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Interventions for actinic keratoses (Review)

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Interventions for actinic keratoses.
Cochrane Database of Systematic Reviews 2012, Issue 12. Art. No.: CD004415.
DOI: 10.1002/14651858.CD004415.pub2.

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[Intervention Review]

Interventions for actinic keratoses

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Editorial group: Cochrane Skin Group
Publication status and date: Edited (no change to conclusions), published in Issue 10, 2019.

Citation: Gupta AK, Paquet M, Villanueva E, Brintnell W. Interventions for actinic keratoses. *Cochrane Database of Systematic Reviews* 2012, Issue 12. Art. No.: CD004415. DOI: 10.1002/14651858.CD004415.pub2.

ABSTRACT

Background

Actinic keratoses are a skin disease caused by long-term sun exposure, and their lesions have the potential to develop into squamous cell carcinoma. Treatments for actinic keratoses are sought for cosmetic reasons, for the relief of associated symptoms, or for the prevention of skin cancer development. Detectable lesions are often associated with alteration of the surrounding skin (field) where subclinical lesions might be present. The interventions available for the treatment of actinic keratoses include individual lesion-based (e.g. cryotherapy) or field-directed (e.g. topical) treatments. These might vary in terms of efficacy, safety, and cosmetic outcomes.

Objectives

To assess the effects of topical, oral, mechanical, and chemical interventions for actinic keratosis.

Search methods

We searched the following databases up to March 2011: the Cochrane Skin Group Specialised Register, CENTRAL in *The Cochrane Library*, MEDLINE (from 2005), EMBASE (from 2010), and LILACS (from 1982). We also searched trials registers, conference proceedings, and grey literature sources.

Selection criteria

Randomised controlled trials (RCTs) comparing the treatment of actinic keratoses with either placebo, vehicle, or another active therapy.

Data collection and analysis

At least two authors independently abstracted data, which included adverse events, and assessed the quality of evidence. We performed meta-analysis to calculate a weighted treatment effect across trials, and we expressed the results as risk ratios (RR) and 95% confidence intervals (CI) for dichotomous outcomes (e.g. participant complete clearance rates), and mean difference (MD) and 95% CI for continuous outcomes (e.g. mean reduction in lesion counts).

Main results

We included 83 RCTs in this review, with a total of 10,036 participants. The RCTs covered 18 topical treatments, 1 oral treatment, 2 mechanical interventions, and 3 chemical interventions, including photodynamic therapy (PDT). Most of the studies lacked descriptions of some methodological details, such as the generation of the randomisation sequence or allocation concealment, and half of the studies had a high risk of reporting bias. Study comparison was difficult because of the multiple parameters used to report efficacy and safety outcomes, as well as statistical limitations. We found no data on the possible reduction of squamous cell carcinoma.

The primary outcome 'participant complete clearance' significantly favoured four field-directed treatments compared to vehicle or placebo: 3% diclofenac in 2.5% hyaluronic acid (RR 2.46, 95% CI 1.66 to 3.66; 3 studies with 420 participants), 0.5% 5-fluorouracil (RR 8.86, 95% CI: 3.67 to 21.44; 3 studies with 522 participants), 5% imiquimod (RR 7.70, 95% CI 4.63 to 12.79; 9 studies with1871 participants), and 0.025% to 0.05% ingenol mebutate (RR 4.50, 95% CI 2.61 to 7.74; 2 studies with 456 participants).

It also significantly favoured the treatment of individual lesions with photodynamic therapy (PDT) compared to placebo-PDT with the following photosensitisers: aminolevulinic acid (ALA) (blue light: RR 6.22, 95% CI 2.88 to 13.43; 1 study with 243 participants, aminolevulinic acid (ALA) (red light: RR 5.94, 95% CI 3.35 to 10.54; 3 studies with 422 participants), and methyl aminolevulinate (MAL) (red light: RR 4.46, 95% CI 3.17 to 6.28; 5 studies with 482 participants). ALA-PDT was also significantly favoured compared to cryotherapy (RR 1.31, 95% CI 1.05 to 1.64).

The corresponding comparative risks in terms of number of participants completely cleared per 1000 were as follows: 313 with 3% diclofenac compared to 127 with 2.5% hyaluronic acid; 136 with 0.5% 5-fluorouracil compared to 15 with placebo; 371 with 5% imiquimod compared to 48 with placebo; 331 with ingenol mebutate compared to 73 with vehicle; 527 to 656 with ALA/MAL-PDT treatment compared to 89 to 147 for placebo-PDT; and 580 with ALA-PDT compared to 443 with cryotherapy.

5% 5-fluorouracil efficacy was not compared to placebo, but it was comparable to 5% imiquimod (RR 1.85, 95% Cl 0.41 to 8.33).

A significant number of participants withdrew because of adverse events with 144 participants affected out of 1000 taking 3% diclofenac in 2.5% hyaluronic acid, compared to 40 participants affected out of 1000 taking 2.5% hyaluronic acid alone, and 56 participants affected out of 1000 taking 5% imiquimod compared to 21 participants affected out of 1000 taking placebo.

Based on investigator and participant evaluation, imiquimod treatment and photodynamic therapy resulted in better cosmetic outcomes than cryotherapy and 5-fluorouracil.

Authors' conclusions

For individual lesions, photodynamic therapy appears more effective and has a better cosmetic outcome than cryotherapy. For field-directed treatments, diclofenac, 5-fluorouracil, imiquimod, and ingenol mebutate had similar efficacy, but their associated adverse events and cosmetic outcomes are different. More direct comparisons between these treatments are needed to determine the best therapeutic approach.

PLAIN LANGUAGE SUMMARY

Interventions for actinic keratoses

Actinic keratoses are a skin disease caused by long-term sun exposure. Damaged skin shows small, red, rough, scaly, flat spots called actinic keratoses or lesions, which feel like patches of dry skin. Symptoms such as bleeding and pain can be associated with actinic keratoses. Moreover, actinic keratoses have the potential to develop into skin cancer if left untreated. The reasons for treatment may include cosmetic appearance, relief of symptoms, or prevention of skin cancer. Treatment can be directed either at individual lesions or to larger areas of the skin where several visible and less visible lesions occur (field-directed treatment).

This systematic review included results from 83 randomised controlled clinical trials evaluating 24 treatments, with a total of 10,036 participants diagnosed with actinic keratosis. We included 18 topical creams or gels applied to a skin area by the participants: adapalene gel, aretinoid methyl sulfone (Ro 14-9706), betulin-based oleogel, calcipotriol (vitamin D), colchicine, diclofenac, 2-(difluoromethyl)-dl-ornithine (DFMO), 5-fluorouracil, ß-1,3-D-glucan, imiquimod, ingenol mebutate (PEP005), isotretinoin, masoprocol, nicotinamide, resiquimod, sunscreen, DL-α-tocopherol (vitamin E), and tretinoin. One treatment, etretinate, was taken orally. Clinical staff administered two mechanical treatments (carbon dioxide and Er:YAG laser resurfacing) on a skin area, and they administered three chemical treatments: cryotherapy on individual lesions, photodynamic therapy on individual lesions or a skin area, and trichloroacetic acid peel on a skin area.

The clinical effects resulting from the treatment of actinic keratoses were reported differently from one study to another. In spite of this inconsistency, it can be concluded that several good treatment options exist for the treatment of actinic keratoses. Actinic keratoses were successfully treated with cryotherapy, diclofenac, 5-fluorouracil, imiquimod, ingenol mebutate, photodynamic therapy, resurfacing, and trichloroacetic acid peel. These different treatments were generally comparably effective. Skin irritation was associated with some of these treatments, such as diclofenac and 5-fluorouracil, but other side-effects were uncommon. The final cosmetic appearance varies from one treatment to another. Imiquimod treatment and photodynamic therapy resulted in better cosmetic appearance than treatment with cryotherapy and 5-fluorouracil.

Treatment with photodynamic therapy gives better therapeutic and cosmetic results than cryotherapy for individual lesions. For field-directed treatments, diclofenac, 5-fluorouracil, imiquimod, and ingenol mebutate are good options associated with different side-effects and cosmetic results. Thus, the choice of treatment option for actinic keratosis depends on the number of lesions, the individual's desired results, and tolerance to the treatments.

BACKGROUND

Description of the condition

Disease definition

Actinic keratoses are scaly lesions on the skin resulting from abnormal growth of atypical epidermal keratinocytes. They are localised at the surface of the skin on the sun-exposed parts of the face or hands, particularly among older fair-skinned individuals. Actinic keratoses are markers for increased rate of non-melanoma skin cancer (Ramsay 2003) and shows the morphological and histological features of squamous cell carcinoma (Cockerell 2000; Feldman 2011). An actinic keratosis could be considered a precancerous lesion or carcinoma in situ based on the fact that the majority of invasive squamous cell carcinomas arise from actinic keratoses. Actinic keratoses are confined to the epidermis, whereas squamous cell carcinoma extends more deeply into the dermis. Thus, to limit the morbidity and mortality associated with squamous cell carcinoma, treatment of actinic keratoses is strongly recommended.

Actinic keratosis is also known as solar keratosis, senile keratosis, senile hyperkeratosis, keratoma senile, keratosis senilis, and actinic cheilitis (actinic keratosis on the lip) (Marks 1993; Rigel 2008; Schwartz 1997).

Clinical Features

The conventional clinical actinic keratosis lesion is a pink, red, or brown scaly patch on the skin, less than one centimetre in diameter (Roewert-Huber 2007). Often, the scaliness of a lesion can be felt before it can be seen; this may progress into thickened or hypertrophic (increased bulk, due to an increase in lesion size) lesions. Actinic keratoses can be clinically graded with grade 1, slightly palpable; grade 2, moderately thick and visible; and grade 3, very thick and hyperkeratotic (Cockerell 2000; Olsen 1991). Accurate clinical diagnosis requires careful observation under adequate lighting conditions and palpation of the lesion texture (Marks 1993). Actinic keratoses are diagnosed histologically with a skin biopsy (Cockerell 2000; Marks 1993). Detectable actinic keratosis lesions are often associated with field change where the surrounding skin is also altered, and subclinical lesions may be present (Vatve 2007).

There are different classifications based on the clinical appearance of actinic keratoses: atrophic, hyperkeratotic, bowenoid, acantholytic, lichenoid, and pigmented (Rigel 2008; Roewert-Huber 2007). Atrophic actinic keratoses are dry, scaly-appearing lesions on a reddened base (due to dilated blood capillaries) without distinct margins. Hyperkeratotic actinic keratoses are papules and plaques with scale or scale-crust that also possibly have cutaneous horns or conical masses. Bowenoid actinic keratoses are scaling red plaques with sharply-established borders that simulate Bowen's Disease (a solitary red plaque with distinct borders) in that the abnormal cells are found throughout the depth of the epidermis. Acantholytic actinic keratoses have focal acantholysis (separation from other cells) occasionally accompanied by clefts. Lichenoid actinic keratoses show dense band-like infiltration of lymphocytes in the papillary dermis and vacuolar alteration at the dermoepidermal junction. Pigmented actinic keratoses have a hyperpigmented or reticulated appearance. Differential diagnosis of actinic keratosis includes Bowen's disease, squamous cell carcinoma, keratoacanthoma, basal cell carcinoma, seborrhoeic keratosis, and lentigo maligna (Holmes 2007).

Symptoms of actinic keratosis include tenderness, itchiness, burning, and a sandpaper-like texture. Over time, lesions may remain unchanged, proliferate, regress, reappear, or develop into squamous cell carcinoma. Microscopically, actinic keratosis lesions show abnormal tissue development (dysplasia) in the skin cells (keratinocytes). During early development of a lesion, the lower layers of the epidermis show the most dysplastic keratinocytes. As a lesion develops, the dysplastic cells permeate the epidermis and form conical-shaped scales when the surface of the epidermis is reached. Acceleration of growth of the epidermal layer and abnormal cellular maturation leads to excessive production of immature adherent scales with a sandpaper or gritty feel (Marks 1993). The lower skin layer (dermis) undergoes patchy inflammation as seen by an increased number of white blood cells (lymphocytes) noted in the dermis (Marks 1993).

Pathogenesis and epidemiology

The anatomical distribution of actinic keratosis lesions correlates with areas of the body that receive the most long-term, chronic, and intense exposure to ultraviolet radiation in sunlight (Marks 1993; Schwartz 1997). More than 80% of the lesions occur on the head, neck, back of the hands, and forearms (Salasche 2000). Chronic exposure to ultraviolet (UV) radiation, mainly UVB (290 to 320 nm), is the major agent leading to mutagenesis (disordered regulation of growth) in keratinocytes (Callen 1997). In fact, mutations in the p53 tumour suppressor gene have been found in 53% of those with actinic keratoses and 69% of squamous cell carcinoma biopsies (Nelson 1994). Ultraviolet radiation can also contribute to suppression of the immune system, resulting in a decreased ability to eliminate over-proliferating cells (Holmes 2007). Moreover, UV light could directly activate human papillomavirus replication. The virus, in turn, degrades a proapoptotic protein BAk, also preventing elimination of tumour cells (Holmes 2007). Thus, sunlight initiates and promotes the formation of non-melanoma skin cancer.

The cause of actinic keratosis involves an interaction between skin colour (melanin protects by absorbing UVB radiation); advancing age (cumulative sun exposure and decrease in the effectiveness of the immune system); gender (actinic keratosis is more prevalent in men); history of severe sunburn in childhood; and sun exposure, which is influenced by latitude and the integrity of the ozone layer (Holmes 2007; Lebwohl 2003; Salasche 2000). Other factors may include occupation (working outdoors), socioeconomic status, and diet (Lebwohl 2003; Marks 1993; Salasche 2000; Schwartz 1997). Immunosuppressive therapy, e.g. in organ transplant recipients, and exhibition of genetic diseases of skin hypopigmentation (low pigmentation), such as xeroderma pigmentosum or albinism (Holmes 2007; Moy 2000), are also risk factors.

The first National Health and Nutrition Examination Survey (NHANES I) found that in healthy white people in the US, the age-adjusted prevalence rate for actinic keratoses was 6.5%. This increases significantly with advancing age: In 65- to 74 year-old men with high sun exposure, the prevalence rate was 55.4% and 18.5% for low sun exposure (Engel 1988). In Australia, where prevalence of actinic keratosis is the highest, as many as 40% of white adults may have an actinic keratosis. For younger adults, aged 30 to 39 years, the rate was 22% for men and 8% for women. In older adults aged 60 to 69 years, 83% of men and 64% of women have an

actinic keratosis. For this population of adults, 42% developed at least 1 new lesion within the year (Frost 2000). Although known to be precancerous, the probability of a lesion undergoing malignant transformation to a squamous cell carcinoma is not clear, but ranges from 0.025% to 16% per year (Glogau 2000; Jeffes 2000).

Description of the intervention

An actinic keratosis may potentially become cancerous; therefore, monitoring is advised. Because of the prevalence of actinic keratoses among an ageing population, treatment has been sought by an increasing number of people (Warino 2006). Reasons for treatment include prevention of cancer development; relief of symptoms, such as bleeding; and improvement of cosmetic appearance. Interventions for actinic keratoses could be divided into individual treatment of lesion and field-directed treatment, i.e. applied to an area of sun-damaged skin where there may be multiple lesions. Individual lesion treatment (spot) might relieve symptoms or cosmetic concerns, whereas field-directed treatment might be more appropriate for prevention of transformation into squamous cell carcinoma. Most of the field-directed treatments are topical treatments where efficacy depends on patient compliance.

Behaviour modifications, including limiting sun exposure between 10am and 4pm, the use of sunscreens with a SPF (sun protection factor) rating of at least 15, and the use of protective clothing, are the best methods for the prevention of actinic keratosis and will help reduce the need for treatment (Schwartz 1997; Wilkerson 1984).

Various strategies for the treatment of actinic keratoses have been developed; these include physician-administered cryotherapy for a few lesions, and topical 5-fluorouracil, topical imiquimod, topical masoprocol, topical diclofenac in 2.5% hyaluronic acid gel, and photodynamic therapy for large numbers of lesions. Salicylic acid may also be used for early lesions, while dermabrasion and laser resurfacing are beneficial when there is coexistent photodamage or multiple recalcitrant lesions. Excision (removal of the lesion, often using a scalpel blade) and chemical peels (use of a caustic agent that causes the lesion to slough off) are both appropriate for hyperkeratotic or recalcitrant lesions. Interferon and oral retinoids are uncommon treatments, and they are still under development. These treatments have varying efficacies and adverse effect profiles (Dinehart 2000; Ibrahim 2009; Marks 1993; Wilkerson 1984).

Thus, the factors to consider when making decisions about treatment include efficacy, tolerability, number of lesions to treat, spot or field-directed treatment, compliance, history of skin cancer, immunosuppression, previous treatment history, and cosmetic appearance.

How the intervention might work

Topical Interventions

Diclofenac gel

One topical treatment for actinic keratoses is the non-steroidal anti-inflammatory drug (NSAID) diclofenac in 2.5% hyaluronic acid gel. The hyaluronic acid vehicle contributes to the success of this treatment by delivering and then retaining diclofenac at the epidermis, protecting against UV radiation and its cosmetic properties (Brown 2005). Although the precise mechanisms of action are not clear, diclofenac is thought to target several aspects of actinic keratosis pathophysiology. One mechanism that has been proposed is the inhibition of cyclooxygenase 2 (COX-2) (Hemmi 2002), which leads to a reduction in prostaglandin synthesis (Rivers 2004). This COX-2 inhibition or other mechanisms may be responsible for diclofenac's inhibition of cell differentiation in vitro, induction of apoptosis in vitro and in vivo, alteration of cell proliferation, and inhibition of angiogenesis (Adamson 2002; Alam 1995; Lu 1995; Seed 1997). Diclofenac has also been shown to activate the nuclear hormone receptors, peroxisome proliferator-activated receptors (PPARs), in vitro; these receptors are involved in many cellular functions including cell differentiation and apoptosis (Adamson 2002).

5-Fluorouracil (5-FU)

This topical agent causes a decrease in cell proliferation and an induction of cell death, particularly in cells with high mitotic (cell division) rates. This occurs through the inhibition of thymidylate synthetase, which blocks the methylation reaction of deoxyuridylic acid to thymidylic acid, thereby, interfering with DNA and RNA synthesis (Berman 2006; Chakrabarty 2004; Eaglstein 1970; Robins 2002b).

Imiquimod

This topical treatment for actinic keratoses is a synthetic compound belonging to the imidazoquinolone family of drugs (Hemmi 2002). It acts as an immune modulator by activating toll-like receptors, ultimately resulting in the modulation of the mRNA expression of many immunomodulatory genes, which induces the production of cytokines by monocytes, macrophages, and epidermal keratinocytes (Correale 2002; Stanley 1999). This has the effect of enhancing innate and acquired immune responses, which leads to strong antiviral and antitumoural activity (Vidal 2006). Imiquimod also induces pro-apoptotic pathways through a variety of mechanisms (Amini 2010).

Chemical Interventions

Cryotherapy

Cryotherapy is often the treatment of choice for individual actinic keratosis lesions (Goldberg 2010). It uses liquid nitrogen to freeze and destroy the epidermis containing actinic keratoses (Goldberg 2010), with efficacy increasing as a function of freezing duration (Thai 2004).

Photodynamic therapy (PDT)

Photodynamic therapy involves the selective accumulation of a photosensitising agent in premalignant or malignant cells (Gold 2008; Juarranz 2008). This is achieved by the application of 5-aminolevulinic acid (5-ALA) or MAL (ALA methyl ester), which are precursors to protoporphyrin IX (PpIX), a potent photosensitiser (Fink-Puches 1997). This causes an excess of PpIX, which selectively accumulates in neoplastic cells. Subsequently, the photosensitiser is activated by visible light, causing the generation of reactive oxygen species in the presence of oxygen. These reactive oxygen species [mainly singlet oxygen ($^1O_2$)] start a cascade of biochemical events that induce damage and the death of neoplastic cells through an apoptotic mechanism (Juzeniene 2007; Moan 1991).

Why it is important to do this review

The existing evidence for use of the various treatment agents for actinic keratoses is varied, and there are concerns regarding

adverse events and cosmetic outcomes. It is vital to critically assess data in terms of the benefits as well as the risks associated with treatment.

OBJECTIVES

To assess the effects of interventions for actinic keratoses.

METHODS

Criteria for considering studies for this review

Types of studies

This review included randomised controlled trials comparing the treatment of actinic keratoses to either placebo, vehicle, other current therapies, or variation in treatment conditions (e.g. different concentrations of the active ingredient or types of light sources for phototherapy). We included cross-over trials and parallel and intraindividual (e.g. left- or right-side comparison) studies.

Types of participants

We included participants with clinical signs of actinic keratoses as assessed by a medical practitioner or histological diagnosis. Diagnostic criteria, such as the Marks definition (Marks 1993) or the Salasche or Schwartz characterisation (Salasche 2000; Schwartz 1997), were acceptable, as was the diagnosis of actinic keratoses by a dermatologist using the terms 'actinic keratosis', 'solar keratosis', 'senile keratosis', 'senile hyperkeratosis', 'keratoma senile', or 'keratosis senilis'. We included studies with immunocompetent and immunosuppressed participants.

Types of interventions

We considered the following interventions:

- prescription-based topical treatments, e.g. diclofenac in hyaluronic gel, 5-fluorouracil, or imiquimod;
- prescription-based oral drugs, e.g. oral retinoids;
- mechanical interventions, e.g. curettage, dermabrasion, or resurfacing;
- chemical interventions, e.g. chemical peels, cryotherapy, or photodynamic therapy; and
- combinations of topical and oral treatments with mechanical or chemical interventions.

The comparators were vehicle, placebo, another active compound or intervention, or a variation of the treatment (duration, concentration, etc).

Types of outcome measures

For actinic keratoses, the outcomes can be expressed per lesion or per participant. Because the participants or body parts of the participants (intraindividual design), not the lesions, were generally randomised, only per-participant outcomes could be included in meta-analyses. Thus, the included outcomes in this review were outcomes reported per participant.

Efficacy outcomes for studies on actinic keratoses are generally based on the clearance of individual lesions. Lesions present at baseline are generally identified, graded (grade I: slightly palpable, better felt than seen; grade II: moderately thick, easily seen and felt; and grade 3: very thick, hyperkeratotic, or both), and mapped. Use of transparencies and photography might help with this process. Sometimes distinction is made between lesions present at the baseline and new lesions appearing during the study. At the end of the study, the assessors evaluate the clearance, or not, of the lesions.

Ideally, complete clearance of actinic keratosis lesions at follow-up would be measured (i.e. number of participants with 100% clearance of target (present at baseline) or all actinic keratosis lesions).

A second outcome measurement, such as partial clearance, is also often used. The definition of partial clearance is subjective but frequently indicates the number of participants with 75% or more of actinic keratosis lesions being completely cleared, i.e. a reduction in the number of lesions by at least 75%.

Alternatively, the mean reduction of total number of lesions at baseline per participant is also used, i.e. the difference between the mean number of lesions at baseline and the mean number of lesions at assessment. The results are then presented as absolute mean or mean percentage of reduction in lesion counts compared to baseline.

We only included outcomes expressed as number of participants experiencing adverse events in this review.

Cosmetic outcomes are really varied from global assessment to individual characteristics, such as changes in pigmentation. We only included outcomes expressed as number of participants or mean per participant in this review.

Primary outcomes

Efficacy outcomes

1. Subjective assessment: global degree of improvement in symptoms or signs as rated by a medical practitioner or participant, or global improvement indices (GII) for completely improved or cleared.
2. Objective assessment: participant complete (100%) or partial (≥ 75%) clearance.
3. Objective assessment: mean reduction in lesion counts (absolute number or percentage).

Secondary outcomes

Safety and cosmetic outcomes

1. Withdrawal due to adverse events.
2. Skin irritation.
3. Minor adverse events excluding skin irritation.
4. Cosmetic outcomes: cosmetic changes, including pigmentation and scarring.

Search methods for identification of studies

We aimed to identify all relevant randomised controlled trials (RCTs) regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We searched the following databases up to 23 March 2011:

- the Cochrane Skin Group Specialised Register using the terms: ((actinic or solar or senile) and keratos*) or hyperkeratos*;
- the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* using the search strategy in Appendix 1:
- PUBMED/MEDLINE via OVID (from 2005) using the strategy in Appendix 2;
- EMBASE via OVID (from 2010) using the strategy in Appendix 3; and
- LILACS (Latin American and Caribbean Health Science Information database, from 1982) using the strategy in Appendix 4.

The UK and US Cochrane Centres have an ongoing project to systematically search MEDLINE and EMBASE for reports of trials, which are then included in the Cochrane Central Register of Controlled Trials. Searching has currently been completed in MEDLINE from inception to 2004 and in EMBASE from inception to 2009. Further searches of these two databases were undertaken for this review by the Cochrane Skin Group to cover the years not searched by the UK and US Cochrane Centres for CENTRAL.

A final prepublication search for this review was undertaken on 4 April 2012. Although it has not been possible to incorporate RCTs identified through this search within this review, relevant references are listed under 'Studies awaiting classification'. They will be incorporated into the next update of the review.

Trials Registers

We searched the following trials registers on 10 March 2011 using the search terms ((actinic, senile, or solar) and keratos) or hyperkeratos.

- The metaRegister of Controlled Trials (www.controlled-trials.com).
- The US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov).
- The Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- The World Health Organisation International Clinical Trials Registry platform (www.who.int/trialsearch).
- The Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

Unpublished literature

We conducted online searches (via pharmaceutical company websites, the U.S. Food and Drug Administration (FDA) website, or both) for the following products and drug companies:

- 3M/Graceway Pharmaceuticals (imiquimod, Aldara, or Zyclara);
- Actavis Mid-Atlantic LLC (imiquimod);
- Allergan (5-fluorouracil, Fluoroplex);
- Apotex (imiquimod);
- Dermik/Sanofi Aventis (5-fluorouracil, Carac);
- DUSA Pharmaceuticals (aminolevulinic acid, Levulan Kerastick);
- Galderma (adapelene, Differin);
- ICN (5-fluorouracil, Efudex);
- Leo Pharmaceuticals (calcipotriol, Dovonex, or Daivonex);
- Mochida Pharmaceuticals (imiquimod, Beselna);
- PharmaDerm/NycoMed US (diclofenac, Solaraze);
- Pharmacia & Upjohn (5-fluorouracil);
- Photocure ASA/Galderma (methyl aminolevulinate, Metvix, or Metvixia);
- Roche (etretinate, Tegison);
- Stiefel/GlaxoSmithKline (isotretinoin, Isotrex, or Isotrexin); and
- URL Pharma (colchicine, Colcrys).

Conference proceedings

We scanned the conference proceedings of the British Association of Dermatologists and the European Academy of Dermatology from 2007 to 2011 for further references to relevant trials. We examined the conference proceedings for 2009 and 2010 of the Annual Meeting of the American Academy of Dermatology, the Annual Meeting of the European Society for Dermatological Research, the Congress of the European Association of Dermatol-Oncology, the Annual Meeting of the British Association of Dermatologists, and the Annual Meeting of the Australasian College of Dermatologists. We scanned the conference proceedings for the 2012 Annual meeting of the American Academy of Dermatology.

Language restrictions

We imposed no language restrictions when we searched for publications. We electronically translated articles published in languages other than English.

Adverse effects

We did not perform a separate search for adverse effects of interventions for actinic keratoses. We looked at reports of adverse events or side-effects in the RCTs identified as a result of our searches, as part of our secondary outcomes.

Data collection and analysis

Selection of studies

At least two authors (WB and MP) independently checked titles and abstracts identified from the searches. We obtained the full text of all studies of possible relevance for independent assessment by two authors (MP and WB). The authors decided which trials fit the inclusion criteria and recorded their methodological quality (MP and WB). They resolved any disagreement by discussion between the authors and a third party arbitrator (AG). Previous contributors also participated in this process in earlier versions of the review.

Data extraction and management

At least two authors extracted and summarised, using data collection forms, the details of eligible trials. One author (MP) double-checked and entered data. The authors were not blinded to the names of the trial authors, journals, or institutions.

Assessment of risk of bias in included studies

Assessment of risk of bias included the Review Manager 5.1 'Risk of bias' assessment tool shown in the 'Risk of bias' tables. In addition, GradePro "quality of evidence" was also used for selected outcomes, and the results are shown in the overview tables for five selected interventions.

Measures of treatment effect

We performed a meta-analysis for each treatment comparison to calculate a weighted treatment effect across trials. We expressed the results as a risk ratio (RR) with 95% confidence intervals (CI) for dichotomous outcomes, and a mean difference (MD) with 95% CI for continuous outcomes. We calculated the number needed to treat (NNT) for significantly different dichotomous outcomes using the following formula: NNT = I 1/ ACR * (1-RR)I where the risk ratios (RR) from the meta-analysis and the moderate assumed control risk (ACR) calculated in GRADEpro was used. For ACR, a mean baseline risk from the study was used for analysis with only one study; and low, median, or high control-group risk were used based on the variation in the included studies in meta-analysis. This previous method would not be applicable to outcomes with an ACR of 0%, i.e. no event in the control group, because of the numerical problems that would ensue.

Unit of analysis issues

The unit of analysis was the participant. We analysed cross-over trials using data from the first phase only and pooled, where possible, with parallel-design studies. We divided results from withinparticipant trials (intraindividual, e.g. split face) into 2 categories: 1) outcomes expressed as number of participants (e.g. participant complete clearance), which could not be included in meta-analyses, were only reported in the text; and 2) outcomes expressed as mean with standard deviation (e.g. mean reduction in lesion counts = mean of reductions observed in each participant), which could be included in meta-analyses using the inverse-variance method. We combined together data from studies with multiple treatments when appropriate (e.g. "all treatment groups" versus "placebo"), or we split the data from the shared group. If studies were using more than one outcome included in this review, we included all outcomes in the analyses.

Assessment of heterogeneity

We assessed heterogeneity using an I^2 statistic value expressed as a percentage. We excluded results from meta-analyses with an I^2 statistic value of 80% or higher. We explored reasons for heterogeneity in studies, and if necessary, sensitivity analyses examined the effects of excluding a study, e.g. those studies with lower methodological quality.

Many studies do not distinguish between the physical location of actinic keratosis lesions on the body. This can introduce heterogeneity, as actinic keratoses of the face and scalp are often more effectively treated by certain topical formulations than lesions located elsewhere. In some studies, pretreatment of lesions to remove hyperkeratosis essentially negated the differences encountered by lesion location, as lower response has been associated with greater hyperkeratosis. Most of the studies included limited their investigation to grade one or two lesions, i.e. minimally to moderate thick lesions. However, when comparing efficacy results from two separate studies using the same treatment, studies incorporating pretreatment of any kind may have accounted for different efficacy rates.

Data synthesis

A random-effects model was prespecified for all meta-analyses. The Mantel-Haenszel method was used for dichotomous outcomes (e.g. cure rates), and an inverse variance model was used for continuous outcomes (e.g. mean reduction in lesion counts).

Subgroup analysis and investigation of heterogeneity

Where appropriate, we undertook subgroup analysis (subgroups of participants) in an attempt to decrease heterogeneity between studies (for example, when different dosing regimens were used or to keep information separated, i.e. when blue or red light was used for photodynamic therapy). In addition, if data were presented for several assessment time points or anatomical locations, we performed subgroup analyses.

RESULTS

Description of studies

See the 'Characteristics of included studies', 'Characteristics of excluded studies', and 'Characteristics of ongoing studies'.

Results of the search

We identified 1001 references from searching bibliographic and trials databases, as well as 28 references through other sources. After removing duplicate references and ongoing studies without results, we had 469 records to screen. We excluded 318 records based on titles and abstracts as they did not meet our eligibility criteria (non-randomised studies, reviews, not interventions to cure). We assessed the full texts of the remaining 151 records. We then excluded a further 55 records, leaving 96 studies. We included 83 of these in our qualitative analysis; 12 are listed under studies awaiting classification, and 1 is an ongoing study. We included 75 studies in our meta-analysis.

The PRISMA study flow chart in Figure 1 summarises the results of the search for studies.

Figure 1. Study flow diagram.

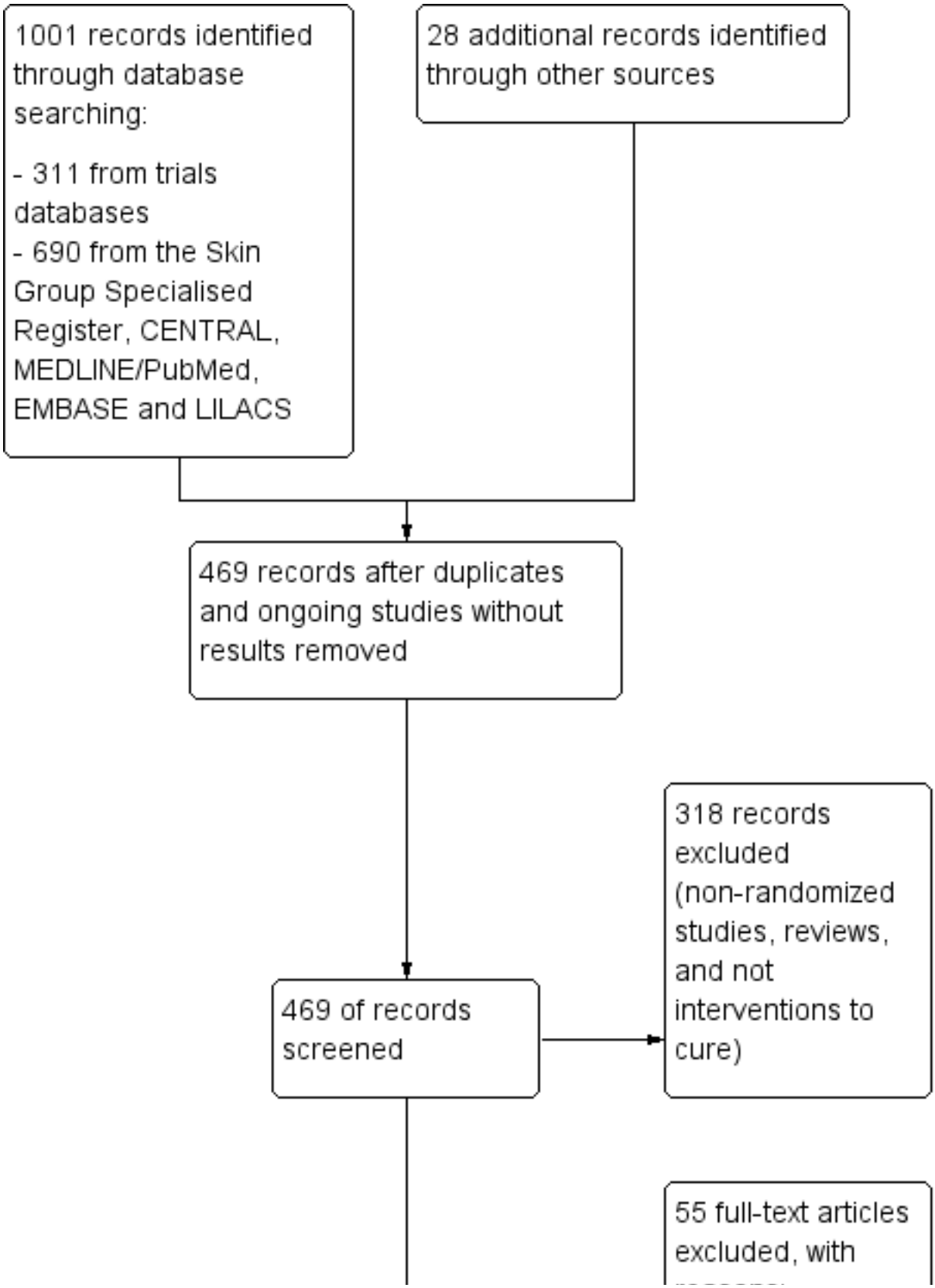


Figure 1. (Continued)

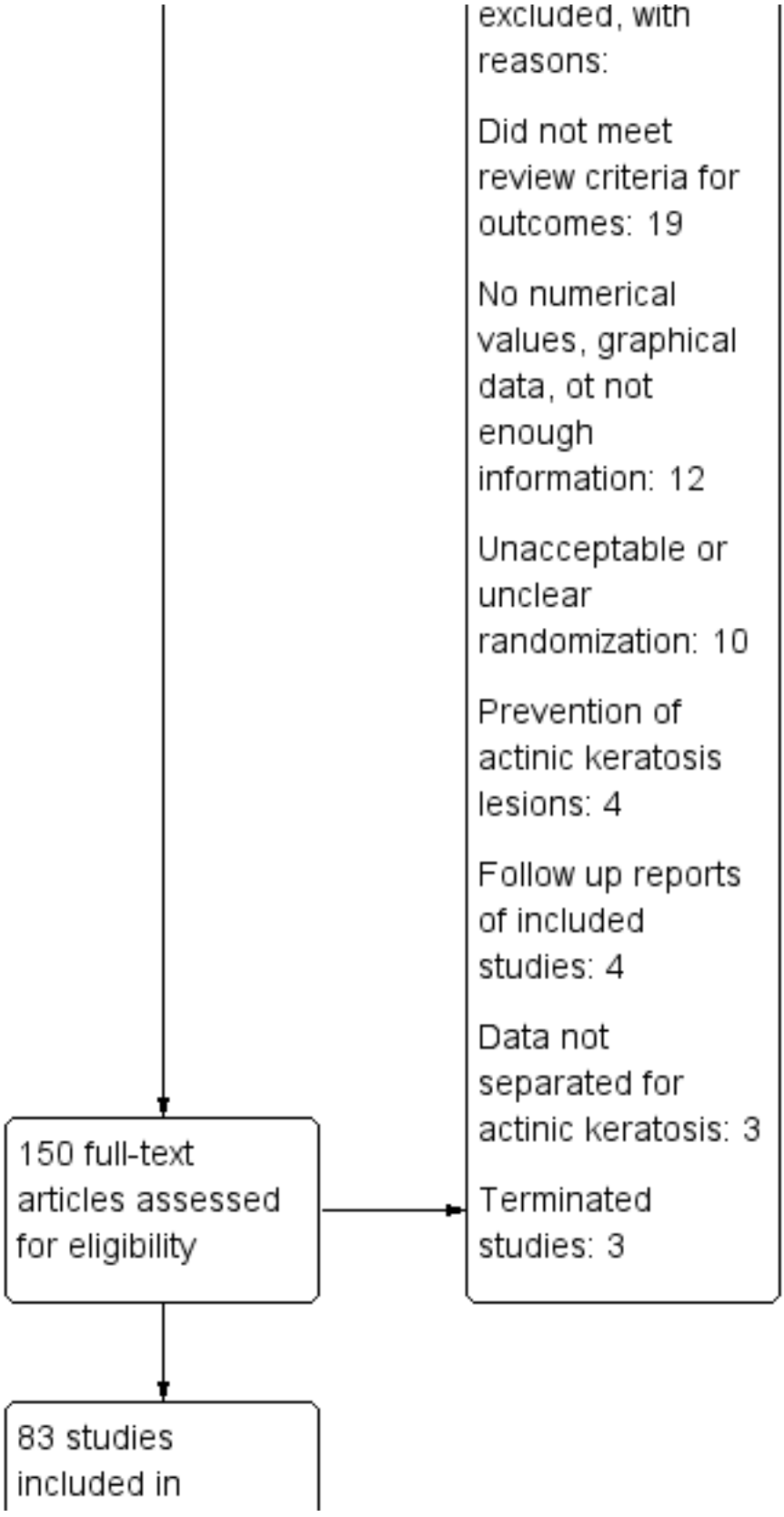
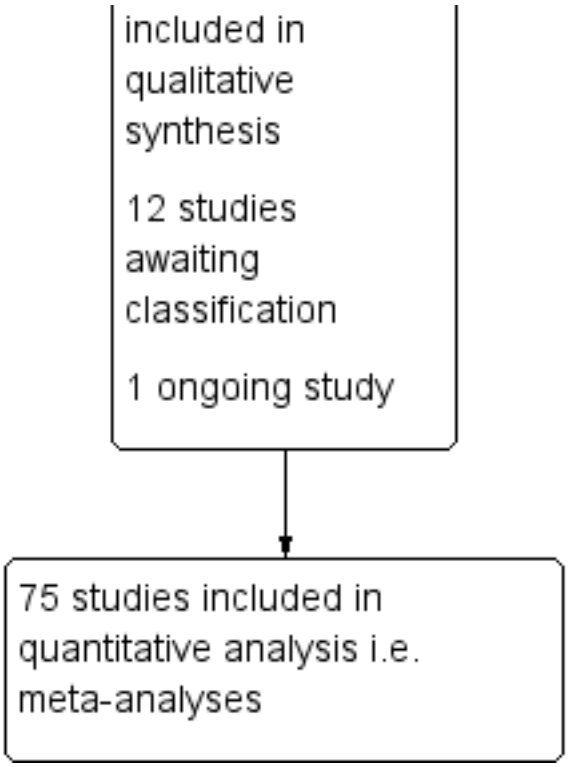


Figure 1. (Continued)



(Please note that in all tables in the results section, the "X" means that the associated outcome was reported, and when there was no participant withdrawal it is specified between parentheses.)

Included studies

We included 83 randomised studies in the review, encompassing 10,036 participants in total.

Design

We only included the randomised (participants or right/left side in intraindividual studies) clinical trials if the interventions were covered by this review and if they reported numerical results for at least one of the review outcomes. This criterion excluded the outcome 'withdrawal due to adverse events', which is generally reported in all studies.

Some studies had more than one design. The design of the studies is summarised in the following table.

	Placebo/vehicle-controlled	**Active-controlled[1]**
Parallel groups	46 studies (including part I of 1 cross-over study)	17 studies
Intraindividual[2]	12 studies	10 studies

1. Active-controlled = compared to another treatment, which could be a different treatment or the same treatment at a different concentration, duration, or types of light used for photodynamic therapy.

2. Intraindividual = within-patients, i.e. different body parts of the same participant received different treatments in parallel (not sequentially).

Sample sizes

Studies ranged in sample size from 4 to 492 participants (124 ± 127, mean ± SD).

Interventions

The interventions assessed in the studies included the following.

Topical treatments

- Adapalene gel
- Aretinoid methyl sulfone (Ro 14-9706)
- Betulin-based oleogel
- Calcipotriol (vitamin D)
- Colchicine
- Diclofenac
- 2-(Difluoromethyl)-dl-ornithine (DFMO)
- 5-fluorouracil (5-FU)
- ß-1,3-D-glucan
- Imiquimod
- Ingenol mebutate (PEP005)
- Isotretinoin
- Masoprocol
- Nicotinamide
- Resiquimod
- Sunscreen
- DL-α-tocopherol (vitamin E)
- Tretinoin

A total of 60 studies investigated topical treatments.

Oral treatments

- Etretinate

One study investigated oral treatment.

Mechanical interventions

- Resurfacing (carbon dioxide and Er:YAG lasers)

Two studies investigated mechanical interventions.

Chemical interventions

- Cryotherapy
- Photodynamic therapy (using a variety of different parameters)
- Chemical peel (trichloroacetic acid)

A total of 37 studies investigated chemical interventions.

Interventions in the included studies could also be segregated based on clinical (e.g. PDT or cryotherapy) or participant (e.g. topical cream) administration, as well as treatments for individual lesions (e.g. cryotherapy) or field-directed treatments (e.g. topical cream).

Participants

Participants in the studies were generally in good health, but a few studies specifically recruited participants with a history of non-melanoma skin cancer. We included studies with organ transplant recipients (immunosuppressed), but these were analysed separately. Responsiveness to immunomodulators may decrease with increasing age, so the age of participants might influence the efficacy of treatments using them. In the included studies, most of the participants were men with mean ages of 60 to 70 years. Lesions were generally grade I (slightly palpable, better felt than seen) or II (moderately thick, easily seen and felt). The location of actinic keratosis lesions, i.e. lesions difficult to access for cream application, could also influence participant compliance and ultimately the efficacy of participant-administered treatments. Lesions were located on the head only (i.e. face, forehead, temples, cheeks, scalp, ear, lips, and neck) in 59 studies, on only non-head locations (upper and lower extremities, legs, arms, elbow, forearms, hands, dorsa of hands, shoulder, décolleté, chest, trunk, and back) in 9 studies, and on both head and non-head locations (including the term "other") in 22 studies. One study did not specify the location of the lesions. In general, lesions were more often located on the face and scalp, which are easy to reach.

Outcomes

Efficacy outcomes

The included studies reported several efficacy outcomes. A lot of the studies did not specify if only target (baseline) lesions or all lesions [i.e. target and subclinical lesions (new lesions appearing during the study)] were included in their analysis. Most of the studies reported more than one outcome. Some of these outcomes corresponded to our primary outcomes or could be transformed into our primary outcomes, whereas others did not meet our criteria for this review. We have summarised the primary and other outcomes in the following table.

Number of studies	Outcomes	Equivalence or transformed into outcome
Primary outcomes		
12	Global improvement indices expressed per participant (Investigator, participant, or both)	Physician global assessment improvement, global therapeutic response or treated area, investigator assessment scale, investigator global assessment, overall response
53	Participant complete clearance (number of participants, rate, proportion, percentages)	Complete responders, total clearance, response to treatment, proportion of participants achieving total clearance, field complete clearance, complete remission, complete response of lesional area, participant's complete resolution, complete clearing, number of participants with 100% clearance, complete participant response, target lesion number score = 0, complete healing, cumulative lesion number score = 0, 100% lesions cleared, percentage of participants who

		experienced 100% clearance of all target lesions, number of participants with all cleared lesions
20	Participant partial (≥ 75%) clearance (number of participants, rate, proportion, percentages)	At least 75% reduction in the number of lesions, at least 75% of lesions cleared, percentage of participants who experienced 75% or greater clearance of all target lesions, therapy responders with at least 75% of clearing of the lesions, participant partial (> 80%) clearance rates
50	Mean reduction in lesion counts (absolute values or percentages)	Mean reduction in the number of actinic keratoses, mean changes of lesion counts, mean numbers of lesions at baseline and assessment time point, mean percentage reduction in the number of actinic keratoses, average changes in lesion counts, mean per cent changes from baseline for all actinic keratoses, mean per cent lesions cleared
Other outcomes		
3	Global improvement indices expressed as scores	Physician global assessment, global improvement score
29	Lesion complete response (per lesions)	Reduction rate in number of actinic keratoses, clearance of individual lesions, rate of totally healed lesions, number of lesions with 0% of remaining area, complete clinical clearance rate on lesion basis, complete clearance rate of lesions, individual lesion clearance, lesion counts at baseline and assessment, percentage lesion reduction, proportion of baseline lesions cleared at the end of treatment, lesions remitted, total lesion counts
9	Median per cent reduction of baseline lesions	Median per cent changes from baseline for all actinic keratoses
6	Participant histological clearance	Histological clearance, histological confirmation
5	Recurrence	-
3	Participant partial (≥ 50%) clearance	Participant with 50% or greater reduction, clearance = resolution of > 50% of the lesions
5	Reduction in lesion size	Overall reduction in lesion area, partial remission (50% size reduction of 75% of lesions), mean diameter of target lesion at baseline and assessment
2	Median number of lesions at baseline and assessment time point	-
1	Participant partial (≥ 66%) clearance	-
1	Participant partial (% not specified) clearance	-
1	Total lesion number score (0 = 0 lesions, 1 = 1 to 3 lesions, 2 = 2 to 4 lesions, 3 = > 6 lesions)	-

1	Negative predictive value, i.e. ratio between histological and clinical clearance	-
1	Participant's perception of efficacy	-
1	Efficacy on a visual analogue scale for field-directed treatment	-
1	Relapse	-

Safety outcomes

There was a lot of variability in the safety outcomes reported by the included studies. Some studies provided briefly qualitative observations on adverse events, whereas others gave detailed quantitative description of adverse events. Intraparticipant studies have limitations in assessing adverse events other than application site and local skin reactions. Adverse events might influence a participant's compliance as well as the maintenance of the blinding. In turn, poor compliance and unblinding could compromise the evaluation of the treatment efficacy. Moreover, adverse events are an important factor in a physician's decision about appropriate treatment for their patients, and a more standardised report of adverse events would be beneficial. The safety outcomes that were our prespecified secondary outcomes found in the included studies, as well as other outcomes, are summarised in the following table.

Number of studies	Outcomes	Equivalence or transformed into outcome
Secondary outcomes		
77	Withdrawal due to adverse events	None lost = all participants completed the trial/study, or lost participants were all justified by other reasons
15	Skin irritation (per participant)	Application site irritation, local irritation, facial irritation, graphical representation of irritation, number of participants reporting relative irritation between treatments
31	Minor adverse events excluding skin irritation (number or percentages of participants)	Most frequent adverse events, number of participants reporting individual adverse events, participants with eye irritation, percentages of participants reporting adverse events for only 1 treatment arm or pooled data, specific treatment-related adverse events
Other outcomes		
16	Application site reactions in general (number or percentages of participants experiencing reactions in general)	Adverse events at treatment sites
15	Application site reactions for specific reactions (number or percentages of participants experiencing specific reactions)	Adverse events at treatment sites
All = 6 Severe = 3	Local skin/adverse reactions - in general (number of percentages of participants)	Local adverse events

All = 33 Severe = 12	Local skin/adverse reactions for specific reactions (number of percentages of participants)	Local skin reactions reported for only 1 treatment arm or pooled data, graphical representation of local skin reactions
20	Participants experiencing at least 1 adverse event (number or percentages of participants)	Number or percentage of participants reporting adverse events, graphical representation of percentages of participants experiencing adverse events
11	Treatment-related adverse events in general (number or percentages of participants)	-
31	Serious adverse events (treatment-related or not)	-
6	Serious adverse events-detection of basal cell carcinoma (presence or not per participant)	-
7	Serious adverse events - detection of squamous cell carcinoma (presence or not per participant)	-
24	Clinical laboratory tests	-
2	Incidences of application site reactions (number of events)	-
1	Application site reactions reported per lesions	-
18	Local tolerability (severe, moderate, mild, absent)	Severity of local skin reactions, global severity rating of local reactions, side-effects (skin reactions) on a scale, irritation severity, severity of facial irritation, severity of local adverse events, grading of individual local reactions, physician's grading of erythema
2	Number of reports of skin irritations	Incidence of local skin reactions
2	Number of participants with strong, moderate, weak, or no inflammatory reaction	-
1	Local phototoxic reactions	-
2	Number of treatment-related adverse events (incidence)	-
1	Qualitative report on treatment-related adverse events	-
22	Qualitative report on skin irritation (types and severity)	Comparison of severity of adverse events between treatments
5	Number of reports of adverse events (incidences)	-
1	Number of reports of serious adverse events	-
12	New actinic keratosis lesions	Subclinical lesions, increase in number of lesions during the study
7	Pain score	Mean visual analogue scale for pain

2	Skin discomfort on a visual analogue scale	-
1	Duration of discomfort	-
1	Erythema measured by skin reflectance meter	-
1	Graft rejection (organ transplant participants)	-
1	Detection of Bowen's disease	-
1	Incidence of new non-melanoma skin cancer	-

The evaluation of the 'skin irritation' outcome was restricted, as only 15 studies had outcomes containing explicitly the term 'irritation'. Several studies reported application site, local skin reactions, or both, which generally included signs and symptoms of skin irritation, such as burning/stinging, erythema, oedema, pruritus, and scaling. We could have included these skin irritation signs and symptoms as more specific 'skin irritation' outcomes if a universal definition of skin irritation existed. Because of the exclusion of skin irritation in the 'minor adverse events' outcome, these reactions as well as the number of participants reporting at least one adverse event, related or not to the treatment (which could include skin irritation), could not be included in any of our secondary outcomes.

Cosmetic outcomes

Only a few studies reported cosmetic outcomes and were varied. In general, cosmetic evaluation was performed on cleared lesions. The cosmetic outcomes that were our prespecified secondary outcomes found in the included studies, as well as other outcomes, are summarised in the following table.

Number of studies	Outcomes	Equivalence or transformed into outcome
Cosmetic outcomes reported per participant		
4	Changes in pigmentation	Hypopigmentation, hyperpigmentation
3	Global cosmetic outcome of "good", "very good", or "excellent"	Final cosmetic results, overall cosmetic outcome
2	Cosmetic appearance score	Total score for cosmetic appearance (erythema, desquamation, induration), cosmetic appearance scores by participant and investigator on a 7-point scale (-3 = much worse to +3 = much better)
4	Skin quality	Decrease in roughness/dryness/scaliness of the skin, normal skin surface, decrease of scarring
4	Improvement in photodamage or photoageing score	Investigator global integrated photodamage, photodamage score (fine lines, mottled pigmentation, tactile roughness, sallowness), photoageing score (global appearance, fine wrinkles, mottled hyperpigmentation, coarse wrinkles, rosy glow)
2	Significantly - or much- improved cosmetic outcome	-
1	Decreased infiltration and disappearance of crust	-

1	Proportion of participants with improvement of surface with actinic damage	Note: the number of participants was not given and could not be included in the analysis
Other outcomes		
5	Cosmetic outcomes per cleared lesions	-
2	Total thickness score	-
1	Changes in pigmentation per lesions	-

Other outcomes

The studies sometimes reported additional outcomes, and they are summarised in the following table. They rarely reported important outcomes, such as compliance, (7 studies) compared to the number of studies investigating participant-administered treatments (63 studies, including 3 daylight photodynamic therapy studies).

Number of studies	Outcomes
10	Participant's satisfaction
8	Rest periods or temporary interruption during treatment
7	Compliance
6	Participant's preference
2	Biological and immunological outcomes
1	Skin concentrations of drug and products due to its mechanism of action
1	Investigator's preference
1	Lesion severity index
1	Quality of life on a visual analogue scale
1	Number of spray cooling for photodynamic therapy

In 2011, we contacted the following authors to get clarification on the studies included.

Author	Topic	Clarification
Kurt Gebauer	Type of analysis used in the study Gebauer 2003	Intention-to-treat
Joseph Jorizzo	Type of analysis used in the studies Jorizzo 2002 and Jorizzo 2006	The type of analysis could not be confirmed
Iraji Fariba	Outcome presented was 'lesions complete response' or 'participant complete clearance' in the study Fariba 2006	No response received
Emil Tanghetti	Type of analysis used in the study Tanghetti 2007	Intention-to-treat

Excluded studies

Generally, we excluded studies if they were not randomised clinical trials on interventions to cure actinic keratosis lesions (actinic keratoses). In addition, we excluded some randomised studies for the reasons cited in the tables of excluded studies in the 'Characteristics of excluded studies' section. The following table summarises the main reasons for the exclusion of these studies.

Data not separated for actinic keratoses	Did not meet review criteria for outcomes	Unacceptable or unclear randomisation	No numerical values, graphical data, or not enough information	Prevention of actinic keratosis lesions	Follow-up reports on included studies
Alberts 2004	Apalla 2010b	Alexiades-Armenakas 2003	Apalla 2010a	Apalla 2010c	Fowler 2002
Green 1998	Babilas 2007	Babilas 2006	Breza 1976	Elmets 2010	Hanke 2011
Humphreys 1996	Babilas 2008	Berlin 2008	de Sévaux 2003	Naylor 1995	Stockfleth 2004
	Bartels 2009	Gold 2006	Dermik 2003	Wennberg 2008	Szeimies 2010a
	Biecha-Thalharnmer 2003	Goldman 2003	Gupta 2004		
	Braathen 2009	Griffin 1991	Robins 2002a		
	Dirschka 2010	Grimaître 2000	Rosen 2010		
	Edwards 1986	Marrero 1998	Simmonds 1973		
	Epstein 2006	Tsoukas 2010	Spencer 2010		
	Ericson 2004	Valeant 2004	Touma 2004		
	Jury 2005		Weinstock 2010		
	Kurwa 1999		Yamauchi 2002		
	Morales 2010				
	Puizina-Ivic 2008a				
	Radakovic-Fijan 2005				
	Shuttleworth 1989				
	Smith 2006				
	Sotiriou 2011				
	Wulf 2006				

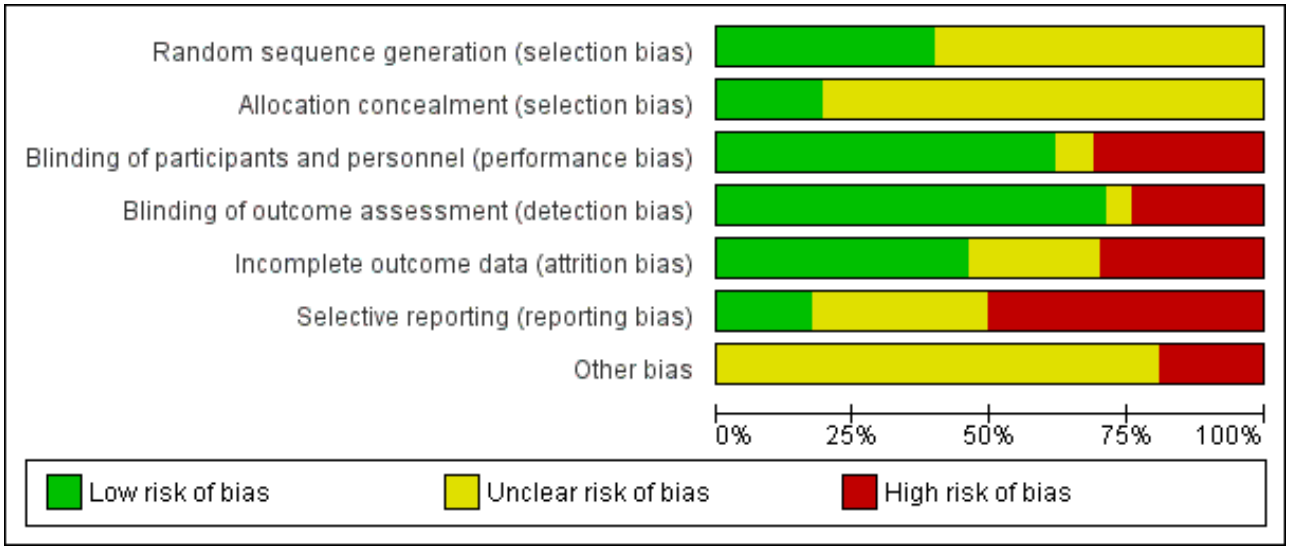
In 2011, we tried to contact the following author to get clarification on the studies excluded.

Author	Topic	Clarification
Barbara A. Gilchrest	1) Number of treatment arms and number of participants allocated 2) Mean numbers of lesions and their standard error of the mean (SEM) for the 3 groups, i.e. 1, 2, and 3 hours	1) 3 groups of 6 participants each incubated for 1, 2, or 3 hours 2) not received

Risk of bias in included studies

Please refer to the 'Risk of bias' tables for each included study, which are part of the 'Characteristics of included studies' tables, and the summary figure, Figure 2 ('Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Ffity studies were judged to be at low risk of bias with regard to the method used to generate the randomisation sequence, which were stratification (Alberts 2000; Foote 2009; Freeman 2003; Hauschild 2009a; Hauschild 2009b; Pariser 2003; Pariser 2008; Szeimies 2002; Thompson 1993), computer-generated randomisation schedule (Gebauer 2009; Huyke 2009; Jorizzo 2004; Jorizzo 2006; Jorizzo 2010; Korman 2005; Lebwohl 2004; Loven 2002; Ooi 2006; Ostertag 2006; Szeimies 2004; Szeimies 2009; Szeimies 2010b; Wiegell 2011a), permuted block randomisation (Anderson 2009; Chen 2003; Kang 2003; McEwan 1997; Moloney 2010; Szeimies 2008; Wiegell 2011a), shuffling of envelopes or drawing of lots (Wiegell 2008; Wiegell 2009), and random digits table or number generator (Seckin 2009; Shaffelburg 2009).

Only 16 studies stated the methods used for allocation concealment before the treatments were assigned, and we judged these studies at low risk of bias. Eight studies used opaque sealed envelopes (Chen 2003; Freeman 2003; Moloney 2010; Szeimies 2004; Tarstedt 2005; Wiegell 2008; Wiegell 2009; Wiegell 2011a). Two studies assigned the next sequential number (Korman 2005; Shaffelburg 2009). An external person (pharmacist, sponsor, or CRO) handled the randomisation process in six studies (Krawtchenko 2007; Pariser 2008; Siller 2009; Stockfleth 2002; Swanson 2010a; Van der Geer 2009).

Blinding

Double-blind or assessor-blind were used in 58 and 10 studies, respectively. Nine studies were open. In some of these studies, blinding was difficult because of the nature of the treatments being compared (e.g. surgical treatment versus topical treatment). Some authors also reported that adverse events, such as the local skin reactions associated with some treatments, might have compromised the blinding. In these cases, different investigators could have been involved in the treatment/safety assessment and the efficacy assessment in order to keep the part of the assessment blinded. Additionally, the use of photography in the evaluation process could help to keep the assessor blinded. The evaluation of the risk of bias for participants, personnel and assessors took into consideration the type of blinding, and when possible, the possibility of unblinding. Of our 83 included studies, we judged 48 as at low risk of bias for both these domains, 19 studies, at high risk of bias, and 3, as unclear for both domains.

Incomplete outcome data

Three studies used intention-to-treat (ITT) analyses, and 25 studies used per-protocol (PP) analyses. Nine studies used both types of analysis. The type of analysis was undetermined in 12 studies. Most studies adequately recorded characteristics of participants not completing the study. We considered studies where $\leq$ 20% of enrolled participants dropped out as acceptable, and only three studies (Alirezai 1994; Persaud 2002; Zeichner 2009) exceeded 20%. For the meta-analyses, we favoured data from ITT analyses over PP analyses, and we converted PP data to ITT data when possible. The evaluation of the risk of bias took into consideration the type of analysis, the number of dropouts, if the reasons for the dropouts were given, and possible discrepancy in the data presented.

Selective reporting

We judged 14 studies as at low risk of bias based on the following criteria: 1) The study protocols were available, and all the prespecified outcomes were presented; 2) the same data were presented in different formats (abstract, protocol with data, product insert, and published report); or 3) non-significant outcomes were reported.

We judged 42 studies as at high risk of bias based on the following criteria: 1) Not all prespecified outcomes in the protocol or methods section were presented (e.g. the percentage in mean reduction in lesion counts was stated, but only absolute counts were presented); or 2) when the outcomes were incompletely reported and could not be entered in meta-analysis (e.g. the standard deviations associated with mean reduction in lesion counts were not reported and the statistical significance between treatments was impossible to determine). We encountered this last example frequently. A few studies only gave data for only one treatment arm or pooled together for different treatment arms. For example, they did not always report adverse events separately for the different treatments. Of course, separate reports were impossible for studies using intraindividual study design.

Twenty-seven studies reported unclear risk of bias. We refer the readers to the 'Risk of bias' tables for each included study for additional information on possible publication bias.

Effects of interventions

We presented the data and analyses of the included studies in two sections.

A) Overviews of the results with five selected outcomes (three primary and two secondary outcomes) expressed as comparative risks and risk ratios (RR) for five selected interventions in immunocompetent participants.

B) Results expressed as risk ratios (RR), number needed to treat (NNT), and mean difference (MD) presented for all interventions and all reported primary and secondary outcomes.

A) Overviews of selected interventions

Because of the variety of data presented for the different outcomes, we made a selection based on the data most frequently presented. For example, 'participant complete clearance' has been reported for target, subclinical, and all lesions, but most of the included studies reported data for all lesions. Thus, to be able to compare the different treatments and keep the summary table simple, we only included 'participant complete clearance' for all lesions. When data were presented for different cycles of treatments, only data for one cycle were included. Selections specific for one treatment are described in the comments section of the overview tables.

Diclofenac in 2.5% hyaluronic acid

Table 1 is an overview for 3% diclofenac in 2.5% hyaluronic acid.

In summary, diclofenac was significantly more efficacious than its vehicle, 2.5% hyaluronic acid. It was also associated with more adverse events, based on the number of participants who withdrew because of adverse events and the number of participants who experienced skin irritation. Diclofenac treatment in 2.5% hyaluronic acid combined with ALA-PDT might increase the long-term efficacy compared to ALA-PDT with 2.5% hyaluronic acid.

5-fluorouracil (5-FU)

Table 2 is an overview for 5-fluorouracil.

In summary, 0.5% and 5% 5-fluorouracil treatments resulted in similar efficacy and safety based on 1 study comparing them directly. 5-Fluorouracil was significantly more efficacious than vehicle and cryotherapy, but similar to ALA-PDT (see PDT overview table: Table 3) and carbon dioxide laser resurfacing. More studies are needed to confirm its superiority to masoprocol and imiquimod and its long-term inferiority to Er:YAG laser resurfacing. In 1 study, additional treatment with 5-fluorouracil increased the efficacy of cryotherapy with vehicle, but the efficacy (illustrative comparative risks) of cryotherapy alone in this study seemed much lower than other studies investigating cryotherapy (see cryotherapy overview table: Table 4). On the other hand, additional treatment with tretinoin did not improve the efficacy of 5-fluorouracil. In general, 5-fluorouracil treatment did not lead to withdrawal because of adverse events; however, substantial skin irritation was associated with this intervention.

Imiquimod

Table 5 is an overview for imiquimod.

In summary, imiquimod was significantly more efficacious than vehicle, but similar to cryotherapy and 3% diclofenac in 2.5% hyaluronic acid (based on another efficacy outcome presented below). More studies are needed to confirm its inferiority to 5% 5-fluorouracil. Additional treatment with 3.75%, but not 5%, imiquimod increased the efficacy of cryotherapy, but the efficacy (illustrative comparative risks) of cryotherapy with vehicle in this study seemed much lower than other studies investigating cryotherapy alone (see cryotherapy overview table: Table 4). More data are needed to be able to compare 5% imiquimod to photodynamic therapy, and additional treatment with imiquimod did not improve the efficacy of photodynamic therapy. Treatment with 5% imiquimod resulted in a larger number of participant withdrawals due to adverse events than treatment with 2.5% and 3.75% imiquimod.

Cryotherapy

Table 4 is an overview for cryotherapy.

In summary, cryotherapy had similar efficacy to betulin-based oleogel and imiquimod. Cryotherapy was significantly inferior to 5-fluorouracil and ALA-PDT. No conclusion could be made on its efficacy compared to MAL-PDT based on our primary outcomes. Additional treatment with 5-fluorouracil or imiquimod might increase the efficacy of cryotherapy, but these studies had generally lower efficacy associated with cryotherapy with vehicle treatment than the other studies with cryotherapy alone. Cryotherapy was generally not associated with withdrawal due to adverse events and had less skin irritation than ALA-PDT3.

Photodynamic therapy (PDT)

Table 3 is an overview for photodynamic therapy.

In summary, similar efficacy was obtained for the two photosensitising agents, ALA and MAL, under similar photodynamic therapy conditions. The use of ALA/MAL with blue or red light PDT resulted in similar results, which were significantly different than vehicle with blue or red light PDT. Longer incubation (4 hours [h]) with ALA resulted in better results compared to shorter incubation time (0.5, 1, and 2 hours). Consequently, 4-hour incubation with ALA followed by PDT was significantly more efficacious than cryotherapy, but 1-hour incubation with ALA followed by PDT (blue light or pulsed dye laser) was not significantly different than 0.5% 5-fluorouracil. Additional treatment with 5% imiquimod

did not improve the efficacy of ALA-PDT. With MAL-PDT, similar efficacy was observed for red light, broad visible light with water-filtered infrared A, and daylight. With daylight PDT, no difference was found between 16% and 8% MAL or between 2-hour and 3-hour incubation with MAL before daylight exposure. Based on our primary outcomes, no conclusion could be made on MAL-red light PDT efficacy compared to cryotherapy or the benefit of multiple versus single treatment. Photodynamic therapy generally did not lead to withdrawal because of adverse events. Based on the only two studies reporting skin irritation, incubation with ALA might cause skin irritation.

B) All interventions

This section is addressed as planned in 'Criteria for considering studies for this review' and 'Types of interventions':

(1) Prescription-based topical treatments
(2) Prescription-based oral drugs
(3) Mechanical interventions
(4) Chemical interventions
(5) Combinations of topical and oral treatments with mechanical or chemical interventions

(1) Prescription-based topical treatments

Prescription-based topical treatments, which are generally field-directed treatments, were addressed in alphabetical order: adapalene gel, aretinoid methyl sulfone (Ro 14-9706), betulin-based oleogel, calcipotriol, colchicine, diclofenac, 2-(Difluoromethyl)-dl-ornithine (DFMO), 5-fluorouracil (5-FU), β-1,3-D-glucan, imiquimod, ingenol mebutate (PEP005), isotretinoin, masoprocol, nicotinamide, resiquimod, sunscreen, DL-α-tocopherol (vitamin E), and tretinoin.

Adapalene gel

This intervention was addressed by only 1 study (Kang 2003), which compared the efficacy of 0.1% adapalene gel, 0.3% adapalene gel, and vehicle gel for the treatment of actinic keratoses on the face, ears, scalp, arms, and back of the hands. Participants were treated with adapalene gel or placebo daily for four weeks, followed by twice-daily applications for up to nine months. The assessment was performed at the end of treatment. There was no major source of possible bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 90 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 90 participants)
Kang 2003	Investigator	-	-	Absolute values

With regard to the outcome 'global Improvement Indices (investigator): completely improved or cleared', we detected no significant difference in efficacy between adapalene and placebo treatments (Analysis 1.1), or between 0.1% and 0.3% adapalene (Analysis 2.1). The proportion of participants who had positive outcomes (clear, marked, moderate, or slight improvements) was higher in participants treated with adapalene (52/60) than those treated with placebo (21/30), and the proportion of participants graded unchanged or worse was higher in those treated with placebo (9/30) than those that were adapalene-treated (8/60) (Kang 2003).

Mean changes [reduction (-) for adapalene and increase (+) for placebo] in the number of actinic keratoses from baseline were the means of measuring efficacy. Compared to placebo, both 0.1% and 0.3% adapalene gel resulted in a significant reduction in mean lesion counts [0.1% = MD -2.00, 95% CI -2.73 to -1.27, and 0.3% = MD -4.00, 95% CI -4.73 to -3.27; Analysis 1.2]. The 0.3% adapalene gel was significantly more efficient than 0.1% adapalene gel in reducing the number of lesions [MD -2.00, 95% CI -2.46 to -1.54; Analysis 2.2].

Secondary outcomes

Study	Withdrawal due to adverse events (N = 90 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 90 participants)	Cosmetic outcome (N = 42 participants)
Kang 2003	x	-	x	Graph

Three participants in the 0.3% adapalene group had to withdraw because of these adverse events: skin irritation, dermatitis, and eye dryness. This number of participants was not significantly different from the placebo group (Analysis 1.3) or the 0.1% adapalene treated-group (Analysis 2.3).

Dermatitis was the only minor adverse event reported quantitatively. Dermatitis was significantly more frequent in the

participants treated with adapalene (20/60) than with placebo (3/30) [RR 3.33, 95% CI 1.08 to 10.34; Analysis 1.4], corresponding to a NNT for an additional harmful outcome of 4.3. In contrast, the number of participants experiencing dermatitis was similar in the 0.1% and 0.3% adapalene-treated groups (Analysis 2.4).

Kang 2003 graphically reported improvements in the following clinical features of photoageing of the skin: mottled hyperpigmentation, fine wrinkles, coarse wrinkles, and rosy glow. The authors stated that a significant difference between adapalene and placebo was detected for global appearance, mottled hyperpigmentation, fine wrinkles, and rosy glow, but not for coarse wrinkles. The exact percentages of participants with improvement in mottled hyperpigmentation were given (55% in the 0.1% group, 65% in the 0.3%, and 25% in the placebo group), but only a subpopulation of participants were evaluated, and the number of participants for each treatment group was not given. Thus, no statistical analysis was performed on this data.

To summarise, adapalene gel was more efficient than placebo in treating actinic keratoses. In addition, 0.3% adapalene gel gave better results than 0.1% adapalene gel, based on the mean reduction in lesion counts without an increase in adverse events.

Aretinoid methyl sulfone (Ro 14-9706)

Ro 14-9706 versus 0.05% tretinoin

This intervention was addressed by only 1 intraindividual study (Misiewicz 1991), which compared the efficacy of 0.05% Ro 14-9706 and 0.05% tretinoin applied twice-daily for 16 weeks for the treatment of facial actinic keratoses. Assessment was performed at the end of the 16-week treatment. There was no major source of possible bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 25 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 25 participants)
Misiewicz 1991	x	-	-	Percentages

Because of the study design, i.e. intraindividual study, the data for 'global improvement indices' for participants receiving the two different interventions could not be included in a meta-analysis, but is presented in the following table.

Number of participants with the following improvements	Ro14-9706	Tretinoin
Complete response	0/25	2/25
Partial response	12/25	10/25
No response	13/25	11/25
Worsening	0/25	2/25

Areas treated with tretinoin cream showed an initial increase in the number of lesions (weeks 3 to 9), which eventually decreased after week 10. Ro 14-9706 showed no initial increase in number of actinic keratoses lesions, but a gradual decline over time. The resulting mean percentage of reduction in lesion counts was significantly higher in the group treated with Ro 14-9706 than the group treated with tretinoin (MD 7.50, 95% CI 6.57 to 8.43; Analysis 3.1).

Secondary outcomes

Misiewicz 1991 reported none of our secondary outcomes.

To summarise, Ro 14-9706 treatment showed better overall reduction in lesion counts, whereas tretinoin treatment, which showed an initial increase in lesions, resulted in more participants with complete response.

Betulin-based oleogel

Studies using betulin-based oleogel used this treatment as a comparator for cryotherapy. The results will be discussed in the cryotherapy section below.

Calcipotriol (vitamin D)

This intervention was addressed by only one study (Seckin 2009), which compared the efficacy of calcipotriol (vitamin D) to placebo treatment for actinic keratoses on the face and scalp. One treatment was applied on 1 randomised side of the face, and the other treatment on the other side twice daily for 12 weeks. Assessment was performed at the end of the 12-week treatment. There was possible attrition and reporting bias associated with this study.

Primary outcomes

Study	Global improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 8 participants)
Seckin 2009	-	-	-	Absolute values, percentages

Mean changes [reduction (-) for calcipotriol and increase (+) for placebo] in the number of actinic keratoses from baseline were the means of measuring efficacy. In contrast to placebo, calcipotriol reduced the number of lesions; however, the overall effect was not statistically different (Analysis 4.1). In addition, no statistical difference in the mean percentage of reduction in lesion counts was detected by the authors (Seckin 2009).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 8 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 8 participants)
Seckin 2009	x (none lost)	-	-	x

There were no participant withdrawals due to adverse events.

The reduction of the total score for cosmetic appearance, which rated erythema, desquamation, and induration of a target lesion, was not different between the calcipotriol and placebo groups (Analysis 4.2).

To summarise, the data available for treatment of actinic keratoses with calcipotriol could not demonstrate its superiority for efficacy or cosmetic outcomes compared to placebo.

Colchicine

This intervention was addressed by only 1 study (Akar 2001), which compared the efficacy of 1% colchicine to 0.5% colchicine for actinic keratosis lesions. Both 0.5% and 1% colchicine were applied twice daily for 10 days on the face, scalp, and upper extremities. Assessment was performed at four weeks. There was no major source of possible bias.

Primary outcomes

Study	Global improvement indices for completely improved or cleared	Participant complete clearance (N = 16 participants)	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 16 participants)
Akar 2001	-	x	-	Absolute values

In general, 0.5% and 1% colchicine treatments resulted in similar efficacy, with 7/8 and 6/8 participants completely cleared (Analysis 5.1) and similar mean reduction in lesion counts for all lesions (Analysis 5.2) or by anatomical locations (Analysis 5.3).

Secondary outcomes

Study	Withdrawal due to adverse events	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 16 participants)
Akar 2001	-	-	-	x

The final cosmetic results in successful cases were good for both colchicine concentrations, as supported by the quantitative analysis of the number of participants with decreased infiltration

and disappearance of crust at one month (Analysis 5.4), which showed no difference between the two treatments.

To summarise, 0.5% and 1% colchicine had similar efficacy and cosmetic outcomes and showed high efficacy (81% of participants completely cleared); however, these conclusions were based on a small sample size.

Diclofenac

Diclofenac versus vehicle

This intervention was addressed by 7 studies (Fariba 2006; Gebauer 2003; McEwan 1997; Rivers 2002; Solaraze study 2; Ulrich 2010; Wolf 2001) comparing 3% diclofenac in 2.5% hyaluronic acid gel to 2.5% hyaluronic acid gel, for the treatment of actinic keratoses. The characteristics of these studies are presented in the following table. There was possible attrition bias (McEwan 1997; Ulrich 2010), reporting bias (Solaraze study 2; Ulrich 2010), and other bias (Fariba 2006; McEwan 1997).

Characteristic	McEwan 1997	Wolf 2001	Rivers 2002	Solaraze study 2	Gebauer 2003	Fariba 2006	Ulrich 2010
Study design	Parallel-group	Parallel-group	Parallel-group	Parallel-group	Parallel-group	Intraindividual	Parallel-group
Anatomical locations	Face, scalp, ear, neck, lower arm/elbow, hand, lower leg/knee	Forehead, central face, scalp, arms, hands	Forehead, central face, scalp, dorsum of hands	Face, scalp, forehead, arm, forearm, back of hands	Head/neck, hands, or arms	Face or scalp	Face, scalp, hands
Diclofenac concentration (%)	3	3	3	3	3	3	3
Frequency of treatment	Twice daily	Twice daily	Twice daily	Twice daily	Twice daily	Twice daily	Twice daily
Duration given (days)	56 to 168	90	30, 60	90	90	90	112
Assessment	At the end of 24-week treatment	4 weeks after the end of treatment	4 weeks after the end of treatment	4 weeks after the end of treatment	At the end of 12-week treatment and 4 weeks after the end of treatment	At the end of 12-week treatment	At the end of 16-week treatment

In Ulrich 2010, participants were immunosuppressed (organ transplant patients). Three of the included studies (Rivers 2002; Solaraze study 2; Wolf 2001) were part of the Solaraze product insert, and the number of participants experiencing at least one adverse event was pooled and reported in the Solaraze study 2.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 312 participants)	Participant complete clearance (N = 490 participants)	Participant partial (≥ 75%) clearance (N = 28 participants)	Mean reduction (changes) in lesion counts (N = 345 participants)
McEwan 1997	-	x	-	-
Wolf 2001	Investigator and participant	x	-	-
Rivers 2002	Investigator and participant	x	-	Absolute values
Solaraze study 2	-	x	-	-
Gebauer 2003	-	x	-	Absolute values
Fariba 2006	-	-	-	-
Ulrich 2010	-	x	x	Percentages

Efficacy measurements using investigator and participant global improvement indices for the outcome 'completely improved' showed the superiority of the 3% diclofenac in 2.5% hyaluronic acid gel over 2.5% hyaluronic acid gel alone for 60-day treatment [investigator: RR 3.06, 95% CI 1.21 and 7.77, NNT= 4.8; participant: RR 2.86, 95% CI 1.12 to 7.32, NNT = 5.3] and 90-day treatment [investigator: RR 2.50, 95% CI 1.37 to 4.55, NNT = 3.6; participant: RR 2.44, 95% CI 1.28 to 4.64], but not for 30-day treatment [investigator and participant: RR 4.00, 95% CI 0.89 to 17.89] (Analysis 6.1; Analysis 6.2).

We performed seven meta-analyses for the outcome 'participant complete clearance'.

1. Analysis for efficacy assessment at the end of treatment: The 2 studies that reported the efficacy assessment at the end of treatment used a treatment period longer than 30 days and showed the superiority of the diclofenac treatment over 2.5% hyaluronic acid gel alone [RR 1.95, 95% CI 1.21 to 3.13, NNT = 7.1] (Analysis 6.3).
2. Analysis for efficacy assessment after a 30-day follow-up for target lesions, i.e. present at baseline: This was similar to the global improvement indices for completely improved 60- and 90-day treatments, but not 30-day treatment. Diclofenac/hyaluronic acid showed superiority over the vehicle for target lesions [(60 days: RR 3.27, 95% CI 1.30 to 8.21, NNT = 4.3) (90 days: RR 2.87, 95% CI 1.84 to 4.48, NNT = 3.4) (Analysis 6.4)].
3. Analysis for efficacy assessment after a 30-day follow-up for all lesions, i.e. target and new lesions: Again, participant complete clearance was significantly different for 60-day therapy (RR 3.83, 95% CI 1.37 to 10.71, NNT = 4.3) and 90-day therapy (RR 2.20, 95% CI 1.40 to 3.44, NNT = 4.5), but not after 30 days of therapy (RR 3.50, 95% CI 0.76 to 16.01). The pooled RR was 2.46 (95% CI 1.66 to 3.66, NNT = 5.4) (Analysis 6.5). The small sample sizes resulted in no significant difference in the RRs for participant complete clearance between the different anatomical locations.
4. Analysis for 30-day treatment with subgroups by anatomical locations (Analysis 6.6).
5. Analysis for 60-day treatment with subgroups by anatomical locations (Analysis 6.7).
6. Analysis for 90-day treatment with subgroups by anatomical locations: In contrast to locations on the face or forehead, the RRs for scalp, arm/forearms, and back of the hands did not favour diclofenac for 90-day treatment over vehicle, because of the variability between studies (Analysis 6.8).
7. Analysis of immunosuppressed participants with efficacy assessment after a 30-day follow-up (Analysis 6.9): In immunosuppressed participants, statistically significant superiority of 16-week treatment with diclofenac over placebo could not be demonstrated despite a large effect for participant complete clearance (RR 5.78, 95% CI 0.38 to 87.35; Analysis 6.9) or partial (> 75%) clearance (RR 3.55, 95% CI 0.57 to 21.94; Analysis 6.10). This was probably due to the small number of participants involved in this single study. Further studies are needed to be able to conclude on the efficacy of diclofenac in immunosuppressed participants.

The healing properties of diclofenac seem to continue after treatment. There was no significant difference in the mean reduction of lesion counts at the end of 60- to 90-day treatment between diclofenac and vehicle (2.5% hyaluronic acid gel) (Analysis 6.11). In contrast, a significantly better reduction in lesion counts was achieved by the diclofenac treatment compared to 2.5% hyaluronic acid gel alone after a 30-day follow-up (MD of at least 2.00; Analysis 6.12). For the immunosuppressed participants, a

mean reduction of 53% in the lesion counts was observed for diclofenac, whereas a mean increase of 17% was observed for 2.5% hyaluronic acid gel alone. A statistical analysis could not be performed because standard deviations were not provided.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 644 participants)	Skin irritation (N = 20 participants)	Minor adverse events excluding skin irritation (N = 462 participants)	Cosmetic outcome (N = 32 participants)
McEwan 1997	x	-	-	-
Wolf 2001	x	-	In general (excluding dermatology because it could include skin irritation) and specific adverse events based on body system	-
Rivers 2002	x	-	x	-
Solaraze study 2	-	-	-	-
Gebauer 2003	x	-	x	-
Fariba 2006	x (intraindividual)	x	-	-
Ulrich 2010	x	-	-	x

None of the participants (N = 20) in the intraindividual study by Fariba 2006 withdrew because of adverse events. In contrast, significantly more participants withdrew because of adverse events in the 3% diclofenac in 2.5% hyaluronic acid group compared to the 2.5% hyaluronic acid group for the other studies (RR 3.59, 95% CI 1.92 to 6.70; Analysis 6.13), corresponding to a NNT of 9.4 for an additional harmful outcome. In the immunosuppressed participants, 2 out of 24 participants in the diclofenac with 2.5% hyaluronic acid group withdrew because of adverse events, whereas none of the 8 participants receiving 2.5% hyaluronic acid alone withdrew.

Fariba 2006 reported irritation only on the side treated with diclofenac in 8 of 20 participants.

Minor adverse events were reported for several body systems, and only the number of participants experiencing minor adverse events related to metabolic and nutritional disorders was significantly higher for diclofenac/hyaluronic acid (RR 5.09, 95% CI 1.16 to 22.22; Analysis 6.28), corresponding to a NNT of 7.2 for an additional harmful outcome. Unfortunately, the authors of the study (Wolf 2001) did not give the details of the adverse events related to metabolic and nutritional disorders. A large number of specific minor adverse events have been reported by only one study, and none of them were significantly different between the two groups. One of the minor adverse events reported by the three studies was dry skin. Dry skin was significantly more frequent in the diclofenac/hyaluronic acid group (RR 2.40, 95% CI 1.20 to 4.78; Analysis 6.20), corresponding to a NNT of 4.4 for an additional harmful outcome.

Two studies reported two adverse events related to the nervous system, hyperaesthesia and paraesthesia, which were localised to treatment sites by Rivers 2002. The number of participants experiencing both neurological adverse events were not different between the two treatment groups.

Ulrich 2010 mentioned that all immunosuppressed participants on the diclofenac treatment group had "cosmetically appealing results" four weeks after the end of the study, but did not mention anything about the hyaluronic acid (vehicle) group.

To summarise, diclofenac was in general significantly more effective than hyaluronic acid alone, but it was associated with significantly more withdrawals due to adverse events. Unfortunately, the data reported by the included studies did not allow comparison of efficacy and safety between immunosuppressed and immunocompetent participants.

Diclofenac versus imiquimod

This intervention was addressed by 1 open-label study (Kose 2008), which compared the efficacy of 3% diclofenac in 2.5% hyaluronic acid (once daily for 12 weeks) and 5% imiquimod (3 times per week for 12 weeks) for the treatment of actinic keratoses on the face and scalp. Assessment was performed at the end of the 12-week treatment. There was possible performance, detection, and reporting bias in this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 49 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts
Kose 2008	Investigators and participants	-	-	-

No significant difference was found between diclofenac or imiquimod either by the investigator global improvement indices (Analysis 7.1) or by the participant global improvement indices (Analysis 7.2).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 49 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Kose 2008	x	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, diclofenac and imiquimod treatments were equivalent.

Other comparisons

The efficacy of diclofenac in combination with photodynamic therapy will be discussed in the phototherapy section.

2-(Difluoromethyl)-dl-ornithine (DFMO)

This intervention was addressed by 1 intraindividual study (Alberts 2000), which compared the efficacy of 10% 2-(Difluoromethyl)-dl-ornithine (DFMO) with placebo for the treatment of actinic keratosis. The creams were applied to the randomised forearms twice daily for six months. Assessment was performed at the end of the 24-week treatment. There was possible reporting bias in this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 42 participants)
Alberts 2000	-	-	-	Absolute values and percentages

The mean numbers of lesions at baseline were high [DFMO-treated arms: 28.1 ± 17.1 (SD); placebo-treated arms: 29.2 ± 18.7], and the reduction rates of lesion counts were relatively low: 23.5% for DFMO and 2.4% for placebo. Moreover, because of the large variability associated with this efficacy outcome, the mean difference (MD) of the absolute mean reduction in lesion counts did not reach statistical significance (MD 5.90, 95% CI -3.84 to 15.64; Analysis 8.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 42 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Alberts 2000	x	-	-	-

Two participants for this intraindividual study withdrew because of adverse events.

To summarise, with severe actinic keratosis, DFMO had limited efficacy and is associated with severe inflammatory reactions.

5-Fluorouracil (5-FU)

5-Fluorouracil versus placebo

This intervention was addressed by 3 studies (Jorizzo 2002; Jorizzo 2004; Weiss 2002). Jorizzo 2002 and Weiss 2002 compared 0.5% 5-fluorouracil to vehicle cream applied daily for 1, 2, or 4 weeks on lesions located on the face or frontal scalp, and the data were part of the Carac product insert. Jorizzo 2004 reported results from an assessment 4 weeks after 1 week of treatment with either 0.5% 5-fluorouracil or vehicle cream prior to cryotherapy treatment on lesions on the face, scalp, ears, neck, and lips. Assessment was performed at four weeks after the end of treatment. There was possible performance, detection, attrition, and reporting bias associated with Jorizzo 2002 and Weiss 2002 studies. The latter also has other possible sources of bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 351 participants)	Participant complete clearance (N = 528 participants)	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 528 participants)
Jorizzo 2002	Scores (not included)	x	-	Absolute values
Jorizzo 2004	Scores (not included)	x	-	Absolute values
Weiss 2002	-	x	-	Absolute values

The data for participant complete clearance from these studies was separated into subgroups based on duration of treatment. Subgroup analyses (Analysis 9.1) showed that treatment with 0.5% 5-fluorouracil treatment resulted in a significantly higher number of completely cleared participants than the placebo cream when applied for 1 week (NNT = 15.4), 2 weeks (NNT = 7.1), and 4 weeks (NNT = 3.2), resulting in an overall significantly better efficacy for 5-fluorouracil (RR 8.86, 95% CI 3.67 to 21.40, NNT = 8.5; Analysis 9.1). When participant complete clearance for the different treatment durations were compared, daily application of 0.5% 5-fluorouracil for 4 weeks was found to have significantly higher efficacy than treatment for 1 week and 2 weeks (RR 0.39, 95% CI 0.19 to 0.81 and RR 0.56, 95% CI 0.36 to 0.87, respectively; Analysis 10.1). No difference was found between treatment for one week and treatment for two weeks. We must be cautious in our interpretation of these results because the design of the studies did not blind the participants and assessor for the treatment duration.

Mean reduction in lesion counts was presented as absolute values, percentages, or both. In Jorizzo 2002, only the percentages without the associated standard deviations were presented, as shown in the following table. Jorizzo 2004 presented both absolute values and percentages (table) with their associated standard deviation. Analysis of the absolute values showed a significant reduction in lesion counts with 1 week of 5-fluorouracil compared to placebo (MD 5.40, 95% CI 2.94 to 7.86; Analysis 9.2). Finally, Weiss 2002 presented the absolute values (placebo: 2.7, 1 week: 8.8, 2 weeks: 11.7, and 4 weeks: 11.1) and percentages (table) without their associated standard deviations. In all studies, the mean percentages of reduction in lesion counts were higher in the 5-fluorouracil-treated groups than placebo.

Mean percentage of reduction in lesion counts	Placebo	5-fluorouracil (1 week)	5-fluorouracil (2 weeks)	5-fluorouracl (4 weeks)	5-fluorouracl (pooled)
Jorizzo 2002 (N = 207 participants)	21.6%	69.5%	86.1%	91.7%	82.4%
Jorizzo 2004 (N = 144 participants)	28.8% ± 32.6% (SD)	62.4% ± 32.6% (SD)	N/A	N/A	62.4%
Weiss 2002 (N = 177 participants)	34.4%	78.5%	83.6%	88.7%	83.6%

N/A = not available

Based on the data from Jorizzo 2004, the mean percentage of reduction in lesion counts for 1 week of treatment with 0.5% 5-fluorouracil compared to vehicle was statistically significant in favour of 5-fluorouracil (MD 33.60, 95% CI 22.88 to 44.32; Analysis 9.3).

Secondary outcomes

Because the safety analysis in Jorizzo 2004 included cryotherapy treatment, this study was excluded from this section. All the safety outcomes, except 'skin irritation' in general, were pooled together in the Carac product insert and were reported as in the Jorizzo 2002 study.

Study	Withdrawal due to adverse events (N = 384 participants)	Skin irritation (N = 384 participants)	Minor adverse events excluding skin irritation (N = 384 participants)	Cosmetic outcome
Jorizzo 2002	x	x	In general (excluding dermatology because it could include skin irritation) and specific adverse events based on body system	-
Weiss 2002	x	x	In general (excluding dermatology because it could include skin irritation) and specific adverse events based on body system	-

Analysis of data reported by Weiss 2002 showed that the number of participants who withdrew because of adverse events had a tendency to be higher in the 5-fluorouracil-treated group compared to the placebo-treated group (Analysis 9.4). The number of withdrawals due to adverse events had a tendency to increase with longer treatment with 5-fluorouracil (Analysis 10.2), but this was not statistically significant. Similar to Weiss 2002, Jorizzo 2002 had 4 treatments arms (1, 2, and 4 weeks of 5-fluorouracil and placebo). In this study, a total of 24 participants out of 207 withdrew because of adverse events, but the authors only mentioned that 12 of them (50%) were in the 4-week group (N = 45). Together, these data suggest that severe adverse events are indeed associated with 4-week treatment with 5-fluorouracil.

Similarly, the number of participants experiencing facial irritation was significantly higher in the 5-fluorouracil-treated group than in the group treated with placebo (RR 1.45, 95% CI 1.27 to 1.65, NNT = 3; Analysis 9.5) without any difference between treatment durations (Analysis 10.3). The number of participants experiencing skin irritation was slightly lower in the 1-week group than the 2 other 5-fluorouracil groups, i.e. 2 and 4 weeks of treatments. Irritation related to treatment was mostly of mild to moderate severity.

None of the analyses for our outcome 'minor adverse events' resulted in significant differences between 5-fluorouracil and vehicle-treated participants (Analysis 9.6; Analysis 9.7; Analysis 9.8; Analysis 9.9; Analysis 9.10; Analysis 9.11; Analysis 9.12; Analysis 9.13; Analysis 9.14; Analysis 9.15; Analysis 9.16). Moreover, no difference was detected between the different 5-fluorouracil treatment durations (Analysis 10.4; Analysis 10.5; Analysis 10.6; Analysis 10.7; Analysis 10.8; Analysis 10.9; Analysis 10.10; Analysis 10.11; Analysis 10.12).

To summarise, 5-fluorouracil was more efficient than vehicle to treat actinic keratoses. Four-week treatment gave better results than one- and two-week treatments, which were comparable. Treatment with 0.5% 5-fluorouracil for 4 weeks could lead to more adverse events as shown by the number of withdrawals due to adverse events. Significant facial irritation was associated with 0.5% 5-fluorouracil treatment.

Different concentrations of 5-fluorouracil

This intervention was addressed by one study (Loven 2002), which used a right/left withinparticipant design (intraindividual) to compare the efficacy of 0.5% to 5% 5-fluorouracil cream or the treatment of actinic keratoses on the face, anterior bald scalp, or forehead. The creams were applied once daily on 1 side of the face with 0.5% cream and twice daily on the other side with 5% cream for 4 weeks. Assessment was performed at 4 weeks after the end of treatment. There was possible performance and reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 21 participants)	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 21 participants)
Loven 2002	-	x	-	Absolute values and percentages

Due to the intraindividual design of the study, no analysis could be performed for the participant-based outcome 'participant complete clearance'; however, a similar total clearance rate was obtained for the 2 treatments, i.e. approximately 43% (9/21) (Loven 2002).

After treatment with 0.5% 5-fluorouracil, participants had a mean reduction of 8.8 lesions, corresponding to 67%, and after 5% 5-fluorouracil, the mean reduction was 6.1 (47%). The authors reported a significant difference (P = 0.044) between the 2 treatments for the absolute mean reduction in lesion counts and graphically represented the standard deviations associated with lesion counts at baseline and week 8. An analysis could not be performed because the numerical values of the standard deviations were not provided.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 21 participants)	Skin irritation (N = 21 participants)	Minor adverse events excluding skin irritation (N = 21 participants)	Cosmetic outcome
Loven 2002	x	x	x	-

Sixteen of 21 participants discontinued treatment but did not withdraw from the study, because of irritation: 4 participants discontinued because of treatment with 0.5% 5-fluorouracil cream, 8 because of 5% cream, and 4 because of both creams.

All participants reported facial irritation in association with both creams.

Eye irritation was reported in 5 out of 21 participants and nasal congestion in 3 out of 21 participants. It was not mentioned if these events were associated with a particular treatment side.

To summarise, 0.5% 5-fluorouracil cream might be more efficient than the 5% cream and is associated with similar skin irritation.

5-fluorouracil with tretinoin

This intervention was addressed by 1 intraindividual study (Bercovitch 1987) comparing 5% fluorouracil treatment combined with 0.05% tretinoin and 5% fluorouracil treatment combined with placebo for treatment of actinic keratoses. 5% fluorouracil was applied twice daily on both forearms and hands, and 0.05% tretinoin cream was applied nightly on a randomised forearm/hand and placebo on the other forearm/hand up to 12 weeks. Assessment was performed at the end of the 12-week treatment. There was possible reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 20 participants)
Bercovitch 1987	-	-	-	Absolute values

The additional treatment with tretinoin did not make any difference in the mean reduction of lesion counts by 5% fluorouracil (Analysis 12.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 20 participants)	Skin irritation (N = 20 participants)	Minor adverse events excluding skin irritation	Cosmetic outcome
Bercovitch 1987	x	x (relative)	-	-

Twelve participants experienced more irritation on the side treated with tretinoin cream, four on the side treated with placebo, and three had equal irritation. One participant withdrew from the study due to irritation, but it was not mentioned if it was due to one treatment in particular.

To summarise, additional treatment with tretinoin did not improve the efficacy of the 5-fluorouracil treatment and was associated with more skin irritation.

5-fluorouracil versus imiquimod

This comparison is discussed in the imiquimod section below, and the results presented in Table 2 correspond to Analysis 13.1.

5-fluorouracil versus masoprocol

This intervention was addressed by 1 study (Kulp-Shorten 1993), comparing 5% 5-fluorouracil and 10% masoprocol for the treatment of actinic keratoses. Both creams were applied twice daily for four weeks on the head or neck. Assessment was performed four weeks after the end of treatment. There was possible bias (other) associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 57 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 49 participants)
Kulp-Shorten 1993	Investigator	-	-	Absolute values and percentages

Analysis of 'investigator global improvement indices' for cleared participants showed a strong and significant risk ratio favouring 5-fluorouracil over masoprocol treatments (RR 3.60, 95% CI 1.57 to 8.26; Analysis 15.1). Two (NTT = 2.1) participants need to be treated to result in 1 clearance with 5-fluorouracil, whereas a larger number would be needed for masoprocol.

No significant difference was detected with the absolute values for mean reduction in lesion counts (Analysis 15.2). In contrast, the mean percentages were significantly different and supported the superiority of 5-fluorouracil in the treatment of actinic keratoses (MD 20.00, 95% CI 11.82 to 28.18; Analysis 15.3).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 57 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 57 participants)	Cosmetic outcome
Kulp-Shorten 1993	x	-	Graph	-

Only 1 participant in the 5-fluorouracil group withdrew because of adverse events (Analysis 15.4).

Minor adverse events were presented graphically based on their severity as percentages of participants experiencing different adverse events, such as necrosis and contact dermatitis. Based on these data and the incidences of these events, the authors concluded that masoprocol treatment was better tolerated than the 5-fluorouracil treatment, and they made a correlation with the number of participants that failed to complete 28 days of treatment. Indeed, a significantly higher percentage (65.5%) of participants treated with 5-fluorouracil failed to complete 28 days of treatment than participants treated with masoprocol (16%).

To summarise, 2 out of 3 efficacy outcome measurements supported the superiority of 5% 5-fluorouracil treatment over 10% masoprocol treatments for actinic keratosis. Masoprocol treatment may be associated with better tolerability.

Other comparisons

The comparisons between 5-fluorouracil and cryotherapy, photodynamic therapy, resurfacing, and chemical peel are discussed in their respective sections. The results presented in Table 2 correspond to the following analyses:
1) cryotherapy (Analysis 14.1);
2) photodynamic therapy (Analysis 11.1; Analysis 11.2);
3) carbon dioxide laser resurfacing (Analysis 16.1; Analysis 16.2);
4) Er:YAG laser resurfacing (Analysis 17.1; Analysis 17.2); and
5) trichloroacetic acid peel (Analysis 18.1).

β-1,3-D-glucan

This intervention was addressed by one study (Tong 1996), which compared β-1,3-D-glucan with placebo for the treatment of solar keratoses. β-1,3-D-glucan was applied twice daily for 7 days to 1 arm with placebo on the other arm. Assessment was performed seven weeks after the end of treatment. There was possible reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 20 participants)
Tong 1996	-	-	-	Absolute values

The mean number of lesions at baseline were respectively 22.5 and 23.9, and the mean reductions after 8 weeks were 5.7 and 8.3 for β-1,3-D-glucan and placebo treatment. Based on the graphical representation of the data (means and standard deviations) over time provided by the authors, β-1,3-D-glucan treatment was not more effective than placebo at reducing actinic keratosis lesions. A statistical analysis was not possible because the numerical values of the standard deviations were not given by the authors.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 20 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 20 participants)	Cosmetic outcome
Tong 1996	x (none lost)	-	x	-

There were no participant withdrawals due to adverse events.

The participants did not report any minor adverse events.

To summarise, β-1,3-D-glucan treatment showed no benefits in treating solar keratoses.

Imiquimod cream

Imiquimod versus placebo

This intervention was addressed by 18 studies (Alomar 2007; Chen 2003; Gebauer 2009; Hanke 2010; Jorizzo 2007; Jorizzo 2010; Korman 2005; Lebwohl 2004; NCT00828568 Taro; NCT00828568 Taro; Persaud 2002; Ooi 2006; Ortonne 2010; Stockfleth 2002; Swanson 2010a; Szeimies 2004; Ulrich 2007; Zeichner 2009) comparing 2.5% to 5% imiquimod cream and placebo in the treatment of actinic keratoses. Two studies had an intraindividual design (Persaud 2002; Zeichner 2009), whereas all the other studies had a parallel design. In only one study the participants were immunosuppressed (organ transplant patients, Ulrich 2007). Dosing regimens were varied and included 2.5%, 3.75%, and 5% imiquimod and 8 dosing regimens with and without repetition of the treatment schedule, which are summarised in the following table. There were possible performance (Gebauer 2009; Hanke 2010; Ortonne 2010), detection (Hanke 2010; Jorizzo 2007; Ortonne 2010), attrition (Chen 2003; Lebwohl 2004; Persaud 2002; Szeimies 2004; Zeichner 2009), reporting (Alomar 2007; Jorizzo 2007; Jorizzo 2010; Korman 2005; Lebwohl 2004; Persaud 2002; Szeimies 2004; Ulrich 2007), and other (Jorizzo 2007) biases.

Study	Anatomical locations	Imiquimod percentage	Number of doses/week	Number of weeks	Number of doses	Time of assessment
Persaud 2002	Face, arms, legs	5	3	8 or less	24 or less	8 weeks after the end of treatment
Stockfleth 2002	Face, scalp, forehead, dorsal forearm, neck, back of hands	5	3	12 or less	36 or less	At the end of the 12-week treatment
Chen 2003	Face, forehead and temples, cheeks	5	3	3 or 6	9 or 18	4 weeks after the end of treatment

Lebwohl 2004	Face or scalp	5	2	16 or less	32 or less	8 weeks after the end of treatment
Szeimies 2004	Face or bald scalp	5	3	16 or less	48 or less	8 weeks after the end of treatment
Korman 2005	Face or bald scalp	5	3	16	48	8 weeks after the end of treatment
Ooi 2006	Scalp, extremities, or upper trunk	5	3	16 or less	48 or less	At the end of treatment
Alomar 2007	Face or bald scalp	5	3	4 or 8	12 or 24	4 weeks after the end of treatment
Jorizzo 2007	Head	5	3	4 or 8	12 or 24	4 weeks after the end of treatment
Ulrich 2007	Face, forehead, or bald scalp	5	3	16	48	8 weeks after the end of treatment
Gebauer 2009	Dorsal of 1 or both forearms and hands	5	2,3,5,7	8	16,24,40,56	8 weeks after the end of treatment
Zeichner 2009	Head	5	1	24	24	4 weeks after the end of treatment
Hanke 2010	Face or bald scalp	2.5, 3.75	7	6 (3 on, 3 off, 3 on)	42	8 weeks after the end of treatment
Jorizzo 2010	Face	3.75	7	4 (2 on, 2 off, 2 on)	28	20 weeks after the end of treatment
Ortonne 2010	Head (bald scalp or face)	5	3	8 (4 on, 4 off, 4 on)	24	At week 20 (6 weeks after the end of treatment)
Swanson 2010a	Face or bald scalp	2.5, 3.75	7	4 (2 on, 2 off, 2 on)	28	8 weeks after the end of treatment
NCT00828568 Aldara	Face or bald scalp	5	2	16	32	8 weeks after the end of treatment
NCT00828568 Taro	Face or bald scalp	5	2	16	32	8 weeks after the end of treatment

Three types of subgroup analyses were performed: 1) by number of doses (from 9 to 56 doses) for 5% imiquimod (in the Analyses 19); 2) by imiquimod concentrations (in the Analyses 20); and 3) by frequency of application, i.e. number per week (in the Analyses 21).

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 20 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction in lesion counts (N = 315 participants)

		(N = 3637 participants)	(N = 2914 participants)	
Persaud 2002	-	-	-	Absolute values
Stockfleth 2002	-	x	-	-
Chen 2003	-	x	x	Absolute values
Lebwohl 2004	-	x	x	-
Szeimies 2004	-	x	x	-
Korman 2005	-	x	x	-
Ooi 2006	-	x	-	-
Alomar 2007	-	x	x	-
Jorizzo 2007	-	x	x	-
Ulrich 2007	-	x	x	-
Gebauer 2009	-	x	x	-
Zeichner 2009	Investigator	-	-	-
Hanke 2010	-	x	x	-
Jorizzo 2010	-	x	-	Percentages
Ortonne 2010	-	-	-	Absolute values
Swanson 2010a	-	x	x	-
NCT00828568 Aldara	-	x	-	-
NCT00828568 Taro	-	x	-	-

Only one intraindividual study, Zeichner 2009, presented the number of participants with global improvement indices for complete clearance. One participant out of 15 was completely cleared on the imiquimod-treated side, whereas none of the participants showed complete clearance on the placebo-treated side. Thus, this dosing regimen was not very effective.

Overall, the risk ratio for participant complete clearance favoured 5% imiquimod treatment over placebo for immunocompetent (RR 6.91, 95% CI 4.25 to 11.26; Analysis 19.1) as well as in immunosuppressed participants (RR 18.50, 95% CI 1.19 to 286.45; Analysis 19.2). Eight immunocompetent participants (NNT = 7.7) must be treated with 5% imiquimod to obtain 1 complete clearance. No immunosuppressed participant in the control group was completely cleared, so the corresponding number, i.e. NNT could not be calculated for this population.

However, 5% imiquimod was not statistically favoured in 4 of the 8 dosing regimens: 9 or 18 doses (3 times/week for 3 weeks on, 4 weeks off), 24 doses (3 times/week for 8 weeks), 40 doses (5 times/week for 8 weeks), and 56 doses (7 times/week for 8 weeks). Increasing the number of doses did not result in an increase in the values of the RRs, suggesting that the number of doses might not be a determining factor for the efficacy of imiquimod. Despite these subgroup analyses, substantial heterogeneity was associated with most of the subgroups of pooled studies. The heterogeneity was particularly high (I^2 statistic = 91%) for the 2 studies, with 1 or 2 courses 3 times/week for 4 weeks on, 4 weeks off, 4 weeks on (Alomar 2007; Jorizzo 2007). The two studies were similar in design. Alomar 2007 was performed in Europe and included participants with five to nine lesions, whereas Jorizzo 2007 was performed in North America and included participants with four to eight lesions. In the European study, 47/126 participants were cleared after 1 course and did not receive a second course, compared to 32/121 in

the American study. This difference might explain the heterogeneity associated with these studies.

Slightly different results were obtained for participant partial (≥ 75%) clearance (Analysis 19.3). One additional dosing regimen did not reach significant difference (12 or 24 doses, 4 weeks on, 4 weeks off). In immunosuppressed participants, the results for partial clearance (RR 23.50, 95% CI 1.53 to 360.94; Analysis 19.4) were similar to complete clearance (Analysis 19.2).

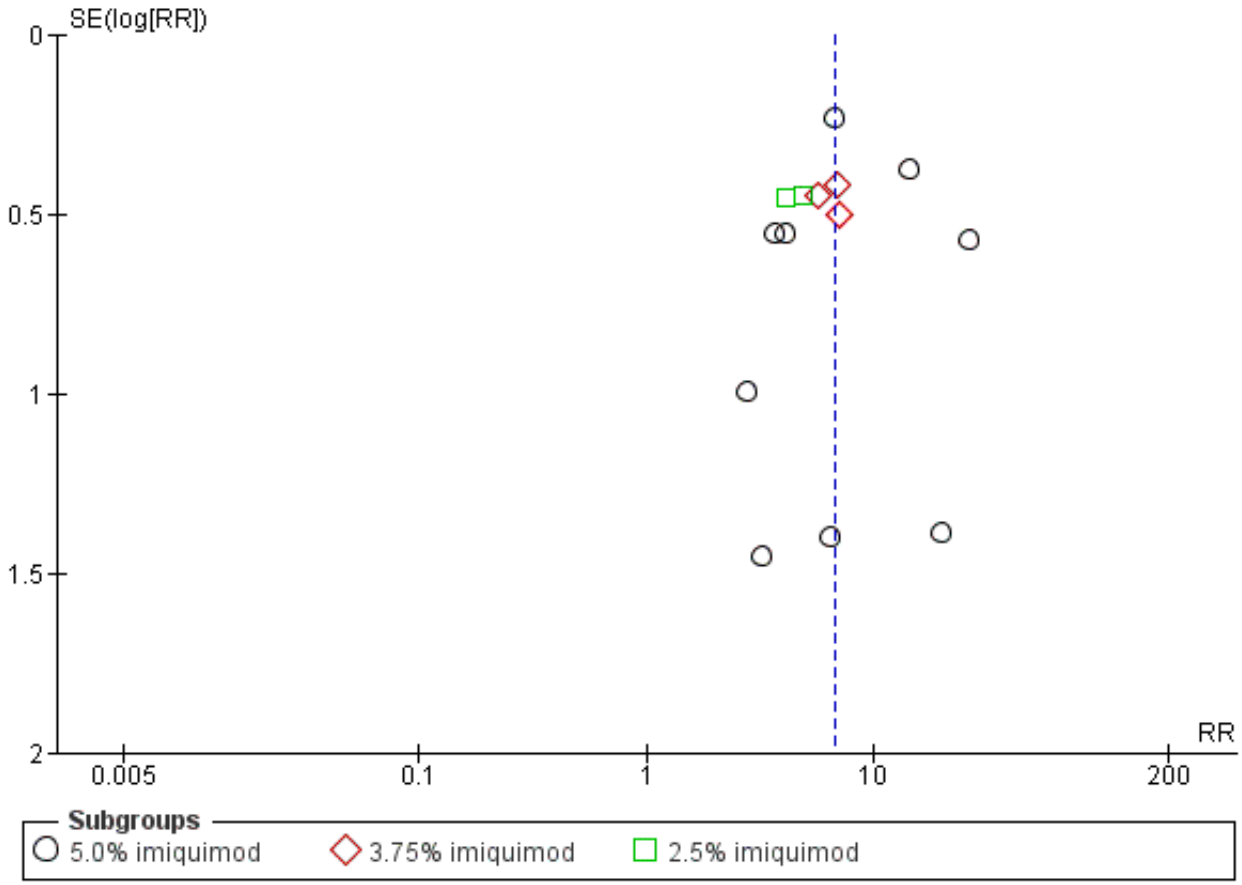
The number of participants with complete clearance was significantly higher in the imiquimod-treated group than the placebo-treated group for the 3 concentrations, i.e. 2.5% (RR 4.49, 95% CI 2.40 to 8.39, NNT = 4.6), 3.75% (RR 6.45, 95% CI 3.87 to 10.73, NNT = 3.7), and 5% (RR 7.70, 95% CI 4.63 to 12.79, NTT = 4.7). Based on the result for the subgroup difference test (P = 0.42; Analysis 20.1), the efficacy of the 3 concentrations compared to placebo was not significantly different despite the fact that the magnitude of the effect increased with the concentration of imiquimod used to treat the actinic keratoses. In contrast, the analysis of the participant partial clearance, which included fewer studies, showed a significant difference between the concentrations of imiquimod (test for subgroup differences: P = 0.01; Analysis 20.2). It is also worth noting that the two studies (Gebauer 2009; Ooi 2006) not including lesions on the face did not favour imiquimod (Analysis 20.1).

The amplitude of the clearance effect increased when the frequency of application was increased from 2 to 3 times per week for both complete clearance (Analysis 21.1) from (RR 5.36, 95% CI 2.03 to 14.16) to (RR 8.38, 95% CI 3.79 to 18.52) and for partial clearance (Analysis 21.2) from (RR 4.99, 95% CI 3.43 to 7.26) to (RR 7.65, 95% CI 2.51 to 23.32), but the difference between the RRs between 2 and 3 times were not significantly different.

Also, no correlation was found for the subgroup analysis of the number of weeks of treatment (not shown).

A funnel plot (Figure 3) for all the studies reporting 'participant complete clearance' suggests that there was no publication bias for this outcome.

Figure 3. Funnel plot of comparison: 15 Imiquimod versus placebo: different concentrations, outcome: 15.1 Participant complete clearance.



Two studies (Ortonne 2010; Persaud 2002) with 24 doses of 5% imiquimod or placebo presented mean reduction in lesion counts as absolute values. Ortonne 2010, but not Persaud 2002, provided the associated standard deviations allowing statistical analysis. The mean reduction in lesion counts were similar for the imiquimod group (2.8 ± 2.1 and 3.9) and for the placebo group (0.6 ± 2.6 and 0.5), but the RR did not significantly favour imiquimod based on Ortonne 2010 alone (Analysis 19.5). In contrast, the mean

percentage of reduction in lesion counts provided by Jorizzo 2010 with 3.75% imiquimod supported the superiority of imiquimod over placebo for treatment of actinic keratoses (MD 46.90, 95% CI 36.68 to 57.12; Analysis 20.3).

Secondary outcomes

In the Jorizzo 2010 study, some lesions also had cryotherapy treatment, and safety outcomes were only reported for the comparison between cryotherapy with and without imiquimod treatment. Thus, this study was not included in the secondary outcomes presented in this section.

Study	Withdrawal due to adverse events (N = 3444 participants)	Skin irritation (N = 1677 participants)	Minor adverse events excluding skin irritation (N = 700 participants)	Cosmetic outcome (N = 1691 participants)
Persaud 2002	x (none lost - intraindividual not included)	-	-	-
Stockfleth 2002	x (none lost)	-	-	-
Chen 2003	x (none lost)	-	-	-
Lebwohl 2004	x	-	-	x
Szeimies 2004	x	x	-	x
Korman 2005	x	-	-	x (imiquimod, not included)
Ooi 2006	x (none lost)	-	x	-
Alomar 2007	x	-	-	-
Jorizzo 2007	x	-	-	
Ulrich 2007	x	-	x (imiquimod only, not included)	x (qualitative, not included)
Gebauer 2009	x	-	x	-
Zeichner 2009	x (none lost - intraindividual not included)	Qualitative (not included)	-	-
Hanke 2010	x	x	x	x
Ortonne 2010	x (none lost)	-	-	-
Swanson 2010a	x	x	-	x
NCT00828568 Taro	x	x	-	-
NCT00828568 Taro	x	x	-	-

All of the studies reported the number of participants who withdrew because of adverse events. Six out of 17 studies reported that no participants withdrew due to adverse events (i.e. "none lost" in the previous table), which are not included in the pooled risk ratio of meta-analysis because of the absence of events. All these studies used 5% imiquimod applied 3 times per week and had a very small sample size (< 50 participants) compared to the other studies. Thus, we have to be careful about the interpretation of the analysed data. When comparing 5% imiquimod application to placebo, there was no significant difference in withdrawals due to adverse effects except at 48 doses. At 48 doses, when 2 studies were combined, there was a significant difference in favour of placebo (RR 2.69, 95% CI 1.48 to 4.90, NNT=16.7; Analysis 19.6).

When 8 of the studies using 5% imiquimod were pooled together (imiquimod N = 1338, placebo N = 952), the number of participant withdrawals due to adverse events was significantly higher in the 5% imiquimod-treated group than the placebo-treated group (RR 2.59, 95% CI 1.59 to 4.23, NNT = 27; Analysis 20.5). The 4 studies with a parallel design (Chen 2003; Ooi 2006; Ortonne 2010; Stockfleth 2002), not included in the calculation of the pooled RR because of the lack of event, represented only 79 participants in the imiquimod group and 31 participants in the placebo group. Thus, we could conclude that 5% imiquimod treatment results in a higher number of participants withdrawn because of adverse events compared to placebo. In contrast, there was no significant difference for 3.75% and 2.5% imiquimod compared to placebo (Analysis 20.5).

For all frequencies of weekly application, there was a tendency to have more participants withdraw because of adverse events in the imiquimod group; a significant difference (RR 2.47, 95% CI 1.42 to 4.30, NTT = 27.2; Analysis 21.3) was reached in the 3 times per week group. Five studies (imiquimod N = 670, placebo N = 649) were included in the calculation of the pooled risk ratio, but 4 smaller studies were not included because of absence of withdrawal in the intervention and control arms (imiquimod N = 79, placebo N = 31). Finally, there was no difference in the number of participants who withdrew because of adverse events in the immunosuppressed participants (Analysis 19.7).

In the studies reporting skin irritation, no significant difference was observed for the separate analysis of the different concentrations. However, the pooled risk ratio did favour placebo, i.e. more participants treated with imiquimod experienced skin irritation compared to participants treated with placebo (RR 3.93, 95% CI 1.56 to 9.88, NNT = 60; Analysis 20.6). In the intraindividual study Zeichner 2009, the participants experienced similar mild irritation with 5% imiquimod and placebo.

Only one study, Gebauer 2009, reported the number of participants experiencing 'minor adverse events excluding skin irritation' in general for different body systems, i.e. body as a whole, digestive system, and nervous system. None of the data were significantly different between the 5% imiquimod- and placebo-treated groups. Few studies reported the number of participants experiencing specific minor adverse events. The following adverse events affecting the body as a whole (pyrexia), the haemic and lymphatic system (lymphadenopathy), the musculoskeletal system (myalgia), the nervous system (fatigue), the respiratory system (cough, sinusitis, and upper respiratory tract infection), and the urogenital system (urinary tract infection) were not different between imiquimod and placebo groups. The number of participants treated with imiquimod experiencing "flu" or "cold"-like symptoms or "headache" was generally not different from placebo-treated participants except for application 7 times per week reported in 1 study by Hanke 2010 (RR 19.68, 95% CI 1.20 to 323.89; Analysis 21.5).

Only a few studies gave quantitative cosmetic outcomes (Lebwohl 2004; Szeimies 2004); a significant decrease in roughness, dryness, and scaliness of the skin was associated with 5% imiquimod treatment compared to placebo (RR 3.23, 95% CI 1.86 to 5.58, NNT = 2.6; Analysis 19.13). In addition, overall cosmetic outcomes were significantly or much improved with 2.5% (RR 2.25, 95% CI 1.62 to 3.14, NNT = 3.1) and 3.75% (RR 2.71, 95% CI 2.05 to 3.58, NNT = 2.3) imiquimod compared to placebo (Analysis 20.16).

To summarise, the efficacy of imiquimod compared to placebo was significantly better based on the participant complete and partial clearance as well as the mean percentage of reduction in lesion counts, but not for the absolute mean reduction in lesion counts. The amplitude of the effect was independent of the number of doses of 5% imiquimod, imiquimod concentrations, or frequency of application on a weekly basis. The number of withdrawals due to adverse events in the imiquimod group compared to placebo was statistically significant in the 48-dose group (although not in the 56-dose group) compared with the lower doses and in the 5% compared to the 2.5% and 3.75% imiquimod concentrations. Significantly better cosmetic outcomes were obtained with imiquimod treatment.

Imiquimod versus diclofenac

This comparison was reported in the diclofenac section above.

Imiquimod versus 5-fluorouracil

This intervention, which was addressed by 2 studies, 1 assessor-blinded (Tanghetti 2007) and 1 open study (Krawtchenko 2007), compared the efficacy of 5% imiquimod and 5% 5-fluorouracil for the treatment of actinic keratoses. In Krawtchenko 2007, imiquimod was applied on the head, neck, or décolleté 3 times per week for 4 weeks on and 4 weeks off, once or twice, and 5-fluorouracil was applied twice daily for 4 weeks. Assessment was performed 4 and 8 weeks after the end of treatment for 5-fluorouracil and imiquimod, respectively. Tanghetti 2007 applied imiquimod on the face, forehead, or scalp twice weekly for 16 weeks and 5-fluorouracil twice daily for 2 to 4 weeks. Assessment was performed at 8 weeks after the end of treatment. There were possible performance (Krawtchenko 2007; Tanghetti 2007), detection (Krawtchenko 2007), and reporting (Tanghetti 2007) biases.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 89 participants)	Participant partial (≥ 75%) clearance	Mean reduction in lesion counts (N = 50 participants)

Tanghetti 2007	-	x	-	-
Krawtchenko 2007	-	x	-	Percentages

With regard to the outcome 'participant complete clearance', no pooled RR can be calculated because of the high heterogeneity (I^2 statistic = 93%; Analysis 22.1) associated with the 2 studies. The data from Krawtchenko 2007, which had no blinding specified, did not favour any treatment (RR 0.88, 95% CI 0.73 to 1.06). In contrast, the data from Tanghetti 2007, which was assessor-blinded, significantly favoured 5-fluorouracil (RR 0.31, 95% CI 0.14 to 0.67). The variability in the dosing regimen might explain the considerable heterogeneity associated with participant complete clearance. Tanghetti 2007 also supported 5-fluorouracil superiority by reporting the mean percentage of reduction in lesion counts of 94% and 66% for 5-fluorouracil and imiquimod, respectively. However, the authors did not provide the standard deviation associated with these values to determine statistically the significance of this difference between the treatments.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 89 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 50 participants)
Tanghetti 2007	x (none lost)	-	-	-
Krawtchenko 2007	x (none lost)	-	-	x

There were no participant withdrawals due to adverse events.

The percentage of participants with a general cosmetic outcome assessed as excellent by the investigator was clearly better for imiquimod (21/26 = 81%) than 5-fluorouracil (1/24 = 4%) (RR 19.38, 95% CI 2.82 to 133.26, NNT = 1.3; Analysis 22.2). Moreover, the skin quality was better in the imiquimod group than the 5-fluorouracil group (RR 1.45, 95% CI 1.00 to 2.11, NNT = 3.8; Analysis 22.3).

To summarise, the superiority of 5-fluorouracil over imiquimod in treating actinic keratoses needs to be supported by additional data. Imiquimod treatment seemed to result in better cosmetic outcomes than 5-fluorouracil.

Other comparisons

The efficacy of imiquimod compared with cryotherapy will be discussed in the cryotherapy section below, and the results presented in the additional Table 5 correspond to Analysis 23.1. Similarly, comparison with photodynamic therapy will be discussed in the phototherapy section.

Ingenol mebutate (PEP005)

This intervention was addressed by three studies (Anderson 2009; Siller 2009; Swanson 2010b). These three studies investigated the efficacy of ingenol mebutate applied once daily for two to three consecutive days or once weekly for two weeks, i.e. two days one week apart (Siller 2009), compared to vehicle for the treatment of actinic keratoses. Treatments were applied to the arms, shoulder, chest, and scalp in both Anderson 2009 and Siller 2009. In addition, the treatments were also applied to the back in Anderson 2009 and the face in Siller 2009, whereas only non-head locations were investigated in Swanson 2010b. Assessment was performed 8 (Anderson 2009; Swanson 2010b) and 12 (Siller 2009) weeks after the first day of treatment. There was possible reporting (Anderson 2009) and other (Siller 2009) bias.

Because different concentrations (0.025%, 0.01%, and 0.05%) of ingenol mebutate and dosing regimens were used in these studies, subgroup analyses were performed for the different ingenol mebutate concentrations (in the Analyses 25) and the number of applications for 0.05% ingenol mebutate (i.e. number of doses or days, in the Analyses 26). Analyses of pooled data were also performed (in the Analyses 24).

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 477 participants)	Participant partial (≥ 75%) clearance (N = 285 participants)	Mean reduction in lesion counts

Anderson 2009	-	x	x	-
Siller 2009	-	-	x	-
Swanson 2010b	-	x	x (percentage not specified and data not included in analysis)	-

Participant complete clearance was evaluated for target lesions (i.e. present at baseline) as well as for all lesions (i.e. target and new lesions). For both, the number of participants completely cleared was significantly higher in the ingenol mebutate group compared to vehicle (target: RR 3.61, 95% CI 1.86 to 7.02, NNT = 2.9; Analysis 24.1) (all lesions: RR 4.50, 95% CI 2.61 to 7.74, NNT = 3.4; Analysis 24.2), which corresponds to 383 per 1000 participants for ingenol mebutate and 73 per 1000 participants for vehicle achieving complete clearance.The amplitude of the effect had a tendency to increase with the concentration of ingenol mebutate (Analysis 25.1; Analysis 25.2), but not with the number of applications of 0.05% ingenol mebutate (Analysis 26.1; Analysis 26.2).

Similar results were obtained for participant partial clearance with a RR of 2.88, 95% CI 1.81 to 4.58 (Analysis 24.3), corresponding to a NNT of 2.8. A possible dependence on the ingenol mebutate concentration (Analysis 25.3), but not on the number of applications for 0.05% ingenol mebutate (Analysis 26.3), was also observed.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 540 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 222 participants)	Cosmetic outcome (N = 540 participants)
Anderson 2009	x	-	x	-
Siller 2009	x	-	-	x
Swanson 2010b	x	-	-	x

No withdrawal due to adverse events was reported in Anderson 2009 and Siller 2009. However, in Swanson 2010b, 1 out of 255 participants withdrew because of an adverse event (pain), but the associated treatment was not specified.

No statistical analyses were performed for minor adverse events because only one participant experienced the individual minor adverse events reported, as shown in the following table, and no statistical significance could be reached. However, based on the incidences, more reports of minor adverse events were associated with the 0.05% ingenol mebutate.

Body system	Minor adverse event	Placebo (N = 60)	0.025% ingenol mebutate for 3 days (N = 50)	0.05% ingenol mebutate for 3 days (N = 57)	0.05% ingenol mebutate for 2 days (N = 55)
Body as a whole	Chills	0	0	1	0
Body as a whole	Fever	0	0	0	1
Body as a whole	Flu or cold	0	0	0	1
Dermatologic	Contact dermatitis	0	0	1	0
Dermatologic	Impetigo	0	0	1	0

Hemic and lymphatic	Traumatic hematoma	0	0	1	0
Metabolic and nutritional disorders	Increase in creatine phosphokinase	0	0	0	1
Musculoskeletal and connective tissue	Muscle spasms	1	0	0	1
Nervous system	Headache	0	0	1	0
Renal and urogenital	Proteinuria	0	0	0	1
Respiratory	Nasal congestion	0	1	0	0
Incidences					
Each treatment arm		1	1	5	5
3 days versus 2 days			6		5
0.025% versus 0.05%			1	10	

There was no scarring, but some pigmentation changes occurred in some participants treated with ingenol mebutate. These changes were not significantly different compared to vehicle (Analysis 24.4).

To summarise, ingenol mebutate was significantly more efficient than vehicle in treating actinic keratoses. When a higher concentration was used (i.e. 0.05%), ingenol mebutate generally resulted in better efficacy. Increasing the number of applications from two to three times did not result in an increase in the number of participants cleared. No significant difference was observed between ingenol mebutate and placebo for adverse events. Thus, ingenol mebutate treatment was relatively safe and efficient for actinic keratosis treatment.

Isotretinoin

This intervention was addressed by 1 study (Alirezai 1994) comparing the efficacy and safety of 0.1% isotretinoin and vehicle cream applied twice daily for 24 weeks for the treatment of actinic keratoses of the face, scalp, and upper extremities. Assessment was performed at the end of treatment. There was possible attrition and other bias in this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 100 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction (changes) in lesion counts (N = 100 participants)
Alirezai 1994	Investigator	-	-	Absolute values

The number of participants experiencing complete clearance, partial clearance, no clearance, and worsening were determined by an investigator global evaluation at the end of treatment. The numbers of participants with complete clearance were low with both isotretinoin and placebo for the three anatomical locations, and the associated risk ratios did not favour any treatment (Analysis 27.1).

The mean reduction of lesion counts for lesions on the face (MD 2.20, 95% CI 1.97 to 2.43) and upper extremities (MD 1.90, 95% CI 1.28 to 2.52), but not on the scalp, did favour isotretinoin over placebo (Analysis 27.2).

Secondary outcomes

Study	Withdrawal due to adverse events	Skin irritation (N = 92 participants)	Minor adverse events excluding skin irritation	Cosmetic outcome

	(N = 100 participants)			
Alirezai 1994	x	x (in general and severe)	-	-

Two of 50 participants in the isotretinoin group withdrew because of adverse events, but it was not statistically different compared to the placebo group (0/50) (Analysis 27.3).

Local irritation on the face, but not on the scalp or upper extremities (Alirezai 1994), was significantly more frequent for the isotretinoin-treated group than for the placebo-treated group for all intensities (RR 1.57, 95% CI 1.23 to 2.01, NNT = 3.0; Analysis 27.4) as well as severe irritation (RR 17.09, 95% CI 2.35 to 124.10, NNT = 3.1; Analysis 27.5).

To summarise, 0.1% isotretinoin with the dosing regimen used was able to significantly reduce actinic keratoses counts on the face or upper extremities but was not sufficient to result in significant participant complete clearance. Isotretinoin treatment was associated with significant local irritation on the face.

Masoprocol

Masoprocol versus vehicle

This intervention was addressed by 1 study (Olsen 1991) comparing 10% masoprocol cream to vehicle cream for the treatment of actinic keratoses. Masoprocol or placebo creams were applied on the head and neck once or twice daily for a maximum of 28 days and follow-up assessment was done at 4 weeks after the last application of the study drug. There was possible attrition and other bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 154 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction in lesion counts (N = 154 participants)
Olsen 1991	Investigator	-	-	Absolute values

Masoprocol-treated participants had a complete cure rate of 12/113 (11%), which was similar to the cure rate of the vehicle cream; 2/41 (5%), as globally assessed by the investigator. Thus, the RR associated with investigator global improvement indices for cured participant did not significantly favour masoprocol.

In contrast, mean reduction in lesion counts was significantly higher for masoprocol than for vehicle-treated groups (MD 7.30, 95% CI 5.77 to 8.83; Analysis 28.2).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 176 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Olsen 1991	x	-	-	-

Two of 131 participants in the masoprocol group withdrew because of adverse events, but it was not statistically different to the placebo group (0/45) (Analysis 28.3).

To summarise, 10% masoprocol with the dosing regimen used was able to significantly reduce actinic keratoses counts but was not sufficient to result in significant participant complete clearance as globally assessed by the investigator. Substantial local skin reactions were also associated with masoprocol treatment compared to vehicle.

Masoprocol versus 5-fluorouracil

This comparison was presented in the 5-fluorouracil section above.

Nicotinamide

This intervention was addressed by 1 study (Moloney 2010) investigating the efficacy of 1% nicotinamide twice daily compared to placebo for the treatment of non-hyperkeratotic actinic keratoses on the face, scalp, and upper limbs. Assessment was performed at three and six months after the beginning of the

treatment. There was possible reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean reduction in lesion counts (N = 30 participants)
Moloney 2010	-	-	-	Percentages

Mean percentage of reduction in lesion counts was assessed at three and six months. At 3 months, the associated RR favoured nicotinamide that reduced by 21.8 ± 10% the number of lesions compared to 10 ± 12% for placebo (MD 11.80, 95% CI 3.92 to 19.68; Analysis 29.1). The superiority of nicotinamide was lost at six months (Analysis 29.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 30 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Moloney 2010	x	-	-	-

None of the 13 participants in the nicotinamide group withdrew because of adverse events; it was not statistically different to the placebo group, which had 2 withdrawals out of 17 participants (Analysis 29.2).

In summary, 1% nicotinamide had very limited short-term efficacy at the dosing regimen used.

Resiquimod

This intervention was addressed by 1 study (Szeimies 2008) investigating different concentrations (0.01%, 0.03%, 0.06%, and 0.1%) of resiquimod for the treatment of actinic keratoses on the face or bald scalp. The cream was applied once daily three times per week for four weeks on and eight weeks off, once or twice, i.e. one or two treatment cycles depending on the participant response to treatment. Assessment was performed at eight weeks after the end of treatment. There was possible other bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 132 participants)	Participant partial (≥ 75%) clearance (N = 132 participants)	Mean reduction in lesion counts
Szeimies 2008	-	x	x	-

Results from individual analyses of participant complete and partial clearance for pairs of resiquimod concentrations are summarised in the following table.

Higher versus lower resiquimod concentrations			
	Participant complete clearance (after 1 cycle)	Participant complete clearance (after 1 or 2 cycles)	Participant partial clearance (after 1 or 2 cycles)

0.1% vs 0.01%	>	≥	≥
0.1% vs 0.03%	>	≤	=
0.1% vs 0.06%	>	≥	≥
0.06% vs 0.01%	≥	=	=
0.06% vs 0.03%	≤	≤	≤
0.03% vs 0.01%	≥	≥	≥

< : significantly inferior, ≤ : tendency to be inferior, = : equal, ≥: tendency to be superior, > : significantly superior, vs = versus

For participant complete clearance, the efficacy of 0.1% resiquimod was generally superior to the other lower concentrations after 1 treatment cycle (0.1% vs 0.01%: RR 2.45, 95% CI 1.64 to 3.65, NNT = 1.7; Analysis 30.1) (0.1% vs 0.03%: RR 1.34, 95% CI 1.09 to 1.66, NNT = 4.0; Analysis 31.1) (0.1% vs 0.06%: RR 1.76, 95% CI 1.30 to 2.38, NNT = 2.3; Analysis 32.1). After the second cycle of treatment, the differences between resiquimod concentrations were lost.

No significant difference was detected between the resiquimod concentrations used with the outcome 'participant partial clearance' (Analysis 30.2; Analysis 31.2; Analysis 32.2; Analysis 33.2; Analysis 34.2; Analysis 35.2).

In general, higher concentrations had a tendency to be more effective. The results obtained with 0.03% and 0.06% resiquimod suggest that these 2 concentrations might have been "switched" or "mislabelled" (Analysis 34.1; Analysis 34.2).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 132 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 132 participants)	Cosmetic outcome
Szeimies 2008	x	-	In general by body system and individual adverse event	-

There were significantly more participants in the 0.1% resiquimod group who withdrew because of adverse events compared to those in the 0.01% (RR 27.77, 95% CI 1.72 to 449.47, NNT = not applicable; Analysis 30.3) and 0.03% (RR 2.96, 95% CI 1.08 to 8.13, NNT = 4.0; Analysis 31.3) resiquimod groups. A significant difference was also found between 0.06% and 0.01% resiquimod (RR 22.91, 95% CI 1.40 to 375.77, NNT = not applicable; Analysis 33.3).

Results from individual analyses of minor adverse events excluding skin irritation for pairs of resiquimod concentrations are summarised in the following table.

Minor adverse events excluding skin irritation							
Higher versus lower resiquimod concentrations							
	Musculoskeletal and connective tissue (in general)				**Nervous system (in general)**		**Skin and subcutaneous tissue disorders (in general)**
0.1% vs 0.01%	≥				>		≥
0.1% vs 0.03%	≥				=		≥
0.1% vs 0.06%	=				=		≤
0.06% vs 0.01%	≥				>		≥
0.06% vs 0.03%	≥				=		≥
0.03% vs 0.01%	≥				>		≤
	Body as a whole		**Musculoskeletal and connective tissue**		**Nervous system**		
	Fatigue	**Rigors**	**Arthralgia**	**Myalgia**	**Headache**	**Lethargy**	**Psychiatric disorders**
0.1% vs 0.01%	≥	≥	≥	≥	≥	≥	≥
0.1% vs 0.03%	=	≥	≥	≥	=	≥	=
0.1% vs 0.06%	≥	≤	≤	≥	=	=	≤
0.06% vs 0.01%	≥	≥	≥	≥	>	≥	≥
0.06% vs 0.03%	≤	≥	≥	=	=	≥	≥
0.03% vs 0.01%	≥	≥	=	≥	≥	≥	≥

< : significantly less participants, ≤ : tendency to have less participants, = : equal number of participants, ≥ : tendency to have more participants, > : significantly more participants

The numbers of participants experiencing adverse events related to musculoskeletal, connective tissue, and skin and subcutaneous tissue disorders, were similar between the different resiquimod concentrations. In contrast, the numbers of participants with adverse events associated with the nervous system in general were significantly lower in the 0.01% resiquimod group compared to all the other groups, which had similar number of participants (0.03%: RR 9.03, 95% CI 1.20 to 68.22, NNT = 4.3; Analysis 35.9) (0.06%: RR 10.94, 95% CI 1.48 to 80.73, NNT = 3.5; Analysis 33.9) (0.1%: RR 10.29, 95% CI 1.39 to 76.12, NNT = 3.7; Analysis 30.9). Headache, the only individual adverse event with significant difference between 2 resiquimod concentrations (0.06% vs 0.01%: RR 18.55, 95% CI 1.11 to 308.90, NNT = not applicable; Analysis 33.10), is a main contributor to the nervous system-related adverse events in this study, with 6/8 participants in the 0.03% group, 8/10 in the 0.06% group, and 7/10 in the 0.1% group suffering from it.

To summarise, 0.1% resiquimod was more effective than the other lower concentrations only if the participants were treated with 1 cycle, i.e. once per day 3 times per week for 4 weeks on and 8 weeks off. Treatment with 0.01% resiquimod was generally associated with less adverse events compared to the other 3 concentrations used.

Sunscreen

Sunscreen is not generally a treatment for actinic keratosis, but it is a means of preventing actinic keratoses. However, one study investigated the role of sunscreen in the cure of existing lesions.

Sunscreen SPF 17 (8% 2-ethyl-hexyl p-methoxycinnamate/2% 4-tert-butyl-4-methoxy-4-dibenzoylmethane) versus placebo

This intervention was addressed by one study (Thompson 1993) comparing sunscreen or placebo creams applied as needed daily for seven months to treat solar keratoses on the head, neck, forearms, and hands. Assessment was performed at the end of the seven-month treatment. There was possible attrition bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 431 participants)
Thompson 1993	-	-	-	Absolute values

Mean changes [reduction (-) or increase (+)] in lesion counts (Analysis 36.1) were assessed at the end of treatment. The sunscreen-treated group showed a small mean decrease in lesion counts (-0.6 ± 4.34, SD), whereas the placebo-treated group showed a mean increase in lesion counts (1 ± 4.46, SD), demonstrating that sunscreen application could not only prevent but also treat actinic keratoses. The resulting mean difference of -1.60 (95% CI -2.43 to -0.77) favoured the use of sunscreen.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 588 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Thompson 1993	x	-	-	-

The authors of the Thompson 1993 study mentioned that 28 and 32 participants in the placebo and sunscreen groups, respectively, withdrew from the study because of skin reactions. We were unable to perform statistical analysis as the participants who withdrew were not grouped by individual reason, and some participants had multiple reasons. Because the number of participants in each treatment group was similar for withdrawal due to skin reactions, withdrawal in general, and who completed the study, we can assume that there was no significant difference in the number of participants who withdrew because of adverse events between the placebo and sunscreen groups.

To summarise, sunscreen might help to treat actinic keratoses in addition to its preventive role, but the efficacy was limited.

DL-α-tocopherol (vitamin E)

This intervention was addressed by 1 study (Foote 2009) comparing 12.5% DL-α-tocopherol (vitamin E) and placebo applied twice daily for 6 months on the right/left arms for treatment of actinic keratoses. Assessment was performed at the end of the six-month treatment. There was possible other bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 42 participants)
Foote 2009	-	-	-	Absolute values

No significant difference in mean reduction in lesion counts (Analysis 37.1) was observed.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 48 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Foote 2009	x	-	-	-

In this intraindividual study, 2 of the 48 participants withdrew from the study because of unrelated illness.

To summarise, vitamin E at the dosing regimen used was not more efficient than placebo to treat actinic keratoses.

Tretinoin

Tretinoin with 5-fluorouracil

This comparison was presented in the 5-fluorouracil section above.

Tretinoin versus arotinoid methyl sulfone (Ro 14-9706)

This comparison was presented in the arotinoid methyl sulfone section above

(2) Prescription-based oral drugs

Only one intervention for the treatment of actinic keratoses was given orally: etretinate.

Etretinate

This intervention was addressed by one study (Moriarty 1982) investigating the efficacy of etretinate for the treatment of actinic keratoses by comparing it to placebo treatment. Two parts were involved in this double-blind cross-over study, and only the first part is presented in this review. The first part involved oral etretinate, a 225 mg tablet 3 times daily for 2 months for 1 group, and the other group taking placebo with the same regimen. Assessment was performed at the end of the two-month treatment. The anatomical locations of the lesions analysed were not specified. There was possible attrition bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 50 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts
Moriarty 1982	-	x	-	-

Complete remission rates (converted to participant complete clearance) after part 1 were better in the etretinate group (5/25 = 20%) compared to placebo (0/25 = 0%), but it was not statistically significant (RR 11.00, 95% CI 0.64 to 188.95; Analysis 38.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 50 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 50 participants)	Cosmetic outcome
Moriarty 1982	x (maybe)	-	x	-

Five (etretinate = 3, placebo = 2) participants out of 50 dropped out of the study, but the reasons were not specified.

Because the adverse events were reported for both parts of the study, the quantitative data were not included in this review. Adverse effects were consistent with vitamin A-type side-effects (i.e. dry mouth, skin rash, desquamation, etc) and were experienced within the first three to four weeks of starting treatment by a large number of participants, but were reversed by reducing dosage. Many participants (17/44 = 39%, at the end of the 2 parts of the cross-over study) required reduction in dosage due to toxicity of etretinate (hepatotoxicity), but response was still maintained when dosage was reduced. Hyperlipidaemia (raised serum lipid levels) associated with etretinate was not assessed in this study.

To summarise, etretinate at the dosing regimen used was not statistically more efficient than placebo to treat actinic keratoses and was associated with adverse events.

(3) Mechanical interventions

The only mechanical intervention reported in the included studies was laser resurfacing, and the different types of laser resurfacing are presented in alphabetical order: carbon dioxide and Er:YAG laser resurfacing. Both interventions are field-directed treatments.

Carbon dioxide laser resurfacing

This intervention was addressed by 1 study (Hantash 2006) comparing the efficacy of 2 passes of carbon dioxide laser resurfacing with 5-fluorouracil applied twice daily for 3 weeks and with trichloroacetic acid peel in the treatment of actinic keratoses on the face. Assessment was performed at 12 weeks after the end of the treatment. There was possible performance, detection, and attrition bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 27 participants)
Hantash 2006	-	-	-	Percentages

The mean percentage of reduction in lesion counts showed a tendency to favour resurfacing compared to 5-fluorouracil treatment (Analysis 39.1) or trichloroacetic acid peel (Analysis 40.1), but the differences were not statistically significant.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 27 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 27 participants)
Hantash 2006	x	-	-	x

Two of 8 participants in the carbon dioxide laser resurfacing group withdrew because of adverse events (incomplete treatment due to intolerance), whereas no participants withdrew in the trichloroacetic acid peel (0/10) and 5-fluorouracil (0/9) groups. However, there was no statistically significant difference (Analysis 39.2; Analysis 40.2) between the treatments.

No postinflammatory pigmentary alteration or scarring was noted in the three treatment arms.

To summarise, the small sample size used in this study did not allow us to conclude on the superiority for efficacy or safety of carbon

dioxide laser resurfacing over fluorouracil or trichloroacetic acid peel.

Er:YAG laser resurfacing

This intervention was addressed by 1 study (Ostertag 2006) comparing the efficacy of Er:YAG laser resurfacing and 5% 5-fluorouracil applied twice daily for 4 to 7 weeks for the treatment of actinic keratoses on the face, scalp, or both. Assessments were performed at 3, 6, and 12 months after the end of treatment. There was possible reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 55 participants)
Ostertag 2006	-	-	-	Absolute values and percentages

A statistical analysis could not be performed because the associated standard deviations were not provided with the mean reductions. The means in Analysis 41.1 suggested that the 2 treatments were equally efficient at reducing actinic keratosis lesions, whereas the mean percentages in Analysis 41.2 suggested better efficacy for laser resurfacing at 6 and 12 months. A statistical significance was stated by the authors.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 55 participants)	Skin irritation (N = 55 participants)	Minor adverse events excluding skin irritation (N = 55 participants)	Cosmetic outcome (N = 55 participants)
Ostertag 2006	x	Overtime	Overtime	x

One participant withdrew due to an adverse event (death) in the 5-fluorouracil-treated group, which was not significantly different to the Er:YAG laser resurfacing group (Analysis 41.3).

The adverse events (skin irritation and minor adverse events) could be categorised into 3 groups:
1) adverse events present only after treatment;
2) adverse events developing after the treatment, i.e. during the follow-up period; and
3) adverse events present after the treatment and at follow-up. Infection was present only at the end of the treatment.

The number of participants who developed an infection was not significantly different between the two treatments but was higher at most time points with laser resurfacing. Acne and milia developed during the follow-up period. The number of participants with acne or milia was higher in the laser resurfacing group. The exception was acne at 12 months, which was similar between the two groups. The number of participants experiencing pain, crustea, and irritation tended to be higher in the fluorouracil treated-group at the end of treatment, but it became higher in the laser resurfacing group during follow-up. Only the number of participants with crustea was significantly different at the end of treatment (RR 0.46, 95% CI 0.27 to 0.79, NNT = 2.4; Analysis 41.6).

In terms of cosmetic outcomes, hypopigmentation got worse over time for laser resurfacing, significantly favouring 5-fluorouracil at 12 months (RR 11.57, 95% CI 1.61 to 83.00; Analysis 41.10), corresponding to a NNT of 2.6 for an additional harmful outcome with laser re-surfacing. Scarring was seen only in the laser resurfacing group but was not significantly different than in the fluorouracil group. In contrast, significantly more participants improved on the photoageing score with the laser resurfacing at 6 months (RR 1.57, 95% CI 1.01 to 2.43, NNT = 3.5) and 12 months (RR 1.70, 95% CI 1.01 to 2.88, NNT = 3.3) (Analysis 41.12) based on evaluation by 2 blinded investigators.

To summarise, the superiority of Er:YAG laser resurfacing over 5-fluorouracil still needs to be demonstrated. More adverse events were associated with Er:YAG laser resurfacing compared to 5-fluorouracil; however, overall ageing scores were better with Er:YAG laser resurfacing.

(4) Chemical interventions

Chemical interventions included studies on cryotherapy, photodynamic therapy, and trichloroacetic acid peel, which are presented in alphabetical order.

Cryotherapy

Cryotherapy was either compared with or combined with topical treatments or other chemical interventions, e.g. photodynamic therapy. Thus, the results are presented in two corresponding sections. Within each section, the comparisons are presented in alphabetical order of the comparison treatment. Cryotherapy is a lesion-directed treatment for detectable lesions, whereas topical treatments are generally field-directed treatments, which treat both detectable and subclinical lesions. Photodynamic therapy can

be used for single lesion or field-directed treatments. Cryotherapy and photodynamic therapy are provider-administered, whereas topical treatments are administered by participants, and their efficacy is highly dependent on the compliance of the participants. These factors might influence the treatment efficacy.

Comparisons with topical treatments

Cryotherapy compared to betulin-based oleogel

This intervention was addressed by one study (Huyke 2009) comparing cryotherapy with liquid nitrogen to betulin-based oleogel alone on the face, scalp, or other locations. Cryotherapy of participant lesions was performed once on lesions on the face and twice on lesions on the rest of the body, whereas betulin-based oleogel was applied twice daily for an unspecified duration. Assessment was performed at three months after the beginning of the treatment. There was possible performance and detection bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 30 participants)	Participant partial (≥ 75%) clearance (N = 30 participants)	Mean (changes) reduction in lesion counts
Huyke 2009	-	x	x	-

Similar participant complete or partial (≥ 75%) clearance rates were observed for the 2 treatments (Analysis 42.1; Analysis 42.2).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 30 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Huyke 2009	x (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, the regimens used in this study for cryotherapy with liquid nitrogen and betulin-based oleogel had similar efficacy for the treatment of actinic keratoses.

Cryotherapy compared to 5-fluorouracil

This intervention was addressed by 1 study (Krawtchenko 2007) comparing cryotherapy with liquid nitrogen performed once or twice with 2-week intervals to 5% 5-fluorouracil applied twice daily for 4 weeks on the head, neck, and décolleté. Assessment was performed at 4 (5-fluorouracil) or 6 (cryotherapy) weeks after the end of treatment and at 1-year follow-up. There was possible performance and detection bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 49 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts
Krawtchenko 2007	-	x	-	-

5% 5-fluorouracil was significantly more effective than cryotherapy to completely clear participants of lesions after the treatment (RR 0.71, 95% CI 0.54 to 0.94, NNT = 3.6) as well as at 12-month follow-up (RR 0.12, 95% CI 0.02 to 0.89, NNT = 3.4; Analysis 43.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 49 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 49 participants)
Krawtchenko 2007	x (none lost)	-	-	x

There were no participant withdrawals due to adverse events.

The same percentage (4%) of the participants in the 5% 5-fluorouracil group and cryotherapy group showed excellent cosmetic outcome as assessed by the investigator. Significantly more participants in the 5-fluorouracil group had better skin appearance (RR 0.27, 95% CI 0.11 to 0.72, NNT = 2.3; Analysis 43.3).

To summarise, cryotherapy was less efficacious than 5% 5-fluorouracil at treating actinic keratoses.

Cryotherapy compared to imiquimod

This intervention was addressed by 1 study (Krawtchenko 2007) comparing cryotherapy and 5% imiquimod. Cryotherapy was performed once or twice with a 2-week interval, whereas imiquimod was applied 3 times per week for 4 weeks followed by 4 weeks rest, and repeated if needed. There was possible performance and detection bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 51 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts
Krawtchenko 2007	-	x	-	-

No significant difference was found in the number of participants completely cleared between 5% imiquimod applied for a total of 4 weeks and cryotherapy treatments, but there were more participants with clearance with imiquimod (22//26 compared with 17/25 on cryotherapy), which may have been due to the additional treatment of subclinical lesions (RR 0.80, 95% CI 0.59 to 1.10; Analysis 44.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 51 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 51 participants)
Krawtchenko 2007	x (none lost)	-	-	x

There were no participant withdrawals due to adverse events.

Assessment by the investigator showed that 4% and 81% of the participants had excellent cosmetic outcomes for cryotherapy and imiquimod treatments, respectively (RR 0.05, 95% CI 0.01 to 0.34, NNT = 1.3; Analysis 44.2). In particular, the skin quality was better with imiquimod treatment (RR 0.19, 95% CI 0.08 to 0.47, NNT = 1.5; Analysis 44.3).

To summarise, cryotherapy and 5% imiquimod had similar efficacy, but imiquimod had significantly better cosmetic outcome.

Comparisons with photodynamic treatments

Cryotherapy versus 5-aminolaevulinic acid (ALA)- photodynamic therapy (PDT)

This intervention was addressed by one open study (Hauschild 2009b) comparing cryotherapy with photodynamic therapy (PDT) using red light and auto-adhesive ALA patches. Both interventions treated participant individual lesions on the head once, and no prior lesion preparation was performed. Assessment was performed 12 weeks after the end of treatment. There was possible performance, detection, attrition, and reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 255 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts
Hauschild 2009b	-	x	-	-

Analysis of participant complete clearance clearly favoured the ALA-PDT treatment over cryotherapy (RR 0.76, 95% CI 0.61 to 0.96, NNT = 7.2; Analysis 46.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 297 participants)	Skin irritation (N = 297 participants)	Minor adverse events excluding skin irritation	Cosmetic outcome
Hauschild 2009b	x (none lost)	x	Qualitative	-

There were no participant withdrawals due to adverse events.

Significantly more participants treated with ALA-PDT experienced skin irritation during (RR 0.63, 95% CI 0.54 to 0.74, NNT = 3.2) and 1 day after (RR 0.27, 95% CI 0.16 to 0.46, NNT = 3.7) treatment compared to cryotherapy (Analysis 46.2).

The minor adverse events reported in the cryotherapy group were eyelid oedema and swollen face, whereas pyoderma and emotional distress were documented for ALA-PDT group. Headaches were reported in both groups.

In summary, in this single study, ALA-PDT treatment was superior to cryotherapy for efficacy outcomes, but more skin irritation was associated with ALA-PDT.

Cryotherapy versus methyl aminolevulinate (MAL)-photodynamic therapy (PDT)

This intervention was addressed by 4 studies (Freeman 2003; Kaufmann 2008; Morton 2006; Szeimies 2002) comparing cryotherapy and PDT with 16% MAL for the treatment of actinic keratoses. All studies were open and used red light PDT. Characteristics of the studies are presented in the following table. There was possible performance, detection, and reporting bias for all studies, attrition bias for all studies except Morton 2006, and other bias for Freeman 2003 and Kaufmann 2008.

Characteristic	Szeimies 2002	Freeman 2003	Morton 2006	Kaufmann 2008
Study design	Parallel	Parallel	Intraindividual	Intraindividual
Anatomical locations	Face, scalp, others (< 10%)	Face or scalp	Face and scalp	Upper and lower extremities (98%), trunk, neck
Prior preparation of lesions (scale and crust removal)	Cryotherapy: yes PDT: yes	Cryotherapy: no PDT: yes	PDT: yes	PDT: yes (except mild lesions = 12%)
Number of treatment cycle	1 (face and scalp) or 2 (other locations)	Cryotherapy : 1 PDT: 2	1 or 2	1 or 2
Number of weeks between treatments	1	1	12	12

Number of freeze-thaw cycles per treatment	2	1	2	2
Total freezing time (sec)	24 ± 18	12 to 26	16	20 ± 14
Individual lesion or field-directed treatment (MAL)	Individual lesions	Individual lesions	Individual lesions	Individual lesions
Occlusion time with 16% MAL (hour)	3	3	3	3
PDT intensity (mW/cm^2)	70 to 200	50 to 250	N/A	N/A
PDT dose (J/cm^2)	75	75	37	37
Type of light source	Non-coherent light	(CureLIght)	LED (Aktilite CL 128 lamp)	LED (Aktilite CL 128 lamp)
Time of assessment	12 weeks after the end of treatment	12 weeks after the end of treatment	12 weeks after the end of treatment	12 weeks after the end of treatment

Primary outcomes

Most of the studies presented 'lesion complete response' as an efficacy outcome, which was not included in this review.

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 240 participants)
Szeimies 2002	-	-	-	-
Freeman 2003	-	-	-	-
Morton 2006	-	-	-	Percentages
Kaufmann 2008	-	-	-	Percentages

Morton 2006 and Kaufmann 2008 presented the percentages without the associated standard deviations. Thus, no statistical analysis could be performed. Based on these percentages presented in Analysis 45.1 and the data presented in the overview tables for cryotherapy and photodynamic therapy, the two treatments seem to have similar efficacy.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 619 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (see table below)
Szeimies 2002	x	-	-	x

Freeman 2003	x	-	Only for MAL-PDT and not included in the analysis	x
Morton 2006	x	-	Intraindividual study not included in meta-analysis	x
Kaufmann 2008	x	-	Intraindividual study not included in meta-analysis	x

In the parallel-group studies, there was no difference in the number of participants who withdrew because of adverse events (Analysis 45.2). In the intraindividual studies, 4 of 119 (Morton 2006) and 2 of 121 (Kaufmann 2008) participants withdrew because of adverse events and 1 of them was related to MAL-PDT treatment.

Kaufmann 2008 mentioned that the types of adverse events observed were mainly photosensitivity reaction (43% of 121 participants) and cold exposure injury (62% of 121 participants) for the MAL-PDT and cryotherapy groups, respectively. Similar qualitative observation was mentioned by Morton 2006 (N = 119).

The types of cosmetic outcomes reported by the four studies are summarised in the following table.

Parameter	**Szeimies 2002** **(N = 122 participants)**	**Freeman 2003** **(N = ? participants)**	**Morton 2006**	**Kaufmann 2008**
Evaluation by investigator	X	X	X	X
Evaluation by participant	X	X	N/A	N/A
Outcome	1) excellent or good 2) fair or poor	Excellent	1) excellent 2) good 3) fair 4) poor	1) excellent 2) good 3) fair 4) poor
Reported per participant	X (only for participants with ≥ 75% reduction of total lesions)	X (only for participants with 100% reduction of total lesions)	N/A	N/A
Reported per lesion	N/A	X	X	X

Because participants or right/left sides were randomised and not the lesions, only the data reported by participants were analysed. Freeman 2003 reported the percentages of completely cleared participants with excellent cosmetic outcome, but the number of participants completely cleared was not specified and the standard deviations associated with the percentages were not provided. Thus, no statistical analysis could be performed on these data. Similar percentages were obtained for investigator and participant assessments for MAL-PDT (83% vs 76%) and cryotherapy (51% vs 56%). The authors reported significant differences between MAL-PDT and cryotherapy groups. The investigator (RR 0.84, 95% CI 0.74 to 0.95, NNT = 6.5; Analysis 45.3) and participant (RR 0.93, 95% CI 0.86 to 1.01, NNT = 14.6; Analysis 45.4) evaluations in the Szeimies 2002 study also supported a better cosmetic outcome in the MAL-PDT group.

To summarise, because most of the efficacy outcomes reported could not be included in our analyses, it is difficult to determine the relative efficacy of MAL-PDT and cryotherapy. Data from one study suggested equivalence between the two treatments. MAL-PDT treatment seems to result in better cosmetic outcomes than cryotherapy.

Photodynamic therapy

Photodynamic therapy employs light sources and photosensitising agents that may differ between studies. As this is a relatively new treatment method, testing different combinations of variables is necessary to attempt to identify the optimal PDT treatment form and regimen. Light sources vary from polychromatic to pulsed laser. Photosensitising agents aminolevulinic acid (ALA) and newer methyl-aminolevulinic acid (MAL) were both used, depending on the study. Thus, results are presented in two sections: photodynamic therapy with ALA and photodynamic therapy with MAL. Within these sections, the results are presented in the following order: 1) comparisons between ALA or MAL and placebo,

2) comparisons with different photodynamic therapy variables, and 3) comparisons with other treatments. Photodynamic therapy could be used to treat individual lesions or a field.

Photodynamic therapy (PDT) with 5-aminolaevulinic acid (ALA)

ALA-PDT versus placebo-PDT

This intervention was addressed by five studies (Hauschild 2009a; Hauschild 2009b; Jeffes 2001; Piacquadio 2004; Szeimies 2010b) investigating the use of aminolevulinic acid (ALA) and photodynamic therapy (PDT) compared to placebo-PDT to treat actinic keratoses. Characteristics of the studies are presented in the following table. There was possible performance (Hauschild 2009b; Jeffes 2001; Piacquadio 2004), detection (Hauschild 2009b; Piacquadio 2004), attrition (Hauschild 2009b; Piacquadio 2004), reporting (Hauschild 2009a; Hauschild 2009b; Piacquadio 2004), and other (Piacquadio 2004) bias.

	Blue light		Red light	
Characteristic	**Jeffes 2001**	**Piacquadio 2004**	**Hauschild 2009a and Hauschild 2009b**	**Szeimies 2010b**
Study design	Assessor-blinded intraindividual	Assessor-blinded parallel	Double-blinded parallel	Double-blinded parallel
Anatomical locations	Face and scalp	Face or scalp	Head	Face, bald scalp, or both
Prior preparation of lesions (e.g. scale and crust removal)	N/A	N/A	No	Yes
Number of treatment cycle	1 or 2	1 or 2	1	1 or 2
Number of weeks between treatments	8	8	N/A	12
Individual lesion or field-directed treatment	Individual lesions	Individual lesions	Individual lesions	Individual lesions
ALA formulation	20% cream	20% cream	Patch containing 8 mg	BF-200 gel
Occlusion time (hour)	14 to 18	14 to 18	4	3
PDT intensity (mW/cm^2)	3, 5, 10	10	N/A	Aktilite: 50-70 PhotoDyn 750: 196
PDT dose (J/cm^2)	2, 5,10	N/A	37	Aktilite: 37 PhotoDyn 750: 170
Illumination time (seconds)	N/A	1000	N/A	Aktilite: N/A PhotoDyn 750: 900
Type of light source	Non-laser fluorescent (Dusa BLU-417)	visible (Blu-U)	LED (Aktilite CL 128 lamp or Omnilux)	LED (Aktilite CL 128 lamp) or incoherent (PhotoDyn 750)

Time of assessment	8 weeks after the end of each treatment	8 weeks after the end of each treatment	12 weeks after the end of each treatment	12 weeks after the end of each treatment

Subgroup analyses were performed to compare blue and red light photodynamic therapies. In addition, one study (Piacquadio 2004) provided efficacy data for individual anatomical locations, i.e. face or scalp, allowing additional subgroup analysis for blue light ALA or placebo with photodynamic treatment.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 701 participants)	Participant partial (≥ 75%) clearance (N = 243 participants)	Mean (changes) reduction in lesion counts
Jeffes 2001	-	intraindividual and not included in meta-analysis	-	-
Piacquadio 2004	-	x	x	-
Hauschild 2009a; Hauschild 2009b	-	x	-	-
Szeimies 2010b	-	x	-	-

Most of the studies gave a second treatment to uncured lesions after the first treatment, and they provided efficacy outcomes 8 to 12 weeks after the first treatment (1 treatment) and after 4 to 12 weeks after the last treatment (1 or 2 treatments). Thus, separate comparisons were performed for the number of treatments received.

In Jeffes 2001, lesions treated with ALA were completely cleared in 45.7% (16/35) of the participants after 1 treatment using blue light PDT, whereas lesions treated with placebo were completely cleared in only 5.7% (2/35). Similarly, the number of participants with complete clearance was significantly higher in the ALA-PDT group than placebo-PDT group for both blue and red light after one treatment (Analysis 47.1). The amplitude of the effect was similar between blue (RR 6.22, 95% CI 2.88 to 13.43, NNT = 2.0; Analysis 47.1) and red light (RR 5.94, 95% CI 3.35 to 10.54, NNT = 2.0; Analysis 47.1), but a larger increase in the RR associated with blue light treatment following an additional treatment on uncured lesions was observed (blue light: RR 9.33, 95% CI 3.59 to 24.26, NNT = 1.8; and red light: RR 6.20, 95% CI 2.40 to 15.99, NNT = 2.0; Analysis 47.2).

This difference might be explained by the fact that only one study with red light performed a second treatment: Szeimies 2010b used two light sources to reflect more medical practices. A lower efficacy was obtained with the ALA/PhotoDyn 750 lamp (26/49 = 53%) than with ALA/Aktilite CL 128 (27/31 = 87%). The PhotoDyn lamp was used in 60% of the ALA and placebo participants, resulting in lower efficacy than the other 2 studies using only the Aktilite lamp after the first treatment.

Similar results were obtained with participant partial clearance for blue light ALA-PDT with a RR of 4.38, 95% CI 2.47 to 7.79, NNT = 1.8 for 1 treatment (Analysis 47.4) and a RR of 6.51, 95% CI 3.22 to 13.15, NNT = 1.6 for 1 or 2 treatments (Analysis 47.5). There was no difference in the RRs for participants completely (Analysis 47.3) or partially (Analysis 47.6) cleared of lesions on the face or scalp. For both outcomes and both sites, ALA-PDT was significantly better than placebo-PDT.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 701 participants)	Skin irritation (N = 300 participants)	Minor adverse events excluding skin irritation (N = 543 participants)	Cosmetic outcome (see table below)
Jeffes 2001	x (none lost)	-	-	x
Piacquadio 2004	x (none lost)	-	x	x

Hauschild 2009a Hauschild 2009b	x (none lost)	x	x	x
Szeimies 2010b	x (none lost)	-	Intraindividual study not included in meta-analysis	x

There were no participant withdrawals due to adverse events.

The number of participants experiencing skin irritation was significantly higher in the ALA-PDT group compared to placebo-PDT during illumination (RR 8.94, 95% CI 4.62 to 17.31, NNT = 1.3; Analysis 47.7) and after the treatment (RR 59.72, 95% CI 3.75 to 952.48, NNT = not applicable; Analysis 47.7).

None of the adverse events reported for blue light photodynamic therapy [injury (Analysis 47.8), hypertension (Analysis 47.9), skin hypertrophy (Analysis 47.11) and headache (Analysis 47.12)] were significantly different between the two treatments. For red light photodynamic therapy, Hauschild 2009a and Hauschild 2009b reported skin discolouration in one participant in the ALA group, which was not significantly different between ALA and placebo-treated participants (Analysis 47.10).

The types of cosmetic outcomes reported by the five studies are summarised in the following table.

Parameter	Jeffes 2001	Piacquadio 2004	Hauschild 2009a; Hauschild 2009b	Szeimies 2010b (N = 114 participants)
Evaluation by investigator	x (not specified)	x	x	x
Evaluation by participant	N/A	N/A	x	N/A
Outcome	Changes in pigmentation	Changes in pigmentation	1) excellent 2) good 3) fair 4) poor	General outcome: 1) very good or good 2) unsatisfactory/impaired outcome Skin quality (qualitative)
Reported per participant	N/A	N/A	N/A	x
Reported per lesion	x	x	x (cleared lesions only)	N/A

Cosmetic outcomes were reported by all studies, but only Szeimies 2010b reported its outcome per participant. The cosmetic outcomes assessed by the investigator were very good or good in 49% of ALA-PDT and 27% in placebo-PDT groups, which was significantly different (RR 1.83, 95% CI 1.03 to 3.25, NNT = 4.5; Analysis 47.13).

To summarise, ALA-PDT was more effective than placebo-PDT, and the efficacy is similar for blue or red light photodynamic therapy. For red light photodynamic therapy, using Aktilite CL 128 lamp gave better results than PhotoDyn 750 lamp. ALA treatment was generally associated with more skin irritation than placebo; however, ALA-PDT resulted in better cosmetic outcomes.

ALA-PDT: comparison between types of light source

This intervention was addressed by one study (Smith 2003) investigating ALA with one hour incubation followed by illumination with blue light or pulsed dye laser (PDL) for field-directed treatment on the face or scalp, twice with a month interval. Assessment was performed at four weeks after the end of treatment. There was possible performance, detection, and reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 24 participants)	Participant partial (≥ 75%) clearance (N = 24 participants)	Mean (changes) reduction in lesion counts

Smith 2003	-	x	x	-

More participants receiving ALA-blue light PDT compared to ALA-PDL had complete (6/12 compared to 1/12) (Analysis 48.1) or partial (>75%) (9/12 compared to 5/12) (Analysis 48.2) clearance, respectively; however, this was not statistically significant.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 24 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 24 participants)
Smith 2003	x (none lost)	-	-	x

There were no participant withdrawals due to adverse events.

None of the three cosmetic outcomes reported, i.e. improvements in global response, tactile roughness, and mottled hyperpigmentation, were significantly different between the two light sources (Analysis 48.3; Analysis 48.4; Analysis 48.5).

To summarise, insufficient data were provided to determine the superiority of one source of light over the other for field-directed treatment of actinic keratoses with ALA-PDT.

ALA-PDT: comparison for different incubation times with ALA

This intervention was addressed by 1 study (Hauschild 2009c) comparing the efficacy of self-adhesive ALA patch treating individual lesions for different incubation times (0.5, 1, 2, and 4 hours) before PDT (red light) treatment to treat actinic keratoses on the head and face. Assessments were performed at 4 and 8 weeks after the end of treatment. There was possible attrition and reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 140 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts
Hauschild 2009c	-	x	-	-

Efficacy was assessed at four (Analysis 49.1) and eight weeks (Analysis 49.2), and participant complete clearance was analysed for subgroups of the different combinations between shorter and longer incubation times. At 4 weeks, analyses of participant complete clearance did not favour shorter or longer times except for comparison between the shortest (0.5 hours) and the longest (4 hours), which favoured the longest incubation time (RR 0.50, 95% CI 0.26 to 0.95, NNT = 3.8). In contrast, all comparisons favoured the longer incubation times with the exception of 1 hour versus 2 hours at week 8 (Analysis 49.2). Thus, a longer incubation with ALA gave better long-term results.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 149 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 149 participants)	Cosmetic outcome
Hauschild 2009c	x (maybe)	-	x	-

Of 149 participants, 9 were not included in the final efficacy analysis and 3 of them terminated the study prematurely; however, the

authors did not give more details about the reasons or associated treatments.

Five of 149 participants experienced adverse events related to treatment, which were 3 headaches (1 in each of the 0.5-, 2-, and 4-hour groups), 1 nose bleed (in the 4-hour group), and a mild increase in alanine transaminase (1 in the 0.5-hour group). None of these adverse events were significantly associated with the incubation time (mild increase in alanine transaminase: Analysis 49.3; headache: Analysis 49.4; and nose bleed: Analysis 49.5). Other adverse events were reported but not in relation to the incubation groups.

To summarise, longer incubation with ALA resulted in an increase in long-term efficacy.

ALA-PDT versus 5-fluorouracil

This intervention was addressed by 1 study (Smith 2003) comparing ALA-PDT field-directed treatment (twice with a 1-month interval) using 2 different types of light sources (blue light and pulse dye laser) with 0.5% fluorouracil applied once or twice daily for 4 weeks on the face or scalp (field-directed treatment). Assessment was performed four weeks after the end of treatment. There was possible performance, detection, and reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 36 participants)	Participant partial (≥ 75%) clearance (N = 36 participants)	Mean (changes) reduction in lesion counts
Smith 2003	-	x	x	-

Analyses of participant complete (Analysis 50.1) and partial (> 75%) (Analysis 50.2) clearance showed that the PDT treatments with blue light and the pulse dye laser (PDL) were comparable to 5-fluorouracil. However, a tendency to favour 5-fluorouracil over ALA-PDT with pulsed dye laser could be observed for both outcomes (complete: RR 0.17, 95% CI 0.02 to 1.18; partial: RR 0.56, 95% CI 0.26 to 1.17), but this was not statistically significant.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 36 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 36 participants)
Smith 2003	x	-	-	x

One of 12 participants in the 5-fluorouracil group withdrew because of adverse events compared to none of the 24 participants in the ALA-PDT groups, which was not significantly different (Analysis 50.3).

None of the 3 cosmetic outcomes reported improvements in global response (RR 0.74, 95% CI 0.44 to 1.25; Analysis 50.4). Tactile roughness (RR 0.92, 95% CI 0.52 to 1.61; Analysis 50.5) and mottled hyperpigmentation (RR 0.65, 95% CI 0.34 to 1.26; Analysis 50.6) were significantly different between 5-fluorouracil and ALA-PDT administered with the 2 light sources, but there was a general tendency to favour 5-fluorouracil treatment. However, this was not statistically significant.

To summarise, no statistical difference could be observed between 5-fluorouracil treatments and ALA with photodynamic therapy because of the small sample of this study. However, 5-fluorouracil treatment had a tendency to result in better outcomes.

ALA-PDT and imiquimod

This intervention was addressed by 1 intraindividual study (Sotiriou 2009) comparing 2 treatments of ALA-red light PDT performed at a 15-day interval on individual lesions and a dosing cycle of 5% imiquimod once per day 3 times per week for 4 weeks on, 4 weeks off, repeated if needed on the dorsal side of the hands and forearms (field-directed treatment). Assessments were performed 4 and 24 weeks after the end of treatment. There was possible performance and detection bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts

Sotiriou 2009	-	-	-	-

The study by Sotiriou 2009 reported "lesion complete response" as an efficacy outcome, which was not one of our primary outcomes.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 30 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome (N = 30 participants)
Sotiriou 2009	X (none lost)	-	-	x

There were no participant withdrawals due to adverse events.

The authors of the Sotiriou 2009 study reported no significant difference in the investigator-assessed excellent cosmetic outcome for lesions in the two treatment groups.

To summarise, the efficacy of ALA-PDT and imiquimod could not be compared.

ALA-PDT versus cryotherapy

This comparison was discussed in the cryotherapy section above, and the results presented in Table 3 correspond to Analysis 51.1 and Analysis 51.2 .

Photodynamic therapy (PDT) with methyl-aminolevulinic (MAL)

MAL-PDT versus placebo-PDT

This intervention was addressed by seven studies (Dragieva 2004a; Freeman 2003; Pariser 2003; Pariser 2008; Photocure-Australian 2004; Photocure-US 2004; Szeimies 2009) investigating the use of methyl-aminolevulinic (MAL) and photodynamic therapy (PDT) compared to placebo-PDT to treat actinic keratoses. The Dragieva 2004a study was performed with immunocompromised participants (organ transplants recipients). Characteristics of the studies are presented in the following table. There was possible performance (Dragieva 2004a; Freeman 2003), detection (Dragieva 2004a; Freeman 2003), attrition (Freeman 2003; Pariser 2003; Photocure-Australian 2004; Photocure-US 2004), reporting (Freeman 2003; Pariser 2003; Photocure-Australian 2004; Photocure-US 2004), and other (Freeman 2003) biases.

	Red light					
Characteristic	**Freeman 2003**	**Pariser 2003**	**Dragieva 2004a**	**Photocure-Australian 2004; Photocure-US 2004**	**Pariser 2008**	**Szeimies 2009**
Study design	Double-blinded parallel	Double-blinded parallel	Double-blinded intraindividual	Double-blinded parallel	Double-blinded parallel	Double-blinded parallel
Anatomical locations	Face or scalp	Face and scalp	Face or scalp, neck, extremities	Face and scalp	Face and scalp	Face and scalp, hand (< 1%)
Prior preparation of lesions (e.g. scale and crust removal)	Yes	Yes	Yes	Yes	Yes	Yes
Number of treatment cycle	2	2	2	2	2	2

Number of weeks between treatments	1	1	1	1	1	1
Individual lesion or field-directed treatment	Individual lesions	Individual lesions	Field-directed treatment	Individual lesions	Individual lesions	Individual lesions
MAL formulation	16% cream	16% cream	N/A	16.8% cream	16.8% cream	16% cream
Occlusion time (hour)	3	3	3	2.5 to 4	3	3
PDT intensity (mW/cm^2)	50 to 250	50 to 200	80	N/A	N/A	56 to 83
PDT dose (J/cm^2)	75	75	75	75	37	37
Illumination time (seconds)	600	480	N/A	N/A	480	540
Type of light source	Broadband (CureLight)	Broadband non-coherent light	Broadband non-coherent (Waldmann PDT 1200)	Broadband (CureLight)	Light-emitting diode (LED) (Aktilite CL 128)	Light-emitting diode (LED) (Aktilite CL 128)
Time of assessment	12 weeks after the end of treatment	12 weeks after the end of treatment	16 weeks after the end of treatment	12 weeks after the end of treatment	12 weeks after the end of treatment	12 weeks after the end of treatment

Primary outcomes

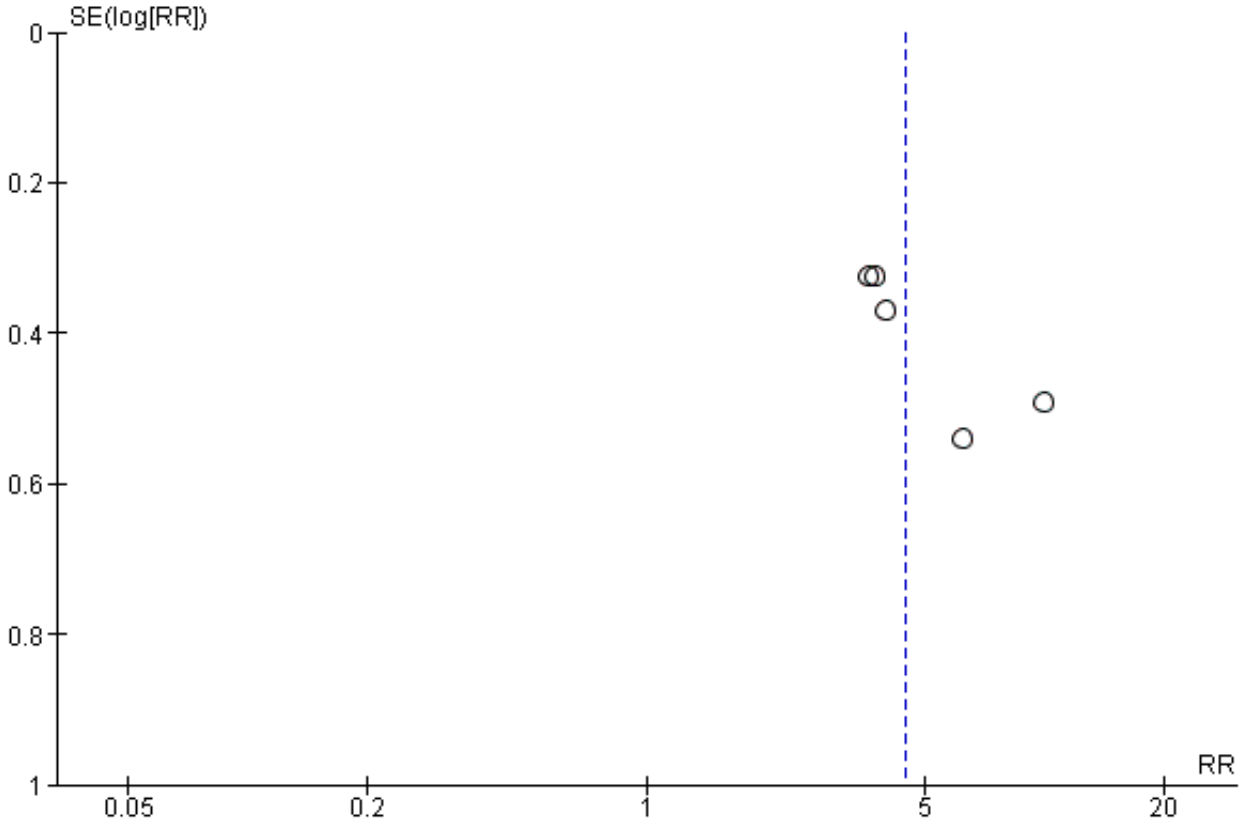
Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 499 participants)	Participant partial (≥ 75%) clearance (N = 191 participants)	Mean (changes) reduction in lesion counts
Freeman 2003	-	-	-	-
Pariser 2003	-	x	-	-
Dragieva 2004a	-	x	-	-
Photocure-Australian 2004; Photocure-US 2004;	-	x	x	-
Pariser 2008	-	x	-	-
Szeimies 2009	-	x	-	-

Freeman 2003 reported only lesion complete response, which is not included in this review.

In immunocompetent participants, pooled RR for participant complete clearance favoured MAL/red light PDT (RR 4.46, 95% CI 3.17 to 6.28, NNT = 1.9; Analysis 52.1). Similarly, pooled RR (Photocure-Australian 2004; Photocure-US 2004) for participant partial (≥ 75%) clearance also favoured MAL-PDT over placebo-PDT (RR 3.28, 95% CI 1.73 to 6.23, NNT = 1.8; Analysis 52.2). In immunosuppressed participants, 13 out of 17 participants were completely cleared on the MAL-PDT-treated side and none on the placebo-PDT-treated side, supporting the superiority of MAL photodynamic therapy in these organ transplants patients.

No publication bias was detected for the studies with immunocompetent participants based on the funnel plot (Figure 4).

Figure 4. Funnel plot of comparison: 50 MAL-PDT (red light) versus placebo-PDT (red light), outcome: 50.1 Participant complete clearance.



Secondary outcomes

Study	Withdrawal due to adverse events (N = 402 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 115 participants)	Cosmetic outcome (see text below)
Freeman 2003	x	-	-	x
Pariser 2003	x	-	-	x
Dragieva 2004a	-	-	-	-
Photocure-Australian 2004; Photocure-US 2004;	-	-	-	x
Pariser 2008	x (none lost)	-	-	-

Szeimies 2009	x (none lost)	-	x	-

The pooled risk ratio for two of the studies showed no significant difference in the number of participants who withdrew because of adverse events between MAL-PDT- and placebo-PDT-treated groups (Analysis 52.3). In addition, two other studies had no withdrawals due to adverse events in both treatment groups. These data together suggest that there is no difference between the two groups.

Szeimies 2009 reported one event of headache (one participant; Analysis 52.4) and three events of eyelid oedema in the MAL-PDT group.

Excellent cosmetic outcomes were observed for MAL-PDT in 81% to 93% of participants completely cleared [Freeman 2003 (N = the number of participants evaluated was not given); Pariser 2003 (N = 32)], but in the absence of data reported for placebo-PDT, these values could not be compared. No significant difference was observed for hyperpigmentation (N = 191; Analysis 52.5).

To summarise, MAL-PDT was clearly more efficient than placebo-PDT to treat actinic keratoses.

MAL-PDT: comparisons between types of light source

This intervention was addressed by two studies (von Felbert 2010; Wiegell 2008). Wiegell 2008 compared field-directed treatment using MAL-PDT with light-emitting diode (LED) red light and field-directed treatment using MAL-PDT with daylight (sun) on the face or scalp (field-directed treatment). After removal of crust and hyperkeratoses, MAL cream was applied for three hours. After 30 minutes occlusion, the daylight-treated side was exposed to outside daylight for 2.5 hours, and then the red light side, which stayed under occlusion for 3 hours, was treated with a LED lamp. von Felbert 2010 compared individual lesion treatment (one or two treatments) using MAL-PDT with red light LED or a broadband visible plus water-filtered infrared A on the face or scalp. Each treatment group was further separated into two subgroups: with and without cooling spray during illumination. Assessments were performed at 12 (von Felbert 2010; Wiegell 2008), 24 (von Felbert 2010), and 48 weeks (von Felbert 2010). There was possible performance (Wiegell 2008) and attrition (von Felbert 2010) bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 80 participants)	Participant partial (≥ 75%) clearance (N = 80 participants)	Mean (changes) reduction in lesion counts (N = 30 participants)
Wiegell 2008	-	-	-	Absolute values and percentages
von Felbert 2010	-	x	x	-

No difference in the mean reduction in lesion counts was found between red (8.0 ± 5.6, mean ± SD, 71%) and daylight (8.4 ± 5.4, 79%) (Analysis 54.1).

At 12 months, the number of participants with complete (RR 1.50, 95% CI 0.90 to 2.51; Analysis 53.1) clearance had a tendency to be higher in the MAL-PDT using red light LED as the illumination source, although this was not statistically significant, compared to broadband visible plus water-filtered infrared A. In contrast, no tendency could be observed for partial clearance (RR 1.03, 95% CI 0.85 to 1.25; Analysis 53.2).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 110 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Wiegell 2008	x (none lost)	-	-	-
von Felbert 2010	x (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

It is worth noting that the authors of the Wiegell 2008 study reported a pain score significantly lower during daylight exposure than red light exposure. The adverse events were more severe in the sun-exposed side for 42% of the participants and more severe in the red light side for 21% following treatment (Wiegell 2008).

To summarise, performing MAL-PDT with daylight exposure resulted in similar efficacy to MAL-PDT with red light treatment. However, a tendency for better results with red light LED compared to broad visible light with water filtered infrared A was observed.

MAL-PDT: comparison for different incubation times with MAL

This intervention was addressed by 1 study (Wiegell 2011a) comparing the efficacy of field-directed treatment MAL-PDT for different illumination times with daylight in the presence of 16% MAL cream. Sunscreen was applied for 15 minutes to the treatment area on the face and scalp, and crusts and scales were gently removed before MAL application. After 30 minutes occlusion with MAL, participants were exposed to the sun for 1.5 or 2.5 hours, resulting in exposure to MAL for 2 and 3 hours. All lesions present in the area were treated, but only grade 1 lesions were included in the data analysis by the authors of the study. Assessment was performed 12 weeks after the end of treatment. There was possible performance bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 120 participants)
Wiegell 2011a	-	-	-	Absolute values and percentages

No difference was found between 2 and 3 hours MAL incubation with daylight PDT for mean reduction of lesion counts (MD 0.10, 95% CI -3.17 to 3.37; Analysis 55.1) or mean percentage reduction in lesion counts (MD 2.60, 95% CI -6.46 to 11.66; Analysis 55.2). The latter had a tendency to favour the shortest incubation time, but this was not statistically significant.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 120 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Wiegell 2011a	x (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, similar efficacy was obtained for 2- or 3-hour incubation with 16% MAL with sun exposure for 1.5 and 2.5 hours, respectively.

MAL-PDT: comparison for different concentrations of MAL

This intervention was addressed by 1 intraindividual study (Wiegell 2009) comparing the efficacy of field-directed treatment with MAL-PDT for different MAL concentrations (16% versus 8%) with daylight PDT for actinic keratoses on the face or scalp. Sunscreen was applied for 15 minutes to the treatment area, and crusts and scales were gently removed before MAL application. The participants were then instructed to spend as much time as possible outside for the rest of the day and wash off the cream at bedtime. The light dose was measured by a dosimeter. Assessment was performed 12 weeks after the end of treatment. There was possible reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 29 participants)
Wiegell 2009	-	-	-	Absolute values and percentages

Similar efficacy was obtained for the 2 concentrations of MAL, i.e. mean reduction in lesion counts of 14.8 ± 8.2 (mean ± SD, 76.9%) for 16% MAL and 14.5 ± 7.6 (79.5%) for 8% MAL (Analysis 56.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 30 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Wiegell 2009	x	-	-	-

One of 30 participants withdrew because of unrelated adverse events (terminal illness).

To summarise, 8% and 16% MAL treatments gave similar results with daylight photodynamic therapy to treat actinic keratoses.

MAL-PDT: comparison between single and multiple MAL-PDT treatment

This intervention was addressed by one study (Tarstedt 2005) comparing the efficacy of one MAL-PDT treatment with red light and three-hour incubation compared to the efficacy of multiple MAL-PDT treatments, which involved two treatment sessions one week apart, on individual lesions on the face and scalp. Lesions not cleared after 12 weeks were retreated. Assessment was performed 12 weeks after the end of each cycle of treatment. There was possible performance, detection, and attrition bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 211 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts
Wiegell 2009	-	x	-	-

The number of participants achieving complete clearance was significantly higher in the single MAL-PDT treatment group compared to the multiple MAL-PDT treatment (RR 1.17, 95% CI 1.03 to 1.33; Analysis 57.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 211 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Tarstedt 2005	x	-	-	Per lesion (not included in analysis)

The number of participants who withdrew because of adverse events was not significantly different between single MAL-PDT and multiple MAL-PDT (Analysis 57.2).

To summarise, multiple MAL-PDT treatments were associated with more adverse events and were less efficacious than a single treatment.

MAL-PDT versus cryotherapy

This comparison was discussed in the cryotherapy section above and the results presented in Table 3 correspond to Analysis 45.1 and Analysis 58.1.

ALA-PDT versus MAL-PDT

This intervention was addressed by 1 intraindividual study (Moloney 2007) comparing 20% ALA incubated for 5 hours and 20% MAL incubated for 3 hours before PDT under identical conditions for field-directed treatment of extensive actinic keratoses on the scalp. Assessment was performed four weeks after the end of treatment. There was possible reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 16 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 15 participants)
Moloney 2007	-	Field complete clearance	-	Absolute values

Because of the intraindividual design of the Moloney 2007 study, participant complete clearance could not be included in meta-analysis, but there was no significant difference between the effectiveness of the 2 treatments in curing actinic keratosis lesions based on participant complete clearance (ALA: 6/16 and MAL: 7/16) and mean reduction in lesion counts (Analysis 59.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 16 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Moloney 2007	x (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, there was no significant difference between the effectiveness of MAL and ALA treatments to treat extensive actinic keratoses.

MAL-PDT versus 5-fluorouracil

This intervention was addressed by 1 intraindividual study (Perrett 2007) comparing 3-hour incubation with MAL followed by red light PDT with 5% 5-fluorouracil twice daily for 3 weeks for treatment of individual actinic keratosis lesions and carcinoma in situ on the forearms and hands of organ transplant participants (immunosuppressed). Assessments were performed at 4, 12, and 24 weeks after the end of treatment. Data for efficacy but not safety outcomes were available separately for actinic keratoses. There was possible performance and detection bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 4 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts
Perrett 2007	-	x	-	-

Because of the intraindividual design of the study, the data for the participant complete clearance could not be included in a meta-analysis. Thus, the efficacy results at one, three, and six months after treatments are presented in the following table.

Assessment at (months)	MAL-PDT	5-fluorouracil
1	4/4	0/4
3	4/4	1/4
6	4/4	1/4

Based on this small sample size study, MAL-PDT seemed to be more effective at treating actinic keratoses in organ transplant participants than 5-fluorouracil under the conditions used.

Secondary outcomes

Because of the pooled data for carcinoma in situ and actinic keratoses, none of our secondary outcomes could be taken from the study by Perrett 2007.

To summarise, despite the small sample size used in Perrett 2007, efficacy data suggested that MAL-PDT was more efficacious than 5-fluorouracil to treat actinic keratoses in immunosuppressed participants

Trichloroacetic acid peel

Trichloroacetic acid peel versus 5-fluorouracil

This intervention was addressed by 1 study (Hantash 2006) comparing trichloroacetic acid peel with 5% 5-fluorouracil applied twice daily for 3 weeks on the face. Assessment was performed 12 weeks after the end of treatment. There was possible performance and detection bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 18 participants)
Hantash 2006	-	-	-	Percentages

Analysis of mean percentage of reduction in lesion counts did not significantly favour any treatment, but there was a tendency to favour the chemical peel (MD 5.80, 95% CI -3.78 to 15.38; Analysis 60.1).

Secondary outcomes

Study	Withdrawal due to adverse events (N = 19 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Hantash 2006	x (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, additional data are needed to confirm the superiority of the trichloroacetic acid chemical peel over 5-fluorouracil to treat actinic keratoses.

Trichloroacetic acid peel versus carbon dioxide laser resurfacing

This comparison was presented in the laser resurfacing section above.

(5) Combinations of topical and oral treatments with mechanical or chemical interventions

Cryotherapy combined with betulin-based oleogel

This intervention was addressed by one study (Huyke 2009) comparing cryotherapy with liquid nitrogen to cryotherapy combined with betulin-based oleogel on the face, scalp, or other locations. Cryotherapy of participant lesions was performed once on lesions on the face and twice on lesions on the rest of the body, whereas betulin-based oleogel was applied twice daily for an unspecified duration. Assessment was performed at three months after the beginning of the treatment. There was possible performance and detection bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 30 participants)	Participant partial (≥ 75%) clearance (N = 30 participants)	Mean (changes) reduction in lesion counts
Huyke 2009	-	x	x	-

Additional treatment with betulin-based oleogel did not significantly change participant complete (Analysis 61.1) or partial (≥ 75%) clearance rates (Analysis 61.2) obtained with cryotherapy.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 30 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Huyke 2009	x (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, the use of betulin-based oleogel after cryotherapy did not improve the efficacy of the cryotherapy.

Cryotherapy combined with 5-fluorouracil

This intervention was addressed by 2 studies (Jorizzo 2004; Jorizzo 2006) comparing 0.5% 5-fluorouracil or placebo applied daily to lesions on the face, scalp, ears, neck, and lips for 7 days combined with cryotherapy at week 4 for uncured lesions for 1 (Jorizzo 2004) to 3 (Jorizzo 2006) cycles. Assessment was performed at 4 weeks after the end of treatment. There was possible reporting (Jorizzo 2006) and other (Jorizzo 2006) bias.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared	Participant complete clearance (N = 144 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 144 participants)
Jorizzo 2004	-	x	-	Absolute values and percentages
Jorizzo 2006	-	x	-	Absolute values and percentages

Pretreatment with 0.5% 5-fluorouracil before cryotherapy for 1 (RR 4.08, 95% CI 1.63 to 10.23, NNT = 4.6) or 2 (RR 3.27, 95% CI 1.82 to 5.88, NNT = 2.8), but not for 3 cycles, resulted in higher participant complete clearance (Analysis 62.1) compared to placebo combined with cryotherapy.

The absolute mean reduction in lesion counts and their associated standard deviations were calculated from the mean lesion counts at baseline and the end of the 3 different treatment cycles. The standard deviation associated with the mean percentage of reduction in lesion counts was only reported for the first treatment cycle in Jorizzo 2004. Thus, statistical analysis of this outcome could not be performed. This difference in efficacy between 0.5% 5-fluorouracil with cryotherapy and vehicle with cryotherapy was supported by the mean percentage of reduction in lesion counts presented in the following table and the significant mean difference for the first cycle (MD 21.40, 95% CI 5.10 to 37.70; Analysis 62.3), but not by the analysis of mean reduction of lesion counts (Analysis 62.2).

Mean percentage of reduction in lesion counts

Study	Number of cycles	Vehicle + cryotherapy (mean ± SD)	5-FU + cryotherapy (mean ± SD)
Jorizzo 2004	1	45.6% ± 54.7%	67% ± 43.6%
Jorizzo 2006	2	57.8%	86.3%

Jorizzo 2006	3	65.7%	77.8%

The results presented in the additional Table 4 comparing vehicle with cryotherapy and 5-FU with cryotherapy correspond to Analysis 63.1, Analysis 63.2, and Analysis 63.3.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 144 participants)	Skin irritation	Minor adverse events excluding skin irritation (N = 144 participants)	Cosmetic outcome
Jorizzo 2004	x (none lost)	-	x (eye irritation)	-
Jorizzo 2006	x	-	x (including Jorizzo 2004)	-

In the first treatment cycle of the Jorizzo 2004 and Jorizzo 2006 study, there were no participant withdrawals due to adverse events. Insufficient information was provided to determine how many participants were lost due to adverse events for the whole study.

None of the adverse events reported were significantly different between cryotherapy alone and cryotherapy combined with 5-fluorouracil. In general, eye irritation (Analysis 62.10) and conjunctivitis (Analysis 62.9) were the most commonly-reported adverse reactions for both groups and the same numbers of participants in each group experiencing it.

To summarise, the efficacy of cryotherapy could be increased with pretreatment with 0.5% 5-fluorouracil if used for 1 or 2, but not 3, cycles.

Cryotherapy combined with imiquimod

This intervention was addressed by three studies (Jorizzo 2010; NCT00774787; Tan 2007). The studies compared cryotherapy followed by vehicle and cryotherapy followed with imiquimod treatment. In Jorizzo 2010, 4 to 14 lesions were treated with cryotherapy, and 5 lesions were left untreated before randomisation. The method used to select which lesions were treated with cryotherapy was not specified. Thus, the data from this study comparing cryotherapy with imiquimod and imiquimod alone could not be used in our analyses. NCT00774787 had an intraindividual study design, whereas all the other studies had a parallel-group design. The anatomical locations, dosing regimens, and assessment time are presented in the following table. There was possible performance (NCT00774787), attrition (Tan 2007), reporting (Jorizzo 2010; NCT00774787; Tan 2007), and other (Tan 2007) biases.

Study	Anatomical locations	Cryotherapy (followed or not with placebo)	Cryotherapy followed by imiquimod	Imiquimod alone	Time of assessment
Tan 2007	Face or scalp	Once	5% imiquimod 2 times/week for 8 weeks	No	4 weeks after the end of treatment
Jorizzo 2010	Face	Once	3.75% imiquimod 3 times/week for 2 weeks on/2 weeks off/2 weeks on	3.75 %imiquimod 3 times/week for 2 weeks on/ 2 weeks off/2 weeks on	20 weeks after the end of treatment
NCT00774787	Face or bald scalp	Once	5% imiquimod 3 times/week for 4 weeks	No	4 to 8 weeks after the end of treatment

Primary outcomes

Study	Global improvement indices for completely improved or cleared	Participant complete clearance (N = 339 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 274 participants)
Tan 2007	-	x	-	-
Jorizzo 2010	-	x	-	Percentages
NCT00774787	-	Intraindividual study	-	Percentages

The primary outcomes were further divided into 3 outcomes: 1) for target lesions, i.e. cryotherapy-treated lesions visible at baseline; 2) for subclinical lesions, i.e. lesions not visible at baseline but visible during the study; and 3) all lesions, i.e. target and subclinical lesions.

More participants had complete clearance on the cryotherapy combined with imiquimod side (8/27 = 30%) than the side that had cryotherapy alone (5/27 = 19%) in the intraindividual study. Cryotherapy combined with imiquimod had a tendency (but this was not statistically significant) to result in more participants with target lesions (cryotherapy-treated: RR 0.62, 95% CI 0.36 to 1.04; Analysis 64.2) or subclinical lesions (RR 0.57, 95% CI 0.33 to 1.01; Analysis 64.3) completely cured compared to cryotherapy. By contrast, there was statistically significant complete clearance of all lesions in participants in Jorizzo 2010 (RR 0.20, 95% CI 0.05 to 0.73; Analysis 64.1); however, this could be due to the fact that the analysis in Jorizzo 2010 included the 5 lesions untreated with cryotherapy.

The combined cryotherapy with 3.75% imiquimod therapy was also significantly favoured compared with the cryotherapy-only treated side for mean percentages of reduction for all lesions (MD -34.10, 95% CI -41.38, to -26.82; Analysis 64.4) but not when 5.0% imiquimod was used (MD -11.20, 95% CI -26.53 to 4.13; Analysis 64.4). The results from the 2 studies could not be pooled due to the high heterogeneity between the 2 studies (I^2 statistic = 86%). It is worth noting that the study favouring the combined therapy had a parallel design, whereas the study not favouring the combined therapy was an intraindividual study. Only the study with 3.75% imiquimod reported the mean percentage of reduction for target lesions only (MD -10.80, 95% CI -17.37 to -4.23; Analysis 64.5), which favoured the combined therapy.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 339 participants)	Skin irritation (N = 312 participants)	Minor adverse events excluding skin irritation (N = 312 participants)	Cosmetic outcome (N = 274 participants)
Tan 2007	x	x	x	-
Jorizzo 2010	x	x	x (only for 2 groups: cryotherapy with placebo and cryotherapy with imiquimod)	x (only for 2 groups: cryotherapy with placebo and cryotherapy with imiquimod)
NCT00774787	x	-	Pooled data not included	x

In the intraindividual study, NCT00774787, there were no participant withdrawals due to adverse events. The pooled risk ratio for Tan 2007 and Jorizzo 2010 showed no difference between cryotherapy with vehicle and cryotherapy with imiquimod groups (RR 0.93, 95% CI 0.28 to 3.07; Analysis 64.6).

The number of participants experiencing skin irritation had a tendency to be higher in the group receiving additional treatment with imiquimod compared to cryotherapy alone (RR 0.39, 95% CI 0.10 to 1.54; Analysis 64.7).

The number of participants experiencing fatigue (RR 0.09, 95% CI 0.01 to 1.69; Analysis 64.8), nausea (RR 0.09, 95% CI 0.01 to 1.69; Analysis 64.9), and myalgia (RR 0.21, 95% CI 0.02 to 1.76; Analysis 64.10) tended to be higher with additional imiquimod treatment, whereas the 3 respiratory adverse events, upper respiratory tract infection (RR 1.34, 95% CI 0.51 to 3.48; Analysis 64.11), bronchitis

(RR 5.21, 95% CI 0.62 to 43.92; Analysis 64.12), and sinusitis (RR 11.45, 95% CI 0.64 to 204.88; Analysis 64.13) tended to be higher in the cryotherapy alone group. None of the minor adverse events were statistically significant. One case of skin infection due to cryotherapy had been reported by Tan 2007, but the treatment group (i.e. placebo or imiquimod) was not specified.

Additional imiquimod treatment with cryotherapy significantly improved the cosmetic outcome compared to cryotherapy alone in all individual cosmetic outcomes reported by Jorizzo 2010 (fine lines, tactile roughness, mottled pigmentation, and sallowness) as well as global photoageing score (RR 0.37, 95% CI 0.25 to 0.56, NNT = 3.1; Analysis 64.15). Cosmetic outcome assessments by participant and investigator in NCT00774787 showed similar results for the additional use of imiquimod with cryotherapy. In this study, analysis of participant assessment favoured the additional use of imiquimod, whereas analysis of investigator assessment did not favour its use. This could be explained by the fact that no placebo was used in this study reporting this cosmetic outcome, making the participants unblinded to the treatment and maybe biased towards the additional treatment with imiquimod; in contrast, the assessor was blinded.

The results presented in the additional Table 5 for imiquimod comparisons correspond to Analysis 65.1, Analysis 65.2, Analysis 65.3, and Analysis 65.4.

To summarise, combination of cryotherapy and imiquimod treatments resulted in significantly better efficacy compared to the cryotherapy alone. Use of imiquimod cream after cryotherapy increased in general the number of participants experiencing adverse events, but resulted in significantly better cosmetic outcome.

ALA-PDT combined with diclofenac in 2.5% hyaluronic acid gel pretreatment

This intervention was addressed by 1 study (Van der Geer 2009) investigating the efficacy of field-directed treatment of ALA-red light PDT on lesions on the dorsal side of the hands pretreated with diclofenac in 2.5% hyaluronic acid gel or 2.5% hyaluronic acid gel, twice daily for 4 weeks. Two weeks after diclofenac treatment, ALA was incubated for 4 hours then PDT with red light fractions at 80 J/cm^2 was performed for 16 minutes. Assessments were performed 6 weeks, and 6 and 12 months after the end of treatment. There was possible reporting bias associated with this study.

Primary outcomes

Study	Global Improvement indices for completely improved or cleared (N = 9 participants)	Participant complete clearance	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 9 participants)
Van der Geer 2009	Mean scores	-	-	Absolute values

The values provided for mean reduction in lesion counts at 6 weeks, 6 and 12 months (Analysis 66.2), and mean global improvement indices scores at 6 months (Analysis 66.1) were all lower in the vehicle group. The authors stated there was a significant difference in the mean number of lesions at 12 months (P = 0.017), but not in the mean reduction of lesion counts (P = 0.34) between the diclofenac and vehicle groups. However, it was impossible to test if these differences were statistically significant because measurement of variability, i.e. standard deviations or standard errors of the mean, were not provided.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 9 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Van der Geer 2009	x (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, pretreatment with diclofenac in 2.5% hyaluronic acid gel did not increase the efficacy of ALA-PDT treatment of actinic keratoses.

ALA-PDT combined with imiquimod

This intervention was addressed by 1 intraindividual study (Shaffelburg 2009) investigating 2 ALA-blue light PDT treatments with an interval of 4 weeks directed to a field of lesions.This was followed after another 4 weeks by 5% imiquimod or placebo applied once per day on the face (field-directed treatment), on 2 days per week for 16 weeks [ALA-blue light PDT followed with imiquimod versus ALA-blue PDT followed with placebo]. Assessments were performed at baseline and months 1, 2, 3, 4, 6, and 12 of the study. There was possible reporting bias.

Primary outcomes

Study	Global improvement indices for completely improved or cleared	Participant complete clearance (N = 25 participants)	Participant partial (≥ 75%) clearance	Mean (changes) reduction in lesion counts (N = 25 participants)
Shaffelburg 2009	-	x	-	Absolute values and percentages

The participant complete clearance was similar with (2/25) or without (2/25) additional imiquimod treatment after ALA-PDT. The mean reduction in lesion counts was 19.9 (86.7%) for the imiquimod-treated group and 16.0 (73.1%) for the placebo group. However, in the absence of standard deviations or standard errors of the mean values, no statistical analysis was possible to determine the significance of these data.

Secondary outcomes

Study	Withdrawal due to adverse events (N = 25 participants)	Skin irritation	Minor adverse events excluding skin irritation	Cosmetic outcome
Shaffelburg 2009	X (none lost)	-	-	-

There were no participant withdrawals due to adverse events.

To summarise, an additional treatment with imiquimod after ALA-PDT did not improve the efficacy of the treatment for actinic keratosis.

DISCUSSION

Summary of main results

Primary outcomes

Actinic keratoses remain unchanged, proliferate, regress, reappear, or develop into squamous cell carcinoma. Thus, comparison to a placebo control group gives a better estimate of the efficacy of an intervention for actinic keratoses. Significant estimate effects compared to vehicle or placebo were obtained for the following interventions.

1) For all reported efficacy outcomes: diclofenac (3/3 outcomes, number of studies (n) = 6, number of participants (N) = 723), 5-fluorouracil (3/3 outcomes, n = 3, N = 528), ingenol mebutate (2/2 outcomes, n = 3, N = 540), sunscreen (1/1 outcome, n = 1, N = 588), ALA-PDT (2/2 outcomes, n = 4, N = 814), and MAL-PDT (2/2 outcomes, n = 5, N = 486).

2) For 50% or more of the reported efficacy outcomes: adapalene (1/2 outcomes, n = 1, N = 90), imiquimod (3/5 outcomes, n = 17, N = 3417), isotretinoin (1/2 outcomes, n = 1, N = 100), and masoprocol (1/2 outcomes, n = 1, N = 176).

3) For none of the reported efficacy outcomes: calcipotriol (vitamin D, 0/2 outcomes, n = 1, N = 9), DFMO (0/1 outcome, n = 1, N = 48), β-1,3-D-glucan (0/1 outcome, n = 1, N = 20), nicotinamide (0/1 outcome, n = 1, N = 30), DL-α-tocopherol (vitamin E, 0/1 outcome, n = 1, N = 48), and etretinate (0/1 outcome, n = 1, N = 50).

Studies that compare the different concentrations of an intervention were included in our analysis. These studies were conducted for adapalene, colchicine, 5-fluorouracil, imiquimod, ingenol mebutate, and MAL. Adalpene was the only intervention to demonstrate a difference in efficacy as a result of different concentrations.

The photosensitiser incubation time and light source were variables that were considered by several studies conducted on photodynamic therapy. One study comparing 0.5-, 1-, 2-, and 4-hour incubations with ALA showed that longer incubation before the photodynamic therapy resulted in better efficacy than a shorter incubation for 4 of the 6 possible comparisons between the different incubation times (see overview for photodynamic therapy in Table 3). In contrast, a similar efficacy was found for two- and three-hour incubation with MAL before photodynamic therapy using daylight. No difference in efficacy was detected between the different light sources for photodynamic therapy (ALA: blue vs red light, blue light vs pulsed dye laser, and MAL: red light LED vs daylight, red light vs broadband visible plus water-filtered infrared A).

We analysed interventions that investigated the efficacy of combined interventions, which generally combined field-directed therapy with treatment for individual lesions. Pretreatment with 0.5% 5-fluorouracil before cryotherapy and imiquimod after cryotherapy significantly improved the efficacy of cryotherapy (see overview for cryotherapy in Table 4). In contrast, no improvement in efficacy was detected when the following interventions were combined: additional tretinoin treatment to 5-fluorouracil, additional betulin-based oleogel to cryotherapy, pretreatment with diclofenac before ALA-PDT, and imiquimod treatment after MAL-PDT.

Several studies compared the efficacy of two different interventions. These interventions may be field-directed

treatments applied to a large area of clinical and subclinical lesions (topical creams, resurfacing, field-directed photodynamic therapy, and chemical peel), or treatments that specifically target clinical lesions, (cryotherapy and individual lesion-directed photodynamic therapy). Topical aretinoid methyl sulfone (Ro 14-9706) was significantly more efficacious than topical tretinoin for only 1 of 2 outcomes reported by one study. Topical 5-fluorouracil was more efficacious than topical masoprocol (2/3 outcomes, n = 1, N = 49) and cryotherapy (1/1 outcome, n = 1, N = 49), but had similar efficacy to topical imiquimod (2/2, n = 2, N = 89), carbon dioxide laser resurfacing (1/1 outcome, n = 1, N = 14), Er:YAG laser resurfacing (2/2 outcomes, n = 1, N = 55), ALA-PDT for individual lesions (2/2 outcomes, n = 1, N = 36), and trichloroacetic acid peel (1/1 outcome, n = 1, N = 18) based on the data provided. However, more data are needed to be able to conclude on the difference in efficacy between 5-fluorouracil and MAL-PDT. Topical imiquimod efficacy was also similar to topical diclofenac (1/1 outcome, n = 1, N = 49) and cryotherapy (1/1 outcome, n = 1, N = 51) efficacies, but more data are needed to be able to compare imiquimod to ALA-PDT for individual lesions. Betulin-based oleogel and cryotherapy had similar efficacy (2/2 outcomes, n = 1, N = 28). Cryotherapy showed lower efficacy compared to ALA-PDT for individual lesions (1/1 outcome, n = 1, N = 72), but more data are needed for the comparison with MAL-PDT for individual lesions. However, field-directed treatments with ALA-PDT and MAL-PDT had similar efficacy (2/2 outcomes, n = 1, N = 15). Based on these comparisons, these interventions could be ranked based on their relative efficacy as follows: (5-fluorouracil = imiquimod = carbon dioxide laser resurfacing = Er:YAG laser resurfacing = ALA-PDT = MAL-PDT = trichloroacetic acid peel = diclofenac) > masoprocol (cryotherapy = betulin-based oleogel). The relative efficacy between masoprocol and cryotherapy was not investigated in any of the studies included. In summary, the comparisons of different interventions showed that these interventions were generally comparable.

In our review, carbon dioxide laser resurfacing has been shown to have a similar efficacy to 5-fluorouracil and trichloroacetic acid peel to treat actinic keratosis. However, the efficiency of carbon dioxide laser resurfacing to prevent short-term (within 12 months) recurrence of actinic keratoses has been questioned (Fulton 1999). Because recurrence, prophylaxis of actinic keratoses, or both, were not in the prespecified outcomes of our review, we will not further discuss this matter, but there might be a need for a future review on the subject.

The relative efficacy of the interventions on various anatomical locations was poorly reported. The majority of studies that investigated different regions of the skin grouped the locations together for each outcome. The only significant difference was reported between lesions on the face and upper extremities during isotretinoin treatment. There was also a decreased tendency to favour imiquimod for the lesions on the face. In summary, there was insufficient data to determine the difference in the lesions' location in this meta-analysis.

For three interventions, the efficacy relative to vehicle/placebo was investigated in immunosuppressed participants. Data from only one study with a small sample was usually included for immunosuppressed participants in the analyses, whereas data from several studies was generally pooled for immunocompetent participants. Thus, it is difficult to compare directly the calculated risk ratios and their 95% CI between studies including immunocompetent versus immunosuppressed participants. A comparison of the unweighted 'participant complete clearance' rates suggests that a similar efficacy is achieved for the two populations. In immunocompetent participants, diclofenac resulted in a 32% (67/208) complete clearance, whereas vehicle had a 13% (27/212) clearance. In immunosuppressed participants the same rates were 41% (9/66) for diclofenac and 0% (0/6) for vehicle. Imiquimod (5%) resulted in 42% (694/1649) vs 62% (18/29) complete clearance, whereas vehicle resulted in 5% (62/1231) and 0% (0/14) for the immunocompetent and immunosuppressed groups, respectively. In PDT, 76% (13/17) of immunosuppressed participants and 74% (204/278) of immunocompetent participants were completely cleared with MAL-PDT compared to 14% (30/204) and 0% (0/17) for placebo-PDT. In summary, the treatments were equally efficacious in immunosuppressed and immunocompetent participants. One ongoing study (NCT01525329) is comparing treatment with MAL-PDT alone and in combination with 5% 5-fluorouracil in both immunocompetent and immunosuppressed participants.

Secondary outcomes

In general, the number of participants withdrawn because of adverse events was not significantly different between interventions. The only exceptions were the following:

1. 3% diclofenac in 2.5% hyaluronic acid compared to 2.5% hyaluronic acid (see overview for diclofenac in Table 1),
2. 5% imiquimod compared to placebo (see overview for imiquimod Table 5), and
3. 0.06% to 0.1% resiquimod compared to 0.01% to 0.03% resiquimod.

The studies reporting skin irritation indicate that diclofenac (see overview for diclofenac in Table 1), 5-fluorouracil (see overview for 5-fluorouracil in Table 2), tretinoin, isotretinoin, and ALA (see overview for photodynamic therapy in Table 3) treatments are associated with significant skin irritation. Topical treatments were associated with different adverse effects than photodynamic therapy and cryotherapy. Topical treatments were associated with "flu" or "cold" symptoms, headache, and conjunctivitis or eye irritation. Photodynamic therapy and cryotherapy were associated with photosensitivity reaction and cold exposure injury, respectively. Most of the minor adverse events that were quantitatively reported were not significantly different between the two interventions that were compared. The only exceptions were the dermatitis associated with adapalene, the metabolic and nutritional disorder and dry skin associated with diclofenac, the "flu" or "cold" symptoms and headache with daily application of imiquimod, and the headache associated with concentrations of resiquimod superior to 0.01%.

Finally, the included studies reported varied cosmetic outcomes. In general, it could be concluded that imiquimod treatment and photodynamic therapy resulted in better cosmetic outcomes than cryotherapy and 5-fluorouracil.

Overall completeness and applicability of evidence

The physician's decision about which treatment to prescribe will depend on each patient's case and their treatment aims. Different interventions might be more effective for cosmetic outcomes, symptom relief, or prevention of squamous cell

carcinoma. In addition, the efficacy, cost, adverse events, length of treatment, ease of treatment, personal preference of the participant, participant compliance, severity of actinic damage, past treatment experiences, and other factors must all be taken into consideration, and the most appropriate treatment will vary from person to person. The completeness of this review will be discussed based on these factors influencing the choice of an intervention for treating actinic keratoses.

Several of these factors (cost, ease of treatment, participant preference, participant compliance, past treatment experiences) were not included in this review. Some of these factors were presented as outcomes in a few studies, and these are summarised in a table in the Included studies section under 'other outcomes'.

This review included several efficacy outcomes. However, the exclusion of an important efficacy outcome, such as 'lesion complete response', limited the evaluation of the relative efficacy of several interventions because some studies only reported this efficacy outcome (see Effects of interventions).

Adverse event reporting was complicated by the use of the generic "skin irritation" outcome. Many studies chose to use categories such as "application site reactions" and "local skin/ adverse reactions" instead of "skin irritation".

The interventions could also be compared based on their length of treatment. A wide variety of treatment options are available for actinic keratosis. Treatments such as cryotherapy or photodynamic therapy are performed once or twice by clinical staff, whereas the duration of topical treatments administered by patients varies from two applications within a few days for ingenol mebutate to daily application for seven months with sunscreen. A decision based on patient compliance and preference could easily be made. The effect of changing the length of a specific treatment was reported in this review where the information was available, but we did not compare different interventions based on their length of treatment. We did not compare continuous therapy with interval/pulse/cycle therapy. The readers are referred to a recent review (Martin 2011), which discusses the efficacy of short-course and interval/pulse/ cycle therapies for 5-fluorouracil, imiquimod, and ALA/MAL-PDT. Outcomes reported over time showed differences between the assessments, but variations in the time of the assessment (follow-up period) were generally not taken into consideration in our evaluation of the relative efficacy between interventions. Long-term (> one year) outcomes were not included in our meta-analysis, but references to these studies were included in the 'Characteristics of included studies' tables.

The severity of the lesions at baseline was not accounted for in our analysis. The studies reported the severity of lesions in different terms; some used the lesion grade, whereas others reported the number of lesions. In some studies, the number of lesions was a criterion for inclusion or exclusion of participants. This information can be found for the individual studies in the 'Characteristics of included studies' tables in the 'participants' sections.

Many patients wish to have their actinic keratoses treated in order to prevent their development into squamous cell carcinoma. The detection of squamous cell carcinoma, basal cell carcinoma, or Bowen's disease was not included in our outcomes, and little is known about their prevention by treating actinic keratoses. This outcome should be addressed in the future. One ongoing study (NCT01453179) will evaluate this issue for 5% imiquimod and 3% diclofenac in hyaluronic acid. However, it is worth noting that the studies included in our analysis did not specify if cancerous lesions were present in the treatment area. This makes the interpretation of this data difficult.

Quality of the evidence

The quality of the evidence presented in this review was evaluated in the 'Risk of bias' graph (Figure 2) and the 'Risk of bias' tables associated with each included study. The major factors decreasing the quality of evidence from the studies on interventions for actinic keratoses are as follows:

1. lack of reporting the methods used for allocation sequence generation and allocation concealment;
2. blinding of studies comparing physically-distinct interventions;
3. the use of per-protocol (PP) analysis instead of intention-to-treat (ITT) analysis (but PP data were converted as much as possible to ITT for meta-analyses); and
4. incomplete reporting of an outcome.

We also noticed another issue with reporting the diagnosis criteria for inclusion of the participants (see 'Characteristics of included studies' tables). Many studies did not specify whether a clinical or histological diagnosis was used to include the participants in the clinical trials.

There were two major limitations in our assessment of the effects of interventions for actinic keratoses. The first was that data from numerous intraindividual studies could not be included in the meta-analyses. The second was the frequent omission of standard deviations in the reporting of the outcome "mean reduction in lesion counts" for both absolute values and percentages, which prevented the statistical analysis of the data. Without the standard deviations, it is difficult to determine if there is a difference between the intervention and the control intervention.

The studies included in the different meta-analyses were generally very consistent, and only a few examples of high heterogeneity were observed. Many of the analyses only included data from an individual study; this included 76% of the efficacy outcomes, 91% of the safety outcomes, and 87% of the cosmetic outcomes.

The frequency of high-quality studies varied based on treatment. Our inclusion criteria fit more studies on imiquimod than 5-fluorouracil or cryotherapy. In contrast, 5-fluorouracil and cryotherapy have been compared to more interventions than imiquimod. The nature of cryotherapy does not allow for double-blinded prospective trials, with the exception of studies investigating the combined therapy with a topical treatment, which resulted in lower quality evidence (see overview for cryotherapy in Table 4).

There were several biases that affected the quality of the evidence. Certain treatments incurred adverse skin reactions (e.g. imiquimod, 5-fluorouracil, ALA, etc) that may indirectly introduce bias into the clinical assessment. Moreover, when comparing self-administered and clinically-administered interventions, such as 5-fluorouracil and photodynamic therapy, the compliance of the participants could have an influence on the outcomes and could introduce selection bias if participants were included or excluded based on their compliance. Reporting bias could also result from

the method used to assess efficacy outcomes. Several studies reported the observation of new actinic keratoses during the clinical trial, and most of the studies did not specify whether they were studying all lesions or a specific subpopulation of clinical, subclinical, or new lesions.

Potential biases in the review process

This review included a broad variety of interventions for actinic keratoses and a large number of outcomes. The search for corresponding studies resulted in a large number of studies, which produced a considerable amount of information. Data extraction sheets were really useful tools for the organisation of this information. However, important details for comparison between studies could have been missed or overlooked in this process. The amount of information presented meant that we were unable to evaluate all of the factors influencing the outcomes, including the methods used for assessment. We searched multiple databases as well as websites and grey literature for randomised clinical trials on all interventions (not prophylaxis) for actinic keratoses in any language. We also contacted pharmaceutical companies to request additional information, but this correspondence was not always successful. There is a possibility that studies may be missing. For example, a study on comparison between 5% 5-fluorouracil and placebo for solar keratoses was registered in the metaRegister of Controlled Trials (mRCT) in 2001 to 2002, but no publication of this study was found.

Our analysis only included randomised controlled trials due to the large scope of this review; all other trial designs were excluded. The randomised clinical trials were only included if all the interventions were covered by this review and if they reported numerical results for at least one of the review outcomes. This criterion excluded the outcome 'Withdrawal due to adverse events', which is generally reported in all the studies. Because the terminology used for the different outcomes was not always consistent in the studies (see the Included studies section under 'Outcomes'), the interpretation of the outcomes' definitions could have introduced some bias in the review process.

Inconsistency in terminology could also have led to misinterpretation during the data extraction process. Some of the review outcomes have been redefined to try to avoid this problem. However, a more precise definition of some outcomes was not always possible. There does not seem to be a common definition of "skin irritation", and many studies included adverse event outcomes that included irritation, symptoms of irritation, or both. The lack of consensus on which symptoms constitute "skin irritation" and the potential for different interpretations by the authors of the studies has resulted in our decision to only include outcomes with the word "irritation" in the label. This adverse event category may also include a pooling of different outcomes, as the skin irritation was not identified by the site (application site vs local irritation).

We separated the studies into two populations of participants: immunocompetent and immunosuppressed. We considered participants to be immunocompetent by default if the studies did not specifically include immunosuppressed participants. However, in 40% of these studies, immunosuppressed participants could have been enrolled based on the inclusion and exclusion criteria reported. It is possible that the immunocompetent population included few immunosuppressed participants.

Data from intention-to-treat analysis was used in the analysis for the review whenever possible to reduce the attrition bias and increase consistency between studies included in the same meta-analysis. The information provided in the studies did not always allow for the conversion of data from per-protocol analysis to intention-to-treat analysis. In some studies, the authors did not observe a significant difference in the outcomes when analysis was conducted with per-protocol analysis, as opposed to intention-to-treat analysis. Thus, the estimated effect size calculated in the meta-analyses should not be affected and our conclusions should remain unchanged. Several studies presented data in a graphical format that was not included in our analysis, either because of unsuccessful correspondence with the authors, time limitations, or both. Statistical limitations due to outcome without event, such as exclusion from meta-analysis or calculation for number needed to treat (NNT) based on assumed control risk (ACR), also restricted our analyses and conclusions.

Agreements and disagreements with other studies or reviews

In a systematic review of randomised controlled trials using 0.5% and 5% 5-fluorouracil for treatment of actinic keratoses, 9 studies were identified (Kaur 2010). We included seven of these studies in our review and excluded two because there was no clear mention of randomisation of the treatments in the published reports. Despite this difference, the authors arrived at a similar conclusion to our review about the participant complete clearance of the 2 concentrations of 5-fluorouracil. In another systematic review (Askew 2009), the authors estimated that about 500 of 1000 of participants receiving 5-fluorouracil for treatment of actinic keratoses could expect complete clearance. An average of our illustrative comparative risks based on study population for 0.5% and 5% 5-fluorouracil treatments (see overview for 5-fluorouracil in Table 2) resulted in 577 of 1000 participants with complete clearance. A similar conclusion was reached by using different methodologies.

A meta-analysis of 5 full journal publications of randomised double-blind clinical trials comparing 5% imiquimod to vehicle concluded that about 50% of participants (500 of 1000) treated with 5% imiquimod achieved complete clearance (Hadley 2006). In this review, the method used to pool data was not specified (but the numbers given suggested that the numbers were added together without any weighting) and a fixed-effect model was used to calculate the relative risk. Our review calculated a lower percentage of 25% to 38% (253 to 382 of 1000; see overview for imiquimod in Table 5) based on 9 studies using a random-effects model to calculate the pooled risk ratio (RR). In contrast to our review, Hadley 2006 did not find any difference in the number of withdrawals due to adverse events between 5% imiquimod and vehicle, but a difference was detected for withdrawal in general, with significantly more in the imiquimod group. Hadley et al detected a greater proportion of local, treatment-related, and overall adverse effects in the 5% imiquimod group, but did not observe any differences in serious adverse events. Thus, 5% imiquimod treatment is generally associated with more adverse events than vehicle.

In a systematic review on photodynamic therapy in the treatment of pre-cancerous skin conditions and cancers (Fayter 2010), the authors reached the following conclusions for the treatment of actinic keratosis: 1) "The only clear evidence of effectiveness" came from the comparison of ALA/MAL-PDT and placebo-PDT, and 2)

"Uncertainties still exist around PDT's effectiveness compared with other topical treatments." Our analyses led to similar conclusions (see the overview for photodynamic therapy in Table 3).

In our review, the efficacy of ALA-PDT was superior to cryotherapy based on 'participant complete clearance', but the efficacy of MAL-PDT compared to cryotherapy could not be assessed. A meta-analysis of 'lesion complete response' was performed in the Fayter 2010 review to compare MAL-PDT to cryotherapy. Unfortunately, this analysis included 4 studies with high heterogeneity (I^2 statistic = 88%), and no definitive conclusion could be made on their relative efficacy. The authors of this review also concluded that the improved cosmetic outcomes obtained for PDT compared to cryotherapy might be due to bias, because in most of the studies the assessors were not blinded.

AUTHORS' CONCLUSIONS

Implications for practice

The treatment of actinic keratoses is generally recommended to limit the morbidity and mortality of squamous cell carcinoma. Surprisingly, there was no evidence in the included studies that treating actinic keratoses prevented squamous cell carcinoma. Only a few studies reported the observation of squamous cell carcinoma, basal cell carcinoma, or both. In these studies, it was not specified if the cell carcinoma was observed in the treated area. Thus, it was impossible to correlate treatment of actinic keratoses with prevention of cell carcinoma. Of course, this lack of information on prevention of squamous cell carcinoma could have been a consequence of our criteria, which included interventions to treat actinic keratoses but not prophylaxis of cancers. As mentioned previously, this review did not cover long-term follow-up studies that could give useful information on recurrence of actinic keratoses as well as prevention of squamous cell carcinoma. We did include the recurrence rates, appearance of new actinic keratoses or incidence of cancer if they were provided in the tables of 'Characteristics of included studies'. Because of the importance of this issue, a systematic review with these long-term outcomes must be performed, and we suggest that randomised clinical trials on interventions for actinic keratoses include observation of squamous cell carcinoma for a follow-up period of at least one year as an efficacy outcome.

Based on the evidence presented in this review, there are many effective options available for the treatment of actinic keratoses. The most effective treatment options were diclofenac, 5-fluorouracil, imiquimod, ingenol mebutate, laser resurfacing, trichloracetic acid peel, ALA-PDT, and MAL-PDT. Other treatment options should not be ruled out as they are still effective, and many have reduced side-effects, which may be preferable or better suited to certain patients.

Ultimately, the decision about which treatment option to use should be agreed upon by both the physician and the patient, based on which intervention suits the participant's specific situation. Certain treatments are better for treating diffuse actinic damage, while others are better for individual lesions. Moreover, the appropriate treatments would depend on the patient's wishes, whether it is cosmetic, symptom relief, or prevention of squamous cell carcinoma. If the risk associated with treatment is greater than the potential benefit, observation without treatment may also be an option.

Implications for research

Our review did not directly compare the methodology used by the studies to evaluate the efficacy outcomes of the interventions for actinic keratoses. Some studies did not give any details on their methodology, whereas others described in detail how individual lesions were mapped, photographed, and followed throughout the study. Mapping of the lesions allowed the investigators to make a distinction between baseline lesions and new or subclinical lesions. For several studies, it was not clear if the efficacy assessment included only target (baseline) lesions or all lesions, which could greatly influence the final outcome. Thus, we recommend that the authors of studies describe in details the methodology used to evaluate the efficacy of the interventions investigated and specify which lesions (baseline/target, subclinical/new, or all lesions) are included in these evaluations.

A clear definition of the lesions being treated is particularly important when comparing individual lesion-based and field-directed treatments, as well as to show that new lesions appeared in response to some treatments. An increase in the number of lesions during treatment was observed for imiquimod (see the 'Notes' section of the 'Characteristics of included studies' tables for Chen 2003; Korman 2005; Lebwohl 2004; and Tan 2007), 5-fluorouracil (Jorizzo 2006; Tanghetti 2007), and tretinoin (Misiewicz 1991). This unmasking of lesions during treatment might have important implications for treatment of actinic keratoses and its associated recurrence. Long-term randomised clinical trials comparing lesion-based and field-directed treatments are needed to address this issue.

Diclofenac in 2.5% hyaluronic acid has been compared directly to 5% 5-fluorouracil (1 excluded study: Smith 2006) and 5% imiquimod for the treatment for actinic keratosis. Diclofenac and 5% imiquimod are both associated with significant adverse events based on the related withdrawals, and 5-fluorouracil treatment is associated with significant skin irritation based on our analyses. It would be advantageous to perform randomised clinical trials comparing diclofenac with other interventions in order to clearly assess its safety outcomes. Similarly, the new treatment ingenol mebutate (PEP005) has only been compared to placebo, and comparison with other interventions for actinic keratosis is needed to evaluate its efficacy and safety compared to established therapy. As mentioned in the summary of main results, additional data are also needed to support or confirm the conclusion of some included studies.

Photodynamic therapy is a newer form of treatment that presents good results in clinical trials. Several studies tried to determine the optimal treatment regimen, output, and photosensitising agents, but most studies did not observe significant changes in efficacy in the variations studied. A few studies investigated the use of daylight for photodynamic therapy using the photosensitiser MAL, and one study showed an efficacy equivalent to MAL-red light PDT. This source of light could be more convenient, more cost effective and easily applicable as field-directed treatment. This is a good prospective area for further research. One ongoing study (NCT01475071) is comparing daylight PDT with conventional PDT.

ACKNOWLEDGEMENTS

The Cochrane Skin Group editorial base wishes to thank Dedee Murrell who was the Key Editor for this review; Jo Leonardi-Bee and

Philippa Middleton who were the Statistical and Methods Editors, respectively; the clinical referees, Hywel Williams and Stephen Keohane; and the consumer referee, Jack Tweed.

The following people contributed to earlier versions of this review; the authors would like to acknowledge their contribution: Kimberley Inniss, Robert Wainwright, Melody Chow, Elizabeth Cooper, Kristy Johnson, and Zbys Fedorowicz. The authors would also like to thank Chris Drummond-Main and Fiona C. Simpson for their input.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Akar 2001

Methods	This was a randomised, active-controlled, double-blind, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Clinical and histological diagnoses • Anatomical locations: face, bald scalp, and dorsal forearms and hands • Single or multiple actinic keratoses **Exclusion criteria of the trial** • Topical agents within the last 3 months • More than 15 lesions or very extensive lesions **Demographics** • 16 white participants • 10 men, 6 women • Age: mean = 64; range = 50 to 82

Akar 2001 *(Continued)*

Interventions	**Intervention** A: 1% colchicine cream twice daily for 10 days + 10 more days if weak response (N = 8 participants) **Control intervention** B: 0.5% colchicine cream twice daily for 10 days + 10 more days if weak response (N = 8 participants)
Outcomes	**Outcomes of the trial** 1) Complete healing (= participant complete clearance) 2) Reduction rate in number of actinic keratoses (= lesion complete response) at 1 month 3) Mean reduction of lesion counts at 1 month 4) Number of participants treated (pooled data) with strong, weak, or no inflammatory reaction 5) Minor adverse events (qualitative) 6) Number of participants with decreased infiltration and disappearance of crust (cosmetic) at 1 month 7) Clinical laboratory tests 8) Relapse at 6 months Efficacy Methods: quantitative assessment by counting visible and palpable actinic keratoses in each test area Time points: at baseline; end of treatment; 1, 2, and 6 months post-treatment Safety Methods: 1. clinical examination, 2. routine laboratory tests (complete blood cell counts, urinalysis, and fasting chemistry) Time points: 1. each study visit (clinical exam), 2. before and after treatment (laboratory tests)
Funding	The drug was provided by Dr. F Frik Drug Company.
Notes	Thick surface scales were removed by 10% salicylic acid 2 days before treatment. There were severe inflammation reactions in the majority of participants (11/16). In cases of inflammation, a weak antiseptic or antibiotic ointment was applied.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 200): "Patients were randomly assigned to treatment with 0.5% colchicine cream or 1% colchicine cream." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both the investigators and the participants were blinded.

Akar 2001 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	An intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropouts Control - B: 0 dropouts
Selective reporting (reporting bias)	Low risk	All outcomes were reported even if there was no difference between treatment groups.
Other bias	Unclear risk	-

Alberts 2000

Methods	This was a randomised, double-blind, placebo-controlled, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Diagnosis by a dermatologist • Men or postmenopausal women, at least 30 years of age • Anatomical location: forearms • Moderate to severe (i.e. ≥ 10 actinic keratoses on the lateral surface) **Exclusion criteria of the trial** • Topical or systematic therapy within 3 months • Any topical medications within 30 days (excluding emollient and sunscreen) • Free of medication or disease that would cause even minor immunosuppression. **Demographics** • 48 participants • 32 men, 10 women • Age: mean = 69
Interventions	A 1-month run-in was performed during which participants used a placebo formulation (hydrophilic ointment) twice daily on both right and left forearms. **Intervention** A: 2-(Difluoromethyl)-dl-ornithine (DFMO) twice daily for 6 months (N = 48 participants) **Control intervention** B: placebo twice daily for 6 months (N = 48 participants)
Outcomes	**Primary outcomes of the trial** 1) Mean numbers of lesions at baseline and 6 months (the mean reduction in lesion counts was calculated) 2) Percentage reduction in the number of actinic keratoses 3) Skin concentrations of drug and products due to its mechanism of action at 6 months

Alberts 2000 *(Continued)*

	Secondary outcomes of the trial 1) Tolerance (qualitative) 2) Compliance Efficacy Methods: quantitative assessment by circling and counting of individual lesions on each arm by a dermatologist and photography using a Nikon N5005 camera with a 60-mm Micor Nikkor lens, SB-21 Macro Speedlight, and Kodachrome ASA 64 film Time points: at baseline and end of treatment Safety Methods: 1. assessment of clinical toxicity frequency and severity [scale 0 (none) to 3 (severe)] by the study dermatologist, 2. complete blood counts and serum chemistry panels (SMA20s) Time points: 1. before the first application of the placebo ointment, at randomisation, and at each monthly visit (toxicity), 2. run-in and at the end of the study (laboratory tests)
Funding	This study was supported by USPHS Grant PO1 CA27502.
Notes	There was no evidence of systemic toxicity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page1282): "Before randomisation, participants were stratified on the basis of gender and numbers of actinic keratoses on the forearms. Participants were then randomly assigned, in a double-blind fashion, to treatment with hydrophilic DFMO ointment on the right versus the left forearm and placebo hydrophilic ointment on the contralateral forearm twice daily for 6 months." Comment: Stratification was used for randomisation sequence generation.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol (PP) analysis was used. Intraindividual study: Intervention - A: 6 dropouts (the reasons were reported) Control - B: 6 dropouts (the reasons were reported) Comment: The associated risk with PP analysis is unclear because the same number of participants were lost in both treatment groups.

Alberts 2000 *(Continued)*

Selective reporting (reporting bias)	High risk	The percentage reduction in lesion counts was given only for the DFMO-treated group.
Other bias	Unclear risk	-

Alirezai 1994

Methods	This was a randomised, double-blind, placebo-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Age 21 years and older • Anatomical locations: face, scalp, upper extremities • ≥ 5 actinic keratoses **Exclusion criteria of the trial** • No topical retinoids or topical steroids in the 2 weeks before treatment • No topical 5-fluorouracil, systemic retinoids, or systemic steroids within 4 weeks before treatment • Pregnant, nursing women, PUVA therapy, skin cancer, or other condition that could interfere with the evaluation **Demographics** • 100 randomised, 93 analysed, 79 completed (no other demographic information was presented)
Interventions	**Intervention** A: isotretinoin 0.1% cream twice daily for 24 weeks (N = 50 participants?) **Control intervention** B: placebo cream twice daily for 24 weeks (N = 50 participants?)
Outcomes	**Outcomes of the trial** 1) Investigators' evaluation of global therapeutic response (= global improvement indice-completely cleared) 2) Mean number of actinic keratosis lesions over time by anatomical area 3) Mean reduction of lesion counts by anatomical area at end of treatment 4) Number of participants with severe, moderate, mild, or no local irritation on the face (= skin irritation) 5) Minor adverse events (qualitative) 6) Serious adverse events (including basal and squamous cell carcinoma) 7) Clinical laboratory tests Efficacy Methods: quantitative assessment by lesion counting and photography Time points: 1. at baseline and every 4 weeks (counting), 2. at baseline, week 12, and end of treatment (photography)

Alirezai 1994 *(Continued)*

	Definitions for the global evaluation: 1. worsening (increase in lesions in treated area), 2. partial response (between 30% < 100% reduction in the number of lesions), and 3. complete response (total clearing) Safety Methods: 1. local tolerability was scored (absent to severe) by investigator, 2. clinical evaluation and reported adverse events, 3. routine laboratory tests Time points: 1. at each visit (tolerability and adverse events), 2. before and after treatment (laboratory tests)
Funding	-
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 448): "Patients were randomly assigned to treatment with 0.1% isotretinoin or a color-matched vehicle." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	2 independent investigators counted lesions.
Incomplete outcome data (attrition bias) All outcomes	High risk	Modified intention-to-treat (ITT) analysis was used (i.e. participants with at least 1 postbaseline assessment were included in the analysis, N = 93), but the number of participants lost to follow up was higher than 20%. The numbers used for analysis were unclear. 1 participant in the isotretinoin group was missing in the data for skin irritation. Intervention - A: 11 dropouts (the reasons were reported) Control - B: 10 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Low risk	A poor efficiency was reported.
Other bias	High risk	The partial response criteria was very large (30% to 100%). Baseline mean withinparticipant differences in lesion number on the face was significantly different between treatment and control groups (P = 0.04).

Alomar 2007

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study.

Alomar 2007 *(Continued)*

	Start date: December 2003 End date: December 2004
Participants	**Inclusion criteria of the trial** • Pre-study clinical diagnosis, 1 lesion confirmed histologically • Aged 18 years and older • Anatomical locations: face or balding scalp • 5 to 9 actinic keratoses within 25 cm^2 area **Exclusion criteria of the trial** • Malignant tumours, dermatological disease, or condition in the treatment or surrounding area that could impede local skin assessments • Unstable cardiovascular, immunosuppressive, haematological, hepatic neurological, renal, endocrine, collagen-vascular, or gastrointestinal abnormalities **Demographics** • 259 white participants • 228 men, 31 women • Age: range = 44 to 94
Interventions	**Intervention** A: 5% imiquimod once per day 3 times per week, 4 weeks on, 4 weeks off (repeated if not cleared) (N = 129 participants) **Control intervention** B: vehicle, once per day 3 times per week, 4 weeks on, 4 weeks off (repeated if not cleared) (N = 130 participants)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at week 8 (1 treatment) and at week 16 (1or 2 treatments) **Secondary outcomes of the trial** 1) Participant partial (≥ 75%) clearance rates at week 16 2) Lesion complete response rates at weeks 8 and 16 **Other outcomes of the trial** 1) Participants experiencing at least 1 adverse event 2) Local skin reactions 3) Minor adverse events 4) Serious adverse events Efficacy Methods: 1. quantitative assessment using lesion counting and mapping with the use of a clear plastic template and photography, 2. histological confirmation using biopsy of a target lesion site Time points: 1. at week 1, week 2, end of treatment (EOT) (week 4 for 1 treatment, week 12 for 2 treatments), and the 4-week post-treatment visit (week 8 for 1 treatment, week 16 form 2 treatments), 2. pretreatment and 8-week post-treatment visit (week 12 for 1 treatment, week 20 for 2 treatments) (biopsy)

Alomar 2007 *(Continued)*

	Safety Methods: 1. assessment of the presence and intensity of specific local skin reactions by the investigator and rating on a scale [0 (none) to 3 (severe)], 2. safety evaluations including clinical laboratory tests (haematology, blood chemistry, and urinalysis) and urine pregnancy tests for women of child-bearing potential, 3. physical examination including vital sign measurements, adverse events, and monitoring of concomitant medications Time points: 1. each visit (local skin reactions, adverse events, and medication monitoring), 2. pre-study and poststudy (safety evaluations), 3. pre-study, week 4 and week 12 visits (physical exam)
Funding	This study was supported by 3M Pharmaceuticals.
Notes	Rest periods were allowed in case of local skin reaction or treatment site adverse events. There were significant differences between imiquimod and vehicle groups in term of numbers and intensities of local skin reactions. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 134): "Eligible patients were randomised to either imiquimod 5% cream or vehicle cream in a 1:1 ratio." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blind and used 2 independent blinded dermatologists for histological evaluation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used, and all subjects were accounted for. Intervention - A: 4 dropouts (the reasons were reported) Control - B: 3 dropouts (the reasons were not all reported)
Selective reporting (reporting bias)	High risk	The participant complete clearance for the face and scalp was reported for the imiquimod group but not the vehicle group.
Other bias	Unclear risk	-

Anderson 2009

Methods	This was a multicentre, randomised, double-blind, double-dummy, vehicle-controlled, parallel-group study. Start date: September 2006 End date: June 2007

Anderson 2009 *(Continued)*

Participants	**Inclusion criteria of the trial** • Clinical typical visible and discreet actinic keratoses • Men and postmenopausal women • Aged 18 years and older • Anatomical locations: arm, shoulder, chest, back, scalp • 4 to 8 actinic keratoses within 25 cm^2 area **Exclusion criteria of the trial** • Women of child-bearing potential • Lesions on the face • Atypical-appearing lesions • Suspected cutaneous malignancy within the selected area • Lesion-directed therapy within 2 cm of the selected area within 4 weeks • Field-directed therapy within 2 cm within 24 months **Demographics** • 222 participants • 178 men, 44 women • Age: mean = 67; range = 43 to 85
Interventions	**Interventions** A: once daily 0.025% ingenol mebutate gel (PEP005) for 3 days (N = 50 participants) B: once daily 0.05% ingenol mebutate gel (PEP005) for 2 days (N = 55 participants) C: once daily 0.05% ingenol mebutate gel (PEP005) for 3 days (N = 57 participants) **Control intervention** D: once daily vehicle for 3 days (N = 60 participants)
Outcomes	**Primary outcome of the trial** 1) Partial clearance rate (= participant partial clearance) **Secondary outcomes of the trial** 1) Complete clearance rate (= participant complete clearance for all lesions) 2) Baseline clearance rate (= participant complete clearance for target lesions) 3) Median percentage reduction of target lesions **Other outcomes of the trial** 1) Application site reactions 2) Local skin reactions overtime (pooled ingenol mebutate data and no data for vehicle) 3) Global severity rating of local reactions 4) Minor adverse events 5) Treatment-related adverse events 6) Serious adverse events 7) Clinical laboratory tests

Anderson 2009 *(Continued)*

8) Cosmetic outcomes: pigmentation and scarring (pooled data)

9) Participants' satisfaction

Efficacy

Methods: quantitative assessment using counting of clinically-visible lesions in the selected treatment area (including baseline and new lesions)

Time points: at day 57 (end-of-study visit)

Definitions: 1. partial clearance rate (proportion of participants with ≥ 75% reduction in the number of lesions identified at baseline), 2. complete clearance rate (proportion of participants with no clinically-visible lesions in the selected treatment area - lesions present at baseline or emergent during the study period), 3. baseline clearance rate (proportion of participants with 100% reduction in the number of lesions identified at baseline), and 4. percentage reduction of the number of lesions (number of lesions present in the treatment area at baseline minus the number of lesions present at the end of the study divided by the number of lesions present at baseline)

Safety

Methods: 1. assessment of any local skin reactions and global severity rating, and monitoring of adverse events by a qualified dermatologist, 2. clinical laboratory tests

Time points: 1. at day 3, follow-up visits on days 8, 15, 29, and 57 (end-of-study visit); 2. at screening visit and on day 8 (laboratory tests)

Cosmetic

Methods: questionnaire with a 7-point Likert scale, in which a score of 1 is very negative, 4 is neutral, and 7 is very positive

Funding	This study was supported by Peplin Ltd.
Notes	Participants' satisfaction (P = 0.0005) and overall satisfaction (P < 0.001) were higher in the treatments groups compared with vehicle. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Each centre was allocated an initial block of 4 randomisation numbers and enrolled participants were assigned a participant number in ascending order.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The centre personnel and the participants were blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigator was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified ITT analysis was used (i.e. at least 1 dose and 1 postbaseline assessment). Intervention - A: 0 dropouts, B: 1 dropout, C: 0 dropouts

Anderson 2009 *(Continued)*

		Control - D: 0 dropouts
Selective reporting (reporting bias)	High risk	Data were pooled for safety and cosmetic outcomes. Based on the protocol NCT00375739, safety was supposed to be the primary outcome. However, efficacy data were presented first.
Other bias	Unclear risk	-

Bercovitch 1987

Methods	The was a single-centre, randomised, double-blind, placebo-controlled, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Clinical and histological diagnoses • Anatomical locations: forearms and hands • Multiple actinic keratoses **Demographics** • 20 participants (no other demographic information was provided) • 8 of 20 participants had history of squamous cell carcinoma
Interventions	**Intervention** A: 5% 5-fluorouracil twice daily on both arms for 2 to 4 weeks and 0.05% tretinoin nightly on 1 randomised arm for 2 to 4 weeks (N = 20 participants) **Control intervention** B: 5% 5-fluorouracil twice daily on both arms for 2 to 4 weeks and placebo nightly on 1 randomised arm for 2 to 4 weeks (N = 20 participants)
Outcomes	**Outcomes of the trial** 1) Mean number of actinic keratosis lesions at baseline and 3 months (mean reduction of lesion counts was calculated) 2) Relative irritation (skin irritation) Efficacy Methods: quantitative assessment using counting of residual actinic keratoses and biopsy of doubtful lesions Time points: at baseline and week 12
Funding	The treatments were provided by Ortho Pharmaceutical Corporation and Hoffman-LaRoche, Inc.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 550): "Tretinoin 0.05% cream (RETIN-A Cream, Ortho Pharmaceutical Corp., Raritan, NJ, U.S.A.) and a placebo cream, Eucerin (Beiersdorf Inc.,

Bercovitch 1987 *(Continued)*

		Norwalk, CT, U.S.A.) were supplied to each patient in unmarked jars labelled only with the randomly assigned side to which the medication was to be applied." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if the only lost participant was included or not in the analysis. Intraindividual study: Intervention - A: 1 dropout (the reasons were reported) Control - B: 1 dropout (the reasons were reported)
Selective reporting (reporting bias)	High risk	Based on the text, the data should have been presented as percentage of reduction in lesion count, but only the absolute counts at baseline and 3 months were presented.
Other bias	Unclear risk	-

Chen 2003

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. Start date: January 2002 End date: August 2002
Participants	**Inclusion criteria of the trial** • Anatomical locations: face, forehead and temples, or both cheeks • 5 to 15 actinic keratoses within 1 treatment area **Exclusion criteria of the trial** • Allergy to any products within the study cream • Pregnancy • Clinically significant and severe systemic disease • Treatment for actinic keratosis within the treatment area with cryotherapy within 6 weeks, with 5-fluorouracil, chemical peels, or dermabrasion within 6 months • Immunosuppressive or immunomodulating drugs including oral or topical corticosteroids within 4 weeks **Demographics** • 34 participants

Chen 2003 *(Continued)*

- 21 men,13 women
- Age: mean = 64

Interventions	**Intervention** A: imiquimod 5% cream once per day, 3 times per week for 3 weeks on, 4 weeks off (repeat once if 75% of lesions hadn't cleared) **Control intervention** B: placebo once per day, 3 times per week for 3 weeks on, 4 weeks off (repeat once if 75% of lesions hadn't cleared)
Outcomes	**Primary outcome of the trial** 1) Participant partial (≥ 75%) clearance rates at 14 weeks **Other outcomes of the trial** 1) Mean number of actinic keratosis lesions overtime (graphical representation) 2) Participant complete clearance 3) Local skin reactions Efficacy Methods: quantitative assessment using counting of the number of lesions in the treatment area by the same investigator and photography Time points: at each weekly visit Safety Methods: reporting of local skin reactions [severity on a 0 (none) to 3 (severe) scale] and adverse events Time points: at each weekly visit
Funding	This study was supported by 3M Pharmaceuticals.
Notes	All adverse effects were gone at follow-up. An increase in the number of lesions during treatment was observed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 252): "Randomisation codes were prepared using permuted blocks of four and stratifying by study centre."
Allocation concealment (selection bias)	Low risk	Quote (page 252): "Randomisation codes were concealed within opaque, sealed envelopes."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind, and randomisation codes were not revealed until all final assessments were completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind, and randomisation codes were not revealed until all final assessments were completed.

Chen 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol analysis was used. Intervention - A: 4 dropouts (the reasons were reported) Control - B: 1 dropout (the reasons were reported) 5 participants with protocol violation (4 imiquimod, 1 placebo) were excluded, and 1 with protocol violation was included (imiquimod not cured).
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Dragieva 2004a

Methods	This was a randomised, double-blind, placebo-controlled, intraindividual study. Start date: July 2001 End date: March 2002
Participants	**Inclusion criteria of the trial** • Organ transplant participants (immunosuppressed) • Multiple mild to moderate actinic keratoses with histological confirmation • Both genders and over 18 years of age • Anatomical locations: face or scalp, neck, extremities • 2 lesional areas (4 X 4 cm) for randomisation **Exclusion criteria of the trial** • Porphyria • Known allergy to any of the compounds or excipients of the cream • Treatment for actinic keratosis within 1 month **Demographics** • 17 participants • 14 men, 3 women • Age: mean = 61; range = 44 to 76 • Face or scalp (N = 107), neck (N = 1), extremities (N = 21) (N = number of lesions)
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) (N = 17 participants) **Control intervention** B: placebo-PDT (N = 17 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment Number of treatments: 2 Interval between treatments: 1 week Preparation of lesions: crusts and scales removed by curettage

Dragieva 2004a *(Continued)*

	Cream concentration (%): -- Application of cream: 1 mm thick to lesional field and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: visible non-coherent light Light source: Waldmann PDT 1200 Wavelength (nm): 600-730 Energy fluence (J/cm^2): 75 inten (mW/cm^2): 80 Exposure time: -- Others: Each participant received 1 g paracetamol orally 1 hour before illumination. Additionally, a fan was used to cool the treated area and to reduce discomfort during illumination.
Outcomes	**Outcomes of the trial** 1) Complete response rates of the lesional area (= participant complete clearance) at 16 weeks after 2nd treatment 2) Reduction in the number of lesions (= lesion complete response) at 16 weeks after 2nd treatment 3) Minor adverse events (qualitative) 4) Discomfort on a visual analogue scale (VAS) Efficacy Methods: quantitative assessment by inspection, photography, and palpation of the lesional area Time points: at 1, 4, 8, and 16 weeks after the 2nd treatment Definitions: 1. complete response (complete clinical regression of all lesions within the treated area), 2. partial response (incomplete reduction in size or number of the lesions within the treated area) Safety Methods: reporting of adverse events including the local phototoxicity reactions Time points: before and after illumination, and at 1, 4, 8, and 16 weeks after the 2nd treatment
Funding	-
Notes	There was no quantification of adverse events, but discomfort was reported higher for MAL than placebo. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 197): "Two lesional areas within a patient, measuring a maximum of 4 X 4 cm, were randomised to receive 2 consecutive treatments of topical PDT 1 week apart using either MAL or placebo cream." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.

Dragieva 2004a *(Continued)*

Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was double-blind, but because discomfort was higher with MAL than placebo cream, the blinding could have been broken.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was double-blind, but because discomfort was higher with MAL than placebo cream, the blinding could have been broken.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropouts Control - B: 0 dropouts
Selective reporting (reporting bias)	Low risk	The same data were reported in the abstract and published paper.
Other bias	Unclear risk	-

Fariba 2006

Methods	This was a randomised, double-blind, placebo-controlled, intraindividual study. Start date: 2003 End date: 2004
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Individuals aged 30 years or older • General good health • Anatomical locations: face or scalp **Exclusion criteria of the trial** • Lesions on lips • Non-postmenopausal women or not using contraception • History or suspected hypersensitivity to any of the ingredients of the active or placebo gel • History of allergy to aspirin or other NSAIDs • Current treatment with disallowed medication (5-fluorouracil, etretinate, cyclosporine, retinoids, topical steroids, or recent trichloroacetic acid or glycolic acid peels) • Unwillingness to discontinue the use of cosmetics or sunscreen on the designated site • Treatment with any other investigational drug or participation in another study within 60 days • Refusal to undergo a wash-out period **Demographics** • 20 participants • 14 men, 6 women • Age: mean = 55, range = 30 to 75

Fariba 2006 *(Continued)*

Interventions	**Intervention** A: 3% diclofenac/2.5% hyaluronic acid twice daily for 90 days (N = 20 participants, 32 lesions) **Control intervention** B: 2.5% hyaluronic acid twice daily for 90 days (N = 20 participants, 32 lesions)
Outcomes	**Outcomes of the trial** 1) Lesion complete response rates 2) Reduction in lesion size 3) Number of participants experiencing irritation (skin irritation) Efficacy Time points: at the end of treatment Definitions: 1. partial response (any reduction in the lesion size compared to baseline), 2. complete response (complete disappearance of the lesion)
Funding	-
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 347): "Sixty-four lesions of actinic keratosis in 20 patients were evaluated, 32 for active treatment and another 32 lesions with relatively similar characteristics but on the opposite side, as controls. Lesions were randomised to receive either 3% diclofenac in 2.5% hyaluronic acid gel or placebo (the inactive gel vehicle, hyaluronic acid only) 0.5 g twice daily in each 5 cm^2 treatment area for 90 days." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropouts Control - B: 0 dropouts
Selective reporting (reporting bias)	Unclear risk	-

Fariba 2006 *(Continued)*

Other bias	High risk	The presentation of the data was confusing. The wording in the manuscript for the efficacy analysis created confusion between 'lesion complete response' and 'participant complete clearance', but based on the numbers and the percentages given, the outcome was lesion complete response.

Foote 2009

Methods	This was a single-centre, randomised, double-blind, placebo-controlled, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Healthy volunteers with clinically diagnosable actinic keratoses • 30 years of age or older • Anatomical locations: arms • ≥ 10 actinic keratoses per forearm **Exclusion criteria of the trial** • Current cancer • Lateral forearm treatment for cancer or actinic keratosis within the past 30 days • Initial chemistry levels (SMA20) outside of normal limits • > 75% compliance during 1-month run-in period **Demographics** • 50 enrolled, 48 randomised participants • 36 men, 6 women • Age: mean = 68
Interventions	**Intervention** A: 12.5% DL-α-tocopherol (vitamin E) on right or left arm twice daily for 6 months (N = 48 participants) **Control intervention** B: placebo on right or left arm twice daily for 6 months (N = 48 participants)
Outcomes	**Primary outcome of the trial** 1) Biochemical and immunological outcomes **Secondary outcome of the trial** 1) Mean reduction of lesion counts **Other outcome of the trial** 1) Number of reports of symptoms (redness, itchiness, burning, dryness) Efficacy Methods: 1. quantitative assessment using circling of lesions and photographs, 2. shave biopsies by physician Time points: before and at the end of treatment Safety

Foote 2009 *(Continued)*

	Methods: 1. physical exams, 2. clinical staff inquired about adverse events (severity, date of onset, duration, and date of resolution) Time points: 1. before treatment and at the end of treatment (physical exams), 2. at monthly visits (adverse events)
Funding	This study was supported by NIH grants CA-27502 and CA-23074.
Notes	This was a phase IIb study. Vitamin E was well tolerated, i.e. only 14 reports for moderate and severe symptoms, which were similar for treatment and placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A progressive randomisation program was used to make sure that allocation did not vary by gender, age, or actinic keratosis lesions (stratification).
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol (PP) analysis was used. Intraindividual study: Intervention - A: 6 dropouts (the reasons were reported) Control - B: 6 dropouts (the reasons were reported) Comment: The associated risk with PP analysis is unclear because the same number of participants were lost in both treatment groups.
Selective reporting (reporting bias)	Low risk	No statistically different results were reported.
Other bias	High risk	Unprecise evaluation: 8 participants at baseline and 6 at the end of treatment had lesions too numerous to count and a number of 78 was used for analysis.

Freeman 2003

Methods	This was a multicentre, randomised, double-blind, open, placebo-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Clincial diagnosis • Anatomical locations: face or scalp

Freeman 2003 *(Continued)*

- Mild-to-moderate non-pigmented actinic keratoses, suitable for cryotherapy with the largest diameter of each lesion being ≥ 5 mm

Exclusion criteria of the trial

- Grade 3 lesions (3 = severe, very thick, or obvious lesion)
- Pigmented lesions
- Recently-treated lesions

Demographics

- 200 participants
- 119 men, 81 women
- Age: range = 33 to 89

Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) (N = 88 participants) **Control interventions** B: placebo -PDT: Placebo (N = 23 participants) C: cryotherapy: no prior preparation, variable liquid nitrogen spray unit, 1 to 2 mm rim of frozen tissue beyond marked outline, a single timed freeze-thaw cycle; mean diameter < 10 mm = mean freeze time of 12 ± 13 seconds, 10 to 20 mm = 16 ± 15 seconds, > 20 mm = 26 ± 11 seconds (N = 89 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 2 Interval between treatments: 1 week Preparation of lesions: crusts and scales removed by curettage Cream concentration (%): 16 Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light Light source: Wavelength (nm): 570-670 Energy fluence (J/cm^2): 75 Intensities (mW/cm^2): 50 to 250 Exposure time: 10 minutes
Outcomes	**Outcomes of the trial** 1) Lesion complete response rates at 3 months 2) Participants experiencing at least 1 adverse event 3) Local skin/adverse reactions 4) Minor adverse events (given only for MAL-PDT)

Freeman 2003 *(Continued)*

	5) Cosmetic outcomes: overall and individual lesions at 3 months (MAL-PDT vs cryotherapy) 6) Participant satisfaction Efficacy Methods: quantitative assessment using mapping with acetate sheets, marking of lesions and anatomical landmarks and Polaroid photography Time points: at 3 months after the beginning of treatment Definitions for lesion response: 1. complete response (complete disappearance of the lesion, both visually and by palpation), 2. non-complete response (incomplete disappearance of the lesion) Safety Methods: adverse events reported by the participant or elicited through open (non-leading) questioning by the investigator Time points: before, during, and after treatment; at 2 weeks by telephone contact; and at a final examination 3 months after treatment Cosmetic Methods: 1. overall cosmetic outcome of completely cleared participants (by investigator and participant), 2. individual lesion cosmetic outcome for completely cleared lesions (hypopigmentation, hyperpigmentation, scar formation and tissue defect rated as none, slight, or obvious) Time points: at 3 months after the beginning of treatment Definitions for overall outcome: 1. excellent (no scarring, atrophy or induration, and no or slight occurrence of redness or change in pigmentation compared with adjacent skin), 2. good (no scarring, atrophy or induration but moderate redness or change in pigmentation compared with adjacent skin), 3. fair (slight to moderate occurrence of scarring, atrophy, or induration), 4. poor (extensive occurrence of scarring, atrophy, or induration)
Funding	This study was supported by Photocure ASA, Olso, Norway.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed per participant for each treatment option (first: PDT or cryo, second: MAL or placebo) and stratified by centre.
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to conceal the allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was double-blind for the comparison between MAL-PDT and placebo-PDT and open for the comparison between MAL-PDT and cryotherapy.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was double-blind for the comparison between MAL-PDT and placebo-PDT and open for the comparison between MAL-PDT and cryotherapy.
Incomplete outcome data (attrition bias) All outcomes	High risk	Both intention-to-treat (ITT) and per-protocol (PP) analyses were used, but only values for PP were presented and the authors only mentioned that results were similar for ITT analysis.

Freeman 2003 *(Continued)*

		Intervention - A: 11 dropouts Control - B: 4 dropouts, C: 3 dropouts Thus, there was less lost in cryotherapy (3.4%) than placebo-PDT (17%) and MAL-PDT (12.5%).
Selective reporting (reporting bias)	High risk	Types of adverse events were not reported separately for PDT and cryotherapy treatments, but more adverse events were reported for PDT than cryotherapy, and more for MAL-PDT than placebo-PDT. Risk of bias for more than 2 groups: cosmetic outcomes were not presented for the placebo-PDT treatment group, and satisfaction was reported only for PDT participants. Similar data were presented in abstract form and published paper.
Other bias	High risk	There was a difference in baseline; the placebo PDT group included a greater proportion of men, and slightly more participants with skin type I and fewer with skin type 2.

Gebauer 2003

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: 1994 End date: 1995
Participants	**Inclusion criteria of the trial** • Solar keratoses • Over 18 years of age • Anatomical locations: head/neck, hands, or arms **Exclusion criteria of the trial** • History of hypersensitivity to non-steroidal anti-inflammatory drugs • Significant current illness • Abnormal liver/renal/haematological tests • Use of concomitant medication that would interfere with the study drug (systemic corticosteroids, antineoplastic, topical and systemic retinoids) • Presence of skin conditions that would confound the study (Bowen's disease, basal cell carcinoma, squamous cell carcinoma) • Involvement in another clinical study in the previous 3 months • Unwillingness to discontinue use of cosmetics • Outdoor occupation or deliberate exposure of skin to sun or UV light • Pregnant women, breastfeeding, or without adequate contraception **Demographics** • 150 participants • 89 men, 61 women • Age: mean = 68
Interventions	**Intervention** A: 0.25 g of 3% diclofenac in 2.5% hyaluronic acid gel twice daily for 12 weeks (N = 73 participants) **Control intervention**

Gebauer 2003 *(Continued)*

	B: 2.5% hyaluronic acid gel alone twice daily for 12 weeks (N = 77 participants)
Outcomes	**Outcomes of the trial** 1) Mean reduction of lesion counts at end of treatment and at 30 days post-treatment 2) Participant complete resolution rates (= participant complete clearance) at end of treatment and at 30 days post-treatment 3) Participant with 50% or greater reduction rates at end of treatment and at 30 days post-treatment 4) Minor adverse events 5) Serious adverse events 6) Clinical laboratory tests 7) Compliance Efficacy Methods: quantitative assessment using lesion counting by a single doctor in each centre throughout the entire study Time points: at baseline, end of treatment (12 weeks), and at 16 weeks Definitions: 1. complete clearance (proportion of participants with complete resolution of lesions), 2. partial clearance (proportion of participants with a ≥ 50% reduction in lesions) Safety Methods: 1. medical history and physical examination (baseline only), 2. haematology and biochemistry testing, 3. adverse events were recorded in the case report form [type (serious or non-serious), onset date, severity (mild, moderate or severe), duration, any action taken, assumed relationship to treatment and outcome] Time points: at baseline, week 12 , and week 16
Funding	This study was supported by Hyal Pharmaceutical Corporation.
Notes	The safety assessment showed no difference between groups. A high compliance was observed for both groups.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 40):"They were randomly allocated to either active treatment (N = 73) or placebo (N = 77)." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind.

Gebauer 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat (ITT) analysis was used and 1 withdrawn participant was accounted for in the wrong treatment group (see below). Intervention - A: 23 dropouts stated but 22 based on the details of the reasons Control - B: 12 dropouts stated but 13 based on the details of the reasons.
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Gebauer 2009

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: April 2000 End date: December 2000

Participants	**Inclusion criteria of the trial**
	• Clinically typical actinic keratosis lesions and histological confirmation
	• Age 18 years and older
	• Anatomical locations: dorsal of 1 or both forearms and hands
	• 10 to 50 lesions
	Exclusion criteria of the trial
	• Dermatological condition in the treatment area that might be exacerbated by treatment or could impair study assessments
	• Allergy to imiquimod or any of the excipients
	• Chemical or alcohol dependency
	• Active malignancy
	• Clinically significant cardiovascular, immunosuppressive, haematological, hepatic, neurological, renal, endocrine, collagen-vascular or gastrointestinal disease or an unstable medical condition
	• Pregnancy or lactation
	• Enrolled in another clinical study
	• No prior treatment in the treatment area as follows:
	  • with imiquimod or systemic retinoids
	  • within the last 2 years with topical retinoids
	  • within the last 3 months with surgical excision
	  • within the last 6 months with psoralen and UVA (PUVA), 5-fluorouracil, masoprocol, chemical peel, or dermabrasion
	  • within the last 4 weeks with cryotherapy or curettage
	  • within the last 24 hours with moisturisers, emollients, or oils
	• No prior treatment outside the area of treatment as follows:
	  • with systemic retinoids
	  • within the last 2 years with topical retinoids
	  • within the last 6 months with psoralen and UVA (PUVA), 5-fluorouracil, masoprocol, chemical peel, or dermabrasion
	  • within the last 1 week with > 2 g daily fluorinated topical corticosteroids or equivalent
	• No prior treatment as follows:

Gebauer 2009 *(Continued)*

- within the last 6 months with cancer chemotherapy
- within the last 3 months with any treatment of SCC or basal cell carcinoma
- within the last 4 weeks with interferon, interferon inducer, immunomodulators, cytotoxic drugs, investigational drugs, drugs with major organ toxicity, immunosuppressives, systemic corticosteroids, inhaled corticosteroids > 1200 ug daily

Demographics

- 149 participants
- 94 men, 54 women
- Age: mean = 71

Interventions	**Interventions** A: 5% imiquimod (2 times/week) for 8 weeks (N = 31 participants) B: 5% imiquimod (3 times/week) for 8 weeks (N = 29 participants) C: 5% imiquimod (5 times/week) for 8 weeks (N = 30 participants) D: 5% imiquimod (7 times/week) for 8 weeks (N = 30 participants) **Control intervention** E: vehicle (2, 3, 5, 7 times/week) for 8 weeks (N = 29 participants, 7 to 8/dosing regimen pooled together)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at week 16 **Secondary outcome of the trial** 1) Participant partial (> 75%) clearance rates at week 16 **Other outcomes of the trial** 1) Application site reactions 2) Local skin reactions 3) Treatment-related adverse events 4) Serious adverse events 5) Clinical laboratory tests 6) Compliance 7) Rest periods Efficacy Methods: 1. quantitative assessment using lesion counts within the target area performed by a qualified dermatologist using a transparent plastic template to track lesions, 2. qualitative assessment using lesion descriptions by investigator, i.e. degree of hyperkeratosis, size and confluence of the lesions, and degree of solar damage between lesions Time points: at baseline, week 4, and end of study (week 16) Definitions: 1. complete clearance rate (proportion of subjects at end of study with no lesions in the treatment area), 2. partial clearance rate (proportion of subjects at their last study visit with at least 75% reduction in lesions in the treatment area) Safety

Gebauer 2009 *(Continued)*

	Methods: 1. recording of vital signs and adverse events, 2. assessment of defined local skin reactions (erythema, oedema, induration, vesicles, erosion, excoriation/flaking, scabbing), 3. photography, 4. physical examination, 5. haematology and chemistry tests and pregnancy testing (adverse events were coded and summarised by body system and preferred term using a modified World Health Organization Adverse Reactions Terminology dictionary) Time points: 1. at weeks 1, 2, 3, 4, 6, 8 (end of treatment), 12, and 16 (8 weeks post-treatment, end of study), 2. at baseline, end of treatment, and end of study (physical exam and laboratory tests) Definitions for grading: 1. mild (subject is aware of the signs and symptoms, but the signs and symptoms are easily tolerated), 2. moderate (signs and symptoms are sufficient to restrict, but not prevent, usual daily activity for the subject), and 3. severe (signs and symptoms are such that the subject is unable to perform usual daily activity)
Funding	This study was supported by 3M Pharmaceuticals.
Notes	The number of local skin reactions and adverse events increased with dosing frequency. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was double-blind for intervention versus control but not for the frequency of application. 4 groups of vehicle were used to match the number of application and conceal treatment allocation, but there was not use of the vehicle to have all groups applying cream for 7 days/week, e.g. tubes labelled for each day of the week (with intervention or control) to conceal frequency allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 4 dropouts, B: 2 dropouts, C: 9 dropouts, D: 12 dropouts Control - E: 1 dropout The imiquimod 5X/week and 7X/week groups lost 30% and 40% of participants, respectively.
Selective reporting (reporting bias)	Low risk	All outcomes were reported even if efficacy was low.
Other bias	Unclear risk	-

Hanke 2010

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

Hanke 2010 *(Continued)*

	Start date: January 2008 End date: July 2008

Participants	**Inclusion criteria of the trial**
	
	• Adults in general good health
	• Anatomical locations: face (70%) or balding scalp
	• 5 to 20 visible and palpable actinic keratoses within 25 cm^2
	
	Exclusion criteria of the trial
	
	• Any condition in the treatment area that might impair evaluation
	• Atypical actinic keratoses
	• Pregnancy, lactation
	• Chemical or alcohol dependency
	• Known allergy to imiquimod or study cream excipients
	• No prior treatment with the following:
	  • within 1 year with imiquimod
	  • within 90 days with interferon, interferon inducers, cytotoxic drugs, immunomodulators, immunosuppressants, oral or parenteral corticosteroids, topical corticosteroids more than 2 g/day, investigational drug or device use outside of the treatment area
	  • within 30 days with imiquimod outside the treatment area, topical prescriptions drugs, and investigational drug or device within treatment
	
	Demographics
	
	• 490 participants
	• 386 men, 104 women
	• Age: mean = 65

Interventions	**Interventions** A: 3.75% imiquimod, once daily for 3 weeks on, 3 weeks off, 3 weeks on (N = 162 participants) B: 2.5% imiquimod, once daily for 3 weeks on, 3 weeks off, 3 weeks on (N = 164 participants) **Control intervention** C: placebo, once daily for 3 weeks on, 3 weeks off, 3 weeks on (N = 164 participants)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at week 17 **Secondary outcomes of the trial** 1) Participant partial (≥ 75%) clearance rates at week 17 2) Median percentage of changes in lesion counts 3) Local skin reactions **Other outcomes of the trial** 1) Participants experiencing at least 1 adverse event 2) Application site reactions (including irritation) 3) Minor adverse events 4) Treatment-related adverse events

Hanke 2010 *(Continued)*

5) Serious adverse events

6) Clinical laboratory tests

7) Investigator global integrated photodamage (IGIP-cosmetic outcome)

8) Temporary treatment interruption

Efficacy

Methods: quantitative assessment using counting of all visible or palpable lesions - baseline or new - in the treatment area by the investigator

Time points: baseline; at weeks 1, 2, 3 (end of cycle 1), 6 (beginning of cycle 2), 7, 8, 9 (end of cycle 2), 13, and 17 (end of study) (subjects who discontinued the study prematurely were requested to return for the end-of-study visit)

Definitions: 1. complete clearance rate (proportion of subjects at the end-of-study visit with a count of zero lesions in the treatment area), 2. partial clearance rates (proportion of subjects with 75% or greater reduction in lesion count in the treatment area at the end-of-study visit as compared with baseline), and 3. percentage of changes in lesion count (per cent change in lesion number at the end-of-study visit as compared with baseline)

Safety

Methods: 1. measurement of vital signs, 2. recording of adverse events, 3. investigator assessment of local skin reactions (erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration) graded as none, mild, moderate, or severe, 4. hematology, serum chemistry, urinalyses, and urine pregnancy tests (treatment-emergent adverse events were summarised for each treatment group by preferred term, intensity, and investigator assessment of relationship to study cream. The local skin reactions were summarised by the most intense score for each reaction and by the sum score at each visit and over the course of the study)

Time points: 1. baseline, at weeks 1, 2, 3 (end of cycle 1), 6 (beginning of cycle 2), 7, 8, 9 (end of cycle 2), 13, and 17 (end of study), 2. pre-study visit and end-of-study visit (laboratory tests)

Cosmetic

Methods: qualitative and quantitative assessment (IGIP score)

Time points: at end-of-study visit

Definition: IGIP score (overall assessment of the subject's photodamage change from baseline in the treatment area including an integrated assessment of fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, sallowness, skin laxity, and telangiectasias) [the details on score were not provided, but both numerical results (score with standard deviation) and the number of participants with "significantly or much improved' cosmetic outcome were presented]

Funding	This study was supported by Graceway Pharmaceuticals.
Notes	Data from 2 studies were pooled together. Temporary dosing interruptions could have been instructed by the investigator to manage local skin reactions and adverse events. 96% of subjects were compliant with dosing. A sample size calculation was provided. There was a follow-up study published (Hanke 2011).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 575): "Eligible subjects were randomised to placebo, imiquimod 2.5%, or imiquimod 3.75% cream in a 1:1:1 treatment allocation."

Hanke 2010 *(Continued)*

		Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was double-blind, but authors mentioned that local effects of imiquimod may have led to investigator and subject bias.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was double-blind, but authors mentioned that local effects of imiquimod may have led to investigator and subject bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 10 dropouts, B: 7 dropouts Control - C: 10 dropouts
Selective reporting (reporting bias)	Unclear risk	All outcomes from the protocol NCT00603798 were reported, but additional outcomes were also presented in the published paper (e.g. cosmetic).
Other bias	Unclear risk	Data for safety were reported differently in the published and the study results section of the protocol NCT00603798 in clinicaltrials.gov.

Hantash 2006

Methods	This was a single-centre, randomised, active-controlled, parallel-group study. Start date: October 1, 2000 End date: October 30, 2002
Participants	**Inclusion criteria of the trial** • Clinical diagnosis confirmed by experienced dermatologist • Anatomical location: face • With a history of facial or scalp non-melanoma skin cancer and numerous actinic keratoses **Exclusion criteria of the trial** • Previous facial resurfacing (laser or chemical peel) within 5 years • Current non-melanoma skin cancer • Topical therapy or cryotherapy within 2 months **Demographics** • 34 participants • 33 men, 1 women
Interventions	**Intervention** A: 2 passes of carbon dioxide laser resurfacing (N = 8 participants) **Control interventions** B: 30% trichloroacetic acid peel (N = 10 participants)

Hantash 2006 *(Continued)*

	C: 5% fluorouracil twice daily for 3 weeks (N = 9 participants) D: not randomised control group without treatment (data not presented and not included in our review) (N = 5 participants, 2 participants not included and reasons were given)
Outcomes	**Outcomes of the trial** 1) Mean number of actinic keratosis lesions at baseline and 3 months (transformed to mean reduction in lesion counts) 2) Mean percentage of reduction of lesion counts at 3 months 3) Incidence of new non-melanoma skin cancer for 5 years (4 groups) 4) Minor adverse events (qualitative) Efficacy Methods: quantitative assessment using the number and locations of existing lesions charted on a diagram of the head (at each visit, any lesions suggestive of basal or squamous cell carcinoma were biopsied. The VA Palo Alto Health Care System (VAPAHCS) medical and pathologic records were reviewed for each participant through June 30, 2005, to evaluate for any subsequent development of skin cancer in treated areas) Time points: at enrolment and every 3 months for a minimum of 24 months (at the end of the 24-month study, participants continued routine general dermatology clinic surveillance) Definitions for rates of cancer formation: 1. cancer incidence rates (ratio of the total number of cancers to the total number of participant-years followed in each group), 2. number of days from baseline/treatment to diagnosis of the first non-melanoma skin cancer Safety Methods: monitoring for any adverse events Time points: at every 3 months for a minimum of 24 months
Funding	-
Notes	Every 3 months, new or remaining lesions were treated with cryosurgery.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 977): "Patients were prospectively randomised to 1 of 3 treatment arms..." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open because physically different treatments were used.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding of assessor was not stated and physically different treatments were used.

Hantash 2006 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	The type of analysis was unclear. Intervention - A: 2 dropouts (the reasons were reported) Controls - B: 0 dropouts, C: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Hauschild 2009a

Methods	This was a multicentre, randomised, double-blinded, placebo-controlled, parallel-group study. Start date: March 2006, End date: December 2007

Participants	**Inclusion criteria of the trial**
	• White men and women with actinic keratoses
	• Skin type I-IV
	• Age 18 years and older
	• Anatomical location: head
	• Mild to moderate grade actinic keratoses with a minimum diameter of 1.8 cm and an interlesional distance of at least 1 cm
	Exclusion criteria of the trial
	• Women of child-bearing potential
	• Non-response to previous photodynamic therapy
	• Dermatological conditions that could influence the study arms
	• Porphyria
	• Clinically relevant immunosuppression or dementia
	• Topical treatment as follows:
	  • within 3 months with urea- and salicylic acid-containing preparations
	  • within 4 weeks with systemic retinoids
	  • within 2 weeks with treatment with cytostatic or radiation
	  • within 3 months and during study, known intolerance to 1 or more ingredients of patches
	Demographics
	• 103 participants
	• 84 men,19 women
	• Age: range = 51 to 89

Interventions	**Intervention** A: 3 to 8 self-adhesive patches of PD P506A (aminolevulinic acid - ALA)-photodynamic therapy (PDT) (N = 69 participants) **Control intervention** B: 3 to 8 self-adhesive patches of placebo-PDT (N = 34 participants) Characteristics of PDT intervention: Type of treatment: individual lesions

Hauschild 2009a *(Continued)*

Number of treatments: 1

Interval between treatments: --

Preparation of lesions: no

Cream concentration (%): patches containing 8 mg

Application of cream: self-adhesive patch

Incubation with cream: 4 hours

Type of light: red light LED

Light source: Aktilite CL 128 or Omnilux

Wavelength (nm): 630

Energy fluence (J/cm^2): 37

Intensities (mW/cm^2): --

Exposure time: --

Outcomes

Primary outcome of the trial

1) Complete clinical clearance rates on lesion basis (= lesion complete response) at 12 weeks post-treatment

Secondary outcomes of the trial

1) Participant complete clearance rates at 12 weeks post-treatment

2) Adverse reactions at the treatment site (= application site reactions) during and the day after the treatment

3) Local skin/adverse reactions (presented for ALA-PDT only)

4) Serious adverse events

5) Treatment-related adverse events

6) Participant and investigator cosmetic outcomes of cleared lesions

7) Participant satisfaction

Efficacy

Methods: clinical diagnosis being regarded as usual procedure in dermatological practice

Time points: at 12 weeks post-treatment

Definitions: complete clinical clearance of a lesion (no visual evidence of persisting lesion on treated surface; no evidence of adherent scaling plaques on treated skin surface when palpated; lesions no longer perceptible to touch; and slight pink or red foci might be visible at lesion sides)

Safety

Methods: 1. recording of local reactions by clinical staff, 2. a diary for the documentation of local reactions by participant during the 4 weeks after therapy, 3. blood samples for monitoring hepatic aminotransferases (alanine aminotransferase and aspartate aminotransferase) and γ-glutamyltransferase, 4. documentation of adverse events

Time points: 1. during patch application, illumination, and thereafter (local reactions), 2. before and day of treatment (blood tests), 3. each study visit (adverse events)

Cosmetic

Hauschild 2009a *(Continued)*

	Methods: 1. participants' and investigators' assessment of the cosmetic outcome of cleared lesions ('excellent', 'good', 'fair', or 'poor'), 2. participants' overall satisfaction with the cosmetic outcome ('very satisfied', 'satisfied', 'poorly satisfied', 'not satisfied') Time points: at 12 weeks post-treatment
Funding	This study was supported by Photonamic GmbH & Co.
Notes	The manuscript included 2 independent phase III studies (AK03 and AK04). This study was AK03. Adverse events were given for individual studies and pooled for ALA-PDT, but pooled only for placebo-PDT. Thus, pooled data were used for analysis (under Hauschild 2009a). A follow-up study was published (Szeimies 2010a). Data for intention-to-treat analysis were used for the meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratification was performed by centre.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind, and treatment was performed by a second investigator to guarantee an observer-blinded status.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Modified ITT analysis was used (4 participants were not included, and the criteria were not specified but the numbers correspond to the following: ALA-PDT: 1 missed control visit, 1 curettage before the study, 1 stop of illumination, and placebo-PDT: 1 consent withdrawn). Intervention - A: 17 dropouts (the reasons were reported) Control - B: 8 dropouts (the reasons were reported) 24% of participants were lost before the end of study, but similar percentages were lost for both treatment arms.
Selective reporting (reporting bias)	High risk	Details on investigator cosmetic outcomes and adverse events for placebo group were not given. Outcomes in protocol (NCT00308854) were all presented in published paper.
Other bias	Unclear risk	-

Hauschild 2009b

Methods	This was a multicentre, randomised, open, parallel-group study. Start date: March 2006 End date: November 2007

Hauschild 2009b *(Continued)*

Participants	**Inclusion criteria of the trial**
	• White men and women with actinic keratoses
	• Skin type I-IV
	• Age18 years and older
	• Anatomical location: head
	• Mild to moderate grade actinic keratoses with a minimum diameter of 1.8 cm and an interlesional distance of at least 1 cm
	Exclusion criteria of the trial
	• Women of child-bearing potential
	• Non-response to previous photodynamic therapy
	• Dermatological conditions which could influence the study arms
	• Porphyria
	• Clinically relevant immunosuppression or dementia
	• Topical treatment as follows:
	  • within 3 months with urea- and salicylic acid-containing preparations
	  • within 4 weeks with systemic retinoids
	  • within 2 weeks with treatment with cytostatic or radiation
	  • within 3 months and during study a known intolerance to 1 or more ingredients of patches or cryosurgery
	Demographics
	• 346 participants
	• 248 men, 98 women
	• Age: mean = 70; range = 41 to 94

Interventions	**Intervention** A: 4 to 8 self-adhesive patches of PD P506A (aminolevulinic acid -ALA)- photodynamic therapy (PDT) (N = 148 participants) **Control interventions** B: 4 to 8 self-adhesive patches of placebo-PDT (N = 49 participants) C: cryosurgery: nozzles of size C, 1 cycle and freeze time between 5 and 10 seconds (N = 149 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 Interval between treatments: -- Preparation of lesions: no Cream concentration (%): patches containing 8 mg Application of cream: self-adhesive patch Incubation with cream: 4 hours Type of light: red light LED Light source: Aktilite CL 128 or Omnilux Wavelength (nm): 630

Hauschild 2009b *(Continued)*

	Energy fluence (J/cm²): 37 Intensities (mW/cm²): -- Exposure time: --
Outcomes	**Primary outcome of the trial** 1) Complete clinical clearance rates on lesion basis (= lesion complete response) at 12 weeks post-treatment **Secondary outcomes of the trial** 1) Participant complete clearance rates at 12 weeks post-treatment 2) Adverse reactions at the treatment site (= application site reactions) during and the day after the treatment 3) Local skin/adverse reactions (presented for ALA-PDT only) 4) Serious adverse events 5) Treatment-related adverse events 6) Participant and investigator cosmetic outcomes of cleared lesions 7) Participant satisfaction Efficacy Methods: clinical diagnosis being regarded as usual procedure in dermatological practice Time points: at 12 weeks post-treatment Definitions: complete clinical clearance of a lesion (no visual evidence of persisting lesion on treated surface; no evidence of adherent scaling plaques on treated skin surface when palpated; lesions no longer perceptible to touch; and slight pink or red foci might be visible at lesion sides) Safety Methods: 1. recording of local reactions by clinical staff, 2. a diary for the documentation of local reactions by participant during the 4 weeks post-treatment, 3. blood samples for monitoring hepatic aminotransferases (alanine aminotransferase and aspartate aminotransferase) and ɣ-glutamyltransferase, 4. documentation of adverse events Time points: 1. during patch application, illumination, and thereafter for PDT, and during the spraying procedure and thereafter for cryotherapy (local reactions), 2. before and day of treatment (blood tests), 3. each study visit (adverse events) Cosmetic Methods: participants' and investigators' assessment of the cosmetic outcome of cleared lesions ('excellent', 'good', 'fair', or 'poor') Time points: at 12 weeks post-treatment
Funding	This study was supported by Photonamic GmbH & Co.
Notes	The manuscript included 2 independent phase III studies (AK03 and AK04). This study was AK04. Adverse events were given for individual studies and pooled for ALA-PDT, but only pooled for placebo-PDT. Thus, pooled data were used for analysis for ALA-PDT vs placebo-PDT (under Hauschild 2009a). A follow-up study was published (Szeimies 2010a). Data for intention-to-treat analysis were used for meta-analyses.

Hauschild 2009b *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratification was performed by centre.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open because the treatments were physically distinct. Similar patches were used for ALA-PDTand placebo-PDT, but no concealment was possible for the physically distinct treatments, i.e. PDT versus cryotherapy.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was open.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Intervention - A: 19 dropouts (the reasons were reported) Controls - B: 6 dropouts (the reasons were reported), C: 23 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	Details on investigator cosmetic outcomes and adverse events for placebo group were not given. Outcomes in protocol (NCT00308867) were all presented in published paper.
Other bias	Unclear risk	-

Hauschild 2009c

Methods	This was a multicentre, randomised, assessor-blinded, active-controlled, parallel group study. Start date: January 2005 End date: July 2005
Participants	**Inclusion criteria of the trial** • Histological diagnosis • White men and women • Aged 18 years and older • Anatomical locations: head and face • 3 to 4 actinic keratoses • Mild to moderate grade • With a maximum diameter of 1.8 cm and an interlesional distance of 1 cm **Exclusion criteria of the trial** • Women of child-bearing potential • Known or suspected acute or chronic hepatic diseases or renal dysfunction • Dermatological conditions that could possibly influence the study aims • Porphyria

Hauschild 2009c *(Continued)*

- Immune system suppression
- Severe concomitant diseases
- Any topical treatment able to affect the disease status was not permitted within the last 4 weeks and during the study (3 months for systemic retinoids)
- Urea and salicylic acid-containing dermatological preparations were not permitted within the last 2 weeks and during the study

Demographics

- 149 randomised, 140 evaluable participants
- 103 men, 37 women
- Age: mean = 71; range = 39 to 91

Interventions	**Interventions** A: 1 hour of PD P506A (aminolevulinic acid (ALA) self-adhesive patch)-photodynamic therapy (PDT) (N = 38 participants) B: 2 hours of PD P506A-PDT (N = 34 participants) C: 4 hours of PD P506A-PDT (N = 34 participants) **Control intervention** D: 0.5 hour of PD P506A-PDT (N = 34 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 Interval between treatments: -- Preparation of lesions: no Cream concentration (%): patches containing 8 mg Application of cream: self-adhesive patch Incubation with cream: 0.5 to 4 hours Type of light: red light Light source: Aktilite CL 128 Wavelength (nm): 630 Energy fluence (J/cm^2): 37 Intensities (mW/cm^2): -- Exposure time: --
Outcomes	**Primary outcome of the trial** 1) Lesion complete response rates at 4 and 8 weeks **Secondary outcomes of the trial** 1) Participant complete clearance rates at 4 and 8 weeks 2) Local skin reactions presented graphically for 3 periods (during ALA patch application, during illumination, and after illumination) as well as by severity of the reactions

Hauschild 2009c *(Continued)*

	3) Treatment-related adverse events (minor adverse events) 4) Minor adverse events (pooled) 5) Serious adverse events 6) Clinical laboratory tests 7) New actinic keratoses Efficacy Methods: clinical diagnosis, the usual procedure in dermatological practice Time points: at 4 and 8 weeks after PDT Definitions: complete clinical clearance of a lesion (no visual evidence of persisting lesions on treated surface, no evidence of adherent scaling plaques on treated skin surface when palpated, lesions no longer perceptible to touch, slight pink or red foci might be visible at lesion sides) Safety Methods: 1. inspection of study lesions for tolerability, 2. recording of local reactions and adverse events (local reactions were always assumed to be related to study therapy. For adverse events, the investigator judged the relation to the study therapy) Time points: 1. at 1 day and 1 week after PDT (tolerability), 2. entire study duration (local reactions and adverse events)
Funding	This study was supported by Photoamic.
Notes	Percentages of participants with local skin reactions were given graphically. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 118): "Patients were randomly allocated to treatment." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was no stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not stated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	To keep the assessor blinded, 1 investigator performed the evaluation, and another investigator administered the treatments.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Lost participants were mentioned (9) but not by treatment group and the reasons were not given.
Selective reporting (reporting bias)	High risk	Adverse events were not always clearly reported by group, and the number of participants included in the safety analysis was not clear.

Hauschild 2009c *(Continued)*

Other bias	Unclear risk	-

Huyke 2009

Methods	This was a single-centre, randomised, active-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Clinical or histological diagnosis • Healthy participants of both sexes older than 18 years with full contractual capability • Anatomical locations: face, scalp, and other • ≤ 10 actinic keratoses **Exclusion criteria of the trial** • Inflammatory skin diseases • Metabolic diseases • Consumption of any drugs except contraceptives • Alcohol consumption • Infections • Pregnancy, lactation • Impaired contractual capability as well as concomitant participation in other clinical studies • Pigmented skin lesions • Concomitant therapy with UV • Medication with immunomodulatory, antibiotic, or anti-inflammatory properties • Treatment for actinic keratosis within 4 weeks • No proper contraceptive method **Demographics** • 45 participants • 36 men, 9 women • Age: mean = 68; range = 50 to 92
Interventions	**Interventions** A: betulin-based oleogel applied twice daily (N = 15) B: combination therapy with initial cryotherapy followed by betulin-based oleogel twice daily (N = 15) **Control intervention** C: cryotherapy in the form of a spray coat method with liquid nitrogen (20 to 40 seconds) (N = 15)
Outcomes	**Outcomes of the trial** 1) Complete clearing (= participant complete clearance) rates at 3 months 2) Therapy responders with ≥ 75% of clearing of the lesions (= participant partial clearance) rates at 3 months 3) Histological analysis of biopsies before treatment and at the end of treatment 4) Minor adverse events (qualitative) Efficacy

Huyke 2009 *(Continued)*

	Methods: 1. quantitative assessment using documentation of visual and photographic evaluation in the case report forms, 2. punch biopsies from 4 participants out of the oleogel group, 2 participants out of the cryotherapy group and 2 participants out of the combination therapy group for evaluation of the degree of dysplasia, number of dyskeratoses and thickness of epidermis and stratum corneum Time points: 1. at 1, 2, and 3 months after the beginning of treatment, 2. before treatment and at the end of treatment (biopsy) Definitions: 1. responders [participants with complete (100 %) and with extensive (≥ 75 %) total clearing of the lesions], and 2. non-responders (participants with disappearance of < 75 % of the lesions) Safety Methods: assessment of the subjective parameters itching and stinging by a questionnaire and grading as follows: 0 = absent, 1 = mild, 2 = moderate, and 3 = severe
Funding	This study was supported by Birken GmbH.
Notes	This study was a Phase II pilot study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation plan was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was open. This study did not use placebo cream to conceal the allocation to cryotherapy only versus cryotherapy with betulin-based oleogel.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was open.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol (PP) analysis was used. Intervention - A: 1 dropout (the reason was reported), B: 1 dropout (the reason was reported) Control - C: 1 dropout (the reason was reported) Comment: The effect of PP analysis is difficult to assess because the same number of participants was lost in each treatment group.
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Jeffes 2001

Methods	This was a multicentre, randomised, assessor-blinded, vehicle-controlled, intraindividual study.

Jeffes 2001 *(Continued)*

	The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	• Clinically typical actinic keratoses (scaly erythematous papules and plaques devoid of cystic pores or a papillomatous surface)
	• Grade 1 (mild, lesions slightly palpable, with lesions more readily felt than seen) or 2 (moderate, moderately thick lesions, easily seen and felt)
	• Anatomical locations: face and scalp
	• ≥ 4 actinic keratoses (2/treatment group)
	Exclusion criteria of the trial
	• Grade 3 (severe, very thick, hypertrophic, or hyperkeratotic)
	• Previous treatment of target actinic keratoses
	• Concurrent use of photosensitising drug
	• Treatment with the following:
	  • within 1 week with non-steroidal anti-inflammatory drugs
	  • within 2 weeks with topical steroids, retinoids (Retin A), or topical alpha hydroxy acids
	  • within 4 weeks with systemic steroids
	  • within 2 months with topical application of 5-fluorouracil, masoprocol, systemic chemotherapeutic agent, immunotherapy, or retinoids
	• Pregnancy or nursing
	• History of cutaneous photosensitivity
	Demographics
	• 36 participants
	• 30 men, 6 women
	• Age: mean = 69; range = 38 to 100

Interventions	**Intervention** A: aminolevulinic acid (ALA)-photodynamic therapy (PDT) (N = 36 participants) **Control intervention** B: vehicle-PDT (N = 36 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 or 2 (if complete response not achieved) Interval between treatments: 8 weeks Preparation of lesions: -- Cream concentration (%): 20% Application of cream: 3 applications onto lesion and a rim of 2 to 4 mm, air dry between applications Incubation with cream: 14 to 18 hours Type of light: blue light Light source: DUSA BLU-417 Wavelength (nm): 417 Energy fluence (J/cm^2): 2, 5, or 10

Jeffes 2001 *(Continued)*

	Intensities (mW/cm^2): -- Exposure time: --
Outcomes	**Outcomes of the trial** 1) Clinical response of actinic keratosis lesions including completely cleared (= lesion complete response) rates for individual (at 8 weeks) and all (at 8 and 16 weeks) light doses 2) Number of participants with 0, 1, 2 (all) cleared lesions (= participant complete clearance) for individual (at 8 weeks) and all [at 8 (ALA and placebo) and 16 (ALA only) weeks] light doses 3) Application site reactions during (illumination) and after treatment reported per lesions 4) Clinical laboratory tests 5) Changes in pigmentation (cosmetic) per lesions 6) PpIX fluorescence Efficacy Time points: at baseline; immediately after PDT; at 24 and 72 hours; and at weeks 1, 4, 8, 9 (retreated participants), 12, and 16 Definitions: 1. complete response (completely cleared with no evidence of adherent scale on the surface of the treated skin when palpated), 2. partial response (≥ 50% reduction in lesion size), and 3. no response (< 50% reduction in lesion size) Safety Methods: 1. evaluation of objective changes in erythema, oedema, wheal, vesiculation, ulceration, haemorrhage, and necrosis on a graded scale (0: none; 1: minimal; 2: moderate; 3: severe), 2. subjective assessment of participant discomfort from pain, burning/stinging, and itching was graded (0: none; 1: minimal; 2: moderate; 3: severe), 3. standard hematologic and biochemical laboratory parameters, 4. reporting of adverse events Time points: 1. at baseline; immediately after PDT; at 24 hours; at 72 hours; and at weeks 1, 4, 8, 9 (retreated participants), 12, and 16, 2. at baseline and again at 1 week post-treatment (laboratory tests)
Funding	This study was supported by DUSA pharmaceuticals, Inc.
Notes	Clinical response was dependant upon dose of light administered (5 or 10 J/cm^2 were more effective than 2 J/cm^2). Visual detection of PpIX confirmed absence of cross contamination of treatment and placebo creams. Grade 1 (30/39 = 77%) lesions had better response than grade 2 (16/31 = 52%). PpIX fluorescence significantly correlated with clinical response (P < 0.001). Only data from 8 week's visit was used, because data from 16 weeks included participants with or without additional treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 97): "Each patient had a minimum of 4 target lesions with 2 lesions being randomised to ALA solution and 2 to vehicle." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.

Jeffes 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	A non-blinded investigator performed treatments.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Different investigators were involved for the treatment and the analysis.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intraindividual study: Intervention - A: 4 dropouts (the reasons were reported) Control - B: 4 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Jorizzo 2002

Methods	This was a multicentre, randomised, double-blind, open (treatment duration), vehicle-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Anatomical locations: face or frontal scalp • ≥ 5 actinic keratoses (≥ 4 mm in diameter) **Exclusion criteria of the trial** • Confounding skin condition (basal cell carcinoma or squamous cell carcinoma) • History of facial skin irritation • Treatment of actinic keratoses within 1 month **Demographics** • 207 participants • 166 men, 41 women
Interventions	**Interventions** A: 0.5% 5-fluorouracil, once daily for 1 week (N = 47 participants) B: 0.5% 5-fluorouracil, once daily for 2 weeks (N = 46 participants) C: 0.5% 5-fluorouracil, once daily for 4 weeks (N = 45 participants) **Control intervention** D: Vehicle, once daily for 1, 2, or 4 weeks (pooling not clear - see page 336 of the study) (N = 69 participants)

Jorizzo 2002 *(Continued)*

Outcomes	**Primary outcomes of the trial** 1) Physician Global Assessment of Improvement (PGAI = Global improvement indices) 2) Per cent reduction of lesions (= mean percentage of reduction in lesion counts) 3) Absolute mean reduction in lesion counts **Other outcomes of the trial** 1) Proportion of participants achieving total clearance (= participant complete clearance) 2) Skin irritation (percentages of participants, severity, overtime) 3) Application and local skin reactions and minor adverse events (pooled data from 2 studies included in Carac product insert, i.e. Jorizzo 2002 and Weiss 2002) 4) Serious adverse events Efficacy Methods: 1. quantitative assessment using lesion counting, 2. qualitative assessment (PGAI mean score, +5 = total clearance and -4 = much worse) Time points: at baseline and 4 weeks post-treatment Safety Methods: 1. adverse events (including details of facial irritation): maximum severity, symptoms, onset and overall duration, post-treatment duration, and summary by visit, 2. facial irritation graded as 0 = none, 1 = mild, 2 = moderate, or 3 = severe (to ensure that all facial irritation was recorded, the last observed value for facial irritation was carried forward if a participant discontinued treatment for any reason)
Funding	This study was supported by Dermik Laboratories.
Notes	Data from this study were included in the Carac product insert.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 336): "Of the 207 randomised participants,..." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was double-blind (treatment vs placebo) and open (treatment duration). No placebo cream was used to conceal the treatment duration.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was double-blind (treatment vs placebo) and open (treatment duration). No placebo cream was used to conceal the treatment duration.
Incomplete outcome data (attrition bias) All outcomes	High risk	It was unclear which type of analysis was used. Intervention - A: 2 dropouts, B: 1 dropout, C: 1 dropout

Jorizzo 2002 *(Continued)*

		Control - D: 0 dropouts (the reasons were not reported)
Selective reporting (reporting bias)	High risk	Values for absolute reductions in lesion numbers, standard deviations on mean percentages, and PGAI were not given. Details on local skin reactions and adverse events, other than facial irritation, was not reported in the published version of the study.
Other bias	Unclear risk	-

Jorizzo 2004

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel group study. Start date: October 2001 End date: February 2002
Participants	**Inclusion criteria of the trial** • Age 18 years and older • Women were eligible if they were postmenopausal or using appropriate contraceptive methods and not pregnant or lactating • Anatomical locations: face, scalp, ears, neck, lips • ≥ 5 actinic keratoses **Exclusion criteria of the trial** • Basal or squamous cell carcinomas • Other potential confounding skin conditions • Known allergies to ingredients of the test drug formulation • Treatment for actinic keratosis within 5 months; cryosurgery within 4 weeks • Engaged in activities that involve excessive or prolonged exposure to sunlight **Demographics** • 144 participants • 119 men, 23 women • Age: mean = 63
Interventions	**Intervention** A: topical 0.5% 5-fluorouracil, once daily for 7 days. At 4 weeks post-treatment, residual lesions treated with cryotherapy. (N = 72 participants) **Control intervention** B: vehicle, once daily for 7 days. At 4 weeks post-treatment, residual lesions treated with cryotherapy (N = 72 participants)
Outcomes	**Primary outcome of the trial** 1) Absolute and per cent of mean reduction in lesion counts at 4 weeks (topical only) and 6 months (topical + cryotherapy) **Other outcomes of the trial** 1) Participant complete clearance rates at 4 weeks and 6 months 2) Application site reactions (also reported in Jorizzo 2006)

Jorizzo 2004 *(Continued)*

	3) Eye irritation (= minor adverse events) Efficacy Methods: quantitative assessment using the counting of visible or palpable lesions, or both, by the same evaluator Time points: before initial treatment and at the 4-week and 6-month follow-up visits Safety Methods: 1. recording of severe application site reactions (erythema, edema, dryness, pain, erosion, burning, and pruritus), 2. eye irritation (burning, sensitivity, itching, stinging, and watering), 3. any other adverse events Time points: at each visit
Funding	This study was supported by Dermik Laboratories.
Notes	This study (interim analysis) is part of a 3-cycle study published in Jorizzo 2006, which was also included in this review. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded. All study personnel, and participants were blinded to actual treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded. Investigators were blinded to actual treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Modified Intention-to-treat (ITT) analysis was used (i.e. participants at 4 week evaluation based on information, efficacy: 142, safety: 143-received one treatment). Intervention - A: 2 dropouts (the reasons were reported) Control - B: 7 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Jorizzo 2006

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. The start and end dates were not specified.

Jorizzo 2006 *(Continued)*

Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Women were eligible if they were postmenopausal or using appropriate contraceptive methods and not pregnant or lactating • Anatomical locations: face, scalp, ears, neck, lips • ≥ 5 actinic keratoses **Exclusion criteria of the trial** • Basal or squamous cell carcinomas • Other potential confounding skin conditions • Known allergies to ingredients of the test drug formulation • Treatment for actinic keratosis within 5 months • Cryosurgery within 4 weeks • Engaged in activities that involve excessive or prolonged exposure to sunlight • Used a tanning parlour • Known dihydropyrimidine dehydrogenase enzyme deficiency • History of drug or alcohol abuse **Demographics** • 144 participants • 119 men, 23 women • Age: mean = 63
Interventions	**Intervention** A: 3 topical/cryosurgery cycles: topical 0.5% 5-fluorouracil, once daily for 7 days. At 4 weeks post-treatment, residual lesions were treated with cryosurgery (N = 72 participants) **Control intervention** B: 3 topical/cryosurgery cycles: topical vehicle, once daily for 7 days. At 4 weeks post-treatment, residual lesions were treated with cryosurgery (N = 70 participants)
Outcomes	**Primary outcomes of the trial** 1) Mean lesion counts at baseline and different treatment cycles (transformed to mean reduction in lesion counts) 2) Mean percentage of reduction in lesion counts 3) Participant complete clearance rates at 3 topical/cryosurgery cycles (before cryosurgery) 4) New involvement of actinic keratosis lesions **Other outcomes of the trial** 1) Application site reactions (severe) 2) Treatment-related adverse events (= minor adverse events) 3) Serious adverse events including basal and squamous cell carcinoma Efficacy Methods: quantitative assessment using the counting of visible or palpable actinic keratoses, or both, by the same evaluator Time points: before initial treatment and at the follow-up visits

Jorizzo 2006 *(Continued)*

	Definitions: 1. actinic keratosis reduction (number of lesions present at the 4-week follow-up visit for each topical/cryosurgery cycle minus the number of baseline lesions for that cycle), 2. clearance (complete lack of lesions in the treatment area at the 4-week follow-up visit for each topical/cryosurgery cycle), 3. new involvement [presence of new lesions in the treatment area at the start of topical/cryosurgery cycle 2 (week 26) or 3 (week 52)] Safety Methods: 1. monitoring the incidence, onset, duration, and severity of adverse events observed, 2. participants reporting the occurrence of any adverse event, and study personnel questioned participants during study visits to monitor safety, 3. all adverse events were categorised by the investigator as serious or not Time points: from time of enrolment to the end of the follow-up period Definitons: serious adverse events [adverse events resulting in death, life threatening; required inpatient hospitalisation or prolongation of existing hospitalisation, resulted in persistent or significant disability or incapacity, those described as important medical events (e.g. diagnosis cancer during the course of treatment)]
Funding	This study was supported by Dermik Laboratories.
Notes	More participants in the vehicle group had cryosurgery. New actinic keratosis lesions were observed over time in both groups, but a lower percentage of participants in the 5-fluorouracil group than the vehicle group was obtained. The number of participants based on ITT analyses were used for meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded. All study personnel and participants were blinded to the actual treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded. Investigators were blinded to the actual treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was stated. Intervention - A: 5 dropouts (the reasons were reported) Control - B: 12 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	Standard deviations on percentage of mean reduction in lesion counts were not reported.
Other bias	High risk	There was some inconsistency in the numbers in the manuscript as well as with the previous paper, Jorizzo 2004, for efficacy outcomes.

Jorizzo 2007

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Clinically typical visible actinic keratoses • Age 18 years and older • Anatomical locations: balding scalp or face • 4 to 8 actinic keratoses **Demographics** • 246 participants
Interventions	**Intervention** A: 5% imiquimod, once per day, 3 days per week for 4 weeks on, 4 weeks off, 1 or 2 courses (N = 123 participants) **Control intervention** B: vehicle: once per day, 3 days per week for 4 weeks on, 4 weeks off, 1 or 2 courses (N = 123 participants)
Outcomes	**Primary outcome of the trial** 1) Recurrence at 1 year **Other outcomes of the trial** 1) Participant complete and partial (≥ 75%) clearance rates after course 1 or overall 2) Individual lesion clearance (= lesion complete response) rates after course 1 or overall 3) Minor adverse events (qualitative) 4) Clinical laboratory tests Efficacy Methods: quantitative assessment using lesion counting Time points: at week 8, 16, and 1 year follow-up (relapse for participants achieving complete clearance) Definitions: 1. complete clearance rate (proportion of participants who cleared all lesions in the treatment area), 2. partial clearance rate (proportion of participants with at least a 75% reduction in baseline lesions) Safety Methods: 1. monitoring for adverse events and local skin reactions, 2. clinical laboratory tests (hematology and chemistry blood tests, and urinalysis), 3. culture of suggested skin infections
Funding	This study was supported by 3M Pharmaceuticals.
Notes	1-year recurrence rate of 39% and 57% were respectively found for imiquimod and vehicle.

Risk of bias

Bias	Authors' judgement	Support for judgement

Jorizzo 2007 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Quote (page 266): "Randomised patients applied imiquimod or vehicle cream (randomised 1:1)..." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Authors reported that blinded investigators may have been biased toward participants treated with imiquimod identified by treatment site reactions.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 4 dropouts (the reasons were not reported) Control - B: 3 dropouts (the reasons were not reported)
Selective reporting (reporting bias)	High risk	Statistically significantly more application site reactions, local skin reactions, and adverse events for imiquimod were reported but not all the numbers supporting it were reported.
Other bias	High risk	There was no demographic description.

Jorizzo 2010

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel group study. Start date: May 2009 End date: February 2010
Participants	**Inclusion criteria of the trial** • Adults in general good health • Anatomical location: face • ≥10 typical visible or palpable actinic keratoses (≤ 1 cm^2 in area and < 1 mm in height) **Exclusion criteria of the trial** • Atypical actinic keratoses (e.g. hyperkeratotic actinic keratoses > 1 cm^2 in area or > 1 mm in height, or both) in the treatment area (face) • Conditions in the facial area that might impair evaluation • Pregnancy or lactation • Chemical or alcohol dependency • Allergy to imiquimod or study cream excipients • The treatment area could not have been treated with the following: within 1 year with imiquimod; within 90 days with dermatologic procedures or surgeries, any actinic keratosis therapy, or investigational drug or device; within 30 days with any topical prescription drug • Exclusive of the treatment area, subjects could not have received treatment with interferon, interferon inducers, cytotoxic drugs, immunomodulators, immunosuppressants, oral or parenteral corticos-

Jorizzo 2010 *(Continued)*

teroids, topical corticosteroids > 2 g/day within 90 days, or an investigational drug or device within 30 days
- Usage of any of these treatments was also prohibited throughout the study.

Demographics

- 247 participants
- 214 men, 33 women
- Age: mean = 67

Interventions	**Interventions** A: cryotherapy followed by 3.75% imiquimod, daily for 2 weeks on, 2 weeks off, 2 weeks on (N = 126 participants) B: no cryotherapy followed by 3.75% imiquimod, daily for 2 weeks on, 2 weeks off, 2 weeks on (N = 126 participants) **Control interventions** C: cryotherapy followed by placebo, daily for 2 weeks on, 2 weeks off, 2 weeks on (N =121 participants) D: no cryotherapy followed by placebo, daily for 2 weeks on, 2 weeks off, 2 weeks on (N =121 participants) Randomisation was performed for imiquimod or placebo treatment, but the method used to select which lesions were treated with or without cryotherapy was not specified. At least 5 lesions were not treated with cryosurgery, and 5 to 14 actinic keratoses were treated with cryosurgery.
Outcomes	**Primary outcome of the trial** 1) Mean and median per cent changes from baseline for all lesions (= mean percentage of reduction in lesion counts) at week 26 **Secondary outcomes of the trial** 1) Participant complete clearance rates for all lesions at week 26 2) Local skin reactions (severe) **Other outcomes of the trial** 1) Application site reactions including irritation 2) Treatment-related adverse events (= minor adverse events) 3) Minor adverse events 4) Serious adverse events including basal and squamous cell carcinoma 5) Cosmetic outcomes (photodamage) 6) Rest periods 7) Participant satisfaction Efficacy Methods: quantitative assessment using lesion counting and mapping on a facial diagram, including lesions that were initially treated with cryosurgery Time points: 1. at each visit (counting), 2. baseline and end of study at week 26 (mapping) Safety

Jorizzo 2010 *(Continued)*

	Methods: investigator assessment of local skin reactions (erythema, oedema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration) graded as none, mild, moderate, or severe and summarised by the most intense score for each reaction, 2. recording of adverse events coded using MedDRA® (Medical Dictionary for Regulatory Activities), Version 12.0 (treatment-emergent AEs were summarised for each treatment group by preferred term, intensity, and investigator assessment of relationship to study cream), 3. serious adverse events and discontinuations due to adverse events Time points: at each clinic visit Cosmetic Methods: assessment of facial photodamage by the investigator using previously published 5-point scales that rated fine lines, mottled pigmentation, tactile roughness, sallowness, and global photoageing Time points: at baseline (prior to cryosurgery) and at weeks 10, 14, 20, and 26/end of study
Funding	This study was supported by Graceway Pharmaceuticals, LLC.
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated allocation sequence was generated.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study was double-blind for imiquimod versus placebo (subject, caregiver, investigator).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study was double-blind for imiquimod versus placebo (outcomes assessor).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A & B: 14 dropouts (the reasons were reported) Controls - C & D: 10 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	All outcomes from the protocol were reported, and the data were consistent in conference abstract, published paper, and the study results section of the protocol (NCT00894647) in clinicaltrials.gov. Additonal outcomes were reported in the published report. The data for "no cryotherapy" was not given for all outcomes. Cosmetic outcomes were reported separately for each criteria but were not reported as a global assessment.
Other bias	Unclear risk	-

Kang 2003

Methods	This was a multicentre, randomised, placebo-controlled, active-controlled, assessor-blinded, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Between 18 and 85 years of age • Anatomical locations: face above the jawline, ear, and scalp, sometimes arms and back of hands • 5 to 25 visible actinic keratoses at least 2 mm diameter but target lesions (maximum of 3 lesions) were at least 5 mm diameter **Exclusion criteria of the trial** • Treatment within the last 6 months with topical retinoids, alpha hydroxy acids, or 5-fluorouracil; within 1 year with systemic retinoids, dermabrasion, or cosmetic operation; within 2 months with oral psoralen-UVA therapy; within 1 month with cryotherapy; within 2 weeks with topical steroids • Dark skin (phototypes V and VI) • Pregnant or lactating women • History of skin cancer in the previous 3 years • Any condition that could interfere with the study evaluation **Demographics** • 90 participants • 69 men, 21 women • Age: mean = 63; range = 43 to 83 • White, 79% with skin phototypes I and II
Interventions	**Interventions** A: 0.1% adapalene gel, once daily for 4 weeks; twice daily from 4 weeks to 36 weeks (N = 30 participants) B: 0.3% adapalene gel, once daily for 4 weeks; twice daily from 4 weeks to 36 weeks (N = 30 participants) **Control intervention** C: placebo, once daily for 4 weeks; twice daily from 4 weeks to 36 weeks (N = 30 participants)
Outcomes	**Primary outcomes of the trial** 1) Mean reduction/changes of lesion counts 2) Morphological changes of target lesions **Secondary outcomes of the trial** 1) Physician global assessment improvement (PGAI) from worse to clear (= Global Improvement Indices) 2) Histological analysis of biopsies before and after treatment **Other outcomes of the trial** 1) Tolerability (= local skin reactions) 2) Minor adverse events 3) Serious adverse events

Kang 2003 *(Continued)*

	4) Photoaging characteristic improvement (cosmetic outcome) Efficacy Methods: 1. quantitative assessment using total lesion counts, 2. assessment of morphologic changes in target actinic keratoses (induration, scaling, and erythema evaluated on a scale of 0 [none] to 3 [severe]), 3. qualitative assessment of improvement (PGAI) as clear, marked, moderate, slight, no change, or worse, 4. biopsy specimens evaluated in a blinded manner by a board-certified dermatopathologist at 1 centre (University of Michigan, Ann Arbor, Michigan) Time points: at week 2, 4, 12, 18, 24, 30, and 36 Cosmetic Methods: standardised photographs were taken of 45 participants by a professional photographer at 1 centre (University of Michigan). [The photographs were evaluated retrospectively in a randomised, blinded fashion to assess the effects of the 3 treatments on photoageing characteristics (mottled hyperpigmentation, fine wrinkles, coarse wrinkles, rosy glow-healthy pink complexion, and global photoageing severity). Each parameter was graded for improvement on a scale of 0 to 6. If there was no difference or worsening between before- and after-treatment photographs, then a score of 0 was given] Time points: at baseline and after 3, 6, and 9 months of treatment
Funding	This study was supported by Galderma Corporation, Texas, US.
Notes	Histology on 36 participants showed no significant difference between treatment groups. There was no follow-up period. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation sequence in blocks of 9 using a unique 4-digit number was generated by a computer program.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not stated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 2 dropouts (the reasons were not reported), B: 3 dropouts (the reasons were reported) Control - C: 2 dropouts (the reasons were not completely reported)
Selective reporting (reporting bias)	High risk	Authors pooled together selected PGAI data, i.e. for clear, marked, moderate (but not slight) improvement to reach statistically significant difference.
Other bias	Unclear risk	-

Kaufmann 2008

Methods	This was a multicentre, randomised, open, active-controlled, intraindividual study. Start date: January 2005 End date: February 2006
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Men and women • Aged 18 years and older • Anatomical locations: upper and lower extremities, trunk, neck • Non-hyperkeratotic lesions of mild or moderate thickness • At least 4 comparable symmetrical lesions of similar severity and total number on both sides of the body (at least 2 lesions on each side and no more than a 2-fold difference between the 2 sides) • Women of child-bearing age were required to have a negative pregnancy test at the beginning of the study and to use effective birth control for the duration of the study **Exclusion criteria of the trial** • Participants receiving topical treatment within the past 3 months or those on ultraviolet therapy • Participants with thick lesions • Participants with pigmented lesions in the target area • Porphyria **Demographics** • 121 participants • 78 men, 43 women • Age: mean = 69; range = 39 to 89
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) (N = 121 participants) **Control intervention** B: cryotherapy: double freeze/thaw (1 to 2 mm frozen rim outside marked outline of lesion), 20 seconds (1 or 2 treatments with a 12-week interval) (N = 121 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 or 2 Interval between treatments: 12 weeks Preparation of lesions: gentle scraping Cream concentration (%): 16 % Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: 3 hours Type of light: red light LED Light source: Aktilite CL128 Wavelength (nm): 630

Kaufmann 2008 *(Continued)*

	Energy fluence (J/cm^2): 37 Intensities (mW/cm^2): -- Exposure time: --
Outcomes	**Primary outcome of the trial** 1) Lesion complete response rates for baseline lesions at week 24 **Secondary outcomes of the trial** 1) Cosmetic outcome assessed by investigator and participants 2) Participant preference **Other outcomes of the trial** 1) Mean percentage of reduction in lesion counts 2) Treatment-related adverse events (= minor adverse events) 3) Participants reporting at least one adverse event 4) Minor adverse events 5) Serious adverse events including squamous cell carcinoma 6) Observation of Bowen's disease and new actinic keratoses Efficacy Methods: quantitative assessment using lesion counting [efficacy evaluations only included lesions present at baseline (i.e. lesions appearing after baseline, if any, were to be reported as an adverse event)] Time points: at baseline and weeks 12 and 24 Definitions for lesion response: 1. complete response (complete disappearance of the lesion), 2. non-complete response (incomplete disappearance) Safety Methods: spontaneous reporting of adverse events by the participant or elicited following non-leading questioning (severity, duration and need for additional therapy) Time points: at each follow-up visit Definitions for adverse events: 1. phototoxic reaction (any observed erythema, oedema, itching, pain, etc), 2. cryotherapy reaction (any observed blisters, infection, etc) Cosmetic Methods: 1. investigator assessment of cosmetic outcome for all lesions with complete response, 2. participant assessment of cosmetic outcome Time points: at week 24 Definitions for investigator assessment: 1. excellent (only slight occurrence of redness or change in pigmentation), 2. good (moderate redness or change in pigmentation), 3. fair (slight to moderate scarring, atrophy or induration), 4. poor (extensive scarring, atrophy, or induration) Definitions for participant assessment on a 5-point scale: –2 (cryotherapy a lot better than MALPDT) to 2 (MAL-PDT a lot better than cryotherapy)

Kaufmann 2008 *(Continued)*

Funding	This study was supported by Galderma.
Notes	A participant questionnaire showed that participants preferred MAL-PDT over cryotherapy for all questions except for effectiveness of treatment. A sample size calculation was provided. Intention-to-treat values were used for meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 995) : "At the baseline visit, eligible patients received treatment with PDT using MAL... and conventional cryotherapy, randomly allocated to alternate sides of the body." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding. This study was open because physically distinct treatments were compared.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no blinding. This study was open because physically distinct treatments were compared.
Incomplete outcome data (attrition bias) All outcomes	High risk	Both per-protocol (PP) and intention-to-treat (ITT) analyses were used. Intraindividual study: Intervention - A: 4 dropouts (the reasons were reported) Control - B: 4 dropouts (the reasons were reported) Comment: ITT and PP populations were respectively 121 and 106. Thus, 11 participants were not accounted for, and it was not always clear which analysis type was used for the different outcomes reported.
Selective reporting (reporting bias)	High risk	The standard deviation associated with the mean percentage of reduction in lesion counts were not provided.
Other bias	High risk	Participant's assessment of cosmetic outcomes has negative value if cryotherapy is better and positive value if MAL-PDT is better. This could influence the participant perception.

Korman 2005

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. Start date: August 2001 End date: August 2002
Participants	**Inclusion criteria of the trial**

Korman 2005 *(Continued)*

- Clinical diagnosis
- Healthy men and women
- Aged 18 years and older
- Anatomical locations: face or bald scalp
- 4 to 8 actinic keratoses within a 25 cm^2 area

Exclusion criteria of the trial

- Any condition that could be exacerbated by treatment or impair the examination area
- Previous treatment with 5% imiquimod cream in the treatment area
- Any known allergies to any excipients in the study cream
- Treatment as follows:
  * within the last 6 months with psoralen plus UVA therapy, UVB therapy, laser abrasion, dermabrasion, or chemical peel
  * within 4 weeks with prescribed topical retinoids, 5-fluorouracil, masoprocol, cryodestruction, chemodestruction, surgical excision, photodynamic therapy, curettage, interferon/interferon inducers, cytotoxic drugs, drugs with major organ toxicity, immunomodulators, immunosuppressive therapies, oral corticosteroids, or topical steroids anywhere on the head
- The use of moisturisers, over-the-counter retinol products, or products containing α or β hydroxy acids in the treatment area

Demographics

- 492 participants
- 431 men, 61 women
- Age: mean = 66.3; range = 41 to 93

Interventions

Intervention

A: 5% imiquimod applied 3 times per week for 16 weeks (N = 242 participants)

Control intervention

B: vehicle cream applied 3 times per week for 16 weeks (N = 250 participants). Applied to entire treatment area at same time of day (before sleeping). Cream to remain in place for approximately 8 hours. Rest periods allowed at discretion of investigator, but did not alter length of 16-week treatment

Outcomes

Primary outcome of the trial

1) Participant complete clearance rates for all lesions at 8 weeks post-treatment

Secondary outcome of the trial

1) Participant partial (> 75%) clearance rates for all lesions at 8 weeks post-treatment

Other outcomes of the trial

1) Median percentage reduction of baseline lesions at 8 weeks post-treatment

2) Participants experiencing at least 1 adverse event
3) Application site reactions

4) Local skin reactions

5) Frequency and severity of adverse events (= minor adverse events)

6) Serious adverse events

7) Rest periods

8) Skin quality (cosmetic outcome)

Korman 2005 *(Continued)*

	Efficacy Methods: quantitative assessment using lesion counting (baseline and new lesions) Time points: at weeks 4, 8, and 16, and post-treatment week 8 Definitions: 1. complete clearance rate (proportion of participants at the 8-week post-treatment visit with no clinically-visible lesions in the treatment area), 2. partial clearance rate (proportion of participants at the 8-week post-treatment visit with at least a 75% reduction in the number of baseline lesions in the treatment area) Safety Methods: 1. reviewing concomitant medication use, 2. assessing the incidence and severity of adverse events spontaneously reported, 3. assessing of local skin reactions (erythema, edema, erosion/ulceration, scabbing/crusting, weeping/exudation, vesicles, and flaking/scaling/dryness) rated as 0 = none, 1= mild, 2 = moderate, and 3 = severe by investigator (reactions within the treatment area that were not assessed as local skin reactions were reported as adverse events) Time points: at weeks 1, 2, 4, 6, 8, 10, 12, 14, and 16, and post-treatment weeks 4 and 8 Cosmetic Methods: investigator-performed (visual, clinical, and tactile examinations) skin quality assessments including skin surface (roughness/dryness/scaliness), hyperpigmentation, hypopigmentation, mottled or irregular pigmentation (hyperpigmentation and hypopigmentation), degree of scarring, and degree of atrophy area rated as 0 = none; 1 = mild; 2 = moderate; and 3 = severe Time points: at the treatment initiation and the 8-week post-treatment visit
Funding	This study was supported by 3M Pharmaceuticals.
Notes	2 phase III studies were included. Clearance rates increased with intensity of erythema. Increase in lesion counts (new or subclinical lesions) was higher in imiquimod group at any point during the treatment period. Long-term clinical outcomes were presented in Lee 2005.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation was achieved by a computer-generated randomisation schedule.
Allocation concealment (selection bias)	Low risk	Participants were assigned the next sequential participant study number and the corresponding study cream.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 15 dropouts (the reasons were reported) Control - B: 15 dropouts (the reasons were reported)

Korman 2005 *(Continued)*

Selective reporting (reporting bias)	High risk	Skin quality rating was not reported for placebo.
Other bias	Unclear risk	-

Kose 2008

Methods	This was a randomised, open-label, active-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Age18 years and older • General good health • Anatomical locations: face and scalp • ≥ 3 actinic keratoses **Exclusion criteria of the trial** • Pregnancy or lactation • Use of medication for actinic keratosis or other systemic treatments within 1 month • Sensitivity to any component of the study medications • Dermatologic conditions, such as psoriasis, eczema, chemical peeling **Demographics** • 49 participants • 28 men, 21 women • Age: mean = 56; range = 41 to 82
Interventions	**Intervention** A: 3% diclofenac sodium in 2.5% hyaluronic acid, once daily for 12 weeks (N = 24 participants) **Control intervention** B: 5% imiquimod, 3 times/week for 12 weeks (N = 25 participants)
Outcomes	**Outcomes of the trial** 1) Investigator (IGII) and participant (PGII) global improvement indices at the end of treatment 2) Lesion severity index 3) Local skin reactions 4) Participants experiencing at least 1 treatment-related adverse event 5) Clinical laboratory tests Efficacy Methods: 1. quantitative assessment using lesion counting, 2. severity of actinic keratoses at baseline, 3. qualitative assessment (GII) by the investigator and participant Time points: at baseline and monthly up to 1 year follow-up

Kose 2008 *(Continued)*

	Definitions for global improvement indices on a 7-point scale: -2 (significantly worse), -1 (slightly worse), 0 (no change), 1 (slightly improved), 2 (moderately improved), 3 (significantly improved), and 4 (completely improved) Definitions for baseline severity index: 0 (no lesions visible), 1 (clearly visible lesions), 2 (many visible, small, moderately-thick lesions, or a few large, thick, rough scaly lesions), 3 (many thick, hypertrophic lesions, which are clearly visible and palpable with well-defined borders) Safety Methods: 1. assessment of tolerability by investigator (erythema, itching, dry skin, and scaling), 2. clinical examination, 3. reporting of adverse events, 4. routine laboratory tests (complete blood cell counts, urine analysis, and fasting chemistry) Time points: 1. monthly up to 1 year follow-up, 2. before and after treatment (laboratory tests)
Funding	-
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 159): "Patients were randomly assigned to treatment with DFS or IMI." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The study was open. The difference in dosing regimen frequency of the 2 topical treatments was not concealed by the use of double-dummy technique.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The study was open.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropout Control - B: 0 dropout
Selective reporting (reporting bias)	High risk	Participant partial (> 75%) clearance was mentioned, but no data were reported.
Other bias	Unclear risk	-

Krawtchenko 2007

Methods	This was a single-centre, randomised, active-controlled, parallel-group study. Start date: August 2004

Krawtchenko 2007 *(Continued)*

End date: February 2005

Participants	**Inclusion criteria of the trial** • White participants • Typical, visible, and histologically-proven actinic keratoses • Anatomical locations: head, neck, and décolleté • 5 to 10 lesions in 1 anatomical area up to 5 X 10 cm **Exclusion criteria of the trial** • Participants using interferon or interferon inducers, immunomodulators, cytotoxic or immunosuppressor drugs, corticosteroids, retinoids, or investigational drugs within 4 weeks • Topical drug for actinic keratoses within 2 weeks • Invasive tumours within the treated area • Cardiovascular, haematological, hepatic, neurological, renal, endocrine, vascular, or gastrointestinal abnormalities or diseases • Dermatological disease within the treated or adjacent (3 cm distance) area • Known allergies to ingredients contained within the drugs studied **Demographics** • 75 participants • 61 men, 14 women • Age: mean = 73; range = 57 to 88
Interventions	**Intervention** A: 0.25 g of 5% imiquimod cream 3 times per week for 8 hours each over a span of 4 weeks, 1 or 2 treatments with a 4-week rest period (N = 26 participants) **Control interventions** B: 5% 5-fluorouracil cream twice daily for 4 weeks (N= 24 participants) C: cryosurgery using bursts of 20 to 40 seconds, 1 or 2 treatments with a 2-week rest period (N = 25 participants)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at test of cure and 12 months after the end of treatment **Other outcomes of the trial** 1) Participant histological clearance rates at test of cure 2) Negative predictive value, i.e. ratio between histological and clinical clearance 3) Serious adverse events 4) Global cosmetic outcome assessments by participant and investigator (presented graphically) 5) Skin quality 6) Recurrence (individual lesion and field) at 12 months after the end of treatment Efficacy Methods: 1. quantitative assessment using precise documentation of location of each lesion on body grid charts with raster and photographs, 2. a 4 mm punch biopsy specimen obtained from 1 of the selected lesions and evaluated independently by 2 expert dermatopathologists

Krawtchenko 2007 *(Continued)*

	Time points: at baseline, test of cure (6, 4, and 8 weeks after last treatment for cryotherapy, 5-fluorouracil and imiquimod, respectively), and 1 year after the end of treatment (recurrence) Definitions: 1. complete clearance (absence of clinically detectable lesions in treated skin regions), 2. recurrence (for cryotherapy: recurrence of initially cleared lesions determined and expressed as percentage of participants with lesion recurrence in relation to all treated participants; for 5-fluorouracil and imiquimod: total recurrences within the cleared cancer field determined and expressed as percentage of participants with field recurrence in relation to all treated participants, new lesions considered; missing values counted as recurrence) Cosmetic Methods: global assessment by investigator and participant based on the amount of scarring, atrophy, or indurations and on pigment change within the treatment area by comparison to adjacent, untreated skin Time points: at test of cure Definitions: 1. excellent (treated skin was indistinguishable from normal skin), 2. good (moderate redness or change in pigmentation), 3. fair (moderate redness or change in pigmentation and slight to moderate scarring, atrophy, or induration), 4. poor (extensive scarring, atrophy, or indurations)
Funding	-
Notes	1 week of rest period for imiquimod and 5-fluorouracil during treatment in case of acute inflammation was allowed. The data on non-recurrence at 1 year follow-up were as follows: 86% (19/22) for imiquimod, 57% (13/23) for 5-fluorouracil, and 41% (7/17) for cryotherapy.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 35): "Each patient was randomly assigned to one of [the] equally sized treatment groups (cryosurgery, 5-FU, or IMIQ) by 'on-call randomisation' provided by a specialised external company." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Low risk	Randomisation involving "on call" randomisation by an external company was used to conceal the allocation. (See previous quote.)
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not stated, but the study compared physically distinct interventions and topical treatments with different application regimens.
Blinding of outcome assessment (detection bias) All outcomes	High risk	There was no statement about assessor-blinding.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropouts at test of cure Control - B: 0 dropouts at test of cure, C: 0 dropouts at test of cure
Selective reporting (reporting bias)	Unclear risk	-

Krawtchenko 2007 *(Continued)*

Other bias	Unclear risk	-

Kulp-Shorten 1993

Methods	This was a multicentre, randomised, double-blind, active-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Men and women • Between 18 and 85 years of age • Good general health • Anatomical locations: head or neck • 3 to 30 actinic keratoses, at least 3 lesions with a minimum diameter of 5 mm **Exclusion criteria of the trial** • Treated with topical steroids or topical antimicrobials with 2 weeks • Tretinoin within 2 months • Systemic corticosteroids within 3 months • Systemic cancer chemotherapy within 6 months • Previous treatment with 5-fluorouracil, masoprocol, isotretinoin, or etretinate • Abnormal skin conditions that might confound interpretation • Known allergy to any of the ingredients in the study drug • Proclivity for facial skin irritation, cutaneous hyperreactivity, or both **Demographics** • 57 randomised, 54 evaluable participants • 49 men, 5 women • Age: range = 18 to 85
Interventions	**Intervention** A: 10% masoprocol applied topically twice daily for 4 weeks (N = 27 participants) **Control intervention** B: 5% 5-fluorouracil applied topically twice daily for 4 weeks (N = 30 participants)
Outcomes	**Outcomes of the trial** 1) Investigator global assessment (= global improvement indices) at week 8 2) Absolute and per cent of mean reduction in lesion counts 3) Number of events for adverse events and their severity 4) Percentage of participants experiencing adverse events represented graphically in function of the event severity (= minor adverse events) 5) Percentage of participants who discontinued treatment 6) Mean max pain score Efficacy

Kulp-Shorten 1993 *(Continued)*

	Methods: 1. quantitative assessment using lesions counting and rating, 2. qualitative assessment (global assessment) Time points: at baseline; days 7, 14, 21, and 28 (the last day of treatment); at day 42 and day 56; and at 1 year and 2 years (recurrence) Definitions for lesion rating: 1. mild (thin actinic keratoses, visible and palpable), 2. moderate (moderately thick actinic keratoses, easily seen and palpated), 3. severe (thick and florid actinic keratoses with distinct borders) Definitions for Global assessment: 1. cured (clear of palpable lesions, slight residual erythema remaining), 2. marked improvement (majority of lesions absent and scales of remaining lesions barely palpable), 3. moderate improvement (many lesions absent and scales decreased in thickness), 4. slight improvement (some lesions cleared, some decreased in scale, but many lesions remain), 5. no change (slightly worse, more or rougher larger lesions remain), 6. much worse (significantly more lesions or majority of lesions rougher, larger, or both) Safety Methods: 1. recording of all adverse experiences noted by participants and questioning of participants; 2. evaluation by investigator on key adverse reactions based on the appearance of the lesions, i.e. degree of erythema, necrosis, ulceration, and erosion in the lesions, and the degree of erythema and contact dermatitis in tissue surrounding and scored as 0 = none, 1 = mild, 2 = moderate, or 3 = severe; 3. intensity of the pain rated by participant on a 9-point scale ranging from 0 = no pain to 8 = severe pain Time points: at each visit
Funding	This study was supported by Reed & Carnrick Pharmaceuticals, A Division of Block Drug Company, Inc.
Notes	The numbers for per-protocol analysis were used for meta-analyses of mean reduction in lesion counts, and intention-to-treat numbers were used for meta-analysis of global improvement indices.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 162): "Patients were randomised in a double-blind fashion to twice-daily treatment with either 10% masoprocol in an emollient cream base or 5% 5-fluorouracil in a vanishing cream base." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded, and treatments were given with the same application regiment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol analysis was used. Intervention - A: 4 dropouts (the reasons were reported) Control - B: 4 dropouts (the reasons were reported)

Kulp-Shorten 1993 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	-
Other bias	High risk	A significantly higher percentage (65.5%) of participants treated with 5-fluorouracil failed to complete 28 days of treatment than participants treated with masoprocol (16%).

Lebwohl 2004

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. Start date: September 2001 End date: August 2002

Participants	**Inclusion criteria of the trial**
	
	• Clinical diagnosis
	• Healthy men and women
	• Aged 18 years and older
	• Anatomical locations: face or bald scalp
	• 4 to 8 actinic keratoses within a 25 cm^2 area
	
	Exclusion criteria of the trial
	
	• Any condition that could be exacerbated by treatment or impair the examination area
	• Previous treatment with 5% imiquimod cream in the treatment area
	• Any known allergies to any excipients in the study cream
	• Treatment as follows:
	  * within the last 6 months with psoralen plus lN A therapy, UVB therapy, laser abrasion, dermabrasion, or chemical peel
	  * within 4 weeks with prescribed topical retinoids, 5-fluorouracil, masoprocol, cryodestruction, chemodestruction, surgical excision, photodynamic therapy, curettage, interferon/interferon inducers, cytotoxic drugs, drugs with major organ toxicity, immunomodulators, immunosuppressive therapies, oral corticosteroids, or topical steroids anywhere on the head
	• The use of moisturisers over-the-counter retinol products or products containing α or β hydroxy acids in the treatment area
	
	Demographics
	
	• 436 participants
	• 380 men, 56 women
	• Age: range = 37 to 88

Interventions	**Intervention** A: 5% imiquimod cream, once per day, twice weekly for 16 weeks or less (N = 215 participants) **Control intervention** B: vehicle, once per day, twice weekly for 16 weeks or less (N = 221 participants)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates (all lesions) at 8 weeks post-treatment **Secondary outcome of the trial**

Lebwohl 2004 *(Continued)*

1) Participant partial (≥ 75% of baseline lesions) clearance rates at 8 weeks post-treatment

Other outcomes of the trial

1) Median per cent reduction in baseline lesions at 8 weeks post-treatment

2) Clinical laboratory tests

3) Participants experiencing at least 1 adverse event

4) Application site reactions
5) Local skin reaction: severe erythema, flaking/scaling/dryness, scabbing/crusting

6) Serious adverse events

7) Skin quality (cosmetic)

8) Increase in the number of lesions during the study

Efficacy

Methods: quantitative assessment using clinical counting

Time points: at baseline; weeks 1, 2, 4, 6, 8, 10, 12, 16 (end of treatment), 20, and 24

Definitions: 1. complete clearance rate (proportion of participants at the 8-week post-treatment visit with a count of 0 clinically-visible lesions in the treatment area), 2. partial clearance rate (proportion of participants at the 8-week post-treatment visit with at least a 75% reduction in the number of lesions counted at baseline in the treatment area)

Safety

Methods: 1. clinical laboratory tests [hematology (haemoglobin, hematocrit, reel blood cell, white blood cell, and platelet counts), serum chemistry (random glucose, blood urea nitrogen, creatinine, total bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, lactate dehydrogenase, alkaline phosphatase, potassium, sodium, calcium, chloride, total protein, albumin, phosphorous, and cholesterol) and urine analysis for colour/appearance, specific gravity, pH, protein, glucose, and ketones and a microscopic examination]; 2. vital sign measurements and physical examinations; 3. photography; 4. recording of adverse events; 5. assessment of local skin reactions (erythema, oedema, erosion/ulceration, scabbing/crusting, weeping/exudate, vesicles, or flaking/scaling/dryness) rated by a study investigator on a scale of 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe; and 6. recording of concomitant medication use

Time points: 1. at each visit, 2. pre-study visit and end of treatment at week 16 (physical exam and laboratory tests)

Definitions for spontaneous participant-reported adverse events: 1. mild (participant was aware of the signs and symptoms, but the signs and symptoms were easily tolerated), 2. moderate (the signs and symptoms were sufficient to restrict, but not prevent, usual daily activity), and 3. severe (the participant was unable to perform usual daily activity)
Cosmetic

Methods: assessment of skin quality by visual, clinical, and tactile examinations of the treatment area by investigator [skin surface, hyperpigmentation, hypopigmentation, mottled or irregular pigmentation (both hyperpigmentation and hypopigmentation), degree of scarring, and atrophy on a scale of 0 to 3, where 0 = none, 1 = mild, 2 = moderate, and 3 = severe]

Time points: at treatment initiation and 8-week post-treatment visit

Funding	This study was supported by 3M Pharmaceuticals, St Paul, Minnesota.
Notes	An increase in lesion counts was observed during treatment. A sample size calculation was provided. Pooled data from 2 phase III studies were presented in Aldara product insert. Long-term clinical outcomes were presented in Lee 2005.

Lebwohl 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 9 dropouts (the reasons were not all reported) Control - B: 11 dropouts (the reasons were not all reported)
Selective reporting (reporting bias)	High risk	As a similar study (Szeimies 2004) was also supported by Graceway/3M Pharmaceuticals, not all skin quality outcomes were reported. All outcomes presented in the product insert were reported in the published paper. Another Graceway clinical trial on the arms and hands (NCT00115154) was not published or included in the product insert.
Other bias	Unclear risk	-

Loven 2002

Methods	This was a randomised, assessor-blinded, active-controlled, intraindividual study. The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	• Aged 18 years and older
	• Men and postmenopausal women (or using appropriate contraception)
	• Anatomical locations: face, anterior bald scalp, or forehead
	• ≥ 6 visible or palpable actinic keratoses, 2 sides within 0.5 of each other of severity scale (based on a 4-point scale with 0.5 increments)
	Exclusion criteria of the trial
	• Basal cell carcinoma, squamous cell carcinoma, or any confounding skin condition
	• Known dihydropyrimidine dehydrogenase deficiency
	• Activities involving excessive or prolonged exposure to sunlight
	• Treatment as follows:
	  • within the last 6 months with 5-fluorouracil or systemic cancer chemotherapy
	  • within 2 months with systemic steroids
	  • within 1 month with topical corticosteroids, tretinoin, or other topical actinic keratosis treatment

Loven 2002 *(Continued)*

	Demographics • 21 participants • 17 men, 4 women • Age: mean = 70
Interventions	**Intervention** A: 0.5% 5-fluorouracil on either side of face, once daily for 4 weeks. Sunscreen/moisturiser was provided when needed (N = 21 participants). **Control intervention** B: 5% 5-fluorouracil on either side of face, twice daily for 4 weeks. Sunscreen/moisturiser was provided when needed (N = 21 participants).
Outcomes	**Primary outcomes of the trial** 1) Absolute and per cent of mean reduction in lesion counts at week 8 2) Total clearance (= participant complete clearance) rates at week 8 **Other outcomes of the trial** 1) Facial irritation (= skin irritation) 2) Eye irritation (= minor adverse events) 3) Serious adverse events including basal cell carcinoma 4) Participant preference Efficacy Methods: quantitative assessment using counting of palpable or visible (to the unaided eye) lesions by a designated blinded evaluator Time points: during screening period and at 4 weeks post-treatment Safety Methods: 1. participant-reported adverse events, 2. photography and evaluation of facial irritation (erythema, edema, dryness, pain, erosion, burning, pruritus, and other signs) on a scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) by the same blinded individual and recording of days of onset and resolution (adverse events that occurred on the head were included in the assessment of facial irritation.) Time points: at baseline and weekly throughout the 4-week treatment (twice weekly for facial irritation) and the post-treatment periods
Funding	-
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation list was used.

Loven 2002 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and clinic staff were not blinded to the difference in dosing regimens (once versus twice daily).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was evaluator blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intraindividual study: Intervention - A: 1 dropout (the reason was reported) Control - B: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	High risk	Only estimates on clearance rates were provided, i.e. exact values were not given and standard deviations for absolute and per cent mean values were not provided.
Other bias	Unclear risk	-

McEwan 1997

Methods	This was a single-centre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: September 1994 End date: January 1996
Participants	**Inclusion criteria of the trial** • Age 21 years and older • Mentally competent • Anatomical locations: face, scalp, ear, neck, lower arm/elbow, hand, lower leg/knee • ≥ 1 actinic keratoses **Exclusion criteria of the trial** • Systemic corticosteroids, retinoids, antineoplastic drugs or cyclosporine • Allergy to the sunscreen preparation (SunSense), diclofenac, or other NSAID • Abnormal blood counts, liver function, urea, or electrolytes • Currently or recently involved in another clinical trial • Women were required to be postmenopausal, sterilised, or taking adequate contraceptive precautions **Demographics** • 130 participants • 73 men, 57 women • Age: range = 48 to 87
Interventions	**Intervention**

McEwan 1997 *(Continued)*

	A: 3% diclofenac in 2.5% hyaluronic acid gel, applied to single keratosis twice daily for 8 to 24 weeks. Sunscreen was applied after morning application (N = 65 participants). **Control intervention** B: 2.5% hyaluronic acid gel alone, applied to single keratosis twice daily for 8 to 24 weeks. Sunscreen was applied after morning application (N = 65 participants).
Outcomes	**Primary outcome of the trial** 1) Response to treatment (including participant complete response) rates at end of treatment **Other outcomes of the trial** 1) Local adverse reactions 2) Serious adverse events Safety Methods: diary recording of any adverse effects and any change in use of concomitant medications Time points: at 8, 16, and 24 weeks
Funding	This study was supported by Hyal Pharmaceutical Australia Ltd.
Notes	There was no follow-up period. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A permuted block randomisation design of size 10 was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants, the investigator, and the data managers were kept "blind" as to the treatment until all assessments and data entry had been completed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The participants, the investigator, and the data managers were kept "blind" as to the treatment until all assessments and data entry had been completed.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 31 participants did not complete the 24-week treatment (the reasons were reported) Control - B: 16 participants did not complete the 24-week treatment (the reasons were reported), and 29 completed. There was no information given for 20 participants. There were also inconsistency between data presented in a table and the description in the text.
Selective reporting (reporting bias)	Unclear risk	-
Other bias	High risk	End of treatment varied as participants ceased treatment at varying times. 34% (diclofenac) and 20% (hyaluronic acid) of participants ceased the treat-

McEwan 1997 *(Continued)*

	ment before 8 weeks. Between 8 and 16 weeks, 11% (diclofenac) and 5% (hyaluronic acid) of participants ceased the treatment. Between 16 and 24 weeks, 55% (diclofenac) and 75% (hyaluronic acid) of participants ceased the treatment.

Misiewicz 1991

Methods	This was a randomised, double-blind, active-controlled, intraindividual study. Start date: January 1988 End date: June 1988
Participants	**Inclusion criteria of the trial** • Anatomical location: face • ≥ 3 actinic keratoses on each face side **Demographics** • 26 participants • 17 men, 9 women • Age: range = 55 to 88
Interventions	**Intervention** A: 0.05% (0.5 g) Ro14-9706 cream (arotinoid methyl sulfone) applied to 1 side of the face twice daily (N = 26 participants) **Control intervention** B: 0.05% tretinoin cream applied to 1 side of the face twice daily (N = 26 participants)
Outcomes	**Outcomes of the trial** 1) Participant overall response (= global improvement indices) rates at 16 weeks 2) Mean per cent decrease in the number of lesions (= mean percentage of reduction in lesion counts) at 16 weeks 3) Clinical laboratory tests 4) Tolerability (erythema and scaling) scoring 5) Increase of lesions during treatment 6) Rest periods Efficacy Methods: 1. quantitative assessment using lesion counting by 2 independent investigators, 2. qualitative assessment using photography of the treated areas Time points: 1. at the beginning of the study and weekly intervals (counting), 2. at baseline and after 4, 8, 12, and 16 weeks (photography) Definitions: healed or completely cleared lesion (the site had been replaced by normal, smooth, hypopigmented or hyperpigmented skin, and lesion not palpable) Definitions for overall response: 1. worsening (increase in the number of lesions), 2. no response (no change or less than 50% reduction in the total number of lesions), 3. partial response (reduction

Misiewicz 1991 *(Continued)*

	greater than 50%, but less than 100%, in the number of lesions), 4. complete response (total clearing of lesions) Safety Methods: 1. assessment of local tolerability (erythema and scaling) on a scale (in case of severe reactions, therapy was interrupted until the inflammation had disappeared), 2. routine laboratory (hematologic and biochemical) tests Time points: 1. weekly, 2. before and after treatment (laboratory tests) Definitions for tolerability scale: 0 (none), 1 (mild, minimal), 2 (moderate, more intense), and 3 (severe, very intense erythema, and scaling with exudation)
Funding	This study was supported by La Roche Ltd.
Notes	Ro 14-9706 had better tolerability. An initial increase in the number of visible actinic keratoses with tretinoin was observed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 448): "The study was randomised, double-blind, with each agent applied to opposite sides of the patient's face at a 0.05% concentration, for a period of 16 weeks." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessment was performed by 2 independent investigators.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol (PP) analysis was used. Intraindividual study: Intervention - A: 1 dropout (the reason was not reported) Control - B: 1 dropout (the reason was not reported)
Selective reporting (reporting bias)	Low risk	Negative (tolerability) data for the sponsored product were reported.
Other bias	Unclear risk	-

Moloney 2007

Methods	This was a single centre, randomised, double-blind, active-controlled, intraindividual study.

Moloney 2007 *(Continued)*

	The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • White men • Anatomical location: scalp • Extensive actinic keratoses for field-directed treatment, grade 1 to 3 (pretreated with white paraffin) **Demographics** • 16 men • Age: mean = 71; range = 59 to 87
Interventions	**Intervention** A: aminolevulinic acid (ALA)-photodynamic therapy (PDT) (N = 16 participants) **Control intervention** B: methyl aminolevulinate (MAL)-PDT (N = 16 participants) There was a 2-week interval between the 2 treatments (right versus left scalp). Characteristics of PDT intervention: Type of treatment: field-directed treatment Number of treatments: 1 Interval between treatments: -- Preparation of lesions: hyperkeratotic lesions were treated with white paraffin gel to remove any keratotic debris Cream concentration (%): 20% Application of cream: visible layer Incubation with cream: occlusive dressing over cream for 3 (MAL) or 5 (ALA) hours Type of light: red light Light source: Waldmann PDT lamp MSR 1200 Wavelength (nm): 580-740 Energy fluence (J/cm^2): 50 Intensities (mW/cm^2): 50 Exposure time: 16 minutes 40 seconds
Outcomes	**Outcomes of the trial** 1) Field complete clearance (= participant complete clearance) rates at 1 month post-treatment 2) Mean number of lesions at baseline and at 1 month post-treatment 3) Mean reduction in lesion counts at 1 month post-treatment 4) Minor adverse events (qualitative) 5) Visual analogue score (VAS) for pain 6) Duration of discomfort

Moloney 2007 *(Continued)*

	7) Participant preference Efficacy Methods: 1. grading of PpIX fluorescence on a scale of 1 to 3 using a Wood's light (1 = light/pale; 2 = moderate; and 3 = strong), 2. clinical response (clear, improved, or no response, and number of residual palpable lesions) assessed by an investigator not involved in safety assessment Time points: 1. before treatment (fluorescence), 2. at baseline and 1 month post-treatment Safety Methods: 1. assessment of pain using a VAS (1 to 100 mm) (If treatment had to be discontinued because of pain, the timing of this was recorded), 2. documentation of adverse effects, and 3. assessment of erythema and erosions by 1 investigator Time points: 1. at 3, 6, 12, and 16 minutes during treatment (pain), 2. 4 days after their first and second treatments (erythema and erosion)
Funding	-
Notes	ALA-PDT was more painful than MAL-PDT.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 88): "Patients were randomised so that half would receive ALA and half MAL as their first split scalp treatment." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 88): "Both patients and investigators remained blinded until study completion."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessment was performed by a second investigator.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol (PP) analysis. Intraindividual study: Intervention - A: 1 dropout (the reason was reported) Control - B: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	High risk	Wood's light was used to look at PpIX fluorescence after cream incubation, but the results were not mentioned.
Other bias	Unclear risk	-

Moloney 2010

Methods	This was a randomised, double-blind, placebo-controlled, parallel-group study. Start date: March 2008 End date: Not available
Participants	**Inclusion criteria of the trial** • Immununocompetent adults • Aged 18 years and older • Anatomical locations: face, scalp, upper limbs • ≥ 4 non-hyperkeratotic actinic keratoses • Symmetrically distributed non-hyperkeratotic actinic keratoses • Grade I (palpable only) or II (visible and palpable) **Exclusion criteria of the trial** • Treatment for actinic keratoses within 1 month • Pregnant or lactating • Taking immunosuppressive or photosensitising medications • Taking nicotinamide or other vitamin supplements • Participants unable to attend for regular follow up • Participants with active dermatitis in the treatment areas • Grade III (thicker hyperkeratotic) **Demographics** • 30 participants • 26 men, 4 women • Age: mean = 74; range = 48 to 89
Interventions	**Intervention** A: 1% nicotinamide, twice daily for 6 months (information from the protocol) (N = 13 participants) **Control intervention** B: placebo, twice daily for 6 months (information from the protocol) (N = 17 participants)
Outcomes	**Primary outcome of the trial** 1) Mean percentage of reduction in lesion counts from baseline at 3 and 6 months **Secondary outcome of the trial** 1) Total count for appearance of new/subclinical lesions at 3 months (protocol) **Other outcome of the trial** 1) Serious adverse events including basal cell carcinoma and squamous cell carcinoma Efficacy Methods: quantitative assessment using counting of lesions by a single observer and photography Safety Methods: reporting of all adverse events
Funding	This study was supported by Cancer Council NSW, the Dermatology Research Foundation and Epiderm.

Moloney 2010 *(Continued)*

Notes	This was a pilot study. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1138): "Participants were randomised (unstratified, size six randomised block)."
Allocation concealment (selection bias)	Low risk	Allocation was concealed within sealed opaque envelopes (protocol).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1138): "Patients and observers (F.M., M.V.) remained blinded until all patients had completed the study."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 1138): "Patients and observers (F.M., M.V.) remained blinded until all patients had completed the study."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	It was unclear if intention-to-treat (ITT) or per-protocol (PP) analysis was used, but ITT was stated in the protocol. Intervention - A: 0 dropouts Control - B: 2 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	Appearance of new/subclinical lesions was not reported, but this outcome was included in the protocol ACTRN12607000428460 at anzctr.org.au.
Other bias	Unclear risk	-

Moriarty 1982

Methods	This was a randomised, double-blind, placebo-controlled, cross-over study (2-part study). The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Histologically-proven actinic keratoses • Anatomical locations: not specified **Demographics** • 50 participants [28 had a history of skin carcinoma, 8 had previously been treated for skin keratoses, 2 had other tumours (breast, parotid), and 7 had concurrent hypertension] • 36 men, 14 women • Age: mean = 71; range = 50 to 85
Interventions	**Intervention** A: etretinate, 75 mg/day (25 mg tablet 3 times daily) for 2 months (N = 25 participants) **Control intervention** B: placebo. 3 times daily for 2 months (N = 25 participants)

Moriarty 1982 *(Continued)*

	Then treatment changes for 2 more months (placebo group gets etretinate, and vice versa)
Outcomes	**Outcomes of the trial** Part 1 1) Complete remission (= participant complete clearance) rates 2) Partial remission (50% size reduction of 75% of lesions) rates 3) Clinical laboratory tests Part 2 (alternate therapy given to each group) 1) Complete remission 2) Partial remission rates 3) Clinical laboratory tests 4) Minor adverse events (for the 2 phases) Efficacy Methods: quantitative assessment using direct measurement and photography of the lesions Time points: every month Safety Methods: 1. haematological and biochemical screen, 2. measurement of plasma vitamin A
Funding	-
Notes	17 participants required dosage reduction due to toxicity. Response was maintained when dosage was reduced. Vitamin A type unwanted effects (dry mouth, skin rash, desquamation, etc) were observed. Only part 1 data has been included in this review. Data for intention-to-treat analysis was used for meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (pages 364 to 365): "Each treatment was given for 2 months and the order of administration was randomised." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias)	High risk	Per-protocol (PP) analysis was used. Intervention - A: 3 dropouts (the reasons were not reported)

Moriarty 1982 *(Continued)*

All outcomes		Control - B: 2 dropouts (the reasons were not reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Morton 2006

Methods	This was a multicentre, randomised, open-label, active-controlled, intraindividual study. Start date: March 2004 End date: April 2005
Participants	**Inclusion criteria of the trial** • Clinical diagnosis of non-hyperkeratotic actinic keratosis • Men and women, • Age 18 years and older (16 years and older in Scotland) • Anatomical locations: face and scalp • ≥ 3 actinic keratoses on each sides of the face and no more than 2 2-fold differences between the 2 sides **Exclusion criteria of the trial** • Topical treatment within 3 months • Regular UV therapy • Thick or pigmented lesions in the target area • Porphyria • Pregnancy and no appropriate birth control **Demographics** • 119 participants • 108 men, 11 women • Age: mean = 75; range = 53 to 93
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic (PDT) (N = 119 participants) **Control intervention** B: cryotherapy: double freeze-thaw (16 seconds total) using liquid nitrogen spray, lesions with non-complete response were retreated at 12 weeks 1 (assessment at 12 weeks) or 2 treatments (assessment at 24 weeks) (N = 119 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 or 2 Interval between treatments: 12 weeks Preparation of lesions: gentle scraping

Morton 2006 *(Continued)*

	Cream concentration (%): 16% Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light LED Light source: AktiliteCL 128 Wavelength (nm): 630 Energy fluence (J/cm^2): 37 Intensities (mW/cm^2): -- Exposure time: 8 to 10 minutes
Outcomes	**Primary outcomes of the trial** 1) Lesion complete response rates of baseline lesions only at 24 weeks 2) Participant preference **Secondary outcomes of the trial** 1) Lesion complete response rates of baseline lesions only at 12 weeks 2) Cosmetic outcomes by investigator at 12 and 24 weeks 3) Investigator preference **Other outcomes of the trial** 1) Mean per cent reduction in lesion counts from baseline at 12 and 24 weeks 2) Skin-related adverse events 3) Skin discomfort and pain after first or second treatments on a visual analogue scale (VAS) Efficacy Methods: quantitative assessment using lesion counting [efficacy evaluations included only lesions present at baseline (i.e. lesions appearing after baseline, if any, were to be reported as adverse events)] Time points: at baseline, and at weeks 12 and 24 Definitions: 1. complete response (complete disappearance of the lesion), 2. non-complete response (incomplete disappearance) Safety Methods: 1. immediate evaluation of skin discomfort by participant after each procedure using a VAS of 0 (no discomfort) to 10 (worst possible skin discomfort), 2. adverse events reported spontaneously by the participant or elicited following non-leading questioning (severity, duration, and need for additional therapy) (If pain was the only reaction and concomitant treatment was not needed, it was not reported as an adverse event, as it was already recorded as skin discomfort) Time points: at each visit (adverse events) Definitions: 1. phototoxic reaction (any observed erythema, oedema, itching, etc), 2. cryotherapy reaction (any observed blisters, infection, etc) Cosmetic Methods: assessment of the overall cosmetic outcome Time points: at weeks 12 and 24

Morton 2006 *(Continued)*

	Definitions: 1. excellent (only slight occurrence of redness or change in pigmentation), 2. good (moderate redness or change in pigmentation), 3. fair (slight to moderate scarring, atrophy, or induration), 4. poor (extensive scarring, atrophy, or induration)
Funding	This study was supported by Galderma France.
Notes	The treatments were comparable in terms of efficacy; however, participants significantly preferred MAL-PDT over cryotherapy. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1030): "At baseline visit, eligible subjects received treatment with PDT using MAL... and conventional cryotherapy, randomly allocated to alternate sides of the face/scalp." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was open because 2 physically distinct treatments were compared.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was open because 2 physically distinct treatments were compared.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocl (PP) and intention-to-treat (ITT) analyses were used. Intraindividual study: Intervention - A: 6 dropouts (the reasons were reported) Control - B: 6 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	Standard deviations for the mean percentages of reduction in lesion counts were not provided.
Other bias	Unclear risk	-

NCT00774787

Methods	This was a randomised, assessor-blinded, active-controlled, intraindividual study. Start date: October 2008 End date: September 2009
Participants	**Inclusion criteria of the trial** • A clinical diagnosis of actinic keratoses • Men and women

NCT00774787 *(Continued)*

- Aged 18 years and older
- Able to comply with all study requirements
- Anatomical locations: face or balding scalp
- Actinic keratoses in 2 reasonably bilaterally symmetric areas: each area with a minimum of 25 cm^2 and a maximum of 50 cm^2 each; area with at least 6 typical, non-hypertrophic target actinic keratoses with target lesion counts of +/- 1 lesion between the areas; each area that the participant can distinguish with respect to study drug application

Exclusion criteria of the trial

- Uncontrolled intercurrent or chronic illness
- Systemic immunocompromised due to disease or treatment
- Clinically relevant systemic autoimmune disease
- Pregnant or nursing
- Dermatologic disease, or condition in the treatment area that may be exacerbated by imiquimod or cause difficulty with examination, or both
- Participation in another clinical study
- Allergies to imiquimod or any of the excipients in the cream
- Treatment as follows:
  * within the past 90 days with psoralens plus ultraviolet A therapy, ultraviolet B therapy, systemic immunomodulators (e.g. oral or parenteral corticosteroids at greater than physiologic doses, interferons, anti-TNF agents, cytokines), chemotherapeutic or cytotoxic agents, or investigational agent
  * within the past 30 days with surgical excision, photodynamic therapy, curettage, topical corticosteroids, laser, dermabrasion, chemical peel, imiquimod 5% cream, topical retinoids, 5-fluorouracil, masoprocol, pimecrolimus, or tacrolimus

Demographics

- 27 participants
- 26 men, 1 women
- Age: mean = 68

Interventions

Intervention

A: cryotherapy followed by 5% imiquimod 3 times per week for 4 weeks (N = 27 participants)

Control intervention

B: cryotherapy (N = 27 participants)

Outcomes

Primary outcome of the trial

1) Mean percentage of reduction in lesion counts at 4 to 8 weeks post-treatment

Secondary outcome of the trial

1) Cosmetic appearance scores by participant and investigator at 4 to 8 weeks post-treatment

Other outcomes of the trial

1) Participant complete clearance rates at 4 to 8 weeks post-treatment (posthoc analysis)

2) Local skin reactions (severity scores)

3) Minor adverse events (pooled)

4) Serious adverse events

Efficacy

NCT00774787 *(Continued)*

Methods: quantitative assessment using counting of all (baseline and new) actinic keratoses in each respective treatment area

Time points: at baseline and 4 to 8 weeks post-treatment

Definitions: 1. per cent change = [(actinic keratoses count at 4 to 8 weeks post-treatment)-(actinic keratoses count at baseline)]/(actinic keratoses count at baseline)]*100%, 2. complete clearance (actinic keratosis count of 0)

Safety

Methods: 1. mean maximum postbaseline intensity of investigator-assessed local skin reactions (erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, erosion/ulceration) scored as 0 = none, 1 = mild, 2 = moderate, 3 = severe per treatment area; 2. serious adverse events; 3. adverse events collected by non-systematic assessment

Time points: postbaseline to the end of study

Cosmetic

Methods: Cosmetic appearance score based on comparison to appearance at baseline by investigator and participant

Time points: at 4 to 8 weeks post-treatment

Definitions for 7-point scale: +3 (treatment area is much better appearing), +2 (treatment area is moderately better appearing), + 1 (treatment area is slightly better appearing), 0 (treatment area appears same), -1 (treatment area is slightly worse appearing), -2 (treatment area is moderately worse appearing), and -3 (treatment area is much worse appearing)

Funding	-
Notes	Local skin reactions were reported as scores, but their values were similar between the imiquimod-treated and topical untreated sides.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1 of study data document): "Study design: Allocation: Randomised..." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was single-blinded (assessor).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was single-blinded (assessor).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis for participant complete clearance and per-protocol (PP) analysis for other analyses were used. Intraindividual study:

NCT00774787 *(Continued)*

		Intervention - A: 1 dropout (the reason was reported) Control - B: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	High risk	A "favourable" efficacy outcome was analysed posthoc, whereas the prespecified outcome was not favourable.
Other bias	Unclear risk	-

NCT00828568 Aldara

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: June 2008 End date: May 2009

Participants	**Inclusion criteria of the trial**
	
	• Men and women
	• Aged 18 years and older
	• Participants must have 4 to 8 clinically diagnosed, non-hyperkeratotic, non-hypertrophic actinic keratosis lesions within a 25 cm^2 contiguous treatment area
	• Anatomical locations: face or balding scalp
	• Women either must be 1-year postmenopausal, surgically sterile, or agree to use a medically-accepted form or birth control
	• Free of any systemic or dermatological disorder
	• Any skin type or race, providing the skin pigmentation will allow discernment of erythema
	
	Exclusion criteria of the trial
	
	• Basal cell or squamous cell carcinoma, or other possible confounding skin conditions (on face and scalp)
	• History of cutaneous hyperreactivity or facial irritation to topical products
	• Engaging in activities involving excessive or prolonged exposure to sunlight
	• Treatment as follows:
	  * within 6 months with systemic cancer chemotherapy, psoralen plus UVA therapy, UVB therapy, laser abrasion, dermabrasion, glycolic acids, or chemical peels
	  * within 2 months with systemic steroids; within 28 days with over-the-counter retinol products, corticosteroids, cryosurgery, curettage, 5-fluorouracil, or other topical actinic keratosis treatments on the treatment area
	• Pregnant or nursing mothers
	• History of allergy or sensitivity to imiquimod or related compounds or other components of the formulation
	• Taking immunosuppressant medication
	
	Demographics
	
	• 422 participants
	• 347 men, 75 women
	• Age: mean = 67

Interventions	**Intervention** A: 5% imiquimod (Taro), once per day, twice weekly for 16 weeks (N = 183 participants) **Control intervention**

NCT00828568 Aldara *(Continued)*

	B: vehicle, once per day, twice weekly for 16 weeks (N = 30 participants)
Outcomes	**Primary outcome of the trial** 1) Number of participants with 100% clearance of lesions (= participant complete clearance) at week 24 **Secondary outcome of the trial** 1) Participants experiencing at least 1 adverse event **Other outcomes of the trial** 1) Application site reactions including irritation 2) Minor adverse events 3) Serious adverse events including squamous cell carcinoma Efficacy Methods: quantitative assessment using lesion counting Time points: at baseline and week 24 Definitions: the participant is 100% clear of lesions (all lesions that were identified at baseline are no longer present, and there are no new lesions) Safety Methods: reporting of adverse events and serious adverse events termed from Medical Dictionary for Regulatory Activities (MedDRA) Time points: at each follow-up visit
Funding	This study was supported by Taro Pharmaceuticals USA.
Notes	This was an equivalence study and was divided into 2 studies for our review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1 of study data document): "Study design: Allocation: Randomised..." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded (subject, caregiver, investigator).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded (outcomes assessor).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocol (PP) and modified (no postbaseline assessment but received treatment) intention-to-treat (ITT) analyses were used.

NCT00828568 Aldara *(Continued)*

		Intervention - A: 31 dropouts (the reasons were reported) Control - B: 7 dropouts of the entire group, i.e. 60 participants (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

NCT00828568 Taro

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: June 2008 End date: May 2009
Participants	**Inclusion criteria of the trial** • Men and women • Aged 18 years and older • Participants must have 4 to 8 clinically diagnosed, non-hyperkeratotic, non-hypertrophic actinic keratosis lesions within a 25 cm^2 contiguous treatment area • Anatomical locations: face or balding scalp • Women either must be 1 year postmenopausal, surgically sterile, or agree to use a medically accepted form or birth control • Free of any systemic or dermatological disorder • Any skin type or race, providing the skin pigmentation will allow discernment of erythema **Exclusion criteria of the trial** • Basal cell or squamous cell carcinoma, or other possible confounding skin conditions (on face and scalp) • History of cutaneous hyperreactivity or facial irritation to topical products • Engaging in activities involving excessive or prolonged exposure to sunlight • Treatment as follows: * within the last 6 months with systemic cancer chemotherapy, psoralen plus UVA therapy, UVB therapy, laser abrasion, dermabrasion, glycolic acids, or chemical peels * within 2 months with systemic steroids * within 28 days with over-the-counter retinol products, corticosteroids, cryosurgery, curettage, 5-fluorouracil, or other topical actinic keratosis treatments on the treatment area • Pregnant or nursing mothers • History of allergy or sensitivity to imiquimod or related compounds or other components of the formulation • Taking immunosuppressant medication • History of allergy or sensitivity to imiquimod or related compounds or other components of the formulation • Taking immunosuppressant medication **Demographics** • 422 participants • 347 men, 75 women • Age: mean = 67

NCT00828568 Taro *(Continued)*

Interventions	**Intervention** A: 5% imiquimod (Aldara), once per day, twice weekly for 16 weeks (N = 179 participants) **Control intervention** B: vehicle, once per day, twice weekly for 16 weeks (N = 30 participants)
Outcomes	**Primary outcome of the trial** 1) Number of participants with 100% clearance of lesions (= participant complete clearance) at week 24 **Secondary outcome of the trial** 1) Participants experiencing at least 1 adverse event **Other outcomes of the trial** 1) Application site reactions including irritation 2) Minor adverse events 3) Serious adverse events including squamous cell carcinoma Efficacy Methods: quantitative assessment using lesion counting Time points: at baseline and week 24 Definitions: the participant is 100% clear of lesions (all lesions that were identified at baseline are no longer present, and there are no new lesions) Safety Methods: reporting of adverse events and serious adverse events termed from Medical Dictionary for Regulatory Activities (MedDRA) Time points: at each follow-up visit
Funding	This study was supported by Taro Pharmaceuticals USA.
Notes	This was an equivalence study and was divided into 2 studies for our review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1 of study data document): "Study design: Allocation: Randomised..." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded (subject, caregiver, investigator).

NCT00828568 Taro *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded (outcomes assessor).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocol (PP) and modified (no postbaseline assessment but received treatment) Intention-to-treat (ITT) analyses were used. Intervention - A: 29 dropouts (the reasons were reported) Control - B: 7 dropouts of the entire group, i.e. 60 participants (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Olsen 1991

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	• White men and women
	• General good health
	• Between 18 and 85 years old
	• Anatomical locations: head and neck
	• ≥ 5 actinic keratoses, at least 5 mm in diameter
	Exclusion criteria of the trial
	• Treatment as follows:
	  * within the last 2 weeks with topical steroids or topical antimicrobials
	  * within 1 month with systemic steroids
	  * within 2 months with tretinoin
	  * within 6 months with topical 5-fluorouracil, systemic chemotherapy
	• Ever used isotretinoin or etretinate
	• Skin cancer
	Demographics
	• 176 participants
	• 129 evaluable men, 25 evaluable women
	• Age: 18 to 85

Interventions	**Intervention** A: 10% masoprocol cream applied twice daily for 14 to 28 days (N = 131 participants) **Control intervention** B: placebo applied twice daily for 14 to 28 days (N = 45 participants)
Outcomes	1) Investigator global assessment (global improvement indices-cured) at 1 month post-treatment

Olsen 1991 *(Continued)*

	2) Mean reduction in lesion counts 3) Median percentage reduction in lesion counts between baseline and 1 month post-treatment 4) Skin irritation Efficacy Methods: 1. quantitative assessment by counting all actinic keratoses in the test area, 2. qualitative assessment (global assessment) Time points: at baseline and 1 month post-treatment Definitions: evaluable (participant who completed at least 14 days of therapy and returned for the follow-up visit 1 month after the drug was stopped) Definitions for global assessment: 1. cured (clear of palpable lesions, slight residual erythema may remain), 2. marked improvement (majority of lesions absent and scales of remaining lesions are barely palpable), 3. moderate improvement (many lesions are now absent and scales have decreased in thickness), 4. slight improvement (some lesions cleared, some decreased in scale, but many lesions remain), 5. no change, 6. slightly worse (more or rougher, larger lesions, or both, remain), and 7. much worse (significantly more lesions or majority of lesions rougher, larger, or both) Safety Methods: clinical assessment and participant history Time points: at each visit (weekly during treatment)
Funding	This study was supported by Chemex Pharmaceuticals, Denver.
Notes	Inflammatory response was not essential for therapeutic activity of masoprocol. The percentage of reduction in lesion counts did not correlate with baseline lesion severity.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 739): "Patients were randomly assigned to treatment with topical masoprocol or vehicle in a 3:1 ratio, respectively." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used, and there was a difference in the percentages of participant lost between treatment (14%) and placebo (9%). Intervention - A: 18 dropouts (the reasons were reported) Control - B: 4 dropouts (the reasons were reported)

Olsen 1991 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	-
Other bias	High risk	25 participants stopped treatment between 14 & 28 days due to adverse reactions, but it was stated that their results were comparable to those who completed the full 28 days of treatment.

Ooi 2006

Methods	This was a single-centre, randomised, double-blind, vehicle-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Histologically-confirmed clinical diagnosis • Aged 18 years and older • Anatomical locations: scalp, extremities, or upper trunk • 6 to 15 actinic keratoses suitable for biopsy **Demographics** • 18 participants • 15 men, 3 women • Age: mean = 68
Interventions	**Intervention** A: 5% imiquimod, applied to 5 lesions, once per day 3 times per week for up to 16 weeks, biopsy of 1 lesion after 2 weeks of treatment (N = 12 participants) **Control intervention** B: vehicle, applied to 5 lesions, once per day 3 times per week for up to 16 weeks, biopsy of 1 lesion after 2 weeks of treatment (N = 6 participants)
Outcomes	**Primary outcome of the trial** 1) Immunological outcome **Other outcomes of the trial** 1) Participant complete clearance rates at the end of treatment 2) Clearance rates 3) Percentage lesion reduction (proportion of baseline lesions cleared at end of treatment = lesion complete response) rates 4) Clinical laboratory tests 5) Application site reactions 6) Local skin reactions 7) Minor adverse events 8) Serious adverse events Efficacy

Ooi 2006 *(Continued)*

	Time points: at the end-of-treatment visit Definitions: 1. clearance (clinical resolution of ≥ 50% of the 4 treated, non-biopsied lesions), 2. complete clearance rate (proportion of participants with 100% clinical clearance of treated lesions) Safety Methods: 1. laboratory tests, 2. recording of local skin reactions and adverse events Time points: pre-study and end of treatment (laboratory tests)
Funding	This study was supported by 3M Pharmaceuticals.
Notes	This was a phase I study, mainly on cutaneous immune response (biomarker changes).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation schedule was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol (PP) analysis was used. Intervention - A: 1 dropout (the reason was reported) Control - B: 0 dropouts
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Ortonne 2010

Methods	This was a randomised, double-blind, vehicle-controlled, parallel-group study. Start date: February 2006 End date: January 2007
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Men and women • Aged 18 years and older

Ortonne 2010 *(Continued)*

- Anatomical locations: head (balding scalp or face, but not both)
- ≥ 5 actinic keratoses, non-hyperkeratotic, non-hypertophic lesions within 20 cm^2 area

Demographics

- 12 participants
- Age: mean = 66

Interventions	**Intervention** A: 5% imiquimod, once per day, 3 times per week, 4 weeks on, 4 weeks off, 4 weeks on (N = 9 participants) **Control intervention** B: vehicle, once per day, 3 times per week, 4 weeks on, 4 weeks off, 4 weeks on (N = 3 participants)
Outcomes	**Primary outcome of the trial** 1) Comparison of evaluation techniques **Secondary outcome of the trial** 1) Histological clearance (confirmation) **Other outcomes of the trial** 1) Mean lesion counts at baseline and week 20 (transformed to mean reduction in lesion counts) 2) New/sub-clinical lesions during the study 3) Minor adverse events (pooled) Efficacy Methods: quantitative assessment using clinical counting Time points: at baseline and weeks 4, 8, 12, and 20 Safety Methods: 1. general physical examination, 2. recording of any adverse events Time points: 1. at the start and end of the study (physical exam), 2. at each visit (adverse events)
Funding	This study was supported by 3M Pharmaceuticals.
Notes	This was a pilot study. Cross polarised light photography, fluorescence diagnostic, and clinical lesion counting were used for efficacy analysis, but only data obtained with clinical counting were used for analyses because it was the technique used in the other studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 641): "Eligible patients were randomised in a 3:1 ratio (active:vehicle) to either imiquimod or vehicle cream." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.

Ortonne 2010 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropouts Control - B: 0 dropouts
Selective reporting (reporting bias)	Low risk	All outcomes in the protocol (NCT00294320) were reported in the published study.
Other bias	Unclear risk	-

Ostertag 2006

Methods	This was a single-centre, randomised, double-blind, active-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Histologically-confirmed clinical diagnosis • Anatomical locations: face, scalp, or both • Widespread actinic keratoses **Exclusion criteria of the trial** • Participants with age above 85 years • Life-expectation less than 3 years • Bad general health • Former total skin treatment with laser or dermabrasion • Untreated facial skin cancer **Demographics** • 55 participants • 50 men, 5 women • Age: mean = 72; range = 52 to 85
Interventions	**Intervention** A: 5% 5-fluorouracil twice daily for 4 to 7 weeks followed by chlorhexidine cream (N = 27 participants) **Control intervention** B: Er:YAG laser resurfacing with oral prophylactic antibiotics and antivirals, Erbium mode: 7 to 28 J/cm^2, 10 to 12 pulses per second with 50% CO_2 from 2 to 4 W (N = 28 participants)
Outcomes	**Primary outcome of the trial** 1) Recurrence rates according to clinical evaluation at 12 months post-treatment

Ostertag 2006 *(Continued)*

Secondary outcomes of the trial

1) Recurrence rates according to clinical evaluation at 3 and 6 months post-treatment

2) Recurrence rates according to histological evaluation at 3 months and at time of recurrence

Other outcomes of the trial

1) Mean reduction in lesion counts at 3, 6, and 12 months post-treatment

2) Mean per cent lesions cleared (= mean percentage of reduction in lesion counts) at 6 and 12 months post-treatment

3) Skin irritation

4) Minor adverse events after treatment, at 3, 6, and 12 months post-treatment

5) Cosmetic outcome: proportion of participants with improvement of surface with actinic damage

6) Cosmetic outcome: proportion of participants with decrease in photoageing score

7) Cosmetic outcome: number of participants with changes in pigmentation or scarring

Efficacy

Methods: 1. quantitative assessment using clinical evaluation including the number of lesions and the surface of actinic damage (0% to 25%, 25% to 50%, 50% to 75%, and 75% to 100%) performed by 2 investigators, 2. histopathological evaluation (3 months after treatment and evaluation of recurrence)

Time points: at baseline; at 3 days (laser only); at 1 (laser only), 2, and 4 weeks; and at 3, 6, and 12 months post-treatment

Safety

Methods: evaluation of adverse effects

Time points: at day 3 (laser only), at weeks 1 (laser only), 2 and 4 , and at 3, 6, and 12 months post-treatment

Cosmetic

Methods: photoageing score (simplified form of the Glogau score) performed by 2 investigators

Time points: at baseline; at day 3 (laser only); at weeks 1 (laser only), 2, and 4; and at 3, 6, and 12 months post-treatment

Funding	-
Notes	There were significantly less recurrences in the laser group than 5-fluorouracil group. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer program, Sampsize 2.0, was used to generate the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias)	Low risk	This study was double-blinded.

Ostertag 2006 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 2 dropouts (the reasons were reported) Control - B: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	High risk	The standard deviations associated with mean values were not provided.
Other bias	Unclear risk	-

Pariser 2003

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Men and women • Aged 18 years and older • Anatomical locations: face and scalp • 4 to 10 previously-untreated mild (slightly palpable, better felt than seen) to moderate (moderately thick, easily felt and seen) non-pigmented actinic keratoses, at least 3 mm in diameter **Exclusion criteria of the trial** • Immunosuppression for idiopathic disease-specific or therapeutic reasons • Porphyria • Pigmented actinic keratoses • Known allergy to methyl aminolevulinate (MAL) or similar photosensitising agents or excipients • Known hypersensitivity to nut products • Current or prior (within the last 30 days) participation in other clinical studies • Pregnancy; lactation; inadequate contraceptive measures during treatment and 1 month thereafter in women of child-bearing potential • Any conditions that might be associated with a risk of poor protocol compliance **Demographics** • 80 participants • 70 men, 10 women • Age: mean = 66
Interventions	**Intervention** A: MAL-photodynamic therapy (PDT) (N = 42 participants) **Control intervention** B: placebo-PDT (N = 38 participants) Characteristics of PDT intervention:

Pariser 2003 *(Continued)*

	Type of treatment: individual lesions Number of treatments: 2 Interval between treatments: 1 week Preparation of lesions: crusts and scales removed by curettage and gentle scraping Cream concentration (%): 16% Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light Light source: -- Wavelength (nm): 570-670 Energy fluence (J/cm^2): 75 Intensities (mW/cm^2): 50 to 200 Exposure time: 8 min
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at 3 months after last treatment **Other outcomes of the trial** 1) Lesion complete response rates at 3 months after last treatment 2) Local adverse events 3) Minor adverse events 4) Serious adverse events 5) Cosmetic outcome with MAL-PDT in completely cleared participants: physician assessment, participant assessment 6) Participants' satisfaction Efficacy Methods: quantitative assessment using inspection, photography, and palpation of each lesion by the same investigator at each centre Time points: at baseline and at 3 months after the second PDT Definitions: complete response (complete disappearance of the lesion) Safety Methods: 1. recording of local skin reactions, phototoxicity reactions, or both, by study-centre personnel who were not involved in evaluation of the participant, 2. adverse events reported spontaneously by the participant or elicited after non-leading questioning (severity, duration, and need for additional therapy) and rated (the clinician assessed the causal relationship of the event to the study treatment as related, uncertain, or not related) Time points: at baseline, during, and immediately after PDT; at week 2; and at 3 months after the second PDT treatment Definitions for adverse events (any unfavourable and unintended sign, symptom, or disease) rating: 1. mild (the event was transient and easily tolerated), 2. moderate (the event caused the participant dis-

Pariser 2003 *(Continued)*

	comfort and interrupted usual activities), and 3. severe (the event caused considerable interference with usual activities and may have been incapacitating or life-threatening) Cosmetic Methods: assessment of overall cosmetic outcome in participants with complete response in all lesions by both the investigator and participant using a 4-point rating scale Definitions for the 4-point scale: 1. excellent (no scarring, atrophy, or induration, and no or slight occurrence of redness or change in pigmentation compared with adjacent skin), 2. good (no scarring, atrophy, or induration, but moderate redness or change in pigmentation compared with adjacent skin), 3. fair (slight to moderate occurrence of scarring, atrophy, or induration), 4. poor (extensive occurrence of scarring, atrophy, or induration)
Funding	This study was supported by PhotoCure ASA.
Notes	The response rate was similar for mild and moderate lesions. Most pain and erythema was gone within 24 hours. Data for intention-to-treat analysis were used for meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prerandomised numbers assigned to participants at screening visit and stratified per centre were used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Intervention - A: 3 dropouts (the reasons were reported) Control - B: 0 dropouts
Selective reporting (reporting bias)	High risk	The cosmetic outcomes were reported for MAL-PDT participants only.
Other bias	Unclear risk	-

Pariser 2008

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. Start date: January 2006 End date: December 2006
Participants	**Inclusion criteria of the trial**

Pariser 2008 *(Continued)*

- Men and women
- Age 18 years and older
- Anatomical locations: face and scalp
- 4 to 10 lesions, untreated, unpigmented, non-hyperkeratotic, grade 1 or 2, at least 3 mm in diameter

Exclusion criteria of the trial

- Immunosuppression
- Porphyria
- Known allergy to methyl aminolevulinate (MAL) or similar photosensitising agents or excipients
- Known hypersensitivity to nut products or other known protein antigens
- Current or prior (within 30 days) participation in other clinical trials
- Pregnancy, lactation, inadequate contraceptive measures during treatment
- Any condition associated with a risk of poor protocol compliance
- Treatment as follows:
  - within the last 30 days with regular UV radiation therapy, local therapy including cryotherapy and curettage
  - within 3 months with topical therapy including imiquimod, 5-fluorouracil, or diclofenac

Demographics

- 100 participants treated and evaluated for safety, 96 randomised and evaluated for efficacy
- 79 men, 17 women
- Age: mean = 66; range = 43 to 89

Interventions	**Intervention** A: MAL-photodynamic therapy (PDT) (N = 49 participants) **Control intervention** B: placebo-PDT (N = 47 participants) Characteristics of PDT intervention: Type of treatment: individual lesions Number of treatments: 2 Interval between treatments: 1 week Preparation of lesions: crusts and scales removed by curettage and gentle scraping Cream concentration (%): 16.8% Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light LED Light source: Aktilite CL 128 Wavelength (nm): 630 Energy fluence (J/cm^2): 37 Intensities (mW/cm^2): -- Exposure time: 8 min
Outcomes	**Primary outcome of the trial**

Pariser 2008 *(Continued)*

1) Complete participant response rates (= participant complete clearance) at 3 months post-treatment

Secondary outcomes of the trial

1) Complete lesion response rates (= lesion complete response) at 3 months post-treatment

2) Application site and local adverse reactions (in general and severe)

Other outcomes of the trial

1) Serious adverse events

2) New lesions during the study

Efficacy

Methods: clinical assessment by inspection, palpation, and characterisation of lesions (in accordance with Olsen 1991) by the same blinded investigator

Time points: at baseline and 3 months post-treatment

Definitions: 1. complete response (complete disappearance of the lesion), 2. non-complete response (incomplete disappearance of the lesion) (non-completely responding lesions were treated at the discretion of the investigator)

Safety

Methods: adverse events reported spontaneously or elicited by non-leading questioning (severity, localisation, duration, and need for additional treatment) (the clinician assessed the causal relationship of the event to the study treatment as related, uncertain, or not related.)

Time points: after lesion preparation before cream application, at the end of the 3-hour cream application and after illumination during each treatment session, and at 2 weeks and 3 months post-treatment

Definitions for the severity of the adverse events: 1. mild (transient and easily tolerated), 2. moderate (caused the participant's discomfort and interrupted usual activities), 3. severe (caused considerable interference with usual activities and may have been incapacitating or life-threatening)

Funding	This study was supported by PhotoCure ASA.
Notes	Within the MAL-PDT group, complete lesion response rates were slightly higher in grade-1 than grade-2 lesions (89% vs 80%), and in lesions on the scalp than on the face (93% vs 87%). Larger lesions (diameter > 20 mm) had lower complete response rates than smaller lesions (74% vs 86% to 90%). At 3 months post-treatment, 31% (15/49) of participants treated with MAL had new lesions compared to 26% (12/47) of participants treated with vehicle. A sample size calculation was provided. This study is study #1 in the Metvixia product insert 2008. The studies included in the Metvixia product insert were changed between 2004 (PhotoCure) and 2008 (Galderma), which correspond to the use of different types of light.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Prerandomised numbers assigned to participants at screening visit and stratified per centre were used for allocation generation.
Allocation concealment (selection bias)	Low risk	Randomisation sequence was prepared by sponsor.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.

Pariser 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was evaluator-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropout Control - B: 0 dropout
Selective reporting (reporting bias)	Low risk	All outcomes from the protocol (NCT00306800) and protocol mistakes were presented.
Other bias	Unclear risk	-

Perrett 2007

Methods	This was a single centre, randomised, active-controlled, intraindividual study. Start date: May 2004 End date: August 2005
Participants	**Inclusion criteria of the trial** • Organ transplant recipients on chronic immunosuppressive therapy • Histologically-confirmed clinical diagnosis • Anatomical locations: forearm, hand • Several actinic keratoses with 2 equivalent areas (clinically and histologically) **Exclusion criteria of the trial** • No wash-out period of 8 weeks for lesion treatments **Demographics** • 3 kidney transplant recipients and 1 kidney and liver transplant recipient • Forearm (1), hand (3), Fitzpatrick skin phototype 1 or 2 • 3 men, 1 woman • Age; range = 49 to 71
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) (N = 4 participants) **Control intervention** B: 5-fluorouracil twice daily for 3 weeks (N = 4 participants) Characteristics of PDT intervention: Type of treatment: field-directed treatment Number of treatments: 2 Interval between treatments: 1 week Preparation of lesions: scales removed by curettage Cream concentration (%): 16%

Perrett 2007 *(Continued)*

	Application of cream: 1 mm thick onto area Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light Light source: Paterson PDT Omnilux Wavelength (nm): 633 ± 15 Energy fluence (J/cm^2): 75 Intensities (mW/cm^2): 80 Exposure time: 8 min
Outcomes	**Outcomes of the trial** 1) Complete resolution of lesional area (= participant complete clearance) rates at 1, 3, and 6 months 2) Overall reduction in lesional area 3) Local skin reactions (pooled for carcinomas in situ and actinic keratoses) 4) Minor adverse events (pooled for carcinomas in situ and actinic keratoses) 5) Cosmestic outcomes by participant and investigator (pooled for carcinomas in situ and actinic keratoses) 6) Treatment-associated pain score 7) Participant's preference Efficacy Methods: quantitative assessment using photographic mapping, tracing of the clinical margins of each lesional area onto transparencies and calculating the surface area by overlaying on 1 mm squared graph paper Time points: before treatment, at 1, 3, and 6 months post-treatment Definitions: 1. complete response (complete clinical resolution of the treated lesion), 2. partial response (at least a 30% reduction in the surface area of the lesion after treatment based upon the European Organisation for Research and Treatment of Cancer (EORTC) guidelines for the evaluation of tumour treatment response), 3. non-responders (lesions that failed to meet the criteria for partial response) Safety Methods: 1. participants kept a record of pain and erythema using a 4-point scale (0 = none, 1 = mild, 2 = moderate, and 3 = severe); 2. documentation of other local skin reactions, such as pruritus, erosions, ulceration, crusting, skin infection, and scarring Time points: daily Cosmetic Methods: cosmetic scoring by clinician and participant Time points: at the 6-month assessment Definitions: 1. poor (extensive scarring, atrophy, or induration), 2. moderate (slight to moderate occurrence of scarring), 3. good (no scarring, atrophy or induration, but moderate redness or pigmentation change compared with adjacent skin), 4. excellent (no scarring, atrophy, or induration, and no or slight occurrence of redness or pigmentation change compared with adjacent skin)

Perrett 2007 *(Continued)*

Funding	The light source was provided by Omnilux.
Notes	This study with immunocompromised participants included participants with actinic keratoses (N = 4) or carcinoma in situ (N = 5). Separated data were presented for efficacy but not for local skin reactions, adverse events, and cosmetic outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 321): "Each patient was randomly assigned to apply topical 5-FU cream to 1 lesional area twice daily for 3 weeks and to receive topical PDT twice at a 1-week interval to the other lesional area." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote (page 322): "Assessments were not blinded."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used for the review based on the individual data presented in a table. Intraindividual study: Intervention - A: 0 dropouts Control - B: 0 dropouts
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Persaud 2002

Methods	This was a randomised, vehicle-controlled, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Anatomical locations: face, arms, legs • ≥ 6 bilateral discrete, visible, palpable, or both, actinic keratoses **Exclusion criteria of the trial** • Previous treatment with 5-fluorouracil, laser resurfacing, chemical peel, or cryotherapy within 28 days

Persaud 2002 *(Continued)*

- Pregnancy, lactation
- Allergy to imiquimod
- Any condition that may have interfered significantly with participation in the study

Demographics

- 22 participants
- 14 evaluable men, 3 evaluable women
- Age: mean = 72; range = 41 to 90

Interventions	**Intervention** A: 5% Imiquimod, 3 times per week for 8 weeks or less (clearance achieved) (N = 22 participants) **Control intervention** B: vehicle, 3 times per week for 8 weeks or less (clearance achieved) (N = 22 participants)
Outcomes	**Outcomes of the trial** 1) Mean lesion counts (transformed to mean reduction of lesion counts) at baseline and week 16 2) Changes in lesion size 3) Participants experiencing at least 1 adverse event (pooled) 4) Local adverse reactions (pooled) 5) Rest periods Efficacy Methods: quantitative assessment using lesion counting and photography (only participants who completed the 8-week course of treatment with imiquimod were assessed for changes in lesion size) Time points: at baseline; at weeks 2, 4, 6, 8, and 16 Safety Methods: 1. monitoring of concomitant medications, and 2. recording of the type and severity (mild, moderate, or severe) of local adverse reactions (erythema, itching, scabbing) Time points: at baseline; at weeks 2, 4, 6, and 8, or until total clearance of lesions
Funding	This study was supported by 3M Pharmaceuticals.
Notes	If needed, a rest period of 3 weeks was allowed and the dosing frequency reduced to 2 times per week.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 554): "Application sites were randomised at the time of treatment." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.

Persaud 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis with 23% of lost participants was used. Intraindividual study: Intervention - A: 5 dropouts (the reasons were reported) Control - B: 5 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	The adverse events were not reported separately for the 2 treatments. The standard deviations associated with mean values were not provided.
Other bias	Unclear risk	-

Photocure-Australian 2004

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Untreated facial and scalp actinic keratoses, slightly palpable (better felt than seen) • Anatomical locations: face and scalp • Non-hyperkeratotic actinic keratoses (maximum of 6 treatment fields) **Exclusion criteria of the trial** • Hyperkeratotic actinic keratoses **Demographics** • 111 participants • 63% (70/111) of participants had less than 4 lesions at baseline; 31% (34/111) of the enrolled participants had 4 to 10 lesions; and 6% (7/111) had more than 10 lesions at baseline
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) (N = 88 participants) **Control intervention** B: placebo-PDT (N = 23 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 2 Interval between treatments: 1 week

Photocure-Australian 2004 *(Continued)*

	Preparation of lesions: debridement Cream concentration (%): 16.8% Application of cream: onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 2.5 to 4 hours Type of light: red light Light source: CureLight BroadBand Model CureLight 01 Wavelength (nm): 570-670 Energy fluence (J/cm^2): 75 Intensities (mW/cm^2): -- Exposure time: --
Outcomes	**Outcomes of the trial** 1) Complete responders (= participant complete clearance) rates at 3 months 2) Participant partial (≥ 75%) clearance rates at 3 months 3) Lesion complete response rates at 3 months 4) Local adverse reactions 5) Cosmetic outcomes: hyperpigmentation Efficacy Time points: at 3 months after the second treatment session Definitions: 1. cleared lesion (not visible and not palpable), 2. complete responder (participant with all treated lesions cleared)
Funding	This study was supported by Photocure ASA.
Notes	Participants with ≥ 4 lesions had lower success rates than those with < 4 lesions when treated with MAL-PDT. Lesions that were slightly palpable, i.e. grade 1, had a better success rate than lesions that were visible and palpable, i.e. grade 2. Local skin reactions and cosmetic outcomes from Photocure ASA Australian and US studies were combined. The studies included in the Metvixia product insert were changed between 2004 (PhotoCure) and 2008 (Galderma), which correspond to the use of different types of light.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2): "These trials were not identical; however, both were randomised, multicenter, and double-blinded with patients randomised to Metvixia-PDT and Vehicle-PDT study arms that required 2 treatment sessions (7 days apart)." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.

Photocure-Australian 2004 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	This was not stated, and the information provided did not allow to make any conclusion. There was no information provided on study dropouts.
Selective reporting (reporting bias)	High risk	The adverse events were reported for the whole study, i.e. not separated for MAL and vehicle.
Other bias	Unclear risk	-

Photocure-US 2004

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Untreated facial and scalp actinic keratoses, slightly palpable (better felt than seen) • Anatomical locations: face and scalp • Non-hyperkeratotic actinic keratoses (maximum of 6 treatment fields) **Exclusion criteria of the trial** • Hyperkeratotic actinic keratoses **Demographics** • 80 participants • 4 to 10 non-hyperkeratotic actinic keratoses
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) (N = 42 participants) **Control intervention** B: placebo-PDT (N = 38 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 2 Interval between treatments: 1 week Preparation of lesions: debridement Cream concentration (%): 16.8% Application of cream: onto lesion and 5 mm of surrounding normal tissue

Photocure-US 2004 *(Continued)*

	Incubation with cream: occlusive dressing over cream for 2.5 to 4 hours Type of light: red light Light source: CureLight BroadBand Model CureLight 01 Wavelength (nm): 570-670 Energy fluence (J/cm^2): 75 Intensities (mW/cm^2): -- Exposure time: --
Outcomes	**Outcomes of the trial** 1) Complete responders (= participant complete clearance) rates at 3 months 2) Participant partial (≥ 75%) clearance rates at 3 months 3) Lesion complete response rates at 3 months 4) Local adverse reactions 5) Cosmetic outcomes: hyperpigmentation Efficacy Time points: at 3 months after the second treatment session Definitions: 1. cleared lesion (not visible and not palpable), 2. complete responder (participant with all treated lesions cleared)
Funding	This study was supported by Photocure ASA.
Notes	Lesions that were slightly palpable, i.e. grade 1, had a better success rate than lesions that were visible and palpable, i.e. grade 2. Local skin/adverse reactions and cosmetic outcomes from Photocure ASA Australian and US studies were combined. The studies included in the Metvixia product insert were changed between 2004 (PhotoCure) and 2008 (Galderma), which correspond to the use of different types of light.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2): "These trials were not identical; however, both were randomised, multicenter, and double-blinded with patients randomised to Metvixia-PDT and Vehicle-PDT study arms that required 2 treatment sessions (7 days apart)." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	This study was double-blinded.

Photocure-US 2004 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	This was not stated and the information provided did not allow to make any conclusion. There was no information provided on study dropouts.
Selective reporting (reporting bias)	High risk	The adverse events were reported for the whole study, i.e. not separated for MAL and vehicle.
Other bias	Unclear risk	-

Piacquadio 2004

Methods	This was a multicentre, randomised, assessor-blinded, vehicle-controlled, parallel group study. The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	
	• Men and non-pregnant, non-lactating women (postmenopausal, surgically sterile, or using a medically-acceptable form of birth control and had a negative urine pregnancy test result)
	• Aged 18 years and older
	• Anatomical locations: face or scalp
	• 4 to 15 actinic keratoses, grade 1 or 2 lesions
	
	Exclusion criteria of the trial
	
	• History of cutaneous photosensitisation
	• Porphyria
	• Hypersensiticity to porphyrins
	• Photodermatosis
	• Use of photosensitising drugs within a given time-frame
	• Very hyperkeratotic, grade 3
	• Treatment as follows:
	  * within the last 2 weeks with topical medications, such as corticosteroids, α hydroxy acids, or retinoids
	  * within 4 weeks with systemic steroid therapy
	  * within 2 months with cryotherapy of target lesions, laser resurfacing, chemical peels, topical application of 5-fluorouracil or masoprocol; systemic treatment with chemotherapeutic agents, sporalens, immunotherapy, or retinoids
	
	Demographics
	
	• 243 participants
	• 203 men, 40 women
	• Age: range = 34 to 89

Interventions	**Intervention** A: aminolevulinic acid (ALA)-photodynamic therapy (PDT) (N = 181 participants) **Control intervention** B: placebo-PDT (N = 62 participants) Characteristics of PDT intervention

Piacquadio 2004 *(Continued)*

	Type of treatment: individual lesions Number of treatments: 1 or 2 Interval between treatments: 8 weeks Preparation of lesions: -- Cream concentration (%): 20% Application of cream: -- Incubation with cream: 14 to 18 hours Type of light: blue light Light source: Blu-U Wavelength (nm): 417 ± 5 Energy fluence (J/cm^2): 10 Intensities (mW/cm^2): 10 Exposure time: 1000 seconds (16 minutes)
Outcomes	**Outcomes of the trial** Assessments at 8 weeks (1 treatment) and 12 weeks (1 or 2 treatments): 1) Clearing of individual lesions (= lesion complete response) rates 2) Percentage of participants who experienced 100% clearance of all target lesions (= participant complete clearance) 3) Percentage of participants who experienced 75% or greater clearance of all target lesions (= participant partial clearance) 4) Clinical laboratory tests 5) Application site reactions 6) Local skin reactions by location, i.e. face or scalp 7) Treatment-related adverse events (= minor adverse events) given for ALA treatment only 8) Minor adverse events in general and by location, i.e. face or scalp 9) Serious adverse events 10) Changes in pigmentation reported per lesion Efficacy Methods: assessments performed by a blinded investigator Time points: at weeks 4, 8, and 12 Safety Methods: 1. laboratory tests, 2. assessment of phototoxic effects such as erythema, edema, stinging or burning, by an unblinded investigator, 3. assessment of adverse events Time points: 1. at baseline and 24 hours after initial light treatment and at week 8 and 24 hours after retreatment (laboratory tests), 2. every visit (phototoxic effect), 3. before, during, and after treatment and at each visit during the study period (adverse events)

Piacquadio 2004 *(Continued)*

	Cosmetic Methods: assessment of changes in pigmentation by an unblinded investigator Time points: at every visit
Funding	This study was supported by DUSA Pharmaceuticals.
Notes	Pooled results from 2 independent and identical phase III clinical trials also presented in the Levulan kerastick product insert. Recurrence was presented in a follow-up paper (Fowler 2002). Data for intention-to-treat analysis were used for the meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method used for allocation generation is unclear, but it was performed separately for each centre.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote (page 42): "Drug application and activation, light treatment, and all safety evaluations were performed by an unblinded investigator..."
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was assessor-blinded for efficacy, but not for safety. Safety and efficacy assessments were performed by different investigators.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Intervention - A: 7 dropouts (the reasons were reported) Control - B: 3 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	The Levulan kerastick product insert mentioned 7 clinical trials. Efficacy data from only 2 randomised phase III (Piacquadio 2004) and open studies were presented. Only safety data from the 2 phase III studies were presented. Levulan kerastick reported efficacy outcomes separately for the face and scalp, but Piacquadio 2004 did not. Piacquadio 2004 reported adverse events for ALA-PDT, whereas Levulan kerastick reported them for both ALA-PDT and placebo-PDT.
Other bias	High risk	Data between Piacquadio 2004 (PP) and the Levulan kerastick (ITT?) product insert was not always the same. Data from Piacquadio 2004 was used for analyses.

Rivers 2002

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: 1995 End date: 1996
Participants	**Inclusion criteria of the trial**

Rivers 2002 *(Continued)*

- Clinical diagnosis
- General good health
- Aged 18 years and older
- Anatomical locations: forehead, central face, scalp, dorsum of hands
- ≥ 5 lesions in 3 treatment blocks

Exclusion criteria of the trial

- Women who were not sterile, not postmenopausal, or not using contraception
- History or suspected hypersensitivity to any of the ingredients of the active or vehicle medication
- Allergy to aspirin or other non-steroidal anti-inflammatory drugs
- Dermatological condition that could affect the absorption, accumulation, metabolism, or both, of the study medication
- Current treatment with a disallowed medication (masoprocol, 5-fluorouracil, etretinate, cyclosporine, retinoids, topical steroids, recent trichloroacetic acid, or glycolic acid peels)
- Unwillingness to discontinue the use of cosmetics or sunscreen on the designated site
- Treatment with any other investigational drug or participation in another study within the previous 60 days
- Refusal to undergo a wash-out period before entry into the study

Demographics

- 195 participants
- 142 men, 53 women
- Age: range = 34 to 90

Interventions

Interventions

A: topical 3% diclofenac in 2.5% hyaluronic acid gel, twice daily for 30 days (0.5 g/treatment with 6 hours between applications) (N = 49 participants)

B: topical 3% diclofenac in 2.5% hyaluronic acid gel, twice daily for 60 days (0.5 g/treatment with 6 hours between applications) (N = 48 participants)

Control interventions

C: topical 2.5% hyaluronic acid gel, twice daily for 30 days (0.5 g/treatment with 6 hours between applications) (N = 49 participants)

D: topical 2.5% hyaluronic acid gel, twice daily for 60 days (0.5 g/treatment with 6 hours between applications) (N = 49 participants)

Outcomes

Primary outcomes of the trial

1) Investigator global improvement indices (IGII)

2) Participant global improvement indices (PGII)

3) Number of participants with complete target lesion clearance at day 60 (target lesion number score = TLNS)
4) Number of participants with complete lesion clearance including new lesions (cumulative lesion number score = CLNS) (TLNS and CLNS transformed to participant complete clearance)

5) Mean numbers of target lesions at baseline and follow-up (transformed to mean reduction in lesion counts).

6) Total thickness score (TTS)

Other outcomes of the trial

1) Clinical laboratory tests

Rivers 2002 *(Continued)*

	2) Application site reactions 3) Minor adverse events 4) Serious adverse events (including basal and squamous cell carcinoma) Efficacy Methods: 1. quantitative assessment using outlining and counting of lesions on a 5 cm^2 transparent grid, 2. TTS determined by palpation and visual assessments, 3. qualitatively assessments of overall improvements by investigator and participant (IGII and PGII), 4. severity of the lesions (mild, moderate, and severe) Time points: at baseline (visit 2, day 1 of treatment) and subsequent visits Definitions for TTS: R (lesion resolved completely), 0 (lesion visible, but not palpable), 1 (lesion visible and palpable), 2 (lesion raised with visible scaling), 3 (lesion hyperkeratotic and > 1 mm in thickness) Definitions for the 7-point scale for IGII and PGII: -2 (significantly worse), -1 (slightly worse), 0 (no change), 1 (slightly improved), 2 (moderately improved), 3 (significantly improved), 4 (completely improved) Safety Methods: 1. participant-recorded concomitant medications taken and side-effects experienced, 2. review of adverse events and photography, 3. clinical laboratory analyses (standard haematological, biochemical parameters, assessment of electrolytes and urinalysis), 4. serology (antidiclofenac antibodies) Time points: 1. daily (participant record), 2. at each visit (adverse events review), 3. at screening and end of treatment or onset of reaction (serology)
Funding	This study was supported by Hyal Pharmaceutical Corporation.
Notes	A sample size calculation was provided. Data were reported in the Solaraze gel product insert.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 95): "This randomised, double-blind, placebo-controlled, parallel-group trial was conducted between 1995 and 1996 at 6 Canadian centres." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 3 dropouts, B: 5 dropouts (the reasons were reported)

Rivers 2002 *(Continued)*

		Control - C: 2 dropouts, D: 1 dropout (the reasons were reported)
Selective reporting (reporting bias)	Low risk	Statistically significant and non-significant outcomes were reported.
Other bias	High risk	There were different safety data between Rivers 2002 and the Solaraze product insert.

Seckin 2009

Methods	This was a single-centre, randomised, assessor-blinded, placebo-controlled, intraindividual study. The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	
	• Between 35 and 85 years of age
	• Anatomical locations: face, scalp, or both
	• ≥ 2 visible, palpable, or both, actinic keratoses with a minimum diameter of 2 mm on each half side
	
	Exclusion criteria of the trial
	
	• Pregnant or lactating women
	• Known hypersensitivity to calcipotriol
	• Participants with hypercalcemia, skin disorder affecting face or scalp
	• Treatment as follows:
	  • within 1 month with topical retinoids, topical 5-fluorouracil, cryotherapy, electrocoterization, photodynamic therapy, oral and topical corticosteroids, topical imiquimod, or topical diclofenac
	  • within 6 months with phototherapy, laser, dermabrasion, chemical peeling, or systemic retinoids
	• Suspected basal or squamous cell carcinoma
	
	Demographics
	
	• 9 participants
	• 6 men, 3 women
	• Age: mean = 70; range = 56 to 79

Interventions	**Intervention** A: calcipotriol (vitamin D), twice daily for 12 weeks on right/left side (N = 9 participants) **Control intervention** B: placebo twice daily for 12 weeks on right/left side (N = 9 participants)
Outcomes	**Outcomes of the trial** 1) Mean numbers of lesions at baseline and week 12 (transformed to mean reduction in lesion counts) 2) Mean diameter of target lesion at baseline and week 12 3) Local skin reactions graded on scale 4) Minor adverse events at week 1 and 12 5) Total score for cosmetic appearance of a target lesion (1 target lesion per treatment side) Efficacy

Seckin 2009 *(Continued)*

	Methods: quantitative assessment using lesion counting and recording of diameters of the target lesions Time points: at baseline and weeks 3, 6, 9, and 12 of therapy Safety Methods: side-effects, such as erythema, dryness, burning sensation, and pruritus, graded from 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe) Time points: at baseline and weeks 3, 6, 9, and 12 of therapy Cosmetic Methods: total scores of the target lesions = the sum of erythema, desquamation, and induration scored between 0 to 3 Time points: at baseline and weeks 3, 6, 9, and 12 of therapy
Funding	-
Notes	Similar number of adverse events reports between to treatment and placebo were reported. Neutrogena sunscreen was used.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation generation was achieved with a random digits table.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not stated.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was assessor-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used, and there was missing information about participants lost after the baseline evaluation.
Selective reporting (reporting bias)	High risk	The severity of local skin reactions was not reported.
Other bias	Unclear risk	-

Shaffelburg 2009

Methods	This was a randomised, double-blind, vehicle-controlled, intraindividual study. The start and end dates were not specified.

Shaffelburg 2009 *(Continued)*

Participants	**Inclusion criteria of the trial**
	• Clinical diagnosis
	• Healthy men and women
	• Aged 18 years and older
	• Anatomical locations: face
	• ≥ 10 actinic keratoses
	Exclusion criteria of the trial
	• Pregnancy or lactation
	• History of photosensitive disorder (porphyries, lupus, dermatomyosis)
	• Known allergy to components of ALA or imiquimod
	• Treatment as follows:
	  • within 1 year with photodynamic therapy, imiquimod, 5-fluorouracil, diclofenac, or oral retinoids
	  • within 6 months with PUVA, UVB therapy, ablative laser procedures, dermabrasion, or chemical peel
	  • within 1 month with topical treatments of the face with retinoids, corticosteroids, or alpha hydroxyl and beta hydroxyl acids
	• Systemic treatments with interferon inducers, cytotoxic drugs, immunomodulators, immunosuppressive therapies, or corticosteroids
	• Cryotherapy, curettage, surgical excision, or chemodestruction
	Demographics
	• 25 participants
	• 20 men, 5 women
	• Age: mean = 70

Interventions	**Intervention** A: aminolevulinic acid (ALA)-photodynamic therapy (PDT) followed by imiquimod once per day, twice per week for 16 weeks (N = 25 participants) **Control intervention** B: ALA-PDT followed by vehicle once per day, twice per week for 16 weeks (N = 25 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment Number of treatments: 2 Interval between treatments: 4 weeks Preparation of lesions: microdermabrasion Cream concentration (%): 20% Application of cream: -- Incubation with cream: 1 hour Type of light: blue light Light source: Blu-U 4170 Wavelength (nm): (417) Energy fluence (J/cm^2): --

Shaffelburg 2009 *(Continued)*

	Intensities (mW/cm^2): -- Exposure time: 8 min
Outcomes	**Primary outcome of the trial** 1) Median and mean per cent reduction of the number of lesions at baseline and month 12 (= mean percentage of reduction in lesion counts) **Secondary outcome of the trial** 1) Severe local skin reactions (pooled) **Other outcomes of the trial** 1) Median and mean lesion counts at baseline and month 12 (converted to mean reduction of lesion counts) 2) Participant complete clearance rates 3) Treatment-related adverse events (= minor adverse events) 4) Rest periods Efficacy Methods: quantitative assessment using lesion counting and mapping by marking their locations on clear acetate templates using permanent marker Time points: at baseline and months 1, 2, 3, 4, 6, and 12 of the study Safety Methods: 1. incidence of severe local skin reactions (erythema, edema, erosion/ulceration, scabbing/crusting, weeping/exudates, vesicles, and flaking/scaling/dryness) associated with imiquimod treatment and compare the incidence to those reported in imiquimod studies in which PDT pretreatment was not utilised, 2. assessment of local skin reactions types on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) by the investigator Time points: at months 2, 3, 4, and 6
Funding	This study was supported by 3M Pharmaceuticals and Graceway Pharmaceuticals.
Notes	The data were changed for intention-to-treat (ITT) analysis for meta-analysis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A previous generated list using a random number generator was used.
Allocation concealment (selection bias)	Low risk	Sequential assignment upon participation enrolment was used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias)	Low risk	This study was double-blinded.

Shaffelburg 2009 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocol (PP) analysis was used. Intraindividual study: Intervention - A: 1 dropout (the reason was reported, and the lost was before treatment) Control - B: 1 dropout (the reason was reported, and the lost was before treatment)
Selective reporting (reporting bias)	High risk	The number of participants with severe local skin reactions was not given separately for the 2 treatments. The standard deviations associated with mean values were not given.
Other bias	Unclear risk	-

Siller 2009

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. Start date: March 2005 End date: September 2005
Participants	**Inclusion criteria of the trial** • Clinically diagnosis and confirmed histologically • Men and women of non-child-bearing potential • Aged 18 years and older • Anatomical locations: arms, shoulders, chest, face, scalp, or both • ≥ 5 actinic keratoses (3 to 15 mm) **Exclusion criteria of the trial** • Any factors with potential influence on treatment outcomes including recurrent lesions, prior or concomitant therapy, immunosuppression, and use of topical corticosteroids • Lesions markedly hyperkeratotic or had atypical histology **Demographics** • 63 randomised participants, 58 participants received treatment • White and 90% had a Fitzpatrick–Pathak skin type of I or II • 52 men, 6 women • Age: mean = 66; range = 44 to 88
Interventions	**Interventions** A: 0.0025% ingenol mebutate, once per day at days 1 & 2 or days 1 & 8 (N = 15 participants) B: 0.01% ingenol mebutate, once per day at days 1 & 2 or days 1 & 8 (N = 16 participants) C: 0.05% ingenol mebutate, once per day at days 1 & 2 or days 1 & 8 (N = 15 participants) **Control intervention** D: vehicle, once per day at days 1 & 2 or days 1 & 8 (N = 12 participants)

Siller 2009 *(Continued)*

Outcomes	**Primary outcomes of the trial** 1) Application site reactions (pain) 2) Local skin responses (= local skin reactions) 3) Treatment-related adverse events (= minor adverse events) 4) Serious adverse events 5) Clinical laboratory tests **Secondary outcomes of the trial** 1) Lesion complete response rates at 85 days (target lesions) 2) Lesion complete and marked clinical clearance rates at 85 days 3) Participant partial (> 80%) clearance rates at 85 days [included in participant partial (≥ 75%) clearance] 4) Participant histological clearance rates at 85 days **Other outcomes of the trial** 1) Cosmetic outcomes: changes in pigmentation Efficacy Methods: 1. clinical evaluation of each lesion by the investigator, 2. histological evaluation by a central blinded dermatopathologist based on a repeat biopsy of the lesion biopsied prior to treatment. Time points: at day 85 (end of study) Definitions: 1. complete clearance (no evidence of residual disease), 2. marked clearance (50% to 90% improvement), 3. slight clearance (10% to 50% improvement), 4. unchanged (10%), and 5. worsened (clinically-observable growth) Safety Methods: 1. vital signs, 2. physical examinations, 3. laboratory tests (haematology, serum chemistry, liver function tests, and urinalysis), 4. recording of local skin reactions (itching, erythema,oedema, erosion/ulceration, scabbing/crusting, weeping/exudates, vesicles, flaking/scaling/dryness) and abnormal skin proliferation (treatment was withheld if a severe local skin reaction occurred prior to the second scheduled dose) Time points: 1. at each visit (vital signs), 2. at screening and final visit (day 85) (physical exam), 3. at screening, last day of treatment, and day 85 (or early exit) (laboratory tests) Cosmetic Methods: recording of hypopigmentation, hyperpigmentation and scarring Time points: at day 85 Definitions for local skin reaction rating: 1. mild (easily tolerated), 2. moderate (associated with discomfort sufficient to interfere with usual activities), and 3. severe (incapacitating with inability to work or perform usual activities).
Funding	This study was supported by Peplin Ltd.
Notes	This was a phase IIa study. Application was done only on predetermined 5 lesions with 2 template diameters. There were 2 application regimens, i.e. days 1 & 2 or days 1 & 8, but no differences were detected and results were pooled together.

Siller 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 17): "Randomisation was performed by an independent clinical research organisation and identical packaging was used to maintain blinding of both investigator and patients regarding allocation to active or vehicle gel." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Low risk	Randomisation sequence was generated by an independent company (see previous quote in random sequence generation).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified intention-to-treat (ITT) analysis was used (participants with no treatment were excluded). Intervention - A: 0 dropouts, B: 1 dropout (the reason was reported), C: 0 dropouts Control - D: 0 dropout
Selective reporting (reporting bias)	Low risk	All outcomes were reported based on protocol NCT00107965, as well as the mistakes made in the dose application schedule.
Other bias	High risk	There were higher percentages of women and scalp lesions in the vehicle group at baseline.

Smith 2003

Methods	This was a randomised, active-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • White participants • Anatomical locations: face or scalp • ≥ 4 non-hyperkeratotic actinic keratoses **Exclusion criteria of the trial** • Hyperkeratotic lesions **Demographics** • 36 participants • 29 men, 7 women

Smith 2003 *(Continued)*

- Age: mean = 61

Interventions	**Interventions** A: aminolevulinic acid (ALA)-blue light photodynamic therapy (PDT) (N = 12 participants) B: ALA-pulsed dye laser (PDL) PDT (N = 12 participants) **Control intervention** C: 0.5% 5-fluorouracil once or twice daily for 4 weeks (N = 12 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment Number of treatments: 2 Interval between treatments: 4 weeks Preparation of lesions: -- Cream concentration (%): 20% Application of cream: -- Incubation with cream: 1 hour Type of light: blue light or pulsed dye laser Light source: Blu-U Photodynamic Therapy Illuminator Wavelength (nm): 595 (PDL) Energy fluence (J/cm^2): 7.5 (PDL) Intensities (mW/cm^2): -- Exposure time: 1000 sec (16 min), 10 ms (PDL)
Outcomes	**Outcomes of the trial** 1) 100% lesions cleared (= participant complete response) at 4 weeks post-treatment 2) ≥ 75% lesions cleared (= participant partial clearance) at 4 weeks post-treatment 3) Tolerability, i.e. grading of local skin reactions 4) Photoageing Efficacy Methods: 1. grading of target lesions on a 4-point scale (from resolved to very thick, markedly keratotic, or both), 2. high magnification digital photography of lesions identified with 3 black ink dots and small adhesive label Time points: at baseline and the end of treatment, 2 weeks and 4 weeks post-treatment Definitions: therapeutic success (sustained clearance of 75% or more of target lesions) Safety Methods: grading of erythema, edema, crusting/erosions, and stinging/ burning Time points: immediately after PDT treatments

Smith 2003 *(Continued)*

Definitions for erythema score: 0 (none), 1 (minimal, scant rare erythema), 2 (mild, easily-seen erythema up to ⅓ of the treated area), 3 (moderate, easily-seen erythema involving between ⅓ to ⅔ of the treated area), 4 (severe, easily-seen erythema involving over ⅔ of the treated area)

Definitions for oedema score: 0 (none), 1 (minimal, scant rare oedema), 2 (mild, easily-seen oedema, minimally palpable, involving up to ⅓ of the treated area), 3 (moderate, easily-seen oedema and typically palpable involving between ⅓ to ⅔ of the treated area), 4 (severe, easily-seen oedema, indurated in some areas involving over ⅔ of the treated area)

Definitions for crusts and erosions score: 0 (none), 1 (rare, a few 3 mm or smaller areas), 2 (mild, up to 12 lesions 3 mm or less, areas readily seen), 3 (moderate), 4 (severe)

Definitions for stinging/burning score: 0 (none), 1 (minimal), 2 (moderate), 3 (severe)

Cosmetic

Methods: 1. global response, 2. assessment of tactile roughness by lightly palpitating by stroking gently with the index finger and molted hyperpigmentation (including area involved, the colour intensity, and the evenness of pigment distribution)

Definitions for global response: 0 (complete response = complete resolution of photodamage), 1 (almost complete response = very significant improvement in photodamage, approximately 90% improvement), 2 (marked response = significant improvement in photodamage, approximately 75% improvement), 3 (moderate response = intermediate improvement in photodamage, approximately 50% improvement), 4 (slight response = some improvement in photodamage), 5 (no response), 6 (condition worsened)
Definitions for tactile roughness grading: 0 (skin is very smooth), 1 (skin is smooth with very occasional rough area), 2 (mild roughness), 3 (moderate roughness), 4 (severe roughness)
Definitions for molted hyperpigmentation grading: 0 (evenly pigmented skin), 1 (light hyperpigmentation involving small areas), 2 (moderate hyperpigmentation involving small areas, light hyperpigmentation involving moderate areas), 3 (moderate hyperpigmentation involving moderate sized areas, light hyperpigmentation involving large areas, small areas of heavy hyperpigmentation), 4 (heavy hyperpigmentation)

Funding	This study was supported by DUSA Laboratories.
Notes	PDT treatments were better tolerated than 5-fluorouracil.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 630): "Caucasian patients with a minimum of 4 nonhyperkeratotic AK of either the face or scalp were recruited and randomised to 3 treatment groups." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The blinding was not stated, but 2 physically distinct treatments were compared.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The blinding was not stated, but 2 physically distinct treatments were compared.

Smith 2003 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A & B: 0 dropouts Control - C: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	High risk	The percentages of participants reporting adverse events were not given except for stinging.
Other bias	Unclear risk	-

Solaraze study 2

Methods	This was a randomised, vehicle-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Men and women • Aged 18 years and older • No clinically-significant medical problems outside of the actinic keratosis lesions • Anatomical locations: face, scalp, forehead, arm/forearm, back of hand • ≥ 5 actinic keratoses within a 5 X 5 cm area in 1 anatomical region, up to 3 anatomical regions per participant **Exclusion criteria of the trial** • No 60-day wash-out period from disallowed medication (masoprocol, 5-fluorouracil, cyclosporine, retinoids, trichloroacetic acid/lactic acid/peel, 50% glycolic acid peel) and hyaluronic acid-containing cosmetics • Known or suspected hypersensitivity to any Solaraze® ingredient • Pregnancy • Allergies to aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) • Other dermatological conditions that might affect the absorption of the study medication • Application of dermatologic products, such as sunscreens, cosmetics, and other drug products, was not permitted **Demographics** • 108 participants
Interventions	**Intervention** A: 3% diclofenac in hyaluronic acid for 90 days (N = 53 participants) **Control intervention** B: hyaluronic acid for 90 days (N = 55 participants)
Outcomes	**Outcomes of the trial** 1) Complete clearing of lesions (= participant complete clearance) rates at 30 days post-treatment 2) Application site reactions (for the 3 studies included in insert, i.e. Rivers 2002; Solaraze study 2; Wolf 2001) reported as incidences (i.e. number of events, not number of participants)

Solaraze study 2 *(Continued)*

	3) Minor adverse events (for the 3 studies included in insert, i.e. Rivers 2002; Solaraze study 2; Wolf 2001) reported as incidences (i.e. number of events, not number of participants)
Funding	This study was supported by Nycomed US Inc.
Notes	This study was included in the product package insert as study 2.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation was not stated in the product insert, but the other 2 studies included were randomised.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The blinding was not stated in the product insert, but the other 2 studies were double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The blinding was not stated in the product insert, but the other 2 studies were double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The type of analysis was not stated, but the 2 other studies had intention-to-treat (ITT) analysis.
Selective reporting (reporting bias)	High risk	This was the only study of 3 presented in the Solaraze product insert that was not published and with no significant difference for participant complete clearance.
Other bias	Unclear risk	-

Sotiriou 2009

Methods	This was a randomised, active-controlled, intraindividual study. Start date: September 2007 End date: July 2008
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Anatomical locations: dorsa of hands and forearms • ≥ 6 comparable non-hyperkeratotic lesions of similar severity (grade 1 or 2) on both sides (3 lesions/side) **Exclusion criteria of the trial** • Other dermatological diseases or conditions in the treatment or surrounding (3 cm distance) area • Topical treatments for actinic keratosis within 2 months in the area • Invasive tumours within the treated area

Sotiriou 2009 *(Continued)*

	Demographics • 30 Participants • 25 men, 5 women • Age: mean = 64; range = 49 to 79
Interventions	**Intervention** A: aminolevulinic acid (ALA)-photodynamic therapy (PDT) (N = 30 participants) **Control intervention** B: 5% imiquimod once per day, 3 times per week for 4 weeks on, 4 weeks off (N = 30 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 2 Interval between treatments: 15 days Preparation of lesions: crust removed by curettage Cream concentration (%): 20% Application of cream: onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 4 hours Type of light: red light Light source: Waldmann PDT 1200 Wavelength (nm): 570-670 Energy fluence (J/cm^2): 75 Intensities (mW/cm^2): 75 Exposure time: --
Outcomes	**Outcomes of the trial** 1) Lesion complete response rates at 1 and 6 months 2) Application site reactions 3) Local skin reactions 4) Investigator-assessed cosmetic outcome 5) Participant's preference Efficacy Methods: quantitative assessment using counting and recording of lesions by the same examiners Time points: at baseline and 1 and 6 months post-treatment Definitions: 1. clinical lesion response (complete response = complete disappearance of the lesion), 2. non-complete response (incomplete disappearance of the lesion). Safety Methods: recording of adverse events (severity, duration, and need for additional therapy)

Sotiriou 2009 *(Continued)*

	Time points: at each visit Cosmetic Methods: assessment by investigators based on the amount of scarring, atrophy, induration, erythema, and pigment change within the treated area in comparison with adjacent, untreated skin Time points: at month 6 post-treatment Definitions: 1. excellent (no erythema, change in pigmentation, scarring, atrophy, or induration), 2. good (slight to moderate erythema or change in pigmentation, but no scarring, atrophy, or induration), 3. fair (slight scarring, atrophy, or induration), 4. poor (moderate to extensive scarring, atrophy, or induration)
Funding	-
Notes	There was a difference in lesion complete response between treatments for grade II lesions, i.e. 57.8% for PDT and 37% for imiquimod, but not for grade I lesions (71% to 72%).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1062): "Eligible patients received PDT treatment and treatment with imiquimod 5% cream randomly allocated to alternate upper extremities." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The blinding was not stated, but 2 physically distinct treatments were compared.
Blinding of outcome assessment (detection bias) All outcomes	High risk	The blinding was not stated, but 2 physically distinct treatments were compared.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Per-protocol (PP) analysis was used. Intraindividual study: Intervention - A: 2 dropouts (the reasons were reported) Control - B: 2 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Low risk	All outcomes were reported, i.e. significantly different or not.
Other bias	Unclear risk	-

Stockfleth 2002

Methods	This was a randomised, double-blind, vehicle-controlled, parallel-group study.

Stockfleth 2002 *(Continued)*

	The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	• Anatomical locations: face, scalp, forehead, dorsal forearm, neck, back of the hand
	• 3 to 10 actinic keratoses within 20 cm^2
	Exclusion criteria of the trial
	• Treatment as follows:
	  • within 4 weeks with interferon/interferon inducers, immunomodulators, immunosuppressants, cytotoxic drugs, or investigational drugs
	  • within 2 weeks with any topical therapy for actinic keratoses lesions
	• Having bacterial or viral infection within 2 weeks
	• Previously treated or currently living with a patient being treated with imiquimod
	• Allergic to components of the vehicle cream
	• Cardiovascular, hematologic, hepatic, neurologic, renal, endocrine, vascular, or gastrointestinal abnormalities or diseases
	• Taking immunosuppressant medication
	• Dependent on alcohol of drugs
	Demographics
	• 52 participants screened, 36 enrolled
	• 38 men, 14 women
	• Age: mean = 68; range = 45 to 85

Interventions	**Intervention** A: 5% imiquimod cream, 3 times (or less based on adverse events) per week for a maximum of 12 weeks (N = 25 participants) **Control intervention** B: placebo, 3 times (or less based on adverse events) per week for a maximum of 12 weeks (N = 11 participants)
Outcomes	**Outcomes of the trial** 1) Participant complete clearance rates at 14 weeks. 2) Participant partial clearance rates 3) Local skin reactions (graphical representation) 4) Minor adverse events (graphical representation) 5) Recurrence 6) Compliance 7) Rest periods Efficacy Methods: 1. clinical evaluation, 2. biopsy (histology) assessed by the same dermatopathologist Time points: at baseline and week 14 after treatment initiation Definitions: 1. complete clearance (complete clinical clearance confirmed histologically), 2. partial clearance (the clearance of 1 or more lesions treated with imiquimod) Safety

Stockfleth 2002 *(Continued)*

	Methods: 1. vital signs recording; 2. photography; 3. assessment and recording of local and systemic adverse or abnormal effects; 4. recording of the incidence and severity of erythema, edema, induration, vesicles, erosion, ulceration, excoriation or flaking, and scabbing on a scale of 1 (mild) to 3 (severe) Time points: at each visit (at weeks 2, 3, 6, 9, and 12)
Funding	This study was supported by 3M Pharmaceuticals.
Notes	The recurrence rate at 1 year was 10% (2/25) for participants treated with imiquimod. A sample size calculation was based on rate of spontaneous healing of actinic keratoses lesions.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1500): "Each patient was randomly assigned a number that was paired with a box containing 12 sachets." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Low risk	The key to codes were held by the pharmaceutical company.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 0 dropouts Control - B: 0 dropouts
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Swanson 2010a

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: January 2008 End date: June 2008
Participants	**Inclusion criteria of the trial** • Clinical assessment by the investigator • Adults in general good health with 5 to 20 visible or palpable actinic keratoses within 25 cm^2 • Anatomical locations: face or balding scalp

Swanson 2010a *(Continued)*

Exclusion criteria of the trial

- Women who were pregnant, lactating, or planning to become pregnant during the study
- Participants who had had a medical event within 90 days of the first visit (such as stroke or heart attack)
- Participants who had had any skin condition in the treatment area that may have been made worse by treatment with imiquimod (e.g. rosacea, psoriasis, atopic dermatitis, or eczema)
- Treatment as follows:
  - within 1 year with 5% imiquimod cream on the head
  - within 90 days, with interferon, interferon, inducers, cytotoxic drugs, immunomodulators, immunosuppressants, oral or parenteral corticosteroids, topical corticosteroids greater than 2 g/d, investigational drug or device use outside of the treatment area, dermatologic procedures or surgeries in the treatment area, and any actinic keratosis therapy in the target treatment area
  - within 30 days, with imiquimod outside of the head, and topical prescription drugs, and investigational drug or device use within treatment area
- Chemical or alcohol dependency
- Allergy to imiquimod or study cream excipients.

Demographics

- 479 participants
- 389 men, 90 women
- Age: mean = 64

Interventions

Interventions

A: 3.75% imiquimod, once daily for 2 weeks on, 2 weeks off, 2 weeks on (N = 160 participants)

B: 2.5% imiquimod, once daily for 2 weeks on, 2 weeks off, 2 weeks on (N = 160 participants)

Control intervention

C: placebo, once daily for 2 weeks on, 2 weeks off, 2 weeks on (N = 159 participants)

Outcomes

Primary outcome of the trial

1) Participant complete clearance rates at week 14

Secondary outcomes of the trial

1) Participant partial (> 75%) clearance rates at week 14

2) Median percentage of reduction in lesion counts

3) Local skin reactions

Other outcomes of the trial

1) Participants experiencing at least 1 adverse event

2) Application site reactions including irritation

3) Treatment-related adverse events (= minor adverse events)

4) Serious adverse events

5) Clinical laboratory tests

6) Investigator global integrated photodamage (IGIP-cosmetic outcome)

7) Number of participants with the different cosmetic outcomes

8) Rest periods

Swanson 2010a *(Continued)*

	Efficacy Methods: quantitative assessment by counting all of the visible or palpable lesions (baseline or new) in the treatment area by the investigator Time points: at each visit Definitions: 1. complete clearance rate (proportion of participants at the end-of-study visit with a count of 0 lesions in the treatment area), 2. partial clearance rates (proportion of participants with 75% or more reduction in lesion count in the treatment area at the end-of-study visit as compared with baseline), 3. per cent change (changes in lesion number at the end-of-study visit as compared with baseline) Safety Methods: 1. measurement of vital signs; 2. recording and coding (Medical Dictionary for Regulatory Activities) of adverse events; 3. investigator assessment of local skin reactions (erythema, edema, weeping/exudate, flaking/scaling/dryness, scabbing/crusting, and erosion/ulceration) graded as none, mild, moderate, or severe; 4. laboratory tests (hematology, serum chemistry, and urinalyses) (treatment-emergent adverse events were summarised for each treatment group by preferred term, intensity, and investigator assessment of relationship to study cream) Time points: 1. at each visit, 2. pre-study visit and end-of-study visit (laboratory tests) Cosmetic Methods: an overall assessment (IGIP score) of the participant's photodamage change from baseline in the treatment area (including an integrated assessment of fine wrinkling, coarse wrinkling, mottled pigmentation, roughness, shallowness, skin laxity, and telangiectasias) rated on a 7-point symmetric scale, ranging from significantly improved = +3 to significantly worse = -3 Time points: at end-of-study visit
Funding	This study was supported by Graceway Pharmaceuticals LLC.
Notes	Data from 2 studies were pooled together. Temporary dosing interruptions could have been instructed by the investigator to manage local skin reactions and adverse events. A sample size calculation was provided. A follow-up study was published (Hanke 2011).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 584): "Eligible patients were centrally randomised to placebo, imiquimod 2.5%, or imiquimod 3.75% cream in a 1:1:1 treatment allocation." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Low risk	Centralised randomisation was used.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was double-blinded (subject, caregiver, investigator), but the authors mentioned that adverse events could be an issue for the concealment of the assigned treatment in some participants.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was double-blinded (outcomes assessor), but authors mentioned that adverse events could be an issue for the concealment of the assigned treatment in some participants.

Swanson 2010a *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 11 dropouts (the reasons were reported), B: 6 dropouts (the reasons were reported) Control - C: 9 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Low risk	All outcomes from the protocol (NCT00605176) were reported.
Other bias	Unclear risk	Data for safety were reported differently in the published study, and the data results linked to the protocol.

Swanson 2010b

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel-group study. Start date: August 2008 End date: February 2009
Participants	**Inclusion criteria of the trial** • Men or women (must have been of non-child-bearing potential or provided negative serum and urine pregnancy test or been using effective contraception) • Aged 18 years and older • Anatomical locations: non-head • 4 to 8 actinic keratoses **Exclusion criteria of the trial** • Cosmetic or therapeutic procedures within 2 weeks and within 2 cm of the selected treatment area. • Treatment with immunomodulators or interferon/interferon inducers or systemic medications that suppress the immune system within 4 weeks • Treatment with 5-fluorouracil, imiquimod, diclofenac, or photodynamic therapy within 8 weeks and 2 cm of treatment area **Demographics** • 255 participants
Interventions	**Intervention** A: 0.05% ingenol mebutate for 2 days (N = 117 participants) **Control intervention** B: vehicle for 2 days (N = 118 participants)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at day 57 **Secondary outcome of the trial** 1) Participant partial (percentage criteria was not specified) clearance rates at day 57 **Other outcomes of the trial** 1) Median percentage reduction in lesion counts

Swanson 2010b *(Continued)*

	2) Local skin reactions (qualitative) 3) Treatment-related adverse events (qualitative) 4) Serious adverse events 5) Pigmentation changes (cosmetic) 6) Compliance Efficacy Time points: on days 3, 8, 15, 29, and 57 Safety Methods: 1. assessment of the incidence rate of adverse events, serious adverse events, and local skin responses; 2. grading of local skin responses Time points: on days 3, 8, 15, 29, and 57 Cosmetic Methods: assessment of pigmentation and scarring Time points: on days 3, 8, 15, 29, and 57
Funding	This study was supported by Peplin Ltd.
Notes	This study report was a conference abstract and was included in the following study awaiting classification Lebwohl 2012.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page AB2): "A total of 255 patients were randomised to treatment with 0.05'X, ingenol mebutate gel or vehicle." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The type of analysis was not stated. Only 1 dropout due to adverse events was reported, but the treatment group was not specified.
Selective reporting (reporting bias)	Unclear risk	All outcomes in the protocol (NCT00742391) were reported in the published study. Another similar study (NCT00942604) has not been published yet.

Swanson 2010b *(Continued)*

Other bias	Unclear risk	-

Szeimies 2002

Methods	This was a multicentre, randomised, open, active-controlled, parallel-group study. Start date: April 1999 End date: November 1999
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Men or women • Age 18 years and older • Anatomical locations: face, scalp, other • ≤ 10 actinic keratoses, suitable to cryotherapy **Exclusion criteria of the trial** • No treatment for last 4 weeks • Participants receiving regular UV therapy • Participants with pigmented lesions • Porphyria **Demographics** • 202 participants • 124 men, 78 women • Face (61% to 65%), scalp (26% to 30%), other (8.9% to 8.0%) • Age: range = 42 to 89
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) (N = 102 participants) **Control intervention** B: cryotherapy: prior skin preparation, variable liquid nitrogen spray unit, 1 to 2 mm rim of frozen tissue beyond marked outline, 2 freeze-thaw cycles in the same session; mean freeze time of 24 ± 18 seconds, (N = 100 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: once for face and scalp, twice for others (8% of lesions) Interval between treatments: 1 week Preparation of lesions: crusts removed by curettage Cream concentration (%): 16% Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light

Szeimies 2002 *(Continued)*

	Light source: --
	Wavelength (nm): 570-670
	Energy fluence (J/cm^2): 75
	Intensities (mW/cm^2): 70 to 200
	Exposure time: 10 min
Outcomes	**Outcomes of the trial**
	1) Lesion complete response rates at 3 months post-treatment
	2) Skin irritation
	3) Local adverse reactions
	4) Investigator's and participant's cosmetic outcomes in participants with > 75% reduction of total lesions: number of participants (excellent and good pooled together)
	5) Participants' satisfaction
	Efficacy
	Time points: at 3 months after the initial treatment
	Definitions: 1. complete response (complete disappearance of the lesion), 2. non-complete response (incomplete disappearance of the lesion)
	Safety
	Methods: recording of adverse events (including the local phototoxicity due to PDT)
	Time points: before and after illumination, after 2 weeks by telephone contact, and after a final examination 3 months post-treatment
	Cosmetic
	Methods: assessment and grading of overall cosmetic outcome
	Time points: at 3 months after the initial treatment
	Definitions: 1. excellent (only slight occurrence of redness or change in pigmentation), 2. good (moderate redness or change in pigmentation), 3. fair (slight to moderate scarring, atrophy, or induration), and 4. poor (extensive scarring, atrophy, or induration)
Funding	This study was supported by Photocure ASA.
Notes	Higher response rates were obtained with thin lesions. High participant satisfaction was obtained with MAL-PDT. 43% of participants treated with MAL-PDT reported local adverse events compared to 26% treated with placebo.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate allocation sequence was generated by stratification with respect to the number of lesions.
Allocation concealment (selection bias)	Unclear risk	This was not stated.

Szeimies 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was open because 2 physically distinct treatments were compared.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was open because 2 physically distinct treatments were compared.
Incomplete outcome data (attrition bias) All outcomes	High risk	There was discrepancy in the text (415) and table (384) for number of lesions in the PDT group. Per-protocol (PP) analysis was used. Intervention - A: 4 dropouts (the reasons were reported) Control - B: 5 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	Overall cosmetic outcomes were pooled together. Satisfaction was reported for PDT participants only.
Other bias	Unclear risk	-

Szeimies 2004

Methods	This was a multicentre, randomised, double-blind, vehicle-controlled, parallel group study. Start date: January 2002 End date: March 2003

Participants	**Inclusion criteria of the trial**
	• Anatomical locations: face or (not and) bald scalp
	• 5 to 9 actinic keratoses
	Exclusion criteria of the trial
	• Any condition in the treatment area that could be exacerbated by treatment with imiquimod 5% cream or that would impair the examination of the treatment area
	• Any known allergies to any excipients in the study cream
	• No prior treatment with imiquimod 5% or topical steroids in the treatment area
	• No prior treatment with corticosteroids causing suppression of the hypothalamic adrenal pituitary axis, suppression of the nuclear factor kappa B, or induction of IL-12, and other cytokines that result in activation of a Th1-immune response with imiquimod
	• No prior treatment with the following:
	  * within 6 months with psoralen plus UVA therapy, UVB therapy, laser abrasion, dermabrasion, or chemical peel
	  * within 4 weeks with prescribed topical retinoids, 5-fluorouracil, masoprocol, cryodestruction, chemodestruction, surgical excision, photodynamic therapy, curettage, IFN/IFN inducers, cytotoxic drugs, drugs with major organ toxicity, immunomodulators, or immunosuppressive therapies
	• Excluded treatments were also prohibited during study participation; exceptions to this criteria included surgical excision, cryodestruction, and curettage (all allowed on areas other than the head), and steroids (topical and inhaled steroids were allowed with restrictions). The use of moisturisers, over-the-counter retinol products, or products containing alpha- or beta-hydroxy acids in thetreatment area was prohibited
	Demographics
	• 286 participants

Szeimies 2004 *(Continued)*

- 248 men, 38 women
- Age: range = 44 to 94

Interventions	**Intervention** A: imiquimod 5% cream, once per day, 3 days per week for 16 weeks or less (N = 147 participants) **Control intervention** B: vehicle, once per day, 3 days per week for 16 weeks or less (N = 139 participants)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at 8 weeks post-treatment **Secondary outcome of the trial** 1) Participant partial (≥ 75%) clearance rates at 8 weeks post-treatment **Other outcomes of the trial** 1) Histological clearance at 8 weeks post-treatment 2) Clinical laboratory tests 3) Application site reactions (including irritation) 4) Local skin reactions 5) Minor adverse events 6) Serious adverse events 7) Skin quality (cosmetic) Efficacy Methods: 1. quantitative assessment using clinical counting and recording the number lesions present in the treatment area, 2. by the histologic result from the biopsy specimen of a predefined lesion biopsy site Time points: 1. at weeks 1, 2, 4, 8, 12, 16 (end of treatment), and 24 (8 weeks post-treatment); 2. at the 8-week post-treatment visit (biopsy) Definitions: 1. complete clearance rate (proportion of participants at the 8-week post-treatment visit with no evidence of lesion on the histology result of the post-treatment target lesion biopsy site and no clinically-visible lesions in the remainder of the treatment area), 2. partial clearance rate (proportion of participants at the 8-week post-treatment visit with at least 75% reduction in the number of lesions counted at baseline in the treatment area) Safety Methods: 1. photography of the treatment area; 2. reviewing adverse events and local skin reactions (erythema, edema, erosion/ulceration, scabbing/crusting, weeping/exudate, vesicles, or flaking/scaling/dryness) rated on a scale of 0 (none) to 3 (severe) and concomitant medication use; 3. clinical laboratory tests (hematology, serum chemistry, urinalyses, and pregnancy test) Time points: 1. at weeks 1, 2, 4, 8, 12, 16 (end of treatment), and 24 (8 weeks post-treatment), 2. pre-study and end-of-study visits (laboratory tests) Cosmetic Methods: visual, clinical, and tactile examinations of skin quality within the treatment area by investigator [skin surface (roughness/dryness/scaliness), hyperpigmentation, hypopigmentation, mottled or irregular pigmentation (both hyperpigmentation and hypopigmentation), degree of scarring, and atrophy] on a scale of 0 (none) to 3 (severe)

Szeimies 2004 *(Continued)*

	Time points: at the treatment initiation and 8-week post-treatment visits
Funding	This study was supported by 3M Pharmaceuticals.
Notes	This was a phase III study. A high rate of agreement was observed between clinical and histologic lesion clearances. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An adequate method of randomisation was achieved by the use of a computer-generated randomisation schedule.
Allocation concealment (selection bias)	Low risk	Adequate allocation concealment was achieved by sealed, tamper-proof envelopes containing a number allocated to each participant.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Intention-to-treat (ITT) analysis was used, but some lost to follow up participants were missing for the description. Intervention - A: 10 dropouts (the reasons were not all reported) Control - B: 18 dropouts (the reasons were not all reported)
Selective reporting (reporting bias)	High risk	As a similar study (Lebwohl 2004) was also supported by 3M Pharmaceuticals not all skin quality outcomes were reported.
Other bias	Unclear risk	-

Szeimies 2008

Methods	This was a multicentre, randomised, active-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Anatomical locations: face or balding scalp • 4 to 8 non-hypertrophic, non-hyperkeratotic actinic keratoses within 25 cm^2 area **Exclusion criteria of the trial** • Dermatological condition in the treatment area that might be exacerbated by treatment or impair • Allergy to resiquimod or gel excipients • Previous imiquimod usage in the treatment area • Unstable medical condition • Pregnancy, lactation

Szeimies 2008 *(Continued)*

- Enrolled in another clinical study
- Treatment as follows:
  - within 6 months with chemotherapy, radiation therapy, systemic retinoids, UVB, topical retinoids, or psoralens with UVA
  - within 2 months with diclofenac, photodynamic treatment, or 5-fluorouracil
  - within 6 weeks with dermabrasion or chemical peel
  - within 4 weeks with immunomodulatory treatment, cytotoxic, investigational, systemic corticosteroids, laser treatment, cryotherapy, surgery or topical corticosteroids
  - within 2 weeks with high-dose vitamin A (> 15000 units/day)

Demographics

- 132 participants
- 109 men, 23 women
- Age: mean = 70

Interventions	**Interventions** A: 0.03% resiquimod, once per day, 3 days per week, 4 week on, 8 weeks off, 1or 2 courses (N = 31 participants) B: 0.06% resiquimod, once per day, 3 days per week, 4 week on, 8 weeks off, 1or 2 courses (N = 32 participants) C: 0.1% resiquimod, once per day, 3 days per week, 4 week on, 8 weeks off, 1or 2 courses (N = 34 participants) **Control intervention** D: 0.01 % resiquimod, once per day, 3 days per week, 4 week on, 8 weeks off, 1or 2 courses (N = 35 participants) The gel application was done using a dosing paper template.
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates after 1 to 2 treatment courses (week 24) **Secondary outcomes of the trial** 1) Participant partial (> 75%) clearance rates after 1 to 2 treatment courses 2) Participant complete clearance rates after 1 course only (week 12) . **Other outcomes of the trial** 1) Application site reactions 2) Severe local skin reactions 3) Treatment-related adverse events (minor adverse events) 4) Serious adverse events 5) Clinical laboratory tests 6) Compliance Efficacy Methods: quantitative assessment using lesion counting and mapping with a transparent plastic template by a qualified dermatologist

Szeimies 2008 *(Continued)*

	Time points: at baseline; weeks 2, 4, 8, and 12 for course 1, and if applicable, at weeks 14, 16, 20, and 24 for course 2 Definitions: 1. overall complete clearance rate (proportion of participants at the end of course 1 (week 12) or course 2 (week 24) with no lesions in the treatment area), 2. partial clearance rate (proportion of participants at their last study visit with at least 75% reduction in the number of lesions in the treatment area) Safety Methods: 1. recording of adverse events, 2. assessment of local skin reactions (erythema, oedema, erosion/ulceration, weeping/exudate, flaking/scaling/dryness, and scabbing/crusting), 3. photographs of treatment area, 4. laboratory tests (haematology, biochemistry, urine analysis, and where applicable, pregnancy tests), 5. vital signs measurements and physical examination, and if appropriate, skin cultures (suspected infection) or skin biopsy (lesion suspicious for malignancy) Time points: at weeks 2, 4, 8, and 12 for course 1, and if applicable, at weeks 14, 16, 20, and 24 for course 2
Funding	This study was supported by 3M Pharmaceuticals.
Notes	This was a phase II study. Serious adverse events and local skin reactions were more frequent with higher doses, and there was lowest compliance in the 0.1% group. A sample size calculation was provided. Intention-to-treat data were used for meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pre-assigned numbering with 1:1:1:1 randomisation with a block size 4 was used for allocation generation.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	This was not stated.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not stated.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) and per-protocol (P) analyses were used. Intervention - A: 5 dropouts (the reasons were reported), B: 10 dropouts (the reasons were reported), C: 14 dropouts (the reasons were reported) Control - D: 2 dropouts (the reasons were reported) Dropping rates were higher for higher doses, i.e. 6%, 16%, 31%, and 41% for 0.01, 0.03, 0.06, and 0.1% resiquimod groups.
Selective reporting (reporting bias)	Unclear risk	-
Other bias	High risk	The values for overall partial (> 75%) clearance were lower than overall complete clearance.

Szeimies 2009

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: March 2006 End date: January 2007

Participants	**Inclusion criteria of the trial**
	
	• Men and women
	• Aged 18 years and older
	• Anatomical locations: face and scalp
	• 4 to 10 previously untreated actinic keratoses, non-pigmented, non-hyperkeratotic, grade 1 or 2, ≥ 3 mm in diameter
	
	Exclusion criteria of the trial
	
	• Immunosuppression for idiopathic, disease-specific or therapeutic reasons
	• Porphyria
	• Pigmented actinic keratoses
	• Known allergy to methyl aminolevulinate (MAL) or similar photosensitising agents or excipients
	• Known hypersensitivity to nut products
	• Current or prior (within the last 30 days) participation in other clinical studies
	• Pregnancy, lactation
	• Treatment as follows:
	  • within 30 days with regular UV radiation therapy or treatment of the face or scalp with local therapy (including cryotherapy and curettage)
	  • within 3 months with topical therapy (including imiquimod, 5-fluorouraccil, and diclofenac)
	
	Demographics
	
	• 115 participants
	• 91 men, 24 women
	• Age: range = 41 to 90

Interventions	**Intervention** A: MAL-photodynamic therapy (PDT) (N = 57 participants) **Control intervention** B: placebo-PDT (N = 58 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 2 Interval between treatments: 1 week Preparation of lesions: crusts and scales removed by curettage Cream concentration (%): 16% Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light LED

Szeimies 2009 *(Continued)*

	Light source: Aktilite CL 128 Wavelength (nm): 630 Energy fluence (J/cm^2): 37 Intensities (mW/cm^2): 56 to 83 Exposure time: 9 min
Outcomes	**Primary outcome of the trial** 1) Participant complete response (= participant complete clearance) rates at 3 months after last treatment **Secondary outcomes of the trial** 1) Lesion complete response rates at 3 months post-treatment 2) Treatment site reactions (= application site reactions) reported by events (i.e. not per participants) 3) Local skin reactions (in general and severe) **Other outcomes of the trial** 1) Participants experiencing at least one adverse event 2) Treatment-related adverse events (= minor adverse events) reported by events (i.e. not per participants) 3) Minor adverse events 4) Serious adverse events including squamous cell carcinoma 5) Percentage of participants with new lesions Efficacy Methods: 1. quantitative assessment using inspection, palpation, and characterisation of lesions (Olsen 1991) by the same investigator, who was not involved in the treatment procedure, 2. documentation of any lesions not present at baseline (lesions with a non-complete response were treated at the discretion of the investigator) Time points: at baseline and 3 months post-treatment Definitions: 1. complete response (complete disappearance of the lesion), 2. non-complete response (incomplete disappearance of the lesion), 3. participant complete response (all participants in whom 100% of lesions had responded completely 3 months post-treatment) Safety Methods: 1. assessment of tolerability, 2. recording of adverse events (severity, localisation, duration, and need for additional treatment) (the clinician assessed the causal relationship of the event to the study treatment as related, uncertain, or not related) Time points: after lesion preparation before cream application, at the end of the 3-hour cream application, after illumination during each treatment session, and at 2 weeks and 3 months post-treatment
Funding	This study was supported by Photocure ASA.
Notes	A sample size calculation was provided. This study was study #2 in the Metvixia product insert 2008. The studies included in the Metvixia product insert were changed between 2004 (PhotoCure) and 2008 (Galderma), which correspond to the use of different types of light.

Szeimies 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated randomisation scheme was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	A clinician not involved in treatment procedure assessed response.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 1 dropout (the reason was reported) Control - B: 0 dropouts
Selective reporting (reporting bias)	Low risk	All outcomes were presented based on the protocol (NCT00304239), and protocol mistakes were acknowledged.
Other bias	Unclear risk	-

Szeimies 2010b

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • White men and women • Between 18 and 85 years of age • Anatomical locations: face, bald scalp, or both • 4 to 8 actinic keratoses, mild to moderate lesions, 0.5 to 1.5 cm in diameter, with a minimum of 1.0 cm interlesional distance **Exclusion criteria of the trial** • All clinical conditions that could influence the study aims and intolerance to any ingredient of BF-200 aminolevulinic acid (ALA) • Known hypersensitivity to ALA • Immunosuppressive therapy • Porphyria • Hypersensitivity to porphyrins • Participants receiving hypericin or systemically acting drugs with phototoxic or photoallergic potential • Participants showing cornu cutaneum-like alterations (cutaneous horns) of the skin in the target area • Dermatoses

Szeimies 2010b *(Continued)*

- Treatment as follows:
  - within 12 weeks with topical treatments within the treatment area
  - within 8 weeks with substances with phototoxic or photoallergic potential
  - within 1 to 6 months with systemic treatments considered to have a possible impact on the outcome, e.g. cytotoxic drugs
- Use of other treatment for actinic keratoses during the study

Demographics

- 122 participants
- 105 men, 17 women
- Age: mean = 71; range = 57 to 85

Interventions	**Intervention** A: ALA-photodynamic therapy (PDT) (N = 81 participants) **Control intervention** B: placebo-PDT (N = 41 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 or 2 Interval between treatments: 12 weeks Preparation of lesions: crusts removed by curettage, roughening, and alcohol wiping Cream concentration (%): BF-200 gel Application of cream: air dry for 10 min Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light Light source: Aktilite CL 128 or PhotoDyn 750 Wavelength (nm): 590-670 (Aktilite), 595-1400 (PhotoDyn) Energy fluence (J/cm^2): 37 (Aktilite), 170 (PhotoDyn) Intensities (mW/cm^2): 50-70 (Aktilite), 196 (PhotoDyn) Exposure time: 15 minutes (PhotoDyn)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance at 12 and 24 weeks **Secondary outcome of the trial** 1) Lesion complete response at 12 and 24 weeks **Other outcomes of the trial** 1) Local skin reactions for first and second treatment by light sources and in general 2) Cosmetic outcomes: general Efficacy

Szeimies 2010b *(Continued)*

	Methods: 1. quantitative assessment of lesion clearance by visual inspection and by palpation by an investigator not involved in treatment and safety evaluation, 2. histological assessment using biopsy of a lesion defined and marked before the PDT treatment Time points: 1. at baseline; 3, and 12 weeks post-treatment, 2. end-of-study visit (biopsy) Definitions: participant complete clearance (all lesions were considered to be cleared both by the clinical and histological assessment) Safety Methods: 1. recording of adverse effects, 2. documentation of local adverse reactions (pain, itching, burning, erythema, oedema, and induration) at the application site and rated as mild, moderate, and severe by the assessing physician or reporting participants, 3. serious adverse events Time points: 1. at 1 week after PDT (by phone) and 3 weeks, 2. during and after PDT (local adverse reactions) Cosmetic Methods: 1. general cosmetic outcome assessed by the investigator as very good, good, unsatisfactory, and impaired; 2. assessment of skin quality Time points: at 12 weeks post-treatment
Funding	This study was supported by Biofrontera Bioscience GmbH.
Notes	Pain, itching, and burning were reported separately for 1st and 2nd treatment, anatomical area, and light sources. In general, more symptoms were reported for Aktilite CL128 than PhotoDyn 750. A sample size calculation was provided. Data with intention-to-treat analyses were used for meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A validated SAS programme based on the random number function RANUNI and random blocks for 6 participants was used.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Treatment and safety assessment were performed by 1 investigator and efficacy assessment by another.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) and per-protocol (PP) analyses were used. Intervention - A: 4 dropouts (the reasons were reported) Control - B: 4 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported, but little information was given on adverse events and cosmetic outcomes.
Other bias	Unclear risk	-

Tan 2007

Methods	This was a randomised, double-blind, vehicle-controlled, parallel-group study (part 1). Start date: April 2005 End date: December 2006

Participants	**Inclusion criteria of the trial**
	
	• Aged 18 years and older
	• Anatomical locations: face or scalp
	• ≥ 4 discreet actinic keratoses in an area ≤ 50 cm^2
	
	Exclusion criteria of the trial
	
	• Known hypersensitivity to imiquimod cream
	• Treatment as follows:
	  • within 5 months with imiquimod in the same area
	  • within 4 weeks with cryosurgery in the same area
	  • within 4 weeks with cytotoxic drugs or investigational drugs
	  • within 2 weeks with bacterial or viral infection
	• previous treatment with interferon or interferon inducers, immunomodulators, immunosuppressants
	• Pregnancy or lactating
	• Concomitant medical conditions that in the investigator's opinion may confounded clinical evaluations
	• Unwillingness to comply with photoprotection throughout the study duration
	• Presence of basal or squamous cell carcinomas in treatment area
	
	Demographics
	
	• 65 participants
	• 57 men, 8 women
	• Age: Imiquimod group: mean = 71.0, Vehicle group = mean 69.4

Interventions	Part 1: **Intervention** A: cryotherapy: 3 to 5 second freeze cycle followed (2 weeks after) by 5% imiquimod cream applied twice weekly for 8 weeks (N = 33 participants) **Control intervention** B: cryotherapy: 3 to 5 second freeze cycle followed (2 weeks after) by vehicle cream for 8 weeks (N = 32 participants) Part 2: Participants with residual actinic keratosis lesions were offered cryotherapy and open-label imiquimod twice weekly for 8 weeks.
Outcomes	**Primary outcomes of the trial (protocol)** 1) Recurrence rate 2) Time to recurrence of lesions **Secondary outcomes of the trial (protocol)** 1) Time to reach treatment success

Tan 2007 *(Continued)*

	2) Proportion of participants completely clear [= participant complete clearance rates for target, subclinical and total lesions at week 22 (i.e. part 1 only)] 3) Participant improvement assessment **Other outcomes of the trial** 1) Clearance rates of target lesion (= lesion complete response) 2) Skin irritation 3) Treatment-related adverse events (= minor adverse events) 4) Serious adverse events 5) New actinic keratoses (subclinical) during the study Efficacy Methods: quantitative assessment using lesion mapping on a transparent overlay map Time points: at baseline, at week 22 after cryotherapy (end of part 1) Definitions: 1. target lesions (those within a designated 50 cm^2 treatment field established at baseline), 2. subclinical lesions (those within the designated treatment field unapparent at baseline), 3. total lesions (the sum of target and subclinical lesions) Safety Methods: monitoring of the frequency and duration of adverse events (local and systemic) Time points: at every study visit
Funding	This study was supported by 3M Pharmaceuticals.
Notes	An increase in subclinical actinic keratoses was observed within the first 3 weeks of imiquimod treatment with a subsequent progressive reduction there after, but this was not observed with vehicle. This was a 2-part study: part 1, included in the meta-analyses, is randomised, double-blind, and controlled, but part 2 is an optional open study not included in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 2): "The initial randomised double-blind phase in which subjects were allocated to either vehicle or imiquimod 5% cream twice weekly for 8 weeks was followed by an optional open-label phase..." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded for part I.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded for part I.

Tan 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Intervention - A: 2 dropouts (the reasons were reported) Control - B: 0 dropouts
Selective reporting (reporting bias)	High risk	Some outcomes (recurrence rate, time to recurrence, time to reach success, participant improvement assessment) in the protocol (NCT00110682) were not presented in the published study.
Other bias	High risk	There were differences between the protocol and the published report. The primary and secondary outcomes in the published report were different than the protocol. The protocol did not mention the second part of the study.

Tanghetti 2007

Methods	This was a multicentre, randomised, assessor-blinded, active-controlled, parallel-group study. The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	• Aged 21 years and older
	• Anatomical locations: face, forehead or scalp
	• ≥ 4 actinic keratoses within 25 cm^2area
	Exclusion criteria of the trial
	• Treatment as follows:
	  • within 1 month with investigational product, liquid nitrogen,
	  • within 2 months with ALA, systemic or topical chemotherapy, systemic, or topical immunotherapy, systemic or topical steroids, oral or topical retinoids diclofenac, topical 5-fluorouracil, or any other treatment that could affect actinic keratoses
	  • within 6 month with facial resurfacing
	• Pregnancy, lactation, of child-bearing potential
	• Immunosuppressed
	• Scheduled elective surgery within 30 days
	• Clinical laboratory value outside the normal range
	• Any organic or psychological disease that could interfere with interpretation
	• Active herpes infection in the 30 days preceding study entry
	• Unwillingness to stop using topical products on the affected area or make-up for the assessment visits
	Demographics
	• 39 participants

Interventions	**Intervention** A: 5% 5-fluorouracil twice daily for 2 to 4 weeks (N = 20 participants) **Control intervention** B: 5% imiquimod twice weekly for 16 weeks (N = 19 participants)
Outcomes	**Outcomes of the trial** 1) Physician global assessment as scores (presented in a graph)

Tanghetti 2007 *(Continued)*

2) Lesion counts at baseline, during and after treatment (= lesion complete response)

3) Participant complete and partial (> 66%) clearance

4) Mean percentage of reduction in lesion counts

5) Physician's grading of erythema (scores represented in a graph)

6) Local skin reactions (qualitative)

7) Participant's perception of efficacy

8) New/subclinical lesions

Efficacy

Methods: 1. quantitative assessment using lesion counting, 2. qualitative assessment using physician's global assessment and participant's perception of efficacy

Time points: at baseline and weeks 4, 8, 12, 16, and 24

Definitions for physician's global assessment and the participant's perception of efficacy scales: 1 (very effective), 2 (moderately effective), 3 (slightly effective), 4 (not effective at all)

Safety

Methods: 1. physician's assessment of erythema on a 0 = none to 3 = severe scale, 2. participant perception of discomfort associated with the treatment.

Time points: at baseline and weeks 4, 8, 12, 16, and 24

Definitions for participant's perception of discomfort scale: 1 (very painful), 2 (moderately painful), 3 (slightly painful), 4 (not painful at all)

Funding	This study was supported by Valeant Pharmaceuticals International.
Notes	Treatment with 5-fluorouracil, but not imiquimod, uncovered and treated subclinical lesions.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 145): "Patients were randomly assigned to receive one of the following treatments to be applied in a thin layer to completely cover each affected cosmetic unit:.." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The 2 distinct dosing schedules were not concealed with a double-dummy technique.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessor was blinded.
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat was used.

Tanghetti 2007 *(Continued)*

All outcomes		Intervention - A: 1 dropout (the reason was reported) Control - B: 2 dropouts (the reasons were provided)
Selective reporting (reporting bias)	High risk	Values for participant's perception of efficacy were not presented.
Other bias	Unclear risk	-

Tarstedt 2005

Methods	This was a randomised, open, active-controlled, parallel-group study. Start date: January 2002 End date: October 2002
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Men and women • Aged 18 years and older • Anatomical locations: face and scalp • ≤ 10 mild (grade 1: slightly palpable, better felt than seen, i.e. thin lesions) or moderate (grade 2: easily palpable lesions) actinic keratoses **Demographics** • 211 participants (413 lesions): 105 - single treatment, 106 - 2 treatments • 82 men, 129 women • Age: mean = 68
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-photodynamic therapy (PDT) once (N = 105 participants) **Control intervention** B: MAL-PDT twice with a 1 week interval (N = 106 participants) There was possible retreatment for single treatment group (not included in meta-analysis). Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 or 2 Interval between treatments: 1 week Preparation of lesions: crusts removed by curettage and gentle scrapping Cream concentration (%): 16 Application of cream: 1 mm thick onto lesion and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: red light Light source: Aktilite CL 16

Tarstedt 2005 *(Continued)*

	Wavelength (nm): 590-670 Energy fluence (J/cm^2): 37 Intensities (mW/cm^2): 750 to 2050 Exposure time: 8 min
Outcomes	**Outcomes of the trial** 1) Lesion complete response at 3 months post-treatment 2) Participant complete response (= participant complete clearance) 3) Participants experiencing at least 1 adverse event 4) Local adverse events 5) Lesion cosmetic outcomes Efficacy Methods: assessment by investigator Time points: at 3 months post-treatment Definitions: 1. lesion complete response (complete disappearance of the lesion), 2. lesion non-complete response (incomplete disappearance of the lesion) Safety Methods: recording of adverse events, including local phototoxicity reactions that normally occur after PDT, and rating as mild, moderate, or severe (the clinician assessed the causal relationship of any adverse events to the study treatment as related, uncertain, or not related) Time points: before and after illumination, and at 3 months post- treatment Cosmetic Methods: assessment of hypopigmentation, hyperpigmentation, scar formation, and tissue defect by their rating as none, slight, or obvious for each lesion that had responded completely Time points: at 3 months post-treatment
Funding	This study was supported by PhotoCure ASA.
Notes	A sample size calculation was provided. Data for intention-to-treat analysis were used for the meta-analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 425): "The randomisation was performed after the patient was included in the study." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to conceal the allocation.

Tarstedt 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was open.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This study was open.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Intervention - A: 0 dropouts Control - B: 6 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Low risk	The results were similar to previously reported data in an abstract.
Other bias	Unclear risk	-

Thompson 1993

Methods	This was a single -centre, randomised, placebo-controlled, parallel-group study. Start date: September 1991 End date: March 1992
Participants	**Inclusion criteria of the trial** • Clinical diagnosis during a by-invitation free skin-cancer screening and histological diagnosis on a randomised subsample of participants • Living in Maryborough and surrounding districts in the state of Victoria, Australia • Aged 40 years and older • Anatomical locations: head, neck, forearms, and hands • 1 to 30 solar keratoses **Exclusion criteria of the trial** • Any lesion treated by a doctor during the course of the study was excluded from analysis **Demographics** • 588 white participants randomised, 431 evaluable participants • 180 men, 251 women • Age: mean = 63; range = 40 to 93
Interventions	**Intervention** A: sunscreen SPF 17 (8% 2-ethyl-hexyl p-methoxycinnamate/2% 4-tert-butyl-4-methoxy-4-dibenzoyl-methane), as needed daily for 7 months (N = 221 evaluable participants) **Control intervention** B: placebo, as needed daily for 7 months (N = 210 evaluable participants)
Outcomes	**Outcomes of the trial**

Thompson 1993 *(Continued)*

	1) Mean reduction/increase in lesion counts at 7 months (= mean reduction in lesion counts) 2) New lesions 3) Number and per cent of baseline lesion remitting (= lesion complete response) 4) Compliance Efficacy Methods: quantitative assessment using recording of lesions Time points: at baseline and 7 months (end of the trial) Definitions: incident lesions (the number of new lesions appearing during the study) Safety Methods: recording of any untoward reactions to the creams
Funding	This study was supported by grants from the Victorian Health Promotion Foundation, Melbourne; the Skin and Cancer Foundation, Sydney; the Skin and Psoriasis Foundation, Melbourne; the Uoyd Williams Trust, Maryborough; the Sydney Melanoma Foundation; and the Australasian College of Dermatologists.
Notes	A sex-based difference in the change in the number of lesions was noted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation was achieved by stratification according to sex and self-rated skin.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This was not stated. Base cream (vehicle) and sunscreen cream had the same consistency by adding 10% mineral oil to the vehicle. Participant blinding concealment was tested by a question at the end of study, and answers were not significant for both treatment arms.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not stated.
Incomplete outcome data (attrition bias) All outcomes	High risk	The type of analysis was unclear. The initial number of participants randomised and the number of dropouts (157) were given for the 2 groups together. The reasons for withdrawal were provided in a table, but because 1 participant could have more than 1 reason, it was impossible to determine how many participants withdrew in each treatment group.
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Tong 1996

Methods	This was a randomised, double-blind, placebo-controlled, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Anatomical locations: arms • 10 to 50 actinic keratoses on each arm **Exclusion criteria of the trial** • Oral steroids • Immunosuppressive therapy • Previously treated with liquid nitrogen or 5-fluorouracil within 30 days **Demographics** • 20 participants • wWhite participants with skin phototype 1 • 11 men, 9 women • Age: mean = 69; range = 52 to 93
Interventions	**Intervention** A: β-1,3-D-glucan, twice daily for 7 days (N = 20 participants) **Control intervention** B: placebo, twice daily for 7 days (N = 20 participants)
Outcomes	**Outcomes of the trial** 1) Mean lesion counts (converted to mean reduction of lesion counts) 2) Tolerability (= local skin/adverse reactions) 3) Minor adverse events Efficacy Methods: quantitative assessment using lesion counting by the same investigator Time points: at baseline, and weeks 1, 4, and 8 Safety Methods: 1. grading of erythema and burning/stinging as absent, mild, moderate, or severe, 2. participant-reported adverse events and concomitant medication use Time points: at baseline and weeks 1, 4, and 8
Funding	-
Notes	This was a pilot study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 137): "...the respective arms to which each preparation was applied were determined by randomisation.

Tong 1996 *(Continued)*

		Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	An unclear type of analysis was used. Intraindividual study: Intervention - A: 0 dropouts Control - B: 0 dropouts
Selective reporting (reporting bias)	High risk	All outcomes were presented even if efficacy was higher for placebo. The standard deviations associated with mean values were not given.
Other bias	Unclear risk	-

Ulrich 2007

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. Start date: November 2002 End date: September 2005

Participants	**Inclusion criteria of the trial**
	• HIstological confirmation of actinic keratosis
	• participants with 1 of 3 organ transplant types (kidney, liver, heart) more than 3 years prior to inclusion into the study, with stable status of the transplanted graft in the 12 months prior to entering the study
	• Immunosuppressive therapy must have been stable within the previous 6 months before enrolment, with an expectation that the therapy would remain stable for 7 months of study participation
	• Anatomical locations: face, forehead, or balding scalp
	• 4 to 10 clinically typical actinic keratoses within a continuous 100 cm^2 area
	Exclusion criteria of the trial
	• Unstable cardiovascular, immunological, haematological, hepatic, neurological, renal, endocrine, collagen-vascular, or gastrointestinal abnormalities or disease
	• Persistent hepatitis B, C infections, or both
	• Treatment as follows:
	  • within 3 days with steroids
	  • within 6 months with any systemic cancer chemotherapy or radiation therapy
	  • within 4 weeks with other systemic treatment including retinoids, interferons, or investigational drugs
	• Used any porphylatic antibody in the first 6 months after transplantation

Ulrich 2007 *(Continued)*

- Invasive malignant tumours of the skin within the treatment area within 6 months
- Vitamin A usage > 15000 units per day

Demographics

- 43 participants
- 29 men, 5 women
- Age: range = 37 to 76

Interventions	**Intervention** A: 5% imiquimod, 3 times per week for 16 weeks (N = 29 participants) **Control intervention** B: vehicle, 3 times per week for 16 weeks (N = 14 participants)
Outcomes	**Primary outcomes of the trial** 1) Safety of the graft (rejection) 2) Application site reactions (imiquimod only) 3) Skin irritation (qualitative) 4) Minor adverse events (imiquimod only) 5) Serious adverse events 6) Clinical laboratory tests **Secondary outcome of the trial** 1) Participant complete or partial (≥ 75%) clearance **Other outcomes of the trial** 1) Lesion complete response 2) Skin quality (cosmetic) Efficacy Methods: 1. quantitative assessment using clinical counting of visible lesions in the treatment area, 2. biopsy of a lesion mapped at baseline (week 24) Time points: at weeks 7, 12, and 16 (treatment period) and weeks 19 and 24 (post-treatment) Safety Methods: 1. monitoring of safety of the graft by an independent and blinded safety committee; monitoring of transplant rejection status, laboratory results, adverse events, local skin reactions, vital signs measurements, and the dosage of immunosuppressive medications, changes in haematology and serum chemistry (specifically: levels of serum creatinine, C-reactive protein, and proteinuria for renal transplant recipients; levels of gamma glutamyl-transpeptidase, glutamic-pyruvic transaminase, glutamic-oxalacetic transaminase, and bilirubin for liver transplant recipients; GOT and GPT, white cell blood count, serum creatinine, haemoglobin, and signs of heart failure for heart transplant recipients), 2. assessment of local skin reactions (erythema, oedema, erosion/ulceration, scabbing/crusting, weeping/exudate, vesicles, and flaking/scaling/dryness) Time points: at weeks 1, 2, 3, 5, 7, 9, 12, and 16 during the treatment period, and weeks 19 and 24 post-treatment Cosmetic

Ulrich 2007 *(Continued)*

	Methods: assessment of skin quality of the treatment area (skin surface, hyperpigmentation, hypopigmentation, the degree of scarring, and any atrophy) Time points: at the 8-week post-treatment visit (week 24)
Funding	This study was supported by 3M Pharmaceuticals.
Notes	The participants were organ transplant recipients, i.e. immunocompromised participants. There was no graft rejection during the study. There was an increase in the number of lesions in the vehicle group only. Clinical clearance was confirmed histologically.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 3): "Baseline data were collected, and the patients were randomised to study drug." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 4 dropouts (the reasons were reported) Control - B: 6 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	Little was reported on skin quality outcomes. A lot of outcomes were reported for the imiquimod-treated group only. All outcomes from the protocol (NCT00189267) were reported in the published study.
Other bias	Unclear risk	-

Ulrich 2010

Methods	This was a randomised, double-blind, vehicle-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Participants with kidney (± pancreas), liver, or heart transplantation within 3 years and stable status of the transplanted graft in the 12 months prior to entering the study • Criteria for determining the stability of grafts were specific to each transplant type • Immunosuppressive therapy must have been stable within the previous 6 months before enrolment and during therapy with the study drug

Ulrich 2010 *(Continued)*

- Anatomical locations: face, forehead, hands, balding scalp
- ≥ 3 actinic keratoses within 50 cm^2

Exclusion criteria of the trial

- Severe renal or hepatic impairment or had any evidence of graft rejection
- Ongoing treatments for actinic keratosis
- Evidence of invasive skin cancers
- Evidence of unstable and severe cardiovascular, immunological, hematologic, hepatic, neurological, renal, endocrine, collagen-vascular, gastrointestinal or non-study related skin abnormalities or disease
- Malignant tumours of the skin within the treatment area within 6 months
- Evidence of systemic cancer or any systemic cancer chemotherapy or radiation therapy within 6 months
- Other systemic treatments, including retinoids, interferons, or investigational drugs, within 4 weeks of study initiation
- Vitamin A usage > 15,000 units per day
- Women of child-bearing potential could not be pregnant or nursing, and they must have been willing to use medically-accepted methods of contraception
- History of hypersensitivity or allergy to any of the ingredients of active drug or vehicle or other non-steroidal anti-inflammatory drugs

Demographics

- 32 participants
- 31 men, 3 women
- Age: range = 49 to 77

Interventions

Intervention

A: 3% diclofenac in 2.5% hyaluronic acid, twice daily for 16 weeks (N = 24 participants)

Control intervention

B: vehicle, 2.5% hyaluronic acid, twice daily for 16 weeks (N = 8 participants)

Outcomes

Outcomes of the trial

1) Participant complete clearance at 20 weeks and 24 months (recurrence)

2) Participant partial (≥ 75%) clearance at 20 weeks and 24 months (recurrence)

3) Average percentage reduction of lesions at 20 weeks (= mean percentage of lesion counts)

4) Safety of the graft (rejection)

5) Minor adverse events (qualitative)

6) Skin irritation (tolerability, presented graphically)

7) Clinical laboratory tests

8) Cosmetic outcomes

9) Skin quality (cosmetic) at 20 weeks

10) 24-month follow up for development of new lesions and invasive squamous cell carcinoma

Efficacy

Methods: 1. quantitative assessment using clinical counting of visible lesions supported by a transparent grid, 2. 3 to 4 mm punch biopsy of a target lesion mapped at the initiation visit

Ulrich 2010 *(Continued)*

	Time points: at baseline, at each visit (weeks 4, 8, 12, 16) and at the post-treatment visit (week 20) Definitions: 1. complete clearance rate (proportion of participants at the 4-week post-treatment visit who had no evidence of lesions on the histology results of a target biopsy lesion site and no clinically-visible lesions in the remainder of the treatment area), 2. partial clearance rate (proportion of participants at the 4-week post-treatment visit who obtained at least 75% reduction in the number of lesions counted at baseline in the treatment area), 3. clearance rate of individual lesions (percentage reduction of lesions from baseline to the 4-weeks post-treatment visit) Safety Methods: monitoring of transplant rejection status, laboratory results, adverse events, local skin reactions, vital signs measurements, and the dosage of immunosuppressive medications; clinical laboratory analyses: serum levels of immunosuppressive medication; levels in serum creatinine, C-reactive protein, and proteinuria for renal transplant recipients; gamma glutamyltranspeptidase, glutamic-pyruvic transaminase, glutamicoxalacetic transaminase, and bilirubin for liver transplant recipients; GOT and GPT, white cell blood count, serum creatinine, hemoglobin, and signs of heart failure for heart transplant recipients) Time points: at each visit (weeks 4, 8, 12, 16) and at the post-treatment visit (week 20) Cosmetic Methods: assessment of skin quality by investigator based on skin surface, hyperpigmentation, hypopigmentation, the degree of scarring, and any atrophy Time points: at the post-treatment visit (week 20)
Funding	This study was supported by Shire Pharmaceuticals.
Notes	New actinic keratoses developed at an average of 9.3 months, but no invasive squamous cell carcinoma developed within a period of 24 months.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page): "Patients with one of three organ transplant types (kidney, liver, heart) were randomised 3:1 (active:vehicle) in this vehicle-controlled, double-blind, parallel group design." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Intervention - A: 2 dropouts (the reasons were reported) Control - B: 2 dropouts (the reasons were reported)

Ulrich 2010 *(Continued)*

Selective reporting (reporting bias)	High risk	There was discrepancy in the number of participants completely cleared between the abstract and published report. The lowest number in the published report was used for meta-analysis.
Other bias	Unclear risk	-

Van der Geer 2009

Methods	This was a randomised, double-blind, vehicle-controlled, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • General good health • Anatomical locations: dorsum of the both hands • With extensive actinic keratosis (minimum affected area of 5 X 5 cm) **Exclusion criteria of the trial** • Allergy to aspirin or other NAIDs • History of gastrointestinal ulcer or bleeding • History of skin cancer on the dorsum of the hands • Dermatologic disease that could affect the amount of absorption or accumulation of diclofenac • Pregnancy, breastfeeding • Participants with actinic keratosis due to immune suppressive disease or immune suppressive medication • Treatment within the last 60 days with topical or oral treatment for actinic keratoses **Demographics** • 10 participants • 6 men, 4 women • Age: mean = 67; range = 50 to 77
Interventions	**Intervention** A: 3% diclofenac in 2.5% hyaluronic acid gel twice daily for 4 weeks, 2 weeks off followed by aminolevulinic acid (ALA)-photodynamic therapy (PDT) (N = 10 participants) **Control intervention** B: 2.5% hyaluronic acid gel twice daily for 4 weeks, 2 weeks off followed by ALA-PDT (N = 10 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment Number of treatments: 1 Interval between treatments: -- Preparation of lesions: no Cream concentration (%): -- Application of cream: --

Van der Geer 2009 *(Continued)*

	Incubation with cream: occlusive dressing over cream for 4 hours Type of light: red light Light source: Omnilux Wavelength (nm): 633 Energy fluence (J/cm^2): 80 Intensities (mW/cm^2): -- Exposure time: 16 minutes (fractions)
Outcomes	**Outcomes of the trial** 1) Mean reduction of lesion counts in a 5 X 5 cm area 2) Participant and investigator global improvement indices (GIIs) expressed as scores 3) Total thickness scores 4) Pain score 5) Severe local adverse reactions (qualitative) Efficacy Methods: 1. quantitative assessment using lesions counting in a 5 X 5 cm area, 2. assessment of lesion thickness visually and by palpation and scored on a 1 to 4 scale, 3. qualitative assessment of global improvement by the investigator and the participant (an independent dermatologist evaluated the efficacy by using photographs) Time points: at baseline, at 6 weeks and 6 months after PDT, and 8 of 10 participants were examined 12 months post-treatment. Definitions: 1. total lesion score (number of lesions counted in 5 × 5 cm area), 2. total thickness score (sum of the thickness scores for individual lesions) Definitions for thickness score: 1 (lesion visible, but not palpable), 2 (lesion visible and palpable), 3 (elevated and keratotic lesion), 4 (hyperkeratotic lesion > 1 mm in thickness) Definitions for GIIs: –2 (significantly worse), –1 (slightly worse), 0 (no change), 1 (some improvement), 2 (moderate improvement), 3 (significant improvement), 4 (complete remission) Safety Methods: 1. scoring of pain, 2. participant-recorded side-effects in daily diary (number and severity) Time points: 1. during PDT (pain), 2. at each visit (side-effects) Definitions for pain score: 0 (painless), 1 (mild pain), 2 (moderate pain), 3 (severe pain), 4 (unbearable pain)
Funding	-
Notes	This was a pilot study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 260): "The pharmacist of the hospital randomly assigned the vehicle to 1 hand and the active drug to the other hand on each patient."

Van der Geer 2009 *(Continued)*

		Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Low risk	A third party (the pharmacist) randomly assigned the vehicle to 1 hand.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent dermatologist evaluated the efficacy.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified intention-to-treat (ITT, exclusion of only 1 participant who withdrew before PDT) was used. Intraindividual study: Intervention - A: 2 dropouts (the reasons were reported) Control - B: 2 dropouts (the reasons were reported)
Selective reporting (reporting bias)	High risk	Only mean values were reported i.e. the associated standard deviations were not provided.
Other bias	Unclear risk	-

von Felbert 2010

Methods	Randomised, double-blind, active-controlled, parallel-group study The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • White participants • Anatomical locations: face or scalp • Untreated, non-pigmented grade I (hardly visible, slightly palpable) or II (easily visible and palpable) actinic keratoses **Exclusion criteria of the trial** • Age under 45 years or over 85 years • Immunosuppression for idiopathic, disease-specific, or therapeutic reasons • Porphyria • Known hypersensitivity to porphyrins • Known photodermatoses or photosensitivity • Known allergy to MAL • Pregnancy, lactation • Diagnosis of basal cell carcinoma • Hyperkeratotic actinic keratoses • Treatment as follows:

von Felbert 2010 *(Continued)*

- within 2 weeks with photosensitising pharmaceuticals; topical treatments with corticosteroids, retinoids, 5-fluorouracil ,or imiquimod
- within 3 months with systemic retinoids, chemotherapy, or immunotherapy
- within 2 months with laser resurfacing, chemical peels, cryotherapy, or photodynamic therapy (PDT)

- Participation in other studies within the last 3 months

Demographics

- 80 participants
- 71 men, 9 women
- Age: mean = 70; range = 56 to 85

Interventions	2 subgroups: with and without cooling spray **Intervention** A: methyl aminolevulinate (MAL)- visible + water-filtered infrared A (VIS + wIRA) PDT (N = 40 participants) **Control intervention** B: MAL-light-emitting diode (LED) red light PDT (N = 40 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment Number of treatments: 1 or 2 Interval between treatments: 3 months Preparation of lesions: gentle removal of scales Cream concentration (%): 16 Application of cream: 1 mm thick to lesion area and 5 mm of surrounding normal tissue Incubation with cream: occlusive dressing over cream for 3 hours Type of light: visible + water-filtered infrared A (VIS + wIRA) or LED red light Light source: Hydrosun type 505 Broadband with 7-mm water cuvette and orange filter OG590 (VIS + wIRA), Aktilite CL 128 (red light) Wavelength (nm): 580-1400 (VIS + wIRA), 630 (red light) Energy fluence (J/cm^2): 240 including 60 VIS (VIS + wIRA), 37 (red light) Intensities (mW/cm^2): 200 including 50 VIS (VIS + wIRA), 75 (red light) Exposure time: 20 minutes (VIS+ wIRA), 8 minutes (red light)
Outcomes	**Outcomes of the trial** 1) Participant complete and partial (≥ 75%) clearance at 3 (1 treatment), 6 (1 or 2 treatments), and 12 (1 or 2 treatments) months 2) Efficacy on a visual assessment scale (VAS) 3) Pain on a VAS (first outcome presented) 4) Local skin reactions 5) Serious adverse events

von Felbert 2010 *(Continued)*

	6) Satisfaction and quality of life on a VAS 7) Number of spray cooling and illumination interruptions Efficacy Methods: 1. documentation of the global aspect of total actinic keratosis area by physicians, 2. rating of efficacy on a VAS [-50 mm (extreme worsening), 0 mm (unchanged), +50 mm (extreme improvement)], 3. rating of efficacy on a five-point scale-rated variable 'percentage of the cleared area in relation to the initial total actinic keratosis area' (100% clearance, ≥ 75% of the total area cleared, ≥ 50% of the total area cleared, ≥ 25% of the total area cleared, no relevant part of the area cleared) Time points: before PDT; at 2 weeks; and at 3, 6, and 12 months after the first PDT Safety Methods: 1. evaluation of the extent of erythema, scaling, crusts, indurations, erosions, ulcerations, and oedema on a VAS [0 (non-existent) to 100 mm (extremely high)] by physicians, 2. evaluation of the intensity of pain, side-effects on a VAS [0 (none) to 100 mm (extremely high)] by participants Time points: 1. before PDT; 2 weeks; and 3, 6, and 12 months after the first PDT, 2. 2, 4, 6, 8, 10, 13, 15, 20, 22, and 25 minutes after the start of PDT (pain) Cosmetic Methods: 1. evaluation of the extent of skin atrophy, scar formation, and pigmentation on a visual analogue scale (VAS) [0 (non-existent) to 100 mm (extremely high)] by physicians, 2. assessment of cosmetic appearance by physicians and participants [VAS: 0 (extremely bad) to 100 mm (extremely good)] Time points: before treatment; at 2 weeks; and at 3, 6, and 12 months after the first PDT
Funding	This study was supported by Erwin Braun Foundation.
Notes	Efficacy was lower in participants receiving cooling spray.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 608): "The patient number was randomly assigned to either group 1 (VIS + wIRA PDT, n = 40 patients) or group 2 (red light PDT, n = 40 patients, Table 1)." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was a double-blinded. Quote (page 609): "Both patients and investigators remained blinded until study completion."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessor was not involved in treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used. Intervention - A: 1 dropout (the reasons were reported)

von Felbert 2010 *(Continued)*

		Control - B: 3 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Weiss 2002

Methods	This was a multicentre, randomised, double-blind (treatment vs placebo),open (treatment duration), vehicle-controlled, parallel-group study. The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	
	• Aged 18 years and older
	• Anatomical locations: face or frontal scalp
	• ≥ 5 actinic keratoses (≥ 4 mm in diameter)
	
	Exclusion criteria of the trial
	
	• Basal or squamous cell carcinoma
	• Other confounding skin conditions
	• History of cutaneous hyperreactivity or facial skin irritation to topical products
	• Excessive sunlight exposure
	• Treatment as follows:
	  • within 6 months with fluorouracil or systemic cancer chemotherapy
	  • within 1 month with other topical treatments for actinic keratoses
	
	Demographics
	
	• 177 participants
	• 152 men, 25 women
	• Age: range = 35 to 89

Interventions	**Interventions** A: 0.5% fluorouracil cream (microsphere) applied once daily to affected areas for 1 week with 4 week follow-up (N = 38 participants) B: 0.5% fluorouracil cream (microsphere) applied once daily to affected areas for 2 weeks with 4 week follow-up (N = 41 participants) C: 0.5% fluorouracil cream (microsphere) applied once daily to affected areas for 4 weeks with 4 week follow-up (N = 40 participants) **Control intervention** D: vehicle applied once daily to affected areas for 1, 2, or 4 weeks with 4-week follow-up (N = 58 participants)
Outcomes	**Outcomes of the trial** 1) Physician global assessment of improvement (PGAI = global improvement indices) 2) Proportion of participants achieving total clearance (= participant complete clearance) 3) Per cent reduction of lesions (= mean percentage of reduction in lesion counts)

Weiss 2002 *(Continued)*

	4) Mean number of lesions at baseline and end of study (transformed to absolute mean reduction in lesion counts) 5) Median number of lesions at baseline and end of study 6) Skin irritation (number of participants, severity, overtime) 7) Serious adverse events Efficacy Methods: 1. quantitative assessment using lesion counting, 2. qualitative assessment using PGAI (+5 = total clearance and -4 = much worse) reported as mean score Time points: at baseline and 4 weeks post-treatment Safety Methods: 1. monitoring of adverse events (onset, duration, severity, and frequency), 2. separate recording for adverse events affecting the facial skin and scalp, 3. monitoring of facial irritation including maximum severity (0 = none, 1 = mild, 2 = moderate, or 3 = severe), symptoms (edema, erythema, dryness, erosion, pain, burning), onset, overall duration, and post-treatment duration Time points: during treatment: days 1 and 8 (1-week groups); days 1, 8, and 15 (2-week groups); or days 1, 8, 15, and 29 (4-week groups); post-treatment: weekly visits and a final evaluation 4 weeks after completing or discontinuing treatment
Funding	-
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 23): "Patients were randomised to receive 0.5% fluorouracil cream or vehicle control for 1, 2, or 4 weeks (Figure 1)." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This study was double-blinded (treatment vs placebo) and open (treatment duration). Indeed, placebo cream was not used to conceal allocation to 1, 2 , or 4 weeks.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Different assessment time points were used for 1-, 2-, or 4-week groups.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat (ITT) analysis was used. Intervention - A: 1 dropout (the reason was not reported), B: 1 dropout (the reason was reported), C: 4 dropouts (the reasons were reported) Control - D: 1 dropout (the reason was not reported)

Weiss 2002 *(Continued)*

Selective reporting (reporting bias)	High risk	The standard deviations associated with the mean number of lesions and percentages were not reported. Adverse events were not reported in this study, but they were reported in a similar study included (Jorizzo 2002).
Other bias	High risk	There was slight difference (P = 0.048) in the women ratio [more in 4-week group (C) and less in placebo group (D)] at baseline.

Wiegell 2008

Methods	This was a single-centre, randomised, assessor-blind, active-controlled, intraindividual study. Start date: May 2006 End date: February 2007
Participants	**Inclusion criteria of the trial** • General good health • Anatomical locations: face or scalp • Symmetrical distribution of actinic keratoses within 80 cm^2 area **Exclusion criteria of the trial** • Pregnancy and lactation **Demographics** • 30 participants • 23 men, 7 women • Age: mean = 78; range = 63 to 90
Interventions	**Intervention** A: methyl aminolevulinate (MAL)-red light photodynamic therapy (PDT) (N = 30 participants) **Control intervention** B: MAL-daylight PDT (N = 30 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment Number of treatments: 1 Interval between treatments: -- Preparation of lesions: crusts and hyperkeratoses removed Cream concentration (%): 16.8 Application of cream: 1 g applied to lesion area Incubation with cream: occlusive dressing over cream for 0.5 hour (daylight) and 3 hours (red light) Type of light: LED red light or daylight Light source: Aktilite CL 128 (red light), sun (daylight) Wavelength (nm): 575-670 (red light), 290-670 (daylight)

Wiegell 2008 *(Continued)*

	Energy fluence (J/cm^2): 37 (red light), 11.7-65.9 (mean = 43.2, measured with a dosimeter) Intensities (mW/cm^2): -- Exposure time: 2.5 hours (daylight)
Outcomes	**Outcomes of the trial** 1) Mean reduction in lesion counts at 3 months post-treatment 2) Local adverse events 3) Participant's pain scores 4) Participant's satisfaction Efficacy Methods: quantitative assessment using counting, grading (Olsen 1991), mapping, and photography of lesions Time points: before treatment and at 3 months post-treatment Definitions: 1. complete response (complete disappearance of the lesion), 2. non-complete response (incomplete disappearance of the lesion) Safety Methods: 1. scoring (0 = no pain to 10 = worst imaginable pain) of the pain in the 2 treated areas by participants, 2. evaluation of adverse events (erythema, crusting or pain) Time points: 1. during daylight exposure, during red LED light illumination, and after treatment (pain), 2. at 1 to 3 days after PDT (adverse events)
Funding	This study was supported by The Eva and Henry Frænkels Memorial Foundation.
Notes	PpIX fluorescence measured before, during, and after treatments showed less fluorescence associated with daylight. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation sequence generation was achieved by drawing lots.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes were used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	The 2 treatments were physically distinct.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The evaluator was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Per-protocol (PP) analysis was used. Intraindividual study: Intervention - A: 1 dropout (the reason was reported)

Wiegell 2008 *(Continued)*

		Control - B: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	Unclear risk	No outcomes were specified in the protocol (NCT00432224).
Other bias	Unclear risk	-

Wiegell 2009

Methods	This was a randomised, double-blind, active-controlled, intraindividual study. Start date: June 2007 End date: December 2007
Participants	**Inclusion criteria of the trial** • General good health • Capable of following the protocol instructions • Anatomical locations: face or scalp • 2 symmetrical areas of 80 cm^2 **Exclusion criteria of the trial** • Pregnant or lactating women **Demographics** • 30 participants • 26 men, 4 women • Age: mean = 71; range = 51 to 94
Interventions	**Intervention** A: 16% methyl aminolevulinate (MAL)-daylight photodynamic therapy (PDT) (N = 30 participants) **Control intervention** B: 8% MAL -daylight PDT (N = 30 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment Number of treatments: 1 Interval between treatments: -- Preparation of lesions: sunscreen SPF20, crusts and hyperkeratoses removed Cream concentration (%):8 or 16 Application of cream: 1 g applied to lesion area Incubation with cream: all day Type of light: daylight Light source: sun (daylight) Wavelength (nm): 290-670 (daylight)

Wiegell 2009 *(Continued)*

	Energy fluence (J/cm^2): measured with dosimeter Intensities (mW/cm^2): -- Exposure time: all day
Outcomes	**Outcomes of the trial** 1) Mean reduction in lesion counts 2) Total lesion count (lesion complete response) 3) Pain scores 4) Erythma scale and per cent by measurements before and after treatment with skin reflectance meter 5) Participant's preference Efficacy Methods: quantitative assessment using counting, grading (Olsen 1991), mapping, and photography of lesions Time points: before treatment and at 3 months post-treatment Definitions: 1. complete response (complete disappearance of the lesion), 2. non-complete response (incomplete disappearance of the lesion) Safety Methods: 1. scoring (0 = no pain to 10 = worst imaginable pain) of the pain in the 2 treated areas by participants in a diary every hour, 2. evaluation of adverse events (erythema, crusting, or pain) visually on a 4-point scale by a dermatologist, 3. quantitative evaluation of erythema [erythema percentage measured with a skin reflectance meter (Optimize Scientific; Chromo Light Aps,Skodsborg, Denmark)] Time points: 1. during daylight exposure, during red LED light illumination, and after PDT (pain), 2. 1 to 3 days after PDT(adverse events), 3. before curettage and on the day after PDT (erythema evaluation) Definitions for visual evaluation of erythema: 1. 0 (no visible erythema), 2. (+) (just perceptible erythema), 3. + (uniform erythema), 4. ++ (bright red erythema and induration)
Funding	-
Notes	PpIX fluorescence was measured using fluorescence camera, and there was no difference between the 2 cream concentrations. There was a correlation with light exposure/dose and response rate. Pain increased with light exposure. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Adequate randomisation sequence was achieved by drawing lots.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes were used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (page 1309): "The evaluating dermatologist and participants were blinded to the concentrations of creams."

Wiegell 2009 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote (page 1309): "The evaluating dermatologist and participants were blinded to the concentrations of creams."
Incomplete outcome data (attrition bias) All outcomes	Low risk	The type of data analysis was unclear, but only 1 participant was lost to follow up. Intraindividual study: Intervention - A: 1 dropout (the reason was reported) Control - B: 1 dropout (the reason was reported)
Selective reporting (reporting bias)	High risk	The number of participants and average time spent outside were different between the abstract and published report. There was a little confusion regarding the type of efficacy outcome reported in the abstract.
Other bias	Unclear risk	-

Wiegell 2011a

Methods	This was a multicentre, randomised, active-controlled, parallel-group study. Start date: June 2008 End date: January 2009

Participants	**Inclusion criteria of the trial**
	• Clinical diagnosis
	• Men and women
	• Aged 18 years and older
	• Anatomical locations: face and scalp
	• ≥ 5 actinic keratoses within 25 cm^2
	• All lesion grades were treated but only grade I (slightly palpable, more easily felt than seen) lesions were included in the data analysis
	Exclusion criteria of the trial
	• Women of child-bearing potential
	• Porphyria
	• Known allergy to any of the constituents of the methyl aminolevulinate (MAL) cream
	• Treatment as follows
	  • within 4 weeks with any actinic keratosis treatment in the treatment area
	  • within 3 months with oral immunosuppressives
	• Any conditions associated with a risk of poor protocol compliance
	Demographics
	• 120 participants
	• 96 men, 24 women
	• Age: mean = 72; range = 47 to 95

Interventions	**Intervention** A: 2h MAL-1.5h daylight photodynamic therapy (PDT) (N = 58 participants)

Wiegell 2011a *(Continued)*

Control intervention

B: 3h MAL-2.5h daylight PDT (N = 62 participants)

Characteristics of PDT intervention

Type of treatment: field-directed treatment

Number of treatments: 1

Interval between treatments: --

Preparation of lesions: sunscreen SPF20, crusts and hyperkeratoses removed

Cream concentration (%): 16

Application of cream: thick layer applied to lesion area

Incubation with cream: 2 or 3 hours (0.5 hour without light exposure)

Type of light: daylight

Light source: sun (daylight)

Wavelength (nm): 290-670 (daylight)

Energy fluence (J/cm^2): 8.6 (1.5 hours), 10.2 (2.5 hours)

Intensities (mW/cm^2): --

Exposure time: 131 ± 37 min (1.5 hours) or 187 ± 52 min (2.5 hours)

Outcomes

Primary outcomes of the trial

1) Mean reduction in lesion counts at 3 months post-treatment

2) Mean percentage of reduction in lesion counts at 3 months post-treatment [which correspond to the primary and only outcome "response rate" in the protocol NCT00711178 based on the published report (see efficacy definitions below)]

Other outcomes of the trial

1) Pain scores

2) Local adverse reactions: erythema and pustular eruptions (pooled data)

3) Participants' satisfaction

4) New actinic keratosis lesions

Efficacy

Methods: quantitative assessment using lesion grading and counting using a template

Time points: at baseline and 3 months post-treatment

Definitions: 1. lesion response rate (number of completely responding lesions divided by the number of lesions treated within the individual participants), 2. complete response (complete disappearance of the lesion, visually and by palpation - mild erythema might
remain), 3. non-complete response (incomplete disappearance of the lesion, visually and by palpation)

Safety

Methods: 1. participant-recorded pain score (0 = no pain and 10 = worst imaginable pain) in diary, 2. erythema and pustular eruption rating by investigators (other adverse events were recorded if the investigators considered these to be related to treatment)

Wiegell 2011a *(Continued)*

	Time points: 1. every half hour during the day of treatment and 4 time-points the following day (pain), 2. at 2 days after PDT (erythema and pustules) Definitions for erythema rating: 1. none (no redness), 2. mild (visibly pink colour), 3. moderate (red colour), 4. severe (dark red purple) Definitions for pustular eruptions rating: 1. none (no pustules), 2. mild (few pustules), 3. moderate (several pustules), 4. severe (severe pustular eruption with yellow crusting)
Funding	This study was supported by Department of dermatology, Bisebjerg Hospital, Copenhagen.
Notes	The effective daylight dose was measured with electronic wristband dosimeter. The weather conditions were monitored every half hour in diary. An increase in pain and erythema was associated with higher effective light dose. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "The randomisation procedure was performed by a computer-generated sequence blocked by centre."
Allocation concealment (selection bias)	Low risk	Quote (page 2): "Allocations were contained in opaque, sequentially numbered, sealed envelopes and were concealed from assessors throughout the study."
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not stated, but the participants were exposed to light for different periods of time.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was assessor-blinded (based on the protocol NCT00711178, clinicaltrials.gov).
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat (ITT) analysis was used for primary outcomes, and per-protocol (PP) analysis was used for secondary outcomes. Intervention - A: 1 dropout (the reason was reported) Control - B: 0 dropouts
Selective reporting (reporting bias)	Unclear risk	All primary outcomes were reported based on the protocol NCT00711178. Additional secondary outcomes, which were not included in our review, were also reported.
Other bias	Unclear risk	-

Wolf 2001

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Good general health • Outpatients

Wolf 2001 *(Continued)*

- Men and women using reliable contraception
- Aged 18 years and older
- Anatomical locations: forehead, central face, scalp, arms, hands
- ≥ 5 actinic keratoses in one to three 5 cm^2 treatment blocks

Exclusion criteria of the trial

- Known allergy to aspirin or other NSAIDs
- Dermatological condition that might interfere with absorption, accumulation or metabolism of the study medication
- Being treated with a disallowed concomitant medication (including masoprocol, 5-fluorouracil, etretinate, cyclosporine, retinoids, trichloroacetic acid peel or glycolic acid)

Demographics

- 120 enrolled participants, 118 received treatment, 117 analysed for safety (1 participant missing)

Interventions	**Intervention** A: 3% diclofenac gel in 2.5% hyaluronic acid gel, 0.5 g twice daily for 90 days (N = 58 participants based on safety data) **Control intervention** B: 2.5% hyaluronic acid gel only, 0.5 g twice daily for 90 days (N = 59 participants based on safety data)
Outcomes	**Primary outcomes of the trial** 1) Participant Global Improvement Indices = 4 2) Investigator Global Improvement Indices = 4 3) Participants with target lesion number score = 0 at 30 days post-treatment (= participant complete clearance) 4) Participants with cumulative lesion number score = 0 at 30 days post-treatment (= participant complete clearance) **Other outcomes of the trial** 1) Participants experiencing at least 1 adverse event 2) Application site reactions 3) Minor adverse events 4) Serious adverse events 5) Clinical laboratory tests Efficacy Methods: 1. quantitative assessment using lesion counting, 2. qualitative assessments (IGII and PGII) Time points: at each visit Definitions: 1. target lesion number score (number of lesions identified in the designated treatment blocks at baseline), 2. cumulative lesion number score (number of lesions identified -target or new-in the designated treatment blocks) Definitions for IGII and PGII 7-point scale: + 2 (significantly worse), +1 (slightly worse), 0 (no change), 1 (slightly improved), 2 (moderately improved), 3 (significantly improved), and 4 (completely improved) Safety

Wolf 2001 *(Continued)*

	Methods: 1. participant-recorded concomitant medications and adverse events in diary; 2. assessment of adverse events for duration, intensity, and causality by physician; 3. standard laboratory analyses [hematology, biochemistry, urinalysis, and serology (antidiclofenac)] Time points: at screening and end of treatment (laboratory tests)
Funding	This study was supported by Hyal Pharmaceutical Co.
Notes	A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 710): "One week after the Screening Visit, patients were randomised to receive either the active treatment, 3% diclofenac in 2.5% hyaluronan gel (SolarazeTM Bioglan) or placebo, which consisted of the inactive gel vehicle, hyaluronan only." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.
Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat (ITT) analysis was used, but the initial randomised numbers for each group were not given explicitly. Intervention - A: 14 dropouts (the reasons were reported) Control - B: 8 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Zeichner 2009

Methods	This was a single-centre, randomised, double-blind, placebo-controlled, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Anatomical locations: head • ≥ 6 actinic keratoses bilaterally symmetrically distributed within a 20 cm^2 area

Zeichner 2009 *(Continued)*

	Demographics • 20 participants • 16 men, 4 women • Age: mean = 75
Interventions	**Intervention** A: 5% imiquimod, once weekly for 24 weeks (N = 20 participants) **Control intervention** B: placebo, once weekly for 24 weeks (N = 20 participants)
Outcomes	**Outcomes of the trial** 1) Investigator assessment scale (= global improvement indice) 2) Total lesion number score 3) Local skin reactions (qualitative) 4) Serious adverse events 5) Skin irritation score (graph) Efficacy Methods: 1. qualitative assessment with an investigator assessment scale (7-point), and 2. quantitative assessment with lesion counting Time points: every 4 weeks during the treatment period and at 4 weeks post-treatment Definitions for the investigator assessment scale: -2 (much worse), -1 (slightly worse), 0 (no change), 1 (mild improvement), 2 (moderate improvement), 3 (marked improvement), 4 (cured) Definitions: total lesion number score (total number of lesions present in the target area was determined for each side, 0 = 0 lesion, 1 = 1 to 3, 2 = 4 to 6, 3 = > 6 lesions) Safety Methods: 1. monitoring the occurrence of local adverse events and systemic adverse events, 2. rating of skin irritation by participants on a 6-point scale (there was no objective measure of local side-effects) Time points: at each visit Definitions for skin irritation scale: 0 (no irritation), 1 (trace irritation), 2 (mild irritation) 3 (moderate irritation), 4 (marked irritation), 5 (severe irritation)
Funding	This study was supported by 3M Pharmaceuticals.
Notes	This was a pilot study. A sample size calculation was provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page): "Enrolled patients were randomised, 1:1, to apply imiquimod to a 20-cm^2area on the right or left side." Comment: Insufficient detail was reported about the method used to generate this allocation sequence.

Zeichner 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	This was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	This study was double-blinded.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This study was double-blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Per-protocol (PP) analysis was used with 25% of subjects lost. Intraindividual study: Intervention - A: 5 dropouts (the reasons were reported) Control - B: 5 dropouts (the reasons were reported)
Selective reporting (reporting bias)	Unclear risk	-
Other bias	Unclear risk	-

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alberts 2004	We assessed actinic damage in general, and the study was not specific to actinic keratoses. Only 60% of participants had clinically-evaluable actinic keratoses on the forearms.
Alexiades-Armenakas 2003	The study did not randomise all the participants.
Apalla 2010a	This was a conference abstract without numerical values for efficacy.
Apalla 2010b	The study did not meet the outcome requirements of the review.
Apalla 2010c	The efficacy of the intervention was on new actinic keratosis lesions (prevention), not on baseline lesions.
Babilas 2006	The study was not randomised. Predefined sides were treated with 2 different light sources for PDT, i.e. always the same side for 1 treatment.
Babilas 2007	The study did not meet the outcome requirements of the review.
Babilas 2008	The study did not meet the outcome requirements of the review.
Bartels 2009	The study did not meet the outcome requirements of the review.
Berlin 2008	The study was not randomised; the participants were allocated based on participant and physician judgement.
Biecha-Thalharnmer 2003	The study did not meet the outcome requirements of the review.

Study	Reason for exclusion
Braathen 2009	The study did not meet the outcome requirements of the review.
Breza 1976	The study did not present efficacy results numerically.
de Sévaux 2003	The study did not present efficacy results numerically; they were given in graphical form.
Dermik 2003	The study did not clearly present efficacy measures. The data were presented in graph form with no quantitative numbers.
Dirschka 2010	The study was randomised (90- versus 180-day treatments), but only partial data at 3 months were presented based on the conference abstract. And only data from the 90-day group were presented in the peer-reviewed paper, i.e. there was no comparison.
DUSA 2009	This trial was terminated due to "Orphan Drug Designation for this indication not granted".
Edwards 1986	The type of interventions were not covered in this review, i.e. injection in participant lesion.
Elmets 2010	This study was on the prevention of actinic keratosis lesions.
Epstein 2006	The study did not meet the outcome requirements of the review.
Ericson 2004	The study did not meet the outcome requirements of the review.
Fowler 2002	This was a follow-up study of an included study.
Gold 2006	It was not clear if the study was randomised.
Goldman 2003	The randomisation was based on participant preference, and there was no efficacy comparison between the 2 treatments.
Green 1998	Out of 80 participants, only 4 had actinic keratosis lesions, and mean lesions counts were reported for all subjects.
Griffin 1991	The randomisation was not mentioned. Little information was given.
Grimaître 2000	The randomisation was not mentioned.
Gupta 2004	The study did not meet the outcome requirements of the review.
Hanke 2011	This was a follow-up study for Hanke 2010; Swanson 2010a.
Humphreys 1996	Actinic keratosis lesions were not distinguished from lentigines for efficacy data.
Jury 2005	The criteria for outcomes was not met, i.e. median lesion counts were provided instead of mean lesion counts.
Kurwa 1999	This study did not meet the outcome requirements of the review; it presented results as the mean reduction in lesion area.
Marrero 1998	There was an inadequate method of randomisation: Every other participant was given a combination treatment on the left side of the face and a monotherapy treatment on the right. All other participants were given the opposite treatment.
Morales 2010	This study did not meet the outcome requirements of the review.

Study	Reason for exclusion
Naylor 1995	This study was on the prevention of actinic keratosis lesions formation, not an intervention to cure.
NCT00005097	The trial was terminated because of the low conditional power for a positive study.
Puizina-Ivic 2008a	This study did not meet the outcome requirements of the review.
Radakovic-Fijan 2005	This study did not meet the outcome requirements of the review.
Robins 2002a	50% of participants were lost to follow up. No statistics were reported. There was too much variability within and between groups as far as following instructions for application. There was no initial counting of lesions.
Rosen 2010	There was not enough information in this conference abstract of a phase II trial to be able to use the data.
Shuttleworth 1989	The type of interventions were not covered in this review, i.e. injection in participant lesion, and it was unclear if the study was randomised
Simmonds 1973	There were no numerical results.
Smith 2006	This study did not meet the outcome requirements of the review.
Sotiriou 2011	This study did not meet the outcome requirements of the review.
Spencer 2010	No enough numerical information was provided, e.g. number of participants in each of the 8 treatment groups.
Stockfleth 2004	This was a long-term follow-up to a previous study: Stockfleth 2002
Szeimies 2010a	This was a follow-up study of Hauschild 2009a; Hauschild 2009b; and Hauschild 2009c.
Touma 2004	The study did not present efficacy results numerically; they were given in graph form.
Tsoukas 2010	It was unclear if the study was randomised based on this conference abstract.
Valeant 2004	The randomisation was not mentioned.
Vbeam 2005	This trial was terminated due low accrual.
Weinstock 2010	The study did not present numerical data.
Wennberg 2008	This study was on prevention of new lesions and mixed lesion types, i.e. not only actinic keratoses.
Wulf 2006	This study does not provide efficacy data on intervention. The primary outcome was mean time to occurrence of first new lesion.
Yamauchi 2002	There was not enough information. Results taken from 2 studies and combined, i.e. no direct comparison.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Akarsu 2011

Methods	This was a single-centre, randomised, open, assessor-blinded, placebo- and active-controlled, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Clinical and histopathological diagnosis • Aged 18 years and older • Men and women who were otherwise healthy • Anatomical locations: face • 1 actinic keratose **Exclusion criteria of the trial** • Pregancy or lactation • Sensitivity to any component of the study medications • Use of medication for actinic keratoses or other systemic treatments within 1 month before the study **Demographics** • 68 participants randomised, 61 participants evaluated • 37 men, 31 women • Age: mean = 66; range = 42 to 87
Interventions	**Intervention** A: 3% diclofenac in 2.5% hyaluronic acid, twice daily for 12 weeks (N = 21 participants) **Control interventions** B: 5% imiquimod, twice per week for 16 weeks (N = 20 participants) C: placebo (Ultrabase cream; Schering Alman, Istanbul, Turkey), twice daily for 12 weeks (N = 20 participants)
Outcomes	**Outcomes of the trial** 1) Total thickness score (TTS) 2) Patient global improvement index (PGII) 3) Complete clearance (= lesion complete response) 4) Local skin reactions Efficacy Methods: quantitative assessment using a scale and photography of lesions Time points: before treatment and at every 4 weeks up to 24 weeks Definitions: 1. TTS scale, 0 = complete clearance, 1 = lesion visible but not palpable, 2 = lesion visible and palpable, 3 = lesion raised with visible scaling, 4 = lesion hyperkeratotic and > 1 mm in thickness; 2. PGII is a self-report scale, and participants evaluated themselves according to a 7-point scale (0 = significantly worse, 1 = slightly worse, 2 = no change, 3 = slightly improved, 4 = moderately improved, 5 = significantly improved, 6 = completely improved) Safety

Akarsu 2011 *(Continued)*

	Methods: evaluation of local skin reactions (erythema, oedema, erosion/ulceration, scabbing/crusting, weeping/exudates, vesicles, and scaling/dryness) on a 0 to 3 scale Time points: at every 4 weeks up to 24 weeks Definitions: 0 = none, 1 = mild, 2 = moderate, 3 =severe
Notes	-

Apalla 2011

Methods	This was a single-centre, randomised, open, assessor-blinded, intraindividual study. Start date: February 2009 End date: May 2010
Participants	**Inclusion criteria of the trial** • Clinical and histological diagnosis • Men and women • Anatomical locations: face or scalp • ≥ 3 actinic keratoses of similar severity, in terms of grade, size, and localisation **Exclusion criteria of the trial** • Dermatological diseases in the treatment area, including pigmented lesions and invasive tumours • Treatment for face and scalp actinic keratoses within the past 3 months • Photosensitivity, hypersensitivity to ALA or ALA-cream excipients • Pregnancy or breastfeeding **Demographics** • 50 white participants (3 lesions/participants were randomised) • 29 men, 21 women • Age: mean = 58; range = 38 to 75
Interventions	**Interventions** A: 50 mW/cm^2 ALA-red light photodynamic therapy (PDT) (N = 50 participants) B: 75 mW/cm^2 ALA-red light PDT (N = 50 participants) **Control intervention** C: 25 mW/cm^2 ALA-red light PDT (N = 50 participants) Characteristics of PDT intervention Type of treatment: individual lesion Number of treatments: 1 Interval between treatments: -- Preparation of lesions: -- Cream concentration (%): 20 Application of cream: --

Apalla 2011 *(Continued)*

	Incubation with cream: 4 hours with occlusion Type of light: red Light source: Waldmann PDT 1200 (non-coherent light) Wavelength (nm): 570-670 Energy fluence (J/cm^2): 75 Intensities (mW/cm^2): 25-75 Exposure time:-- At the 3-month follow-up visit, lesions without a complete response were treated with surgical techniques (cryosurgery or excision).
Outcomes	**Primary outcomes of the trial** 1) Pain on a visual analogue scale (VAS) during illumination **Secondary outcomes of the trial** 1) Lesion complete response at 3 and 12 months post-treatment 2) Adverse events (qualitative) Efficacy Methods: 1. quantitative assessment using lesion counting, Time points: at baseline; and at 3, 6, and 12 months post-treatment Definitions: 1. complete response (CR): complete absence of any clinical sign indicative of actinic keratoses, 2. non-complete response (non-CR): remaining clinical signs indicative of actinic keratoses Safety Methods: recording of adverse events Time points: from 5-ALA application time point until the end-of-study
Notes	-

Azimi 2012

Methods	This was a randomised, double-blind, placebo-controlled, parallel-group study. Start date: January 2010 End date: March 2011
Participants	**Inclusion criteria of the trial** • Aged 0 to 150 years • Men and women • Clinical diagnosis of actinic keratoses • ≥ 5 lesions • Willing to participate in the study **Exclusion criteria of the trial**

Azimi 2012 *(Continued)*

	• Pregnancy (first trimester)
	• Previous history of allergy to drugs of study
	• Treatment as follows:
	  • within 1 month with destructive methods, peeling methods, or drugs for treatment of lesions
	  • within 2 months with isotretinoin
	• Participation in the other clinical studies over the past month
	
	Demographics
	
	• 112 participants randomised, 100 evaluated
	• 88 men, 12 women
	• Age: mean = 67; range = 46 to 86

Interventions	**Intervention** A: cryotherapy followed by Acnalene 0.1% gel at day 10, twice daily for 3 months **Control intervention** B: cryotherapy followed by placebo at day 10, twice daily for 3 months
Outcomes	**Primary outcomes of the trial** 1) Changes in the average number of actinic keratosis lesions (= mean reduction in lesion counts) 2) Mean frequency of reduction (= mean percentage of reduction in lesion counts) 3) Clinical outcome based on change in lesion number [including 'recovery rate of over 75%' (= participant partial (≥ 75%) clearance)] **Secondary outcomes of the trial** 1) Adverse events 2) Cosmetic outcomes Efficacy Methods: quantitative assessment by lesion counting and photography Time points: at baseline and monthly after the beginning of the topical treatment Definitions: 1. full recovery (greater than or equal to 75% reduction in the number of lesions), 2. relative recovery (30 to 75 per cent reduction in the number of lesions), 3. no response (no reduction or [greater than or equal to] 30% reduction in the number of lesions), 4. worsening (an increase in the number of lesions) Safety Methods: clinical examination and questioning of participants Cosmetic Methods: assessment of changes in pigmentation and scar formation
Notes	This study corresponded to the protocol IRCT201010104901N1.

Damian 2011

Methods	This was a single-centre, randomised, double-blind, placebo-controlled, parallel-group study.

Damian 2011 *(Continued)*

	The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Men and women • Symmetrically distributed non-hyperkeratotic actinic keratoses on face/scalp/upper limbs • ≥ 4 actinic keratoses in one or more treatment areas • Participants have received no other treatments for actinic keratoses within the last month **Exclusion criteria of the trial** • Pregnant or lactating • Taking immunosuppressive or photosensitising medications • Taking nicotinamide or other vitamin supplements • Participants unable to attend for regular follow up • Participants with active dermatitis in the treatment areas • Liver disease • Currently taking Carbamazepine **Demographics** • 35 participants
Interventions	**Intervention** A: administration of 500 mg nicotinamide tablet, twice daily for 4 months **Control intervention** B: placebo tablet made of lactose. The dose, frequency, and duration of treatment are the same as for the nicotinamide group (i.e. 500 mg twice a day for 4 months)
Outcomes	**Primary outcomes of the trial** 1) Reduction in total actinic keratosis count at 4 months compared with baseline count **Secondary outcomes of the trial** 1) Reduction in site-specific (i.e. face, arms, scalp) actinic keratosis count at 2 and 4 months compared with baseline count 2) Reduction in skin cancers (posthoc) Efficacy Methods: quantitative assessment by blinded clinical examination by a medically-qualified observer Time points: at baseline, and 2 and 4 months
Notes	-

Deonizio 2011

Methods	Randomised, open, active-controlled, intraindividual study The start and end dates were not specified.

Deonizio 2011 *(Continued)*

Participants	**Inclusion criteria of the trial** • Aged 50 to 80 years • Men and women • Multiple actinic keratoses • Anatomical location: upper limbs **Exclusion criteria of the trial** • Uncompensated chronic diseases • Coagulation disorders **Demographics** • 16 participants (limbs were randomised)
Interventions	**Intervention** A: topical anaesthetic with occlusion (lidocaine 5% and prilocaine 5%) was applied for 2 hours before cryopeeling (on a field) followed by treatment of individual lesions with liquid nitrogen (LN) (N = 16 participants) **Control intervention** B: topical anaesthetic with occlusion (lidocaine 5% and prilocaine 5%) was applied for 2 hours before cryopeeling (on a field) followed by treatment of individual lesions with dimethyl ether, propane, and isobutane gases in a portable system (PS) (N = 16 participants) Topical Vaseline was used in the postoperative period to moisturise the skin and reduce the discomfort of healing.
Outcomes	**Outcomes of the trial** 1) Percentage of lesions completely healed (= lesion complete response) at 2 months post-treatment 2) Pain on the visual analogue scale (VAS) from zero (no discomfort) to 10 (worst discomfort possible) 3) Global preference of physician and participant based on a 5-point scale, which ranged from -2 (right much better than left) to +2 (left much better than right) 4) Cosmetic outcomes Efficacy Methods: quantitative assessment using marking of the lesions with acetate sheets and permanent-ink pen, standardised photographic documentation, and counting Time points: at baseline and days 7, 14, 21, 3, and 60 Definitions: lesions that had healed completely (showed no sign of a previous lesion) Cosmetic Methods: 3 blinded dermatologists evaluated how much the appearance of the skin had improved following a standardised scale based on comparison with pictures taken at baseline Time points: at 60 days Definitions: 0 (no improvement), 1 (a little better), 2 (much better)
Notes	-

Dirschka 2012

Methods	This was a multicentre, randomised, assessor-blind, placebo- and active-controlled, parallel-group study. The start and end dates were not specified.

Participants	**Inclusion criteria of the trial**
	
	• Clinical and histological diagnosis
	• White men and women
	• Between 18 and 85 years of age
	• Anatomical locations: face, bald scalp, or both
	• 4 to 8 actinic keratoses, mild to moderate lesions, 0.5 to 1.5 cm in diameter, with a minimum of 1.0 cm interlesional distance
	
	Exclusion criteria of the trial
	
	• All clinical conditions that could influence the study aims and intolerance to any ingredient of BF-200 aminolevulinic acid (ALA) or MAL cream
	• Porphyria
	• Photodermatoses
	• Treatment as follows:
	  • within 12 weeks with topical treatments within the treatment area
	  • within 8 weeks with substances with phototoxic or photoallergic potential
	  • within 1 to 6 months with systemic treatments considered to have a possible impact on the outcome, e.g. cytotoxic drugs
	• Use of other treatment for actinic keratoses during the study
	
	Demographics
	
	• 571 participants
	• 479 men, 91 women
	• Age: mean = 71; range = 39 to 87

Interventions	**Intervention** A: BF-200 (10%) ALA gel-photodynamic therapy (PDT) (N = 248 participants) **Control interventions** B: 16% MAL cream -PDT (N = 247 participants) C: placebo gel-PDT (N = 76 participants) Characteristics of PDT intervention Type of treatment: individual lesions Number of treatments: 1 or 2 Interval between treatments: 12 weeks Preparation of lesions: mild curettage, roughening and alcohol wiping Cream concentration (%): -- Application of cream: -- Incubation with cream: occlusive dressing over cream for 3 hours

Dirschka 2012 *(Continued)*

	Type of light: red light Light source: Aktilite CL 128, PhotoDyn 750/505, Omnilux PDT, Waldmann PDT 1200L Wavelength (nm): 630 (Aktilite, Omnilux), 580-1400 (PhotoDyn), 600-750 (Waldmann) Energy fluence (J/cm^2): 37 (Aktilite, Omnilux), 170 (PhotoDyn), 100 (Waldmann) Intensities (mW/cm^2): -- Exposure time: --
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance at 12 weeks after the first and last PDT **Secondary outcome of the trial** 1) Lesion complete response at 12 weeks after the last PDT **Other outcomes of the trial** 1) Local skin reactions at application sites before and after PDT 2) Adverse events 3) Serious adverse events 3) Pain on a visual analogue scale (VAS: 0 represents no pain, 1 to 3 are interpreted as 'mild', 4 to 7 as 'moderate', and 8 to 10 as 'severe' pain) during PDT 4) Cosmetic outcomes: general Outcomes were stratified for different light sources, mild and moderate lesions, and lesions on the face and scalp. Efficacy Methods: quantitative assessment of lesion clearance by visual inspection and by palpation by an investigator not involved in treatment and safety evaluation Time points: at baseline, and 3 and 12 weeks post-treatment Definitions: participant complete clearance (all lesions were considered to be cleared both by the clinical assessment) Safety Methods: 1. recording of adverse effects, 2. documentation of local adverse reactions (pain, itching, burning, erythema, oedema, and induration) at the application site and rated as mild, moderate, and severe by the assessing physician or reporting participants, 3. serious adverse events Time points: 1. at 1 week after PDT (by phone) and 3 weeks, 2. during and after PDT (local adverse reactions), 3. throughout the study (serious adverse events) Cosmetic Methods: 1. general cosmetic outcome assessed by the investigator as very good, good, unsatisfactory, and impaired; 2. assessment of skin quality Time points: at 12 weeks post-treatment
Notes	This was a confirmatory phase III study.

Galitzer 2011

Methods	This was a multicentre, randomised, assessor-blind, intraindividual study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Men and women • Anatomical locations: dorsal forearm or hand • 3 actinic keratoses within a continuous 25 cm^2 area (= target area) **Exclusion criteria of the trial** • Participation in other trials • Porphyrin abnormalities • Sensitivity to trial components • Tanning • Use of photosensitising drugs or other medications that might interfere • Recent procedures or topical preparations directed at the target areas **Demographics** • 10 participants (forearms or arms were randomised) • 7 men, 3 women • Age: mean = 75
Interventions	**Intervention** A: pretreatment with tazarotene gel (0.1 %) twice daily for 1 week + ALA-blue light photodynamic therapy (PDT) on the entire treatment area, e.g. extensor surface of the hand or forearm between the elbow and the base of the fingers, which includes target area (N = 10 participants) **Control intervention** B: no pretreatment + ALA-blue light PDT on the entire treatment area (N = 10 participants) Characteristics of PDT intervention Type of treatment: field-directed Number of treatments: 1 Interval between treatments: -- Preparation of lesions: -- Cream concentration (%): 20 Application of cream: first applied to individual lesions and then to entire treatment area Incubation with cream: 1 hour, with occlusion on the control side Type of light: blue light Light source: BLU-U Wavelength (nm): -- Energy fluence (J/cm^2): 10 Intensities (mW/cm^2): 10

Galitzer 2011 *(Continued)*

	Exposure time: 16 minutes 40 seconds
Outcomes	**Outcomes of the trial** 1) Lesion counts on the target and entire treatment areas after pretreatment and 8 weeks after PDT compared to baseline 2) Median per cent reduction in lesion counts in the target and entire treatment areas after pretreatment and 8 weeks after PDT 3) Participants with different percentage reduction in lesion counts in the target and entire treatment areas (100% = participant complete clearance) after pretreatment (target area only) and 8 weeks after PDT 4) Investigator global assessment (IGA) after pretreatment and 8 weeks after PDT 5) Tolerance (pigmentary changes, erythema, edema, stinging/burning, scaling/dryness, and oozing/vesiculation) at baseline, after pretreatment, after PD, and 8 weeks after PDT 6) Participant satisfaction on 5-point scale in which 0 = poor and 4 = excellent Efficacy Methods: 1. quantitative assessment by lesion counting, 2. qualitative assessment by investigator (IGA) on a 5-point scale Time points: at baseline, after pretreatment, and 8 weeks after PDT Definitions: IGA: 0 = clear and 5 = very severe Safety Methods: 1. postinflammatory hyperpigmentation, erythema, scaling & dryness, edema, and oozing/crusting/vesiculation were assessed using a 5-point ordinal scale (0 = none to 4 = severe), 2. participants rated stinging and burning on a 4-point scale (0 = none and 3 = severe), 3. adverse events were recorded Time points: at each visit and phone call 24 to 48 hours after PDT
Notes	-

Haddad 2011

Methods	This was a randomised, parallel-group study. The start and end dates were not specified.
Participants	**Inclusion criteria of the trial** • Anatomical locations: face or scalp • ≥ 5 actinic keratoses, not treated during the previous 6 months • Fitzpatrick skin types I to IV **Exclusion criteria of the trial** • History of porphyria or photosensitivity • Active infectious disease • Systemic retinoid treatment during the previous year • Hypertrophic or keloidal scars • Fitzpatrick skin type V and VI

Haddad 2011 *(Continued)*

- Pregnancy or lactation
- Use of photosensitising drugs (tetracycline, retinoid)
- Presence of systemic uncontrolled diabetes, hypertension, or or cardiovascular disease

Demographics

- 24 participants randomised, 21 participants evaluated

Interventions	**Interventions** A: 20 J/cm^2 ALA-Intense Pulsed Light (IPL) PDT (N = 4 participants) B: 25 J/cm^2 ALA-IPL PDT (N = 4 participants) C: 40 J/cm^2 (2 passes of 20 J/cm^2) ALA-IPL PDT (N = 5 participants) D: 50 J/cm^2 (2 passes of 25 J/cm^2) ALA-IPL PDT (N = 5 participants) **Control intervention** E: IPL PDT (N = 3 participants) Characteristics of PDT intervention Type of treatment: -- Number of treatments: 1 Interval between treatments: -- Preparation of lesions: -- Cream concentration (%): 20 Application of cream: twice Incubation with cream: 2 hours Type of light: IPL Light source: -- Wavelength (nm): -- Energy fluence (J/cm^2): -- Intensities (mW/cm^2): -- Exposure time: --
Outcomes	**Outcomes of the trial** 1) Global response to treatment (actinic keratoses and photodamage) was determined by a 7-point scale (= grade) 2) Mean clearance rates for actinic keratoses only (= difference between mean grades before PDT and 8 weeks after PDT) 3) Tolerability (adverse reactions) at 48 hours after PDT 4) Participant discomfort during PDT Efficacy Methods: 1. quantitative assessment of 5 previously identified lesions (non-hyperkeratotic, < 1 cm in diameter, dry, rough, yellowish, with scales) marked in each participant, numbered from 1 to 5,

Haddad 2011 *(Continued)*

	and documented by the FotoFindermediscope system (photography); 2. qualitative assessment (global response) on a 7-point scale Time points: at baseline, and 48 hours and 8 weeks after PDT Definitions: 7-point scale: 0 = complete response, 1 = 90% improvement, 2 = 75% improvement, 3 = 50% improvement, 4 = 10% improvement, 5 = no improvement, and 6 = condition worsened Safety Methods: 1. erythema, edema, crusts, and erosions were graded on a 5-point scale (0= none to 4= severe), 2. burning or stinging during treatment was graded on a 4-point scale (0 = none to 3 = severe). Time points: at 48 hours after PDT
Notes	The study included participants with actinic keratoses, photodamage, or both.

Lebwohl 2012

Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group studies (4 studies). Start date: September 2008 End date: October 2009

Participants	**Inclusion criteria of the trial**
	
	• Men or women
	• Aged 18 years and older
	• Women must be of either non-child-bearing potential, postmenopausal, or of child-bearing potential but having had a negative serum and urine pregnancy test results prior to study treatment to rule out pregnancy
	• Anatomical location: face or scalp (2 studies), trunk or extremities (2 studies)
	• 4 to 8 clinically typical, visible, and discrete actinic keratoses within a 25 cm^2 contiguous field
	
	Exclusion criteria of the trial
	
	• Target treatment area within 5 cm of an incompletely-healed wound or within 10 cm of a suspected basal cell or squamous cell carcinoma
	• Previous treatment with ingenol mebutate gel (PEP-005)
	• Target treatment area contained hypertrophic and hyperkeratotic lesions, or cutaneous horns
	• Lesions that had not responded to repeated cryosurgery
	• Treatment as follows:
	  • within 2 weeks with cosmetic or therapeutic procedures within 2 cm of the selected treatment area
	  • within 4 weeks with immunomodulators, interferon/interferon inducers, or systemic medications that suppress the immune system
	  • within 8 weeks with 5-fluorouracil, imiquimod, diclofenac, or photodynamic therapy within 2 cm of the selected treatment area
	
	Demographics
	
	• 1005 participants
	• 751 men, 254 women
	• Age: mean = 65; range = 34 to 89

Lebwohl 2012 *(Continued)*

Interventions	**Intervention** A: face or scalp: 0.015% PEP005 gel, once daily for 3 days (N = 277 participants) trunk or extremities: 0.05% PEP005 gel, once daily for 2 days (N = 226 participants) **Control intervention** B: vehicle gel, once daily for 2 or 3 days (N = 502 participants)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates at day 57 **Secondary outcomes of the trial** 1) Participant partial (≥ 75%) clearance rates at day 57 2) Median percentage changes from baseline in total number of lesions at day 57 and 12 months follow-up (posthoc) **Other outcomes of the trial** 1) New actinic keratosis lesions or recurrence at 12 months follow-up for participants complete cleared in 3 of the studies (posthoc) 2) Local skin reactions on a 5-point scale (individual scores and time course of the mean composite score) 3) Application-site adverse reactions 4) Adverse events 5) Serious adverse events 6) Pigmentation changes and scarring (cosmetic) Efficacy Methods: quantitative assessment by a study investigator who examined the selected treatment area in person Time points: at baseline, and day 57 and 12 months follow-up Safety Methods: 1. assessment of the incidence rate of adverse events, serious adverse events, and local skin responses; 2. grading of local skin responses with photographic guides to ensure uniform reporting for the following: erythema, flaking or scaling, crusting, swelling, vesiculation or pustulation, and erosion or ulceration Time points: on days 3 (trunk or extremities), 4 (face or scalp), 8, 15, 29, and 57 Definitions: composite local-skin response score (sum of the 6 individual scores that were reported at each study visit for each participant - maximum composite score = 24) Cosmetic Methods: assessment of pigmentation and scarring Time points: on days 3, 8, 15, 29, and 57
Notes	This included 4 studies: NCT00742391 (= Swanson 2010b included in analyses), NCT0091551, NTC00916006, and NCT00942604.

Serra-Guillen 2012

Methods	This was a randomised, active-controlled, parallel-group study. Start date: January 2009 The end date was not specified.
Participants	**Inclusion criteria of the trial** • Anatomical locations: face or scalp • ≥ 5 non-hyperkeratotic actinic keratoses or skin alterations indicating field cancerisation in a 25 cm^2 area of skin **Exclusion criteria of the trial** • Previously received imiquimod or PDT on the face or scalp for any lesion • Received any other treatment within 3 months • Immunosuppressive treatment • Hereditary diseases that predispose to skin cancer (Gorlin syndrome, xeroderma pigmentosum) **Demographics** • 136 participants randomised, 105 participants evaluated • 92 men, 13 women • Age: mean = 73
Interventions	**Intervention** A: MAL-red light PDT followed 1 month later by 5% imiquimod, 3 times per week for 4 weeks (N = 32 participants) **Control interventions** B: MAL-red light PDT (N = 40 participants) C: 5% imiquimod, 3 times per week for 4 weeks (N = 33 participants) Characteristics of PDT intervention Type of treatment: field-directed Number of treatments: 1 Interval between treatments: -- Preparation of lesions: curettage of the most hyperkeratotic lesions Cream concentration (%): 16 Application of cream: whole treatment area Incubation with cream: 3 hours with occlusion Type of light: red light Light source: Aktilite CL 1 Wavelength (nm): -- Energy fluence (J/cm^2): 37 Intensities (mW/cm^2): --

Serra-Guillen 2012 *(Continued)*

	Exposure time: 8 minutes
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rates (clinical) at 1 month post-treatment **Other outcomes of the trial** 1) Participant partial (≥ 75%) clearance rates (clinical) at 1 month post-treatment 2) Clinicopathologic response (= clinical complete clearance and histological clearance) at 1 month post-treatment 3) Local skin reactions for imiquimod treatment at week 4 4) Tolerance (comfort, discomfort, pain, local skin reaction, side-effects, waiting time, and duration of treatment) evaluated on an analogue scale of 0 (well tolerated) to 10 (very poorly tolerated) after PD, imiquimod treatment, or both 5) Participant satisfaction (benefit, improvement achieved, side-effects, and tolerance) on an analogue scale of 0 (very dissatisfied) to 10 (very satisfied) at 1 month post-treatment Efficacy Methods: 1. quantitative assessment by visual examination and palpation, 2. histological evaluation (biopsy) on 2 prespecified lesions identified by photography: lesion 1 before treatment and lesion 2 after treatment Time points: at baseline, and at 1 month post-treatment Definitions: 1. complete clinical clearance (total absence of actinic keratoses or lesions clinically suspected of being actinic keratoses), 2. clinicopathologic response (complete clinical response and absence of actinic keratoses in the biopsy specimen of lesion 2), 3. absence of actinic keratoses (normalisation of the stratum corneum with no parakeratosis and normal maturation of epidermal keratinocytes with no atypical keratinocytes) Safety Methods: evaluation of the intensity of the local reaction (mild, moderate, or severe) Time points: at week 4 of treatment Definitions: 1. mild local reaction (occasional appearance of limited edema and mild erythema in the treatment area), 2. moderate local reaction (erythema, edema, ulceration, and flaking in at least 50% of the treatment area), 3. severe local reaction (erythema, edema, ulceration, and crusts occupying almost all of the treatment area and even extending beyond the treatment area)
Notes	-

Stockfleth 2011

Methods	This was a multicentre, randomised, double-blind, placebo- and active-controlled, parallel-group study. Start date: 2008 End date: 2009
Participants	**Inclusion criteria of the trial** • Participants with general good and stable health

Stockfleth 2011 *(Continued)*

- Histological diagnosis
- Men and women
- Between 18 and 85 years of age
- Anatomical locations: face, forehead, or bald scalp
- Skin type I to IV
- 4 to 10 actinic keratoses within an area of 25 cm^2, grade I (mild) and II (moderate), with diameter between 0.5 cm and 1.5 cm

Exclusion criteria of the trial

- Any treatment for actinic keratosis within the treatment area in the previous 3 months
- Women of child-bearing potential without a highly effective method of contraception

Demographics

- 470 participants
- 398 men, 72 women
- Age: mean = 72

Interventions

Intervention

A: 0.5% 5-FU in combination with 10% salicylic acid (SA) solution (LAS41005), once daily for up to 12 weeks (N = 98 participants)

Control interventions

B: 5-FU/SA vehicle, once daily for up to 12 weeks (N = 187 participants)

C: 3% diclofenac in hyaluronic acid (HA)(LAS106521), twice daily for up to 12 weeks (N = 185 participants)

If severe side-effects occurred, frequency of drug application could be reduced to 3 times per week (5-FU/SA and vehicle) or to once daily (diclofenac/HA).

Outcomes

Primary outcome of the trial

1) Histological clearance rate of 1 predefined lesion

Secondary outcomes of the trial

1) Lesion counts at baseline, and at week 12 (end of treatment) and 20 (8 weeks post-treatment)

2) Mean total lesion area at baseline and week 20 (8 weeks post-treatment)

3) Participant complete clearance (clinical) at week 20

4) Investigator's and participant's global assessment at weeks 6, 12, and 20

5) Treatment-emergent adverse events (including application site reactions)

6) Tolerance (inflammation and burning)

7) Serious adverse events

Efficacy

Methods: 1. quantitative assessment by visual inspection of the treatment area and determination of the number and size of lesions, 2. biopsy of 1 representative target lesion performed by 3 mm punch biopsy and a second predefined clinically identical lesion for the biopsy at the post-treatment visit evaluated by an independent and blinded dermatopathologist. Biopsy sites were selected on the basis of clinical appearance (clinical grade, area, and size). Photodocumentation and grid documentation were performed for the purposes of lesion identification. No skin tattoos were

Stockfleth 2011 *(Continued)*

	used, and no photodocumentation was performed during interim visits, 3. qualitative assessment by physician and participant ranging from 'very good' to 'none' Time points: at weeks 2, 4, 6, 10, 12 (end of treatment), and 20 (8 weeks post-treatment) Safety Methods: participant-reported adverse events Time points: at each visit
Notes	This corresponded to protocol NCT00987246 and EudraCT No. 2007-003889-18.

Wiegell 2011b

Methods	This was a randomised, assessor-blinded, active-controlled, intraindividual study. Start date: December 2008 End date: May 2009
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Men and women • Aged 18 years and older • Anatomical locations: face and scalp • Multiple actinic keratoses, symmetrically distributed **Demographics** • 20 participants (areas randomised) • 19 men, 1 women • Age: mean = 74; range = 58 to 90
Interventions	**Intervention** A: MAL-2.5h low-intensity artificial daylight photodynamic therapy (PDT) (N = 20 participants) **Control intervention** B: MAL-red light-emitting diode (LED) PDT (N = 20 participants) Characteristics of PDT intervention Type of treatment: field-directed treatment (100 cm^2) Number of treatments: 1 Interval between treatments: -- Preparation of lesions: scales and hyperkeratoses removed with a curette Cream concentration (%): 16 Application of cream: -- Incubation with cream: 3 hours (under occlusion for 0.5 hours for daylight and 3 hours for red LED) Type of light: artificial daylight, red light

Wiegell 2011b *(Continued)*

	Light source: Xenon H4 light bulbs (daylight) Wavelength (nm): -- Energy fluence (J/cm^2): 37 (red LED) Intensities (mW/cm^2): -- Exposure time: 2.5 hours for artificial daylight
Outcomes	**Primary outcome of the trial** 1) Lesion complete response **Other outcomes of the trial** 1) Mean reduction in lesion counts at 3 months post-treatment 2) Participant complete response (= participant complete clearance) at 3 months post-treatment 3) Pain scores (0 = no pain and 10 = worst imaginable pain) every half hour during 'daylight' exposure and every 1.5 minutes during red LED treatment 4) New actinic keratosis lesions 5) PpIX fluorescence Efficacy Methods: quantitative assessment using lesion grading and counting using a template Time points: at baseline and 3 months post-treatment Definitions: complete response (complete disappearance of the lesion, visually and by palpation - mild erythema might remain)
Notes	-

Characteristics of ongoing studies *[ordered by study ID]*

ACTRN12610000689077

Trial name or title	Randomised, double-blind, placebo-controlled study to assess efficacy of oral nicotinamide (500 mg daily) in the treatment and prevention of actinic keratoses
Methods	This is a randomised, double-blind, placebo-controlled, parallel-group.
Participants	**Inclusion criteria of the trial** • Men and women • Aged 18 years and older • Symmetrically distributed non-hyperkeratotic actinic keratoses on the face/scalp/upper limbs • ≥ 4 actinic keratoses in 1 or more treatment areas • Participants have received no other treatments for actinic keratoses within the last month **Exclusion criteria of the trial** • Under 18 years old • Pregnant or lactating • Taking immunosuppressive or photosensitising medications • Immune suppressive concurrent illness (e.g. human immunodeficiency virus - HIV - infection)

ACTRN12610000689077 *(Continued)*

	• Malignancy (excluding non-melanoma skin cancer) in the previous 5 years • Taking nicotinamide supplements within the last month • Participants unable to attend for regular follow up • Participants with active dermatitis in assessment areas • Liver disease (although hepatic effects of nicotinamide are rare, in contrast to nicotinic acid) • Currently taking carbamazepine (case reports of interaction with nicotinamide) **Demographics** • 40 participants
Interventions	**Intervention** A: oral nicotinamide 500 mg daily for 4 months **Control intervention** B: placebo tablets (lactose tablets identical in appearance and size to nicotinamide tablets but without active ingredient) daily for 4 months
Outcomes	**Primary outcome of the trial** 1) Reduction in total actinic keratosis count at 2 and 4 months from baseline
Starting date	August 2010
Contact information	A/Prof Diona Damian (diona.damian@sswahs.nsw.gov.au) Dermatology Gloucester House Level 3 Royal Prince Alfred Hospital Missenden Rd Camperdown 2050 Australia
NCT	-
Notes	This study is ongoing and the last update was in August 2010. (April 2012)

NCT00115154

Trial name or title	Vehicle-Controlled, Double-Blind Study to Assess the Safety and Efficacy of Imiquimod 5% Cream for the Treatment of Actinic Keratosis on the Upper Extremities
Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Have actinic keratoses on arm or hand • Discontinuation of sun tanning and the use of tanning beds • Discontinuation of the use of moisturisers, body oils, over-the-counter retinol products, and products containing alpha or beta hydroxy acid in the treatment and surrounding area • Withholding from the use of sunscreen in the treatment area for 24 hours prior to all study visits and for 8 hours before applying study cream

NCT00115154 *(Continued)*

	• Postponement of the treatment of non-study actinic keratosis lesions anywhere on the arm being treated until study participation is complete **Exclusion criteria of the trial** • Subjects must not have any evidence of systemic cancer, immunosuppression, or other unstable health conditions • Participation in another clinical study • Have previously received treatment with imiquimod within the treatment area • Have squamous cell carcinoma (SCC), basal cell carcinoma (BCC), or other malignancy in the treatment or surrounding area that requires treatment **Demographics** • 270 participants
Interventions	**Intervention** A: imiquimod 5% cream, once per day, 2 days per week for 16 weeks **Control intervention** B: vehicle cream, once per day, 2 days per week for 16 weeks
Outcomes	**Primary outcome of the trial** 1) Efficacy of imiquimod 5% cream compared to vehicle cream **Secondary outcome of the trial** 1) Safety of treatment with imiquimod 5% cream
Starting date	May 2005
Contact information	Graceway Pharmaceuticals, LLC
NCT	NCT00115154
Notes	This study has been completed and the last update was in February 2007 (April 2012).

NCT00204542

Trial name or title	Comparison of the Efficacy and Tolerability of Solaraze for 3 vs. 6 Months in Patients With Mild to Moderate Actinic Keratosis Located at the Face and Head
Methods	This is a multicentre, randomised, open, active-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Aged 18 to 80 years • Men and women • Visible and histologically-proven actinic keratosis • Prepared and able to give written informed consent • Prepared to comply with all study requirements, including the following: application of gel on the treatment area twice a day, and 5/7 clinic visits during the pre-study, treatment, post-treatment, and follow-up period • Pre- and post-treatment biopsy for histological confirmation (of clearance) of actinic keratosis diagnosis

NCT00204542 *(Continued)*

	Exclusion criteria of the trial • Data of clinically significant, unstable, cardiovascular or haematologic, hepatic, neurologic, renal, endocrine, collagen-vascular, or gastrointestinal abnormalities or diseases • Known allergies to any excipient in the study drug • Any dermatological disease, condition, or both, in the treatment or surrounding area (3 cm distances from treatment area) that may be exacerbated by treatment with diclofenac or cause difficulty with examination • Active chemical dependency or alcoholism, as assessed by the investigator • Currently participating in another clinical study or have completed another clinical study with an investigational drug within the past 30 days • Received topical treatment at the treatment area with imiquimod or 5-fluorouracil within a time period of 1 month • Invasive tumours within the treatment area, e.g. merkel cell carcinoma, squamous cell carcinoma, or basal cell carcinoma; the latter is accepted if completely surgically removed **Demographics** • 418 participants
Interventions	**Intervention** A: diclofenac, twice daily for 3 months **Control intervention** B: diclofenac, twice daily for 6 months
Outcomes	**Primary outcome of the trial** 1) Histologically controlled complete clearance of the actinic keratosis at 6 weeks post-treatment
Starting date	June 2005
Contact information	Claus Garbe, MD Skin Cancer Program, Department of Dermatology, University Hospital Tübingen
NCT	NCT00204542
Notes	This study has been completed in December 2010, and the last update was in August 2011 (April 2012).

NCT00472459

Trial name or title	A Multicentre, Randomised Study of Photodynamic Therapy(PDT) With Metvix® 160 mg/g Cream in Immuno-compromised Patients With Non-melanoma Skin Cancer
Methods	This was a multicentre, randomised, open, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Transplant recipients with at least 2 clinically-diagnosed actinic keratosis lesions and maximum 10 skin lesions [actinic keratoses (AK), basal cell carcinoma (BCC), squamous cell carcinoma (SCC)

NCT00472459 *(Continued)*

	in situ, warts, or both) in each of the 2 contralateral areas (diameter 5 x 10 cm) in the face, the scalp, the extremities, or on the trunk/neck • Transplant recipients who previously are treated more than once for their skin lesions • Transplant recipients who have received immunosuppressive therapy for more than 3 years • Men or women above 18 years of age • Written informed consent **Exclusion criteria of the trial** • Participants with more than 10 skin lesions (AK, BCC, SCC in situ, warts) in 1 of the 2 areas • Participants with SCC (not SCC in situ) in 1 of the 2 areas • Participants not previously treated or treated only once for their skin lesions • Participants with rosacea in 1 of the 2 areas • Participants with morpheaform/highly infiltrating BCC • Known allergy to methyl-aminolevulinate, a similar compound or excipients of the cream • Participation in other clinical studies either concurrently or within the last 30 days • Pregnant or breastfeeding (all women of child-bearing potential must document a negative pregnancy test and use the pill or intrauterine device (IUD) during the treatments and for at least 1 month thereafter) • Conditions associated with a risk of poor protocol compliance **Demographics** • 81 participants
Interventions	**Intervention** A: the treatment area on a randomised side (5 x 10 cm^2) will be treated at baseline and at visits at 3, 9, and 15 months. At baseline the area will be treated with fractionated Metvix® PDT treatment consisting of 2 treatments 1 week apart and at visits at 3, 9, and 15 months with single Metvix® PDT treatment **Control intervention** B: in the contralateral control area (5 x 10 cm^2), new and recurrent lesions and lesions in non-complete response will be treated with lesion-specific treatment at the discretion of the investigator at each study visit
Outcomes	**Primary outcomes of the trial** 1) Occurrence of new lesions (actinic keratosis, basal cell carcinoma, squamous cell carcinoma and warts) at 3, 9, 15, 21, and 27 months after first treatment 2) Number of actinic keratosis lesions that show complete response at 3, 9, 15, 21, and 27 months after first treatment **Secondary outcomes of the trial** 1) Number of BCC lesions that show complete response in the treated area with the contralateral control area at 3, 9, 15, 21, and 27 months after first treatment 2) Number of recurrent lesions at 9, 15, 21, and 27 months after first treatment 3) Assess the cosmetic outcome at 3, 9, 15, 21, and 17 months after first treatment 4) Investigate product safety in this participant population at 3, 9, 15, 21, and 27 months after first treatment
Starting date	July 2003
Contact information	Ann-Marie Wennberg, MD, PhD (PI) Sahlgrenska University Hospital Gothenburg,

NCT00472459 *(Continued)*

	Sweden
NCT	NCT00472459
Notes	This study has been completed in July 2006, and the last update was in September 2010 (April 2012).

NCT00608634

Trial name or title	Phase 2a Randomized, Placebo-Controlled, Double-Blind Trial of Topical Perillyl Alcohol in Sun Damaged Skin
Methods	This is a single-centre, randomised, double-blind, placebo-controlled, parallel-group study.

Participants	**Inclusion criteria of the trial**
	• Aged 18 years and older
	• Women must not be of child-bearing potential, and therefore must be postmenopausal or surgically sterile by hysterectomy
	• Not pregnant or nursing
	Disease characteristics
	• Resident of Pima or adjoining Southern Arizona county
	• Participants outside of Pima County are also eligible
	• Sun-damaged skin as judged by the study physician and quantifiable, clinically-diagnosed, and visible actinic keratoses on both dorsal forearms, with at least 2 AK on each arm
	• AK lesions must not be clustered, confluent, or too numerous to count accurately
	• Presence of actinic keratoses on sites other than the test area allowed
	• No significant inflammation or irritation of the skin of the upper extremities that is not clinically-diagnosed as sun damage, or AK participants must agree to limit sun exposure as much as possible and may continue their normal pattern of sunscreen use
	Exclusion criteria of the trial
	• Concurrent skin malignancy or disorder of the upper extremities
	• Participants with squamous or basal cell carcinoma in an area other than the test area are eligible upon excision of the squamous or basal cell carcinoma
	• Participants who are immunosuppressed by virtue of medication or disease
	• Serious concurrent illness that could interfere with study regimen
	• Invasive cancer within the past 5 years
	• Treatment as follows:
	  • within 30 days with prior topical medications to the skin of the upper extremities, except for emollients or sunscreens; concurrent mega-doses of vitamins, defined as any of the following: more than 5 times the recommended daily allowance, more than 5 capsules of multivitamins, 400 IU of vitamin E, 200 µg of selenium, or 1 g of vitamin C
	  • within 6 months with concurrent therapy for squamous cell carcinoma or basal cell carcinoma anywhere in the test area (i.e. the forearms or hands), treatment for squamous cell carcinoma or basal cell carcinoma on sites other than the test area is allowed, within 4 weeks, with surgical biopsy, surgical excision, or cryotherapy for actinic keratosis in the test area and the sites must have healed
	  • within 6 months with topical treatment (e.g. 5-fluorouracil or imiquimod) for actinic keratosis
	• No concurrent therapy that may interfere with clinical evaluations
	• No concurrent topical drug treatment (e.g. retinoids, aminolevulinic acid, diclofenac sodium, imiquimod, or fluorouracil) to any area of skin, including test area

NCT00608634 *(Continued)*

	• No concurrent enrolment in another clinical trial • No concurrent topical citrus peel or consumption of citrus peel • No chemotherapy for cancer within the past 5 years **Demographics** • 94 participants
Interventions	**Interventions** A: perillyl alcohol (POH) cream (0.3%) applied topically to each dorsal forearm twice daily for 3 months in the absence of unacceptable toxicity B: perillyl alcohol (POH) cream (0.76%) applied topically to each dorsal forearm twice daily for 3 months in the absence of unacceptable toxicity **Control intervention** C: placebo cream applied topically to each dorsal forearm twice daily for 3 months in the absence of unacceptable toxicity
Outcomes	**Primary outcome of the trial** 1) To determine if topical administration of perillyl alcohol (POH) cream can reverse actinic damage as evidenced by normalisation of quantitative skin histopathology scores in skin tissue biopsy samples from participants with moderate to severe sun damage **Secondary outcomes of the trial** 1) To determine if topically-administered POH results in significant alterations in surrogate end point biomarkers of epidermal cell proliferation, including optical coherence tomography, p53 expression, c-Fos expression, and apoptosis (as measured by activated caspase-3 expression) 2)To determine if topically-administered POH results in normalisation of nuclear chromatin patterns in skin biopsy tissue from these participants, as determined by karyometric analysis 3) To determine if topical POH can be administered safely to the forearms of these participants
Starting date	May 2004
Contact information	Steve Stratton, MD (study chair) University of Arizona
NCT	NCT00608634
Notes	The status of this study is unknown, and the last update was in September 2010 (April 2012).

NCT00695578

Trial name or title	A Randomized Right/Left Clinical Trial to Evaluate the Use of Biafine Cream Versus Standard Care in Subjects With Actinic Keratosis Post Cryotherapy
Methods	This is a single-centre, randomised, assessor-blinded, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Subject must give written consent • Aged 50 years and older

NCT00695578 *(Continued)*

	• Men and women • Subjects must have had cryotherapy treatment of at least 1 actinic keratosis on each forearm in the dermatology clinic (Wake Forest University Health Sciences Dermatology) **Exclusion criteria of the trial** • Subjects age < 50 years of age • Subjects with known allergy or sensitivity to topical Biafine or polysporin ointment • Inability to complete all study-related visits • Introduction of any other prescription medication, topical or systemic, for actinic keratoses while participating in the study • Subjects using other topical agent's glycolic acid products, alpha hydroxy acid products, retinoids, and chemical peel agents in the treatment areas while on study **Demographics** • 20 participants
Interventions	**Intervention** A: cryotherapy followed by Biafine cream **Control intervention** B: cryotherapy followed by standard care
Outcomes	**Primary outcome of the trial** 1) The change of the target lesions from baseline to end of treatment in the IGA at 4 weeks
Starting date	October 2006
Contact information	Steve Feldman, MD, PhD (PI) Wake Forest University
NCT	NCT00695578
Notes	This study has been completed in February 2008, and the last update was in February 2009 (April 2012).

NCT00700063

Trial name or title	A Multicenter, Randomized, Double-blind, Vehicle-controlled, Dose-ranging Study to Evaluate the Safety and Efficacy of 0.005%, 0.01% and 0.015% PEP005 Topical Gel When Used to Treat Actinic Keratoses on the Head (Face or Scalp)
Methods	This is a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Men or women • Women must be of non-child-bearing potential; child-bearing potential provided negative pregnancy test and using effective contraception • 4 to 8 actinic keratosis lesions on the face or scalp **Exclusion criteria of the trial**

NCT00700063 *(Continued)*

	• Treatment as follows: * within 2 weeks with cosmetic or therapeutic procedures within 2 cm of the selected treatment area * within 4 weeks with immunomodulators, interferon/interferon inducers, or systemic medications that suppress the immune system * within 8 weeks with 5-fluorouracil, imiquimod, diclofenac, or photodynamic therapy within 2 cm of treatment area **Demographics** • 265 participants
Interventions	**Interventions** A: PEP005 topical gel 0.005%, 2-day treatment B: PEP005 topical gel 0.01%, 2-day treatment C: PEP005 topical gel 0.015%, 2-day treatment D: PEP005 topical gel 0.005%, 3-day treatment E: PEP005 topical gel 0.01%, 3-day treatment F: PEP005 topical gel 0.015%, 3-day treatment **Control interventions** G: vehicle gel, 2-day treatment H: vehicle gel, 3-day treatment
Outcomes	**Primary outcome of the trial** 1) Safety and toleration (incidence of adverse events, serious adverse events, and skin responses) at 57 days **Secondary outcome of the trial** 1) Efficacy (clearance of actinic keratosis lesions) at 57 days
Starting date	June 2008
Contact information	Peplin
NCT	NCT00700063
Notes	This study has been completed in October 2008, and the last update was in July 2010 (April 2012). Incomplete data were published in abstract form in an excluded study (Spencer 2010).

NCT00756288

Trial name or title	A Randomized Controlled Paired Comparison of Photo-therapy With a Topical Retinoid Cream Pre-treatment Versus PDT Alone for Actinic Keratoses
Methods	This is a single-centre, randomised, double-blind, parallel-group study.
Participants	**Inclusion criteria of the trial** • Aged 18 to 80 years old

NCT00756288 *(Continued)*

- Participants with actinic keratosis lesions who will receive PDT
- Participants with actinic keratosis lesions in 2 areas other than the face and scalp, each with a surface area of 10 cm^2 or greater and at least 3 clinically-diagnosed non-hypertrophic actinic keratosis lesions in each
- Participants in good health
- Participants with willingness and the ability to understand and provide informed consent

Exclusion criteria of the trial

- Participants who are pregnant or lactating
- Participants with a history of cutaneous photosensitivity or porphyria, hypersensitivity to porphyrins, or photodermatosis
- Treatment as follows:
  - within 1 week with photosensitising drugs
  - within 2 weeks with topical medications, such as corticosteroids, alpha hydroxy acids, or retinoids
  - within 4 weeks with previous treatment of target actinic keratoses
- Participants who are unable to understand the protocol or give informed consent

Demographics

- 20 participants

Interventions	**Intervention** A: topical retinoid, for 4 weeks followed by blue-light photodynamic therapy with photosensitising agent (at week 4) **Control intervention** B: blue-light photodynamic therapy with photosensitising agent at week 4
Outcomes	**Primary outcomes of the trial** 1) Live blinded rater and blinded photo rater analysis of areas at week 0 and week 6 for erythema, edema, crusting, ulceration, palpability, and the need to cease/delay treatment 2) Overall response in reduction of number of AKs at 6 weeks **Secondary outcomes of the trial** 1) Participants will assess pain, burning, and itching on a scale of 0 to 3 at week 0, during retinoid treatment, during phototherapy, 1 day after, and at week 6 2) Principal investigator will evaluate adverse events at week 6
Starting date	August 2008
Contact information	Murad Alam, MD (PI) Department of Dermatology Northwestern University
NCT	NCT00756288
Notes	This study is ongoing and the last update was in April 2011 (April 2012).

NCT00786994

Trial name or title	Randomized, Multicenter, Double Blind Study to Compare the Efficacy and Tolerability of Oleogel-S-10 for 3 Month Versus Placebo Only in Patients With Mild to Moderate Actinic Keratoses Located at the Face and Head Oleogel-S-10 in Actinic Keratoses Trial
Methods	This is a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Histologically-proven actinic keratoses within 3 months before study entry • Aged 18 years and older • ≥ 2 mild to moderate actinic keratoses located at the facial skin or the head (except lips) • Actinic keratoses with a diameter of 0.5 to 2 cm that are definitely distinguished from other lesions and display a minimum distance of 0.5 cm to neighboured lesions that are evaluated as histopathological grade 1 to 3 • Prepared and able to give written informed consent • In case of women: postmenopause defined as natural menopause with menses > 1 year ago serum FSH (> 20 IU/l) and E2 levels in the postmenopausal range or participants who had bilateral oophorectomy • Prepared and comply with all study requirements, including the following: application of Oleogel-S10 on the treatment area once or twice a day; 4 clinic visits during the pre-study, treatment, post-treatment, and follow-up period; pre- and post-treatment biopsy for histological confirmation (of clearance) of actinic keratosis-diagnosis • Representative histologic slide and tissue block were shipped **Exclusion criteria of the trial** • Active immunosuppressive therapy • Data of clinically significant, unstable, cardiovascular or hematologic, hepatic, neurologic, renal, endocrine, collagen-vascular, or gastrointestinal abnormalities or diseases (note: participants with clinically-stable medical conditions including, but not limited to, controlled hypertension, diabetes mellitus type II, hypercholesterolemia, or osteoarthritis will be allowed to enter the study • Known allergies to any excipient in the study drug • Any dermatological disease, condition, or both, in the treatment or surrounding area (3 cm distances from treatment area) that may be exacerbated by treatment with Oleogel-S-10 or cause difficulty with examination • Active chemical dependency or alcoholism, as assessed by the investigator • Pregnant and lactating women • Currently participating in another clinical study or have completed another clinical study with an investigational drug within the past 30 days • Treatment as follows: within 1 month with topical treatment at the treatment area with diclofenac gel, imiquimod, or 5-fluorouracil • Concomitant existence of non-treated (non-excised) basal cell carcinoma, squamous cell carcinoma, or malignant melanoma • Invasive tumours within the treatment area, e.g. merkel cell carcinoma, squamous cell carcinoma, basal cell carcinoma; the latter is accepted if completely surgically removed. Note: a biopsy of any lesion within the treatment or surrounding area suggestive of malignancy should be performed at the pre-study screening visit. If invasive SCC or other malignant conditions are confirmed within the treatment area, the participant will not be included in the study **Demographics** • 165 participants
Interventions	**Interventions** A: oleogel-S-10 for 3 months once a day (N = 54 participants) B: oleogel-S-10 for 3 months twice a day (N = 54 participants)

NCT00786994 *(Continued)*

	Control interventions C: placebo (petroleum jelly) for 3 months once a day (N = 27 participants) D: placebo (petroleum jelly) for 3 months twice a day (N = 27 participants)
Outcomes	**Primary outcome of the trial** 1) Objective response of the marker actinic keratosis, defined as histologically complete or partial clearance (partial clearance = down-grading in Cockerell-classification) assessed at 18 weeks. The marker actinic keratosis is defined as an initially-selected lesion within the target area that will be used for final biopsy **Secondary outcomes of the trial** 1) Histologically-controlled complete clearance, 2) Histologically-controlled down staging 75% clearance rate 3) Dose response relationship 4)Time to clinically complete response 5) Tolerability Assessment at 18 weeks
Starting date	October 2008
Contact information	Birken GmbH Principal investigator Claus Garbe, Prof. Dr, Universitätshautklinik Tübingen
NCT	NCT00786994
Notes	This study has been completed in November 2010 and the last update was in January 2012 (April 2012).

NCT00859105

Trial name or title	A Multicenter, Double-Blind, Vehical-Controlled Study Comparing Imiquimod Cream, 5% (Apotex Inc.) to Aldara™ Cream, 5%(3M Pharmaceutials, U.S.) and Aldara™ Cream, 5%(3M Pharmaceuticals, Canada) in the Treatments of Actinic Keratosis
Methods	This is a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • 4 to 8 clinically-diagnosed, non-hyperkeratotic, non-hypertrophic actinic keratosis lesions within a 25 cm^2 contiguous treatment area on either the face or balding scalp • Women either must be 1 year postmenopausal, surgically sterile, or agree to use a medically-accepted form of birth control • Free of any systemic or dermatological disorder • Any skin type or race, providing the skin pigmentation will allow discernment of erythema **Exclusion criteria of the trial** • Basal cell or squamous cell carcinoma, or other possible confounding skin conditions (on face and scalp) • History of cutaneous hyperreactivity or facial irritation to topical products • Engaging in activities involving excessive or prolonged exposure to sunlight

NCT00859105 *(Continued)*

	• Treatment as follows:
	  • within 6 months with systemic cancer chemotherapy, psoralen plus UVA therapy, UVB therapy, laser abrasion, dermabrasion, glycolic acids, or chemical peels
	  • within 2 months with systemic steroids
	  • within 28 days with over-the-counter retinol products, corticosteroids, cryosurgery, curettage, 5-fluorouracil, or other topical actinic keratosis treatments in the treatment area
	• Pregnant or nursing mothers
	• History of allergy or sensitivity to imiquimod or related compounds or other components of the formulation
	• Taking immunosuppressant medication
	
	Demographics
	
	• 497 participants

Interventions	**Interventions** A: Apotex, 5% imiquimod applied as a thin layer to target area once a day, 2 days each week, 16 weeks B: Aldara US, 5% imiquimod applied as a thin layer to target area once a day, 2 days each week, 16 weeks C: Aldara Canada, 5% imiquimod applied as a thin layer to target area once a day, 2 days each week, 16 weeks **Control intervention** D: vehicle applied as a thin layer to target area once a day, 2 days each week, 16 weeks
Outcomes	**Primary outcomes of the trial** 1) The primary objectives are to establish the therapeutic equivalence of imiquimod cream 5%, manufactured by Apotex Inc. and 2 Aldara (imiquimod) creams, manufactured by 3M (US & Canada) at 24 weeks 2) Superiority over vehicle in the treatment of AK at 24 weeks **Secondary outcome of the trial** 1) The secondary objective is to compare the safety profiles of the 3 creams at 24 weeks
Starting date	February 2008
Contact information	William Brooks (study director) Apotex Inc
NCT	NCT00859105
Notes	This study has been completed in November 2008, and the last update was in March 2009 (April 2012).

NCT00948428

Trial name or title	A Multicenter, Double-Blind, Randomized, Parallel Group, Vehicle-Controlled Study to Determine the Clinical Equivalence of a Generic Imiquimod Cream, 5% and Aldara™ Cream in Subjects With Actinic Keratosis

NCT00948428 *(Continued)*

Methods	This is a multicentre, randomised, double-blind, placebo- and active-controlled, parallel-group.

Participants	**Inclusion criteria of the trial**
	• Men or non-pregnant women
	• Aged 18 years and older
	• In general good health
	• Women who were postmenopausal, surgically sterile, or using a medically acceptable form of birth control with a negative urine pregnancy test at the baseline visit
	• Participants provided written and verbal informed consent.
	• 4 to 12 visible, discrete non-hyperkeratotic, non-hypertrophic actinic keratosis lesions within a 25 cm^2 treatment area on the face, anterior scalp, or both
	• Participants were willing and able to comply with study instructions and return to the clinic for required visits.
	Exclusion criteria of the trial
	• Participants who were lactating, or planning to become pregnant during the study
	• Participants had hyperkeratotic, hypertrophic or large mat-like actinic keratoses within the 25 cm^2 treatment area
	• Participants who had the need or were planning to be exposed to artificial tanning devices or excessive sunlight during the trial
	• Participants who were immunosuppressed (e.g. HIV, systemic malignancy, graft vs host disease, etc)
	• Participants who experienced an unsuccessful outcome from previous imiquimod therapy
	• Participants with known hypersensitivity or previous allergic reaction to any of the active or inactive components of the study drugs
	• Treatment as follows:
	  • within 2 months with laser resurfacing, photodynamic therapy, chemical peels, dermabrasion, topical application of 5-fluorouracil, imiquimod, diclofenac sodium, or other treatments for actinic keratoses or photodamage
	  • within 2 days with topicals of any kind to the selected treatment area
	  • within 2 weeks with facial topical medications: corticosteroids; alpha hydroxy acids (e.g. glycolic acid, lactic acid, etc, greater than 5%); beta hydroxy acid (salicylic acid greater than 2%); urea - greater than 5% or prescription retinoids (e.g. tazarotene, adapalene, tretinoin) to the face, anterior scalp, or both; or cryotherapy to lesions adjacent to or within the 25 cm^2 treatment area
	  • within 4 weeks with systemic steroid therapy: chemotherapeutic agents, psoralens, immunotherapy, or retinoids
	Demographics
	• 462 participants

Interventions	**Intervention** A: generic 5% topical cream dispensed in individual 0.25 g sachets applied twice a week for 16 weeks **Control interventions** B: Aldara 5% topical cream dispensed in individual 0.25 g sachets applied twice a week for 16 weeks C: topical cream vehicle matching generic imiquimod dispensed in individual 0.25 g sachets applied twice a week for 16 weeks
Outcomes	**Primary outcome of the trial**

NCT00948428 *(Continued)*

	1) Proportion of participants in each treatment group with complete clearance of actinic keratosis lesions at 8 weeks post-treatment (week 24, test of cure/TOC) visit **Secondary outcomes of the trial** 1) The partial clearance rates, defined as the proportion of subjects with at least a 75% reduction in the number of lesions counted at baseline 2) Proportion of participants with complete clearance of lesions at week 16 (end of treatment) and week 24 (TOC)
Starting date	May 2008
Contact information	Christine M. Winslow, Ph.D. (study director) Actavis Mid-Atlantic LLC
NCT	NCT00948428
Notes	This study has been completed in April 2009, and last update was in August 2010 (April 2012).

NCT00991861

Trial name or title	Double-blind, Randomized, Multi-centre Phase II Study to Evaluate the Efficacy and Safety of Topically Applied LAS41007 Once Daily and LAS41007 Twice Daily Versus LAS106521 Gel Twice Daily in the Treatment of Actinic Keratosis Grade I to II
Methods	This is a multicentre, randomised, double-blind, active-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Men and women • At least 4 to 10 clinically-assessed actinic keratoses grade I to II (according to Olsen 1991) in the face/forehead, on the bald scalp, or both • The diameter of each actinic keratosis target lesion is not less than 0.5 cm and not greater than 1.5 cm • The target lesions must be located in overall 2 treatment areas with a size of 25 cm^2 per treatment area **Exclusion criteria of the trial** • Have evidence of clinically-significant or unstable medical conditions, such as metastatic tumour or tumour with high probability of metastatic spread; heart failure (NYHA class III or higher); immunosuppressive disorder (e.g. HIV); hematologic, hepatic, renal, neurologic, or endocrine disorder; collagen-vascular disorder (e.g. cerebrovascular disorder or other bleedings); or gastrointestinal disorder (e.g. active ulcera or history of recurrent peptic ulcera or haemorrhage) • Suffer from paraesthesia in the treatment areas • Show Cornu cutaneum of the skin, hypertrophic actinic keratosis lesions in the treatment areas, or both **Demographics** • 100 participants
Interventions	**Interventions** A: LAS41007 once daily

NCT00991861 *(Continued)*

	B: LAS41007 twice daily **Control intervention** C: LAS106521 (3% diclofenac in hyaluronic acid)
Outcomes	**Primary outcomes of the trial** 1) Histological clearance of 1 pre-selected target lesion at day 120 2) Complete clinical clearance of all target lesions in the treatment areas at day 120 **Secondary outcome of the trial** 1) Physician's Global Tolerability Assessment (PGT) at day 120
Starting date	August 2009
Contact information	Christoph Willers, MD, MBA Almirall Hermal GmbH
NCT	NCT00991861
Notes	This study has been completed in February 2010, and the last update was in July 2010 (April 2012).

NCT01203878

Trial name or title	An Exploratory, Open-label Study of Sequential Field-directed Treatment of Actinic Keratoses of the Face With Imiquimod 3.75% Cream Followed by Photodynamic Therapy
Methods	This was a multicentre, randomised, open, parallel-group study.

Participants	**Inclusion criteria of the trial**
	
	• Men and women
	• Aged 18 years and older
	• 10 to 30 clinically typical actinic keratoses on the face
	
	Exclusion criteria of the trial
	
	• Hypertrophic actinic keratoses or other skin lesions on the head that might require excluded treatment during the study
	• Known contraindication to treatment with imiquimod or photodynamic therapy
	• Condition that would limit compliance, be a potential safety risk, or require therapy with an excluded treatment
	• Systemically immunocompromised
	• Pregnant or nursing
	• Dermatologic disease, condition, or both in the treatment area that might be exacerbated by treatment with imiquimod, cause difficulty with examination, or require therapy with an excluded treatment
	• Participation in another clinical study
	• Treatment as follows:
	  • within 60 days with ultraviolet therapy, systemic immunomodulators, chemotherapeutic or cytotoxic agentsInvestigational agents
	  • on the head with imiquimod, photodynamic therapy, red or blue light source therapy, cryotherapy or chemotherapy, surgical excision or curettage, topical corticosteroids, laser dermabrasion, chemical peel, topical retinoids, topical 5-fluorouracil, topical pimecrolimus or tacrolimus, or topical diclofenac

NCT01203878 *(Continued)*

	Demographics • 60 participants
Interventions	**Intervention** A: imiquimod 3.75% cream, up to 2 packets, applied topically daily for 2 2-week cycles separated by a no-treatment interval of 2 weeks, followed 4 weeks later by photodynamic therapy with 20% aminolevulinic acid and blue light exposure of the entire face **Control intervention** B: Imiquimod 3.75% cream, up to 2 packets, applied topically daily for 2 2-week cycles separated by a no-treatment interval of 2 weeks, followed by observation
Outcomes	**Primary outcomes of the trial** 1) Actinic keratosis count at week 18 2) The per cent change in actinic keratosis count as compared to the baseline lesion count **Secondary outcomes of the trial** 1) Complete clearance at week 18 2) The proportion of participants with complete clearance of actinic keratoses in the treatment area (entire face) 3) Cosmetic appearance at week 18 4) Change in investigator and participant scores of cosmetic appearance of the treatment area (entire face)
Starting date	September 2010
Contact information	Julie Biron jbiron@goldskincare.com
NCT	NCT01203878
Notes	This study is currently recruiting, and the last update was in July 2011 (April 2012).

NCT01229319

Trial name or title	An Investigator-Initiated Study to Assess the Safety and Efficacy of Imiquimod 3.75% Cream When Used After Cryotherapy in the Treatment of Hypertrophic Actinic Keratoses (AK) on Dorsal Hands and Forearms
Methods	This is a single-centre, randomised, assessor-blinded, intraindividual study.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Participants must be in good general health as confirmed by the medical history • Participants must be able to read, sign, and understand the informed consent • Prior to cryosurgery, participants have at least 3 hypertrophic actinic keratoses on each dorsal hand/forearm • Participant must be willing to forego any other treatments on the dorsum of the hands and or/forearms, including tanning bed use and excessive sun exposure while in the study

NCT01229319 *(Continued)*

	• Participant is willing and able to participate in the study as an outpatient, making frequent visits to the study centre during the treatment and follow-up periods and to comply with all study requirements including concomitant medication and other treatment restrictions
	• If the participant is a woman of child-bearing potential, she must have a negative urine pregnancy test result prior to study treatment initiation and must agree to use an approved method of birth control while enrolled in the study
	
	Exclusion criteria of the trial
	
	• Participants with a history of melanoma anywhere on the body
	• Participants with an unstable medical condition as deemed by the clinical investigator
	• Participants with non-melanoma skin cancer on the dorsum of the hands or forearms
	• Participants with any dermatologic disease in the treatment area that may be exacerbated by the treatment proposed or that might impair the evaluation of AKs
	• Treatment as follows:
	  • within 6 months with imiquimod on the dorsum of the hands or forearms
	  • within 30 days with imiquimod outside of the study area, any topical prescription medications on the study area
	• Women who are pregnant, lactating, or planning to become pregnant during the study period
	• Participants who have experienced a clinically-important medical event within 90 days of the visit (e.g. stroke, myocardial infarction, etc)
	• Participants who have active chemical dependency or alcoholism as assessed by the investigator
	• Participants who have known allergies to any excipient in the study cream
	• Participants who are currently participating in another clinical study or have completed another clinical study with an investigational drug or device on the study area within 30 days prior to study treatment initiation
	
	Demographics:
	
	• 20 participants

Interventions	**Intervention** A: cryotherapy + imiquimod 3.75% daily for 2 weeks on, 2 weeks off, 2 weeks on on one arm **Control intervention** B: cryotherapy alone on the other arm
Outcomes	**Primary outcomes of the trial** 1) Clearance of actinic keratoses assessed at 14 weeks 2) Actinic keratosis lesion count 3) Photography **Secondary outcome of the trial** 1) Local skin reactions assessed at 14 weeks
Starting date	October 2010
Contact information	Gary S Goldenberg, MD (garygoldenbergmd@gmail.com) Giselle Singer, BS (giselle.singer@mssm.edu)
NCT	NCT01229319
Notes	This study is currently recruiting, and the last update was in June 2011 (April 2012).

NCT01260987

Trial name or title	Conventional Versus Fractional CO2 Laser Assisted Photodynamic Therapy for Basal Call Carcinomas and Actinic Keratoses
Methods	This is a single-centre, randomised, assessor-blinded, active-controlled, intraindividual.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Skin type I to III • Fertile women using secure birth control • Moderate to severe actinic keratoses in the face or on the hands • Difficult-to-treat nodular basal cell carcinomas in the face **Exclusion criteria of the trial** • Pregnancy or breastfeeding participants • Participants with porphyria • Participants with Gorlins syndrome • Participants with a tendency to produce hypertrophic scars or keloids • Participants with known allergy to Metvix • Participants who are not considered able to follow the treatment protocol (e.g. severely alcoholic, dementia, mentally ill, etc) • Participants with pigmented or morphea basal cell carcinomas • Known herpes simplex virus infection in treatment areas **Demographics** • 47 participants
Interventions	**Intervention** A: fractional CO_2 laser assisted photodynamic therapy (PDT) pretreatment with fractional CO_2 laser before methyl-aminolevulinate (MAL)-red light PDT (37 J/cm^2) **Control intervention** B: conventional photodynamic therapy using methyl-aminolevulinate (MAL) and red light (37 J/cm^2)
Outcomes	**Primary outcomes of the trial** 1) Treatment response at 3 months, clinical evaluation by a blinded physician 2) Reoccurrence at 12 months, clinical evaluation by a blinded physician 3) Treatment response at 12 months **Secondary outcomes of the trial** 1) Pain during treatment, participant score (VAS 0 to 10) 2) Adverse effects at 12 months 3) Scaring, hyper- and hypopigmentation 4) Fluorescence at 3 hours, MAL uptake 5) Cosmetic result at 12 months, 4-point scale
Starting date	October 2010
Contact information	Christina S Haak, MD (christinahaak@dadlnet.dk)

NCT01260987 *(Continued)*

	Katrine Togsverd-Bo, MD (KTOG0001@regionh.bbh.dk)
NCT	NCT01260987
Notes	This study is currently recruiting, and the last update was June 2011 (April 2012).

NCT01265602

Trial name or title	Double-blind, Randomized, Vehicle- and Comparator-controlled, Multi-center Trial to Evaluate the Efficacy and Safety of LAS41007 in the Treatment of Actinic Keratosis
Methods	This is a multicentre, randomised, double-blind, placebo- and active-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Aged 18 years and older • Men and women • 6 to 16 clinically-confirmed actinic keratosis target lesions of mild to moderate (grade I to II, according to Olsen 1991) intensity in the whole treatment area (TA) (and additionally 1 representative lesion for histological diagnosis of actinic keratosis), which must be located in the face including the forehead (excluding eyelids, lips, and mucosa), bald scalp, or both • The actinic keratosis target lesions must be discrete and quantifiable; the distance from 1 lesion to its neighbour lesion must be greater than 1.0 cm • The diameter of each target lesion should be not less than 0.5 cm and not greater than 1.5 cm • The target lesions must be located in up to 3 TAs with a size of 25 cm^2 per TA (i.e. total area of TA is up to 75 cm^2) • Diagnosis of actinic keratosis histologically confirmed **Exclusion criteria of the trial** • Have known hypersensitivity, intolerance, or allergies against ingredients of the IMPs and other non-steroidal anti-inflammatory agents • Have a history of bronchospasm, asthma, urticaria, or rhinitis after the intake of non-steroidal anti-inflammatory drugs (NSAIDs) • Have a history of gastrointestinal bleeding or perforation associated with prior therapy with NSAIDs • Have evidence of clinically significant or unstable medical conditions • Have currently and within the past 3 months other malignant tumours of the skin in the TAs • Suffer from paraesthesia in the TAs • Show cornu cutaneum of the skin, hypertrophic, or both, actinic keratosis lesions in the TAs • Are known to be pregnant or lactating (currently or within the past 3 months) • Any clinically relevant abnormal finding during screening, baseline, or both • Specific topical treatments in the target area within defined time periods • Specific physical treatments in the TAs within defined time periods • Specific systemic treatments within defined time periods • Participants suffering from actinic keratoses in locations other than the target areas, receiving any topical therapy throughout the interventional phase of the study until termination of V6 • Participants who need a permanent therapy with any other NSAID. The use of NSAIDs as "prn" (pro re nata), i.e. to be taken as needed (≤ 3 days at a stretch) and the use of ASA as anticoagulative therapy will be allowed • Participants taking methotrexate or sulfonylurea during the interventional phase of the study

NCT01265602 *(Continued)*

- Anticoagulative therapy, e.g. with cumarines or heparines throughout the interventional phase of the study. Treatment with ASA at a dose not exceeding 100 mg/d and clopidogrel at a dose not exceeding 75 mg/d will be allowed
- Participants having any significant physical abnormalities in the potential TAs that may cause difficulty with examination or final evaluation
- Have any dermatological disease in the TAs or surrounding area that may be exacerbated by treatment with topical diclofenac or cause difficulty with examination
- Physical or mental inability, unwillingness, or both, to apply the study preparations correctly and to follow the study restrictions and visits
- Any suspicion of current drug or alcohol abuse, or both, as assessed by the investigator
- Anticipated non-availability for study visits/procedures
- Exposure to an investigational product within the last 3 months
- Any previous randomisation into this trial
- Participant is institutionalised because of legal or regulatory order
- Employee of the study site or of the Sponsor's company or the CRO

Demographics

- 915 participants

Interventions

Intervention

A: LAS41007, twice daily, once in the morning and once in the evening. Per application, not more than 1.5 g of the immunologically mediated photodermatoses (IMP) should be applied, which is sufficient to cover a total area of 75 cm^2 (corresponding to 3 single TAs, each with a size of 25 cm^2) in maximum. The IMPs will be applied for 90 days in maximum

Control interventions

B: LASW1510, twice daily, once in the morning and once in the evening. Per application, not more than 1.5 g of the IMP should be applied, which is sufficient to cover a total area of 75 cm^2 (corresponding to 3 single TAs, each with a size of 25 cm^2) in maximum. The IMPs will be applied for 90 days in maximum

C: vehicle, twice daily, once in the morning and once in the evening. Per application, not more than 1.5 g of the IMP should be applied, which is sufficient to cover a total area of 75 cm^2 (corresponding to 3 single TAs, each with a size of 25 cm^2) in maximum. The IMPs will be applied for 90 days in maximum

Outcomes

Primary outcomes of the trial

1) Superiority of LAS41007 compared to vehicle at day 1

2) Superiority of LAS41007 compared to LASW1510 assessed by histology to evaluate the histological clearance of one pre-selected target lesion
3) Superiority of LAS41007 compared to vehicle at day 150

4) Superiority of LAS41007 compared toLASW1510 each assessed by histology to evaluate the histological clearance of one pre-selected target lesion
Secondary outcomes of the trial

1) Superiority of LAS41007 compared to vehicle at day 1

2) Improved clinical efficacy of LAS41007 compared to LASW1510 with respect to clinical efficacy at day 1
3) Superiority of LAS41007 compared to vehicle at day 21

4) Improved clinical efficacy of LAS41007 compared to LASW1510 with respect to clinical efficacy at day 21
5) Superiority of LAS41007 compared to vehicle at day 56

NCT01265602 *(Continued)*

	6) Improved clinical efficacy of LAS41007 compared to LASW1510 with respect to clinical efficacy at day 56 7) Superiority of LAS41007 compared to vehicle at day 90 8) Improved clinical efficacy of LAS41007 compared to LASW1510 with respect to clinical efficacy at day 90 9) Superiority of LAS41007 compared to vehicle at day 150 10) Improved clinical efficacy of LAS41007 compared to LASW1510 with respect to clinical efficacy at day 150
Starting date	November 2010
Contact information	Sven Silberborth, PhD (sven.silberborth@almirall.com)
NCT	NCT01265602
Notes	This study is currently recruiting, and the last update was in December 2010 (April 2012).

NCT01354717

Trial name or title	Phase 3 Study of Brand Generic and Placebo in Treatment of Actinic Keratosis
Methods	This is a randomised, double-blind, placebo- and active-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Men and women • Between 48 and 85 year • Women who have had surgical sterilisation or are postmenopausal (absence of menses for at least 1 year) are eligible. Women of child-bearing potential who are non-pregnant and non-nursing and willing to avoid pregnancy during the course of the study and during the menstrual cycle following completion of their participation in the study are eligible. (Adequate contraception is defined as regular use of, diaphragm with condoms, IUD with condoms, or systemic contraceptives - if used for at least 3 months prior to enrolment in the study). A negative pregnancy test is required at entry into the study • Able to refrain from the use of all other topical medications to the facial area during the treatment period • Considered reliable and capable of understanding their responsibility and role in the study. Have provided written informed consent **Exclusion criteria of the trial** • History of allergy or hypersensitivity to 5-fluorouracil • Known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency • > 10 lesions total on the face [lesions that are hyperkeratotic, thicker than 1 mm (a piece of paper) or larger than 9 mm, or lesions suspicious for squamous cell carcinoma will not be included in lesion counts] • Clinical evidence of severe, uncontrolled autoimmune, cardiovascular, gastrointestinal, hematological, hepatic, neurological, pancreatic, pulmonary or renal disease • Dermatologic conditions if present on the face, such as atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, or albinism • Positive urine pregnancy test in women of child-bearing potential • Inability to use adequate birth control measures for women of child-bearing potential, as defined above • Serious psychological illness

NCT01354717 *(Continued)*

	• Significant history (within the past year) of alcohol or drug abuse
	• Participation in any clinical research study during the 30 day period preceding study initiation
	• Medical history which, based on the clinical judgment of the investigator, implies an unlikelihood of successful completion of the study
	• Treatment for actinic keratosis or skin cancer as follows:
	  • within 2 weeks and until day 42 visit with sun lamps or sun tanning beds or booths
	  • within 28 days with topical 5 fluorouracil, cryodestruction (liquid nitrogen spray), curettage (scraping of pre-cancer or skin cancers), surgical removal of skin cancer, photodynamic therapy, surgical excision, topical diclofenac (Solaraze), topical imiquimod (Aldara), or topical retinoids if used for actinic keratosis or other treatments for actinic keratoses
	  • within 1 month with any immunomodulators like interferon or cytotoxic drugs, any oral (systemic steroids) or topical corticosteroids, except for subjects on chronic low dose corticosteroids less than 5 mg daily for greater than 1 year
	  • within 6 months with chemical peel, dermabrasion, laser abrasion, PUVA (psoralen plus ultraviolet A) therapy, or UVB therapy to the face or bald scalp, systemic 5-fluorouracil, or systemic cancer therapy
	• Subjects with lesions suspicious for squamous cell carcinoma
	
	Demographics
	
	• 377 participants

Interventions	**Intervention** A: generic 0.5% 5-fluorouracil, once daily (duration of treatment was not specified) **Control interventions** B: carac 0.5% 5-fluorouracil, once daily (duration of treatment was not specified) C: placebo, once daily (duration of treatment was not specified)
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance at 6 weeks
Starting date	September 2010
Contact information	-
NCT	NCT01354717
Notes	This study has been completed in March 2011, and the last update was in JUne 2011 (April 2012).

NCT01358851

Trial name or title	Prospective Comparator Controlled Randomized Exploratory Study on the Efficacy of LAS 41005 Compared to Cryotherapy in Subjects With Hyperkeratotic Actinic Keratosis
Methods	This is a multicentre, randomised, open, active-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • General good and stable health confirmed by a physical examination and by medical history • Men or women • Between 18 and 85 years • Anatomical location: face/forehead or bald scalp

NCT01358851 *(Continued)*

- 4 to 10 clinically-confirmed hyperkeratotic target lesions of moderate to severe intensity
- Skin type I to IV according to Fitzpatrick's
- Free of any significant physical abnormalities (e.g. tattoos, dermatoses) in the potential treatment area that may cause difficulty with examination or final evaluation
- Physical ability to apply the study preparation correctly and to follow the study restrictions and visit
- Women of child-bearing potential are allowed to participate in this study, but only if they use a highly effective method of contraception

Exclusion criteria of the trial

- Immunosuppressive therapy
- Known hypersensitivity to the ingredients
- Coagulation defects that are inherited or acquired
- Evidence of clinically significant, unstable medical conditions
- Current other malignant or benign tumours of the skin within the treatment area
- Current treatment of actinic keratosis within the treatment area (face/scalp) within 3 months with phenytoin, methotrexate or sulfonylurea, or inhibitors of DPD (e.g. Brivudin, Sorivudin)
- Participants who have taken topical or systemic treatments that might interfere with the study end points, within a time window that is not allowed, or who are currently taking phenytoin, methotrexate, or sulfonylurea
- Pregnancy or lactation (currently or within the past 3 months)
- Any dermatological disease in the treatment area or surrounding area that may be exacerbated by treatment
- Currently or within the past 8 weeks participating in another clinical study
- Active chemical dependency or alcoholism as assessed by the investigator
- Institutionalised because of legal or regulatory order
- Any dermatological disease in the treatment area or surrounding area that may be exacerbated by treatment
- Currently or within the past 8 weeks participating in another clinical study
- Active chemical dependency or alcoholism as assessed by the investigator
- Institutionalised because of legal or regulatory order
- Pregnancy or lactation (currently or within the past 3 months)
- Any dermatological disease in the treatment area or surrounding area that may be exacerbated by treatment
- Currently or within the past 8 weeks participating in another clinical study
- Active chemical dependency or alcoholism as assessed by the investigator
- Institutionalised because of legal or regulatory order
- Pregnancy or lactation (currently or within the past 3 months)
- Any dermatological disease in the treatment area or surrounding area that may be exacerbated by treatment
- Currently or within the past 8 weeks participating in another clinical study
- Active chemical dependency or alcoholism as assessed by the investigator
- Institutionalised because of legal or regulatory order

Demographics

- 67 participants

Interventions

Intervention

A: LAS41005 (0.5% 5-fluorouracil/ 10% salicylic acid) once daily (number of weeks was not specified)

Control intervention

NCT01358851 *(Continued)*

	B: cryotherapy 1 to 2 times during the treatment time
Outcomes	**Primary outcome of the trial** 1) Histological clearance of 1 predefined target lesion at 8 weeks after the end of treatment with LAS41005 or 14 weeks after first cryotherapy **Secondary outcomes of the trial** 1) Participant complete clearance rates at days 21, 42, and 98 2) Participant partial (% was not specified) clearance rates at days 21, 42, and 98
Starting date	April 2011
Contact information	Rosario Rodríguez Almirall, S.A.
NCT	NCT01358851
Notes	This study is ongoing, and the last update was January 2012 (April 2012).

NCT01413763

Trial name or title	A Double-blind, Randomized, Placebo-controlled, 2-way Crossover Study to Assess the Potential Effect of Topically Applied Imiquimod Cream on Atrial Ectopy in Patients With Actinic Keratosis
Methods	This is a single-centre, randomised, double-blind, placebo-controlled, cross-over study.
Participants	**Inclusion criteria of the trial** • General good health • Men and women • Aged18 years and older • Anatomical location: face or balding scalp • ≥ 5 typical visible or palpable actinic keratoses • Women of child-bearing potential must be non-pregnant and non-lactating **Exclusion criteria of the trial** • Previous clinical study participation within 30 days (drug or device) • Evidence of clinically significant diseases • History of drug or alcohol abuse • Uncontrolled systemic hypertension, NYHA heart failure classification Class > II, or a history of atrial fibrillation or atrial flutter • Treatment within 30 days with imiquimod or interferon • Known allergies to any excipient in the study cream • Melanoma anywhere on the body **Demographics** • 50 participants
Interventions	**Intervention** A: 3.75% imiquimod cream, daily for 2 weeks

NCT01413763 *(Continued)*

	Control intervention B: placebo cream, daily for 2 weeks
Outcomes	**Primary outcome of the trial** 1) Change in 24-hour supraventricular beat count at day 14 **Secondary outcomes of the trial** 1) Change in 24-hour supraventricular premature couplet and run counts and atrial fibrillation (per cent time) at day 14 2) Change in 24-hour mean heart rate at day 14 3) Change in 24-hour ventricular premature beat count, ventricular premature couplet, and run counts at day 14
Starting date	July 2011
Contact information	Irma Benavides (ibenavides@cnsmail.com)
NCT	NCT01413763
Notes	This study is recruiting, and the last update was in August 2011 (April 2012).

NCT01453179

Trial name or title	Long-term Effects of Aldara® 5% Cream and Solaraze® 3% Gel in the Treatment of Actinic Keratoses on the Face or Scalp With Respect to the Risk of Progression to In-situ and Invasive Squamous Cell Carcinoma
Methods	This is a multicentre, randomised, open, active-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Histological diagnosis • Immunocompetent • Men and women • Aged18 years and older • Anatomical location: face or scalp • 5 to 10 typical visible actinic keratoses in 1 contiguous area of up to 50 cm^2 (the eyelids, the inside of the nostrils or ears, or the lip area inside the vermilion border must not be part of this area), grade I or II • Willingness to comply with the obligations of the study **Exclusion criteria of the trial** • History of hypersensitivity to imiquimod, diclofenac, acetyl salicylic acid, other non-steroidal anti-inflammatory drugs (NSAID), hyaluronic acid, or relevant excipients • Pregnancy, breastfeeding, or planned pregnancy during the study. Women of child-bearing potential not using a highly effective method of birth control defined as those which result in a low failure rate (i.e. < 1% per year) when used consistently and correctly, such as implants, injectables, combined oral contraceptives, hormonal IUDs, tubal ligation, or vasectomised partner • Presence of actinic keratosis lesions in the treatment area with clinically-excessive hyperkeratosis as seen in cutaneous horns • Persisting actinic keratoses at screening visit following topical treatment with imiquimod or diclofenac in the treatment area

NCT01453179 *(Continued)*

- Presence of any histologically-confirmed skin tumour in the treatment area: in situ SCC including Bowen's disease, invasive SCC, basal cell carcinoma, or other malignant tumours
- Any dermatological disease or condition that may exacerbate by treatment with imiquimod or diclofenac (e.g. rosacea, psoriasis, atopic dermatitis)
- Any dermatological disease or condition in the treatment area that causes difficulty with examination (e.g. eczema)
- History of any malignant tumour with high tumour burden or any systemic antitumour treatment (including radiotherapy)
- History of any malignant skin tumour having metastasised or in which metastasis within the study period is likely
- History of severe cardiovascular, pulmonary, hepatic, renal, gastrointestinal, haematological, endocrine, metabolic, mental, neurological, or other disease within the last two years which might hinder regular treatment and supervision and might lead to premature withdrawal from the study
- Mentally incapacitated participant. Present or history of drug or alcohol abuse within the last 3 years
- Treatment as follows
  - within 4 weeks with systemic immunomodulatory treatment, such as interferon, azathioprine, cyclosporine, retinoids, any oral or injectable corticosteroids, or inhaled or nasal corticosteroids with dosages of > 1200 µg/day beclomethasone or equivalent
  - within 2 months with any topical treatment including imiquimod or diclofenac; any systemic treatment, such as systemic retinoids; or any surgical treatment
- Exposure to an investigational product within the last 3 months
- Lack of ability or willingness to give informed consent
- Age below 18 years
- Lack of willingness to have personal study related data collected, archived, or transmitted according to protocol
- Anticipated non-availability for study visits/procedures
- Vulnerable subjects (such as persons kept in detention)

Demographics

- 220 participants

Interventions	**Intervention** A: 5% imiquimod, 3 times per week for 4 weeks on, 4 weeks off, once or twice **Control intervention** B: 3% diclofenac in hyaluronic acid, twice daily for 12 weeks
Outcomes	**Primary outcome of the trial** 1) Long-term outcome (3 years) with respect to the risk of progression to SCC (in situ, invasive, or both) **Secondary outcomes of the trial** 1) Recurrence rate at 3 years post-treatment 2) Time to recurrence at 3 years post-treatment 3) Need of rescue treatment at 3 years post-treatment 4) Cosmetic outcome at 3 years post-treatment
Starting date	October 2011
Contact information	Dr Ursula Petzold

NCT01453179 *(Continued)*

	MEDA Pharma GmbH & Co. KG
NCT	NCT01453179
Notes	This study is ongoing, and the last update was in March 2012 (April 2012).

NCT01458587

Trial name or title	A Phase II Study of Photodynamic Therapy With LEVULAN® Topical Solution + Blue Light Versus LEVULAN® Topical Solution Vehicle + Blue Light for the Treatment of Actinic Keratoses on the Upper Extremities
Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

Participants	**Inclusion criteria of the trial**
	• Men and women
	• Aged 18 years and older
	• Anatomical location: upper extremities
	• ≥ 4 grade I/II actinic keratoses on each upper extremity
	Exclusion criteria of the trial
	• Pregnancy
	• History of cutaneous photosensitisation, porphyria, hypersensitivity to porphyrins, or photodermatosis
	• Lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the treatment area
	• Skin pathology or condition which could interfere with the evaluation of the test product or requires the use of interfering topical or systemic therapy
	• Immunosuppressed
	• Unsuccessful outcome from previous ALA-PDT therapy
	• Currently enrolled in an investigational drug or device study or has received an investigational drug or been treated with an investigational device within 30 days prior to the initiation of treatment
	• Known sensitivity to one or more of the vehicle components (ethyl alcohol, isopropyl alcohol, laureth 4, polyethylene glycol)
	• Treatment on the extremities to be treated as follows:
	  • within 2 days with keratolytics including urea (greater than 5%), alpha hydroxy acids [e.g. glycolic acid, lactic acid, etc, greater than 5%], or salicylic acid (greater than 2%)
	  • within 2 weeks with cryotherapy
	  • within 4 weeks with retinoids, including tazarotene, adapalene, tretinoin, or retinol
	  • within 8 weeks with microdermabrasion, laser ablative treatments, ALA-PDT, chemical peels, 5-FU, diclofenac, imiquimod, or other topical treatments for actinic keratosis
	  • within 6 months with 2 or more ALA PDT treatments or systemic retinoid therapy
	Demographics
	• 64 participants

Interventions	**Intervention** A: 3 hours 20% ALA-blue light PDT **Control intervention**

NCT01458587 *(Continued)*

	B: 3 hours vehicle-blue light PDT
Outcomes	**Primary outcome of the trial** 1) Clearance rate for baseline grade I/II lesions at week 12 **Secondary outcomes of the trial** 1) Clearance rate for all baseline lesions at weeks 8 and 12 2) Clearance rate for baseline grade I/II lesions at week 8 3) Per cent change in total actinic keratoses at weeks 8 and 12 4) Participant complete clearance at weeks 8 and 12 5) Participant complete clearance excluding grade III lesions at weeks 8 and 12 6) Participant partial (≥ 75%) clearance at weeks 8 and 12 7) Participant satisfaction score 8) Changes in pigmentation (hypo and hyper) at 2, 8, and 12 weeks after PDT 9) Local skin reactions during PDT (stinging/burning); 5 minutes after PDT (erythema, edema); and 2, 8, and 12 weeks after PDT (erythema, edema, stinging/burning, scaling/dryness, oozing/vesiculation/crusting)
Starting date	November 2011
Contact information	Jim Berg (jberg@therapeuticsinc.com) Dan Piacquadio, MD (danp@therapeuticsinc.com)
NCT	NCT01458587
Notes	This study is recruiting, and the last update was in November 2011 (April 2012).

NCT01459393

Trial name or title	Evaluation of the Formulation of 5-aminolevulinic Acid With Dimethylsulfoxide in Photodynamic Therapy for Treatment of Actinic Keratosis
Methods	This is a single-centre, randomised, open, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Men and women • Aged18 years and older • Anatomical location: upper limbs • Symmetrical actinic keratoses, same grade, I, II, or III **Exclusion criteria of the trial** • Concomitant skin diseases, congenital or acquired (albinism, vitiligo, xeroderma, Gorlin, etc) • Immunosuppression (HIV, transplanted patients, etc) • Pregnancy or lactation • Participants who do not agree with the informed consent initially or during the protocol • Presence of pigmented lesions near the keratoses • Porphyria

NCT01459393 *(Continued)*

	• Treatment for keratosis within 2 months in the upper limbs **Demographics** • 137 participants
Interventions	**Intervention** A: 4 hours 20% ALA-red light PDT, once or twice with a 3-month interval **Control intervention** B: cryotherapy, once or twice with a 3-month interval
Outcomes	**Primary outcome of the trial** 1) Changes in lesion area at 0, 3, and 6 months **Secondary outcomes of the trial** 1) Pain on a visual analogue scale (VAS) and a graduated scale at the time 0 and 15 minutes after each intervention 2) Cosmetic outcome evaluated subjectively by the participant and investigator (awful, bad, regular, good, excellent) and objectively by the investigator (presence or absence of 1 or more of these criteria: hypochromia, hyperpigmentation, hyperemia, scar)
Starting date	November 2010
Contact information	Catarina Robert, MD René AC Vieira, PHD Fundação Pio XII - Hospital de Câncer de Barretos
NCT	NCT01459393
Notes	This study is ongoing, and the last update was in October 2011 (April 2012).

NCT01475071

Trial name or title	IIntra-individual Comparison of Efficacy and Safety of Metvix® Natural Daylight Photodynamic Therapy Versus Conventional Metvix® Photodynamic Therapy in Subject With Mild Actinic Keratoses
Methods	This is a multicentre, randomised, assessor-blind, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Men and women • Aged 18 years or older • Anatomical location: face or the scalp • Mild (with or without moderate in the treatment area) actinic keratoses **Exclusion criteria of the trial** • Clinical diagnosis of at least 1 severe actinic keratose on the treatment area • Clinical diagnosis of other skin disease (including non-melanoma skin cancer) on the treatment area

NCT01475071 *(Continued)*

	• Pigmented actinic keratoses on the treatment area **Demographics** • 100 participants
Interventions	**Intervention** A:16% MAL-daylight photodynamic therapy (PDT), once or twice with a 12-week interval **Control intervention** B: 16% MAL-conventional PDT, once or twice with a 12-week interval
Outcomes	**Primary outcome of the trial** 1) Per cent change from baseline in total number of treated mild lesions per side at week 12 2) Participant assessment of maximal pain on a scale from 0 (no pain) to 10 (extreme pain) per side at baseline
Starting date	March 2012
Contact information	Catherine Bosc (catherine.bosc@galderma.com)
NCT	NCT01475071
Notes	This study is recruiting, and the last update was in March 2012 (April 2012).

NCT01475955

Trial name or title	A Phase II Study of Photodynamic Therapy With LEVULAN® Topical Solution + Blue Light Versus LEVULAN® Topical Solution Vehicle + Blue Light Using Spot and Broad Area Application and Incubation Times of 1, 2 and 3 Hours for the Treatment of Multiple Actinic Keratoses on the Face or Scalp
Methods	This is a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Men and women • Aged 18 years or older • Anatomical location: face or scalp • 6 to 20 actinic keratoses, grade I/II • History of actinic keratosis therapy within the treatment area at least twice in the 2 years prior to study entry **Exclusion criteria of the trial** • Pregnancy • Grade III or atypical actinic keratoses (e.g. > 1 cm^2 in size) within the treatment area • Lesions suspicious for skin cancer (skin cancer not ruled out by biopsy) or untreated skin cancers within the treatment area • Plans to be exposed to artificial tanning devices or excessive sunlight during the trial • Immunosuppressed • Unsuccessful outcome from previous ALA-PDT therapy • History of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins or photodermatosis

NCT01475955 *(Continued)*

- Skin pathology or condition that could interfere with the evaluation of the test product or requires the use of interfering topical or systemic therapy
- Skin pathology or condition that could interfere with the evaluation of the test product or requires the use of interfering topical or systemic therapy
- Any condition which would make it unsafe for the subject to participate in this research study
- Currently enrolled in an investigational drug or device study or has received an investigational drug or been treated with an investigational device within 30 days prior to the initiation of treatment
- Known sensitivity to one or more of the vehicle components (ethyl alcohol, isopropyl alcohol, laureth 4, polyethylene glycol)
- An active herpes simplex infection or a history of 2 or more outbreaks within the past 12 months, in the treatment area
- Treatment on the treatment area as follows:
  - within 2 days with keratolytics including urea (greater than 5%), alpha hydroxy acids [e.g. glycolic acid, lactic acid, etc, greater than 5%], or salicylic acid (greater than 2%)
  - within 2 weeks with cryotherapy
  - within 4 weeks with retinoids, including tazarotene, adapalene, tretinoin, or retinol within 8 weeks with microdermabrasion, laser ablative treatments, ALA-PDT, chemical peels, 5-FU, diclofenac, imiquimod, or other topical treatments for actinic keratosis
  - within 6 months with 2 or more ALA PDT treatments
  - systemic retinoid therapy within 6 months of initiation of treatment

Demographics

- 220 participants

Interventions	**Interventions** A: field application 1 hours 20% ALA-blue light photodynamic therapy (PDT) B: field application 2 hours 20% ALA-blue light PDT C: field application 3 hours 20% ALA-blue light PDT D: Individual lesion application 2 hours 20% ALA-blue light PDT **Control intervention** E: field/individual application 1 to 3 hours 20% ALA-blue light PDT
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rate at week 12 **Secondary outcomes of the trial** 1) Participant complete clearance rate at weeks 4, 8, and 24 2) Participant partial (≥ 75%) clearance rate at weeks 4, 8, 12, and 24 3) Per cent change in lesion number at weeks 4, 8, 12, and 24 4) Participant satisfaction score on a 0 to 3 scale 5) Changes in pigmentation (hyper- and hypo-) at 24 to 48 hours after PDT, and at weeks 2, 4, 8, 12, and 24 6) Local skin reactions during PDT (stinging/burning); at 5 minutes after PDT (erythema, edema); at 24 to 48 hours after PDT; and weeks 2, 4, 8, 12, and 24 (erythema, edema, stinging/burning, scaling/dryness, oozing/vesiculation/crusting)
Starting date	December 2011

NCT01475955 *(Continued)*

Contact information	Jim Berg (jberg@therapeuticsinc.com) Dan Piacquadio, MD (danp@therapeuticsinc.com)
NCT	NCT01475955
Notes	This study is recruiting, and the last update was in March 2012 (April 2012).

NCT01481155

Trial name or title	Prospective, Single-center, Investigator-blinded, Randomized, Half-side, Comparative Study of Photodynamic Therapy vs. CO2 Laser Therapy in Treatment of Actinic Keratoses
Methods	This is a single-centre, randomised, assessor-blind, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Clinical and histological (on a lesion ≥ 4 mm diameter in treatment area) diagnosis • Men and women • Aged 18 years or older • ≥ 2 symmetrical clinically-visible actinic keratoses (at least 1 per treatment area) **Exclusion criteria of the trial** • Aged 17 years or younger • Lack of participant's informed consent for any of the 2 treatments • Contraindication for CO_2 therapy or for photodynamic therapy • Skin infection in the treatment area **Demographics** • 21 participants
Interventions	**Intervention** A: CO_2 laser therapy **Control intervention** B: 4h ALA- red light photodynamic therapy (PDT)
Outcomes	**Primary outcome of the trial** 1) Number of actinic keratoses at 3 months post-treatment **Secondary outcomes of the trial** 1) Histologic features at 1 month post-treatment 2) Epidermal thickness in optical coherence tomography at 1 month post-treatment
Starting date	March 2011
Contact information	Dr. Nina Scola, Consultant in Ruhr University of Bochum, Ruhr University of Bochum
NCT	NCT01481155

NCT01481155 *(Continued)*

Notes	This study is ongoing, and the last update was in December 2011 (April 2012).

NCT01493921

Trial name or title	A Randomized, Double-Blind, Parallel, Vehicle-Controlled Phase III Trial to Assess the Efficacy and Safety of Topical SR-T100 Gel in the Treatment of Patients With Actinic Keratosis
Methods	This is a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

Participants	**Inclusion criteria of the trial**
	• Clinical and histological (on a lesion ≥ 4 mm diameter in treatment area) diagnosis
	• Men and women
	• Aged 20 years or older
	• Anatomical location: arms, shoulder, chest, face, and scalp
	• ≥ 2 clinically-visible, discrete, non-hyperkeratotic, hypertrophic AK lesions located within a 25 cm^2 contiguous or non-contiguous treatment area
	Exclusion criteria of the trial
	• Dermatological disease and condition, such as atopic dermatitis, basal cell carcinoma, eczema, psoriasis, rosacea, squamous cell carcinoma, melanoma, or other possible confounding skin conditions in the treatment or surrounding area within 5 cm distances from treatment area
	• Treatment as follows:
	  • within 4 weeks with immunomodulators or immunosuppressive therapy, interferon and cytotoxic drugs
	  • on the treatment area with topical 5-FU, diclofenac gel, imiquimod, corticosteroids, retinoids, masoprocol, cryodestruction, chemodestruction, curettage, photodynamic therapy, or surgical excision
	  • within 6 months on the treatment area with psoralen plus UVA therapy, UVB therapy, laser abrasion, or dermabrasion chemical peel
	• Participant is known to be hypersensitive to the study medication
	• Women who are pregnant, breastfeeding, or considering becoming pregnant while on the study
	• Participant who had used of any investigational drug within the past 30 days before enrolment
	Demographics
	• 113 participants

Interventions	**Intervention** A: SR-T100 gel, once daily with an occlusive dressing for 16 weeks **Control intervention** B: vehicle gel, once daily with an occlusive dressing for 16 weeks
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance at 8 weeks post-treatment (week 24) **Secondary outcomes of the trial** 1) Lesion size reduction at 8 weeks post-treatment (week 24) 2) Participant partial (≥ 75%) clearance at 8 weeks post-treatment (week 24) 3)Tolerance

NCT01493921 *(Continued)*

Starting date	October 2011
Contact information	Kou-Wha Kuo, Ph.D (kwkuo@geherbs.com.tw) Tony Chiu, B.S (tonychiu@geherbs.com.tw)
NCT	NCT01493921
Notes	This study is recruiting, and the last update in March 2012 (April 2012).

NCT01502020

Trial name or title	A Multicenter, Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Comparison Study to Determine the Therapeutic Equivalence of Generic Imiquimod Cream, 3.75% and Zyclara™ (Imiquimod) Cream, 3.75% in Subjects With Actinic Keratoses
Methods	This was a multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

Participants	**Inclusion criteria of the trial**
	• Good general health and free of any disease state or physical condition that might have impaired evaluation of lesions or which, in the investigator's opinion, exposed the subject to an unacceptable risk by study participation
	• Men and women
	• Aged 18 years or older
	• Anatomical location: face (excluding ears) or balding scalp, but not both
	• 5 to 20 clinically typical, visible, or palpable actinic keratoses, each at least 4 mm in diameter, in an area greater than 25cm^2
	• Women of child-bearing potential (WOCBP) must have had a negative urine pregnancy test (UPT) and agreed to use an effective form of birth control for the duration of the study (e.g. abstinence, stabilised on hormonal contraceptives for at least 3 months [oral, implant, injection, IUD, patch, or NuvaRing], condom and spermicidal, or diaphragm and spermicidal). Abstinence was an acceptable form of birth control for subjects who were not sexually active. Subjects who became sexually active during the trial had to agree to use an effective, non-prohibited form of birth control for the duration of the study
	• Participant was willing and able to apply the test article as directed, comply with study instructions, and commit to all follow-up visits for the duration of the study
	Exclusion criteria of the trial
	• Pregnancy, lactation, or planning to become pregnant during the study
	• Hyperkeratotic, hypertrophic, or atypical actinic keratose (e.g. > 1 cm^2 in size) in the treatment area
	• Enrollement in an investigational drug or device study during the study period
	• Panning to be exposed to artificial tanning devices or excessive sunlight during the trial
	• Immunosuppressed (e.g. HIV, systemic malignancy, graft versus host disease, etc)
	• Unsuccessful outcome from previous imiquimod therapy (i.e. after a reasonable therapeutic trial with no compliance issues, topical application did not work)
	• Treatment as follows:
	  • within 30 days with investigational drug or investigational device
	  • within 6 months with laser resurfacing, PUVA (Psoralen + ultraviolet A) therapy, UVB therapy, chemical peels, or dermabrasion on the face or balding scalp
	  • within 1 month with cryodestruction or chemodestruction, curettage, photodynamic therapy, surgical excision or other treatments for actinic keratosis on the face or scalp, corticosteroid therapy, interferon, cytotoxic drugs, immunomodulators, immunosuppressive thera-

NCT01502020 *(Continued)*

	pies or retinoids, corticosteroids, alpha hydroxy acids (e.g. glycolic acid, lactic acid etc > 5%), beta hydroxy acid (salicylic acid > 2%), urea > 5%, 5-fluorouracil, diclofenac, imiquimod, or prescription retinoids (e.g. tazarotene, adapalene, or tretinoin) • within 1 day with topical creams, lotions, or gels of any kind to the selected treatment area • Basal cell or squamous cell carcinoma within the treatment area within 1 year of study enrolment • History of sensitivity to any of the ingredients in the test articles • Any skin pathology or condition (e.g. facial/scalp psoriasis, atopic dermatitis, acne, rosacea, etc) that, in the investigator's opinion, could have interfered with the evaluation of the test article, worsened due to the treatment or required the use of interfering topical, systemic, or surgical therapy • Any condition which, in the investigator's opinion, would have made it unsafe or precluded the participant's ability to fully participate in the research study • Known to be non-compliant or was unlikely to comply with the requirements of the study protocol (e.g. due to alcoholism, drug dependency, or mental incapacity) in the opinion of the investigator **Demographics** • 410 participants
Interventions	**Intervention** A: generic 3.75% imiquimod, once daily for 2 weeks on, 2 weeks off, 2 weeks on **Control interventions** B: placebo, once daily for 2 weeks on, 2 weeks off, 2 weeks on C: Zyclara 3.75% imiquimod, once daily for 2 weeks on, 2 weeks off, 2 weeks on
Outcomes	**Primary outcomes of the trial** 1) Participant complete clearance rate at 8 weeks post-treatment (week 14) 2) Compliance 3) Severity and frequency of adverse events 4) Severity and frequency of local skin reactions **Secondary outcome of the trial** 1) Participant partial (≥ 75%) clearance rate at 8 weeks post-treatment (week 14) 2) Per cent change in the lesion number at 8 weeks post-treatment (week 14)
Starting date	February 2011
Contact information	Daniel Piacquadio, M.D Therapeutics, Inc
NCT	NCT01502020
Notes	This study has been completed in November 2011, and the last update was in December 2011 (Apil 2012).

NCT01516515

Trial name or title	A Double-blind, Randomized, Vehicle-controlled, Parallel-group, Phase II Dose-ranging Study to Evaluate the Efficacy and Safety of SR-T100 Gel in Patients With Actinic Keratosis (AK) on the Head (Face and/or Scalp)
Methods	This is a randomised, double-blind, placebo-controlled, parallel-group study.

Participants	**Inclusion criteria of the trial**
	• Good general health condition (performance status ≤ 2 Eastern Cooperative Oncology Group (ECOG)
	• Men and women
	• Aged 20 years or older
	• Anatomical location: face, balding scalp, or both
	• 4 to 8 clinically diagnosed, discrete, non-hyperkeratotic, non-hypertrophic actinic keratoses, located with or without a contiguous 25 cm^2 areas
	• Biopsy allowed to be performed on selected lesion.
	• Photographs allowed on selected lesion and used as part of the study data package
	• Women with child-bearing potential must take reliable contraception method(s) during the participation of the study
	Exclusion criteria of the trial
	• Recurrent invasive squamous cell carcinoma (SCC).
	• Grossly suspicious or inflamed lymph nodes on physical examination.
	• Clinically significant or unstable medical conditions
	• Skin condition in the treatment area that may be made worse by treatment.
	• Treatment as follows:
	  • within 28 days on the treatment area(s), OTC retinol products, corticosteroids, cryosurgery, curettage, 5-fluorouracil (5-FU), imiquimod, topical diclofenac, retinoids, or other topical AK treatments (such as laser abrasion, dermabrasion, glycolic acids, or chemical peels)
	  • within 6 months with systemic cancer chemotherapy or immunosuppressant; on the target evaluation area, psoralen plus UVA therapy, UVB therapy
	  • within 12 months with prednisone, prednisolone, or both (≥ 10 mg or the equivalent) for more than 2 weeks continuously
	• Engaging in activities involving excessive or prolonged exposure to sunlight
	• History of allergy or sensitivity to related compounds or other components of the investigational product formulation
	• Woman who is pregnant, lactating, or planning to become pregnant during the study
	• Participant used any investigational drug within 8 weeks prior to the screening visit
	Demographics
	• 87 participants

Interventions	**Interventions** A: SR-T100 with 1.0% of SM in Solanum undatum plant extract for 16 weeks B: SR-T100 with 2.3% of SM in Solanum undatum plant extract for 16 weeks **Control intervention** B: placebo for 16 weeks
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance rate at 8 weeks post-treatment (week 24) **Secondary outcome of the trial**

NCT01516515 *(Continued)*

	1) Participant partial (≥ 75%) clearance rate at 8 weeks post-treatment (week 24)
Starting date	-
Contact information	Dr Kou-Wha Kuo (kwkuo@geherbs.com.tw)
NCT	NCT01516515
Notes	This study is not yet recruiting, and the last update was January 2012 (April 2012).

NCT01525329

Trial name or title	Combination Therapy With 5-Fluorouracil and Photodynamic Therapy for the Treatment of Post-transplant Premalignant Skin Disease
Methods	This is a single-centre, randomised, open, parallel-group (1 arm with immunocompetent controls and 1 arm with immunosuppressed organ transplant recipients), intraindividual (1 side with topical and PDT and 1 side with only PDT) study.
Participants	**Inclusion criteria of the trial** • Men and women • Aged 18 years or older • Anatomical location: face, scalp, or ears • ≥ 4 actinic keratoses • Participants in the solid organ transplant arm of the study must have had either a kidney or liver transplant, and the transplantation surgery must have occurred at least 2 years prior to enrolment **Exclusion criteria of the trial** • Pregnant or nursing • Currently participating in another clinical trial • Using any topical treatment for their actinic keratoses • Currently being treated for other cancers with medical or radiation therapy • Known hypersensitivity to 5-aminolevulinic acid, 5-fluorouracil, or any component of the study material • History of a photosensitivity disease, including porphyria cutanea tarda **Demographics** • 40 participants
Interventions	**Intervention** A: 5% 5-fluorouracil once daily for 6 days followed by 3 hours MAL-red light phototherapy (PDT) in immunocompetent and immunosuppressed participants **Control intervention** B: 3 hours MAL-red light PDT in immunocompetent and immunosuppressed participants
Outcomes	**Primary outcome of the trial** 1) Accumulation of PpIX at 3 hours after MAL application **Secondary outcomes of the trial** 1) Rate of lesion clearance at day 14 and at 3 months

NCT01525329 *(Continued)*

	2) Rate of development of new AK at months 3, 6 9, and 12
Starting date	September 2011
Contact information	Margo Riha, BSN, RN (riham@ccf.org) Sara Lohser, MD (lohsers@ccf.org)
NCT	NCT01525329
Notes	This study is recruiting, and the last update was in February 2012 (April 2012).

NCT01538901

Trial name or title	Topical Imiquimod 5% Cream Therapy Versus Photodynamic Therapy With Methyl-aminolaevulinate 16% Cream of Actinic Keratoses in Organ Transplant Recipients
Methods	This is a single-centre, randomised, open, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Clinical diagnosis • Men and women • Aged 18 years or older • Participants who had received a kidney, liver, lung, or heart transplant more than 3 years prior to inclusion into the study • Participants who had been treated at least 6 months prior to study entry with a stable 2-fold or 3-fold immunosuppressive treatment • Anatomical location: face, scalp, or both • Actinic keratoses in at least 2 anatomically separated contralateral areas with comparable size and extension and minimum distance of 5 cm **Exclusion criteria of the trial** • Invasive squamous cell carcinoma or basal cell carcinoma in the treatment area • Known allergy to imiquimod, methyl-aminolaevulinate, or both, or 1 of the other components of the investigational products, peanut oil, or both • Treatment within 4 weeks with retinoids, interferons, or investigational drugs • Participants who are participating in other dermatological study • Persistent Hepatitis B or C infections • Any evidence of systemic cancer • Participants who have received any systemic cancer chemotherapy or radiation therapy • Pregnant or lactating women **Demographics** • 34 participants
Interventions	**Intervention** A: 3 hours 16% MAL-red light photodynamic therapy (PDT) (70 J/cm^2), twice with a 2 week interval **Control intervention** B: 5% imiquimod, 3 times per week for 4 weeks
Outcomes	**Primary outcome of the trial**

NCT01538901 *(Continued)*

	1) Lesion complete response rate at 4 weeks post-treatment **Secondary outcomes of the trial** 1) Lesion complete response rate at 6 and 12 months post-treatment 2) Global reduction in the area of specific PpIX fluorescence at 1, 6, and 12 months post-treatment 3) Global participant's satisfaction on a 10 cm visual analogue scale (VAS, 0 means extremely unsatisfied, 1 to 3 means unsatisfied, 5 to 7 means moderately satisfied, 8 to 10 means highly satisfied) at 3, 6, and 12 months post-treatment
Starting date	April 2012
Contact information	Stanislava Tzaneva, Doz. Dr (stanislava.tzaneva@meduniwien.ac.at) Alexandra Geusau, Prof. Dr (alexandra.geusau@meduniwien.ac.at)
NCT	NCT01538901
Notes	This study is not yet recruiting, and the last update was in February 2012 (April 2012).

NCT01541228

Trial name or title	Clinical Effect of Photodynamic Treatment When Treating Actinic Keratoses With Different Light Doses
Methods	This is a single-centre, randomised, participant-blinded, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Clinically and histologically diagnosed • Men and women • Age older than 50 years • Anatomical location: face or scalp • 2 to 5 actinic keratoses with symmetrical distribution, largest diameter ≤ 3 cm (measuring the longest axis), grade I or II • Participant must be willing and capable of co-operating to the extent and degree required by the protocol • Participant is not the subject of the administrative or legal judicial proceeding • Participant has social health security required by laws of healthcare institutions. **Exclusion criteria of the trial** • > 5 actinic keratoses in the planned treatment area • Recurrent actinic keratoses, i.e. previously treated in the study area • Very hyperkeratotic, grade 3 (on a 0 to 3 scale) lesions among the target lesions • Actinic keratoses located on the nose • Other skin lesions (diseases) in the tumour study area • Subject with known hereditary basal cell carcinoma syndromes (Gorlin-Goltz, Basex-Dupre-Christol, et al) • Subject with a history of cutaneous photosensitization or porphyria or Xeroderma pigmentosum, hypersensitivity to porphyrins, or photodermatosis • Treatment

NCT01541228 *(Continued)*

	• within 30 days with photosensitising drugs • within 6 months with immunomodulatory or immunosuppressive therapies, including systemic and topical steroids, imiquimod or solaraze, interferon, and acitretin • within 2 months in the study area with laser resurfacing, chemical peels, topical application fluorouracil, or other drugs for the treatment of actinic keratoses • Participant who had participated in another investigational drug or device research study within 30 days of enrolment • Participant with known hypersensitivity to 5-aminolevulinc acid, a similar compound or excipients of the cream • Participant with known status after organ transplantation **Demographics** • 38 participants
Interventions	**Intervention** A: 20% ALA-red light photodynamic therapy (PDT) (70 J/cm^2), twice with a 2-week interval **Control intervention** B: 20% ALA-red light PDT (100 J/cm^2), twice with a 2-week interval
Outcomes	**Primary outcome of the trial** 1) Relapse of clinically cleared actinic keratosis, evaluation by two investigators for clinical/histological relapse at 1, 3, 6, 12, and 24 months post-treatment **Secondary outcome of the trial** 1) Pain during treatment, participant scoring on a visual analogue scale (VAS)
Starting date	April 2010
Contact information	Evelina Buinauskaite, MD Skaidra Valiukeviciene, Prof. Lithuanian University of Health Sciences, Medical Academy, Department of Skin and Venereal Diseases
NCT	NCT01541228
Notes	This study is ongoing, and the last update was in February 2012 (April 2012).

NCT01541553

Trial name or title	A Sequential Treatment Regimen of Cryotherapy and Picato® for the Treatment of Actinic Keratosis on the Face and Scalp
Methods	This is a multicentre, randomised, double-blinded, placebo-controlled, parallel-group study.
Participants	**Inclusion criteria of the trial** • Men and women • Aged 18 years and older

NCT01541553 *(Continued)*

- Anatomical location: face or scalp
- 4 to 8 clinically typical, visible and discrete actinic keratoses within a contiguous 25 cm^2 treatment area
- Women must be of either: non-child-bearing potential, i.e. postmenopausal or have a confirmed clinical history of sterility (e.g. the subject is without a uterus), or child-bearing potential provided there is a confirmed negative urine pregnancy test prior to study treatment, to rule out pregnancy
- Women of child-bearing potential must be willing to use effective contraception

Exclusion criteria of the trial

- Location of the selected treatment area: on any location other than the face or scalp, within 5 cm of an incompletely healed wound, within 10 cm of a suspected basal cell carcinoma (BCC) or SCC
- Prior treatment with PEP005 Gel on face or scalp
- Selected treatment area lesions that have atypical clinical appearance, recalcitrant disease, or both
- History or evidence of skin conditions other than the trial indication that would interfere with evaluation of the trial medication
- Clinical diagnosis/history or evidence of any medical condition that would expose a subject to an undue risk of a significant adverse event or interfere with assessments of safety and efficacy
- Any abnormal vital signs measurements that are medically significant or would impact the safety of the subject or the interpretation of the trial results
- Anticipated need for hospitalisation or outpatient surgery during the first 15 days after the first trial medication application
- Known sensitivity or allergy to any of the ingredients in PEP005 gel
- Recent excessive exposure to ultraviolet light
- Current enrolment or participation in a clinical trial within 30 days of entry into this study
- Participants previously randomised in the trial
- Women who are breastfeeding
- Treatment as follows:
  - within 2 weeks prior to visit 1 with cosmetic or therapeutic procedures, use of acid-containing therapeutic products, or use of topical medicated creams, ointments, lotions, gels, foams, or sprays within 2 cm of the selected treatment area
  - within 4 weeks prior to visit 1 with immunomodulators, cytotoxic drugs or interferon /interferon inducers, systemic medications that suppress the immune system, treatment/therapy with ultraviolet light A (UVA), or ultraviolet light B (UVB).
  - within 8 weeks prior to visit 1 with 5-FU, imiquimod, diclofenac sodium, or photodynamic therapy within 2 cm of the selected treatment area
  - within 6 months prior to visit 1 with systemic retinoids or biologic/monoclonal antibody therapies

Demographics

- 326 participants

Interventions	**Intervention** A: cryotherapy followed by 0.015% PEP005 (ingenol mebutate) gel (field) daily for 3 consecutive days **Control intervention** B: cryotherapy followed by vehicle gel (field) daily for 3 consecutive days
Outcomes	**Primary outcome of the trial** 1) Participant complete clearance at week 11 **Secondary outcomes of the trial** 1) Per cent reduction from baseline in number of lesions at week 11

NCT01541553 *(Continued)*

	2) Participant complete clearance for 12 months (recurrence) 3) Per cent reduction from baseline in number of lesions at week 11 through to month 12 4) Participant partial (≥ 75%) clearance at week 11 4) Participant partial (≥ 75%) clearance at week 11 through to month 12
Starting date	March 2012
Contact information	Birgitte Vestbjerg (birgitte.vestbjerg@leo-pharma.com)
NCT	NCT01541553
Notes	This study is recruiting, and the last update was in March 2012 (April 2012).

Willey 2011

Trial name or title	Temperature modulated photodynamic therapy for the treatment of actinic keratoses on the extremities
Methods	This is a randomised, blinded, active-controlled, intraindividual study.
Participants	**Inclusion criteria of the trial** • Anatomical location: upper and lower extremities **Demographics** • 20 participants
Interventions	**Intervention** A: ALA + heat followed by blue light photodynamic therapy (PDT) (N= 20 participants) **Control interventions** B: ALA + no heat followed by blue light PDT (N = 20 participants) Characteristics of PDT intervention Type of treatment: -- Number of treatments: 1 Interval between treatments: -- Preparation of lesions: -- Cream concentration (%): 20 Application of cream: -- Incubation with cream: 1 hour under occlusion Type of light: blue light Light source: -- Wavelength (nm): 417 nm Energy fluence (J/cm^2): 10 Intensities (mW/cm^2): --

Willey 2011 *(Continued)*

	Exposure time: --
Outcomes	**Outcomes of the trial** 1) Clearance rates 2) Tolerability during and following treatment on a 4-point scale Efficacy Methods: quantitative assessment by lesion counting performed by an unblinded investigator and photographs evaluation by a blinded investigator Time points: at baseline, and 2 and 6 months post-treatment
Starting date	-
Contact information	-
NCT	-
Notes	Abstract from 31st Annual Conference of the American Society for Laser Medicine and Surgery, ASLMS 2011

DATA AND ANALYSES

Comparison 1. Adapalene gel versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Improvement Indices (investigator)-cleared	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Mean changes in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 0.1% adapalene gel	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 0.3% adapalene gel	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Minor adverse events excluding skin irritation: dermatitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Adapalene gel versus placebo, Outcome 1 Global Improvement Indices (investigator)-cleared.

Study or subgroup	Adapalene n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2003	2/60	0/30		2.54[0.13,51.31]

Favours placebo 0.001 0.1 1 10 1000 Favours adapalene

Analysis 1.2. Comparison 1 Adapalene gel versus placebo, Outcome 2 Mean changes in lesion counts.

Study or subgroup	Adapalene N	Adapalene Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.2.1 0.1% adapalene gel						
Kang 2003	30	-0.5 (0.9)	15	1.5 (1.3)		-2[-2.73,-1.27]
1.2.2 0.3% adapalene gel						
Kang 2003	30	-2.5 (0.9)	15	1.5 (1.3)		-4[-4.73,-3.27]

Favours adapalene -5 -2.5 0 2.5 5 Favours placebo

Analysis 1.3. Comparison 1 Adapalene gel versus placebo, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	0.1-0.3% Adapelene n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2003	3/60	0/30		3.56[0.19,66.72]

Favours 0.1-0.3%adapalene 0.01 0.1 1 10 100 Favours placebo

Analysis 1.4. Comparison 1 Adapalene gel versus placebo, Outcome 4 Minor adverse events excluding skin irritation: dermatitis.

Study or subgroup	adapalene n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2003	20/60	3/30		3.33[1.08,10.34]

Favours adapalene 0.01 0.1 1 10 100 Favours placebo

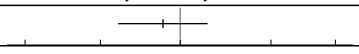
Comparison 2. 0.1% adapalene vs 0.3% adapalene

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Improvement Indices (investigator)-cleared	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Mean changes in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Minor adverse events excluding skin irritation: dermatitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

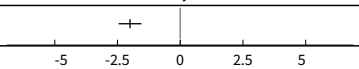
Analysis 2.1. Comparison 2 0.1% adapalene vs 0.3% adapalene, Outcome 1 Global Improvement Indices (investigator)-cleared.

Study or subgroup	0.1% adapalene n/N	0.3% adapalene n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2003	25/30	27/30		0.93[0.76,1.13]



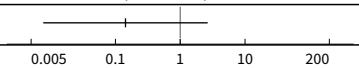
Analysis 2.2. Comparison 2 0.1% adapalene vs 0.3% adapalene, Outcome 2 Mean changes in lesion counts.

Study or subgroup	0.3% adapalene N	0.3% adapalene Mean(SD)	0.1% adapalene N	0.1% adapalene Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kang 2003	30	-2.5 (0.9)	30	-0.5 (0.9)		-2[-2.46,-1.54]



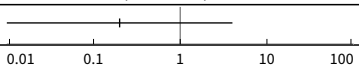
Analysis 2.3. Comparison 2 0.1% adapalene vs 0.3% adapalene, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	0.1% adapelene n/N	0.3% adapelene n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2003	0/30	3/30		0.14[0.01,2.65]



Analysis 2.4. Comparison 2 0.1% adapalene vs 0.3% adapalene, Outcome 4 Minor adverse events excluding skin irritation: dermatitis.

Study or subgroup	0.1% adapalene n/N	0.3% adapalene n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kang 2003	0/30	2/30		0.2[0.01,4]

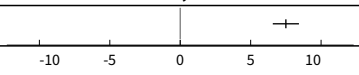


Comparison 3. Arotinoid Methyl Sulfone (Ro 14-9706) versus Tretinoin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Arotinoid Methyl Sulfone (Ro 14-9706) versus Tretinoin, Outcome 1 Mean percentage of reduction in lesion counts.

Study or subgroup	Arotinoid Methyl Sulfone N	Arotinoid Methyl Sulfone Mean(SD)	Tretinoin N	Tretinoin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Misiewicz 1991	25	37.8 (1.3)	25	30.3 (2)		7.5[6.57,8.43]

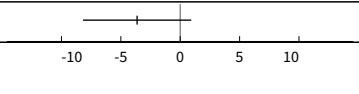


Comparison 4. Calcipotriol (vitamin D) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean changes in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Cosmetic outcomes: Reduction in total cosmetic appearance score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

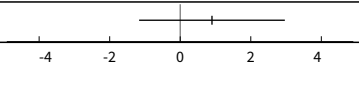
Analysis 4.1. Comparison 4 Calcipotriol (vitamin D) versus placebo, Outcome 1 Mean changes in lesion counts.

Study or subgroup	Calciprotriol N	Calciprotriol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Seckin 2009	8	-2.9 (2.6)	8	0.8 (6)		-3.63[-8.19,0.93]



Analysis 4.2. Comparison 4 Calcipotriol (vitamin D) versus placebo, Outcome 2 Cosmetic outcomes: Reduction in total cosmetic appearance score.

Study or subgroup	Calciprotriol N	Calciprotriol Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Seckin 2009	8	2 (1.9)	8	1.1 (2.3)		0.9[-1.17,2.97]



Comparison 5. 1% colchicine cream versus 0.5% colchicine cream

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Mean reduction in lesion counts-total	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Mean reduction in lesion counts-per anatomical locations	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Face	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Scalp	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Upper extremities	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cosmetic outcomes: Number of participants with decreased infiltration and disappearance of crust	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 5.1. Comparison 5 1% colchicine cream versus 0.5% colchicine cream, Outcome 1 Participant complete clearance.

Study or subgroup	1% cochicine n/N	0.5% colchicine n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Akar 2001	6/8	7/8		0.86[0.53,1.38]
		Favours 0.5%	0.5 0.7 1 1.5 2	Favours 1%

Analysis 5.2. Comparison 5 1% colchicine cream versus 0.5% colchicine cream, Outcome 2 Mean reduction in lesion counts-total.

Study or subgroup	1% cochicine N	Mean(SD)	0.5% colchicine N	Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Akar 2001	8	2 (2.4)	8	2.1 (2.7)		-0.1[-2.6,2.4]
				Favours 0.5%	-2 -1 0 1 2	Favours 1.0%

Analysis 5.3. Comparison 5 1% colchicine cream versus 0.5% colchicine cream, Outcome 3 Mean reduction in lesion counts-per anatomical locations.

Study or subgroup	1% cochicine N	1% cochicine Mean(SD)	0.5% colchicine N	0.5% colchicine Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
5.3.1 Face						
Akar 2001	8	3.3 (2.9)	8	3.6 (3.1)		-0.3[-3.24,2.64]
5.3.2 Scalp						
Akar 2001	8	1 (1.7)	8	1.5 (2.4)		-0.5[-2.54,1.54]
5.3.3 Upper extremities						
Akar 2001	8	1.6 (1.8)	8	1.3 (2.1)		0.3[-1.62,2.22]
				Favours 0.5%	-2 -1 0 1 2	Favours 1.0%

Analysis 5.4. Comparison 5 1% colchicine cream versus 0.5% colchicine cream, Outcome 4 Cosmetic outcomes: Number of participants with decreased infiltration and disappearance of crust.

Study or subgroup	1% cochicine n/N	0.5% colchicine n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Akar 2001	6/8	7/8		0.86[0.53,1.38]
		Favours 0.5%	0.5 0.7 1 1.5 2	Favours 1.0%

Comparison 6. 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Investigator Global Improvement Indices-completely improved	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 30 day treatment/30 day follow-up	1	98	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.89, 17.89]
1.2 60 day treatment/30 day follow-up	1	97	Risk Ratio (M-H, Random, 95% CI)	3.06 [1.21, 7.77]
1.3 90 day treatment/30 day follow-up	1	117	Risk Ratio (M-H, Random, 95% CI)	2.50 [1.37, 4.55]
2 Participant Global Improvement Indices-completely improved	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 30 day treatment/30 day follow-up	1	98	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.89, 17.89]
2.2 60 day treatment/30 day follow-up	1	97	Risk Ratio (M-H, Random, 95% CI)	2.86 [1.12, 7.32]

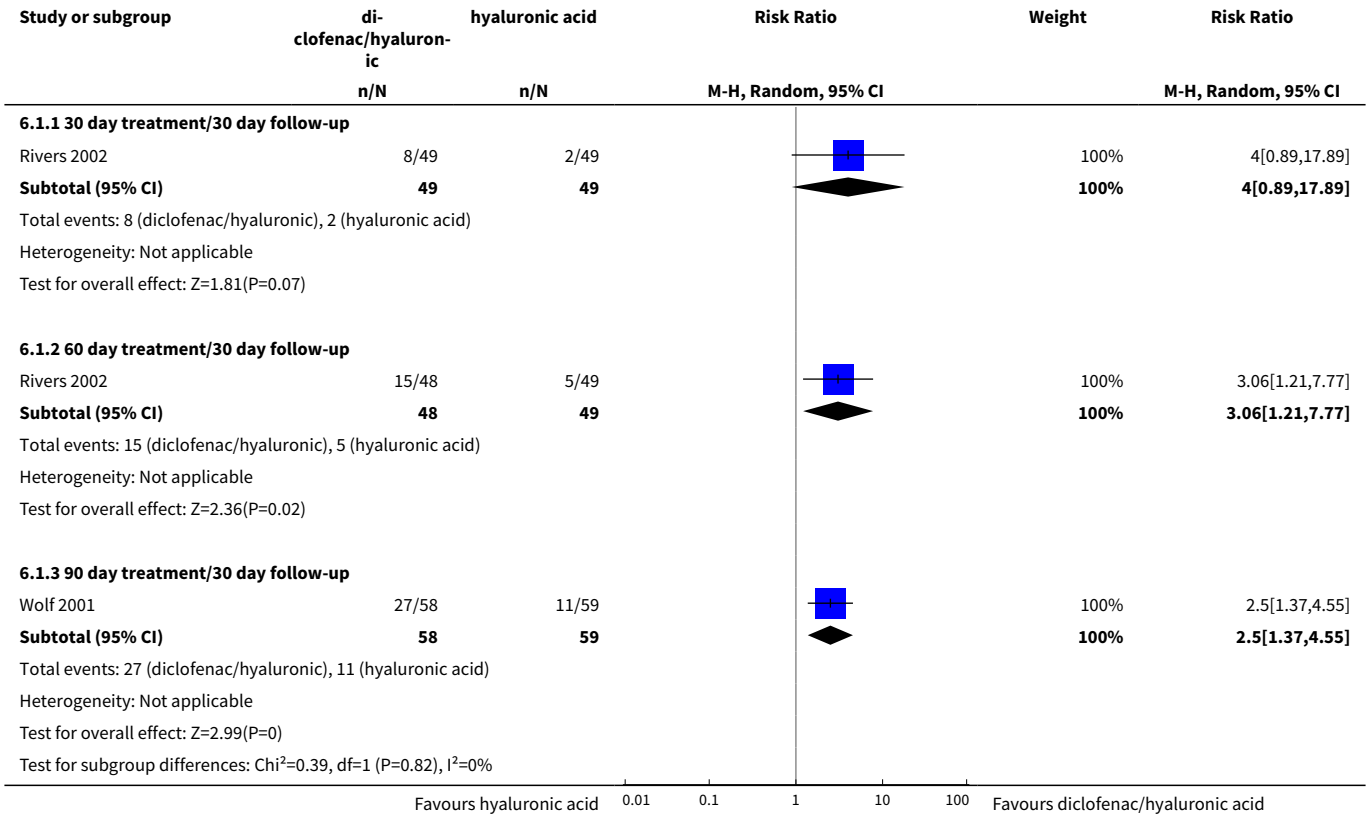
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 90 day treatment/30 day follow-up	1	117	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.28, 4.64]
3 Participant complete clearance at end of treatment (>56 days)	2	280	Risk Ratio (M-H, Random, 95% CI)	1.95 [1.21, 3.13]
4 Participant complete clearance (target lesions)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 30 day treatment/ 30 day follow-up	1	98	Risk Ratio (M-H, Random, 95% CI)	3.5 [0.76, 16.01]
4.2 60 day treatment/ 30 day follow-up	1	97	Risk Ratio (M-H, Random, 95% CI)	3.27 [1.30, 8.21]
4.3 90 day treatment/ 30 day follow-up	2	267	Risk Ratio (M-H, Random, 95% CI)	2.87 [1.84, 4.48]
5 Participant complete clearance (all lesions)	3	420	Risk Ratio (M-H, Random, 95% CI)	2.46 [1.66, 3.66]
5.1 30 day treatment/ 30 day follow-up	1	98	Risk Ratio (M-H, Random, 95% CI)	3.5 [0.76, 16.01]
5.2 60 day treatment/ 30 day follow-up	1	97	Risk Ratio (M-H, Random, 95% CI)	3.83 [1.37, 10.71]
5.3 90 day treatment/30 day follow-up	2	225	Risk Ratio (M-H, Random, 95% CI)	2.20 [1.40, 3.44]
6 Participant complete clearance for 30 day treatment by locations	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Scalp	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Forehead	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Face	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 Back of hand	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Participant complete clearance for 60 day treatment by locations	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Scalp	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Forehead	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Face	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.4 Arm/forearm	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.5 Back of hand	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Participant complete clearance for 90 day treatment by locations	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 Scalp	2	23	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.25, 6.08]
8.2 Forehead	2	95	Risk Ratio (M-H, Random, 95% CI)	1.71 [1.03, 2.85]
8.3 Face	2	47	Risk Ratio (M-H, Random, 95% CI)	2.15 [1.05, 4.40]
8.4 Arm/forearm	2	37	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.26, 14.40]
8.5 Back of hand	2	63	Risk Ratio (M-H, Random, 95% CI)	1.71 [0.04, 65.87]
9 Participant complete clearance in immunosuppressed participants	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Participant partial (>75%) clearance in immunosuppressed participants	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Mean reduction of lesion counts (30-90 days): At the end of study	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
11.1 90 days	1	150	Mean Difference (IV, Random, 95% CI)	0.80 [-1.48, 3.08]
12 Mean reduction of lesion counts (30-90 days): 30 day follow-up	2	345	Mean Difference (IV, Random, 95% CI)	2.55 [1.56, 3.53]
12.1 30 days	1	98	Mean Difference (IV, Random, 95% CI)	2.00 [0.63, 3.37]
12.2 60 days	1	97	Mean Difference (IV, Random, 95% CI)	2.40 [0.73, 4.07]
12.3 90 days	1	150	Mean Difference (IV, Random, 95% CI)	3.80 [1.83, 5.77]
13 Withdrawal due to adverse events	4	592	Risk Ratio (M-H, Random, 95% CI)	3.59 [1.92, 6.70]
14 Minor adverse event: body as a whole : in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Minor adverse event: body as a whole : "flu"	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
16 Minor adverse event:: body as a whole : infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17 Minor adverse event: cardiovascular: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

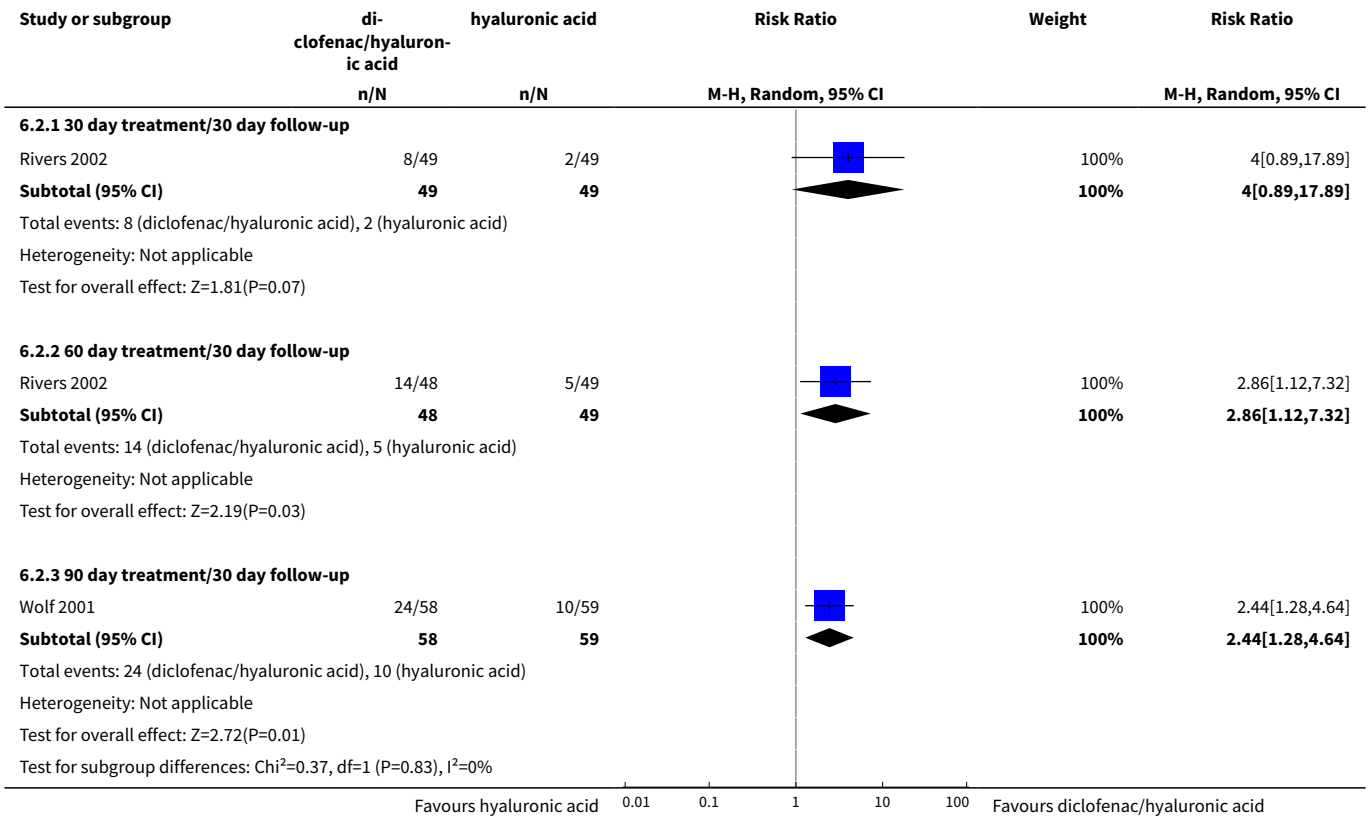
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Minor adverse event: cardiovascular: sinus bradycardia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19 Minor adverse event: dermatological: bursitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20 Minor adverse event: dermatological: dry skin	3	462	Risk Ratio (M-H, Random, 95% CI)	2.40 [1.20, 4.78]
21 Minor adverse event: dermatological: herpes zoster	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
22 Minor adverse event: dermatological: rash vesiculobullous	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
23 Minor adverse event::dermatological: seborrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
24 Minor adverse event: dermatological: skin exfoliation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
25 Minor adverse event: dermatological: ulcerated skin	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
26 Minor adverse event: digestive : in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
27 Minor adverse event: hemic and lymphatic: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
28 Minor adverse event: metabolic and nutritional disorders : in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
29 Minor adverse event: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
30 Minor adverse event: musculoskeletal and connective tissue: hypokinesia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
31 Minor adverse event: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
32 Minor adverse event: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
33 Minor adverse event: nervous system: hyperaesthesia	2	345	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.30, 2.60]
34 Minor adverse event: nervous system: paraesthesia	2	345	Risk Ratio (M-H, Random, 95% CI)	2.53 [0.57, 11.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
35 Minor adverse event: respiratory: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
36 Minor adverse event: respiratory: bronchitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
37 Minor adverse event: respiratory: pharyngitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
38 Minor adverse event: respiratory: upper respiratory tract infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
39 Minor adverse event: special senses: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
40 Minor adverse event: urogenital: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

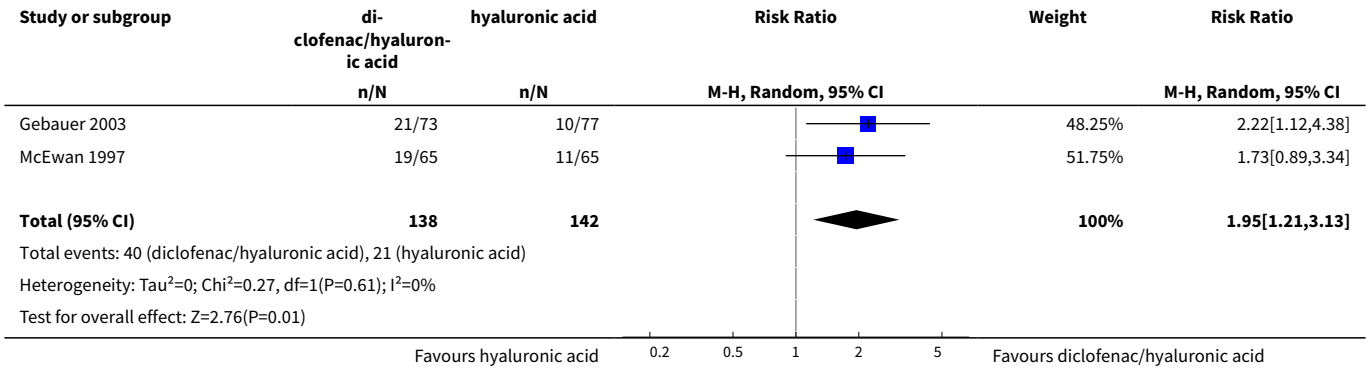
Analysis 6.1. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 1 Investigator Global Improvement Indices-completely improved.



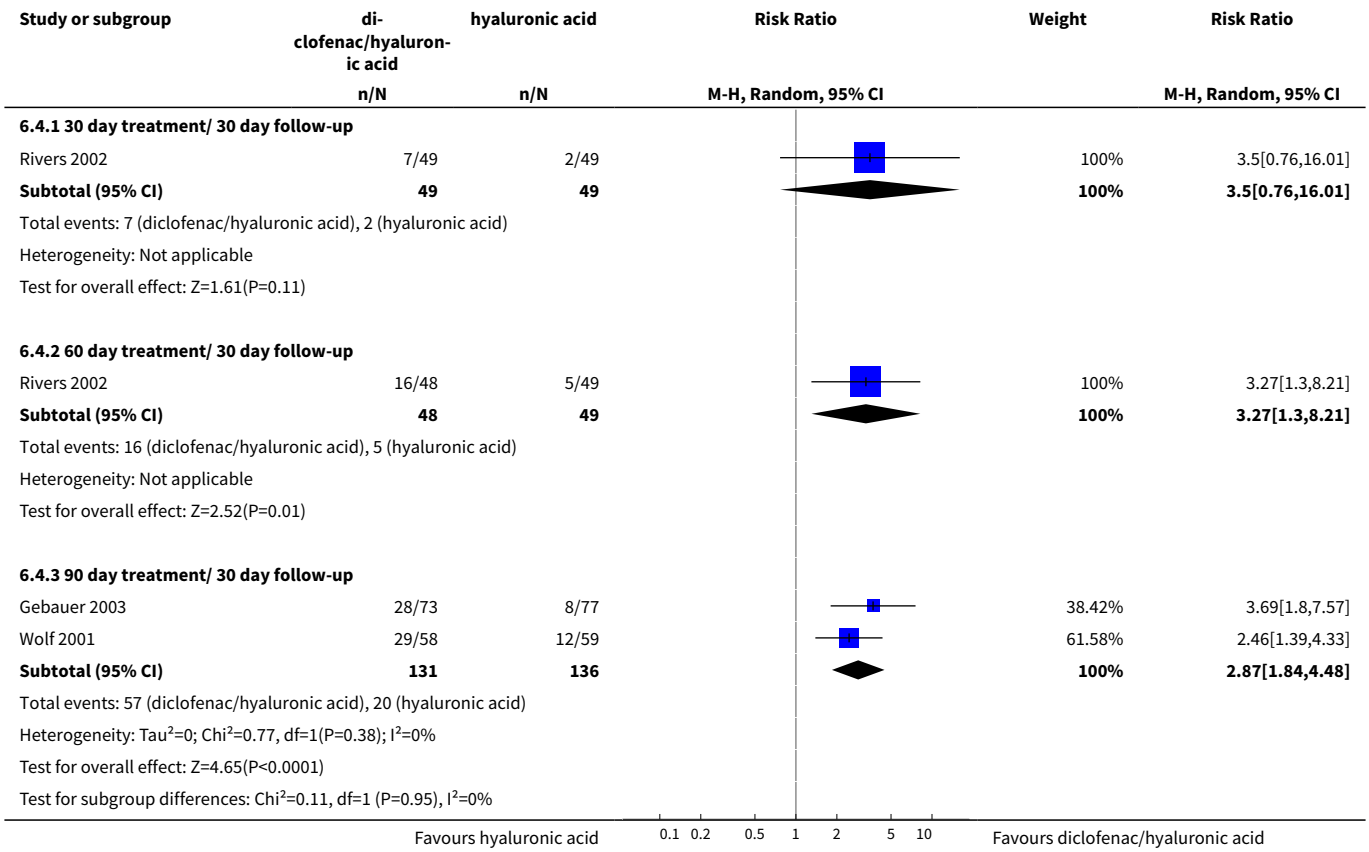
Analysis 6.2. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 2 Participant Global Improvement Indices-completely improved.



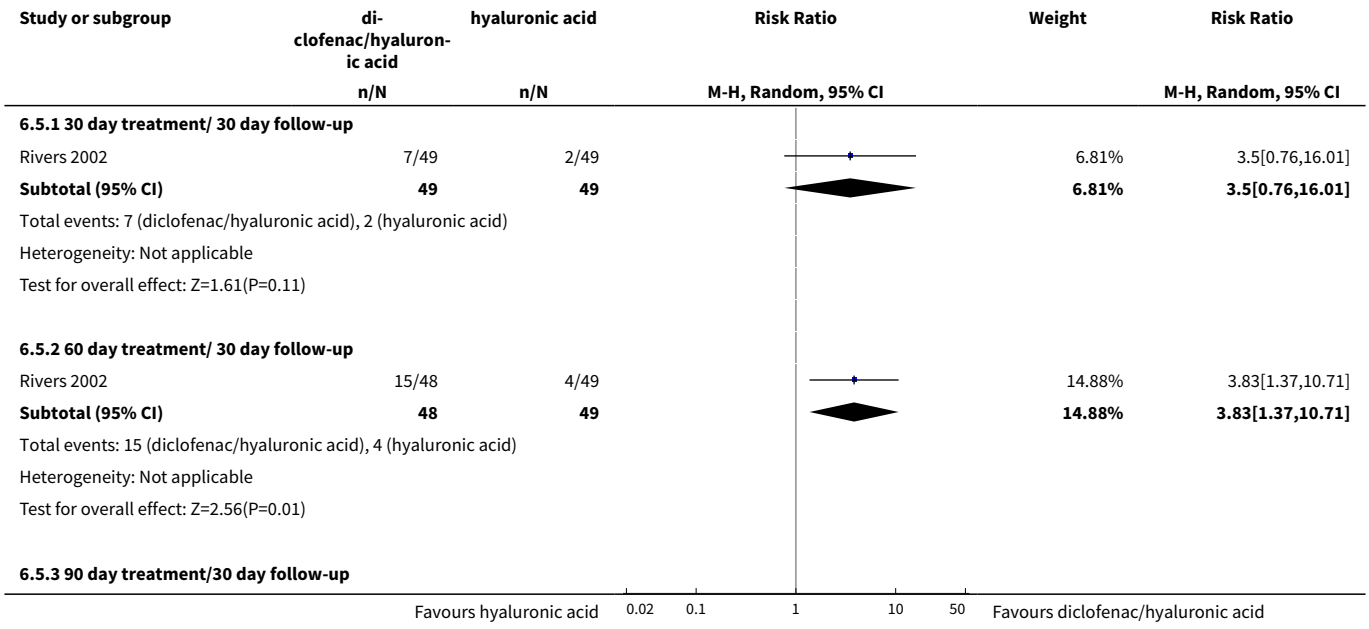
Analysis 6.3. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 3 Participant complete clearance at end of treatment (>56 days).

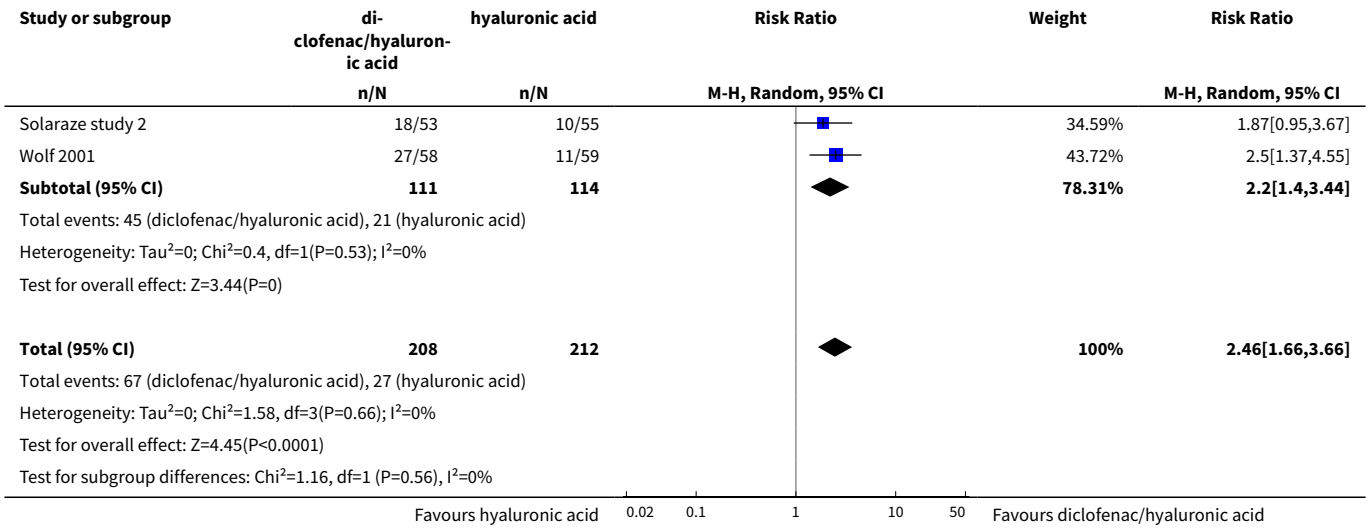


Analysis 6.4. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 4 Participant complete clearance (target lesions).

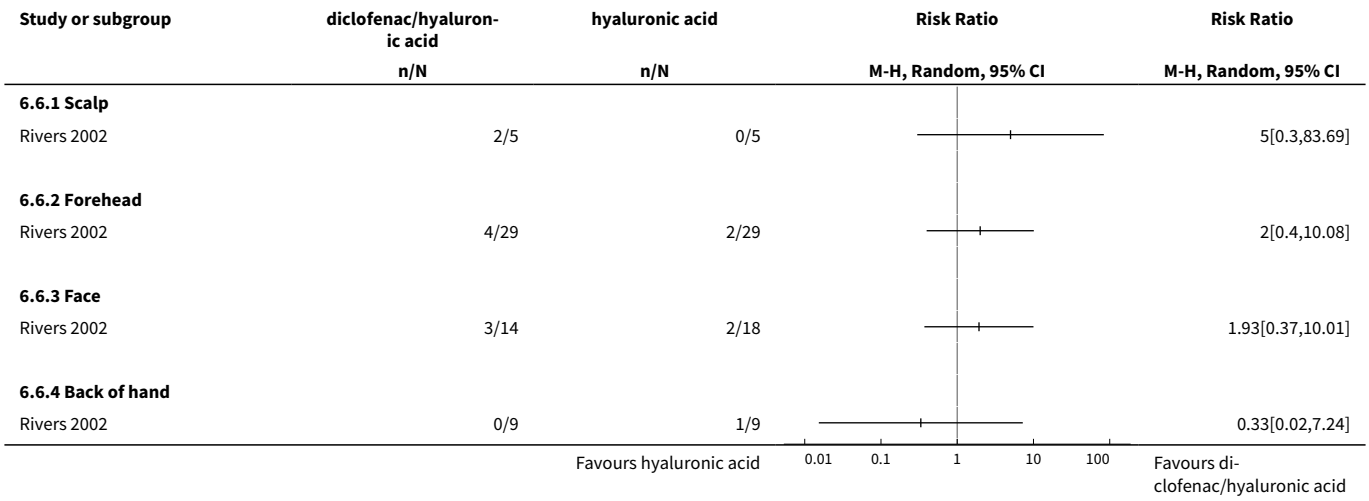


Analysis 6.5. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 5 Participant complete clearance (all lesions).

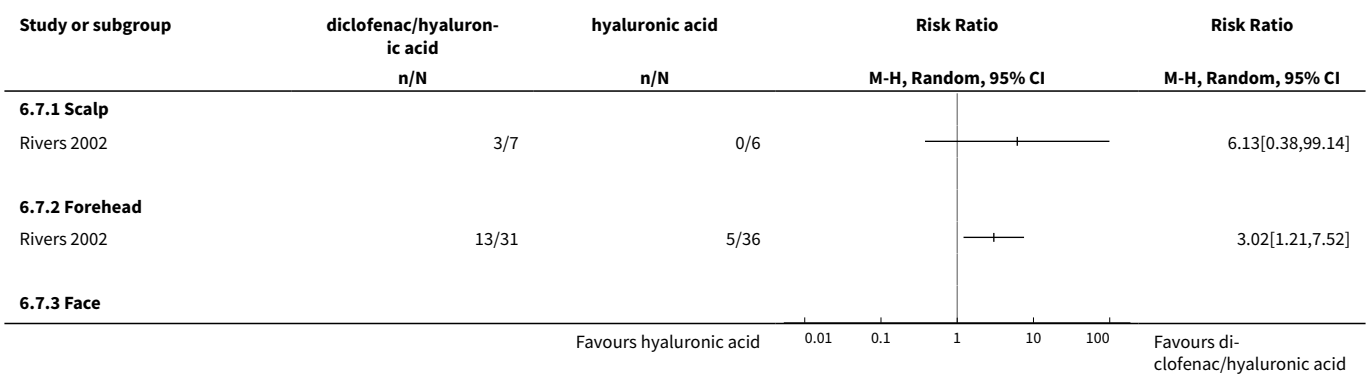


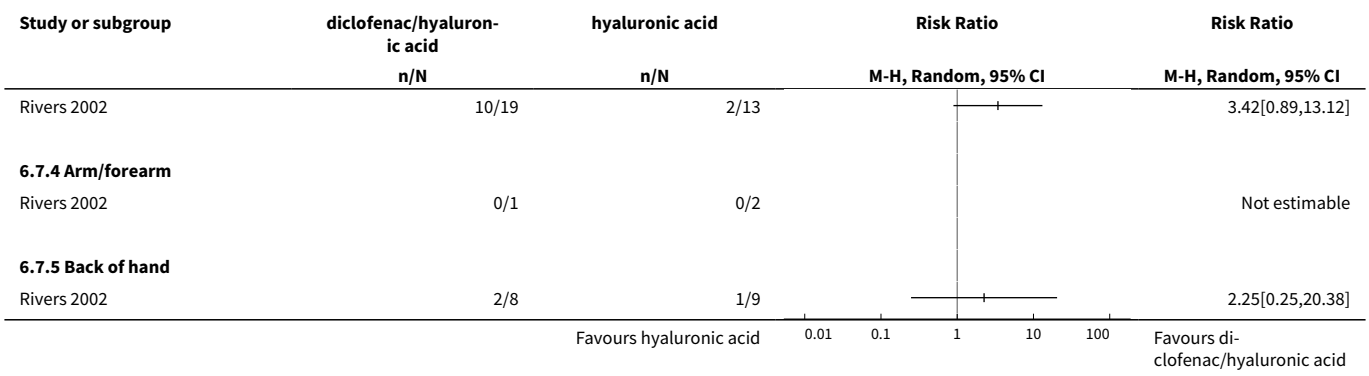


Analysis 6.6. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 6 Participant complete clearance for 30 day treatment by locations.

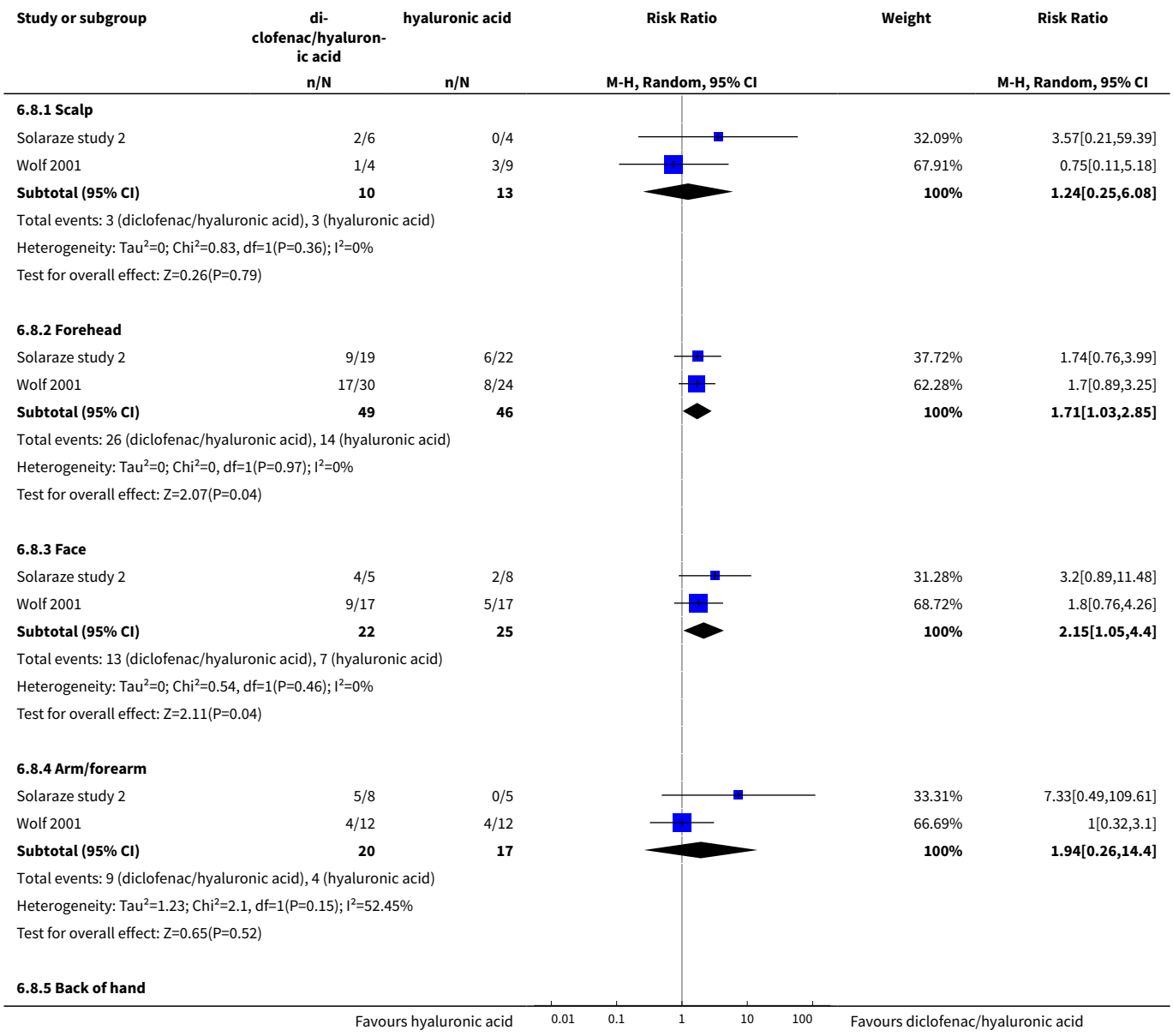


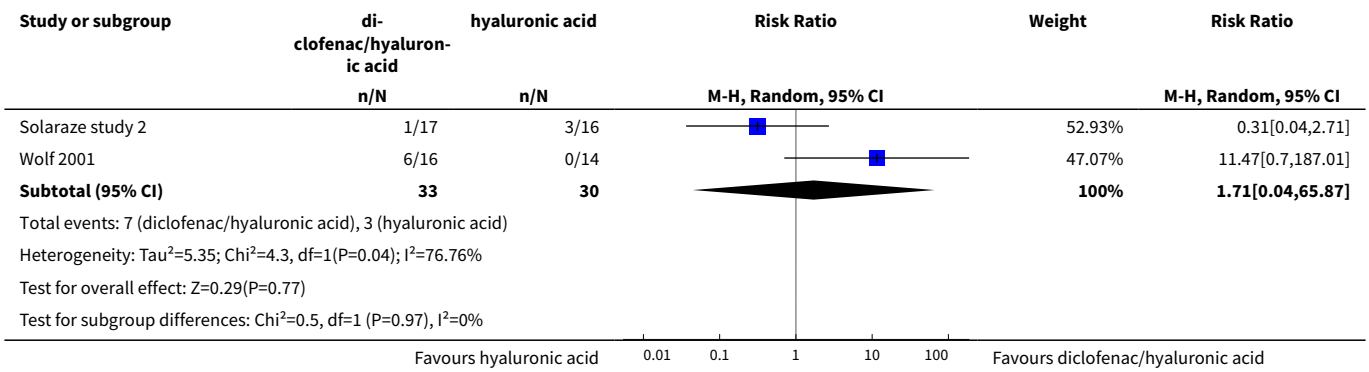
Analysis 6.7. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 7 Participant complete clearance for 60 day treatment by locations.



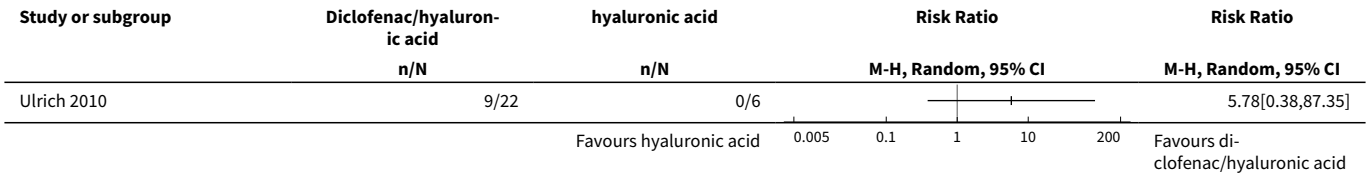


Analysis 6.8. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 8 Participant complete clearance for 90 day treatment by locations.

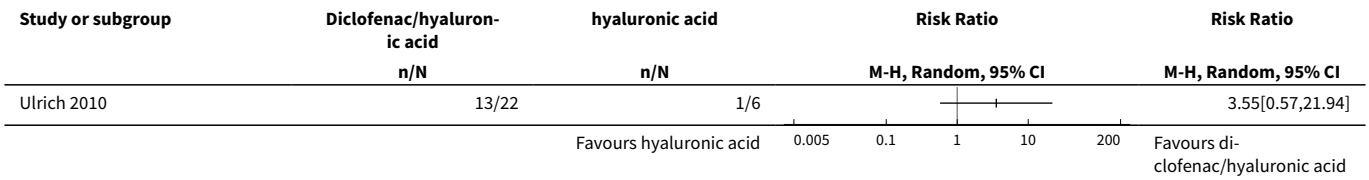




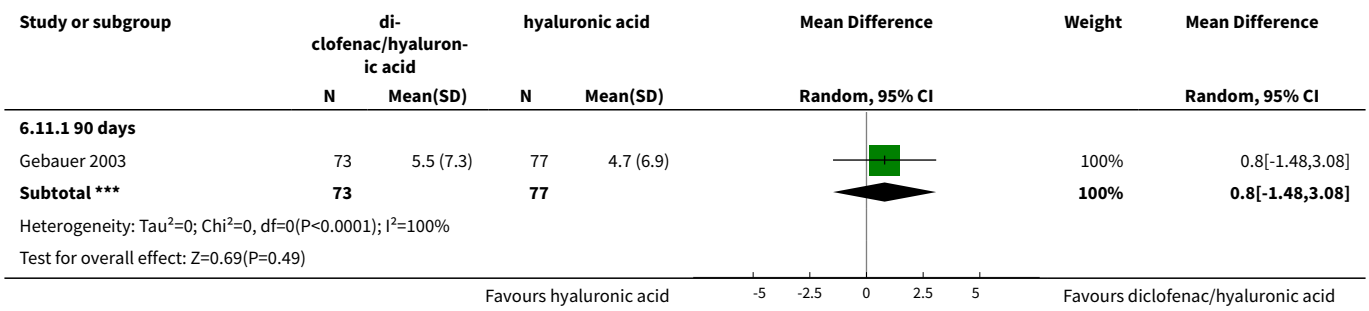
Analysis 6.9. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 9 Participant complete clearance in immunosuppressed participants.



Analysis 6.10. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 10 Participant partial (>75%) clearance in immunosuppressed participants.

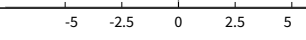


Analysis 6.11. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 11 Mean reduction of lesion counts (30-90 days): At the end of study.



Analysis 6.12. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 12 Mean reduction of lesion counts (30-90 days): 30 day follow-up.

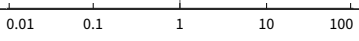
Study or subgroup	di-clofenac/hyaluron-ic acid		hyaluronic acid		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
6.12.1 30 days							
Rivers 2002	49	4.4 (3.3)	49	2.4 (3.6)		45.2%	2[0.63,3.37]
Subtotal ***	**49**		**49**			**45.2%**	**2[0.63,3.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.87(P=0)							
6.12.2 60 days							
Rivers 2002	48	4.9 (4)	49	2.5 (4.4)		31.51%	2.4[0.73,4.07]
Subtotal ***	**48**		**49**			**31.51%**	**2.4[0.73,4.07]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.81(P=0)							
6.12.3 90 days							
Gebauer 2003	73	6.2 (7.5)	77	2.4 (4.3)		23.28%	3.8[1.83,5.77]
Subtotal ***	**73**		**77**			**23.28%**	**3.8[1.83,5.77]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.78(P=0)							
Total ***	**170**		**175**			**100%**	**2.55[1.56,3.53]**
Heterogeneity: Tau^2=0.07; Chi^2=2.2, df=2(P=0.33); I^2=8.93%							
Test for overall effect: Z=5.07(P<0.0001)							
Test for subgroup differences: Chi^2=2.2, df=1 (P=0.33), I^2=8.93%							



Favours hyaluronic acid — Favours diclofenac/hyaluronic acid

Analysis 6.13. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 13 Withdrawal due to adverse events.

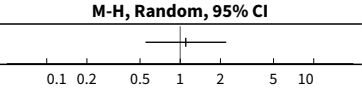
Study or subgroup	3% di-clofenac/2.5% HA	2.5% hyaluron-ic acid (HA)	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Gebauer 2003	15/73	3/77		27.14%	5.27[1.59,17.47]
McEwan 1997	15/65	3/65		27.44%	5[1.52,16.45]
Rivers 2002	6/97	2/98		15.68%	3.03[0.63,14.65]
Wolf 2001	8/58	4/59		29.73%	2.03[0.65,6.39]
Total (95% CI)	**293**	**299**		**100%**	**3.59[1.92,6.7]**
Total events: 44 (3% diclofenac/2.5% HA), 12 (2.5% hyaluronic acid (HA))					
Heterogeneity: Tau^2=0; Chi^2=1.7, df=3(P=0.64); I^2=0%					
Test for overall effect: Z=4.02(P<0.0001)					



Favours diclofenac — Favours hyaluronic acid

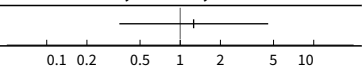
Analysis 6.14. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 14 Minor adverse event: body as a whole : in general.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	13/58	12/59		1.1[0.55,2.21]



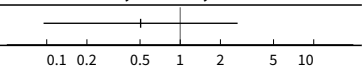
Analysis 6.15. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 15 Minor adverse event: body as a whole : "flu".

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rivers 2002	5/97	4/98		1.26[0.35,4.56]



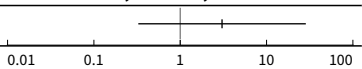
Analysis 6.16. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 16 Minor adverse event:: body as a whole : infection.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rivers 2002	2/97	4/98		0.51[0.09,2.69]



Analysis 6.17. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 17 Minor adverse event: cardiovascular: in general.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	3/58	1/59		3.05[0.33,28.49]



Analysis 6.18. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 18 Minor adverse event: cardiovascular: sinus bradycardia.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	1/73	0/77		3.16[0.13,76.4]

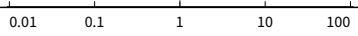
Analysis 6.19. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 19 Minor adverse event: dermatological: bursitis.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	0/73	1/77		0.35[0.01,8.49]

Favours diclofenac/hyaluronic acid | Favours hyaluronic acid

Analysis 6.20. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 20 Minor adverse event: dermatological: dry skin.

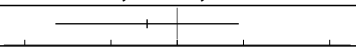
Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	16/73	2/77		16.79%	8.44[2.01,35.43]
Rivers 2002	26/97	16/98		43.9%	1.64[0.94,2.86]
Wolf 2001	21/58	10/59		39.31%	2.14[1.1,4.13]
Total (95% CI)	**228**	**234**		**100%**	**2.4[1.2,4.78]**
Total events: 63 (diclofenac/hyaluronic acid), 28 (hyaluronic acid)					
Heterogeneity: Tau^2=0.2; Chi^2=4.6, df=2(P=0.1); I^2=56.55%					
Test for overall effect: Z=2.48(P=0.01)					



Favours diclofenac/hyaluronic acid | Favours hyaluronic acid

Analysis 6.21. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 21 Minor adverse event: dermatological: herpes zoster.

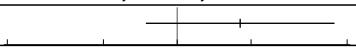
Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	0/73	1/77		0.35[0.01,8.49]



Favours diclofenac/hyaluronic acid | Favours hyaluronic acid

Analysis 6.22. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 22 Minor adverse event: dermatological: rash vesiculobullous.

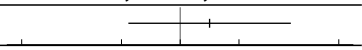
Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	3/58	0/59		7.12[0.38,134.83]



Favours diclofenac/hyaluronic acid | Favours hyaluronic acid

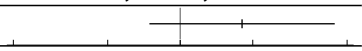
Analysis 6.23. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 23 Minor adverse event::dermatological: seborrhoea.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	1/73	0/77		3.16[0.13,76.4]



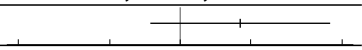
Analysis 6.24. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 24 Minor adverse event: dermatological: skin exfoliation.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	3/58	0/59		7.12[0.38,134.83]



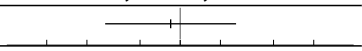
Analysis 6.25. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 25 Minor adverse event: dermatological: ulcerated skin.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	3/58	0/59		7.12[0.38,134.83]



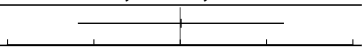
Analysis 6.26. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 26 Minor adverse event: digestive : in general.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	5/58	6/59		0.85[0.27,2.62]



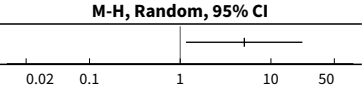
Analysis 6.27. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 27 Minor adverse event: hemic and lymphatic: in general.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	1/58	1/59		1.02[0.07,15.88]



Analysis 6.28. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 28 Minor adverse event: metabolic and nutritional disorders : in general.

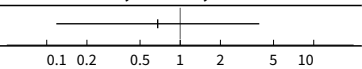
Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	10/58	2/59		5.09[1.16,22.22]



Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

Analysis 6.29. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 29 Minor adverse event: musculoskeletal and connective tissue: in general.

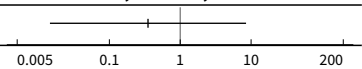
Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	2/58	3/59		0.68[0.12,3.91]



Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

Analysis 6.30. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 30 Minor adverse event: musculoskeletal and connective tissue: hypokinesia.

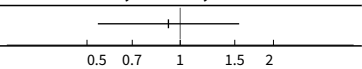
Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	0/73	1/77		0.35[0.01,8.49]



Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

Analysis 6.31. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 31 Minor adverse event: nervous system: in general.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	18/58	20/59		0.92[0.54,1.55]



Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

Analysis 6.32. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 32 Minor adverse event: nervous system: headache.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rivers 2002	0/97	5/98		0.09[0.01,1.64]

Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

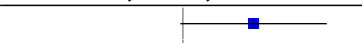
Analysis 6.33. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 33 Minor adverse event: nervous system: hyperaesthesia.

Study or subgroup	di-clofenac/hyaluron-ic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	1/73	2/77		20.48%	0.53[0.05,5.69]
Rivers 2002	5/97	5/98		79.52%	1.01[0.3,3.38]
Total (95% CI)	**170**	**175**		**100%**	**0.88[0.3,2.6]**
Total events: 6 (diclofenac/hyaluronic acid), 7 (hyaluronic acid)					
Heterogeneity: Tau^2=0; Chi^2=0.23, df=1(P=0.63); I^2=0%					
Test for overall effect: Z=0.22(P=0.82)					

Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

Analysis 6.34. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 34 Minor adverse event: nervous system: paraesthesia.

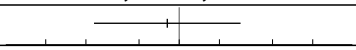
Study or subgroup	di-clofenac/hyaluron-ic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	7/73	1/77		32.37%	7.38[0.93,58.55]
Rivers 2002	12/97	8/98		67.63%	1.52[0.65,3.54]
Total (95% CI)	**170**	**175**		**100%**	**2.53[0.57,11.2]**
Total events: 19 (diclofenac/hyaluronic acid), 9 (hyaluronic acid)					
Heterogeneity: Tau^2=0.66; Chi^2=2.02, df=1(P=0.16); I^2=50.46%					
Test for overall effect: Z=1.22(P=0.22)					



Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

Analysis 6.35. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 35 Minor adverse event: respiratory: in general.

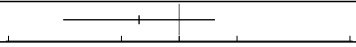
Study or subgroup	diclofenac/hyaluron-ic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	4/58	5/59		0.81[0.23,2.88]



Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

Analysis 6.36. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 36 Minor adverse event: respiratory: bronchitis.

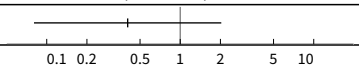
Study or subgroup	diclofenac/hyaluron-ic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rivers 2002	0/97	2/98		0.2[0.01,4.15]



Favours diclofenac/hyaluronic acid — Favours hyaluronic acid

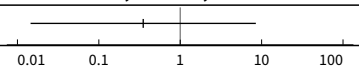
Analysis 6.37. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 37 Minor adverse event: respiratory: pharyngitis.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Rivers 2002	2/97	5/98		0.4[0.08,2.03]



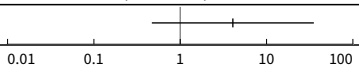
Analysis 6.38. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 38 Minor adverse event: respiratory: upper respiratory tract infection.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Gebauer 2003	0/73	1/77		0.35[0.01,8.49]



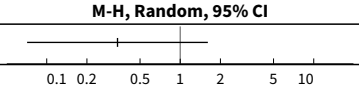
Analysis 6.39. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 39 Minor adverse event: special senses: in general.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	4/58	1/59		4.07[0.47,35.32]



Analysis 6.40. Comparison 6 3% diclofenac in 2.5% hyaluronic acid versus 2.5% hyaluronic acid (vehicle), Outcome 40 Minor adverse event: urogenital: in general.

Study or subgroup	diclofenac/hyaluronic acid n/N	hyaluronic acid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Wolf 2001	2/58	6/59		0.34[0.07,1.61]



Comparison 7. 3% diclofenac in 2.5% hyaluronic acid versus 5% imiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Investigator Global Improvement Indices-Complete improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Participant Global Improvement Indices-Complete improvement	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 3% diclofenac in 2.5% hyaluronic acid versus 5% imiquimod, Outcome 1 Investigator Global Improvement Indices-Complete improvement.

Study or subgroup	Diclofenac n/N	Imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kose 2008	3/24	6/25		0.52[0.15,1.85]
		Favours imiquimod	0.01 0.1 1 10 100	Favours diclofenac

Analysis 7.2. Comparison 7 3% diclofenac in 2.5% hyaluronic acid versus 5% imiquimod, Outcome 2 Participant Global Improvement Indices-Complete improvement.

Study or subgroup	Diclofenac n/N	Imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kose 2008	7/24	6/25		1.22[0.48,3.1]
		Favours imiquimod	0.01 0.1 1 10 100	Favours diclofenac

Comparison 8. 2-(Difluoromethyl)-dl-ornithine (DFMO) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in lesions counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 2-(Difluoromethyl)-dl-ornithine (DFMO) versus placebo, Outcome 1 Mean reduction in lesions counts.

Study or subgroup	DFMO N	DFMO Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Alberts 2000	42	6.6 (20.9)	42	0.7 (24.5)		5.9[-3.84,15.64]
				Favours placebo	-20 -10 0 10 20	Favours DFMO

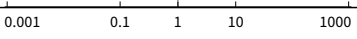
Comparison 9. 0.5% 5-FU versus vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	3	522	Risk Ratio (M-H, Random, 95% CI)	8.86 [3.67, 21.40]
1.1 1 week treatment with 4 week follow-up	3	267	Risk Ratio (M-H, Random, 95% CI)	8.30 [2.04, 33.76]
1.2 2 week treatment with 4 week follow-up	2	128	Risk Ratio (M-H, Random, 95% CI)	6.42 [1.27, 32.59]
1.3 4 week treatment with 4 week follow-up	2	127	Risk Ratio (M-H, Random, 95% CI)	13.07 [2.68, 63.66]
2 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Mean percentage of reduction in lesion counts	1	142	Mean Difference (IV, Random, 95% CI)	33.60 [22.88, 44.32]
4 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Skin irritation	2	384	Risk Ratio (M-H, Random, 95% CI)	1.45 [1.27, 1.65]
6 Minor adverse event excluding skin irritation: body as a whole : in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Minor adverse event excluding skin irritation: body as a whole : allergy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Minor adverse event excluding skin irritation: body as a whole : "flu" or common cold	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse event excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse event excluding skin irritation: musculoskeletal and connective tissue: soreness	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse event excluding skin irritation:nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Minor adverse event excluding skin irritation: respiratory: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse event excluding skin irritation: respiratory: sinusitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Minor adverse event excluding skin irritation: respiratory: upper respiratory tract infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Minor adverse event excluding skin irritation: special senses: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Minor adverse event excluding skin irritation:special senses: eye irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

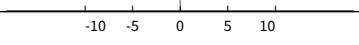
Analysis 9.1. Comparison 9 0.5% 5-FU versus vehicle, Outcome 1 Participant complete clearance.

Study or subgroup	0.5% fluorouracil n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 1 week treatment with 4 week follow-up					
Jorizzo 2002	7/45	0/23		9.78%	7.83[0.47,131.28]
Jorizzo 2004	12/72	0/70		9.87%	24.32[1.47,402.97]
Weiss 2002	10/38	1/19		19.83%	5[0.69,36.23]
Subtotal (95% CI)	**155**	**112**		**39.49%**	**8.3[2.04,33.76]**
Total events: 29 (0.5% fluorouracil), 1 (Vehicle)					
Heterogeneity: Tau^2=0; Chi^2=0.86, df=2(P=0.65); I^2=0%					
Test for overall effect: Z=2.95(P=0)					
9.1.2 2 week treatment with 4 week follow-up					
Jorizzo 2002	17/45	0/23		10.16%	18.26[1.15,290.68]
Weiss 2002	8/41	1/19		19.33%	3.71[0.5,27.57]
Subtotal (95% CI)	**86**	**42**		**29.48%**	**6.42[1.27,32.59]**
Total events: 25 (0.5% fluorouracil), 1 (Vehicle)					
Heterogeneity: Tau^2=0; Chi^2=0.94, df=1(P=0.33); I^2=0%					
Test for overall effect: Z=2.24(P=0.02)					
9.1.3 4 week treatment with 4 week follow-up					
Jorizzo 2002	26/45	0/23		10.26%	27.65[1.76,434.27]
Weiss 2002	19/40	1/19		20.77%	9.03[1.3,62.51]
Subtotal (95% CI)	**85**	**42**		**31.03%**	**13.07[2.68,63.66]**
Total events: 45 (0.5% fluorouracil), 1 (Vehicle)					
Heterogeneity: Tau^2=0; Chi^2=0.46, df=1(P=0.5); I^2=0%					
Test for overall effect: Z=3.18(P=0)					
Total (95% CI)	**326**	**196**		**100%**	**8.86[3.67,21.4]**
Total events: 99 (0.5% fluorouracil), 3 (Vehicle)					
Heterogeneity: Tau^2=0; Chi^2=2.69, df=6(P=0.85); I^2=0%					
Test for overall effect: Z=4.85(P<0.0001)					
Test for subgroup differences: Chi^2=0.39, df=1 (P=0.82), I^2=0%					

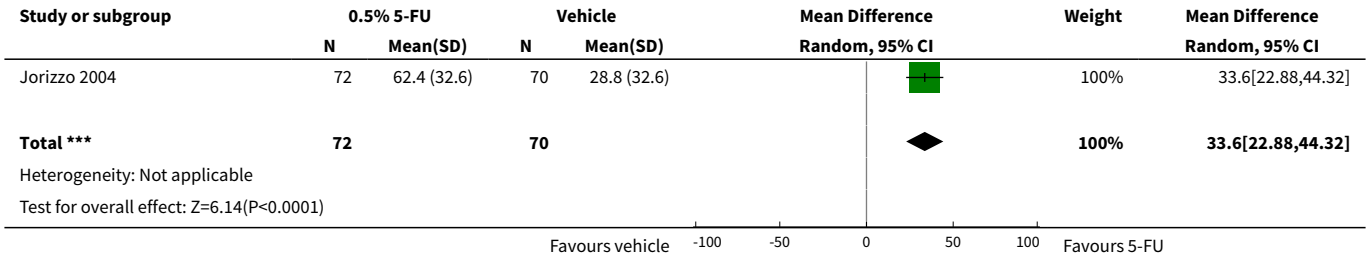


Analysis 9.2. Comparison 9 0.5% 5-FU versus vehicle, Outcome 2 Mean reduction in lesion counts.

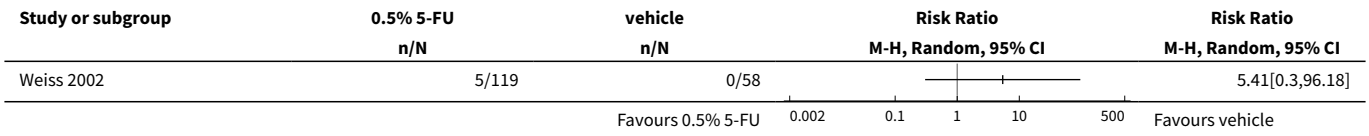
Study or subgroup	5-FU N	5-FU Mean(SD)	vehicle N	vehicle Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Jorizzo 2004	72	9.4 (9.2)	70	4 (5.3)		5.4[2.94,7.86]



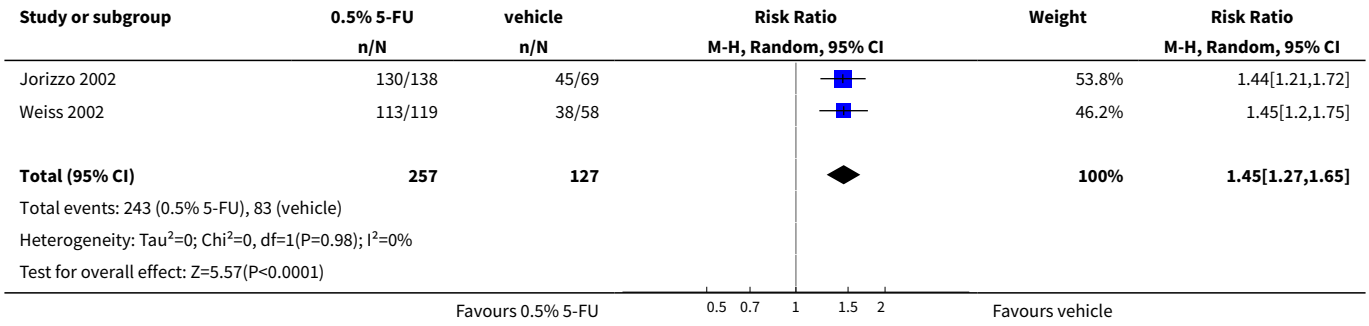
Analysis 9.3. Comparison 9 0.5% 5-FU versus vehicle, Outcome 3 Mean percentage of reduction in lesion counts.



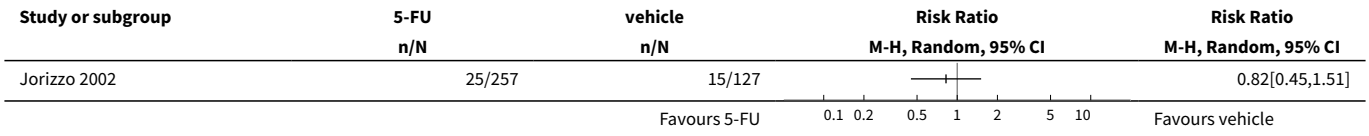
Analysis 9.4. Comparison 9 0.5% 5-FU versus vehicle, Outcome 4 Withdrawal due to adverse events.



Analysis 9.5. Comparison 9 0.5% 5-FU versus vehicle, Outcome 5 Skin irritation.

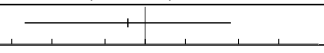


Analysis 9.6. Comparison 9 0.5% 5-FU versus vehicle, Outcome 6 Minor adverse event excluding skin irritation: body as a whole : in general.



Analysis 9.7. Comparison 9 0.5% 5-FU versus vehicle, Outcome 7 Minor adverse event excluding skin irritation: body as a whole : allergy.

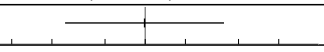
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	3/257	2/127		0.74[0.13,4.38]



Favours 5-FU — Favours vehicle

Analysis 9.8. Comparison 9 0.5% 5-FU versus vehicle, Outcome 8 Minor adverse event excluding skin irritation: body as a whole : "flu" or common cold.

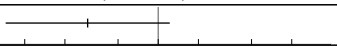
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	6/257	3/127		0.99[0.25,3.89]



Favours 5-FU — Favours vehicle

Analysis 9.9. Comparison 9 0.5% 5-FU versus vehicle, Outcome 9 Minor adverse event excluding skin irritation: musculoskeletal and connective tissue: in general.

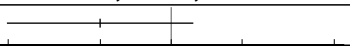
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	3/257	5/127		0.3[0.07,1.22]



Favours 5-FU — Favours vehicle

Analysis 9.10. Comparison 9 0.5% 5-FU versus vehicle, Outcome 10 Minor adverse event excluding skin irritation: musculoskeletal and connective tissue: soreness.

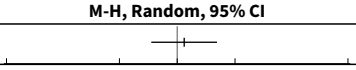
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	0/257	2/127		0.1[0,2.05]



Favours 5-FU — Favours vehicle

Analysis 9.11. Comparison 9 0.5% 5-FU versus vehicle, Outcome 11 Minor adverse event excluding skin irritation:nervous system: headache.

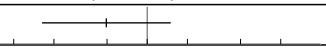
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	8/257	3/127		1.32[0.36,4.88]



Favours 5-FU — Favours vehicle

Analysis 9.12. Comparison 9 0.5% 5-FU versus vehicle, Outcome 12 Minor adverse event excluding skin irritation: respiratory: in general.

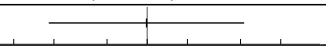
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	6/257	6/127		0.49[0.16,1.5]



Favours 5-FU — Favours vehicle

Analysis 9.13. Comparison 9 0.5% 5-FU versus vehicle, Outcome 13 Minor adverse event excluding skin irritation: respiratory: sinusitis.

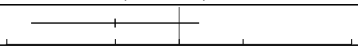
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	4/257	2/127		0.99[0.18,5.32]



Favours 5-FU — Favours vehicle

Analysis 9.14. Comparison 9 0.5% 5-FU versus vehicle, Outcome 14 Minor adverse event excluding skin irritation: respiratory: upper respiratory tract infection.

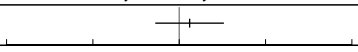
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	0/257	2/127		0.1[0,2.05]



Favours 5-FU — Favours vehicle

Analysis 9.15. Comparison 9 0.5% 5-FU versus vehicle, Outcome 15 Minor adverse event excluding skin irritation: special senses: in general.

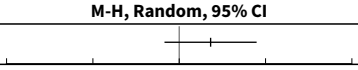
Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	16/257	6/127		1.32[0.53,3.29]



Favours 5-FU — Favours vehicle

Analysis 9.16. Comparison 9 0.5% 5-FU versus vehicle, Outcome 16 Minor adverse event excluding skin irritation:special senses: eye irritation.

Study or subgroup	5-FU n/N	vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2002	14/257	3/127		2.31[0.67,7.88]



Favours 5-FU — Favours vehicle

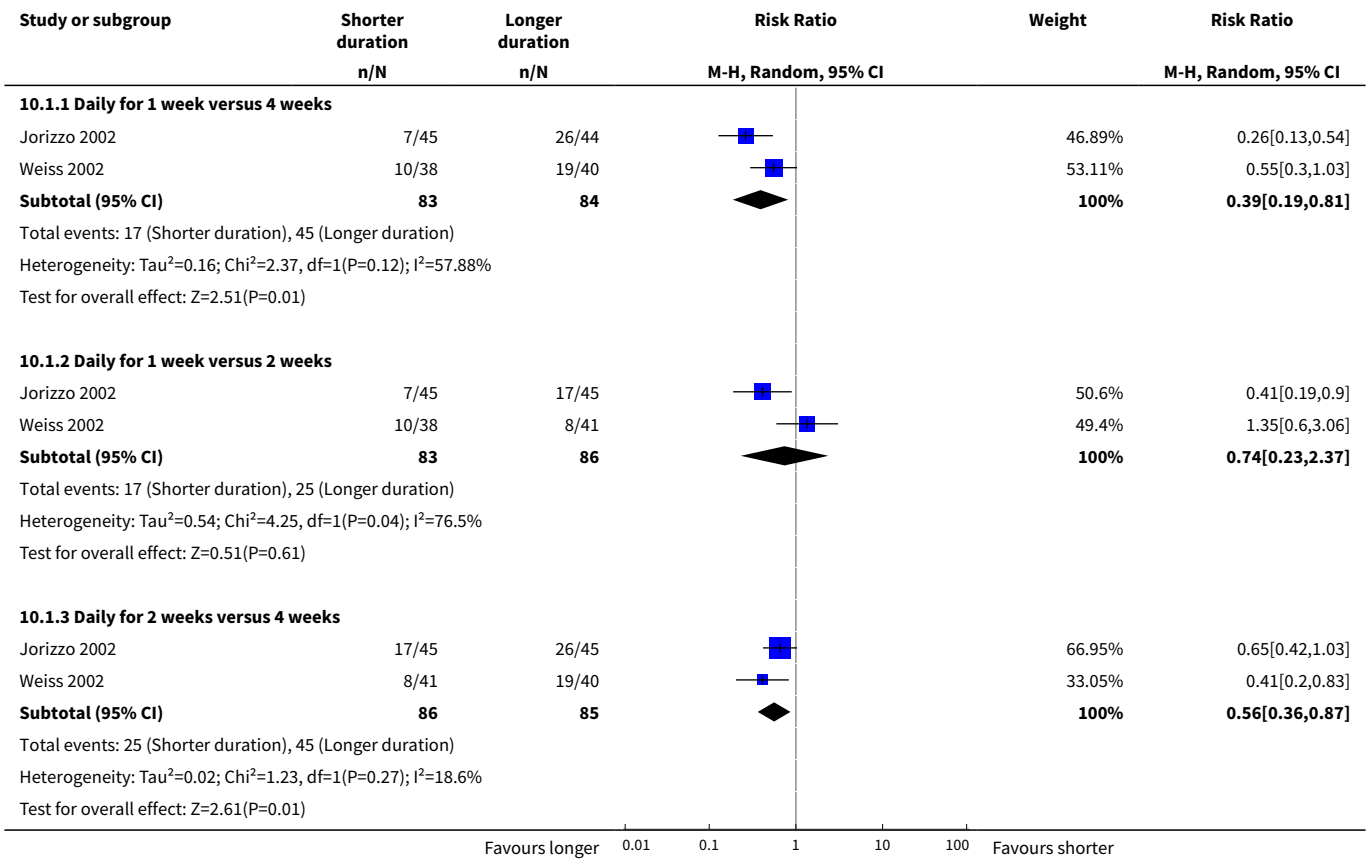
Comparison 10. 0.5% 5-FU at varying application durations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Daily for 1 week versus 4 weeks	2	167	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.19, 0.81]
1.2 Daily for 1 week versus 2 weeks	2	169	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.23, 2.37]
1.3 Daily for 2 weeks versus 4 weeks	2	171	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.36, 0.87]
2 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Skin irritation	2	515	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.91, 1.00]
3.1 Daily for 1 week versus 4 weeks	2	170	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.89, 1.03]
3.2 Daily for 1 week versus 2 weeks	2	172	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.08]
3.3 Daily for 2 weeks versus 4 weeks	2	173	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.02]
4 Minor adverse events excluding skin irritation: body as a whole : in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Minor adverse events excluding skin irritation: body as a whole : allergy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Minor adverse events excluding skin irritation: body as a whole : "flu" or common cold	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Minor adverse events excluding skin irritation: respiratory: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Minor adverse events excluding skin irritation: respiratory: sinusitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Minor adverse events excluding skin irritation: special senses: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

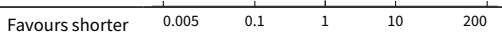
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Minor adverse events excluding skin irritation: special senses: eye irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1 Daily for 1 week versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 Daily for 1 week versus 2 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 Daily for 2 weeks versus 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 10.1. Comparison 10 0.5% 5-FU at varying application durations, Outcome 1 Participant complete clearance.



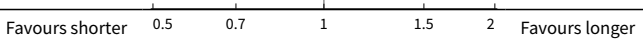
Analysis 10.2. Comparison 10 0.5% 5-FU at varying application durations, Outcome 2 Withdrawal due to adverse events.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.2.1 Daily for 1 week versus 4 weeks				
Weiss 2002	0/38	4/40		0.12[0.01,2.1]
10.2.2 Daily for 1 week versus 2 weeks				
Weiss 2002	0/38	1/41		0.36[0.02,8.55]
10.2.3 Daily for 2 weeks versus 4 weeks				
Weiss 2002	1/41	4/40		0.24[0.03,2.09]



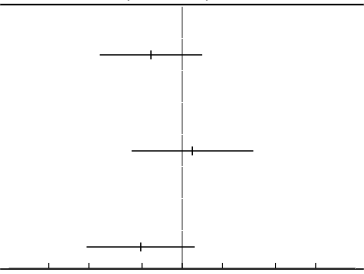
Analysis 10.3. Comparison 10 0.5% 5-FU at varying application durations, Outcome 3 Skin irritation.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.3.1 Daily for 1 week versus 4 weeks					
Jorizzo 2002	42/47	43/45		13.66%	0.94[0.83,1.05]
Weiss 2002	36/38	39/40		23.17%	0.97[0.89,1.06]
Subtotal (95% CI)	**85**	**85**		**36.82%**	**0.96[0.89,1.03]**
Total events: 78 (shorter), 82 (longer)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=1.18(P=0.24)					
10.3.2 Daily for 1 week versus 2 weeks					
Jorizzo 2002	42/47	45/46		16.15%	0.91[0.82,1.02]
Weiss 2002	36/38	38/41		14.38%	1.02[0.91,1.15]
Subtotal (95% CI)	**85**	**87**		**30.53%**	**0.96[0.86,1.08]**
Total events: 78 (shorter), 83 (longer)					
Heterogeneity: Tau^2=0; Chi^2=1.97, df=1(P=0.16); I^2=49.36%					
Test for overall effect: Z=0.64(P=0.52)					
10.3.3 Daily for 2 weeks versus 4 weeks					
Jorizzo 2002	42/47	43/45		13.66%	0.94[0.83,1.05]
Weiss 2002	38/41	39/40		18.98%	0.95[0.86,1.05]
Subtotal (95% CI)	**88**	**85**		**32.64%**	**0.94[0.88,1.02]**
Total events: 80 (shorter), 82 (longer)					
Heterogeneity: Tau^2=0; Chi^2=0.05, df=1(P=0.83); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					
Total (95% CI)	**258**	**257**		**100%**	**0.95[0.91,1]**
Total events: 236 (shorter), 247 (longer)					
Heterogeneity: Tau^2=0; Chi^2=2.43, df=5(P=0.79); I^2=0%					
Test for overall effect: Z=2.09(P=0.04)					
Test for subgroup differences: Chi^2=0.13, df=1 (P=0.94), I^2=0%					



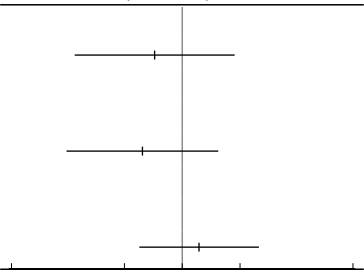
Analysis 10.4. Comparison 10 0.5% 5-FU at varying application durations, Outcome 4 Minor adverse events excluding skin irritation: body as a whole : in general.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.4.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	7/85	12/85		0.58[0.24,1.41]
10.4.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	7/85	6/87		1.19[0.42,3.41]
10.4.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	6/87	12/85		0.49[0.19,1.24]



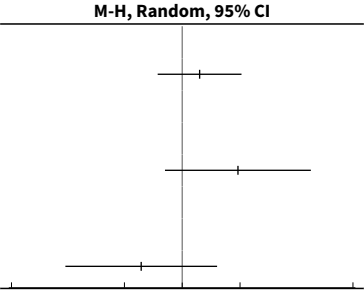
Analysis 10.5. Comparison 10 0.5% 5-FU at varying application durations, Outcome 5 Minor adverse events excluding skin irritation: body as a whole : allergy.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.5.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	0/85	1/85		0.33[0.01,8.07]
10.5.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	0/85	2/87		0.2[0.01,4.2]
10.5.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	2/87	1/85		1.95[0.18,21.15]



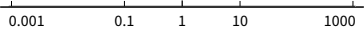
Analysis 10.6. Comparison 10 0.5% 5-FU at varying application durations, Outcome 6 Minor adverse events excluding skin irritation: body as a whole : "flu" or common cold.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.6.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	4/85	2/85		2[0.38,10.63]
10.6.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	4/85	0/87		9.21[0.5,168.48]
10.6.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	0/87	2/85		0.2[0.01,4.01]



Analysis 10.7. Comparison 10 0.5% 5-FU at varying application durations, Outcome 7 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.7.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	1/85	1/85		1[0.06,15.73]
10.7.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	1/85	1/87		1.02[0.07,16.1]
10.7.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	1/87	1/85		0.98[0.06,15.37]



Analysis 10.8. Comparison 10 0.5% 5-FU at varying application durations, Outcome 8 Minor adverse events excluding skin irritation: nervous system: headache.

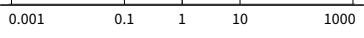
Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.8.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	3/85	3/85		1[0.21,4.82]
10.8.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	3/85	2/87		1.54[0.26,8.96]
10.8.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	2/87	3/85		0.65[0.11,3.8]

Analysis 10.9. Comparison 10 0.5% 5-FU at varying application durations, Outcome 9 Minor adverse events excluding skin irritation: respiratory: in general.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.9.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	5/85	1/85		5[0.6,41.9]
10.9.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	5/85	0/87		11.26[0.63,200.47]
10.9.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	0/87	1/85		0.33[0.01,7.89]

Analysis 10.10. Comparison 10 0.5% 5-FU at varying application durations, Outcome 10 Minor adverse events excluding skin irritation: respiratory: sinusitis.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.10.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	4/85	0/85		9[0.49,164.62]
10.10.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	4/85	0/87		9.21[0.5,168.48]
10.10.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	0/87	0/85		Not estimable



Analysis 10.11. Comparison 10 0.5% 5-FU at varying application durations, Outcome 11 Minor adverse events excluding skin irritation: special senses: in general.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.11.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	6/85	6/85		1[0.34,2.98]
10.11.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	6/85	3/87		2.05[0.53,7.92]
10.11.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	3/87	6/85		0.49[0.13,1.89]

Analysis 10.12. Comparison 10 0.5% 5-FU at varying application durations, Outcome 12 Minor adverse events excluding skin irritation: special senses: eye irritation.

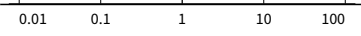
Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
10.12.1 Daily for 1 week versus 4 weeks				
Jorizzo 2002	5/85	6/85		0.83[0.26,2.63]
10.12.2 Daily for 1 week versus 2 weeks				
Jorizzo 2002	5/85	3/87		1.71[0.42,6.92]
10.12.3 Daily for 2 weeks versus 4 weeks				
Jorizzo 2002	3/87	6/85		0.49[0.13,1.89]

Comparison 11. 0.5% 5-FU versus ALA-PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 11.1. Comparison 11 0.5% 5-FU versus ALA-PDT, Outcome 1 Participant complete clearance.

Study or subgroup	0.5% 5-FU n/N	ALA-PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.1.1 Blue light				
Smith 2003	6/12	6/12		1[0.45,2.23]
11.1.2 Pulsed dye laser				
Smith 2003	6/12	1/12		6[0.85,42.59]
11.1.3 Combined				
Smith 2003	6/12	7/24		1.71[0.74,3.98]



Analysis 11.2. Comparison 11 0.5% 5-FU versus ALA-PDT, Outcome 2 Withdrawal due to adverse events.

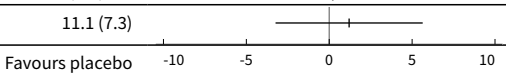
Study or subgroup	5-FU n/N	ALA-PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.2.1 Blue light				
Smith 2003	1/12	0/12		3[0.13,67.06]
11.2.2 Pulsed dye laser				
Smith 2003	1/12	0/12		3[0.13,67.06]
11.2.3 Combined				
Smith 2003	1/12	0/24		5.77[0.25,131.92]

Comparison 12. 5% 5-FU with 0.05% tretinoin versus 5% 5-FU with placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 12.1. Comparison 12 5% 5-FU with 0.05% tretinoin versus 5% 5-FU with placebo, Outcome 1 Mean reduction in lesion counts.

Study or subgroup	Tretinoin N	Tretinoin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Bercovitch 1987	19	12.3 (6.6)	19	11.1 (7.3)		1.2[-3.24,5.64]

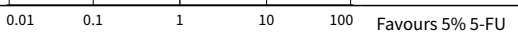


Comparison 13. 5% 5-FU versus 5% imiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	2	89	Risk Ratio (M-H, Random, 95% CI)	1.85 [0.41, 8.33]

Analysis 13.1. Comparison 13 5% 5-FU versus 5% imiquimod, Outcome 1 Participant complete clearance.

Study or subgroup	5% 5-FU n/N	Imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	23/24	22/26		53.12%	1.13[0.94,1.36]
Tanghetti 2007	17/20	5/19		46.88%	3.23[1.49,7.01]
Total (95% CI)	**44**	**45**		**100%**	**1.85[0.41,8.33]**
Total events: 40 (5% 5-FU), 27 (Imiquimod)					
Heterogeneity: Tau^2=1.1; Chi^2=14.33, df=1(P=0); I^2=93.02%					
Test for overall effect: Z=0.8(P=0.42)					



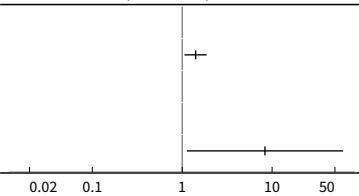
Comparison 14. 5% 5-FU versus cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.2 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 14.1. Comparison 14 5% 5-FU versus cryotherapy, Outcome 1 Participant complete clearance.

Study or subgroup	5% 5-FU n/N	Cryotherapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
14.1.1 After treatment				
Krawtchenko 2007	23/24	17/25		1.41[1.06,1.87]
14.1.2 At 12 months				
Krawtchenko 2007	8/24	1/25		8.33[1.13,61.7]

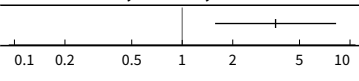


Comparison 15. 5% 5-FU versus 10% masoprocol

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Investigator Global Improvement Indices -cleared	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Mean reduction of lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Mean percentage of reduction of lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

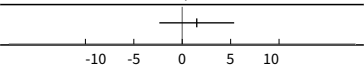
Analysis 15.1. Comparison 15 5% 5-FU versus 10% masoprocol, Outcome 1 Investigator Global Improvement Indices -cleared.

Study or subgroup	5-FU n/N	Masoprocol n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kulp-Shorten 1993	20/30	5/27		3.6[1.57,8.26]



Analysis 15.2. Comparison 15 5% 5-FU versus 10% masoprocol, Outcome 2 Mean reduction of lesion counts.

Study or subgroup	5-FU N	5-FU Mean(SD)	Masoprocol N	Masoprocol Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kulp-Shorten 1993	26	12.8 (7.3)	23	11.3 (6.5)		1.5[-2.36,5.36]

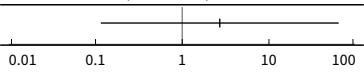


Analysis 15.3. Comparison 15 5% 5-FU versus 10% masoprocol, Outcome 3 Mean percentage of reduction of lesion counts.

Study or subgroup	5-FU N	5-FU Mean(SD)	Masoprocol N	Masoprocol Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Kulp-Shorten 1993	26	97.6 (5.6)	23	77.6 (19.3)		20[11.82,28.18]

Analysis 15.4. Comparison 15 5% 5-FU versus 10% masoprocol, Outcome 4 Withdrawal due to adverse events.

Study or subgroup	5-FU n/N	Masoprocol n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Kulp-Shorten 1993	1/30	0/27		2.71[0.12,63.84]

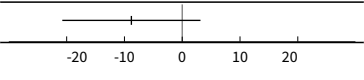


Comparison 16. 5% 5-FU versus carbon dioxide laser resurfacing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of reduction of lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

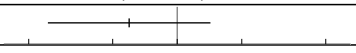
Analysis 16.1. Comparison 16 5% 5-FU versus carbon dioxide laser resurfacing, Outcome 1 Mean percentage of reduction of lesion counts.

Study or subgroup	5% 5-FU N	5% 5-FU Mean(SD)	Resurfacing N	Resurfacing Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Hantash 2006	8	83.2 (12.5)	6	92 (10.3)		-8.8[-20.76,3.16]



Analysis 16.2. Comparison 16 5% 5-FU versus carbon dioxide laser resurfacing, Outcome 2 Withdrawal due to adverse events.

Study or subgroup	5% 5-FU n/N	Resurfacing n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hantash 2006	0/9	2/8		0.18[0.01,3.27]



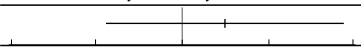
Favours 5-FU | Favours laser resurfacing

Comparison 17. 5% 5-FU versus Er:YAG laser resurfacing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Skin irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 At the end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 17.1. Comparison 17 5% 5-FU versus Er:YAG laser resurfacing, Outcome 1 Withdrawal due to adverse events.

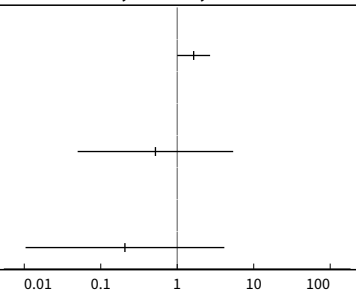
Study or subgroup	5-FU n/N	Er:YAG laser resurfacing n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ostertag 2006	1/27	0/28		3.11[0.13,73.11]



Favours 5-FU | Favours Er:YAG

Analysis 17.2. Comparison 17 5% 5-FU versus Er:YAG laser resurfacing, Outcome 2 Skin irritation.

Study or subgroup	5-FU n/N	Er:YAG laser resurfacing n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
17.2.1 At the end of treatment				
Ostertag 2006	19/27	12/28		1.64[1,2.69]
17.2.2 At 3 months				
Ostertag 2006	1/27	2/28		0.52[0.05,5.39]
17.2.3 At 6 months				
Ostertag 2006	0/27	2/28		0.21[0.01,4.13]



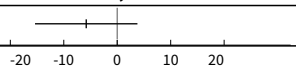
Favours 5-FU | Favours Er:YAG

Comparison 18. 5% 5-FU versus Trichloroacetic acid peel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of reduction in lesions	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 18.1. Comparison 18 5% 5-FU versus Trichloroacetic acid peel, Outcome 1 Mean percentage of reduction in lesions.

Study or subgroup	5% 5-FU N	5% 5-FU Mean(SD)	Peel N	Peel Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Hantash 2006	8	83.2 (12.5)	10	89 (6.6)		-5.8[-15.38,3.78]



Comparison 19. 5% Imiquimod versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance-number of doses	11	2880	Risk Ratio (M-H, Random, 95% CI)	6.91 [4.25, 11.26]
1.1 9 or 18 doses (3 times/week for 3 weeks on, 4 weeks off)	1	39	Risk Ratio (M-H, Random, 95% CI)	2.76 [0.39, 19.40]
1.2 12-16 doses (2 times/week for 8 weeks or 3 times/week for 4 weeks)	3	543	Risk Ratio (M-H, Random, 95% CI)	7.88 [1.09, 56.67]
1.3 12 or 24 doses (3 times/week for 4 weeks on , 4 weeks off, 4 weeks on)	2	505	Risk Ratio (M-H, Random, 95% CI)	8.81 [1.15, 67.32]
1.4 24 doses (3 times/week for 8 weeks)	1	36	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.07, 25.08]
1.5 32-36 doses (2 times/ week for 16 weeks or 3 times/ week for 12 weeks)	4	888	Risk Ratio (M-H, Random, 95% CI)	7.12 [3.06, 16.58]
1.6 40 doses (5 times/week for 8 weeks)	1	37	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.03, 17.27]
1.7 48 doses (3 times/ week for 16 weeks)	3	795	Risk Ratio (M-H, Random, 95% CI)	10.90 [3.59, 33.15]
1.8 56 doses (7 times/week for 8 weeks)	1	37	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.07, 24.29]

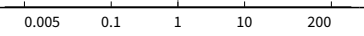
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Participant complete clearance in immunosuppressed participants	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Participant partial (>75%) clearance	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 9 or 18 doses (3 times/ week for 3 weeks on, 4 weeks off. 3 weeks on)	1	39	Risk Ratio (M-H, Random, 95% CI)	2.41 [0.91, 6.39]
3.2 12-16 doses (3 times/week for 4 weeks or 2 times/week for 8 weeks)	2	284	Risk Ratio (M-H, Random, 95% CI)	2.86 [1.53, 5.34]
3.3 12 or 24 doses (3 times/week for 4 weeks on, 4 weeks off)	2	505	Risk Ratio (M-H, Random, 95% CI)	6.23 [0.70, 55.10]
3.4 24 doses (3 times/week for 8 weeks)	1	36	Risk Ratio (M-H, Random, 95% CI)	4.0 [0.25, 62.85]
3.5 32 doses (2 times/week for 16 weeks)	1	436	Risk Ratio (M-H, Random, 95% CI)	5.02 [3.44, 7.33]
3.6 40 doses (5 times/week for 8 weeks)	1	37	Risk Ratio (M-H, Random, 95% CI)	3.35 [0.21, 53.51]
3.7 48 doses (3 times/ week for 16 weeks)	2	778	Risk Ratio (M-H, Random, 95% CI)	8.46 [2.29, 31.16]
3.8 56 doses (7 times/week for 8 weeks)	1	37	Risk Ratio (M-H, Random, 95% CI)	5.94 [0.39, 90.34]
4 Participant partial (>75%) clearance in immunosuppressed participants	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Withdrawal due to adverse events	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 12-16 doses (2 times/week for 8 weeks or 3 times/week for 4 weeks)	1	38	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.03, 16.74]
6.2 12 or 24 doses (3 times/week for 4 weeks on , 4 weeks off, 4 weeks on)	2	505	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.31, 8.23]
6.3 24 doses (3 times/week for 8 weeks)	1	36	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.07, 25.08]

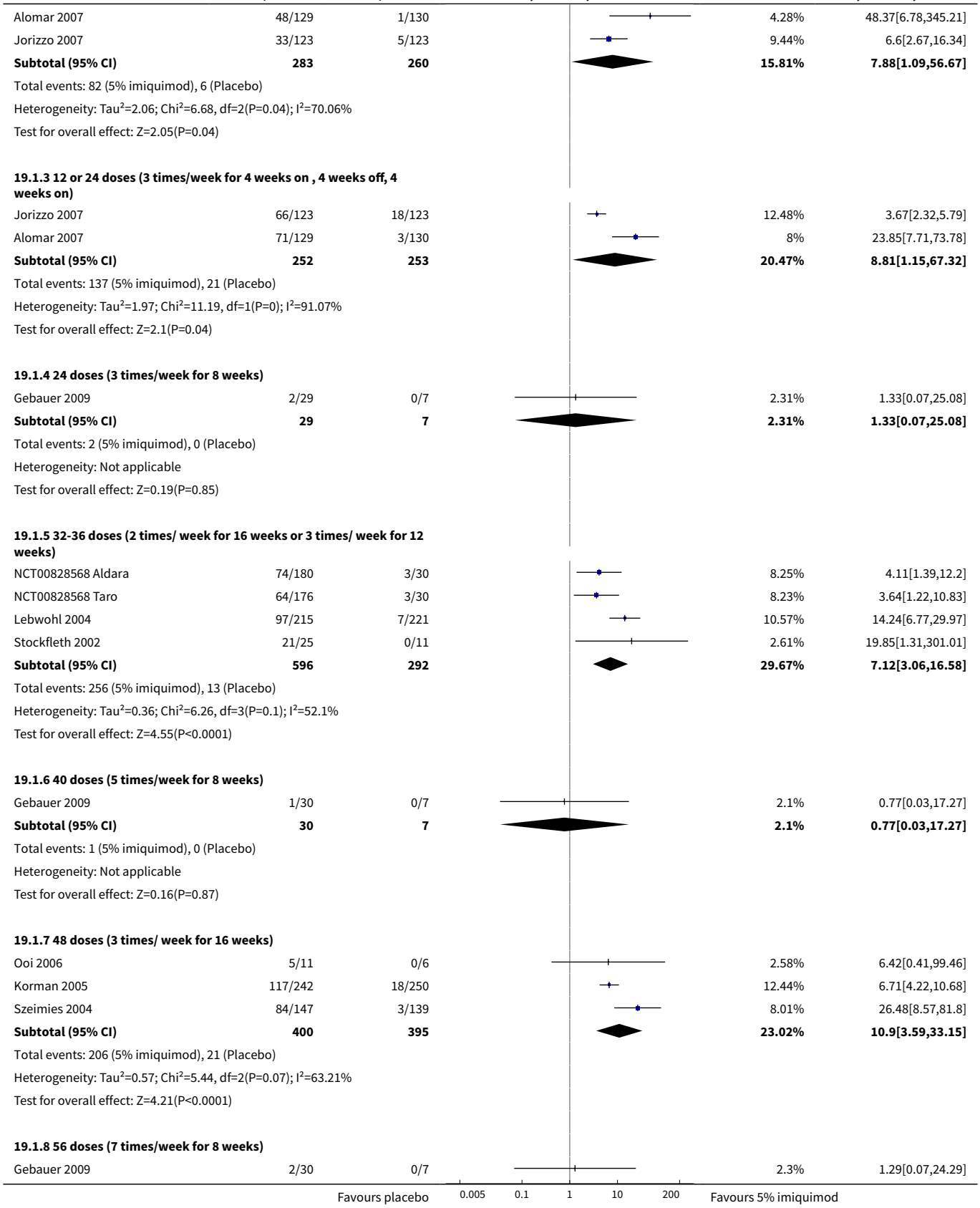
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.4 32-36 doses (2 times/ week for 16 weeks or 3 times/ week for 12 weeks)	3	858	Risk Ratio (M-H, Random, 95% CI)	2.29 [0.80, 6.57]
6.5 40 doses (5 times/week for 8 weeks)	1	37	Risk Ratio (M-H, Random, 95% CI)	4.90 [0.32, 75.60]
6.6 48 doses (3 times/ week for 16 weeks)	2	778	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.48, 4.90]
6.7 56 doses (7 times/week for 8 weeks)	1	37	Risk Ratio (M-H, Random, 95% CI)	5.42 [0.35, 82.97]
7 Withdrawal due to adverse events in immunosuppressed participants	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 48 doses (3 times/ week for 16 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Minor adverse events excluding skin irritation: body as a whole: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 12-16 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 24-28 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 40 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.4 56 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Minor adverse events excluding skin irritation: body as a whole: "flu" or "cold"	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 12-16 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 24-28 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.3 40 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.4 56 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Minor adverse events excluding skin irritation: digestive: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1 12-16 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 24-28 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.3 40 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

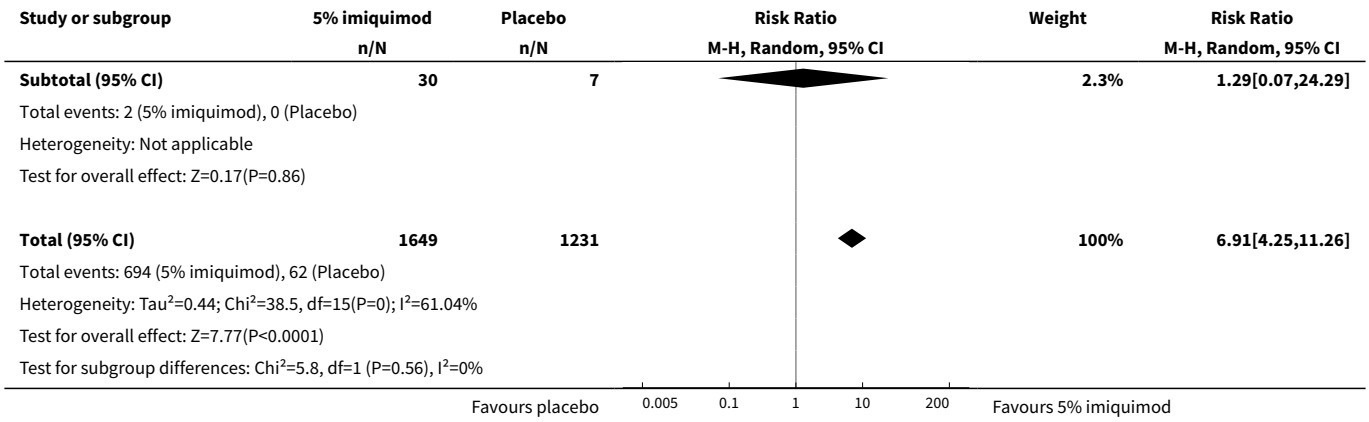
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.4 56 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Minor adverse events excluding skin irritation: digestive: nausea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1 12-16 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 24-28 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 40 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.4 56 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1 12-16 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 24-28 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 40 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.4 56 doses	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Cosmetic outcome: decrease in roughness/dryness/scaliness of the skin	2	683	Risk Ratio (M-H, Random, 95% CI)	3.23 [1.86, 5.58]
13.1 32-36 doses	1	415	Risk Ratio (M-H, Random, 95% CI)	2.54 [1.91, 3.37]
13.2 48 doses	1	268	Risk Ratio (M-H, Random, 95% CI)	4.43 [2.69, 7.30]

Analysis 19.1. Comparison 19 5% Imiquimod versus placebo, Outcome 1 Participant complete clearance-number of doses.

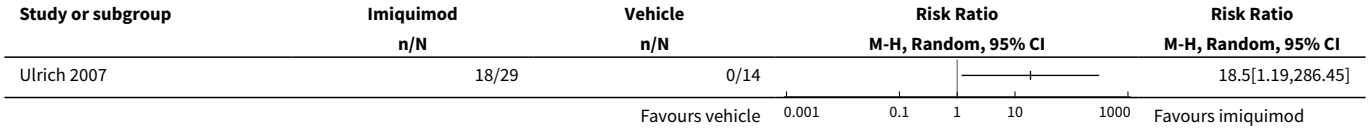
Study or subgroup	5% imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
19.1.1 9 or 18 doses (3 times/week for 3 weeks on, 4 weeks off)					
Chen 2003	8/29	1/10		4.32%	2.76[0.39,19.4]
Subtotal (95% CI)	**29**	**10**		**4.32%**	**2.76[0.39,19.4]**
Total events: 8 (5% imiquimod), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.02(P=0.31)					
19.1.2 12-16 doses (2 times/week for 8 weeks or 3 times/week for 4 weeks)					
Gebauer 2009	1/31	0/7		2.1%	0.75[0.03,16.74]



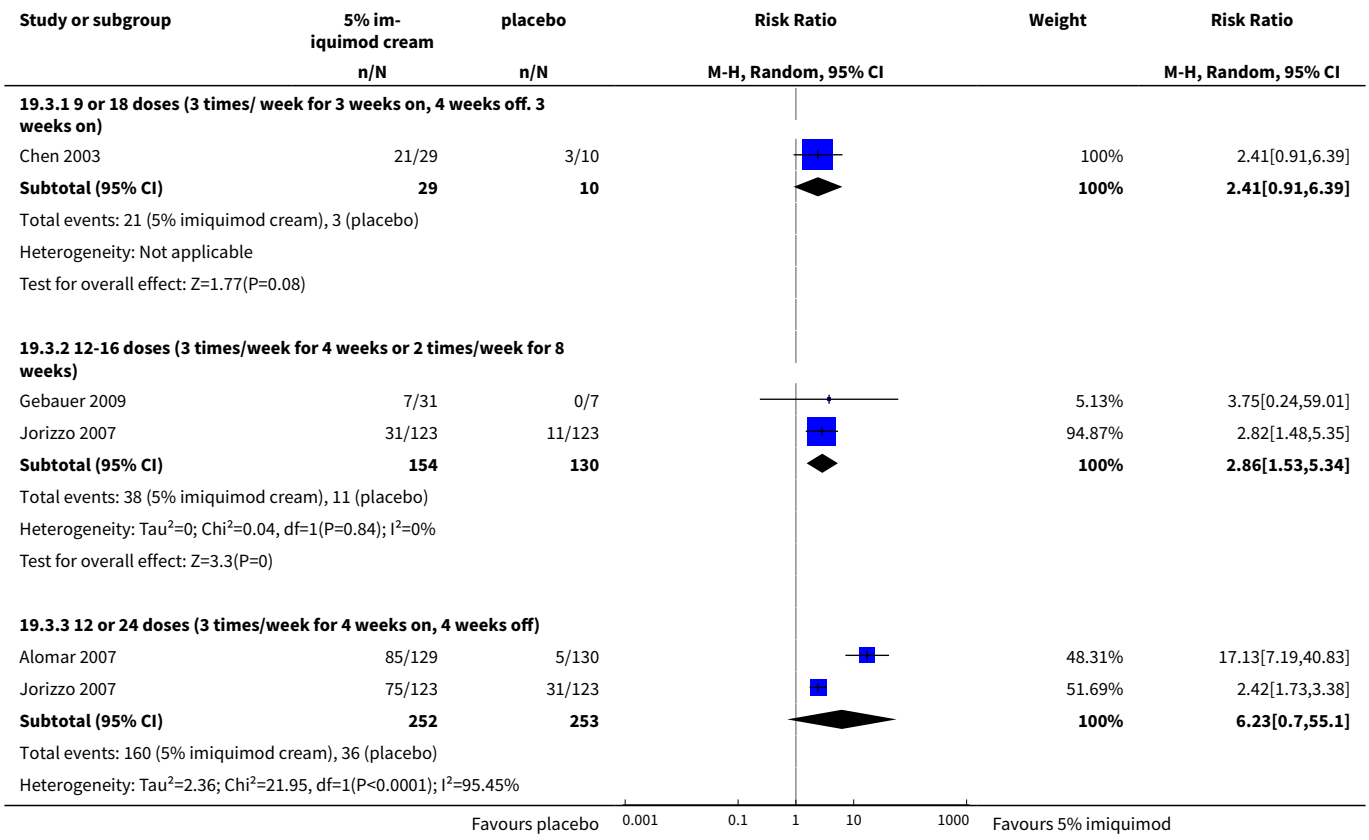


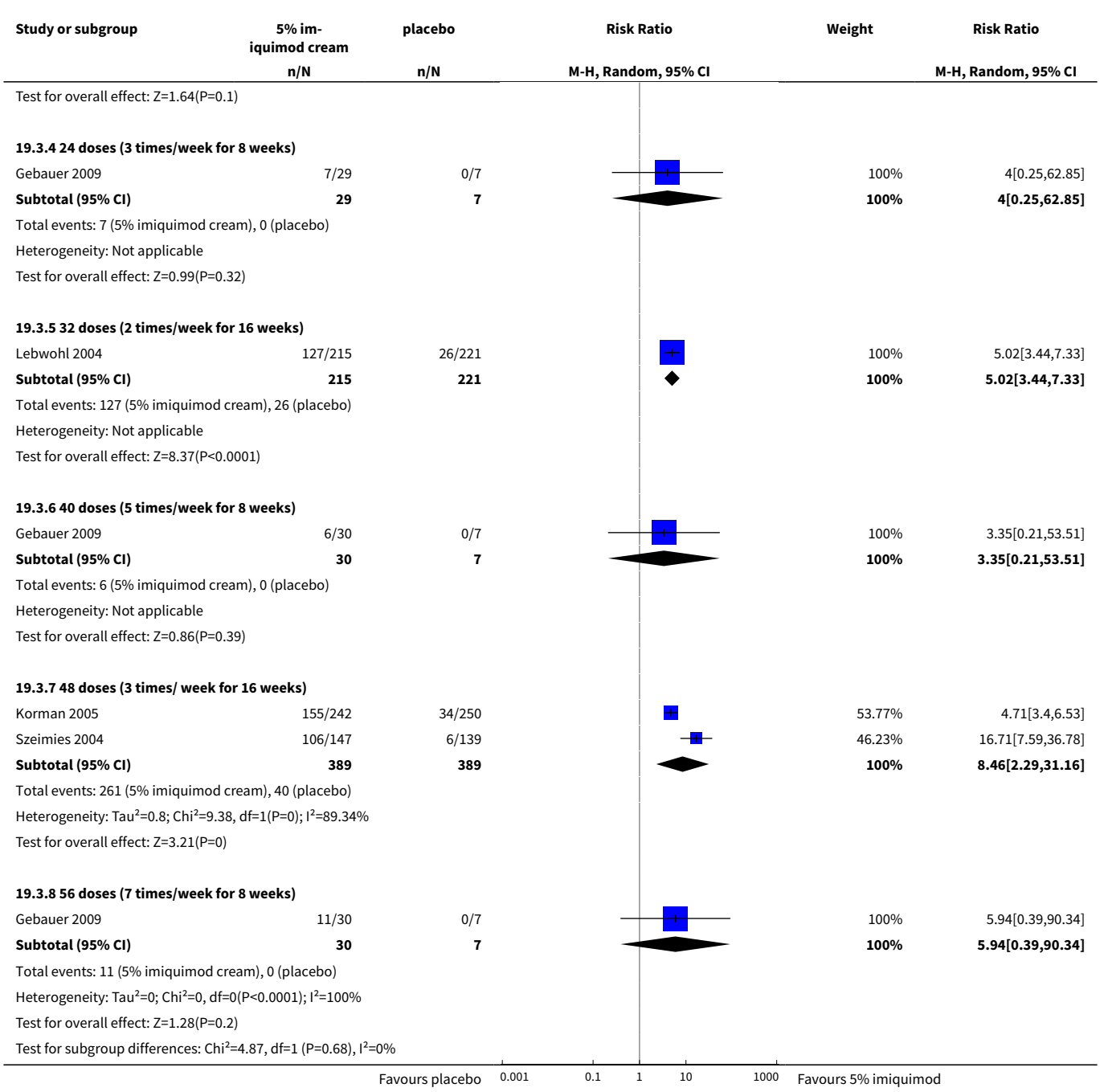


Analysis 19.2. Comparison 19 5% Imiquimod versus placebo, Outcome 2 Participant complete clearance in immunosuppressed participants.

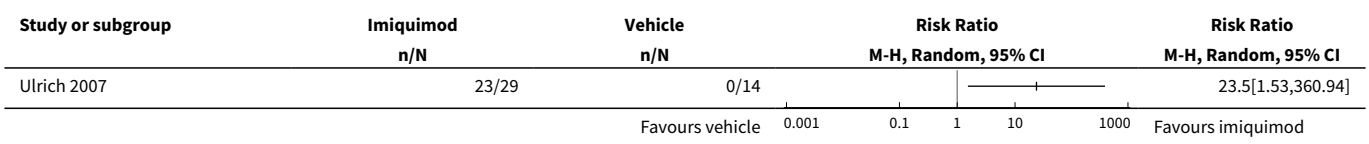


Analysis 19.3. Comparison 19 5% Imiquimod versus placebo, Outcome 3 Participant partial (>75%) clearance.



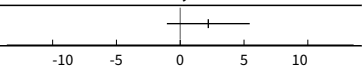


Analysis 19.4. Comparison 19 5% Imiquimod versus placebo, Outcome 4 Participant partial (>75%) clearance in immunosuppressed participants.



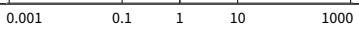
Analysis 19.5. Comparison 19 5% Imiquimod versus placebo, Outcome 5 Mean reduction in lesion counts.

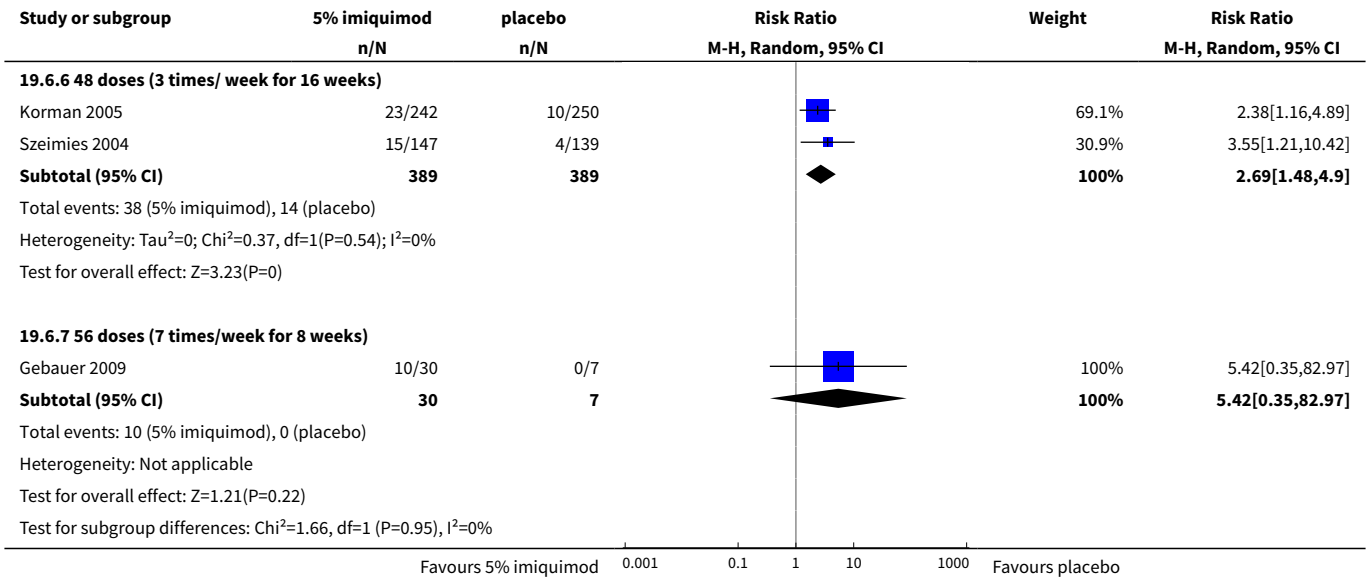
Study or subgroup	Imiquimod		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Ortonne 2010	9	2.8 (2.1)	3	0.6 (2.6)		2.2[-1.05,5.45]



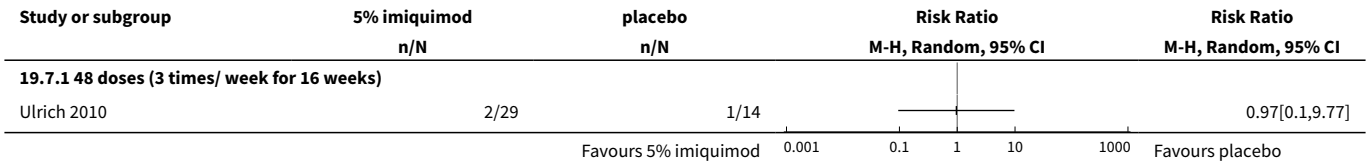
Analysis 19.6. Comparison 19 5% Imiquimod versus placebo, Outcome 6 Withdrawal due to adverse events.

Study or subgroup	5% imiquimod	placebo	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
19.6.1 12-16 doses (2 times/week for 8 weeks or 3 times/week for 4 weeks)					
Gebauer 2009	1/31	0/7		100%	0.75[0.03,16.74]
Subtotal (95% CI)	**31**	**7**		**100%**	**0.75[0.03,16.74]**
Total events: 1 (5% imiquimod), 0 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.18(P=0.86)					
19.6.2 12 or 24 doses (3 times/week for 4 weeks on , 4 weeks off, 4 weeks on)					
Alomar 2007	2/129	0/130		29.2%	5.04[0.24,103.93]
Jorizzo 2007	2/123	2/123		70.8%	1[0.14,6.99]
Subtotal (95% CI)	**252**	**253**		**100%**	**1.6[0.31,8.23]**
Total events: 4 (5% imiquimod), 2 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.8, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.57(P=0.57)					
19.6.3 24 doses (3 times/week for 8 weeks)					
Gebauer 2009	2/29	0/7		100%	1.33[0.07,25.08]
Subtotal (95% CI)	**29**	**7**		**100%**	**1.33[0.07,25.08]**
Total events: 2 (5% imiquimod), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					
19.6.4 32-36 doses (2 times/ week for 16 weeks or 3 times/ week for 12 weeks)					
Lebwohl 2004	7/215	2/221		45.75%	3.6[0.76,17.12]
NCT00828568 Aldara	11/183	1/30		27.56%	1.8[0.24,13.46]
NCT00828568 Taro	8/179	1/30		26.69%	1.34[0.17,10.34]
Subtotal (95% CI)	**577**	**281**		**100%**	**2.29[0.8,6.57]**
Total events: 26 (5% imiquimod), 4 (placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.64, df=2(P=0.73); I^2=0%					
Test for overall effect: Z=1.53(P=0.12)					
19.6.5 40 doses (5 times/week for 8 weeks)					
Gebauer 2009	9/30	0/7		100%	4.9[0.32,75.6]
Subtotal (95% CI)	**30**	**7**		**100%**	**4.9[0.32,75.6]**
Total events: 9 (5% imiquimod), 0 (placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.14(P=0.25)					

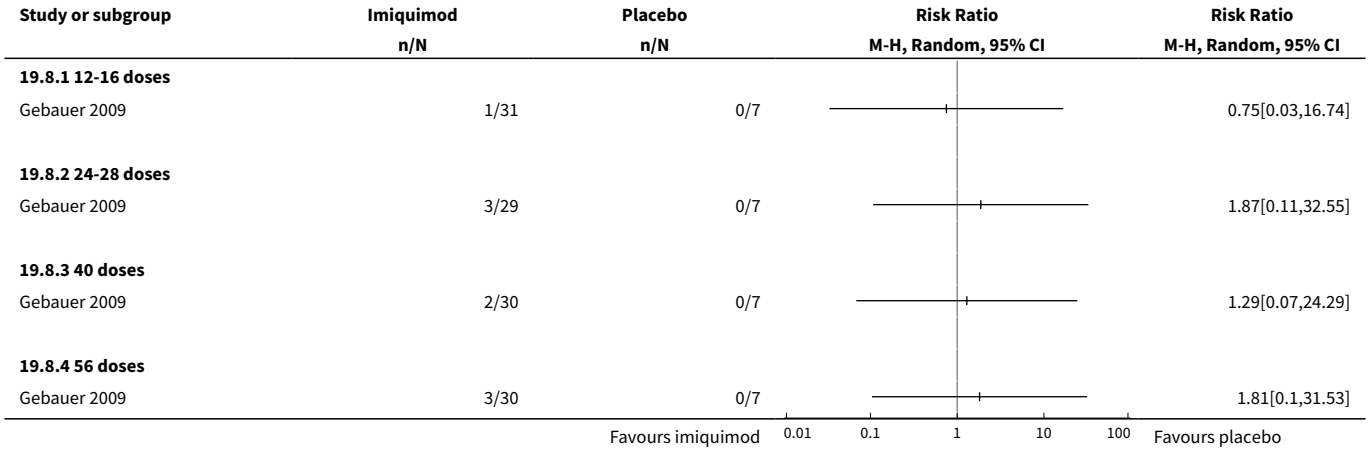




Analysis 19.7. Comparison 19 5% Imiquimod versus placebo, Outcome 7 Withdrawal due to adverse events in immunosuppressed participants.

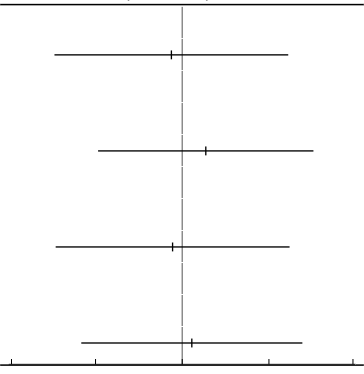


Analysis 19.8. Comparison 19 5% Imiquimod versus placebo, Outcome 8 Minor adverse events excluding skin irritation: body as a whole: in general.



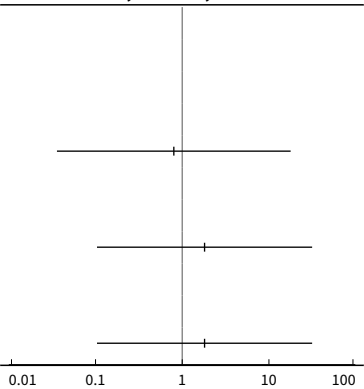
Analysis 19.9. Comparison 19 5% Imiquimod versus placebo, Outcome 9 Minor adverse events excluding skin irritation: body as a whole: "flu" or "cold".

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.9.1 12-16 doses				
Gebauer 2009	1/31	0/7		0.75[0.03,16.74]
19.9.2 24-28 doses				
Gebauer 2009	3/29	0/7		1.87[0.11,32.55]
19.9.3 40 doses				
Gebauer 2009	1/30	0/7		0.77[0.03,17.27]
19.9.4 56 doses				
Gebauer 2009	2/30	0/7		1.29[0.07,24.29]



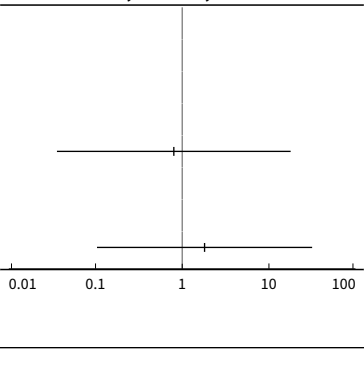
Analysis 19.10. Comparison 19 5% Imiquimod versus placebo, Outcome 10 Minor adverse events excluding skin irritation: digestive: in general.

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.10.1 12-16 doses				
Gebauer 2009	0/31	0/7		Not estimable
19.10.2 24-28 doses				
Gebauer 2009	1/29	0/7		0.8[0.04,17.83]
19.10.3 40 doses				
Gebauer 2009	3/30	0/7		1.81[0.1,31.53]
19.10.4 56 doses				
Gebauer 2009	3/30	0/7		1.81[0.1,31.53]



Analysis 19.11. Comparison 19 5% Imiquimod versus placebo, Outcome 11 Minor adverse events excluding skin irritation: digestive: nausea.

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.11.1 12-16 doses				
Gebauer 2009	0/31	0/7		Not estimable
19.11.2 24-28 doses				
Gebauer 2009	1/29	0/7		0.8[0.04,17.83]
19.11.3 40 doses				
Gebauer 2009	3/30	0/7		1.81[0.1,31.53]



Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.11.4 56 doses				
Gebauer 2009	2/30	0/7		1.29[0.07,24.29]

Favours imiquimod 0.01 0.1 1 10 100 Favours placebo

Analysis 19.12. Comparison 19 5% Imiquimod versus placebo, Outcome 12 Minor adverse events excluding skin irritation: nervous system: in general.

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
19.12.1 12-16 doses				
Gebauer 2009	0/31	0/7		Not estimable
19.12.2 24-28 doses				
Gebauer 2009	0/29	0/7		Not estimable
19.12.3 40 doses				
Gebauer 2009	4/30	0/7		2.32[0.14,38.83]
19.12.4 56 doses				
Gebauer 2009	4/30	0/7		2.32[0.14,38.83]

Favours imiquimod 0.01 0.1 1 10 100 Favours placebo

Analysis 19.13. Comparison 19 5% Imiquimod versus placebo, Outcome 13 Cosmetic outcome: decrease in roughness/dryness/scaliness of the skin.

Study or subgroup	5% Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
19.13.1 32-36 doses					
Lebwohl 2004	114/205	46/210		56.89%	2.54[1.91,3.37]
Subtotal (95% CI)	**205**	**210**		**56.89%**	**2.54[1.91,3.37]**
Total events: 114 (5% Imiquimod), 46 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=6.45(P<0.0001)					
19.13.2 48 doses					
Szeimies 2004	76/143	15/125		43.11%	4.43[2.69,7.3]
Subtotal (95% CI)	**143**	**125**		**43.11%**	**4.43[2.69,7.3]**
Total events: 76 (5% Imiquimod), 15 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=5.84(P<0.0001)					
Total (95% CI)	**348**	**335**		**100%**	**3.23[1.86,5.58]**
Total events: 190 (5% Imiquimod), 61 (Placebo)					
Heterogeneity: Tau^2=0.12; Chi^2=3.72, df=1(P=0.05); I^2=73.15%					
Test for overall effect: Z=4.19(P<0.0001)					
Test for subgroup differences: Chi^2=3.61, df=1 (P=0.06), I^2=72.33%					

Favours placebo 0.01 0.1 1 10 100 Favours imiquimod

Comparison 20. Imiquimod versus placebo: different concentrations

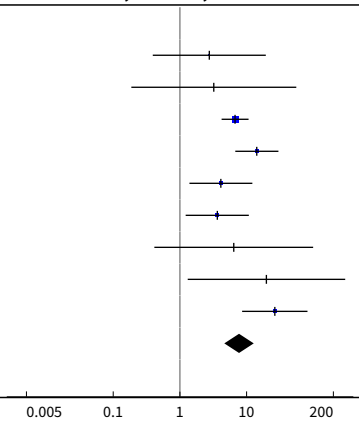
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	12	3087	Risk Ratio (M-H, Random, 95% CI)	6.73 [5.03, 9.00]
1.1 5.0% imiquimod	9	1871	Risk Ratio (M-H, Random, 95% CI)	7.70 [4.63, 12.79]
1.2 3.75% imiquimod	3	730	Risk Ratio (M-H, Random, 95% CI)	6.45 [3.87, 10.73]
1.3 2.5% imiquimod	2	486	Risk Ratio (M-H, Random, 95% CI)	4.49 [2.40, 8.39]
2 Participant partial (>75%) clearance	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 5.0% imiquimod	4	1363	Risk Ratio (M-H, Random, 95% CI)	6.71 [3.89, 11.57]
2.2 3.75% imiquimod	2	484	Risk Ratio (M-H, Random, 95% CI)	3.11 [2.08, 4.66]
2.3 2.5% imiquimod	2	485	Risk Ratio (M-H, Random, 95% CI)	2.48 [1.67, 3.68]
3 Mean percentage of reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 3.75% imiquimod	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Minor adverse events excluding skin irritation: body as a whole: 'flu" or "cold"	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 5.0% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Withdrawal due to adverse events	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 5.0% imiquimod	8	2290	Risk Ratio (M-H, Random, 95% CI)	2.59 [1.59, 4.23]
5.2 3.75% imiquimod	2	483	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.22, 3.93]
5.3 2.5% imiquimod	2	486	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.09, 2.70]
6 Skin irritation	5	1678	Risk Ratio (M-H, Random, 95% CI)	3.93 [1.56, 9.88]
6.1 5.0% imiquimod	3	708	Risk Ratio (M-H, Random, 95% CI)	3.68 [0.86, 15.74]
6.2 3.75% imiquimod	2	484	Risk Ratio (M-H, Random, 95% CI)	4.86 [0.92, 25.83]
6.3 2.5% imiquimod	2	486	Risk Ratio (M-H, Random, 95% CI)	3.45 [0.63, 18.97]

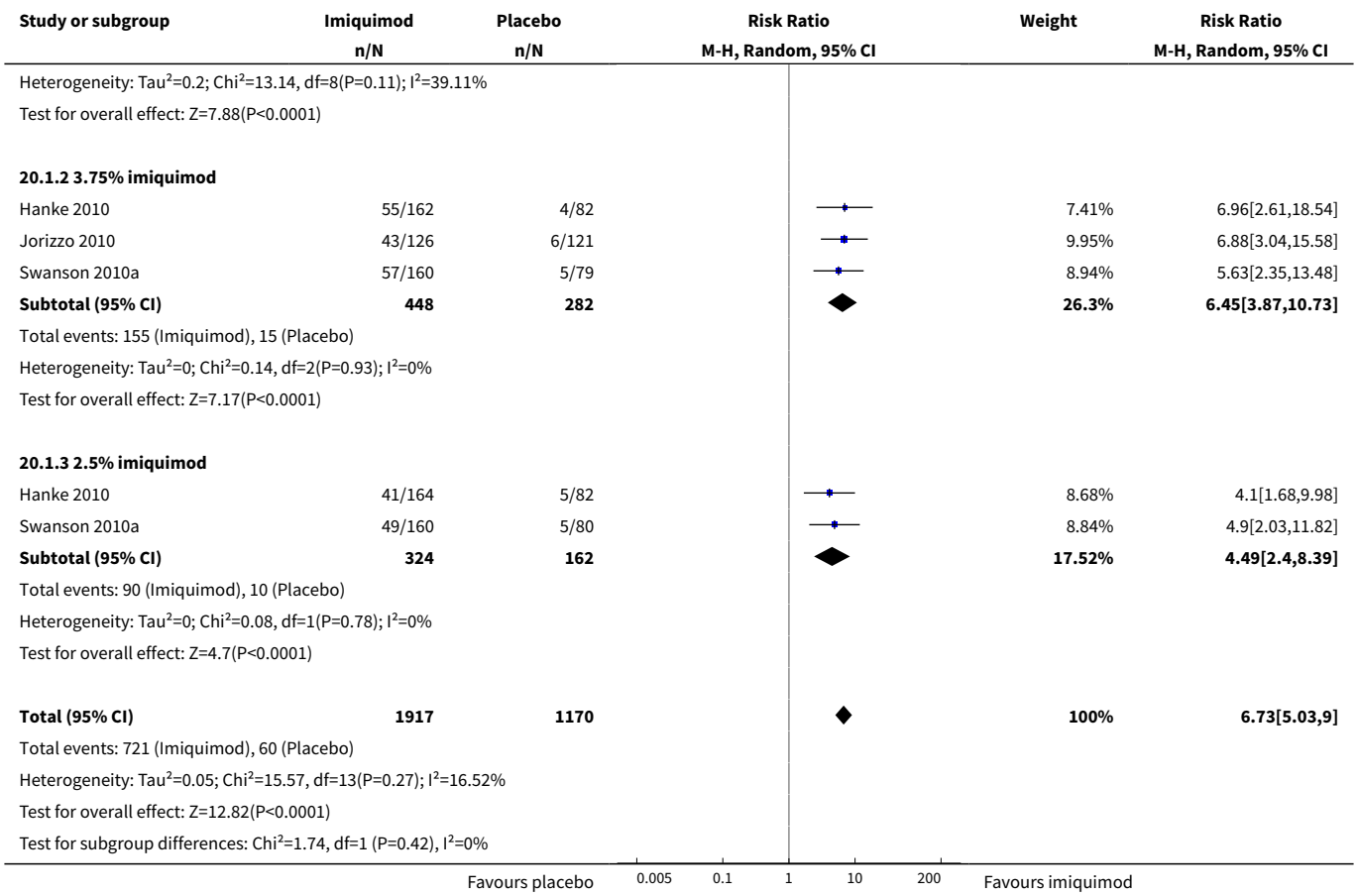
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Minor adverse events excluding skin irritation: body as a whole: pyrexia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Minor adverse events excluding skin irritation: hemic and lymphatic: lymphadenopathy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Minor adverse events excluding skin irritation: nervous system: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Minor adverse events excluding skin irritation: nervous system: headache	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1 5.0% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.3 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Minor adverse events excluding skin irritation: respiratory: cough	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Minor adverse events excluding skin irritation: respiratory: sinusitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13.2 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14 Minor adverse events excluding skin irritation: respiratory: upper respiratory tract infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
14.2 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 Minor adverse events excluding skin irritation: urogenital: urinary tract infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15.1 3.75% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15.2 2.5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
16 Cosmetic outcome: Participant's significantly or much improved cosmetic outcome assessed by investigator	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
16.1 3.75% imiquimod	2	470	Risk Ratio (M-H, Random, 95% CI)	2.71 [2.05, 3.58]
16.2 2.5% imiquimod	2	475	Risk Ratio (M-H, Random, 95% CI)	2.25 [1.62, 3.14]

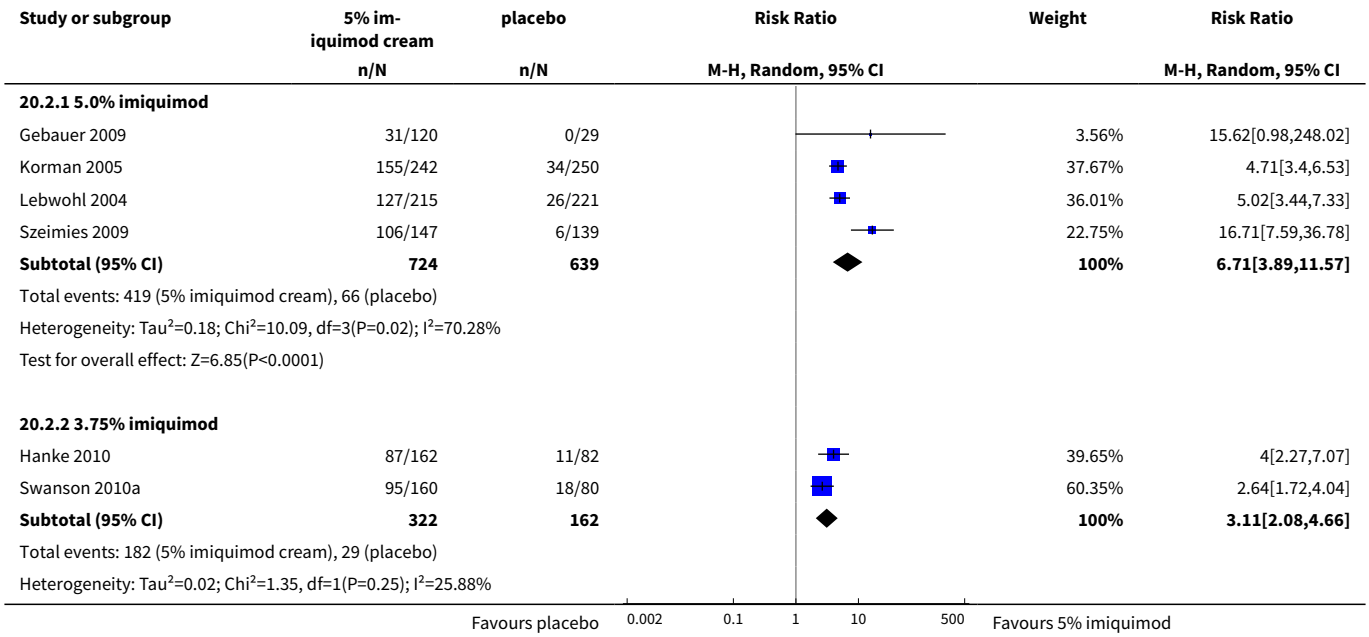
Analysis 20.1. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 1 Participant complete clearance.

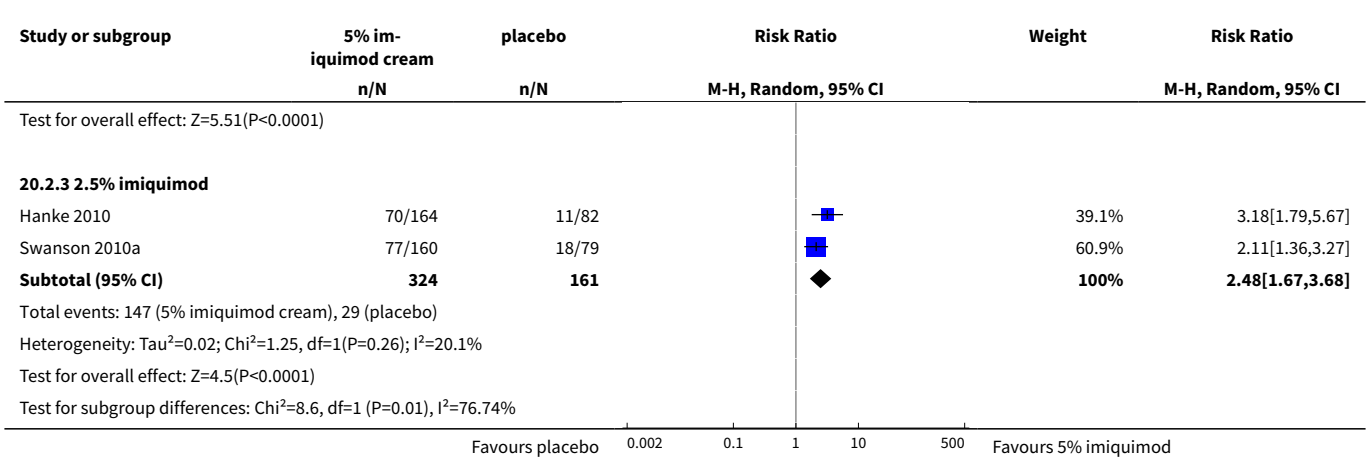
Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
20.1.1 5.0% imiquimod					
Chen 2003	8/29	1/10		2.13%	2.76[0.39,19.4]
Gebauer 2009	6/120	0/29		1.02%	3.22[0.19,55.64]
Korman 2005	117/242	18/250		21.14%	6.71[4.22,10.68]
Lebwohl 2004	97/215	7/221		11.48%	14.24[6.77,29.97]
NCT00828568 Aldara	74/180	3/30		6.2%	4.11[1.39,12.2]
NCT00828568 Taro	64/176	3/30		6.17%	3.64[1.22,10.83]
Ooi 2006	5/11	0/6		1.1%	6.42[0.41,99.46]
Stockfleth 2002	21/25	0/11		1.12%	19.85[1.31,301.01]
Szeimies 2004	84/147	3/139		5.82%	26.48[8.57,81.8]
Subtotal (95% CI)	**1145**	**726**		**56.19%**	**7.7[4.63,12.79]**
Total events: 476 (Imiquimod), 35 (Placebo)					



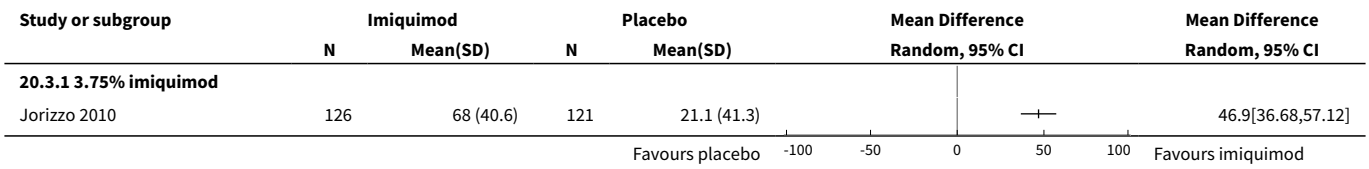


Analysis 20.2. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 2 Participant partial (>75%) clearance.

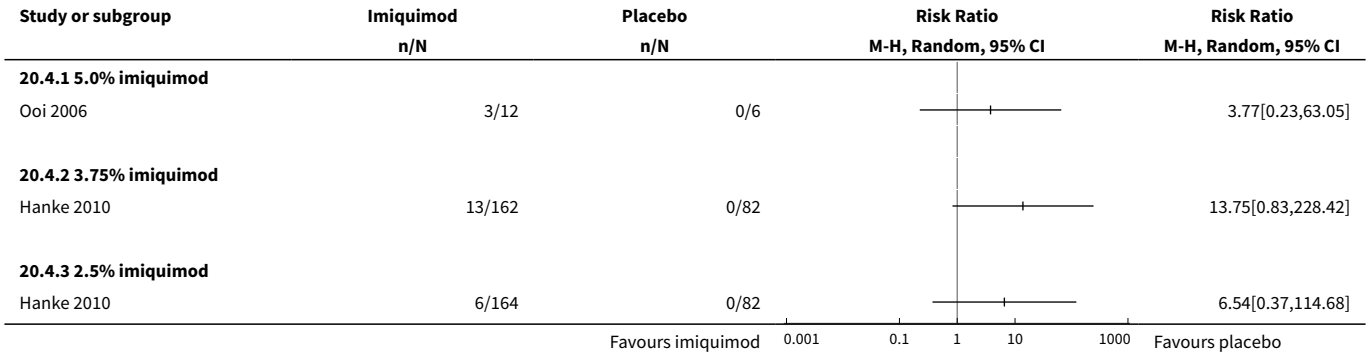




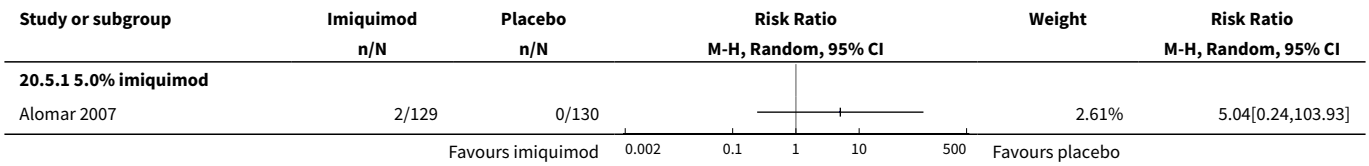
Analysis 20.3. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 3 Mean percentage of reduction in lesion counts.

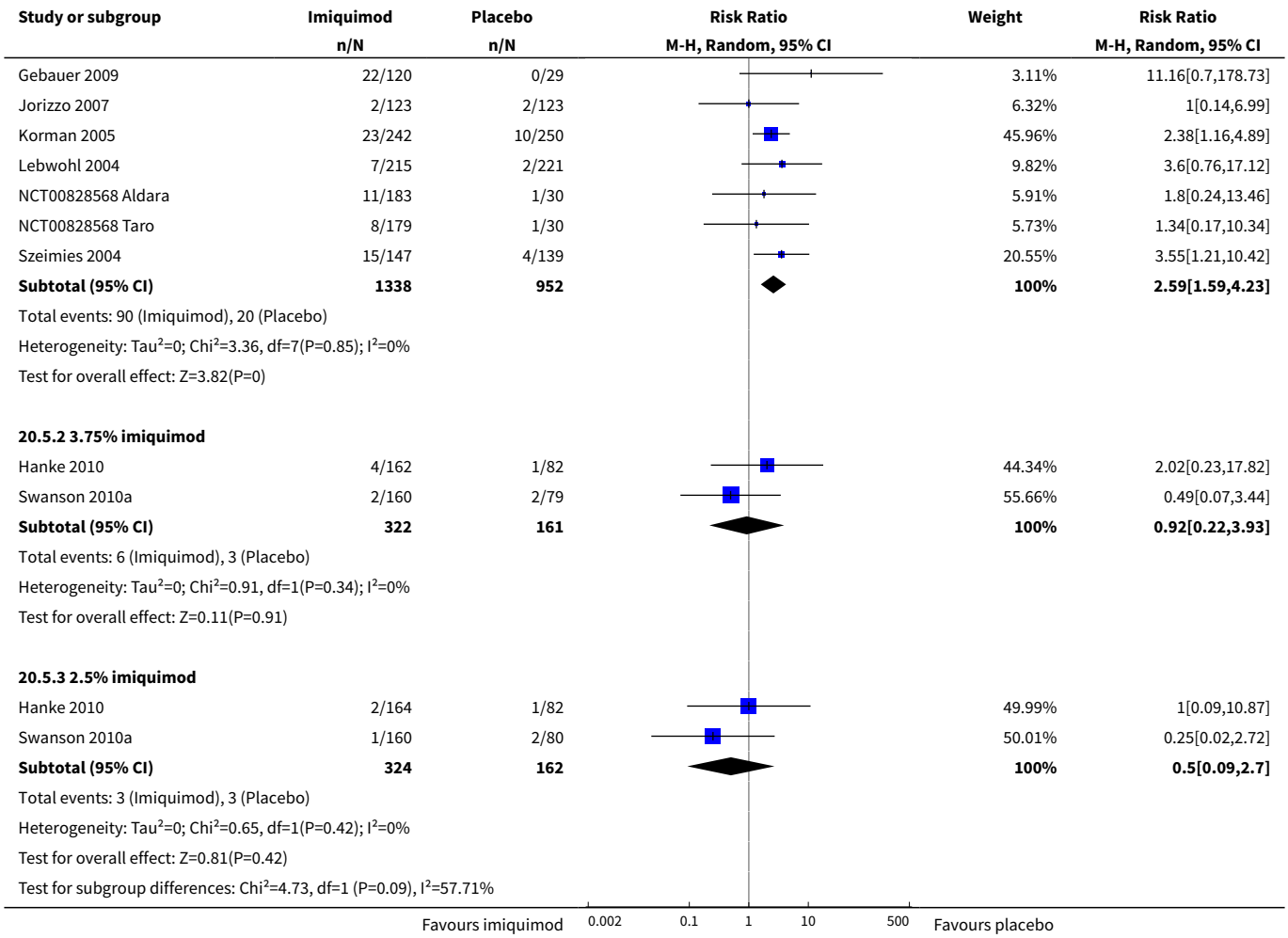


Analysis 20.4. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 4 Minor adverse events excluding skin irritation: body as a whole: 'flu" or "cold".

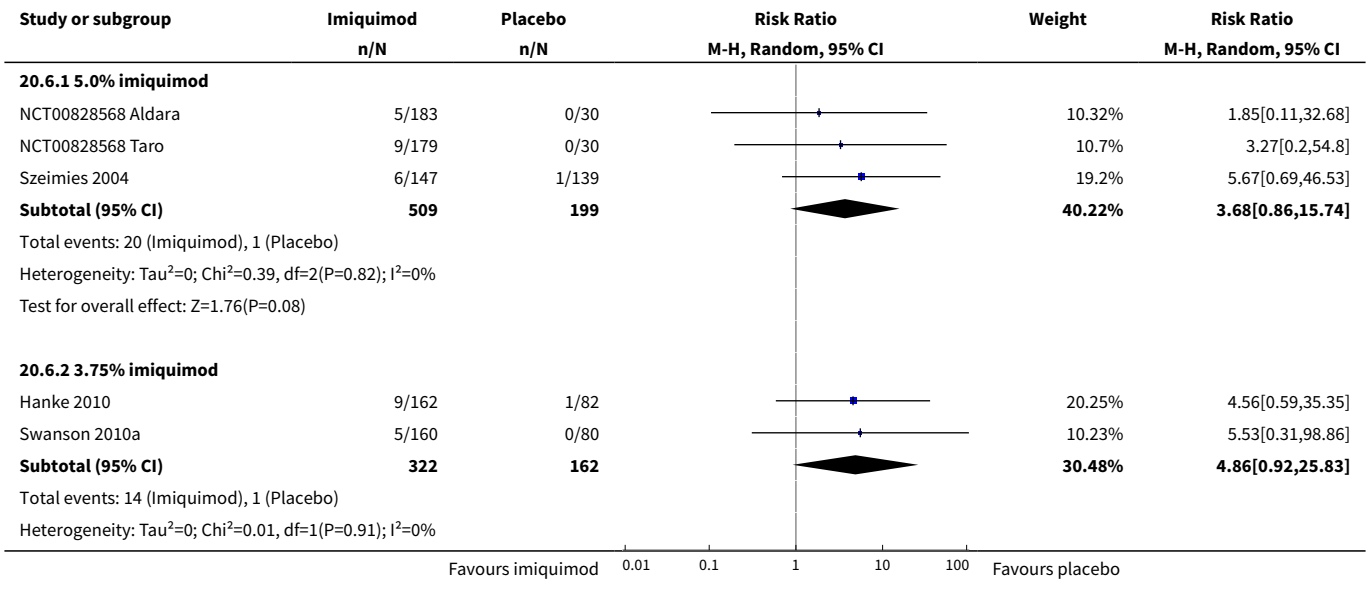


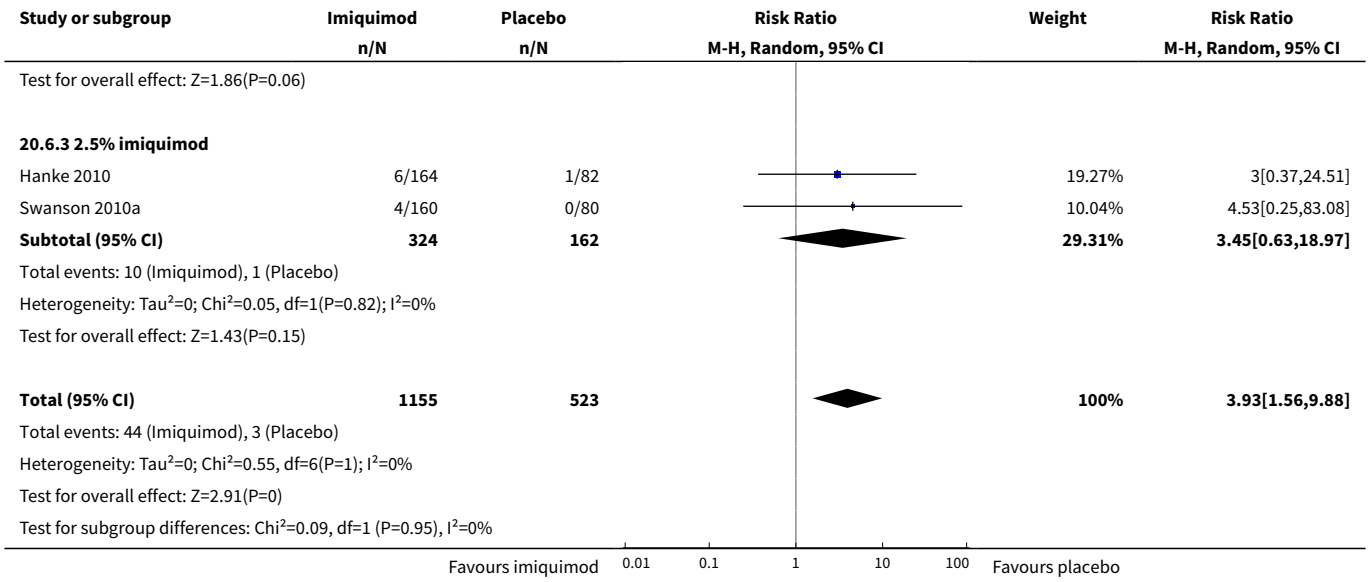
Analysis 20.5. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 5 Withdrawal due to adverse events.



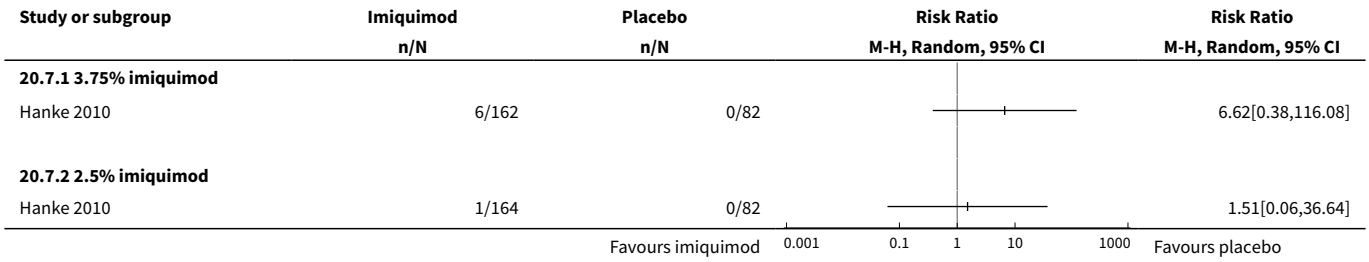


Analysis 20.6. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 6 Skin irritation.

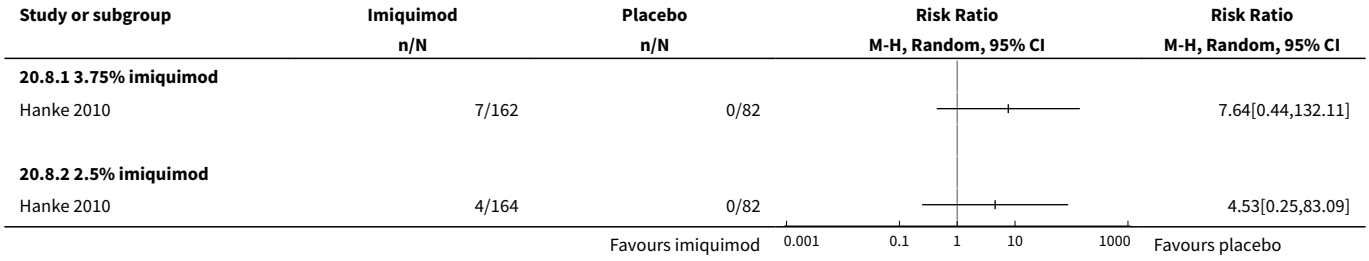




Analysis 20.7. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 7 Minor adverse events excluding skin irritation: body as a whole: pyrexia.



Analysis 20.8. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 8 Minor adverse events excluding skin irritation: hemic and lymphatic: lymphadenopathy.



Analysis 20.9. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 9 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
20.9.1 3.75% imiquimod				
Hanke 2010	5/162	0/82		5.6[0.31,100.08]

Favours imiquimod 0.002 0.1 1 10 500 Favours placebo

Analysis 20.10. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 10 Minor adverse events excluding skin irritation: nervous system: fatigue.

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
20.10.1 3.75% imiquimod				
Hanke 2010	8/162	1/82		4.05[0.52,31.83]
20.10.2 2.5% imiquimod				
Hanke 2010	5/164	1/82		2.5[0.3,21.05]

Favours imiquimod 0.005 0.1 1 10 200 Favours placebo

Analysis 20.11. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 11 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
20.11.1 5.0% imiquimod				
Ooi 2006	3/12	0/6		3.77[0.23,63.05]
20.11.2 3.75% imiquimod				
Hanke 2010	8/162	1/82		4.05[0.52,31.83]
20.11.3 2.5% imiquimod				
Hanke 2010	6/164	1/82		3[0.37,24.51]

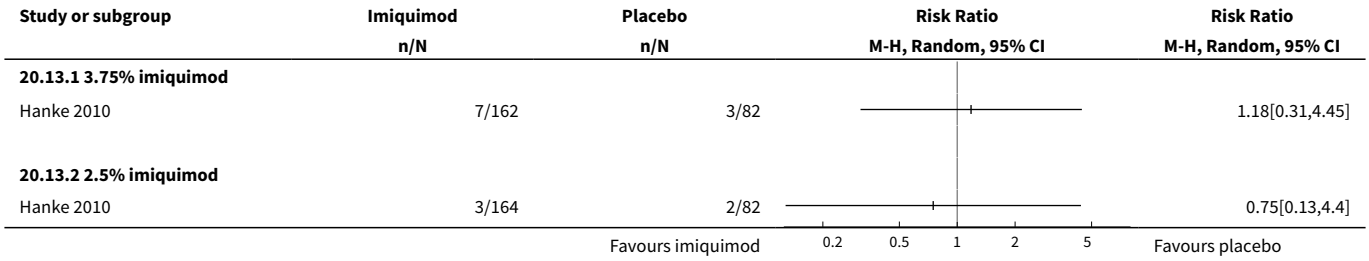
Favours imiquimod 0.001 0.1 1 10 1000 Favours placebo

Analysis 20.12. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 12 Minor adverse events excluding skin irritation: respiratory: cough.

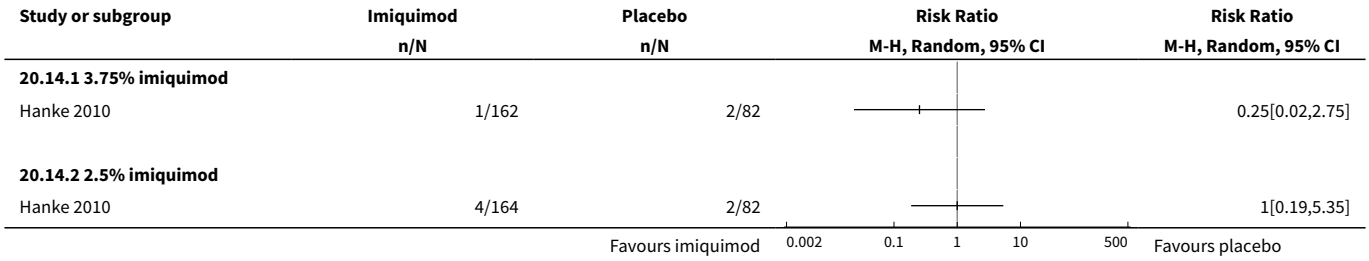
Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
20.12.1 3.75% imiquimod				
Hanke 2010	4/162	1/82		2.02[0.23,17.82]
20.12.2 2.5% imiquimod				
Hanke 2010	0/164	1/82		0.17[0.01,4.07]

Favours imiquimod 0.005 0.1 1 10 200 Favours placebo

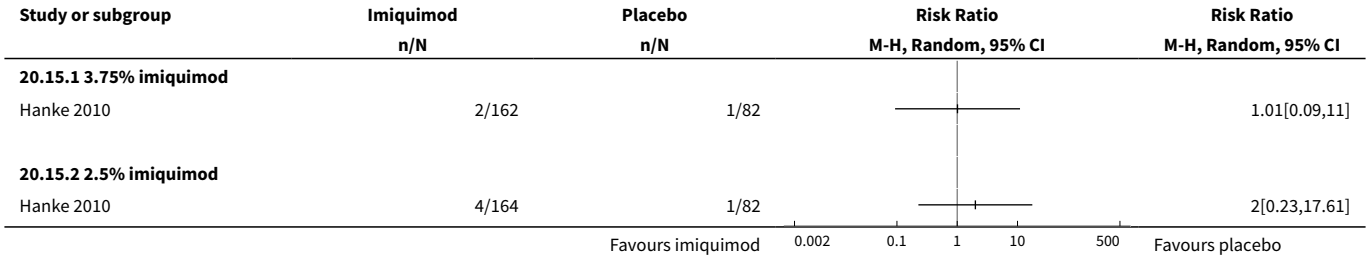
Analysis 20.13. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 13 Minor adverse events excluding skin irritation: respiratory: sinusitis.



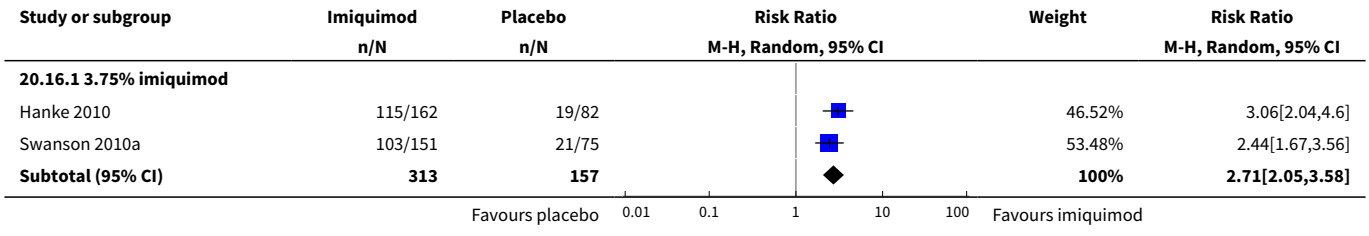
Analysis 20.14. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 14 Minor adverse events excluding skin irritation: respiratory: upper respiratory tract infection.

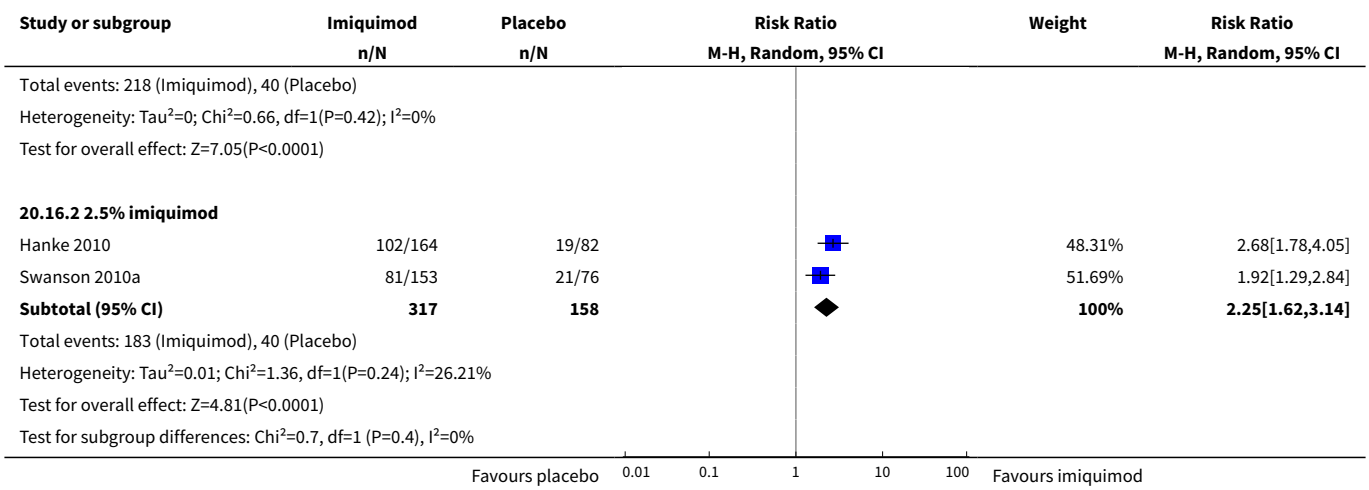


Analysis 20.15. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 15 Minor adverse events excluding skin irritation: urogenital: urinary tract infection.



Analysis 20.16. Comparison 20 Imiquimod versus placebo: different concentrations, Outcome 16 Cosmetic outcome: Participant's significantly or much improved cosmetic outcome assessed by investigator.





Comparison 21. Imiquimod versus placebo: frequency of application

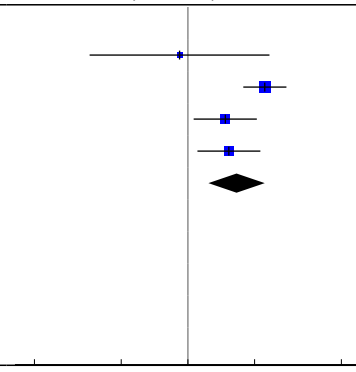
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	12		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 2 times/week	4	890	Risk Ratio (M-H, Random, 95% CI)	5.36 [2.03, 14.16]
1.2 3 times/week	6	1336	Risk Ratio (M-H, Random, 95% CI)	8.38 [3.79, 18.52]
1.3 5 times/week	1	37	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.03, 17.27]
1.4 7 times/week	4	1253	Risk Ratio (M-H, Random, 95% CI)	5.39 [3.65, 7.98]
2 Participant partial (>75%) clearance	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 2 times/week	2	474	Risk Ratio (M-H, Random, 95% CI)	4.99 [3.43, 7.26]
2.2 3 times/week	3	814	Risk Ratio (M-H, Random, 95% CI)	7.65 [2.51, 23.32]
2.3 5 times/week	1	37	Risk Ratio (M-H, Random, 95% CI)	3.35 [0.21, 53.51]
2.4 7 times/week	3	1006	Risk Ratio (M-H, Random, 95% CI)	2.95 [1.99, 4.37]
3 Withdrawal due to adverse events	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

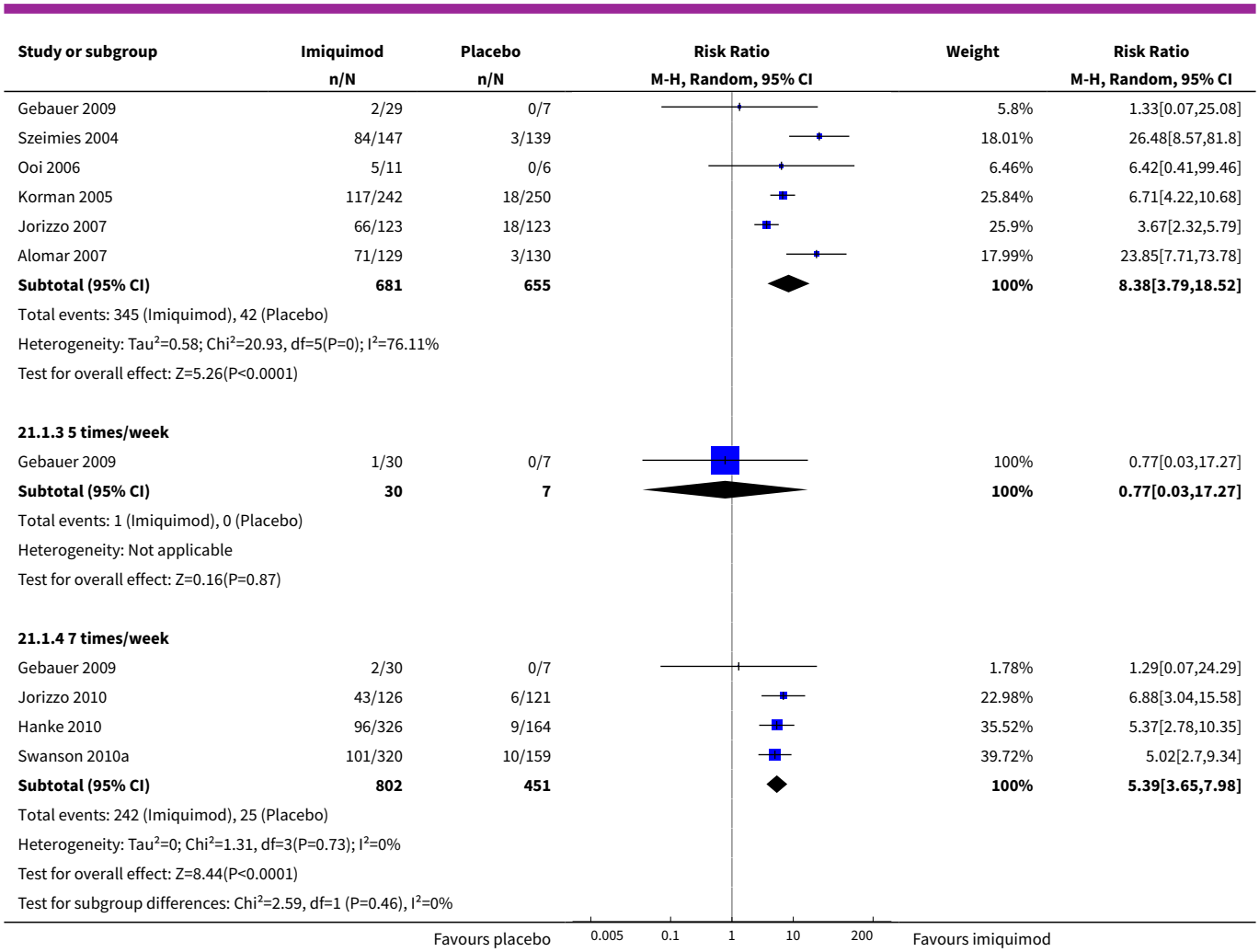
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 2 times/week	4	896	Risk Ratio (M-H, Random, 95% CI)	2.04 [0.75, 5.53]
3.2 3 times/week	5	1319	Risk Ratio (M-H, Random, 95% CI)	2.47 [1.42, 4.30]
3.3 5 times/week	1	37	Risk Ratio (M-H, Random, 95% CI)	4.90 [0.32, 75.60]
3.4 7 times/week	3	1006	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.33, 7.18]
4 Minor adverse events excluding skin irritation:body as a whole: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 2 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 3 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 5 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 7 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Minor adverse events excluding skin irritation: body as a whole:"flu" or "cold"	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 2 times/week	1	38	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.03, 16.74]
5.2 3 times/week	2	54	Risk Ratio (M-H, Random, 95% CI)	2.67 [0.36, 19.83]
5.3 5 times/week	1	37	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.03, 17.27]
5.4 7 times/week	2	527	Risk Ratio (M-H, Random, 95% CI)	5.20 [0.28, 95.18]
6 Minor adverse events excluding skin irritation: digestive: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 3 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 5 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 7 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Minor adverse events excluding skin irritation: digestive: nausea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 3 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 5 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.3 7 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 3 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 7 times/week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Minor adverse events excluding skin irritation: nervous system: headache	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9.1 3 times/week	1	18	Risk Ratio (M-H, Random, 95% CI)	3.77 [0.23, 63.05]
9.2 5 times/week	1	37	Risk Ratio (M-H, Random, 95% CI)	1.81 [0.10, 31.53]
9.3 7 times/week	2	527	Risk Ratio (M-H, Random, 95% CI)	4.48 [0.86, 23.31]

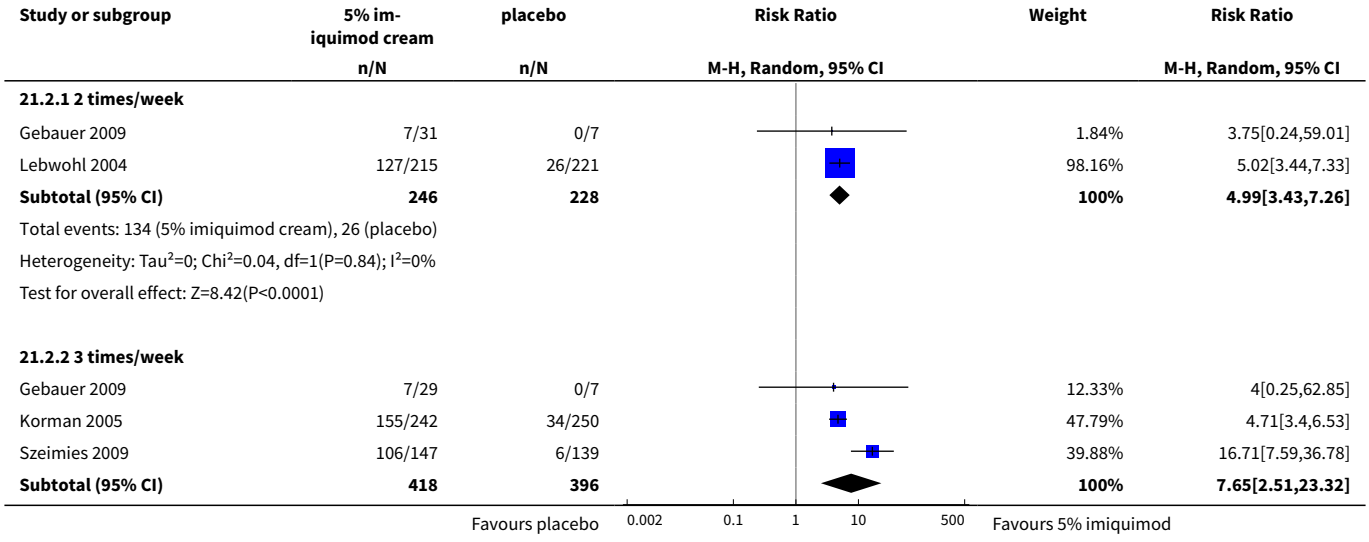
Analysis 21.1. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 1 Participant complete clearance.

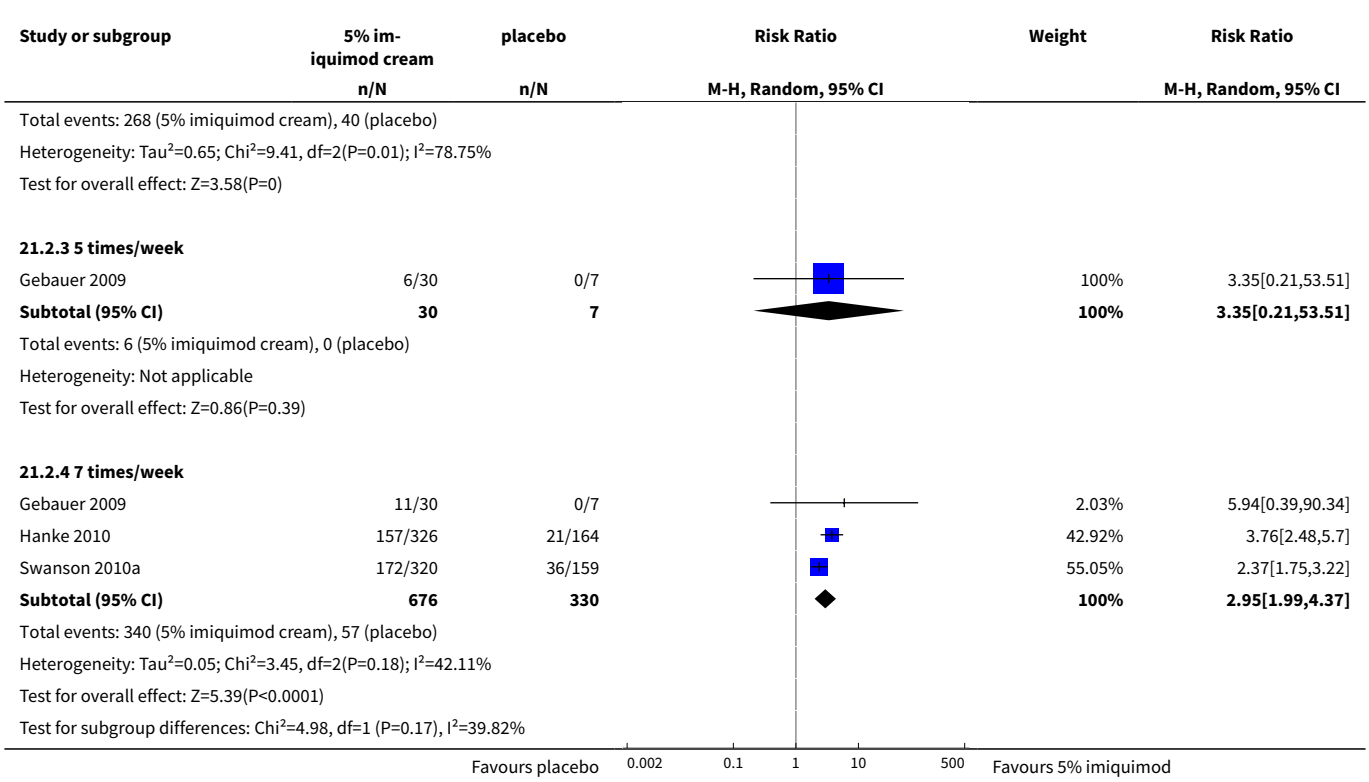
Study or subgroup	Imiquimod n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
21.1.1 2 times/week					
Gebauer 2009	1/31	0/7		8.02%	0.75[0.03,16.74]
Lebwohl 2004	97/215	7/221		35.13%	14.24[6.77,29.97]
NCT00828568 Taro	64/176	3/30		28.39%	3.64[1.22,10.83]
NCT00828568 Aldara	74/180	3/30		28.46%	4.11[1.39,12.2]
Subtotal (95% CI)	**602**	**288**		**100%**	**5.36[2.03,14.16]**
Total events: 236 (Imiquimod), 13 (Placebo)					
Heterogeneity: Tau²=0.56; Chi²=7.89, df=3(P=0.05); I²=61.97%					
Test for overall effect: Z=3.39(P=0)					
21.1.2 3 times/week					



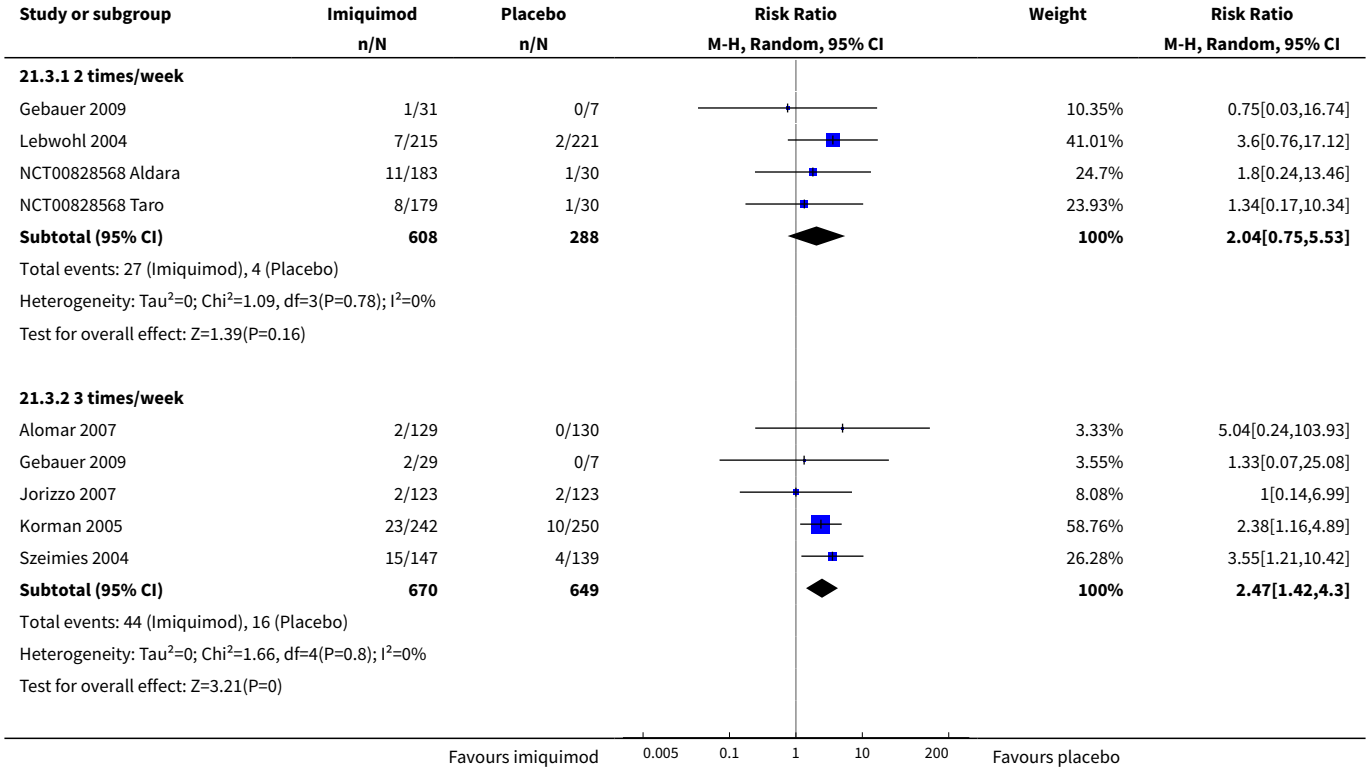


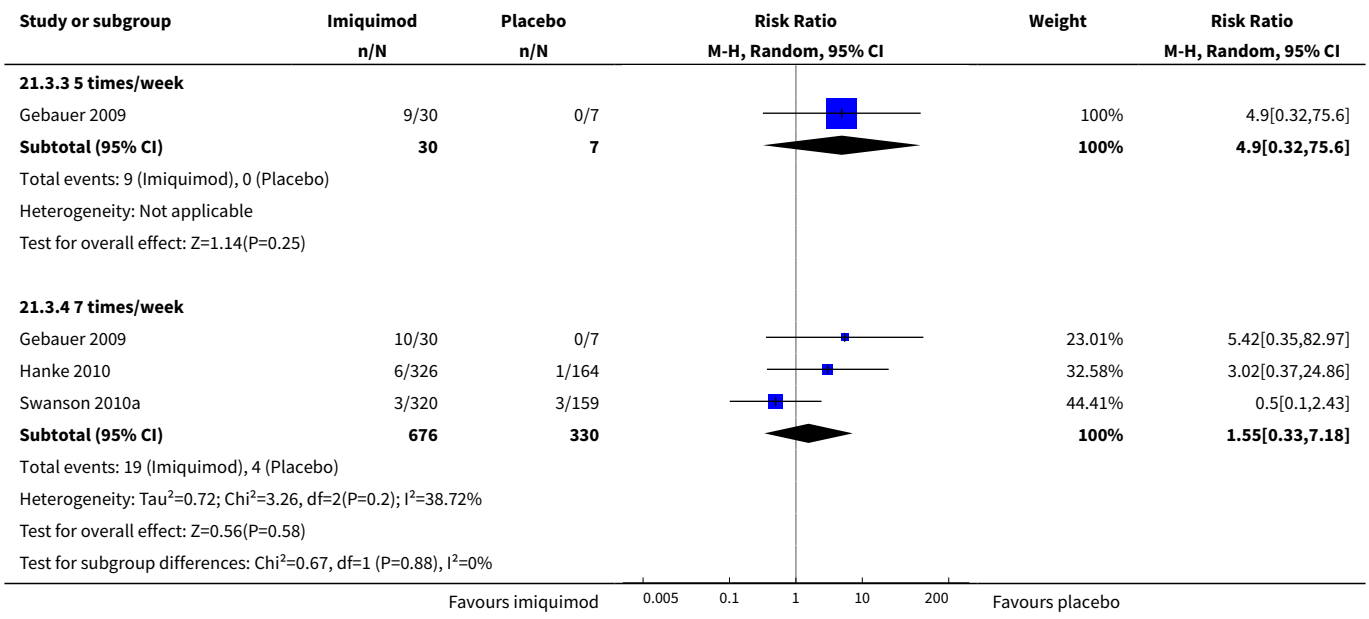
Analysis 21.2. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 2 Participant partial (>75%) clearance.



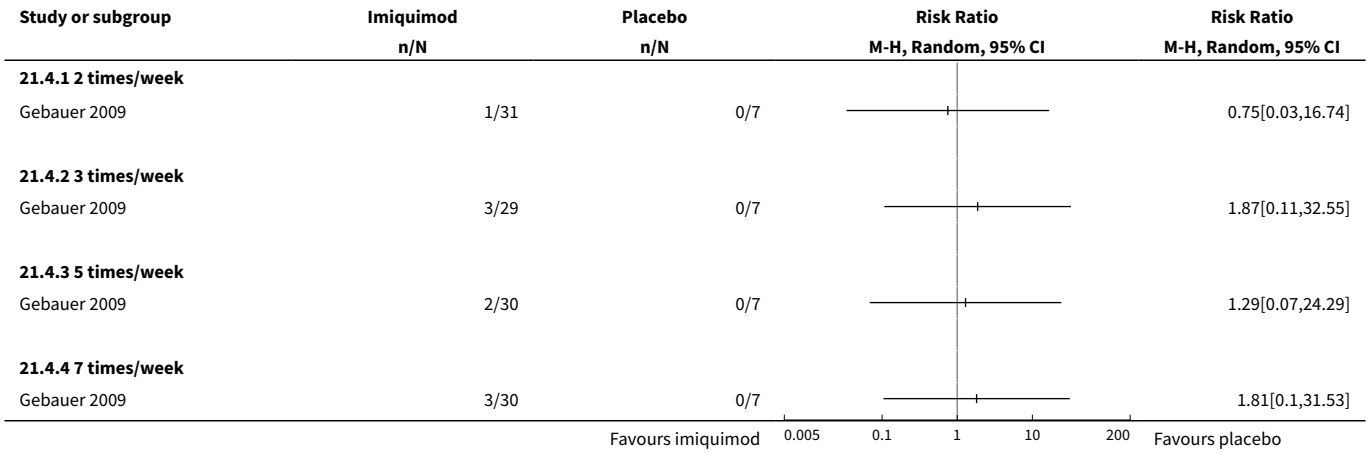


Analysis 21.3. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 3 Withdrawal due to adverse events.

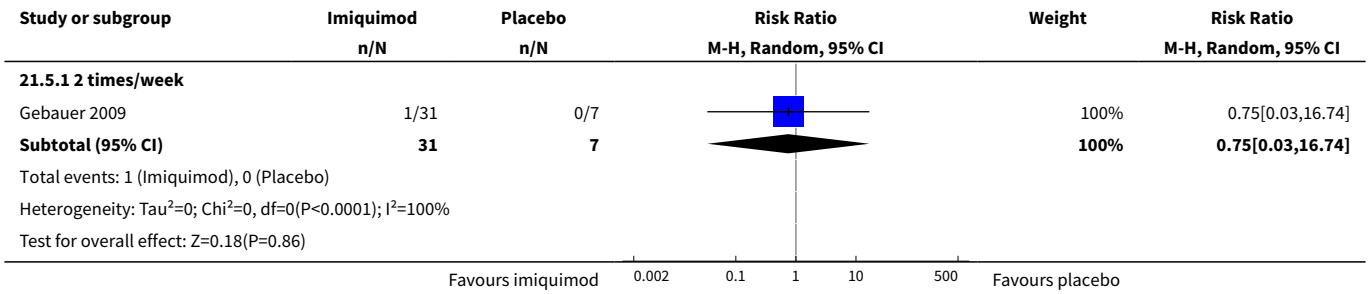


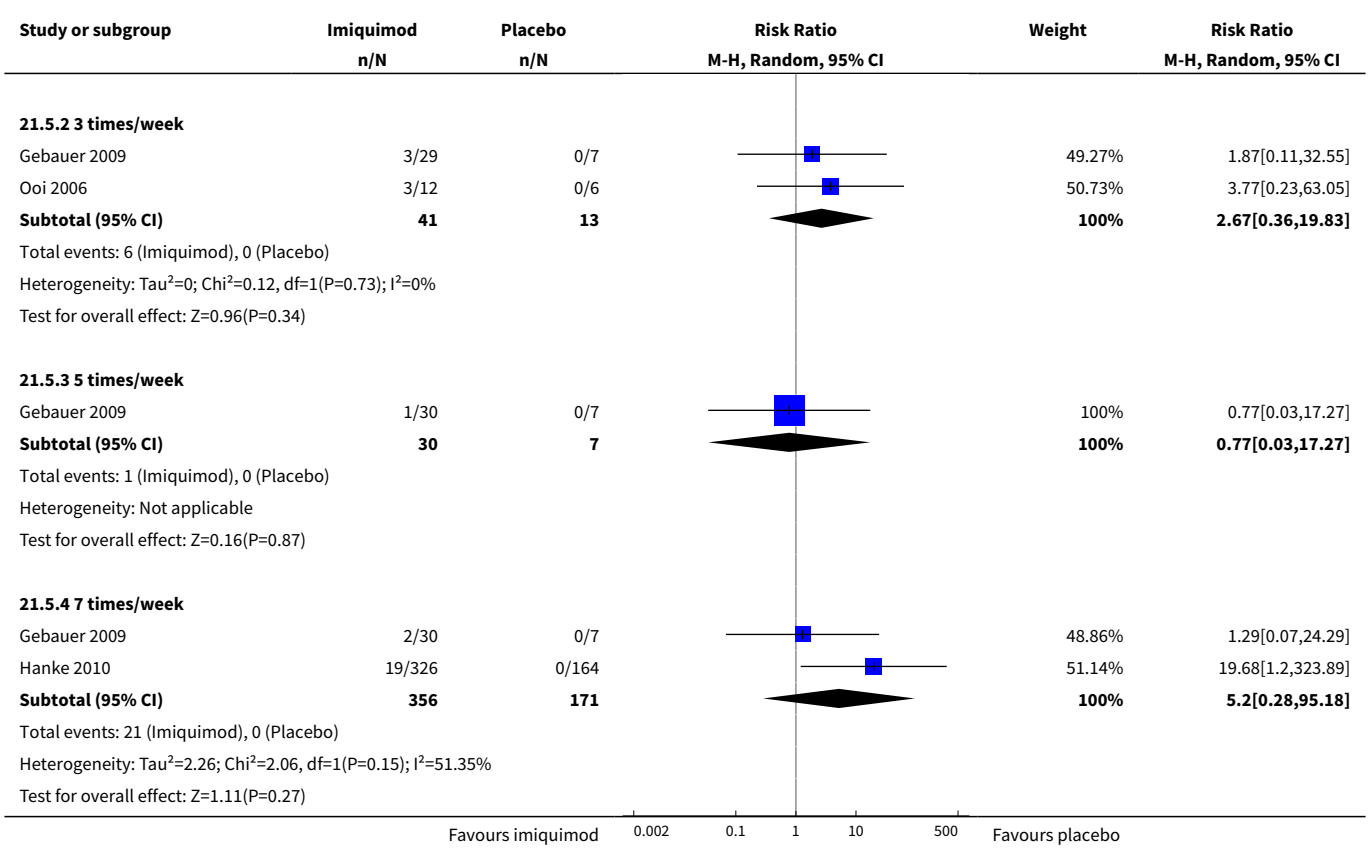


Analysis 21.4. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 4 Minor adverse events excluding skin irritation:body as a whole: in general.

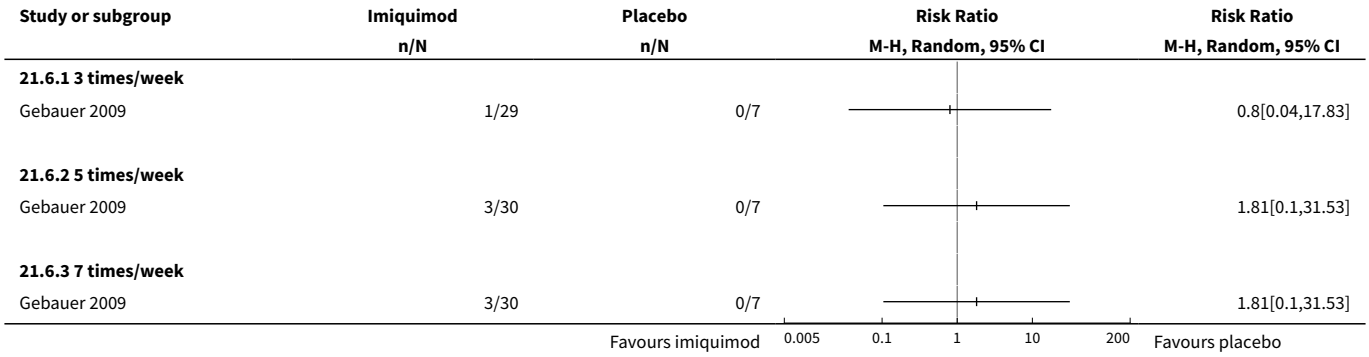


Analysis 21.5. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 5 Minor adverse events excluding skin irritation: body as a whole:"flu" or "cold".

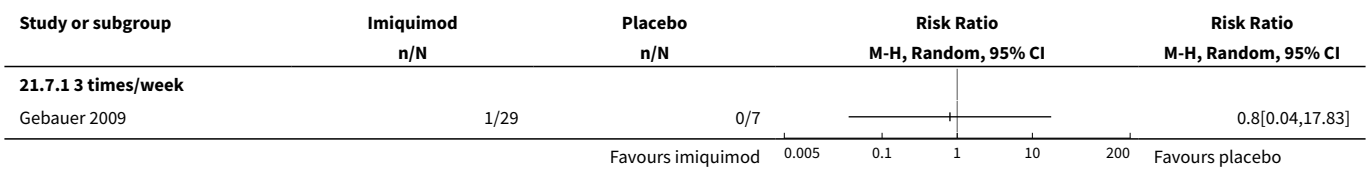


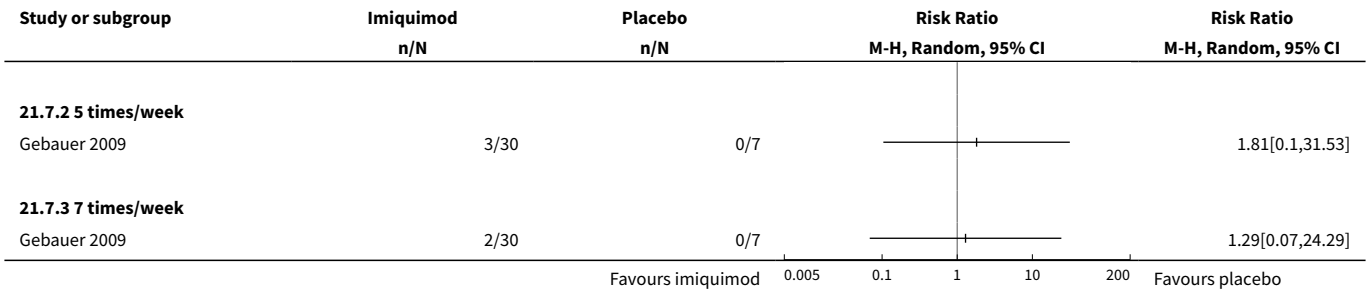


Analysis 21.6. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 6 Minor adverse events excluding skin irritation: digestive: in general.

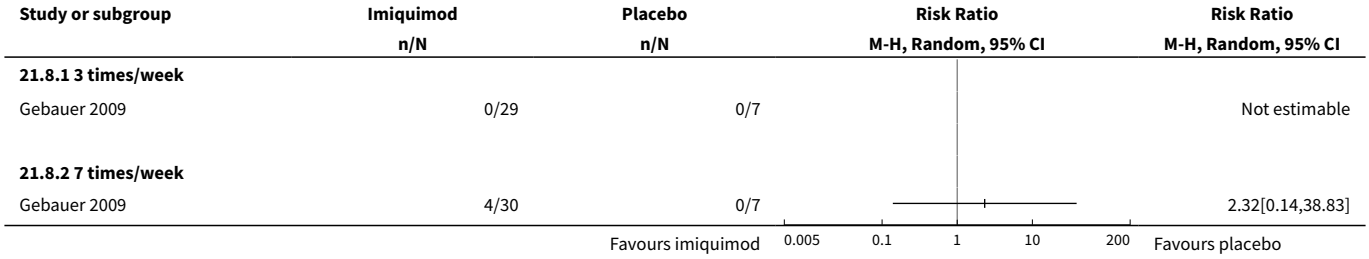


Analysis 21.7. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 7 Minor adverse events excluding skin irritation: digestive: nausea.

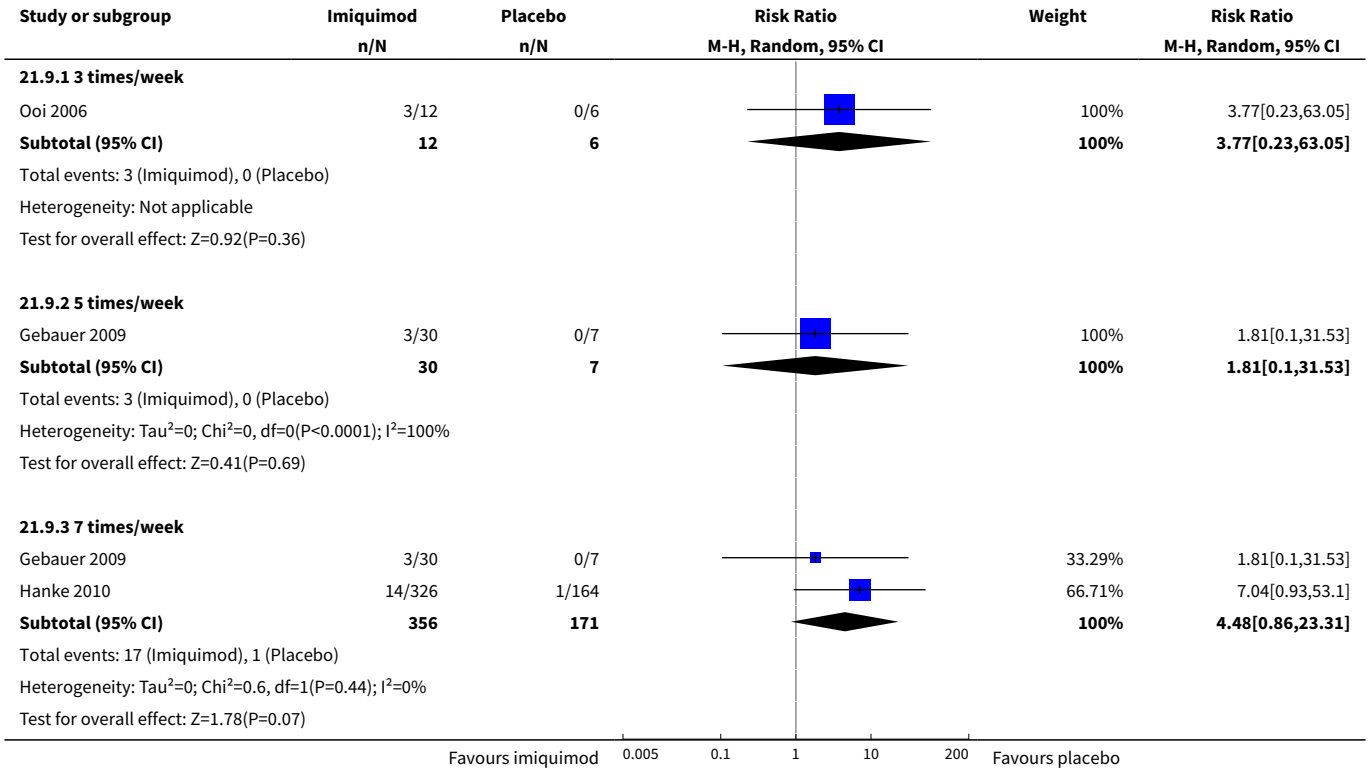




Analysis 21.8. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 8 Minor adverse events excluding skin irritation: nervous system: in general.



Analysis 21.9. Comparison 21 Imiquimod versus placebo: frequency of application, Outcome 9 Minor adverse events excluding skin irritation: nervous system: headache.

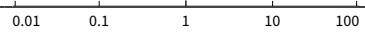


Comparison 22. 5% imiquimod versus 5% 5-FU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Cosmetic outcome: Investigator cosmetic outcome "excellent"	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Cosmetic outcome: normal skin surface	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

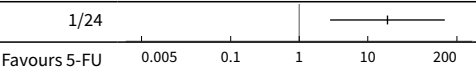
Analysis 22.1. Comparison 22 5% imiquimod versus 5% 5-FU, Outcome 1 Participant complete clearance.

Study or subgroup	Imiquimod n/N	5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	22/26	23/24		0%	0.88[0.73,1.06]
Tanghetti 2007	5/19	17/20		0%	0.31[0.14,0.67]



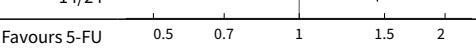
Analysis 22.2. Comparison 22 5% imiquimod versus 5% 5-FU, Outcome 2 Cosmetic outcome: Investigator cosmetic outcome "excellent".

Study or subgroup	Imiquimod n/N	5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	21/26	1/24		19.38[2.82,133.26]



Analysis 22.3. Comparison 22 5% imiquimod versus 5% 5-FU, Outcome 3 Cosmetic outcome: normal skin surface.

Study or subgroup	Imiquimod n/N	5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	22/26	14/24		1.45[1,2.11]



Comparison 23. 5% imiquimod versus cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 23.1. Comparison 23 5% imiquimod versus cryotherapy, Outcome 1 Participant complete clearance.

Study or subgroup	Imiquimod n/N	Cryotherapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
23.1.1 5% imiquimod				
Krawtchenko 2007	22/26	17/25		1.24[0.91,1.7]
		Favours cryotherapy	0.2 0.5 1 2 5	Favours imiquimod

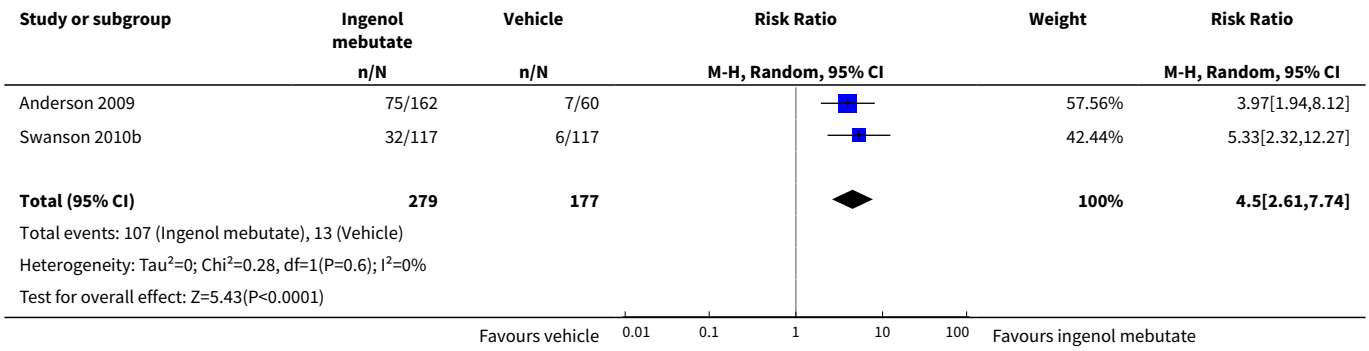
Comparison 24. Ingenol mebutate (PEP005) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance of target lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participant complete clearance of all lesions	2	456	Risk Ratio (M-H, Random, 95% CI)	4.50 [2.61, 7.74]
3 Participant partial (>75%) clearance of target lesions	2	280	Risk Ratio (M-H, Random, 95% CI)	2.88 [1.81, 4.58]
4 Cosmetic outcomes: changes in pigmentation	3	514	Risk Ratio (M-H, Random, 95% CI)	3.36 [0.63, 17.80]

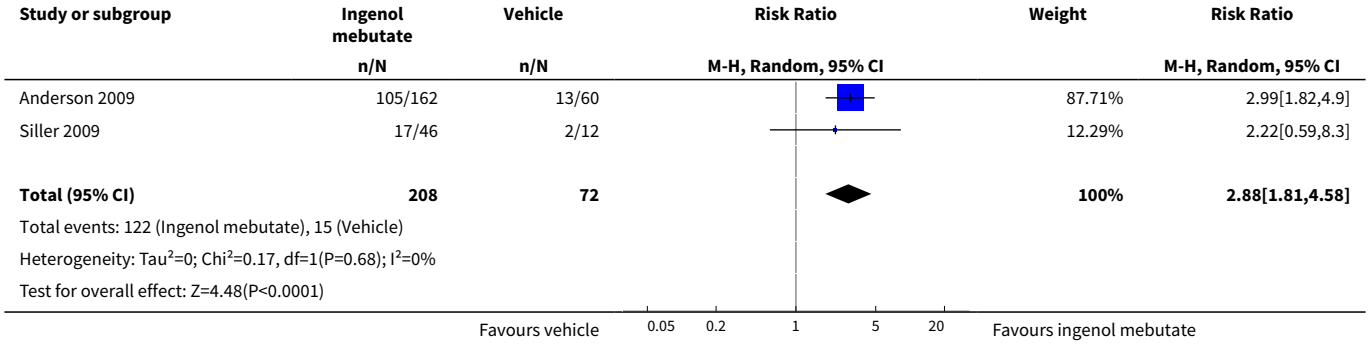
Analysis 24.1. Comparison 24 Ingenol mebutate (PEP005) versus placebo, Outcome 1 Participant complete clearance of target lesions.

Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Anderson 2009	78/162	8/60		3.61[1.86,7.02]
		Favours vehicle	0.01 0.1 1 10 100	Favours ingenol mebutate

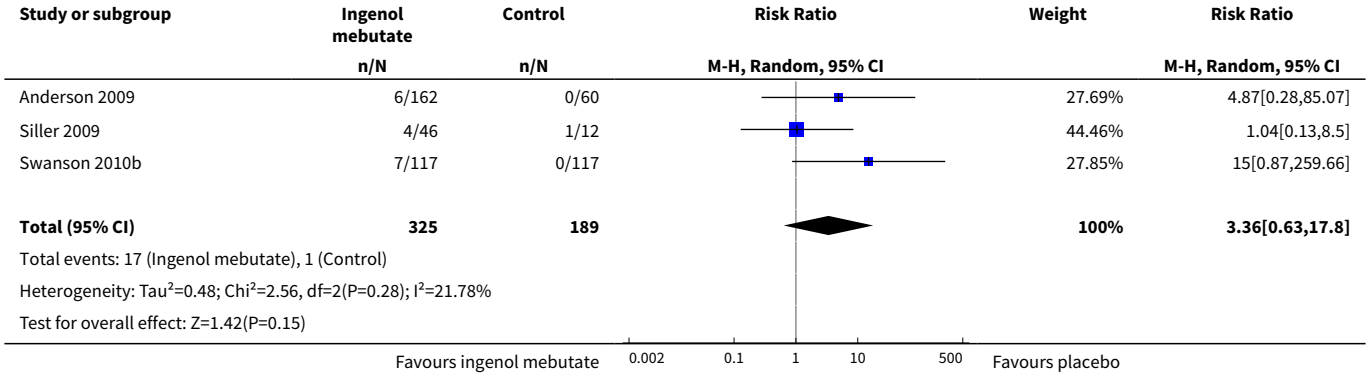
Analysis 24.2. Comparison 24 Ingenol mebutate (PEP005) versus placebo, Outcome 2 Participant complete clearance of all lesions.



Analysis 24.3. Comparison 24 Ingenol mebutate (PEP005) versus placebo, Outcome 3 Participant partial (>75%) clearance of target lesions.



Analysis 24.4. Comparison 24 Ingenol mebutate (PEP005) versus placebo, Outcome 4 Cosmetic outcomes: changes in pigmentation.

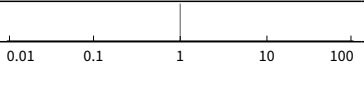


Comparison 25. Ingenol mebutate (PEP005) versus placebo: different concentrations

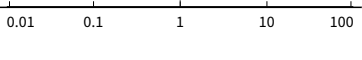
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance of target lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 0.025% 3 days	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 0.05% 2-3 days	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant complete clearance of all lesions	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 0.025% 3 days	1	70	Risk Ratio (M-H, Random, 95% CI)	4.0 [1.03, 15.55]
2.2 0.05% 2-3 days	2	386	Risk Ratio (M-H, Random, 95% CI)	5.14 [2.75, 9.62]
3 Participant partial (>75%) clearance of target lesions	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 0.0025% 2 days	1	19	Risk Ratio (M-H, Random, 95% CI)	1.33 [0.21, 8.41]
3.2 0.01% 2 days	1	20	Risk Ratio (M-H, Random, 95% CI)	0.5 [0.06, 4.23]
3.3 0.025% 3 days	1	70	Risk Ratio (M-H, Random, 95% CI)	2.8 [1.13, 6.96]
3.4 0.05% 2-3 days	2	171	Risk Ratio (M-H, Random, 95% CI)	3.34 [1.84, 6.04]
4 Cosmetic outcomes: changes in pigmentation	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 0.01% 2 days	1	20	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.08, 25.88]
4.2 0.05% 2 days	2	253	Risk Ratio (M-H, Random, 95% CI)	4.86 [0.48, 49.39]

Analysis 25.1. Comparison 25 Ingenol mebutate (PEP005) versus placebo: different concentrations, Outcome 1 Participant complete clearance of target lesions.

Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
25.1.1 0.025% 3 days				

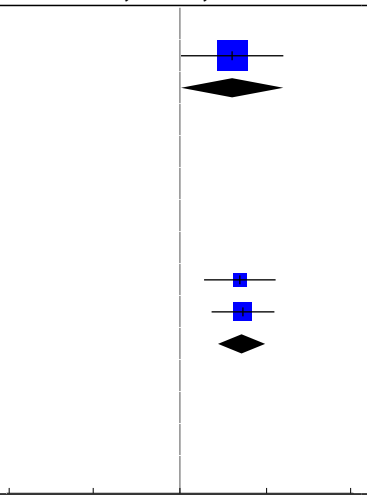


Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Anderson 2009	21/50	3/20		2.8[0.94,8.35]
25.1.2 0.05% 2-3 days				
Anderson 2009	57/112	6/40		3.39[1.59,7.25]



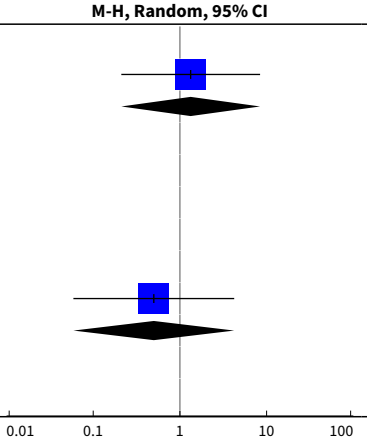
Analysis 25.2. Comparison 25 Ingenol mebutate (PEP005) versus placebo: different concentrations, Outcome 2 Participant complete clearance of all lesions.

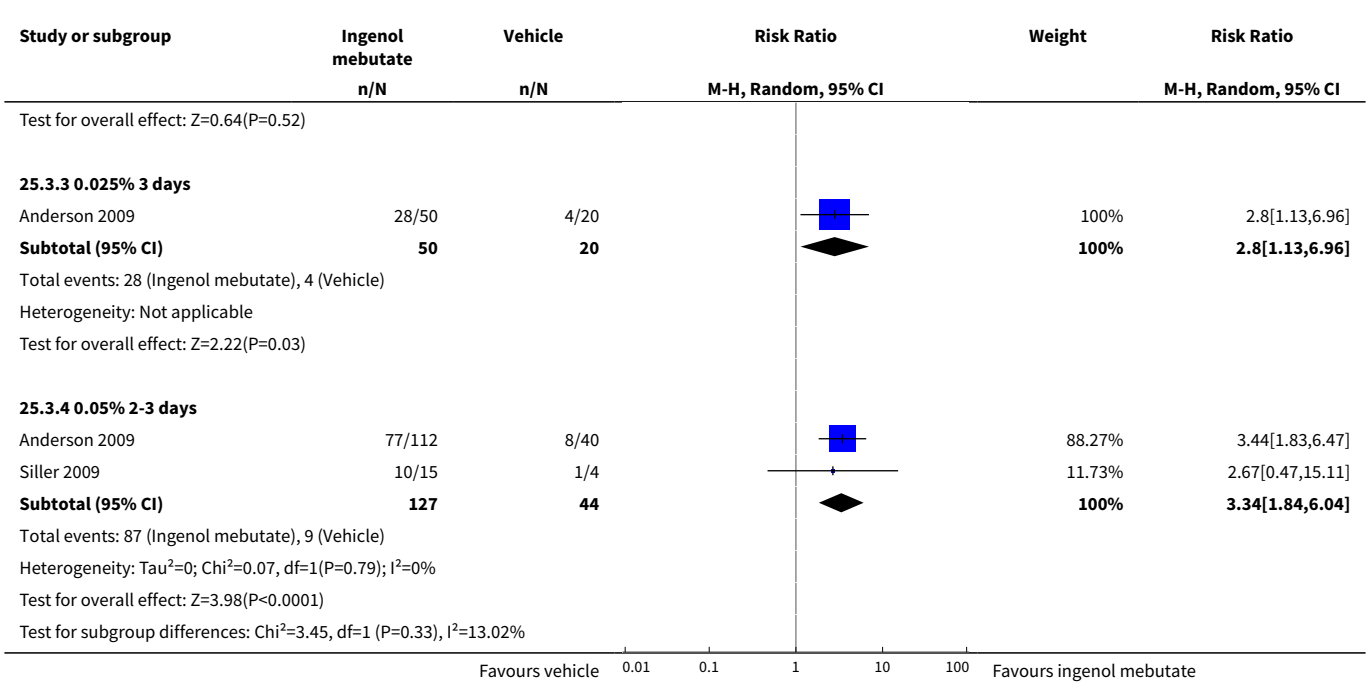
Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
25.2.1 0.025% 3 days					
Anderson 2009	20/50	2/20		100%	4[1.03,15.55]
Subtotal (95% CI)	**50**	**20**		**100%**	**4[1.03,15.55]**
Total events: 20 (Ingenol mebutate), 2 (Vehicle)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2(P=0.05)					
25.2.2 0.05% 2-3 days					
Anderson 2009	55/112	4/40		43.56%	4.91[1.9,12.68]
Swanson 2010b	32/117	6/117		56.44%	5.33[2.32,12.27]
Subtotal (95% CI)	**229**	**157**		**100%**	**5.14[2.75,9.62]**
Total events: 87 (Ingenol mebutate), 10 (Vehicle)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=5.13(P<0.0001)					
Test for subgroup differences: Chi^2=0.11, df=1 (P=0.74), I^2=0%					



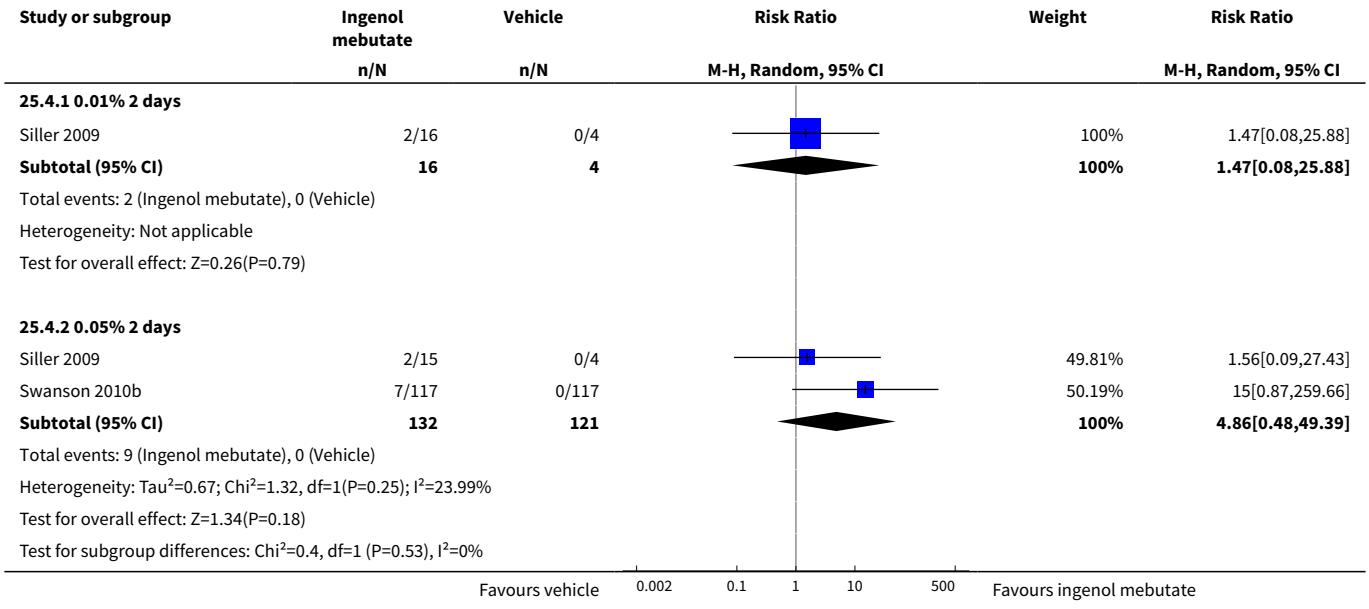
Analysis 25.3. Comparison 25 Ingenol mebutate (PEP005) versus placebo: different concentrations, Outcome 3 Participant partial (>75%) clearance of target lesions.

Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
25.3.1 0.0025% 2 days					
Siller 2009	5/15	1/4		100%	1.33[0.21,8.41]
Subtotal (95% CI)	**15**	**4**		**100%**	**1.33[0.21,8.41]**
Total events: 5 (Ingenol mebutate), 1 (Vehicle)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.76)					
25.3.2 0.01% 2 days					
Siller 2009	2/16	1/4		100%	0.5[0.06,4.23]
Subtotal (95% CI)	**16**	**4**		**100%**	**0.5[0.06,4.23]**
Total events: 2 (Ingenol mebutate), 1 (Vehicle)					
Heterogeneity: Not applicable					





Analysis 25.4. Comparison 25 Ingenol mebutate (PEP005) versus placebo: different concentrations, Outcome 4 Cosmetic outcomes: changes in pigmentation.

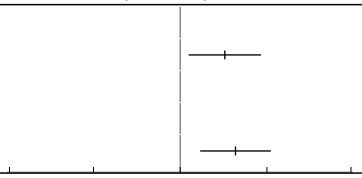


Comparison 26. 0.05% Ingenol mebutate (PEP005) versus placebo: number of doses

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance of target lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 0.05% 2 days	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 0.05% 3 days	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant complete clearance of all lesions	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 0.05% 2 days	2	319	Risk Ratio (M-H, Random, 95% CI)	4.32 [2.30, 8.11]
2.2 0.05% 3 days	1	87	Risk Ratio (M-H, Random, 95% CI)	4.08 [1.59, 10.47]
3 Participant partial (>75%) clearance of target lesions	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 0.05% 2 days	2	104	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.41, 5.00]
3.2 0.05% 3 days	1	87	Risk Ratio (M-H, Random, 95% CI)	3.23 [1.66, 6.29]

Analysis 26.1. Comparison 26 0.05% Ingenol mebutate (PEP005) versus placebo: number of doses, Outcome 1 Participant complete clearance of target lesions.

Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
26.1.1 0.05% 2 days				
Anderson 2009	24/55	4/30		3.27[1.25,8.55]
26.1.2 0.05% 3 days				
Anderson 2009	33/57	4/30		4.34[1.7,11.1]



Analysis 26.2. Comparison 26 0.05% Ingenol mebutate (PEP005) versus placebo: number of doses, Outcome 2 Participant complete clearance of all lesions.

Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
26.2.1 0.05% 2 days					
Anderson 2009	24/55	4/30		42.95%	3.27[1.25,8.55]
Swanson 2010b	32/117	6/117		57.05%	5.33[2.32,12.27]
Subtotal (95% CI)	**172**	**147**		**100%**	**4.32[2.3,8.11]**
Total events: 56 (Ingenol mebutate), 10 (Vehicle)					
Heterogeneity: Tau^2=0; Chi^2=0.57, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=4.56(P<0.0001)					
26.2.2 0.05% 3 days					
Anderson 2009	31/57	4/30		100%	4.08[1.59,10.47]
Subtotal (95% CI)	**57**	**30**		**100%**	**4.08[1.59,10.47]**
Total events: 31 (Ingenol mebutate), 4 (Vehicle)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.92(P=0)					
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.92), I^2=0%					

Analysis 26.3. Comparison 26 0.05% Ingenol mebutate (PEP005) versus placebo: number of doses, Outcome 3 Participant partial (>75%) clearance of target lesions.

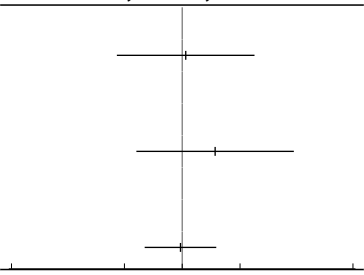
Study or subgroup	Ingenol mebutate n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
26.3.1 0.05% 2 days					
Anderson 2009	34/55	7/30		86.64%	2.65[1.34,5.24]
Siller 2009	10/15	1/4		13.36%	2.67[0.47,15.11]
Subtotal (95% CI)	**70**	**34**		**100%**	**2.65[1.41,5]**
Total events: 44 (Ingenol mebutate), 8 (Vehicle)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=3.01(P=0)					
26.3.2 0.05% 3 days					
Anderson 2009	43/57	7/30		100%	3.23[1.66,6.29]
Subtotal (95% CI)	**57**	**30**		**100%**	**3.23[1.66,6.29]**
Total events: 43 (Ingenol mebutate), 7 (Vehicle)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.46(P=0)					

Comparison 27. Isotretinoin versus vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Investigator global improvement indices-completely cleared	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Face	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Scalp	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Upper extremities	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Mean reduction of lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Face	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Scalp	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Upper extremities	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Skin irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Severe-Skin irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

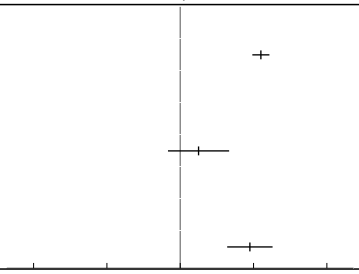
Analysis 27.1. Comparison 27 Isotretinoin versus vehicle, Outcome 1 Investigator global improvement indices-completely cleared.

Study or subgroup	Isotretinoin n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
27.1.1 Face				
Alirezai 1994	1/41	1/47		1.15[0.07,17.75]
27.1.2 Scalp				
Alirezai 1994	1/16	0/20		3.71[0.16,85.29]
27.1.3 Upper extremities				
Alirezai 1994	3/15	3/14		0.93[0.22,3.88]



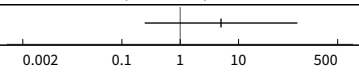
Analysis 27.2. Comparison 27 Isotretinoin versus vehicle, Outcome 2 Mean reduction of lesion counts.

Study or subgroup	Isotretinoin N	Isotretinoin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
27.2.1 Face						
Alirezai 1994	41	3.9 (0.6)	47	1.7 (0.5)		2.2[1.97,2.43]
27.2.2 Scalp						
Alirezai 1994	16	4.1 (1.5)	20	3.6 (0.9)		0.5[-0.33,1.33]
27.2.3 Upper extremities						
Alirezai 1994	15	2.9 (0.9)	14	1 (0.8)		1.9[1.28,2.52]



Analysis 27.3. Comparison 27 Isotretinoin versus vehicle, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Isotretinoin n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Alirezai 1994	2/50	0/50		5[0.25,101.58]



Analysis 27.4. Comparison 27 Isotretinoin versus vehicle, Outcome 4 Skin irritation.

Study or subgroup	Isotretinoin n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Alirezai 1994	40/43	29/49		1.57[1.23,2.01]

Analysis 27.5. Comparison 27 Isotretinoin versus vehicle, Outcome 5 Severe-Skin irritation.

Study or subgroup	Isotretinoin n/N	Vehicle n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Alirezai 1994	15/43	1/49		17.09[2.35,124.1]

Comparison 28. Masoprocol versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global improvement indices-cured	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 28.1. Comparison 28 Masoprocol versus placebo, Outcome 1 Global improvement indices-cured.

Study or subgroup	Masoprocol n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Olsen 1991	12/113	2/41		2.18[0.51,9.31]
		Favours placebo	0.1 0.2 0.5 1 2 5 10	Favours masoprocol

Analysis 28.2. Comparison 28 Masoprocol versus placebo, Outcome 2 Mean reduction in lesion counts.

Study or subgroup	masprocol N	masprocol Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Olsen 1991	113	9.6 (5.6)	41	2.3 (3.7)		7.3[5.77,8.83]
				Favours vehicle	-10 -5 0 5 10	Favours masoprocol

Analysis 28.3. Comparison 28 Masoprocol versus placebo, Outcome 3 Withdrawal due to adverse events.

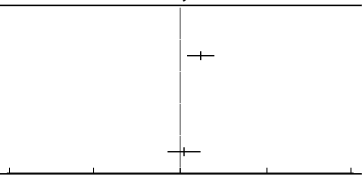
Study or subgroup	Masoprocol n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Olsen 1991	2/131	0/45		1.74[0.09,35.62]
		Favours masoprocol	0.01 0.1 1 10 100	Favours placebo

Comparison 29. 1% nicotinamide versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mean percentage of reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 At 3 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 months	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

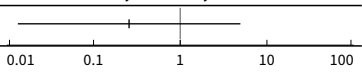
Analysis 29.1. Comparison 29 1% nicotinamide versus placebo, Outcome 1 Mean percentage of reduction in lesion counts.

Study or subgroup	nicotinamide N	nicotinamide Mean(SD)	placebo N	placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
29.1.1 At 3 months						
Moloney 2010	13	21.8 (10)	17	10 (12)		11.8[3.92,19.68]
29.1.2 At 6 months						
Moloney 2010	13	24.6 (15.4)	17	22.4 (9.6)		2.2[-7.33,11.73]



Analysis 29.2. Comparison 29 1% nicotinamide versus placebo, Outcome 2 Withdrawal due to adverse events.

Study or subgroup	nicotinamide n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Moloney 2010	0/13	2/17		0.26[0.01,4.94]



Comparison 30. 0.1% resiquimod versus 0.01% resiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After 1 cycle	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Minor adverse events excluding skin irritation: body as a whole: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Minor adverse events excluding skin irritation: body as a whole: rigors	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse events excluding skin irritation: nervous system: lethargy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 30.1. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 1 Participant complete clearance.

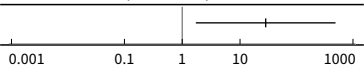
Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
30.1.1 After 1 cycle				
Szeimies 2008	34/34	14/35		2.45[1.64,3.65]
30.1.2 After 1 or 2 cycles				
Szeimies 2008	29/34	27/35		1.11[0.88,1.39]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 30.2. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
30.2.1 After 1 or 2 cycles				
Szeimies 2008	26/34	22/35		1.22[0.89,1.67]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

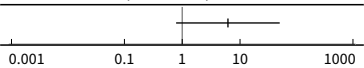
Analysis 30.3. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	13/34	0/35		27.77[1.72,449.47]



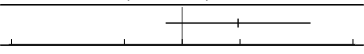
Analysis 30.4. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 4 Minor adverse events excluding skin irritation: body as a whole: fatigue.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	6/34	1/35		6.18[0.78,48.64]



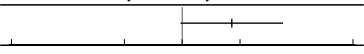
Analysis 30.5. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 5 Minor adverse events excluding skin irritation: body as a whole: rigors.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/34	0/35		9.26[0.52,165.65]



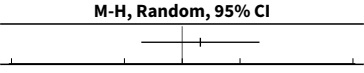
Analysis 30.6. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	7/34	1/35		7.21[0.94,55.5]



Analysis 30.7. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	2/34	1/35		2.06[0.2,21.67]



Analysis 30.8. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/34	0/35		11.31[0.65,197.06]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 30.9. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 9 Minor adverse events excluding skin irritation: nervous system: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	10/34	1/35		10.29[1.39,76.12]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 30.10. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 10 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	7/34	0/35		15.43[0.92,260.05]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 30.11. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 11 Minor adverse events excluding skin irritation: nervous system: lethargy.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/34	0/35		9.26[0.52,165.65]

Favours higher 0.001 0.1 1 10 1000 Favours lower

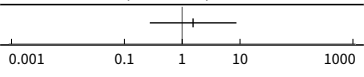
Analysis 30.12. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/34	1/35		3.09[0.34,28.25]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 30.13. Comparison 30 0.1% resiquimod versus 0.01% resiquimod, Outcome 13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/34	2/35		1.54[0.27,8.67]



Comparison 31. 0.1% resiquimod versus 0.03% resiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After 1 cycle	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Minor adverse events excluding skin irritation: body as a whole: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Minor adverse events excluding skin irritation: body as a whole: rigors	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse events excluding skin irritation: nervous system: lethargy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 31.1. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 1 Participant complete clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
31.1.1 After 1 cycle				
Szeimies 2008	34/34	23/31		1.34[1.09,1.66]
31.1.2 After 1 or 2 cycles				
Szeimies 2008	29/34	28/31		0.94[0.79,1.13]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 31.2. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 2 Participant partial (>75%) clearance.

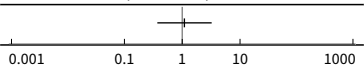
Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
31.2.1 After 1 or 2 cycles				
Szeimies 2008	26/34	25/31		0.95[0.74,1.22]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 31.3. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	13/34	4/31		2.96[1.08,8.13]
		Favours higher dose	0.1 0.2 0.5 1 2 5 10	Favours lower dose

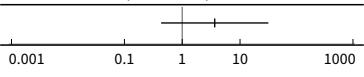
Analysis 31.4. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 4 Minor adverse events excluding skin irritation: body as a whole: fatigue.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	6/34	5/31		1.09[0.37,3.23]



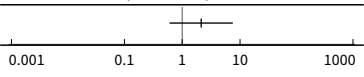
Analysis 31.5. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 5 Minor adverse events excluding skin irritation: body as a whole: rigors.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/34	1/31		3.65[0.43,30.89]



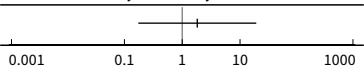
Analysis 31.6. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	7/34	3/31		2.13[0.6,7.51]



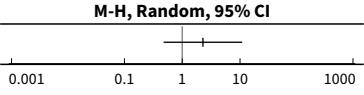
Analysis 31.7. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	2/34	1/31		1.82[0.17,19.13]



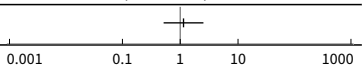
Analysis 31.8. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/34	2/31		2.28[0.48,10.91]



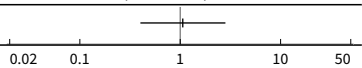
Analysis 31.9. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 9 Minor adverse events excluding skin irritation: nervous system: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	10/34	8/31		1.14[0.52,2.52]



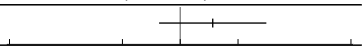
Analysis 31.10. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 10 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	7/34	6/31		1.06[0.4,2.82]



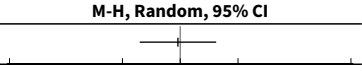
Analysis 31.11. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 11 Minor adverse events excluding skin irritation: nervous system: lethargy.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/34	1/31		3.65[0.43,30.89]



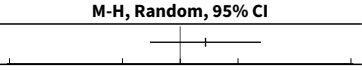
Analysis 31.12. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/34	3/31		0.91[0.2,4.19]



Analysis 31.13. Comparison 31 0.1% resiquimod versus 0.03% resiquimod, Outcome 13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/34	1/31		2.74[0.3,24.94]



Comparison 32. 0.1% resiquimod versus 0.06% resiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After 1 cycle	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Minor adverse events excluding skin irritation: body as a whole: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Minor adverse events excluding skin irritation: body as a whole: rigors	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse events excluding skin irritation: nervous system: lethargy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 32.1. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 1 Participant complete clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
32.1.1 After 1 cycle				
Szeimies 2008	34/34	18/32		1.76[1.3,2.38]
32.1.2 After 1 or 2 cycles				
Szeimies 2008	29/34	25/32		1.09[0.87,1.37]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 32.2. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
32.2.1 After 1 or 2 cycles				
Szeimies 2008	26/34	20/32		1.22[0.88,1.7]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 32.3. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	13/34	10/32		1.22[0.63,2.39]
		Favours higher dose	0.1 0.2 0.5 1 2 5 10	Favours lower dose

Analysis 32.4. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 4 Minor adverse events excluding skin irritation: body as a whole: fatigue.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	6/34	3/32		1.88[0.51,6.9]
		Favours higher	0.001 0.1 1 10 1000	Favours lower

Analysis 32.5. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 5 Minor adverse events excluding skin irritation: body as a whole: rigors.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/34	5/32		0.75[0.22,2.56]
		Favours higher	0.001 0.1 1 10 1000	Favours lower

Analysis 32.6. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	7/34	6/32		1.1[0.41,2.92]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 32.7. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	2/34	5/32		0.38[0.08,1.8]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 32.8. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/34	2/32		2.35[0.49,11.28]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 32.9. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 9 Minor adverse events excluding skin irritation: nervous system: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	10/34	10/32		0.94[0.45,1.96]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 32.10. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 10 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	7/34	8/32		0.82[0.34,2.01]

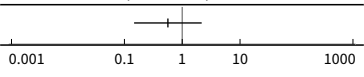
Favours higher 0.05 0.2 1 5 20 Favours lower

Analysis 32.11. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 11 Minor adverse events excluding skin irritation: nervous system: lethargy.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/34	4/32		0.94[0.26,3.45]

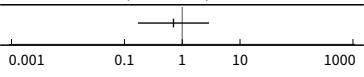
Analysis 32.12. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/34	5/32		0.56[0.15,2.17]



Analysis 32.13. Comparison 32 0.1% resiquimod versus 0.06% resiquimod, Outcome 13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/34	4/32		0.71[0.17,2.91]



Comparison 33. 0.06% resiquimod versus 0.01% resiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After 1 cycle	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Minor adverse events excluding skin irritation: body as a whole: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Minor adverse events excluding skin irritation: body as a whole: rigors	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse events excluding skin irritation: nervous system: lethargy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 33.1. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 1 Participant complete clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
33.1.1 After 1 cycle				
Szeimies 2008	18/32	14/35		1.41[0.85,2.34]
33.1.2 After 1 or 2 cycles				
Szeimies 2008	25/32	27/35		1.01[0.78,1.31]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 33.2. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
33.2.1 After 1 or 2 cycles				
Szeimies 2008	20/32	22/35		0.99[0.69,1.44]

Favours lower dose — 0.5 0.7 1 1.5 2 — Favours higher dose

Analysis 33.3. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	10/32	0/35		22.91[1.4,375.77]

Favours higher dose — 0.001 0.1 1 10 1000 — Favours lower dose

Analysis 33.4. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 4 Minor adverse events excluding skin irritation: body as a whole: fatigue.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/32	1/35		3.28[0.36,29.97]

Favours higher — 0.001 0.1 1 10 1000 — Favours lower

Analysis 33.5. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 5 Minor adverse events excluding skin irritation: body as a whole: rigors.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/32	0/35		12[0.69,208.76]

Favours higher — 0.001 0.1 1 10 1000 — Favours lower

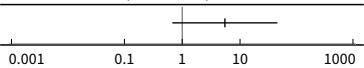
Analysis 33.6. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	6/32	1/35		6.56[0.83,51.59]

Favours higher — 0.001 0.1 1 10 1000 — Favours lower

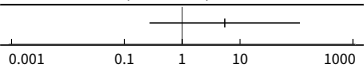
Analysis 33.7. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/32	1/35		5.47[0.67,44.34]



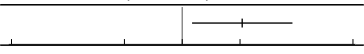
Analysis 33.8. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	2/32	0/35		5.45[0.27,109.49]



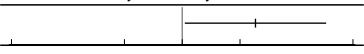
Analysis 33.9. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 9 Minor adverse events excluding skin irritation: nervous system: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	10/32	1/35		10.94[1.48,80.73]



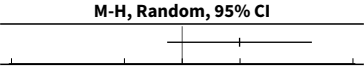
Analysis 33.10. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 10 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	8/32	0/35		18.55[1.11,308.9]



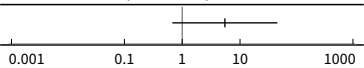
Analysis 33.11. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 11 Minor adverse events excluding skin irritation: nervous system: lethargy.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/32	0/35		9.82[0.55,175.48]



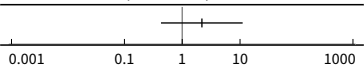
Analysis 33.12. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/32	1/35		5.47[0.67,44.34]



Analysis 33.13. Comparison 33 0.06% resiquimod versus 0.01% resiquimod, Outcome 13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/32	2/35		2.19[0.43,11.15]



Comparison 34. 0.06% resiquimod versus 0.03% resiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After 1 cycle	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Minor adverse events excluding skin irritation: body as a whole: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Minor adverse events excluding skin irritation: body as a whole: rigors	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse events excluding skin irritation: nervous system: lethargy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse events excluding skin irritation:skin and subcutaneous disorders: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 34.1. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 1 Participant complete clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
34.1.1 After 1 cycle				
Szeimies 2008	18/32	23/31		0.76[0.52,1.1]
34.1.2 After 1 or 2 cycles				
Szeimies 2008	25/32	28/31		0.86[0.7,1.07]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 34.2. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
34.2.1 After 1 or 2 cycles				
Szeimies 2008	20/32	25/31		0.78[0.56,1.07]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 34.3. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	10/32	4/31		2.42[0.85,6.91]

Favours higher dose 0.001 0.1 1 10 1000 Favours lower dose

Analysis 34.4. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 4 Minor adverse events excluding skin irritation: body as a whole: fatigue.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/32	5/31		0.58[0.15,2.23]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.5. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 5 Minor adverse events excluding skin irritation: body as a whole: rigors.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/32	1/31		4.84[0.6,39.14]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.6. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	6/32	3/31		1.94[0.53,7.07]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.7. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/32	1/31		4.84[0.6,39.14]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.8. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	2/32	2/31		0.97[0.15,6.46]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.9. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 9 Minor adverse events excluding skin irritation: nervous system: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	10/32	8/31		1.21[0.55,2.66]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.10. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 10 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	8/32	6/31		1.29[0.51,3.29]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.11. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 11 Minor adverse events excluding skin irritation: nervous system: lethargy.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/32	1/31		3.88[0.46,32.77]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.12. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/32	3/31		1.61[0.42,6.19]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Analysis 34.13. Comparison 34 0.06% resiquimod versus 0.03% resiquimod, Outcome 13 Minor adverse events excluding skin irritation:skin and subcutaneous disorders: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/32	1/31		3.88[0.46,32.77]

Favours higher 0.001 0.1 1 10 1000 Favours lower

Comparison 35. 0.03% resiquimod versus 0.01% resiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After 1 cycle	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 After 1 or 2 cycles	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Minor adverse events excluding skin irritation: body as a whole: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Minor adverse events excluding skin irritation: body as a whole: rigors	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: nervous system: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse events excluding skin irritation: nervous system: lethargy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 35.1. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 1 Participant complete clearance.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
35.1.1 After 1 cycle				
Szeimies 2008	23/31	14/35		1.85[1.18,2.93]
35.1.2 After 1 or 2 cycles				
Szeimies 2008	28/31	27/35		1.17[0.95,1.45]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 35.2. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 2 Participant partial (>75%) clearance.

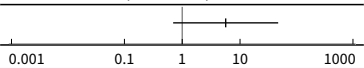
Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
35.2.1 After 1 or 2 cycles				
Szeimies 2008	25/31	22/35		1.28[0.94,1.75]
		Favours lower dose	0.5 0.7 1 1.5 2	Favours higher dose

Analysis 35.3. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	4/31	0/35		10.13[0.57,180.85]
		Favours higher dose	0.001 0.1 1 10 1000	Favours lower dose

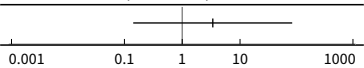
Analysis 35.4. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 4 Minor adverse events excluding skin irritation: body as a whole: fatigue.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	5/31	1/35		5.65[0.7,45.73]



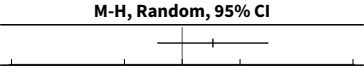
Analysis 35.5. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 5 Minor adverse events excluding skin irritation: body as a whole: rigors.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	1/31	0/35		3.38[0.14,79.95]



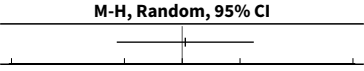
Analysis 35.6. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 6 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/31	1/35		3.39[0.37,30.9]



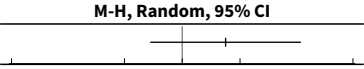
Analysis 35.7. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 7 Minor adverse events excluding skin irritation:musculoskeletal and connective tissue: arthralgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	1/31	1/35		1.13[0.07,17.3]



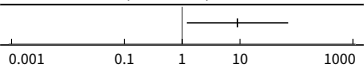
Analysis 35.8. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 8 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	2/31	0/35		5.63[0.28,112.84]



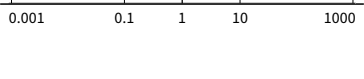
Analysis 35.9. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 9 Minor adverse events excluding skin irritation: nervous system: in general.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	8/31	1/35		9.03[1.2,68.22]



Analysis 35.10. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 10 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	6/31	0/35		14.63[0.86,249.51]



Analysis 35.11. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 11 Minor adverse events excluding skin irritation: nervous system: lethargy.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	1/31	0/35		3.38[0.14,79.95]

Analysis 35.12. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 12 Minor adverse events excluding skin irritation: nervous system: psychiatric disorders.

Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	3/31	1/35		3.39[0.37,30.9]

Analysis 35.13. Comparison 35 0.03% resiquimod versus 0.01% resiquimod, Outcome 13 Minor adverse events excluding skin irritation: skin and subcutaneous disorders: in general.

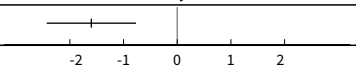
Study or subgroup	Higher dose n/N	Lower dose n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2008	1/31	2/35		0.56[0.05,5.93]

Comparison 36. Sunscreen SPF 17 (8% 2-ethyl-hexyl p-methoxycinnamate/2% 4-tert-butyl-4-methoxy-4-dibenzoylmethane) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean change in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 36.1. Comparison 36 Sunscreen SPF 17 (8% 2-ethyl-hexyl p-methoxycinnamate/2% 4-tert-butyl-4-methoxy-4-dibenzoylmethane) versus placebo, Outcome 1 Mean change in lesion counts.

Study or subgroup	Sunscreen		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Thompson 1993	210	-0.6 (4.3)	221	1 (4.5)		-1.6[-2.43,-0.77]

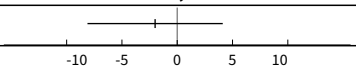


Comparison 37. 12.5% DL-α-tocopherol (vitamin E) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction of lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 37.1. Comparison 37 12.5% DL-α-tocopherol (vitamin E) versus placebo, Outcome 1 Mean reduction of lesion counts.

Study or subgroup	DL-α-tocophero		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Foote 2009	42	6 (14.3)	42	8 (14.3)		-2[-8.12,4.12]



Comparison 38. Etretinate versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 38.1. Comparison 38 Etretinate versus placebo, Outcome 1 Participant complete clearance.

Study or subgroup	etretinate n/N	placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Moriarty 1982	5/25	0/25		11[0.64,188.95]
		Favours placebo	0.005 0.1 1 10 200	Favours etretinate

Comparison 39. Carbon dioxide laser resurfacing versus 5% 5-FU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of reduction of lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 39.1. Comparison 39 Carbon dioxide laser resurfacing versus 5% 5-FU, Outcome 1 Mean percentage of reduction of lesion counts.

Study or subgroup	Resurfacing N	Resurfacing Mean(SD)	5% 5-FU N	5% 5-FU Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Hantash 2006	6	92 (10.3)	8	83.2 (12.5)		8.8[-3.16,20.76]
				Favours 5-FU	-20 -10 0 10 20	Favours resurfacing

Analysis 39.2. Comparison 39 Carbon dioxide laser resurfacing versus 5% 5-FU, Outcome 2 Withdrawal due to adverse events.

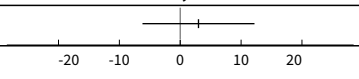
Study or subgroup	Resurfacing n/N	5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hantash 2006	2/8	0/9		5.56[0.31,100.94]
		Favours laser resurfacing	0.005 0.1 1 10 200	Favours 5-FU

Comparison 40. Carbon dioxide laser resurfacing versus Trichloroacetic acid peel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of reduction of lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

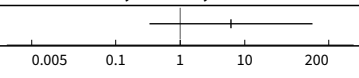
Analysis 40.1. Comparison 40 Carbon dioxide laser resurfacing versus Trichloroacetic acid peel, Outcome 1 Mean percentage of reduction of lesion counts.

Study or subgroup	Resurfacing		Peel		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Hantash 2006	6	92 (10.3)	10	89 (6.6)		3[-6.2,12.2]



Analysis 40.2. Comparison 40 Carbon dioxide laser resurfacing versus Trichloroacetic acid peel, Outcome 2 Withdrawal due to adverse events.

Study or subgroup	Resurfacing	Peel	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Hantash 2006	2/8	0/10		6.11[0.33,111.71]



Comparison 41. Er:YAG laser resurfacing versus 5% 5-FU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in lesion counts			Other data	No numeric data
2 Mean percentage of reduction in lesion counts			Other data	No numeric data
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Skin irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 At the end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Minor adverse events excluding skin irritation: dermatology: acne	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.3 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Minor adverse events excluding skin irritation: dermatology:crustea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 At the end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.4 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Minor adverse events excluding skin irritation: dermatology: infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 At the end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Minor adverse events excluding skin irritation: dermatology: milia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.3 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Minor adverse events excluding skin irritation: dermatology:pain	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 At the end of treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.2 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Cosmetic outcomes: changes in pigmentation (hypo)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10.2 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Cosmetic outcomes: scarring	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.2 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Cosmetic outcomes: improvement in photoageing score	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.2 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12.3 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 41.1. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 1 Mean reduction in lesion counts.

		Mean reduction in lesion counts		
Study	Intervention	At 3 months	At 6 months	At 12 months
Ostertag 2006	5-fluorouracil	13.2	12.5	12.4
Ostertag 2006	Er:YAG laser resurfacing	13.8	13.9	14.2

Analysis 41.2. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 2 Mean percentage of reduction in lesion counts.

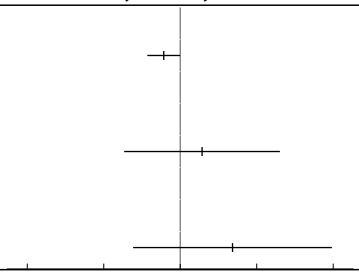
		Mean percentage of reduction in lesion counts	
Study	Assessment	Resurfacing	5-FU
Ostertag 2006	At 6 months	94.4%	79.2%
Ostertag 2006	At 12 months	91.1%	76.6%

Analysis 41.3. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Ostertag 2006	0/28	1/27		0.32[0.01,7.57]

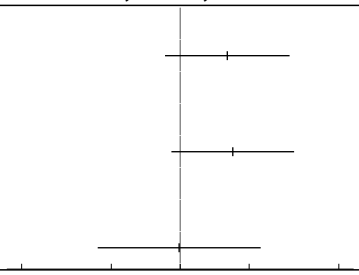
Analysis 41.4. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 4 Skin irritation.

Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
41.4.1 At the end of treatment				
Ostertag 2006	12/28	19/27		0.61[0.37,1]
41.4.2 At 3 months				
Ostertag 2006	2/28	1/27		1.93[0.19,20.05]
41.4.3 At 6 months				
Ostertag 2006	2/28	0/27		4.83[0.24,96.16]



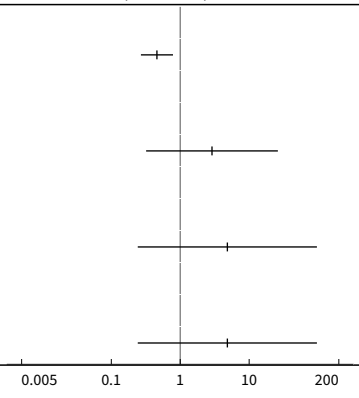
Analysis 41.5. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 5 Minor adverse events excluding skin irritation: dermatology: acne.

Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
41.5.1 At 3 months				
Ostertag 2006	5/28	1/27		4.82[0.6,38.63]
41.5.2 At 6 months				
Ostertag 2006	6/28	1/27		5.79[0.74,44.94]
41.5.3 At 12 months				
Ostertag 2006	1/28	1/27		0.96[0.06,14.65]



Analysis 41.6. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 6 Minor adverse events excluding skin irritation: dermatology:crustea.

Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
41.6.1 At the end of treatment				
Ostertag 2006	10/28	21/27		0.46[0.27,0.79]
41.6.2 At 3 months				
Ostertag 2006	3/28	1/27		2.89[0.32,26.12]
41.6.3 At 6 months				
Ostertag 2006	2/28	0/27		4.83[0.24,96.16]
41.6.4 At 12 months				
Ostertag 2006	2/28	0/27		4.83[0.24,96.16]

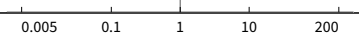


Analysis 41.7. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 7 Minor adverse events excluding skin irritation: dermatology: infection.

Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
41.7.1 At the end of treatment				
Ostertag 2006	4/28	0/27		8.69[0.49,154.06]

Analysis 41.8. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 8 Minor adverse events excluding skin irritation: dermatology: milia.

Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
41.8.1 At 3 months				
Ostertag 2006	2/28	0/27		4.83[0.24,96.16]
41.8.2 At 6 months				
Ostertag 2006	4/28	0/27		8.69[0.49,154.06]
41.8.3 At 12 months				
Ostertag 2006	2/28	0/27		4.83[0.24,96.16]

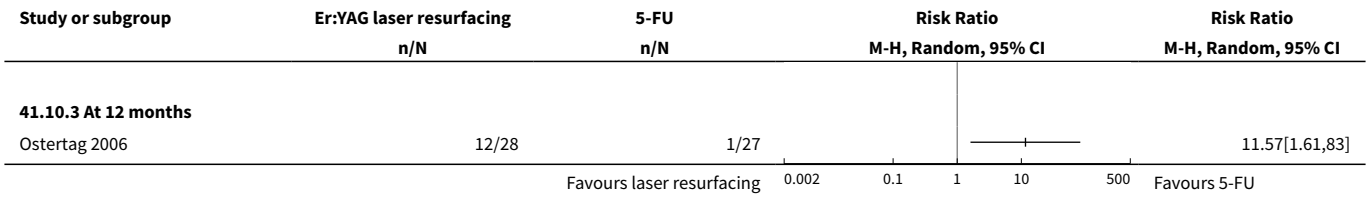


Analysis 41.9. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 9 Minor adverse events excluding skin irritation: dermatology:pain.

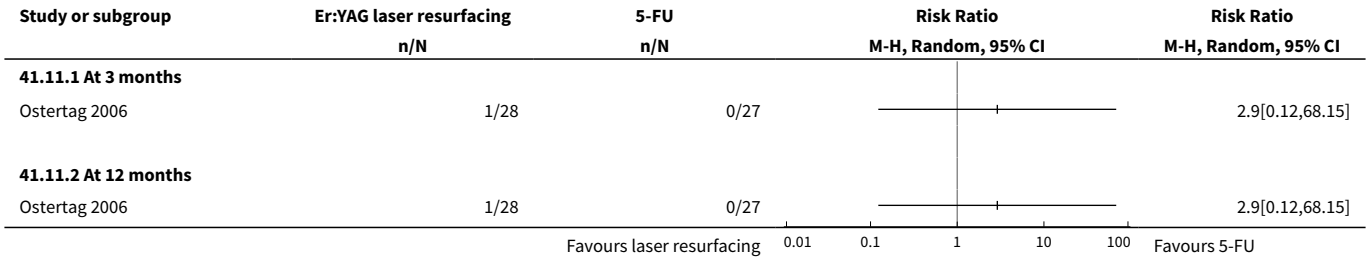
Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
41.9.1 At the end of treatment				
Ostertag 2006	6/28	8/27		0.72[0.29,1.81]
41.9.2 At 3 months				
Ostertag 2006	2/28	1/27		1.93[0.19,20.05]

Analysis 41.10. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 10 Cosmetic outcomes: changes in pigmentation (hypo).

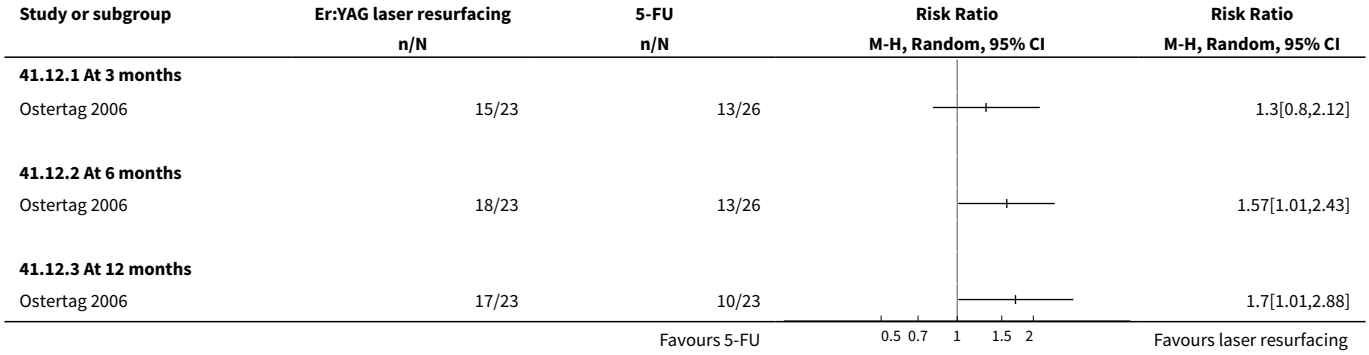
Study or subgroup	Er:YAG laser resurfacing n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
41.10.1 At 3 months				
Ostertag 2006	1/28	0/27		2.9[0.12,68.15]
41.10.2 At 6 months				
Ostertag 2006	5/28	0/27		10.62[0.62,183.26]



Analysis 41.11. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 11 Cosmetic outcomes: scarring.



Analysis 41.12. Comparison 41 Er:YAG laser resurfacing versus 5% 5-FU, Outcome 12 Cosmetic outcomes: improvement in photoageing score.



Comparison 42. Cryotherapy versus betulin-based oleogel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 42.1. Comparison 42 Cryotherapy versus betulin-based oleogel, Outcome 1 Participant complete clearance.

Study or subgroup	Cryotherapy n/N	Betulin-based oleogel n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Huyke 2009	11/14	9/14		1.22[0.76,1.97]
		Favours oleogel	0.5 0.7 1 1.5 2	Favours cryotherapy

Analysis 42.2. Comparison 42 Cryotherapy versus betulin-based oleogel, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Cryotherapy n/N	Betulin-based oleogel n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Huyke 2009	13/14	12/14		1.08[0.84,1.4]
		Favours oleogel	0.5 0.7 1 1.5 2	Favours cryotherapy

Comparison 43. Cryotherapy versus 5% 5-FU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 After treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Cosmetic outcomes: excellent global cosmetic outcome	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Cosmetic outcomes: better skin appearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 43.1. Comparison 43 Cryotherapy versus 5% 5-FU, Outcome 1 Participant complete clearance.

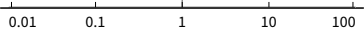
Study or subgroup	Cryotherapy n/N	5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
43.1.1 After treatment				
Krawtchenko 2007	17/25	23/24		0.71[0.54,0.94]
43.1.2 At 12 months				
Krawtchenko 2007	1/25	8/24		0.12[0.02,0.89]
		Favours 5% 5-FU	0.02 0.1 1 10 50	Favours cryotherapy

Analysis 43.2. Comparison 43 Cryotherapy versus 5% 5-FU, Outcome 2 Cosmetic outcomes: excellent global cosmetic outcome.

Study or subgroup	Cryotherapy n/N	5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	1/25	1/24		0.96[0.06,14.5]

Analysis 43.3. Comparison 43 Cryotherapy versus 5% 5-FU, Outcome 3 Cosmetic outcomes: better skin appearance.

Study or subgroup	Cryotherapy n/N	5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	4/25	14/24		0.27[0.11,0.72]



Comparison 44. Cryotherapy versus imiquimod

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Cosmetic outcomes: excellent global cosmetic outcome	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Cosmetic outcomes: better skin appearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 44.1. Comparison 44 Cryotherapy versus imiquimod, Outcome 1 Participant complete clearance.

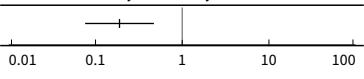
Study or subgroup	Cryotherapy n/N	Imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
44.1.1 5% imiquimod				
Krawtchenko 2007	17/25	22/26		0.8[0.59,1.1]

Analysis 44.2. Comparison 44 Cryotherapy versus imiquimod, Outcome 2 Cosmetic outcomes: excellent global cosmetic outcome.

Study or subgroup	Cryotherapy n/N	Imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	1/25	21/26		0.05[0.01,0.34]

Analysis 44.3. Comparison 44 Cryotherapy versus imiquimod, Outcome 3 Cosmetic outcomes: better skin appearance.

Study or subgroup	Cryotherapy n/N	Imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Krawtchenko 2007	4/25	22/26		0.19[0.08,0.47]



Comparison 45. Cryotherapy versus MAL-red light PDT

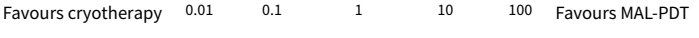
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of reduction in lesion counts			Other data	No numeric data
2 Withdrawal due to adverse events	2	379	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.16, 7.16]
3 Cosmetic outcomes: excellent or good cosmetic outcomes by investigator	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Cosmetic outcomes: excellent or good cosmetic outcomes by participant	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Analysis 45.1. Comparison 45 Cryotherapy versus MAL-red light PDT, Outcome 1 Mean percentage of reduction in lesion counts.

		Mean percentage of reduction in lesion counts	
Study	Assessment at	Cryotherapy	MAL-PDT
Kaufmann 2008	12 weeks	N/A	N/A
Kaufmann 2008	24 weeks	87%	75%
Morton 2006	12 weeks	74.5%	84.4%
Morton 2006	24 weeks	83.9%	86.7%

Analysis 45.2. Comparison 45 Cryotherapy versus MAL-red light PDT, Outcome 2 Withdrawal due to adverse events.

Study or subgroup	Cryotherapy n/N	MAL-PDT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Freeman 2003	0/89	1/88		35.89%	0.33[0.01,7.98]
Szeimies 2002	2/100	1/102		64.11%	2.04[0.19,22.14]
Total (95% CI)	**189**	**190**		**100%**	**1.06[0.16,7.16]**
Total events: 2 (Cryotherapy), 2 (MAL-PDT)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.06(P=0.95)					



Analysis 45.3. Comparison 45 Cryotherapy versus MAL-red light PDT, Outcome 3 Cosmetic outcomes: excellent or good cosmetic outcomes by investigator.

Study or subgroup	Cryotherapy n/N	MAL-PDT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Szeimies 2002	55/68	52/54		0%	0.84[0.74,0.95]

Favours MAL-PDT 0.5 0.7 1 1.5 2 Favours cryotherapy

Analysis 45.4. Comparison 45 Cryotherapy versus MAL-red light PDT, Outcome 4 Cosmetic outcomes: excellent or good cosmetic outcomes by participant.

Study or subgroup	Cryotherapy n/N	MAL-PDT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Szeimies 2002	62/68	53/54		0%	0.93[0.86,1.01]

Favours MAL-PDT 0.5 0.7 1 1.5 2 Favours cryotherapy

Comparison 46. Cryotherapy versus ALA-red light PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Skin irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 During treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 One day after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 46.1. Comparison 46 Cryotherapy versus ALA-red light PDT, Outcome 1 Participant complete clearance.

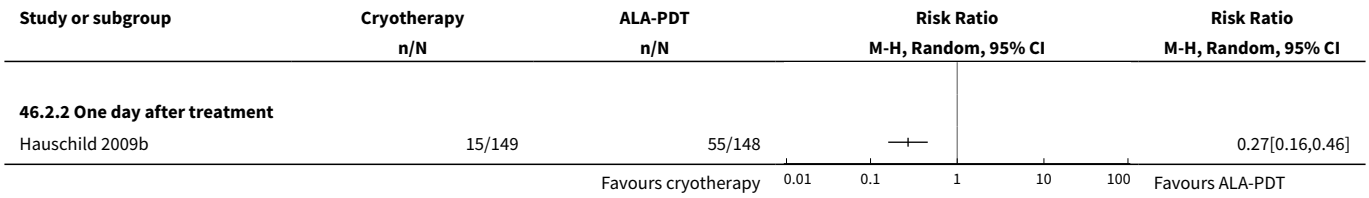
Study or subgroup	Cryotherapy n/N	ALA-PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hauschild 2009b	66/149	86/148		0.76[0.61,0.96]

Favours ALA-PDT 0.5 0.7 1 1.5 2 Favours cryotherapy

Analysis 46.2. Comparison 46 Cryotherapy versus ALA-red light PDT, Outcome 2 Skin irritation.

Study or subgroup	Cryotherapy n/N	ALA-PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
46.2.1 During treatment				
Hauschild 2009b	80/149	126/148		0.63[0.54,0.74]

Favours cryotherapy 0.01 0.1 1 10 100 Favours ALA-PDT



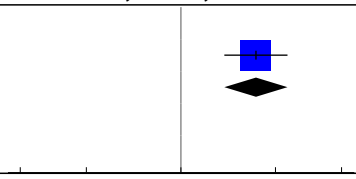
Comparison 47. ALA-PDT versus placebo-PDT

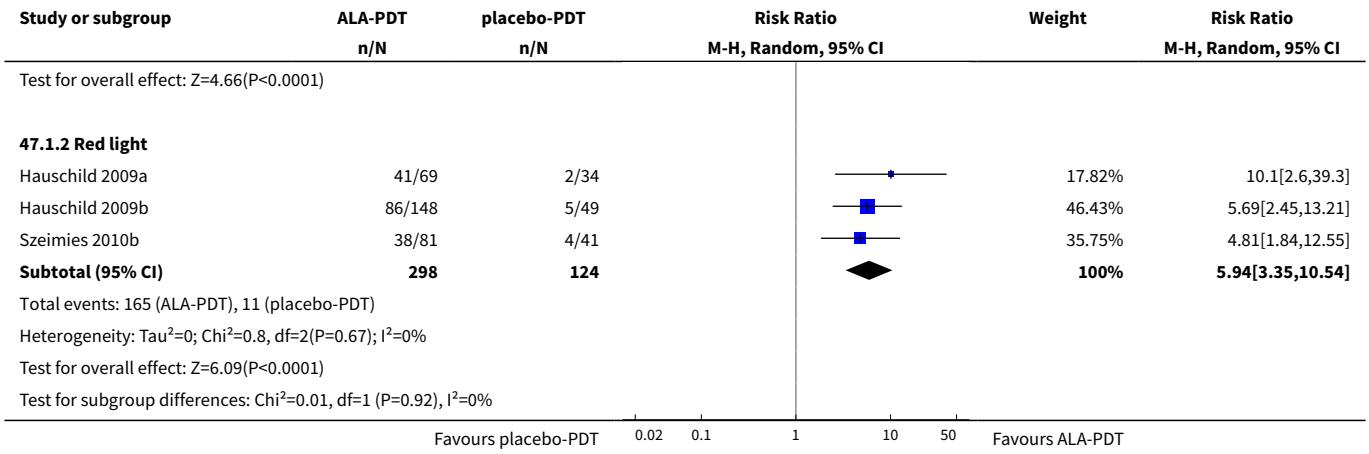
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance [1 treatment]	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Blue light	1	243	Risk Ratio (M-H, Random, 95% CI)	6.22 [2.88, 13.43]
1.2 Red light	3	422	Risk Ratio (M-H, Random, 95% CI)	5.94 [3.35, 10.54]
2 Participant complete clearance [1 or 2 treatments]	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Red light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Participant complete clearance [1 or 2 treatments] by anatomical location	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Face	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Scalp	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Participant partial (> 75%) clearance [1 treatment]	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Participant partial (>75%) clearance[1 or 2 treatments]	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Participant partial (>75%) clearance [1 or 2 treatment] by anatomical location	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Face	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Scalp	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Skin irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Red light-during illumination	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Red light-after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Minor adverse events excluding skin irritation: body as a whole: injury	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Minor adverse events excluding skin irritation: cardiovascular: hypertension	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Minor adverse events excluding skin irritation: dermatology: skin discolouration	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10.1 Red light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11 Minor adverse events excluding skin irritation: dermatology: skin hypertrophy	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
12 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
13 Cosmetic outcome: very good or good general cosmetic outcome	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

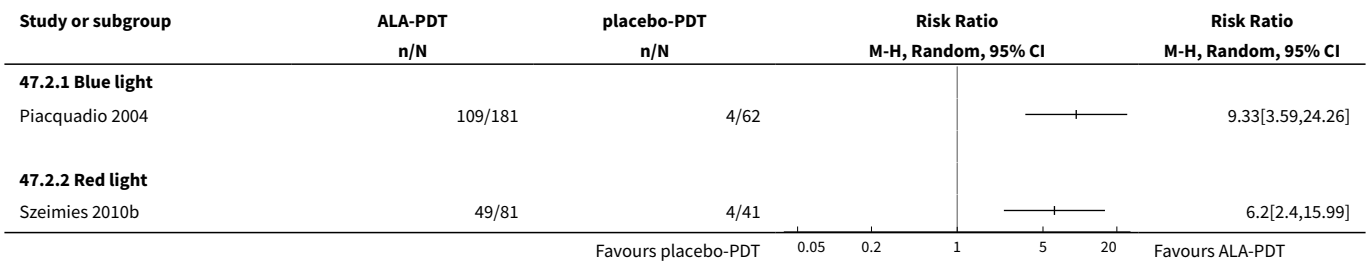
Analysis 47.1. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 1 Participant complete clearance [1 treatment].

Study or subgroup	ALA-PDT n/N	placebo-PDT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
47.1.1 Blue light					
Piacquadio 2004	109/181	6/62		100%	6.22[2.88,13.43]
Subtotal (95% CI)	**181**	**62**		**100%**	**6.22[2.88,13.43]**
Total events: 109 (ALA-PDT), 6 (placebo-PDT)					
Heterogeneity: Not applicable					

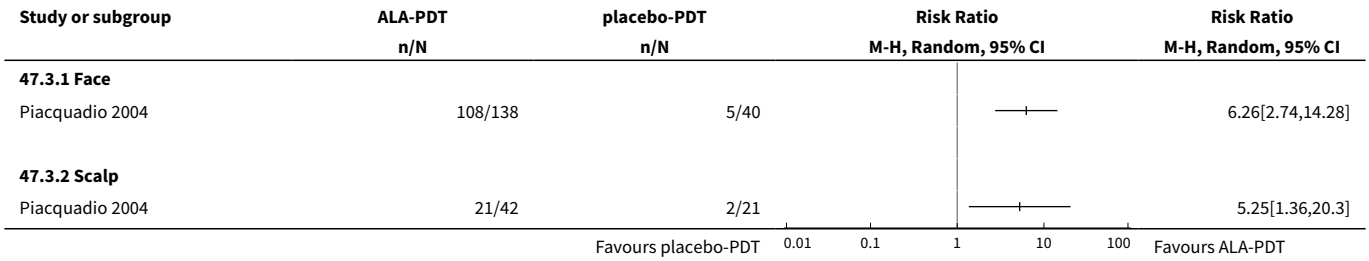




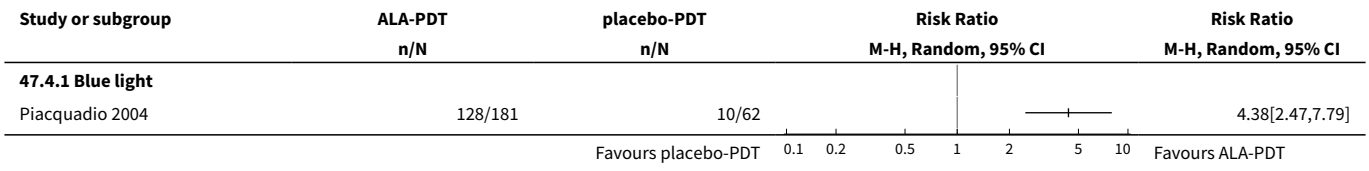
Analysis 47.2. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 2 Participant complete clearance [1 or 2 treatments].



Analysis 47.3. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 3 Participant complete clearance [1 or 2 treatments] by anatomical location.

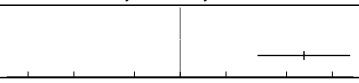


Analysis 47.4. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 4 Participant partial (> 75%) clearance [1 treatment].



Analysis 47.5. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 5 Participant partial (>75%) clearance[1 or 2 treatments].

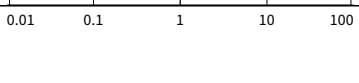
Study or subgroup	ALA-PDT n/N	placebo-PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.5.1 Blue light				
Piacquadio 2004	133/181	7/62		6.51[3.22,13.15]



Favours placebo-PDT — Favours ALA-PDT

Analysis 47.6. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 6 Participant partial (>75%) clearance [1 or 2 treatment] by anatomical location.

Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.6.1 Face				
Piacquadio 2004	127/138	8/40		4.6[2.47,8.57]
47.6.2 Scalp				
Piacquadio 2004	31/42	4/21		3.88[1.58,9.53]



Favours placebo-PDT — Favours ALA-PDT

Analysis 47.7. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 7 Skin irritation.

Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.7.1 Red light-during illumination				
Hauschild 2009a	187/217	8/83		8.94[4.62,17.31]
47.7.2 Red light-after treatment				
Hauschild 2009a	77/217	0/83		59.72[3.75,952.48]

Favours ALA-PDT — Favours placebo-PDT

Analysis 47.8. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 8 Minor adverse events excluding skin irritation: body as a whole: injury.

Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.8.1 Blue light				
Piacquadio 2004	9/181	1/62		3.08[0.4,23.85]

Favours ALA-PDT — Favours placebo-PDT

Analysis 47.9. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 9 Minor adverse events excluding skin irritation: cardiovascular: hypertension.

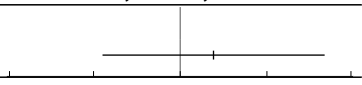
Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.9.1 Blue light				
Piacquadio 2004	3/181	0/62		2.42[0.13,46.26]

Analysis 47.10. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 10 Minor adverse events excluding skin irritation: dermatology: skin discolouration.

Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.10.1 Red light				
Hauschild 2009a	1/217	0/83		1.16[0.05,28.1]

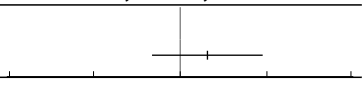
Analysis 47.11. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 11 Minor adverse events excluding skin irritation: dermatology: skin hypertrophy.

Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.11.1 Blue light				
Piacquadio 2004	3/181	0/62		2.42[0.13,46.26]



Analysis 47.12. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 12 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
47.12.1 Blue light				
Piacquadio 2004	12/181	2/62		2.06[0.47,8.93]



Analysis 47.13. Comparison 47 ALA-PDT versus placebo-PDT, Outcome 13 Cosmetic outcome: very good or good general cosmetic outcome.

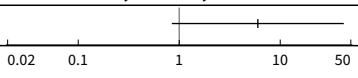
Study or subgroup	ALA-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Szeimies 2010b	38/77	10/37		1.83[1.03,3.25]

Comparison 48. ALA- blue light PDT versus ALA-pulsed laser PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 Cosmetic outcome: improvement in global response	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4 Cosmetic outcome: improvement in tactile roughness	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Cosmetic outcome: improvement in mottled hyperpigmentation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

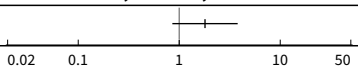
Analysis 48.1. Comparison 48 ALA- blue light PDT versus ALA-pulsed laser PDT, Outcome 1 Participant complete clearance.

Study or subgroup	Blue light n/N	Pulsed dye laser n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Smith 2003	6/12	1/12		6[0.85,42.59]



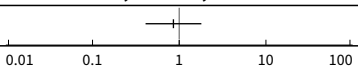
Analysis 48.2. Comparison 48 ALA- blue light PDT versus ALA-pulsed laser PDT, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Blue light n/N	Pulsed dye laser n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Smith 2003	9/12	5/12		1.8[0.85,3.79]



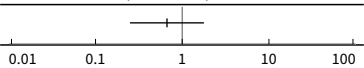
Analysis 48.3. Comparison 48 ALA- blue light PDT versus ALA-pulsed laser PDT, Outcome 3 Cosmetic outcome: improvement in global response.

Study or subgroup	Blue light n/N	Pulsed dye laser n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Smith 2003	6/12	7/12		0.86[0.41,1.8]



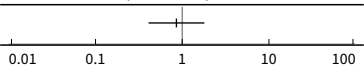
Analysis 48.4. Comparison 48 ALA- blue light PDT versus ALA-pulsed laser PDT, Outcome 4 Cosmetic outcome: improvement in tactile roughness.

Study or subgroup	Blue light n/N	Pulsed dye laser n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Smith 2003	4/12	6/12		0.67[0.25,1.78]



Analysis 48.5. Comparison 48 ALA- blue light PDT versus ALA-pulsed laser PDT, Outcome 5 Cosmetic outcome: improvement in mottled hyperpigmentation.

Study or subgroup	Blue light n/N	Pulsed dye laser n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Smith 2003	6/12	7/12		0.86[0.41,1.8]



Comparison 49. ALA-red light PDT at different application times

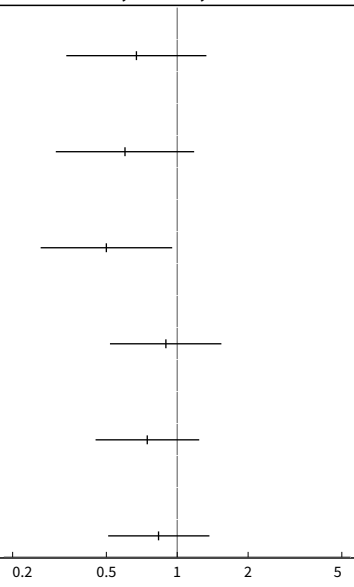
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Participant complete clearance at 4 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 0.5h versus 1.0h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 0.5h versus 2 h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 0.5h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 1h versus 2h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 1h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 2h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant complete clearance at 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 0.5h versus 1.0h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 0.5h versus 2 h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 0.5h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.4 1h versus 2h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.5 1h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 2h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Minor adverse events excluding skin irritation: metabolic and nutritional disorders: elevated alanine transaminase (ALT)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 0.5h versus 1.0h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 0.5h versus 2 h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 0.5h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Minor adverse events excluding skin irritation: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 0.5h versus 1h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 0.5h versus 2h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 0.5h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 1h versus 2h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 1h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.6 2h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Minor adverse events excluding skin irritation: other: epistaxis (nose bleeding)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 0.5h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 1h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.3 2h versus 4h	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

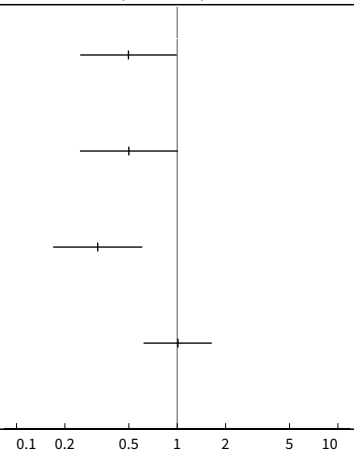
Analysis 49.1. Comparison 49 ALA-red light PDT at different application times, Outcome 1 Participant complete clearance at 4 weeks.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
49.1.1 0.5h versus 1.0h				
Hauschild 2009c	9/34	15/38		0.67[0.34,1.33]
49.1.2 0.5h versus 2 h				
Hauschild 2009c	9/34	15/34		0.6[0.31,1.18]
49.1.3 0.5h versus 4h				
Hauschild 2009c	9/34	18/34		0.5[0.26,0.95]
49.1.4 1h versus 2h				
Hauschild 2009c	15/38	15/34		0.89[0.52,1.54]
49.1.5 1h versus 4h				
Hauschild 2009c	15/38	18/34		0.75[0.45,1.24]
49.1.6 2h versus 4h				
Hauschild 2009c	15/34	18/34		0.83[0.51,1.37]

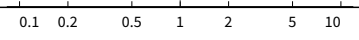


Analysis 49.2. Comparison 49 ALA-red light PDT at different application times, Outcome 2 Participant complete clearance at 8 weeks.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
49.2.1 0.5h versus 1.0h				
Hauschild 2009c	8/34	18/38		0.5[0.25,0.99]
49.2.2 0.5h versus 2 h				
Hauschild 2009c	8/34	16/34		0.5[0.25,1.01]
49.2.3 0.5h versus 4h				
Hauschild 2009c	8/34	25/34		0.32[0.17,0.61]
49.2.4 1h versus 2h				
Hauschild 2009c	18/38	16/34		1.01[0.62,1.64]
49.2.5 1h versus 4h				

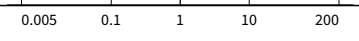


Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hauschild 2009c	18/38	25/34		0.64[0.44,0.95]
49.2.6 2h versus 4h				
Hauschild 2009c	16/34	25/34		0.64[0.42,0.96]



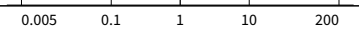
Analysis 49.3. Comparison 49 ALA-red light PDT at different application times, Outcome 3 Minor adverse events excluding skin irritation: metabolic and nutritional disorders: elevated alanine transaminase (ALT).

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
49.3.1 0.5h versus 1.0h				
Hauschild 2009c	1/34	0/38		3.34[0.14,79.42]
49.3.2 0.5h versus 2 h				
Hauschild 2009c	1/34	0/34		3[0.13,71.15]
49.3.3 0.5h versus 4h				
Hauschild 2009c	1/34	0/34		3[0.13,71.15]



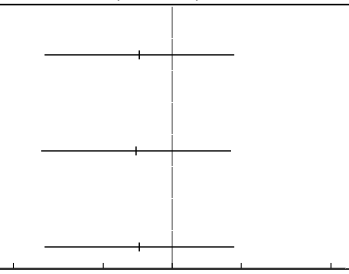
Analysis 49.4. Comparison 49 ALA-red light PDT at different application times, Outcome 4 Minor adverse events excluding skin irritation: nervous system: headache.

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
49.4.1 0.5h versus 1h				
Hauschild 2009c	1/34	0/38		3.34[0.14,79.42]
49.4.2 0.5h versus 2h				
Hauschild 2009c	1/34	1/34		1[0.07,15.34]
49.4.3 0.5h versus 4h				
Hauschild 2009c	1/34	1/34		1[0.07,15.34]
49.4.4 1h versus 2h				
Hauschild 2009c	0/38	1/34		0.3[0.01,7.11]
49.4.5 1h versus 4h				
Hauschild 2009c	0/38	1/34		0.3[0.01,7.11]
49.4.6 2h versus 4h				
Hauschild 2009c	1/34	1/34		1[0.07,15.34]



Analysis 49.5. Comparison 49 ALA-red light PDT at different application times, Outcome 5 Minor adverse events excluding skin irritation: other: epistaxis (nose bleeding).

Study or subgroup	shorter n/N	longer n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
49.5.1 0.5h versus 4h				
Hauschild 2009c	0/34	1/34		0.33[0.01,7.91]
49.5.2 1h versus 4h				
Hauschild 2009c	0/38	1/34		0.3[0.01,7.11]
49.5.3 2h versus 4h				
Hauschild 2009c	0/34	1/34		0.33[0.01,7.91]



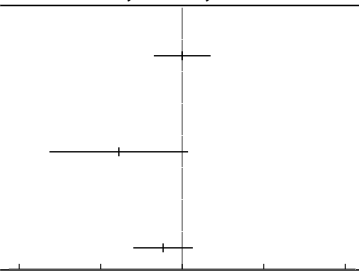
Comparison 50. ALA-PDT versus 0.5% 5-FU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Cosmetic outcome: improvement in global response	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5 Cosmetic outcome: improvement in tactile roughness	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Cosmetic outcome: improvement in mottled hyperpigmentation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Blue light	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Pulsed dye laser	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Combined	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

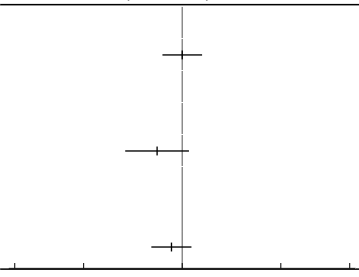
Analysis 50.1. Comparison 50 ALA-PDT versus 0.5% 5-FU, Outcome 1 Participant complete clearance.

Study or subgroup	ALA-PDT n/N	0.5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
50.1.1 Blue light				
Smith 2003	6/12	6/12		1[0.45,2.23]
50.1.2 Pulsed dye laser				
Smith 2003	1/12	6/12		0.17[0.02,1.18]
50.1.3 Combined				
Smith 2003	7/24	6/12		0.58[0.25,1.35]



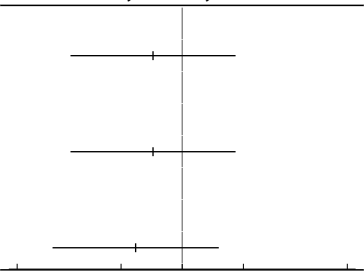
Analysis 50.2. Comparison 50 ALA-PDT versus 0.5% 5-FU, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	ALA-PDT n/N	0.5% 5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
50.2.1 Blue light				
Smith 2003	9/12	9/12		1[0.63,1.59]
50.2.2 Pulsed dye laser				
Smith 2003	5/12	9/12		0.56[0.26,1.17]
50.2.3 Combined				
Smith 2003	14/24	9/12		0.78[0.49,1.24]



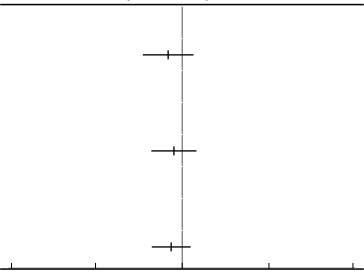
Analysis 50.3. Comparison 50 ALA-PDT versus 0.5% 5-FU, Outcome 3 Withdrawal due to adverse events.

Study or subgroup	ALA-PDT n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
50.3.1 Blue light				
Smith 2003	0/12	1/12		0.33[0.01,7.45]
50.3.2 Pulsed dye laser				
Smith 2003	0/12	1/12		0.33[0.01,7.45]
50.3.3 Combined				
Smith 2003	0/24	1/12		0.17[0.01,3.96]



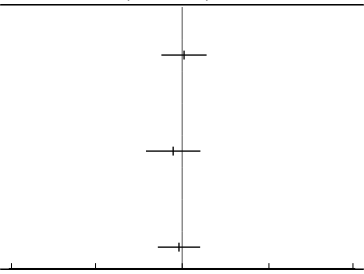
Analysis 50.4. Comparison 50 ALA-PDT versus 0.5% 5-FU, Outcome 4 Cosmetic outcome: improvement in global response.

Study or subgroup	ALA-PDT n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
50.4.1 Blue light				
Smith 2003	6/12	8/11		0.69[0.35,1.35]
50.4.2 Pulsed dye laser				
Smith 2003	7/12	8/11		0.8[0.44,1.46]
50.4.3 Combined				
Smith 2003	13/24	8/11		0.74[0.44,1.25]



Analysis 50.5. Comparison 50 ALA-PDT versus 0.5% 5-FU, Outcome 5 Cosmetic outcome: improvement in tactile roughness.

Study or subgroup	ALA-PDT n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
50.5.1 Blue light				
Smith 2003	8/12	7/11		1.05[0.58,1.91]
50.5.2 Pulsed dye laser				
Smith 2003	6/12	7/11		0.79[0.38,1.62]
50.5.3 Combined				
Smith 2003	14/24	7/11		0.92[0.52,1.61]



Analysis 50.6. Comparison 50 ALA-PDT versus 0.5% 5-FU, Outcome 6 Cosmetic outcome: improvement in mottled hyperpigmentation.

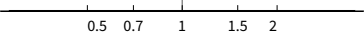
Study or subgroup	ALA-PDT n/N	5-FU n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
50.6.1 Blue light				
Smith 2003	4/12	7/11		0.52[0.21,1.31]
50.6.2 Pulsed dye laser				
Smith 2003	6/12	7/11		0.79[0.38,1.62]
50.6.3 Combined				
Smith 2003	10/24	7/11		0.65[0.34,1.26]

Comparison 51. ALA-red light PDT vs cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Skin irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 During treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 One day after treatment	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 51.1. Comparison 51 ALA-red light PDT vs cryotherapy, Outcome 1 Participant complete clearance.

Study or subgroup	ALA-PDT n/N	Cryotherapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Hauschild 2009b	86/148	66/149		1.31[1.05,1.64]



Analysis 51.2. Comparison 51 ALA-red light PDT vs cryotherapy, Outcome 2 Skin irritation.

Study or subgroup	ALA-PDT n/N	Cryotherapy n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
51.2.1 During treatment				
Hauschild 2009b	126/148	80/149		1.59[1.35,1.87]
51.2.2 One day after treatment				
Hauschild 2009b	55/148	15/149		3.69[2.19,6.23]

Comparison 52. MAL-red light PDT versus placebo-red light PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	5	482	Risk Ratio (M-H, Random, 95% CI)	4.46 [3.17, 6.28]
2 Participant partial (>75%) clearance	2	191	Risk Ratio (M-H, Random, 95% CI)	3.28 [1.73, 6.23]
3 Withdrawal due to adverse events	2	191	Risk Ratio (M-H, Random, 95% CI)	2.00 [0.23, 17.74]
4 Minor adverse event: nervous system: headache	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Cosmetic outcome: hyperpigmentation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

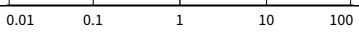
Analysis 52.1. Comparison 52 MAL-red light PDT versus placebo-red light PDT, Outcome 1 Participant complete clearance.

Study or subgroup	MAL-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Pariser 2003	32/42	8/38		27.65%	3.62[1.91,6.85]
Pariser 2008	29/49	7/47		21.79%	3.97[1.93,8.18]
Photocure-Australian 2004	71/88	3/23		10.25%	6.19[2.14,17.86]
Photocure-US 2004	33/42	8/38		27.89%	3.73[1.98,7.05]
Szeimies 2009	39/57	4/58		12.42%	9.92[3.79,25.96]
Total (95% CI)	**278**	**204**		**100%**	**4.46[3.17,6.28]**
Total events: 204 (MAL-PDT), 30 (Placebo/PDT)					
Heterogeneity: Tau^2=0; Chi^2=4.1, df=4(P=0.39); I^2=2.42%					
Test for overall effect: Z=8.58(P<0.0001)					

Favours placebo-PDT — Favours ALA-PDT

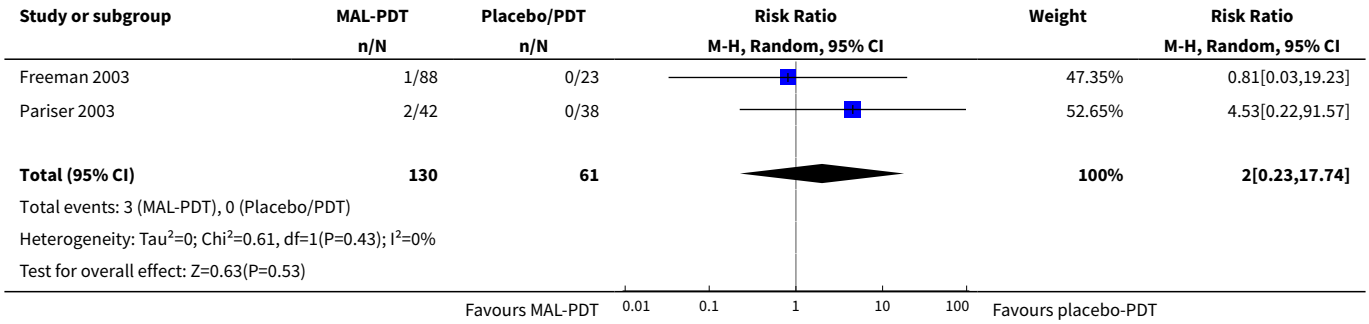
Analysis 52.2. Comparison 52 MAL-red light PDT versus placebo-red light PDT, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	MAL-PDT n/N	Placebo/PDT n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Photocure-Australian 2004	76/88	4/23		34.53%	4.97[2.03,12.15]
Photocure-US 2004	35/42	12/38		65.47%	2.64[1.62,4.3]
Total (95% CI)	**130**	**61**		**100%**	**3.28[1.73,6.23]**
Total events: 111 (MAL-PDT), 16 (Placebo/PDT)					
Heterogeneity: Tau^2=0.1; Chi^2=1.75, df=1(P=0.19); I^2=42.96%					
Test for overall effect: Z=3.63(P=0)					

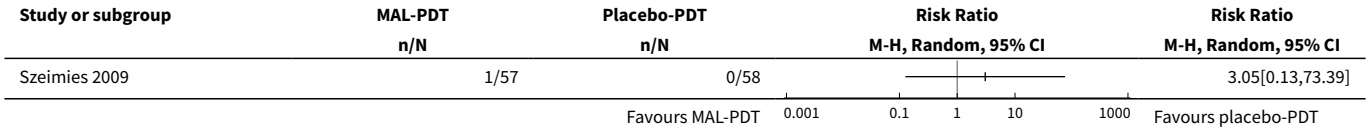


Favours placebo-PDT — Favours MAL-PDT

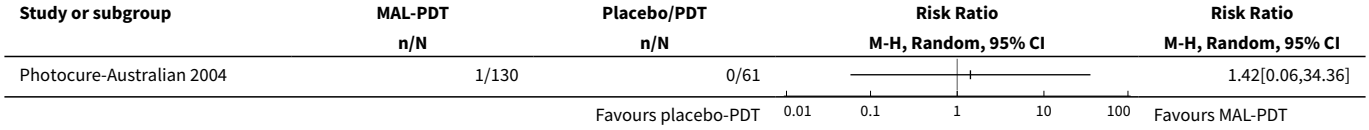
Analysis 52.3. Comparison 52 MAL-red light PDT versus placebo-red light PDT, Outcome 3 Withdrawal due to adverse events.



Analysis 52.4. Comparison 52 MAL-red light PDT versus placebo-red light PDT, Outcome 4 Minor adverse event: nervous system: headache.



Analysis 52.5. Comparison 52 MAL-red light PDT versus placebo-red light PDT, Outcome 5 Cosmetic outcome: hyperpigmentation.



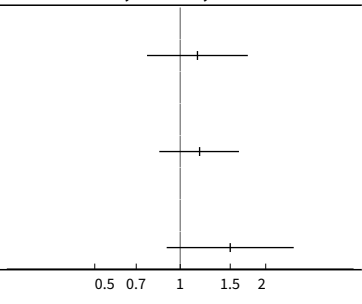
Comparison 53. MAL-red light LED PDT versus MAL-broad visible + water-filtered infrared A PDT (1 or 2 treatments)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 At 3 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 At 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 At 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

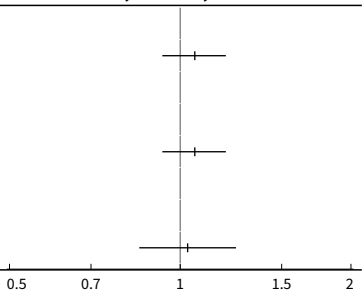
Analysis 53.1. Comparison 53 MAL-red light LED PDT versus MAL-broad visible + water-filtered infrared A PDT (1 or 2 treatments), Outcome 1 Participant complete clearance.

Study or subgroup	Red light LED n/N	visible + wIRA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
53.1.1 At 3 months				
von Felbert 2010	23/40	20/40		1.15[0.76,1.73]
53.1.2 At 6 months				
von Felbert 2010	28/40	24/40		1.17[0.84,1.61]
53.1.3 At 12 months				
von Felbert 2010	21/40	14/40		1.5[0.9,2.51]



Analysis 53.2. Comparison 53 MAL-red light LED PDT versus MAL-broad visible + water-filtered infrared A PDT (1 or 2 treatments), Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Red light LED n/N	visible + wIRA n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
53.2.1 At 3 months				
von Felbert 2010	38/40	36/40		1.06[0.93,1.2]
53.2.2 At 6 months				
von Felbert 2010	38/40	36/40		1.06[0.93,1.2]
53.2.3 At 12 months				
von Felbert 2010	34/40	33/40		1.03[0.85,1.25]

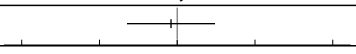


Comparison 54. MAL-red light LED PDT versus MAL-daylight PDT

Outcome or subgroup title	No. of studies	No. of par-ticipants	Statistical method	Effect size
1 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 54.1. Comparison 54 MAL-red light LED PDT versus MAL-daylight PDT, Outcome 1 Mean reduction in lesion counts.

Study or subgroup	Red light LED N	Red light LED Mean(SD)	Daylight N	Daylight Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Wiegell 2008	29	8 (5.6)	29	8.4 (5.4)		-0.4[-3.23,2.43]



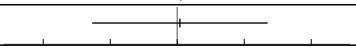
Favours daylight — Favours red light LED

Comparison 55. 2h MAL-day light PDT versus 3h MAL-daylight PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Mean percentage of reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 55.1. Comparison 55 2h MAL-day light PDT versus 3h MAL-daylight PDT, Outcome 1 Mean reduction in lesion counts.

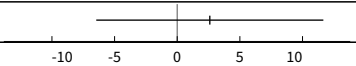
Study or subgroup	2h MAL N	2h MAL Mean(SD)	3h MAL N	3h MAL Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Wiegell 2011a	58	9.8 (8.8)	62	9.7 (9.5)		0.1[-3.17,3.37]



Favours 3h MAL — Favours 2h MAL

Analysis 55.2. Comparison 55 2h MAL-day light PDT versus 3h MAL-daylight PDT, Outcome 2 Mean percentage of reduction in lesion counts.

Study or subgroup	2h N	2h Mean(SD)	3h N	3h Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Wiegell 2011a	58	77.2 (23.3)	62	74.6 (27.3)		2.6[-6.46,11.66]



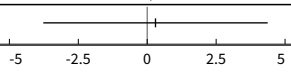
Favours 3h — Favours 2h

Comparison 56. 16% MAL-daylight PDT versus 8% MAL-daylight PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 56.1. Comparison 56 16% MAL-daylight PDT versus 8% MAL-daylight PDT, Outcome 1 Mean reduction in lesion counts.

Study or subgroup	16% MAL N	16% MAL Mean(SD)	8% MAL N	8% MAL Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Wiegell 2009	29	14.8 (8.2)	29	14.5 (7.6)		0.3[-3.77,4.37]

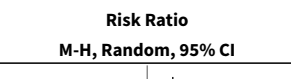


Comparison 57. Single MAL-red light PDT versus multiple MAL-red light PDT (2 treatments 1 week apart)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Withdrawal due to adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

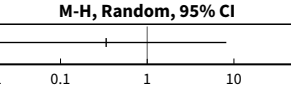
Analysis 57.1. Comparison 57 Single MAL-red light PDT versus multiple MAL-red light PDT (2 treatments 1 week apart), Outcome 1 Participant complete clearance.

Study or subgroup	Single MAL-PDT n/N	Multiple MAL-PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Tarstedt 2005	93/105	80/106		1.17[1.03,1.33]



Analysis 57.2. Comparison 57 Single MAL-red light PDT versus multiple MAL-red light PDT (2 treatments 1 week apart), Outcome 2 Withdrawal due to adverse events.

Study or subgroup	Single MAL-PDT n/N	Multiple MAL-PDT n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Tarstedt 2005	0/105	1/106		0.34[0.01,8.17]

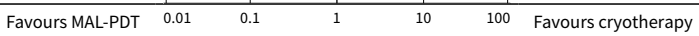


Comparison 58. MAL- red light PDT vs cryotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawal due to adverse events	2	379	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.14, 6.36]

Analysis 58.1. Comparison 58 MAL- red light PDT vs cryotherapy, Outcome 1 Withdrawal due to adverse events.

Study or subgroup	MAL-PDT n/N	Cryotherapy n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Freeman 2003	1/88	0/89		35.89%	3.03[0.13,73.48]
Szeimies 2002	1/102	2/100		64.11%	0.49[0.05,5.32]
Total (95% CI)	**190**	**189**		**100%**	**0.94[0.14,6.36]**
Total events: 2 (MAL-PDT), 2 (Cryotherapy)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.06(P=0.95)					

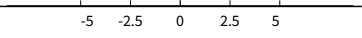


Comparison 59. ALA-red light PDT versus MAL-red light PDT

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 59.1. Comparison 59 ALA-red light PDT versus MAL-red light PDT, Outcome 1 Mean reduction in lesion counts.

Study or subgroup	ALA-PDT N	ALA-PDT Mean(SD)	MAL-PDT N	MAL-PDT Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Moloney 2007	15	6.2 (1.9)	15	5.6 (3.2)		0.6[-1.28,2.48]



Comparison 60. Trichloroacetic acid peel versus 5% 5-FU

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of reduction in lesions	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 60.1. Comparison 60 Trichloroacetic acid peel versus 5% 5-FU, Outcome 1 Mean percentage of reduction in lesions.

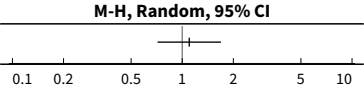
Study or subgroup	Peel N	Peel Mean(SD)	5% 5-FU N	5% 5-FU Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Hantash 2006	10	89 (6.6)	8	83.2 (12.5)		5.8[-3.78,15.38]

Comparison 61. Cryotherapy versus cryotherapy with betulin-based oleogel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Participant partial (>75%) clearance	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

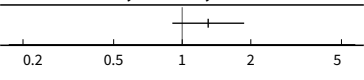
Analysis 61.1. Comparison 61 Cryotherapy versus cryotherapy with betulin-based oleogel, Outcome 1 Participant complete clearance.

Study or subgroup	Cryotherapy n/N	Combination n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Huyke 2009	11/14	10/14		1.1[0.72,1.69]



Analysis 61.2. Comparison 61 Cryotherapy versus cryotherapy with betulin-based oleogel, Outcome 2 Participant partial (>75%) clearance.

Study or subgroup	Cryotherapy n/N	Combination n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Huyke 2009	13/14	10/14		1.3[0.91,1.87]

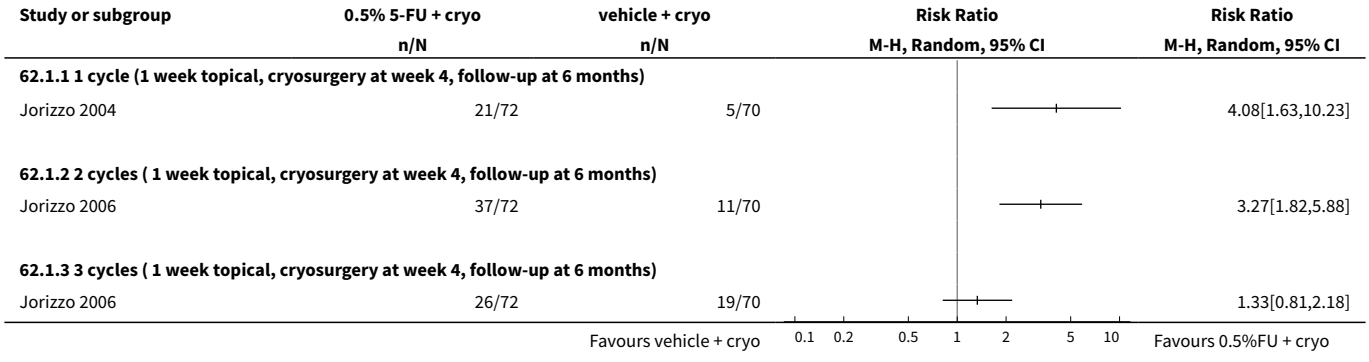


Comparison 62. (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance at 6 months	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 1 cycle (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 2 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 3 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Mean reduction in lesion counts at 6 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

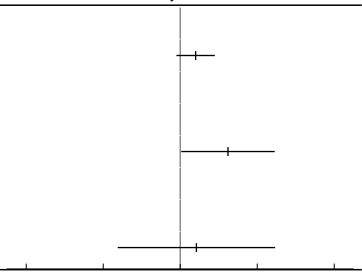
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 1 cycle (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 2 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 3 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mean percentage of reduction in lesion counts at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 1 cycle (1 week topical, cryosurgery at 4 weeks, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Minor adverse events excluding skin irritation: body as a whole: allergic reaction	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5 Minor adverse events excluding skin irritation: dermatology: hyperesthesia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Minor adverse events excluding skin irritation: dermatology: skin discoloration	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Minor adverse events excluding skin irritation: dermatology: vesiculobullous rash	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Minor adverse events excluding skin irritation: digestive: cheilitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: special senses: conjunctivitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: special senses: eye irritation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 62.1. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 1 Participant complete clearance at 6 months.



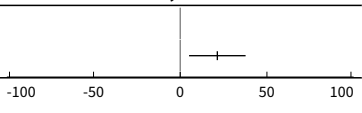
Analysis 62.2. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 2 Mean reduction in lesion counts at 6 months.

Study or subgroup	5-FU + cryo N	5-FU + cryo Mean(SD)	Vehicle + cryo N	Vehicle + cryo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
62.2.1 1 cycle (1 week topical, cryosurgery at week 4, follow-up at 6 months)						
Jorizzo 2004	72	8.6 (7)	70	6.6 (8.1)		2[-0.49,4.49]
62.2.2 2 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)						
Jorizzo 2006	72	18.1 (20.2)	70	11.9 (16.6)		6.2[0.13,12.27]
62.2.3 3 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)						
Jorizzo 2006	72	14.7 (41.1)	70	12.6 (16.2)		2.1[-8.12,12.32]



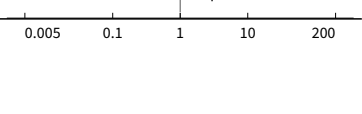
Analysis 62.3. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 3 Mean percentage of reduction in lesion counts at 6 months.

Study or subgroup	5-FU + cryo N	5-FU + cryo Mean(SD)	Vehicle + cryo N	Vehicle + cryo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
62.3.1 1 cycle (1 week topical, cryosurgery at 4 weeks, follow-up at 6 months)						
Jorizzo 2004	72	67 (43.6)	70	45.6 (54.7)		21.4[5.1,37.7]



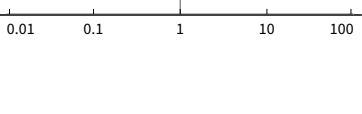
Analysis 62.4. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 4 Minor adverse events excluding skin irritation: body as a whole: allergic reaction.

Study or subgroup	5-FU + cryo n/N	Vehicle + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2006	1/72	0/71		2.96[0.12,71.44]



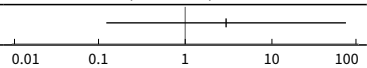
Analysis 62.5. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 5 Minor adverse events excluding skin irritation: dermatology: hyperesthesia.

Study or subgroup	5-FU + cryo n/N	Vehicle + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2006	1/72	0/71		2.96[0.12,71.44]



Analysis 62.6. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 6 Minor adverse events excluding skin irritation: dermatology: skin discoloration.

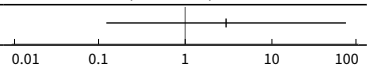
Study or subgroup	5-FU + cryo n/N	Vehicle + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2006	1/72	0/71		2.96[0.12,71.44]



Favours 5-FU + cryo — Favours vehicle + cryo

Analysis 62.7. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 7 Minor adverse events excluding skin irritation: dermatology: vesiculobullous rash.

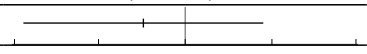
Study or subgroup	5-FU + cryo n/N	Vehicle + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2006	1/72	0/71		2.96[0.12,71.44]



Favours 5-FU + cryo — Favours vehicle + cryo

Analysis 62.8. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 8 Minor adverse events excluding skin irritation: digestive: cheilitis.

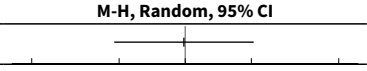
Study or subgroup	5-FU + cryo n/N	Vehicle + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2006	0/72	1/71		0.33[0.01,7.94]



Favours 5-FU + cryo — Favours vehicle + cryo

Analysis 62.9. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 9 Minor adverse events excluding skin irritation: special senses: conjunctivitis.

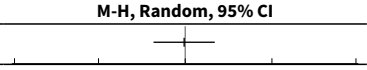
Study or subgroup	5-FU + cryo n/N	vehicle + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2006	12/72	12/71		0.99[0.48,2.05]



Favours 5-FU + cryo — Favours vehicle + cryo

Analysis 62.10. Comparison 62 (0.5% 5-FU + cryotherapy) versus (vehicle + cryotherapy), Outcome 10 Minor adverse events excluding skin irritation: special senses: eye irritation.

Study or subgroup	5-FU + cryo n/N	vehicle + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2004	10/72	10/70		0.97[0.43,2.19]



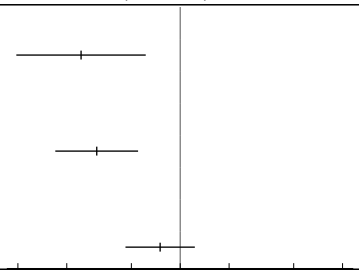
Favours 5-FU + cryo — Favours vehicle + cryo

Comparison 63. (vehicle + cryotherapy) versus (0.5% 5-FU + cryotherapy)

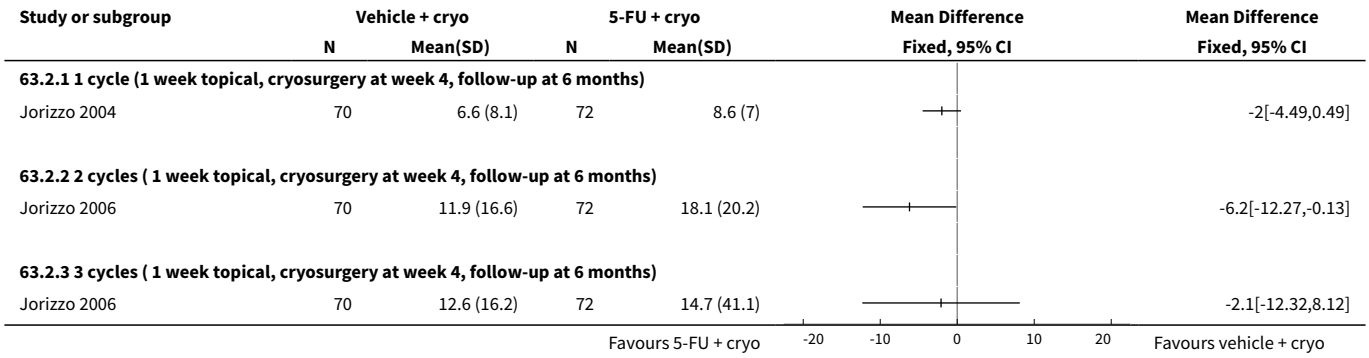
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance at 6 months	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 1 cycle (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 2 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 3 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Mean reduction in lesion counts at 6 months	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 1 cycle (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 2 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 3 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Mean percentage of reduction in lesion counts at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 1 cycle (1 week topical, cryosurgery at 4 weeks, follow-up at 6 months)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 63.1. Comparison 63 (vehicle + cryotherapy) versus (0.5% 5-FU + cryotherapy), Outcome 1 Participant complete clearance at 6 months.

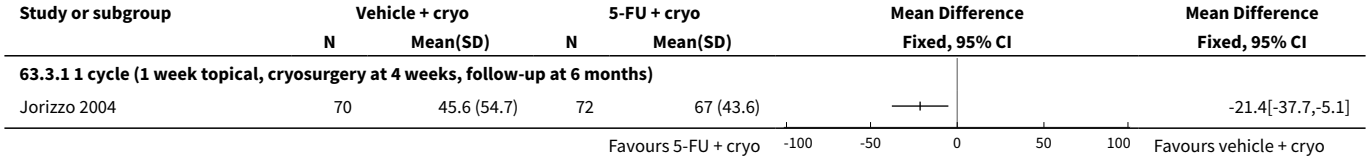
Study or subgroup	vehicle + cryo n/N	0.5% 5-FU + cryo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
63.1.1 1 cycle (1 week topical, cryosurgery at week 4, follow-up at 6 months)				
Jorizzo 2004	5/70	21/72		0.24[0.1,0.61]
63.1.2 2 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)				
Jorizzo 2006	11/70	37/72		0.31[0.17,0.55]
63.1.3 3 cycles (1 week topical, cryosurgery at week 4, follow-up at 6 months)				
Jorizzo 2006	19/70	26/72		0.75[0.46,1.23]



Analysis 63.2. Comparison 63 (vehicle + cryotherapy) versus (0.5% 5-FU + cryotherapy), Outcome 2 Mean reduction in lesion counts at 6 months.



Analysis 63.3. Comparison 63 (vehicle + cryotherapy) versus (0.5% 5-FU + cryotherapy), Outcome 3 Mean percentage of reduction in lesion counts at 6 months.



Comparison 64. Cryotherapy with vehicle versus cryotherapy with imiquimod

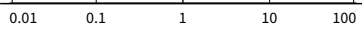
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance of all lesions	2	311	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.05, 0.73]
1.1 5% imiquimod	1	64	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.11, 1.42]
1.2 3.75% imiquimod	1	247	Risk Ratio (M-H, Random, 95% CI)	0.11 [0.04, 0.30]
2 Participant complete clearance of target (cryotherapy treated) lesions	2	311	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.36, 1.04]
2.1 5% imiquimod	1	64	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.47, 1.60]
2.2 3.75% imiquimod	1	247	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.37, 0.68]
3 Participant complete clearance of subclinical lesions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 5% imiquimod	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Mean percentage of reduction in all lesion counts	2	301	Mean Difference (IV, Random, 95% CI)	-23.69 [-46.03, -1.34]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 5% imquimod	1	54	Mean Difference (IV, Random, 95% CI)	-11.20 [-26.53, 4.13]
4.2 3.75% imiquimod	1	247	Mean Difference (IV, Random, 95% CI)	-34.10 [-41.38, -26.82]
5 Mean percentage of reduction in target (cryotherapy treated) lesion counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 3.75% imiquimod	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Withdrawal due to adverse events	2	312	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.28, 3.07]
6.1 5% imiquimod	1	65	Risk Ratio (M-H, Random, 95% CI)	2.91 [0.12, 68.95]
6.2 3.75% imiquimod	1	247	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.21, 2.79]
7 Skin irritation	2	311	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.10, 1.54]
7.1 5% imiquimod	1	64	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.20, 2.01]
7.2 3.75% imiquimod	1	247	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.02, 1.19]
8 Minor adverse events excluding skin irritation: body as a whole: fatigue	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Minor adverse events excluding skin irritation: digestive: nausea	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Minor adverse events excluding skin irritation: respiratory: upper respiratory tract infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Minor adverse events excluding skin irritation: respiratory: bronchitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
13 Minor adverse events excluding skin irritation: respiratory: sinusitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
14 Minor adverse events excluding skin irritation: special senses: conjunctivitis	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
15 Cosmetic outcomes: Improved global photoageing score	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
16 Cosmetic outcomes: Improved fine lines	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
17 Cosmetic outcomes: Improved tactile roughness	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
18 Cosmetic outcomes: Improved mottled pigmentation	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
19 Cosmetic outcomes: Improved sallowness	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
20 Cosmetic outcomes: cosmetic appearance score	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
20.1 Investigator	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
20.2 Participant	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

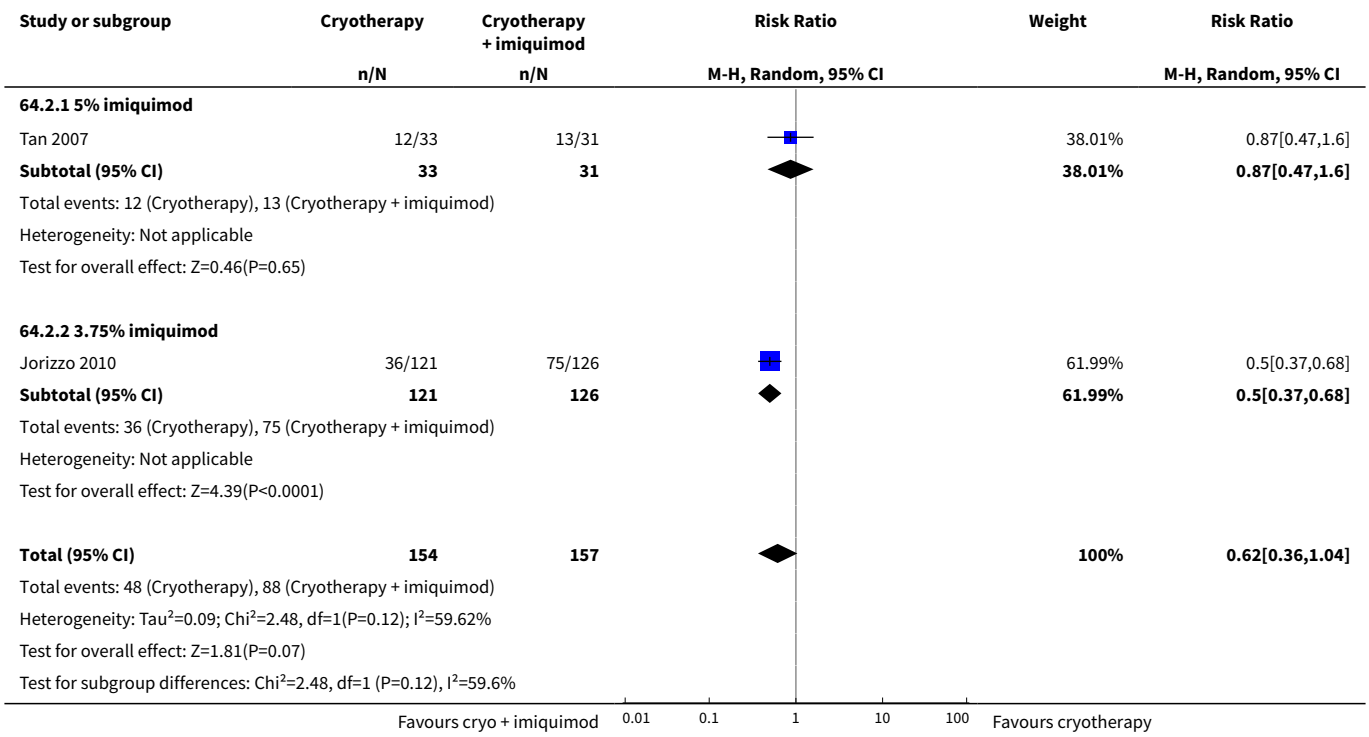
Analysis 64.1. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 1 Participant complete clearance of all lesions.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
64.1.1 5% imiquimod					
Tan 2007	3/33	7/31		45.68%	0.4[0.11,1.42]
Subtotal (95% CI)	**33**	**31**		**45.68%**	**0.4[0.11,1.42]**
Total events: 3 (Cryotherapy), 7 (Cryotherapy + imiquimod)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					
64.1.2 3.75% imiquimod					
Jorizzo 2010	4/121	38/126		54.32%	0.11[0.04,0.3]
Subtotal (95% CI)	**121**	**126**		**54.32%**	**0.11[0.04,0.3]**
Total events: 4 (Cryotherapy), 38 (Cryotherapy + imiquimod)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.33(P<0.0001)					
Total (95% CI)	**154**	**157**		**100%**	**0.2[0.05,0.73]**
Total events: 7 (Cryotherapy), 45 (Cryotherapy + imiquimod)					
Heterogeneity: Tau^2=0.55; Chi^2=2.64, df=1(P=0.1); I^2=62.09%					
Test for overall effect: Z=2.43(P=0.01)					
Test for subgroup differences: Chi^2=2.51, df=1 (P=0.11), I^2=60.19%					

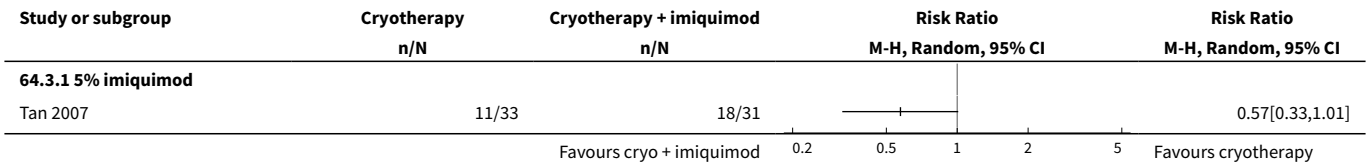


Favours cryo + imiquimod — Favours cryotherapy

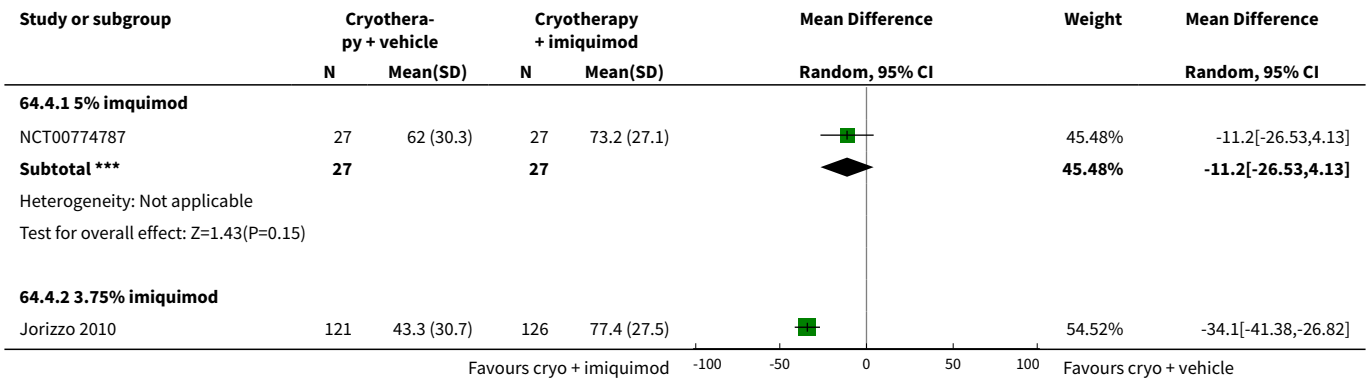
Analysis 64.2. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 2 Participant complete clearance of target (cryotherapy treated) lesions.

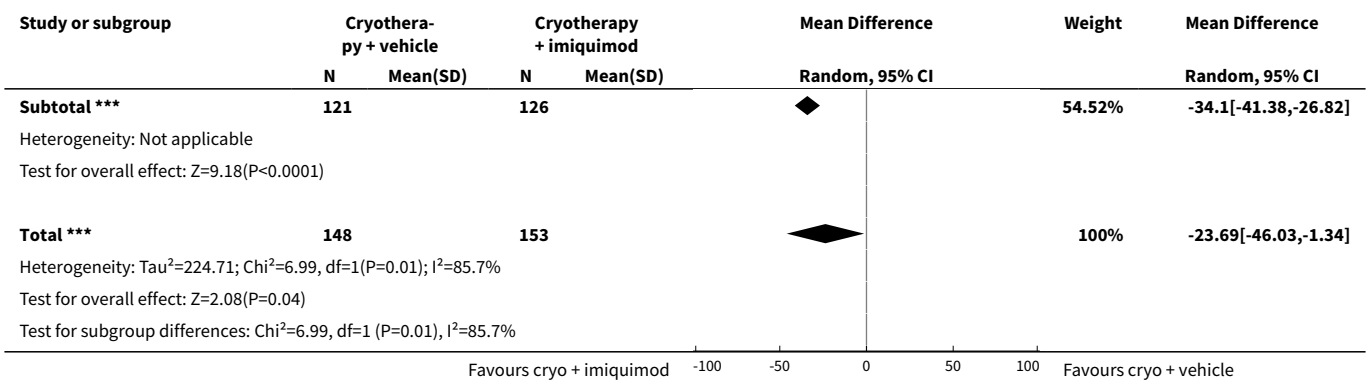


Analysis 64.3. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 3 Participant complete clearance of subclinical lesions.

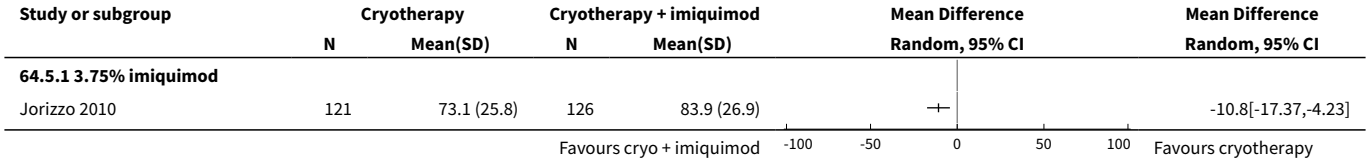


Analysis 64.4. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 4 Mean percentage of reduction in all lesion counts.

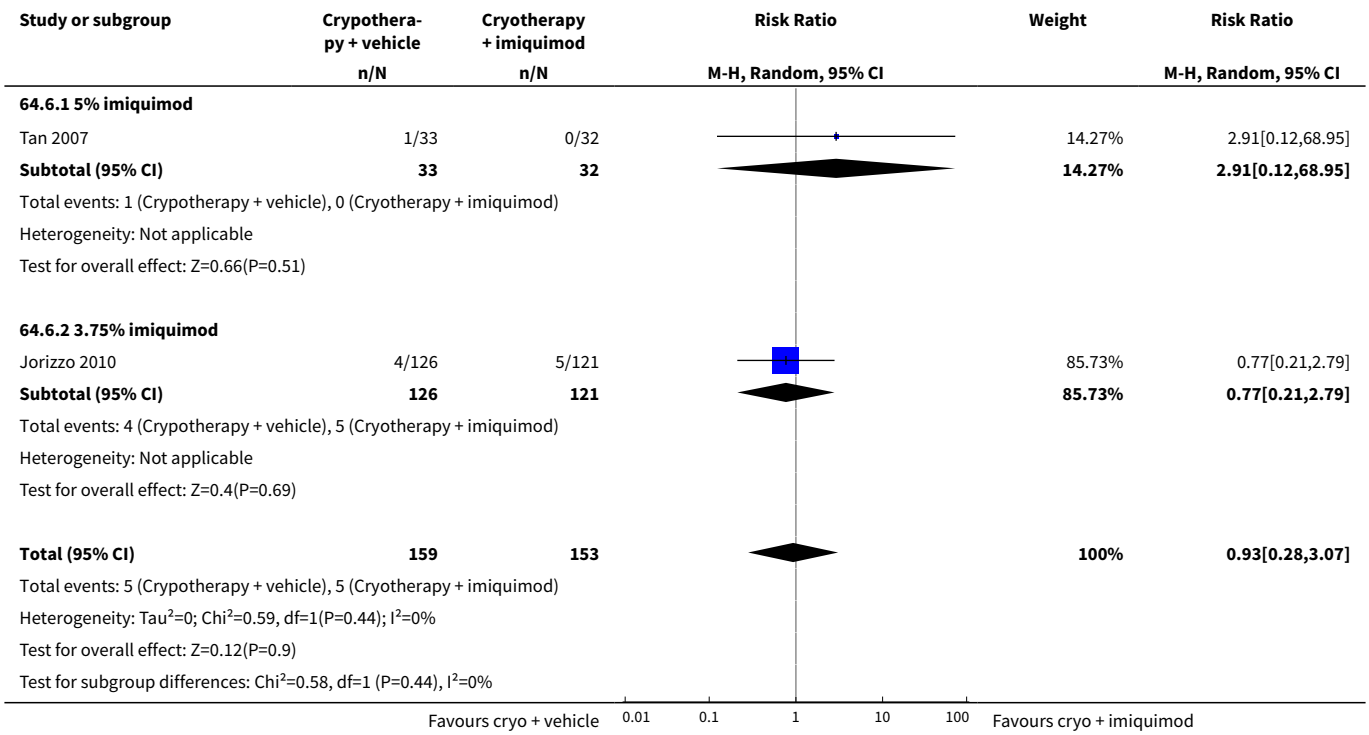




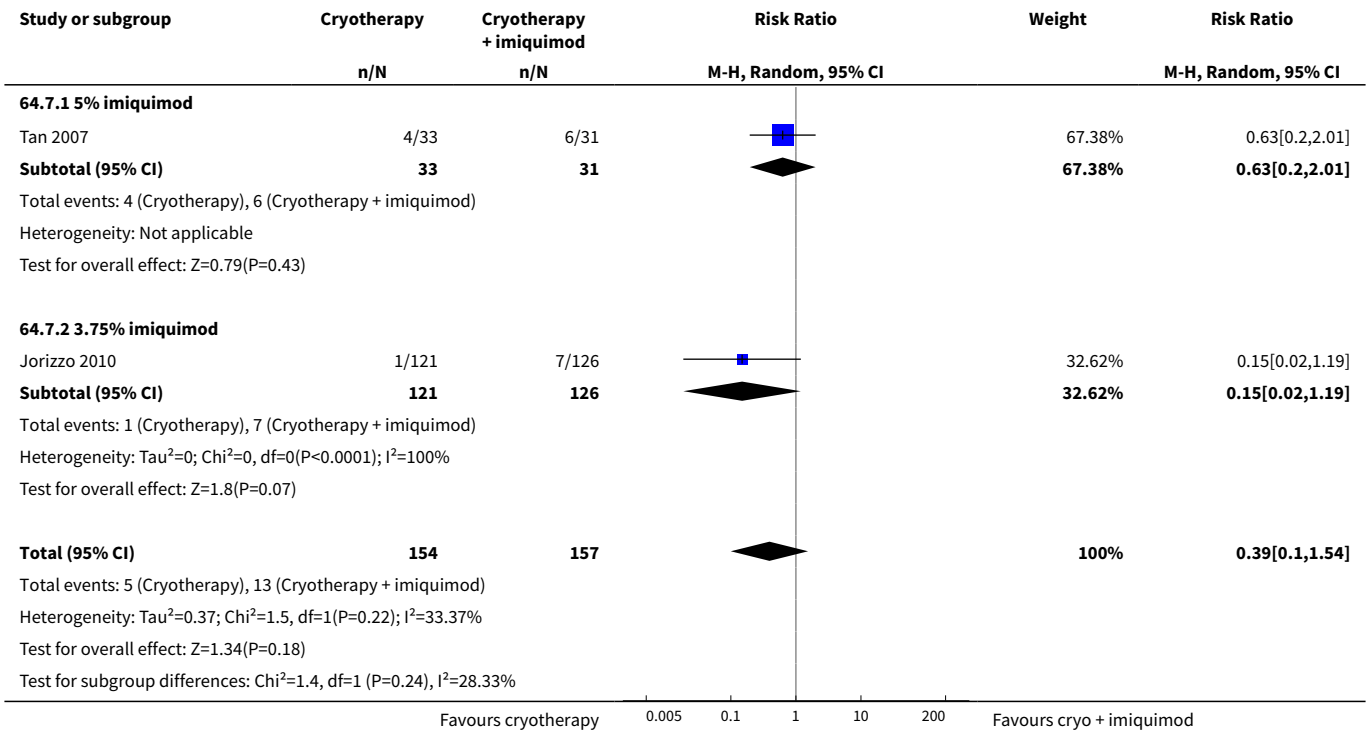
Analysis 64.5. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 5 Mean percentage of reduction in target (cryotherapy treated) lesion counts.



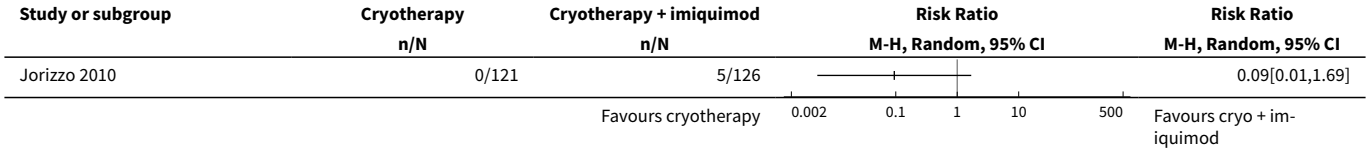
Analysis 64.6. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 6 Withdrawal due to adverse events.



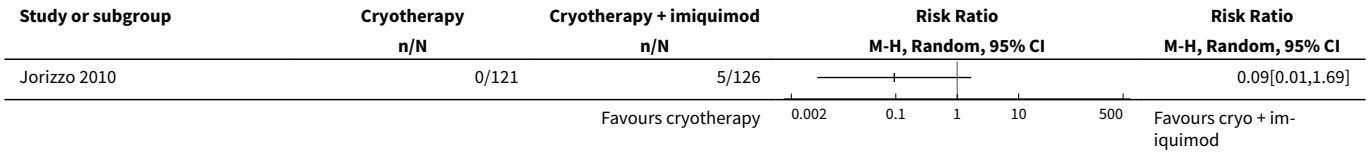
Analysis 64.7. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 7 Skin irritation.



Analysis 64.8. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 8 Minor adverse events excluding skin irritation: body as a whole: fatigue.

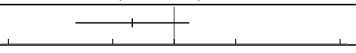


Analysis 64.9. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 9 Minor adverse events excluding skin irritation: digestive: nausea.



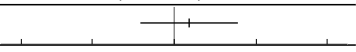
Analysis 64.10. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 10 Minor adverse events excluding skin irritation: musculoskeletal and connective tissue: myalgia.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	1/121	5/126		0.21[0.02,1.76]



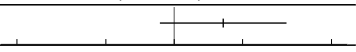
Analysis 64.11. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 11 Minor adverse events excluding skin irritation: respiratory: upper respiratory tract infection.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	9/121	7/126		1.34[0.51,3.48]



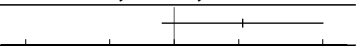
Analysis 64.12. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 12 Minor adverse events excluding skin irritation: respiratory: bronchitis.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	5/121	1/126		5.21[0.62,43.92]



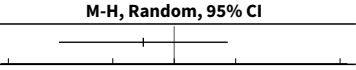
Analysis 64.13. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 13 Minor adverse events excluding skin irritation: respiratory: sinusitis.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	5/121	0/126		11.45[0.64,204.88]



Analysis 64.14. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 14 Minor adverse events excluding skin irritation: special senses: conjunctivitis.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Tan 2007	0/33	1/31		0.31[0.01,7.42]



Analysis 64.15. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 15 Cosmetic outcomes: Improved global photoageing score.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	23/119	63/122		0.37[0.25,0.56]

Favours cryo + imiquimod 0.01 0.1 1 10 100 Favours cryotherapy

Analysis 64.16. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 16 Cosmetic outcomes: Improved fine lines.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	18/119	40/122		0.46[0.28,0.76]

Favours cryo + imiquimod 0.01 0.1 1 10 100 Favours cryotherapy

Analysis 64.17. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 17 Cosmetic outcomes: Improved tactile roughness.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	27/119	75/122		0.37[0.26,0.53]

Favours cryo + imiquimod 0.01 0.1 1 10 100 Favours cryotherapy

Analysis 64.18. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 18 Cosmetic outcomes: Improved mottled pigmentation.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	22/119	57/122		0.4[0.26,0.6]

Favours cryo + imiquimod 0.01 0.1 1 10 100 Favours cryotherapy

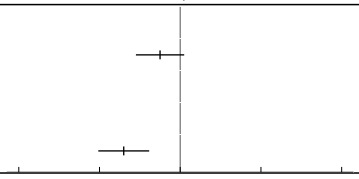
Analysis 64.19. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 19 Cosmetic outcomes: Improved sallowness.

Study or subgroup	Cryotherapy n/N	Cryotherapy + imiquimod n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Jorizzo 2010	15/119	31/122		0.5[0.28,0.87]

Favours cryo + imiquimod 0.01 0.1 1 10 100 Favours cryotherapy

Analysis 64.20. Comparison 64 Cryotherapy with vehicle versus cryotherapy with imiquimod, Outcome 20 Cosmetic outcomes: cosmetic appearance score.

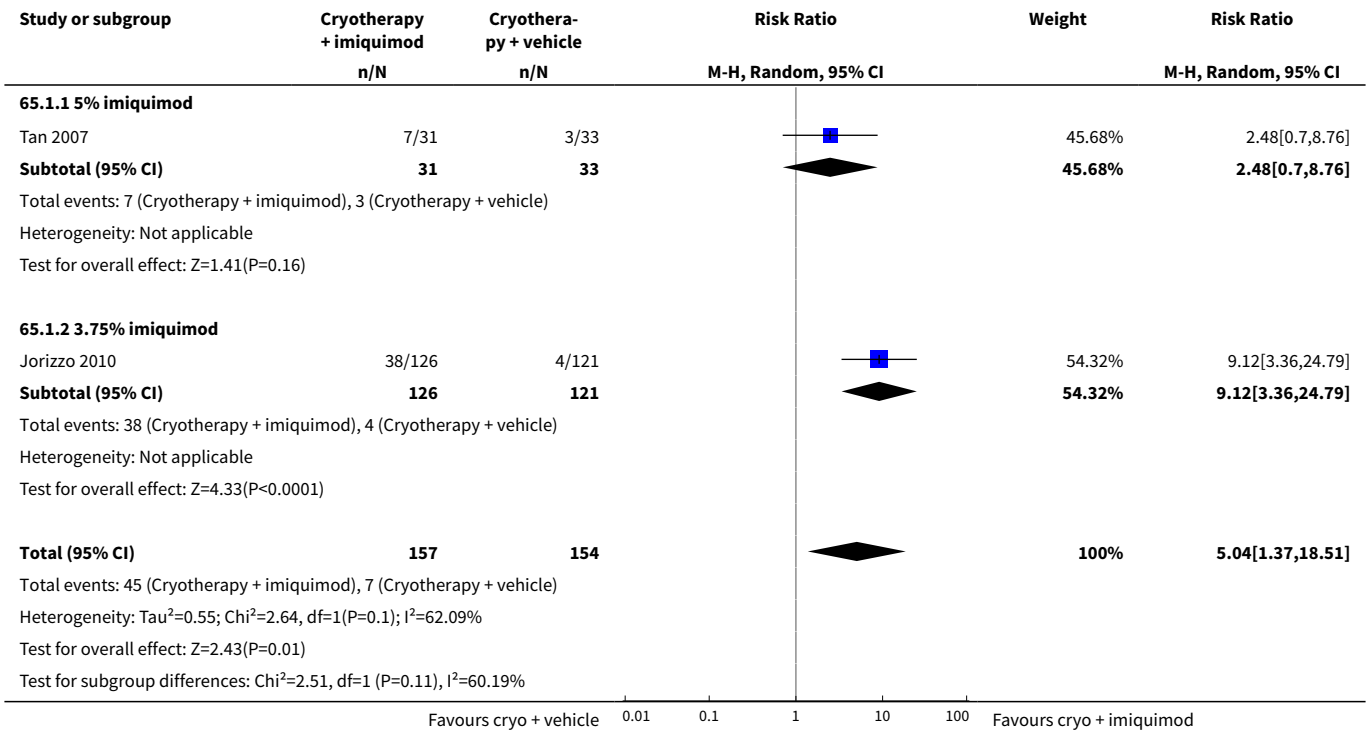
Study or subgroup	Cryotherapy N	Cryotherapy Mean(SD)	Cryotherapy + imiquimod N	Cryotherapy + imiquimod Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
64.20.1 Investigator						
NCT00774787	26	1.6 (1.1)	26	2.1 (1.1)		-0.5[-1.1,0.1]
64.20.2 Participant						
NCT00774787	26	1.2 (1.3)	26	2.6 (1)		-1.4[-2.03,-0.77]



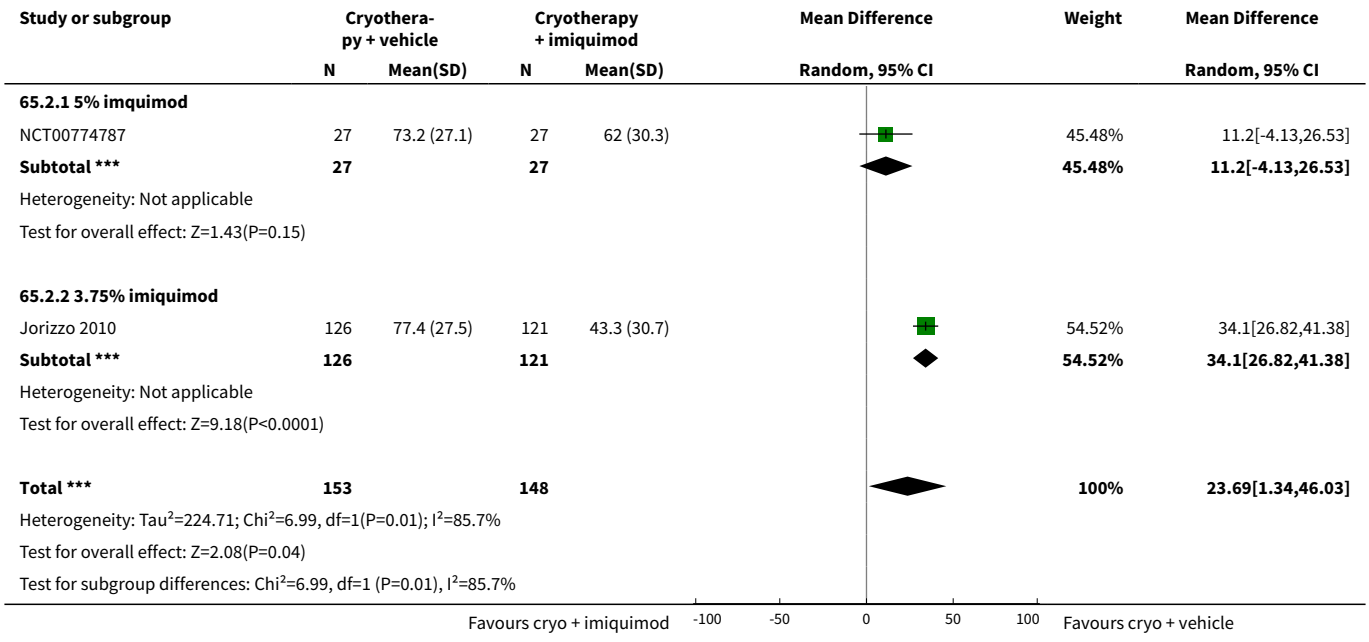
Comparison 65. Cryotherapy with imiquimod versus cryotherapy with vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participant complete clearance of all lesions	2	311	Risk Ratio (M-H, Random, 95% CI)	5.04 [1.37, 18.51]
1.1 5% imiquimod	1	64	Risk Ratio (M-H, Random, 95% CI)	2.48 [0.70, 8.76]
1.2 3.75% imiquimod	1	247	Risk Ratio (M-H, Random, 95% CI)	9.12 [3.36, 24.79]
2 Mean percentage of reduction in all lesion counts	2	301	Mean Difference (IV, Random, 95% CI)	23.69 [1.34, 46.03]
2.1 5% imquimod	1	54	Mean Difference (IV, Random, 95% CI)	11.20 [-4.13, 26.53]
2.2 3.75% imiquimod	1	247	Mean Difference (IV, Random, 95% CI)	34.10 [26.82, 41.38]
3 Withdrawal due to adverse events	2	312	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.33, 3.56]
3.1 5% imiquimod	1	65	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.01, 8.13]
3.2 3.75% imiquimod	1	247	Risk Ratio (M-H, Random, 95% CI)	1.30 [0.36, 4.73]
4 Skin irritation	2	311	Risk Ratio (M-H, Random, 95% CI)	2.55 [0.65, 10.04]
4.1 5% imiquimod	1	64	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.50, 5.13]
4.2 3.75% imiquimod	1	247	Risk Ratio (M-H, Random, 95% CI)	6.72 [0.84, 53.83]

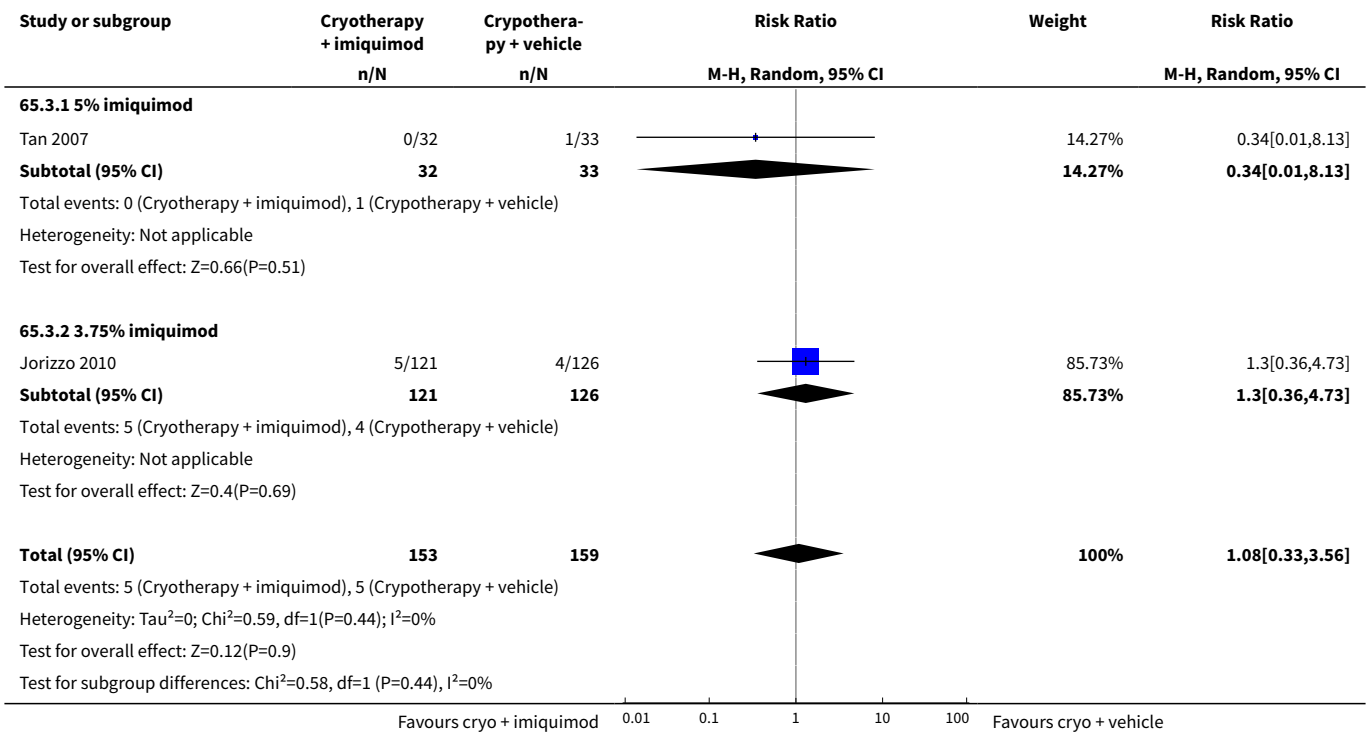
Analysis 65.1. Comparison 65 Cryotherapy with imiquimod versus cryotherapy with vehicle, Outcome 1 Participant complete clearance of all lesions.



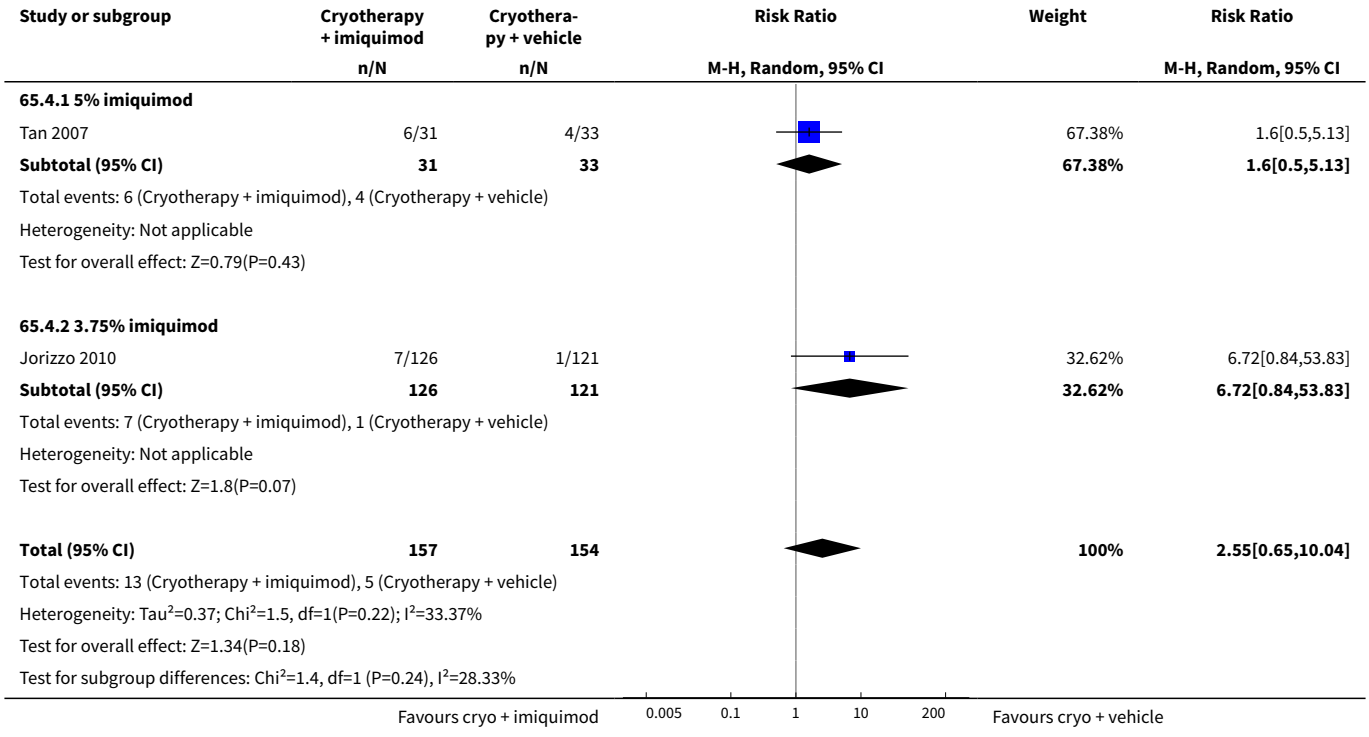
Analysis 65.2. Comparison 65 Cryotherapy with imiquimod versus cryotherapy with vehicle, Outcome 2 Mean percentage of reduction in all lesion counts.



Analysis 65.3. Comparison 65 Cryotherapy with imiquimod versus cryotherapy with vehicle, Outcome 3 Withdrawal due to adverse events.



Analysis 65.4. Comparison 65 Cryotherapy with imiquimod versus cryotherapy with vehicle, Outcome 4 Skin irritation.



Comparison 66. (3% diclofenac in 2.5% hyaluronic acid + ALA-red light PDT) versus (2.5% hyaluronic acid + ALA-red light PDT)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global Improvement Indices (-2 to 4) at 6 months			Other data	No numeric data
2 Mean reduction of lesion counts			Other data	No numeric data

Analysis 66.1. Comparison 66 (3% diclofenac in 2.5% hyaluronic acid + ALA-red light PDT) versus (2.5% hyaluronic acid + ALA-red light PDT), Outcome 1 Global Improvement Indices (-2 to 4) at 6 months.

		Global Improvement Indices (-2 to 4) at 6 months	
Study	Intervention	Patient	Investigator
Van der Geer 2009	Diclofenac in 2.5% hyaluronic acid + ALA-PDT	3.3	3.4
Van der Geer 2009	2.5% hyaluronic acid + ALA-PDT	2.4	2.7

Analysis 66.2. Comparison 66 (3% diclofenac in 2.5% hyaluronic acid + ALA-red light PDT) versus (2.5% hyaluronic acid + ALA-red light PDT), Outcome 2 Mean reduction of lesion counts.

		Mean reduction of lesion counts		
Study	Intervention	At 6 weeks	At 6 months	At 12 months
Van der Geer 2009	Diclofenac in 2.5% hyaluronic acid + ALA-PDT	10.13	11.56	12.5
Van der Geer 2009	2.5% hyaluronic acid + ALA-PDT	9.9	10.56	8.8

ADDITIONAL TABLES

Table 1. Overview for 3% diclofenac in 2.5% hyaluronic acid

Diclofenac in 2.5% hyaluronic acid compared to interventions for actinic keratoses in immunocompetent participants						
Intervention/Comparison intervention	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk **With comparator**	Corresponding risk **With intervention**				
Participant complete clearance						
3% diclofenac in 2.5% hyaluronic acid/2.5% hyaluronic acid	**Study population**		**RR 2.46** (1.66 to 3.66)	420 (3 studies)	⊕⊕⊕⊖ **moderate**	For all lesions, data from 30, 60, and 90 day treatments

Table 1. Overview for 3% diclofenac in 2.5% hyaluronic acid *(Continued)*

	127 per 1000	**313 per 1000** (211 to 466)				pooled together, assessment at 30 days after the end of treatment (Analysis 6.5)
	Moderate					
	132 per 1000	**325 per 1000** (219 to 483)				
3% diclofenac in 2.5% hyaluronic acid/5% imiquimod	-	-	-	-	-	Not reported
3% diclofenac in 2.5% hyaluronic acid + ALA-red light PDT/2.5% hyaluronic acid + ALA-red light PDT	-	-	-	-	-	Not reported
Mean reduction in lesion counts						
3% diclofenac in 2.5% hyaluronic acid/2.5% hyaluronic acid	The mean reduction in lesion counts in the control groups was **2.5 lesions**	The mean reduction of lesion counts in the intervention groups was **2.55 higher** (1.56 to 3.53 higher)	-	345 (2 studies)	⊕⊕⊕⊕ **high**	Data from 30, 60, and 90 day treatments pooled together, assessment 30 days after the end of treatment (Analysis 6.12)
3% diclofenac in 2.5% hyaluronic acid/ 5% imiquimod	-	-	-	-	-	Not reported
3% diclofenac in 2.5% hyaluronic acid + ALA-red light PDT/2.5% hyaluronic acid + ALA-red light PDT	See comment	See comment	Not estimable	10 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: at 6 weeks; diclofenac/hyaluronic acid (HA) + ALA-PDT = 10.13, HA + ALA-PDT= 9.9, at 6 months; diclofenac/HA + ALA-PDT = 11.56, HA + ALA-PDT = 10.56, at 12 months; diclofenac/HA + ALA-PDT = 12.5, HA + ALA-PDT = 8.8
Mean percentage of reduction in lesion counts						
All comparisons	-	-	-	-	-	Not reported
Withdrawal due to adverse events						
3% diclofenac in 2.5% hyaluronic acid/2.5% hyaluronic acid	**Study population**		**RR 3.59**	592 (4 studies)	⊕⊕⊕⊕ **high**	(Analysis 6.13)

Table 1. Overview for 3% diclofenac in 2.5% hyaluronic acid *(Continued)*

	40 per 1000	**144 per 1000** (77 to 269)	(1.92 to 6.7)			Additional data from intraindividual study: no participant withdrew because of adverse events (N = 20). GRADE = low.
	Moderate					
	43 per 1000	**154 per 1000** (83 to 288)				
3% diclofenac in 2.5% hyaluronic acid/5% imiquimod	**0 per 1000**	**0 per 1000**	Not estimable	49 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
3% diclofenac in 2.5% hyaluronic acid + ALA-red light PDT/2.5% hyaluronic acid + ALA-red light PDT	**0 per 1000**	**0 per 1000**	Not estimable	10 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Skin irritation						
3% diclofenac in 2.5% hyaluronic acid/2.5% hyaluronic acid	See comment	See comment	Not estimable	20 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study reported irritation only on the diclofenac treated side of 8 out of 20 participants
3% diclofenac in 2.5% hyaluronic acid/5% imiquimod	-	-	-	-	-	Not reported
3% diclofenac in 2.5% hyaluronic acid + ALA-red light PDT/2.5% hyaluronic acid + ALA-red light PDT	-	-	-	-	-	Not reported

Table 2. Overview for 5-fluorouracil

5-fluorouracil (5-FU) compared to interventions for actinic keratoses in immunocompetent participants

Intervention/Comparison intervention	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	Corresponding risk				
	With comparator	**With intervention**				
Participant complete clearance						
0.5% 5-FU/Vehicle	**Study population**		**RR 8.86** (3.67 to 21.40)	522 (3 studies)	⊕⊕⊕⊕ **high**	Data from 1, 2, and 4 week treatments were pooled together (Analysis 9.1)
	15 per 1000	**136 per 1000** (56 to 328)				

Table 2. Overview for 5-fluorouracil *(Continued)*

	Moderate					
	0 per 1000	**0 per 1000** (0 to 0)				
0.5% 5-FU with cryotherapy/Vehicle with cryotherapy	**71 per 1000**	**291 per 1000** (116 to 731)	**RR 4.08** (1.63 to 10.23)	142 (1 study)	⊕⊕⊖⊖ **low**	1 cycle (Analysis 62.1)
0.5% 5-FU/ALA-PDT	**292 per 1000**	**499 per 1000** (239 to 1000)	**RR 1.71** (0.74 to 3.98)	48 (1 study)	⊕⊖⊖⊖ **very low**	Data from blue light and pulsed dye laser were pooled (Analysis 11.1)
0.5% 5-FU/5.0% 5-FU	See comment	See comment	Not estimable	21 (1 study)	⊕⊖⊖⊖ **very low**	Intraindividual study: 0.5% and 5.0% 5-FU = 9/21
5% 5-FU with 0.05% tretinoin /5% 5-FU with placebo	-	-	-	-	-	Not reported
5% 5-FU /10% masoprocol	-	-	-	-	-	Not reported
5% 5-FU/5% Imiquimod	**Study population**		**RR 1.85** (0.41 to 8.33)	89 (2 studies)	⊕⊖⊖⊖ **very low**	(Analysis 13.1)
	600 per 1000	**1000 per 1000** (246 to 1000)				
	Moderate					
	555 per 1000	**1000 per 1000** (230 to 1000)				
5% 5-FU/Carbon dioxide laser resurfacing	-	-	-	-	-	Not reported
5% 5-FU/Er:YAG laser resurfacing	-	-	-	-	-	Not reported
5% 5-FU/Cryotherapy	**680 per 1000**	**959 per 1000** (721 to 1000)	**RR 1.41** (1.06 to 1.87)	49 (1 study)	⊕⊕⊖⊖ **low**	Only data after the treatment (Analysis 14.1)
5% 5-FU/ Trichloroacetic acid peel	-	-	-	-	-	Not reported
Mean reduction in lesion counts						
0.5% 5-FU/Vehicle	The mean reduction in lesion counts in the control groups was	The mean reduction in lesion counts in the intervention groups was **5.40 higher** (2.94 to 7.86 higher)	-	142 (1 study)	⊕⊕⊕⊖ **moderate**	Data from 1, 2, and 4 week treatment were pooled. (Analysis 9.2) Results from another study (N = 177) with

Table 2. Overview for 5-fluorouracil *(Continued)*

	4 lesions					no SD: placebo: 2.7 lesions, 5-FU = 8.8 lesions, GRADE = moderate
0.5% 5-FU with cryotherapy/Vehicle with cryotherapy	The mean reduction in lesion counts in the control groups was **6.6 lesions**	The mean reduction in lesion counts in the intervention groups was **2 higher** (0.49 lower to 4.49 higher)		142 (1 study)	⊕⊕⊕⊖ **moderate**	1 cycle (Analysis 62.2)
0.5% 5-FU/ALA-PDT	-	-	-	-	-	Not reported
0.5% 5-FU/5.0% 5-FU	See comment	See comment	Not estimable	21 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: results with no SD: 0.5% 5-FU = 8.8 lesions, 5.0% 5-FU = 6.1 lesions
5% 5-FU with 0.05% tretinoin /5% 5-FU with placebo	The mean reduction in lesion counts in the control groups was **11.1 lesions**	The mean reduction in lesion counts in the intervention groups was **1.2 higher** (3.24 lower to 5.64 higher)	-	19 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 12.1)
5% 5-FU /10% masoprocol	The mean reduction in lesion counts in the control groups was **11.3 lesions**	The mean reduction in lesion counts in the intervention groups was **1.5 higher** (2.36 lower to 5.36 higher)	-	49 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 15.2)
5% 5-FU/5% Imiquimod	-	-	-	-	-	Not reported
5% 5-FU/Carbon dioxide laser resurfacing	-	-	-	-	-	Not reported
5% 5-FU/Er:YAG laser resurfacing	See comment	See comment	Not estimable	55 (1 study)	⊕⊕⊖⊖ **low**	Results with no SD: number of lesions at 3 months:5-FU = 13.2, resurfacing = 13.8, at 6 months:5-FU = 12.5, resurfacing = 13.9, at 12 months: 5-FU = 12.4, resurfacing = 14.2
5% 5-FU/Cryotherapy	-	-	-	-	-	Not reported
5% 5-FU/ Trichloroacetic acid peel	-	-	-	-	-	Not reported
Mean percentage of reduction in lesion counts						

Table 2. Overview for 5-fluorouracil *(Continued)*

0.5% 5-FU/Vehicle	The mean percentage of reduction in lesion counts ranged across control groups from **28.8 per cent**	The mean percentage of reduction in lesion counts in the intervention groups was **33.60 higher** (22.88 to 44.32 higher)	-	142 (1 study)	⊕⊕⊕⊖ **moderate**	Data from 1 week treatment.(Analysis 9.3) Results from two other studies with no SD 1) (N = 207) placebo = 21.6%, 5-FU = 69.5%, GRADE = low, 2)(N = 177) placebo = 34.4%, 5-FU = 78.5%, GRADE = moderate
0.5% 5-FU with cryotherapy/Vehicle with cryotherapy	The mean percentage of reduction in lesion counts in the control groups was **45.6 per cent**	The mean percentage of reduction in lesion counts in the intervention groups was **21.4 higher** (5.1 to 37.7 higher)	-	142 (1 study)	⊕⊕⊕⊖ **moderate**	(Analysis 62.3)
0.5% 5-FU/ALA-PDT	-	-	-	-	-	Not reported
0.5% 5-FU/5.0% 5-FU	See comment	See comment	Not estimable	21 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: results with no SD: 0.5% 5-FU = 67% and 5.0% 5-FU = 47%
5% 5-FU with 0.05% tretinoin /5% 5-FU with placebo	-	-	-	-	-	Not reported
5% 5-FU /10% masoprocol	The mean percentage of reduction in lesion counts in the control groups was **77.6 percent**	The mean percentage of reduction in lesion counts in the intervention groups was **20 higher** (11.82 to 28.18 higher)	-	49 (1 study)	⊕⊕⊕⊖ **moderate**	(Analysis 15.3)
5% 5-FU/5% Imiquimod	See comment	See comment	Not estimable	39 (1 study)	⊕⊕⊖⊖ **low**	Results with no SD: 5% 5-FU = 94%, 5% imiquimod = 66%
5% 5-FU/Carbon dioxide laser resurfacing	The mean percentage of reduction in lesion counts in the control groups was **92 percent**	The mean percentage of reduction in lesion counts in the intervention groups was **8.80 lower** (20.76 lower to 3.16 higher)	-	14 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 16.1)
5% 5-FU/Er:YAG laser resurfacing	See comment	See comment	Not estimable	55 (1 study)	⊕⊕⊖⊖ **low**	Results with no SD: at 6 months: 5-FU = 79.2%, resurfacing 94.5%, at 12 months: 5-FU = 76.6%, resurfacing = 91.1%

Table 2. Overview for 5-fluorouracil *(Continued)*

5% 5-FU/Cryotherapy	-	-	-	-	-	Not reported
5% 5-FU/ Trichloroacetic acid peel	The mean percentage of reduction in lesion counts in the control groups was **89 per cent**	The mean percentage of reduction in lesion counts in the intervention groups was **5.8 lower** (15.38 lower to 3.78 higher)	-	18 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 18.1)
Withdrawal due to adverse events						
0.5% 5-FU/Vehicle	**0 per 1000**	**N/A** (5/119 = 42/1000)	**RR 5.41** (0.3 to 96.18)	177 (1 study)	⊕⊖⊖⊖ **very low**	Data from 1, 2, and 4 week treatments were pooled.(Analysis 9.4) Another study reported 24/207 participants withdrew because of adverse events and 12 of them were in 4 week 5-FU group. GRADE = low
0.5% 5-FU with cryotherapy/Vehicle with cryotherapy	See comment	See comment	Not estimable	142 (1 study)	⊕⊕⊖⊖ **low**	There were no participant withdrawals in the first part of this three part study (incomplete data were given for the whole study).
0.5% 5-FU/ALA-PDT	**0 per 1000**	**N/A** (1/12 = 83/1000)	**RR 5.77** (0.25 to 131.92)	36 (1 study)	⊕⊕⊖⊖ **low**	Data from blue light and pulsed dye laser were pooled (Analysis 11.2)
0.5% 5-FU/5.0% 5-FU	See comment	See comment	Not estimable	21 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: 16/21 discontinued treatment but did not withdraw: 4 because of 0.5%, 8 because of 5.0% , 4 because of both creams.
5% 5-FU with 0.05% tretinoin /5% 5-FU with placebo	See comment	See comment	Not estimable	19 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: 1 participant withdrew because of irritation but associated treatment was not specified.
5% 5-FU /10% masoprocol	**0 per 1000**	**N/A** (1/30 = 33/1000)	**RR 2.71** (0.12 to 63.84)	57 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 15.4)

Table 2. Overview for 5-fluorouracil *(Continued)*

5% 5-FU/5% Imiquimod	**0 per 1000**	**0 per 1000**	Not estimable	89 (2 studies)	⊕⊕⊖⊖ **low**	There were no participant withdrawals due to adverse events.
5% 5-FU/Carbon dioxide laser resurfacing	**250 per 1000**	**45 per 1000** (2 to 817)	**RR 0.18** (0.01 to 3.27)	17 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 16.2)
5% 5-FU/Er:YAG laser resurfacing	**0 per 1000**	**N/A** (1/27 = 37/1000)	**RR 3.11** (0.13 to 73.11)	55 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 17.1)
5% 5-FU/Cryotherapy	**0 per 1000**	**0 per 1000**	Not estimable	49 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
5% 5-FU/ Trichloroacetic acid peel	**0 per 1000**	**0 per 1000**	Not estimable	18 (1 study)	⊕⊕⊖⊖ **low**	There were no participant withdrawals due to adverse events.
Skin irritation						
0.5% 5-FU/Vehicle	**654 per 1000**	**948 per 1000** (830 to 1000)	**RR 1.45** (1.27 to 1.65)	384 (2 studies)	⊕⊕⊕⊖ **moderate**	Data from 1, 2, and 4 week treatments were pooled (Analysis 9.5)
0.5% 5-FU with cryotherapy/Vehicle with cryotherapy	-	-	-	-	-	Not reported
0.5% 5-FU/ALA-PDT	-	-	-	-	-	Not reported
0.5% 5-FU/5.0% 5-FU	**1000 per 1000**	**1000 per 1000**	-	21 (1 study)	⊕⊕⊕⊖ **moderate**	Intraindividual study: All participants reported facial irritation in association with both creams
5% 5-FU with 0.05% tretinoin /5% 5-FU with placebo	See comment	See comment	Not estimable	19 (1 study)	⊕⊕⊕⊖ **moderate**	Intraindividual study: 12 had more irritation with tretinoin, 4 had more with placebo, and 3 had equal irritation.
5% 5-FU /10% masoprocol	-	-	-	-	-	Not reported
5% 5-FU/5% Imiquimod	-	-	-	-	-	Not reported
5% 5-FU/Carbon dioxide laser resurfacing	-	-	-	-	-	Not reported

Table 2. Overview for 5-fluorouracil *(Continued)*

5% 5-FU/Er:YAG laser resurfacing	**429 per 1000**	**703 per 1000** (429 to 1000)	**RR 1.64** (1 to 2.69)	55 (1 study)	⊕⊕⊖⊖ **low**	At the end of treatment (Analysis 17.2)
5% 5-FU/Cryotherapy	-	-	-	-	-	Not reported
5% 5-FU/ Trichloroacetic acid peel	-	-	-	-	-	Not reported

Table 3. Overview for photodynamic therapy

Photodynamic therapy compared to interventions for actinic keratoses in immunocompetent participants

Intervention/Comparison intervention	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk **With comparator**	Corresponding risk **With intervention**				
Participant complete clearance						
ALA-PDT						
1h ALA-blue light PDT /1h ALA-pulsed dye laser PDT (field-directedtreatments)	**83 per 1000**	**500 per 1000** (71 to 1000)	**RR 6** (0.85 to 42.59)	24 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 48.1)
1h ALA-blue light PDT /0.5% 5-FU (field-directedtreatments)	**500 per 1000**	**500 per 1000** (225 to 1000)	**RR 1** (0.45 to 2.23)	24 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 50.1)
14-18h ALA-blue light PDT /14-18h placebo-blue light PDT (individual lesions)	**97 per 1000**	**602 per 1000** (279 to 1000)	**RR 6.22** (2.88 to 13.43)	243 (1 study)	⊕⊖⊖⊖ **very low**	1 treatment. (Analysis 47.1) Additional intraindividual study: ALA-PDT: 16/35, placebo-PDT = 2/35. GRADE = moderate
1h ALA-pulsed dye laser PDT /0.5% 5-FU (field-directedtreatments)	**500 per 1000**	**85 per 1000** (10 to 590)	**RR 0.17** (0.02 to 1.18)	24 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 50.1)
0.5h ALA-red light PDT/1h ALA-red light PDT (individual lesions)	**474 per 1000**	**237 per 1000** (118 to 469)	**RR 0.5** (0.25 to 0.99)	72 (1 study)	⊕⊕⊖⊖ **low**	Data from assessment at 8 weeks after the end of treatment (Analysis 49.2)

Table 3. Overview for photodynamic therapy *(Continued)*

0.5h ALA-red light PDT/2h ALA-red light PDT (individual lesions)	**471 per 1000**	**235 per 1000** (118 to 475)	**RR 0.5** (0.25 to 1.01)	68 (1 study)	⊕⊖⊖⊖ **very low**	Data from assessment at 8 weeks after the end of treatment (Analysis 49.2)
0.5h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	**735 per 1000**	**235 per 1000** (125 to 449)	**RR 0.32** (0.17 to 0.61)	68 (1 study)	⊕⊕⊖⊖ **low**	Data from assessment at 8 weeks after the end of treatment (Analysis 49.2)
1h ALA-red light PDT /2h ALA-red light PDT (individual lesions)	**471 per 1000**	**475 per 1000** (292 to 772)	**RR 1.01** (0.62 to 1.64)	72 (1 study)	⊕⊖⊖⊖ **very low**	Data from assessment at 8 weeks after the end of treatment (Analysis 49.2)
1h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	**735 per 1000**	**471 per 1000** (324 to 699)	**RR 0.64** (0.44 to 0.95)	72 (1 study)	⊕⊕⊖⊖ **low**	Data from assessment at 8 weeks after the end of treatment (Analysis 49.2)
2h ALA-red light PDT/4h ALA-red light PDT (individual lesions)	**735 per 1000**	**471 per 1000** (309 to 706)	**RR 0.64** (0.42 to 0.96)	68 (1 study)	⊕⊕⊖⊖ **low**	Data from assessment at 8 weeks after the end of treatment (Analysis 49.2)
3-4h ALA-red light PDT/3 to 4h placebo-red light PDT (individual lesions)	**89 per 1000**	**527 per 1000** (297 to 935)	**RR 5.94** (3.35 to 10.54)	422 (3 studies)	⊕⊕⊕⊕ **high**	1 treatment (Analysis 47.1)
3% diclofenac in 2.5% hyaluronan gel + 4h ALA-red light PDT /2.5% hyaluronan gel + 4h ALA-red light PDT (field-directedtreatments)	-	-	-	-	-	Not reported
4h ALA-red light PDT/Cryotherapy (individual lesions)	**443 per 1000**	**580 per 1000** (465 to 726)	**RR 1.31** (1.05 to 1.64)	297 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 51.1)
ALA-red light PDT (individual lesions)/5% imiquimod (field-directedtreatment)	-	-	-	-	-	Not reported
ALA-blue light PDT + 5% imiquimod / ALA-blue light PDT + placebo (field-directedtreatments)	See comment	See comment	Not estimable	25 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: ALA-PDT + 5% imiquimod = 2/25; ALA-PDT + placebo = 2/25
ALA-PDT versus MAL-PDT						
5h ALA-red light PDT /3h MAL-red light PDT	See comment	See comment	Not estimable	16 (1 study)	⊕⊕⊕⊖ **moderate**	Intraindividual study: ALA-PDT = 6/16, MAL-PDT = 7/16

Table 3. Overview for photodynamic therapy *(Continued)*

(field-directedtreatments)						
MAL-PDT						
All day 16% MAL-daylight PDT / All day 8% MAL-daylight PDT (field-directedtreatments)	-	-	-	-	-	Not reported
2h MAL-daylight PDT /3h MAL-daylight PDT (field-directedtreatments)	-	-	-	-	-	Not reported
2.5-4h MAL-red light PDT /2.5-4h placebo-red light PDT (individual lesions)	**147 per 1000**	**656 per 1000** (466 to 924)	**RR 4.46** (3.17 to 6.28)	482 (5 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 52.1)
3h MAL-red light LED PDT /3h MAL-broad visible + water-filtered infrared A PDT (individual lesions)	**500 per 1000**	**575 per 1000** (380 to 865)	**RR 1.15** (0.76 to 1.73)	80 (1 study)	⊕⊕⊖⊖ **low**	Data from assessment at 12 weeks after the end of treatment.(Analysis 53.1)
3h MAL-red light LED PDT /3h MAL-daylight PDT (field-directedtreatments)	-	-	-	-	-	Not reported
Single 3h MAL-red light PDT / Multiple 3h MAL-red light PDT [2 treatments 1 week apart] (individual lesions)	**755 per 1000**	**883 per 1000** (777 to 1000)	**RR 1.17** (1.03 to 1.33)	211 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 57.1)
3h MAL-red light PDT /Cryotherapy (individual lesions)	-	-	-	-	-	Not reported
Mean reduction in lesion counts						
ALA-PDT						
1h ALA-blue light PDT /1h ALA-pulsed dye laser PDT (field-directedtreatments)	-	-	-	-	-	Not reported
1h ALA-blue light PDT /0.5% 5-FU (field-directedtreatments)	-	-	-	-	-	Not reported
14-18h ALA-blue light PDT /14-18h placebo-blue light PDT (individual lesions)	-	-	-	-	-	Not reported

Table 3. Overview for photodynamic therapy *(Continued)*

1h ALA-pulsed dye laser PDT /0.5% 5-FU (field-directedtreatments)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT/1h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT/2h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-red light PDT /2h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
2h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
3-4h ALA-red light PDT /3-4h placebo-red light PDT (individual lesions)	-	-	-	-	-	Not reported
3% diclofenac in 2.5% hyaluronic acid gel + 4h ALA-red light PDT /2.5% hyaluronic acid gel + 4h ALA-red light PDT (field-directedtreatments)	See comment	See comment	Not estimable	10 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: at 6 weeks; diclofenac/hyaluronic acid (HA) + ALA-PDT = 10.13, HA + ALA-PDT= 9.9, at 6 months:; diclofenac/HA + ALA-PDT = 11.56, HA + ALA-PDT = 10.56, at 12 months; diclofenac/HA + ALA-PDT = 12.5, HA + ALA-PDT = 8.8
4h ALA-red light PDT /Cryotherapy (individual lesions)	-	-	-	-	-	Not reported
ALA-red light PDT (individual lesions)/5% imiquimod (field-directedtreatment)	-	-	-	-	-	Not reported
ALA-blue light PDT + 5% imiquimod / ALA-blue light PDT + placebo (field-directedtreatments)	See comment	See comment	Not estimable	25 (1 study)	⊕⊕⊖⊖ **low**	Results from intraindividual study without SD: ALA-PDT + 5% imiquimod = 19.9 lesions; ALA-PDT + placebo = 16.0 lesions
ALA-PDT versus MAL-PDT						
5h ALA-red light PDT /3h MAL-red light PDT	The mean reduction	The mean reduction	-	15 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 59.1)

Table 3. Overview for photodynamic therapy *(Continued)*

(field-directedtreatments)	in lesion counts in the control groups was **5.6 lesions**	in lesion counts in the intervention groups was **0.6 higher** (1.28 lower to 2.48 higher)				
MAL-PDT						
All day 16% MAL-daylight PDT / All day 8% MAL-daylight PDT (field-directedtreatments)	The mean reduction in lesion counts in the control groups was **14.5 lesions**	The mean reduction in lesion counts in the intervention groups was **0.3 higher** (3.77 lower to 4.37 higher)	-	29 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 56.1)
2h MAL-daylight PDT /3h MAL-daylight PDT (field-directedtreatments)	The mean reduction in lesion counts in the control groups was **9.7 lesions**	The mean reduction in lesion counts in the intervention groups was **0.1 higher** (3.17 lower to 3.37 higher)		120 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 55.1)
2.5-4h MAL-red light PDT /2.5-4h placebo-red light PDT (individual lesions)	-	-	-	-	-	Not reported
3h MAL-red light LED PDT /3h MAL-broad visible + water-filtered infrared A PDT (individual lesions)	-	-	-	-	-	Not reported
3h MAL-red light LED PDT /3h MAL-daylight PDT (field-directedtreatments)	The mean reduction in lesion counts in the control groups was **8.4 lesions**	The mean reduction in lesion counts in the intervention groups was **0.4 lower**	-	29 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 54.1)

Table 3. Overview for photodynamic therapy *(Continued)*

		(3.23 lower to 2.43 higher)				
Single 3h MAL-red light PDT / Multiple 3h MAL-red light PDT [2 treatments 1 week apart] (individual lesions)	-	-	-	-	-	Not reported
3h MAL-red light PDT /Cryotherapy (individual lesions)	-	-	-	-	-	Not reported
Mean percentage of reduction in lesion count						
ALA-PDT						
1h ALA-blue light PDT /1h ALA-pulsed dye laser PDT (field-directedtreatments)	-	-	-	-	-	Not reported
1h ALA-blue light PDT /0.5% 5-FU (field-directedtreatments)	-	-	-	-	-	Not reported
14-18h ALA-blue light PDT /14-18h placebo-blue light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-pulsed dye laser PDT /0.5% 5-FU (field-directedtreatments)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT/1h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT/2h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-red light PDT /2h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
2h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported

Table 3. Overview for photodynamic therapy *(Continued)*

3-4h ALA-red light PDT /3-4h placebo-red light PDT (individual lesions)	-	-	-	-	-	Not reported
3% diclofenac in 2.5% hyaluronic acid gel + 4h ALA-red light PDT /2.5% hyaluronic acid gel + 4h ALA-red light PDT (field-directedtreatments)	-	-	-	-	-	Not reported
4h ALA-red light PDT /Cryotherapy (individual lesions)	-	-	-	-	-	Not reported
ALA-red light PDT (individual lesions)/5% imiquimod (field-directedtreatment)	-	-	-	-	-	Not reported
ALA-blue light PDT + 5% imiquimod / ALA-blue light PDT + placebo (field-directedtreatments)	See comment	See comment	Not estimable	25 (1 study)	⊕⊕⊖⊖ **low**	Results from intraindividual study without SD: ALA-PDT + 5% imiquimod = 86.7%; ALA-PDT + placebo = 73.1%
ALA-PDT versus MAL-PDT						
5h ALA-red light PDT /3h MAL-red light PDT (field-directedtreatments)	-	See comment	-	-	-	Not reported
MAL-PDT						
All day 16% MAL-daylight PDT / All day 8% MAL-daylight PDT (field-directedtreatments)	See comment	See comment	Not estimable	29 (1 study)	⊕⊕⊖⊖ **low**	Data with no SD: 16% MAL-daylight PDT = 76.9%, 8% MAL-daylight PDT = 79.5%.
2h MAL-daylight PDT /3h MAL-daylight PDT (field-directedtreatments)	The mean percentage of reduction in lesion counts in the control groups was **74.6 percent**	The mean percentage of reduction in lesion counts in the intervention groups was **2.6 higher** (6.46 lower to 11.66 higher)	-	120 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 55.2)
2.5-4h MAL-red light PDT /2.5-4h placebo-red light PDT	-	-	-	-	-	Not reported

Table 3. Overview for photodynamic therapy *(Continued)*

(individual lesions)						
3h MAL-red light LED PDT /3h MAL-broad visible + water-filtered infrared A PDT (individual lesions)	-	-	-	-	-	Not reported
3h MAL-red light LED PDT /3h MAL-daylight PDT (field-directedtreatments)	See comment	See comment	Not estimable	29 (1 study)	⊕⊕⊖⊖ **low**	Data with no SD: MAL-red light LED PDT = 71%, MAL-daylight PDT = 79%.
Single 3h MAL-red light PDT / Multiple 3h MAL-red light PDT [2 treatments 1 week apart] (individual lesions)	-	-	-	-	-	Not reported
3h MAL-red light PDT /Cryotherapy (individual lesions)	See comment	See comment	Not estimable	240 (2 studies)	⊕⊖⊖⊖ **very low**	Intraindividual studies with no SD: at 12 weeks: MAL-PDT = 84.4%, cryotherapy = 74.5%, at 24 weeks: MAL-PDT = 75-86.7%, cryotherapy = 83.9-87%
Withdrawal due to adverse events						
ALA-PDT						
1h ALA-blue light PDT /1h ALA-pulsed dye laser PDT (field-directedtreatments)	**0 per 1000**	**0 per 1000**	Not estimable	24 (1 study)	⊕⊕⊖⊖ **low**	There were no participant withdrawals due to adverse events.
1h ALA-blue light PDT /0.5% 5-FU (field-directedtreatments)	**83 per 1000**	**28 per 1000** (1 to 621)	**RR 0.33** (0.01 to 7.45)	24 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 50.3)
14-18h ALA-blue light PDT /14-18h placebo-blue light PDT (individual lesions)	**0 per 1000**	**0 per 1000**	Not estimable	271 (2 studies)	⊕⊕⊖⊖ **low**	There were no participant withdrawals due to adverse events.
1h ALA-pulsed dye laser PDT /0.5% 5-FU (field-directedtreatments)	**83 per 1000**	**28 per 1000** (1 to 621)	**RR 0.33** (0.01 to 7.45)	24 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 50.3)
0.5h ALA-red light PDT/1h ALA-red light PDT (individual lesions)	See comment	See comment	Not estimable	72 (1 study)	⊕⊖⊖⊖ **very low**	No details were given for the reasons for withdrawal.
0.5h ALA-red light PDT/2h ALA-red light PDT (individual lesions)	See comment	See comment	Not estimable	68 (1 study)	⊕⊖⊖⊖ **very low**	No details were given for the reasons for withdrawal.

Table 3. Overview for photodynamic therapy *(Continued)*

0.5h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	See comment	See comment	Not estimable	68 (1 study)	⊕⊝⊝⊝ **very low**	No details were given for the reasons for withdrawal.
1h ALA-red light PDT /2h ALA-red light PDT (individual lesions)	See comment	See comment	Not estimable	72 (1 study)	⊕⊝⊝⊝ **very low**	No details were given for the reasons for withdrawal.
1h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	See comment	See comment	Not estimable	72 (1 study)	⊕⊝⊝⊝ **very low**	No details were given for the reasons for withdrawal.
2h ALA-red light PDT /4h ALA-red light PDT (individual lesions)	See comment	See comment	Not estimable	68 (1 study)	⊕⊝⊝⊝ **very low**	No details were given for the reasons for withdrawal.
3-4h ALA-red light PDT /3-4h placebo-red light PDT (individual lesions)	**0 per 1000**	**0 per 1000**	Not estimable	391 (3 studies)	⊕⊕⊕⊕ **high**	There were no participant withdrawals due to adverse events.
3% diclofenac in 2.5% hyaluronic acid gel + 4h ALA-red light PDT /2.5% hyaluronic acid gel + 4h ALA-red light PDT (field-directedtreatments)	**0 per 1000**	**0 per 1000**	Not estimable	10 (1 study)	⊕⊕⊕⊝ **moderate**	There were no participant withdrawals due to adverse events.
4h ALA-red light PDT /Cryotherapy (individual lesions)	**0 per 1000**	**0 per 1000**	Not estimable	255 (1 study)	⊕⊕⊕⊝ **moderate**	There were no participant withdrawals due to adverse events.
ALA-red light PDT (individual lesions)/5% imiquimod (field-directedtreatment)	**0 per 1000**	**0 per 1000**	Not estimable	30 (1 study)	⊕⊕⊝⊝ **low**	There were no participant withdrawals due to adverse events.
ALA-blue light PDT + 5% imiquimod / ALA-blue light PDT + placebo (field-directedtreatments)	**0 per 1000**	**0 per 1000**	Not estimable	25 (1 study)	⊕⊕⊝⊝ **low**	There were no participant withdrawals due to adverse events.
ALA-PDT versus MAL-PDT						
5h ALA-red light PDT /3h MAL-red light PDT (field-directedtreatments)	**0 per 1000**	**0 per 1000**	Not estimable	15 (1 study)	⊕⊕⊕⊝ **moderate**	There were no participant withdrawals due to adverse events.
MAL-PDT						
All day 16% MAL-daylight PDT / All day 8% MAL-daylight PDT (field-directedtreatments)	See comment	See comment	Not estimable	29 (1 study)	⊕⊕⊕⊝ **moderate**	One of 30 participants withdrew because of adverse events unrelated to treatments.
2h MAL-daylight PDT /3h MAL-daylight PDT (field-directedtreatments)	**0 per 1000**	**0 per 1000**	Not estimable	120 (1 study)	⊕⊕⊕⊝ **moderate**	There were no participant withdrawals due to adverse events.

Table 3. Overview for photodynamic therapy *(Continued)*

2.5-4h MAL-red light PDT /2.5-4h placebo-red light PDT (individual lesions)	**0 per 1000**	**N/A** (3/130 = 23/1000)	**RR 2** (0.23 to 17.74)	191 (2 studies)	⊕⊖⊖⊖ **very low**	(Analysis 52.3) Two additional studies with no participant withdrawals because of adverse events (N = 211). GRADE = low
3h MAL-red light LED PDT /3h MAL-broad visible + water-filtered infrared A PDT (individual lesions)	**0 per 1000**	**0 per 1000**	Not estimable	78 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
3h MAL-red light LED PDT /3h MAL-daylight PDT (field-directedtreatments)	**0 per 1000**	**0 per 1000**	Not estimable	29 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Single 3h MAL-red light PDT / Multiple 3h MAL-red light PDT [2 treatments 1 week apart] (individual lesions)	**9 per 1000**	**3 per 1000** (0 to 77)	**RR 0.34** (0.01 to 8.17)	211 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 57.2)
3h MAL-red light PDT /Cryotherapy (individual lesions)	**11 per 1000**	**10 per 1000** (1 to 67)	**RR 0.94** (0.14 to 6.36)	379 (2 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 58.1) Two additional intraindividual studies: 4 of 119 and 2 of 121 participants withdrew because of adverse events and one of them was related to MAL-PDT. GRADE = low
Skin irritation						
ALA-PDT						
1h ALA-blue light PDT /1h ALA-pulsed dye laser PDT (field-directedtreatments)	-	-	-	-	-	Not reported
1h ALA-blue light PDT /0.5% 5-FU (field-directedtreatments)	-	-	-	-	-	Not reported
14-18h ALA-blue light PDT /14-18h placebo-blue light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-pulsed dye laser PDT /0.5% 5-FU (field-directedtreatments)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT/1h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported

Table 3. Overview for photodynamic therapy *(Continued)*

0.5h ALA-red light PDT/2h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
0.5h ALA-red light PDT/4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-red light PDT/2h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
1h ALA-red light PDT/4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
2h ALA-red light PDT/4h ALA-red light PDT (individual lesions)	-	-	-	-	-	Not reported
3 to 4h ALA-red light PDT /3 to 4h placebo-red light PDT (individual lesions)	**0 per 1000**	**N/A (77/217 = 355/1000)**	**RR 59.72** (3.75 to 952.48)	300 (2 studies)	⊕⊕⊕⊖ **moderate**	Data for ALA-PDT was given separately for two studies but not for placebo. Data from assessment after treatment (Analysis 47.7)
3% diclofenac in 2.5% hyaluronic acid gel + 4h ALA-red light PDT /2.5% hyaluronic acid gel + 4h ALA-red light PDT (field-directedtreatments)	-	-	-	-	-	Not reported
4h ALA-red light PDT /Cryotherapy (individual lesions)	**101 per 1000**	**371 per 1000** (220 to 627)	**RR 3.69** (2.19 to 6.23)	297 (1 study)	⊕⊕⊖⊖ **low**	Assessment one day after the treatment (Analysis 51.2)
ALA-red light PDT (individual lesions)/5% imiquimod (field-directedtreatment)	-	-	-	-	-	Not reported
ALA-blue light PDT + 5% imiquimod / ALA-blue light PDT + placebo (field-directedtreatments)	-	-	-	-	-	Not reported
ALA-PDT versus MAL-PDT						
5h ALA-red light PDT /3h MAL-red light PDT (field-directedtreatments)	-	-	-	-	-	Not reported
MAL-PDT						
All comparisons	-	-	-	-	-	Not reported

Table 4. Overview for cryotherapy

Cryotherapy compared to interventions for actinic keratoses in immunocompetent participants						
Intervention/ Comparison intervention	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	Corresponding risk				
-	**With comparator**	**With intervention**	-	-	-	-
Participant complete clearance						
Cryotherapy /Betulin-based oleogel	**643 per 1000**	**784 per 1000** (489 to 1000)	**RR 1.22** (0.76 to 1.97)	28 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 42.1)
Cryotherapy/cryotherapy with betulin-based oleogel	**714 per 1000**	**786 per 1000** (514 to 1000)	**RR 1.1** (0.72 to 1.69)	28 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 61.1)
Cryotherapy/5% 5-FU	**958 per 1000**	**680 per 1000** (518 to 901)	**RR 0.71** (0.54 to 0.94)	49 (1 study)	⊕⊕⊖⊖ **low**	Assessment after treatment (Analysis 43.1)
Vehicle with cryotherapy/0.5% 5-FU with cryotherapy	**292 per 1000**	**70 per 1000** (29 to 178)	**RR 0.24** (0.1 to 0.61)	142 (1)	⊕⊕⊖⊖ **low**	1 cycle (Analysis 63.1)
Cryotherapy /Imiquimod	**846 per 1000**	**677 per 1000** (499 to 931)	**RR 0.8** (0.59 to 1.10)	51 (1 study)	⊕⊖⊖⊖ **very low**	5% imiquimod (Analysis 44.1)
Cryotherapy with vehicle / Cryotherapy with imiquimod	**Study population**		**RR 0.2** (0.05 to 0.73)	311 (2 studies)	⊕⊕⊕⊕ **high**	Pooled data (5% and 3.75% imiquimod)(Analysis 64.1) Results from an additional intraindividual study: cryotherapy + vehicle = 5/27, cryotherapy+imiquimod = 8/27 GRADE = moderate
	287 per 1000	**57 per 1000** (14 to 209)				
	Moderate					
	264 per 1000	**53 per 1000** (13 to 193)				
Cryotherapy /ALA-red light PDT	**581 per 1000**	**442 per 1000** (354 to 558)	**RR 0.76** (0.61 to 0.96)	297 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 46.1)
Cryotherapy/MAL-red light PDT	-	-	-	-	-	Not reported
Mean reduction in lesion counts						
Cryotherapy /Betulin-based oleogel	-	-	-	-	-	Not reported

Table 4. Overview for cryotherapy *(Continued)*

Cryotherapy/cryotherapy with betulin-based oleogel	-	-	-	-	-	Not reported
Cryotherapy/5% 5-FU	-	-	-	-	-	Not reported
Vehicle + cryotherapy/0.5% 5-FU + cryotherapy	The mean reduction in lesion counts in the control groups was **8.6 lesions**	The mean reduction in lesion counts in the intervention groups was **2 lower** (4.49 lower to 0.49 higher)	-	142 (1)	⊕⊕⊕⊖ **moderate**	1 cycle (Analysis 63.2)
Cryotherapy /Imiquimod	-	-	-	-	-	Not reported
Cryotherapy with vehicle / Cryotherapy with imiquimod	-	-	-	-	-	Not reported
Cryotherapy /ALA-red light PDT	-	-	-	-	-	Not reported
Cryotherapy/MAL-red light PDT	-	-	-	-	-	Not reported
Mean percentage of reduction in lesion counts						
Cryotherapy /Betulin-based oleogel	-	-	-	-	-	Not reported
Cryotherapy/cryotherapy with betulin-based oleogel	-	-	-	-	-	Not reported
Cryotherapy/5% 5-FU	-	-	-	-	-	Not reported
Vehicle with cryotherapy/0.5% 5-FU with cryotherapy	The mean percentage of reduction in lesion counts in the control groups was **67 percent**	The mean percentage of reduction in lesion counts in the intervention groups was **21.4 lower** (37.7 to 5.1 lower)	-	142 (1)	⊕⊕⊕⊖ **moderate**	(Analysis 63.3)
Cryotherapy /Imiquimod	-	-	-	-	-	Not reported
Cryotherapy with vehicle / Cryotherapy with imiquimod	See comment	See comment	-	301 (2 studies)	⊕⊖⊖⊖ **very low**	High heterogeneity (I^2=86%) between 3.75% (parallel group, MD -34.10, 95% CI -41.38 to -26.82)) and 5.0% (intraindividual, MD -11.20, 95% CI -26.53 to 4.13) im-

Table 4. Overview for cryotherapy *(Continued)*

						iquimod studies. (Analysis 64.4)
Cryotherapy /ALA-red light PDT	-	-	-	-	-	Not reported
Cryotherapy/MAL-red light PDT	See comment	See comment	Not estimable	240 (2 studies)	⊕⊖⊖⊖ **very low**	Intraindividual studies with no SD: at 12 weeks: cryotherapy = 74.5%, MAL-PDT= 84.4%, at 24 weeks: cryotherapy = 83.9-87%, MAL-PDT = 75-86.7%
Withdrawal due to adverse events						
Cryotherapy /Betulin-based oleogel	**0 per 1000**	**0 per 1000**	Not estimable	28 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Cryotherapy/cryotherapy with betulin-based oleogel	**0 per 1000**	**0 per 1000**	Not estimable	28 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Cryotherapy/5% 5-FU	**0 per 1000**	**0 per 1000**	Not estimable	49 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Vehicle with cryotherapy/0.5% 5-FU with cryotherapy	See comment	See comment	Not estimable	142 (1 study)	⊕⊕⊖⊖ **low**	There were no participant withdrawals due to adverse events in the first part of this three part study (incomplete data were given for the whole study).
Cryotherapy /Imiquimod	**0 per 1000**	**0 per 1000**	Not estimable	51 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Cryotherapy with vehicle / Cryotherapy with imiquimod	**Study population**		**RR 0.93** (0.28 to 3.07)	312 (2 studies)	⊕⊕⊕⊖ **moderate**	Pooled data (5% and 3.75% imiquimod) (Analysis 64.6)
	33 per 1000	**30 per 1000** (9 to 100)				
	Moderate					
	21 per 1000	**20 per 1000** (6 to 64)				
Cryotherapy /ALA- red light PDT	**0 per 1000**	**0 per 1000**	Not estimable	297 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Cryotherapy/MAL- red light PDT	**11 per 1000**	**11 per 1000** (2 to 75)	**RR 1.06** (0.16 to 7.16)	379 (2 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 45.2) Two additional intraindividual stud-

Table 4. Overview for cryotherapy *(Continued)*

						ies: 4 of 119 and 2 of 121 participants withdrew because of adverse events and one of them was related to MAL-PDT. GRADE = low
Skin irritation						
Cryotherapy /Betulin-based oleogel	-	-	-	-	-	Not reported
Cryotherapy/cryotherapy with betulin-based oleogel	-	-	-	-	-	Not reported
Cryotherapy/5% 5-FU	-	-	-	-	-	Not reported
Vehicle with cryotherapy/0.5% 5-FU with cryotherapy	-	-	-	-	-	Not reported
Cryotherapy /Imiquimod	-	-	-	-	-	Not reported
Cryotherapy with vehicle / Cryotherapy with imiquimod	**Study population**		**RR 0.39** (0.1 to 1.54)	311 (2 studies)	⊕⊕⊕⊖ **moderate**	Pooled data (5% and 3.75% imiquimod) (Analysis 64.7)
	83 per 1000	**32 per 1000** (8 to 128)				
	Moderate					
	125 per 1000	**49 per 1000** (13 to 192)				
Cryotherapy /ALA-red light PDT	**372 per 1000**	**100 per 1000** (59 to 171)	**RR 0.27** (0.16 to 0.46)	297 (1 study)	⊕⊕⊖⊖ **low**	Assessment one day after the treatment (Analysis 46.2)
Cryotherapy/MAL-red light PDT	-	-	-	-	-	Not reported

Table 5. Overview for imiquimod

Imiquimod compared to interventions for actinic keratoses in immunocompetent participants						
Intervention/Comparison intervention	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	Corresponding risk				
-	**With comparator**	**With intervention**	-	-	-	-
Participant complete clearance						
2.5% imiquimod/placebo	**62 per 1000**	**277 per 1000** (148 to 518)	**RR 4.49**	486 (2 studies)	⊕⊕⊕⊕ **high**	(Analysis 20.1)

Table 5. Overview for imiquimod *(Continued)*

			(2.4 to 8.39)			
3.75% imiquimod/placebo	**Study population**		**RR 6.45** (3.87 to 10.73)	730 (3 studies)	⊕⊕⊕⊕ **high**	(Analysis 20.1)
	53 per 1000	**343 per 1000** (206 to 571)				
	Moderate					
	50 per 1000	**322 per 1000** (193 to 536)				
Cryotherapy + 3.75% imiquimod/Cryotherapy + vehicle	**33 per 1000**	**301 per 1000** (111 to 820)	**RR 9.12** (3.36 to 24.79)	247 (1 study)	⊕⊕⊕⊖ **moderate**	For all lesions (Analysis 65.1)
5% imiquimod/placebo	**Study population**		**RR 7.70** (4.63 to 12.79)	1871 (9 studies)	⊕⊕⊕⊕ **high**	(Analysis 20.1)
	48 per 1000	**371 per 1000** (223 to 617)				
	Moderate					
	32 per 1000	**246 per 1000** (148 to 409)				
5% imiquimod/3% diclofenac in 2.5% hyaluronic acid	-	-	-	-	-	Not reported
5% imiquimod /5% 5-FU	See comment	See comment	-	89 (2 studies)	⊕⊖⊖⊖ **very low**	The two studies was associated with high heterogeneity (I^2= 93%) and the results could not be pooled together. One study favoured 5-FU (RR 0.31, 95% CI 0.14 to 0.67] whereas the other did not (RR 0.88, 95% CI 0.73 to 1.06] (Analysis 22.1)
5% imiquimod/Cryotherapy	**680 per 1000**	**843 per 1000** (619 to 1000)	**RR 1.24** (0.91 to 1.7)	51 (1 study)	⊕⊖⊖⊖ **very low**	(Analysis 23.1)
Cryotherapy + 5% imiquimod/Cryotherapy + vehicle	**91 per 1000**	**225 per 1000** (64 to 796)	**RR 2.48** (0.70 to 8.76)	64 (1 study)	⊕⊕⊖⊖ **low**	For all lesions.(Analysis 65.1) Results from an additional intraindividual study: cryotherapy + imiquimod side (8/27 = 30%), cryotherapy alone side (5/27 = 19%), GRADE = low
5% imiquimod/ALA-PDT				-		Not reported

Table 5. Overview for imiquimod *(Continued)*

ALA-PDT + 5% imiquimod/ALA-PDT + placebo	See comment	See comment	Not estimable	25 (1 study)	⊕⊕⊖⊖ **low**	Intraindividual study: ALA-PDT + 5% imiquimod = 2/25; ALA-PDT + placebo = 2/25
Mean reduction in lesion counts						
2.5% imiquimod/placebo	-	-	-	-	-	Not reported
3.75% imiquimod/placebo	-	-	-	-	-	Not reported
Cryotherapy + 3.75% imiquimod/Cryotherapy + vehicle	-	-	-	-	-	Not reported
5% imiquimod/placebo	The mean reduction in lesion counts in the control groups was **0.6 lesions**	The mean reduction in lesion counts in the intervention groups was **2.20 higher** (1.05 lower to 5.45 higher)	-	12 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 19.5) Results from an additional intraindividual study with no SD (N = 21): 5% imiquimod: 3.9 lesions, placebo = 0.5 lesions, GRADE = very low
5% imiquimod/3% diclofenac in 2.5% hyaluronic acid	-	-	-	-	-	Not reported
5% imiquimod /5% 5-FU	-	-	-	-	-	Not reported
5% imiquimod/Cryotherapy	-	-	-	-	-	Not reported
Cryotherapy + 5% imiquimod/Cryotherapy + vehicle	-	-	-	-	-	Not reported
5% imiquimod/ALA-PDT	-	-	-	-	-	Not reported
ALA-PDT + 5% imiquimod/ALA-PDT + placebo	See comment	See comment	Not estimable	25 (1 study)	⊕⊕⊖⊖ **low**	Results from intraindividual study without SD: ALA-PDT + 5% imiquimod= 19.9 lesions; ALA-PDT + placebo= 16.0 lesions
Mean percentage of reduction in lesion counts						
2.5% imiquimod/placebo	-	-	-	-	-	Not reported
3.75% imiquimod/placebo	The mean percentage of reduction in lesion counts in the control groups was	The mean percentage of reduction in lesion counts in the intervention groups was **46.90 higher** (36.68 to 57.12 higher)	-	247 (1 study)	⊕⊕⊕⊖ **moderate**	(Analysis 20.3)

Table 5. Overview for imiquimod *(Continued)*

	21.1 per cent					
Cryotherapy + 3.75% imiquimod/Cryotherapy + vehicle	The mean percentage of reduction in lesion counts in the control groups was **43.3 per cent**	The mean percentage of reduction in lesion counts in the intervention groups was **34.1 higher** (26.82 to 41.38 higher)	-	247 (1 study)	⊕⊕⊕⊖ **moderate**	For all lesions (Analysis 65.2)
5% imiquimod/placebo	-	-	-	-	-	Not reported
5% imiquimod/3% diclofenac in 2.5% hyaluronic acid	-	-	-	-	-	Not reported
5% imiquimod /5% 5-FU	See comment	See comment	Not estimable	39 (1 study)	⊕⊕⊖⊖ **low**	Results with no SD: 5% imiquimod = 66%, 5% 5-FU = 94%
5% imiquimod/Cryotherapy	-	-	-	-	-	Not reported
Cryotherapy + 5% imiquimod/Cryotherapy + vehicle	The mean percentage of reduction in lesion counts in the control groups was **62 per cent**	The mean percentage of reduction in lesion counts in the intervention groups was **11.2 higher** (4.13 lower to 26.53 higher)	-	27 (1 study)	⊕⊕⊖⊖ **low**	For all lesions.(Analysis 65.2) Results from an additional intraindividual study: cryotherapy-5% imiquimod = 73.2±27.1%, cryotherapy + vehicle = 62.0±30.3%. GRADE = moderate
5% imiquimod/ALA-PDT	-	-	-	-	-	Not reported
ALA-PDT + 5% imiquimod/ALA-PDT + placebo	See comment	See comment	Not estimable	25 (1 study)	⊕⊕⊖⊖ **low**	Results from intraindividual study without SD: ALA-PDT + 5% imiquimod = 86.7% ; ALA-PDT + placebo = 73.1 %
Withdrawal due to adverse events						
2.5% imiquimod/placebo	**19 per 1000**	**9 per 1000** (2 to 50)	**RR 0.5** (0.09 to 2.7)	486 (2 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 20.5)
3.75% imiquimod/placebo	**19 per 1000**	**17 per 1000** (4 to 73)	**RR 0.92** (0.22 to 3.93)	483 (2 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 20.5)
Cryotherapy + 3.75% imiquimod/Cryotherapy + vehicle	**32 per 1000**	**41 per 1000** (11 to 150)	**RR 1.3** (0.36 to 4.73)	247 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 65.3)

Table 5. Overview for imiquimod *(Continued)*

5% imiquimod/placebo	**Study population**		**RR 2.59** (1.59 to 4.23)	2290 (8 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 20.5) Four small sample size studies with no participant withdrawal are not included in meta-analysis: pooled data, imiquimod 0/79 and placebo 0/31. Additional two intraindividual studies: no participant withdrew because of adverse events (0/42) GRADE = very low (both studies had more than 20% participant lost).
	21 per 1000	**56 per 1000** (34 to 91)				
	Moderate					
	5 per 1000	**13 per 1000** (8 to 22)				
	High					
	0 per 1000	**0 per 1000** (0 to 0)				
5% imiquimod/3% diclofenac in 2.5% hyaluronic acid	**0 per 1000**	**0 per 1000**	Not estimable	49 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
5% imiquimod /5% 5-FU	**0 per 1000**	**0 per 1000**	Not estimable	50 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
5% imiquimod/Cryotherapy	**0 per 1000**	**0 per 1000**	Not estimable	51 (1 study)	⊕⊕⊕⊖ **moderate**	There were no participant withdrawals due to adverse events.
Cryotherapy + 5% imiquimod/Cryotherapy + vehicle	**30 per 1000**	**10 per 1000** (0 to 246)	**RR 0.34** (0.01 to 8.13)	65 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 65.3)
5% imiquimod/ALA-PDT	**0 per 1000**	**0 per 1000**	Not estimable	30 (1 study)	⊕⊕⊖⊖ **low**	There were no participant withdrawals due to adverse events.
ALA-PDT + 5% imiquimod/ALA-PDT + placebo	**0 per 1000**	**0 per 1000**	Not estimable	25 (1 study)	⊕⊕⊖⊖ **low**	There were no participant withdrawals due to adverse events.
Skin irritation						
2.5% imiquimod/placebo	**6 per 1000**	**21 per 1000** (4 to 117)	**RR 3.45** (0.63 to 18.97)	486 (2 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 20.6)
3.75% imiquimod/placebo	**6 per 1000**	**30 per 1000** (6 to 159)	**RR 4.86** (0.92 to 25.83)	484 (2 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 20.6)
Cryotherapy + 3.75% imiquimod/Cryotherapy + vehicle	**8 per 1000**	**56 per 1000** (7 to 445)	**RR 6.72** (0.84 to 53.83)	247 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 65.4)
5% imiquimod/placebo	**5 per 1000**	**18 per 1000** (4 to 79)	**RR 3.68** (0.86 to 15.74)	708 (3 studies)	⊕⊕⊕⊖ **moderate**	(Analysis 20.6) Additional intraindividual study: similar mild irritation between the

Table 5. Overview for imiquimod *(Continued)*

						two treatment sides (N = 20) GRADE = very low
5% imiquimod/3% diclofenac in 2.5% hyaluronic acid	-	-	-	-	-	Not reported
5% imiquimod/5% 5-FU	-	-	-	-	-	Not reported
5% imiquimod/Cryotherapy	-	-	-	-	-	Not reported
Cryotherapy + 5% imiquimod/Cryotherapy + vehicle	**121 per 1000**	**194 per 1000** (61 to 622)	**RR 1.6** (0.5 to 5.13)	64 (1 study)	⊕⊕⊖⊖ **low**	(Analysis 65.4)
5% imiquimod/ALA-PDT	-	-	-	-	-	Not reported
ALA-PDT + 5% imiquimod/ALA-PDT + placebo	-	-	-	-	-	Not reported

APPENDICES

Appendix 1. CENTRAL (Cochrane Library) search strategy

#1 (actinic and keratos*) or (solar and keratos*) or (senile and keratos) or (hyperkeratos*)
#2 MeSH descriptor Keratosis, Actinic explode all trees
#3 (#1 OR #2)

Appendix 2. MEDLINE (OVID) search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. (animals not (human and animals)).sh.
10. 8 not 9
11. actinic keratos$.mp. or exp Keratosis, Actinic/
12. solar keratos$.mp.
13. senile keratos$.mp.
14. hyperkeratos$.mp.
15. 11 or 12 or 13 or 14
16. 10 and 15

Appendix 3. EMBASE (OVID) search strategy

1. random$.mp.
2. factorial$.mp.
3. (crossover$ or cross-over$).mp.
4. placebo$.mp. or PLACEBO/
5. (doubl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl$ adj blind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. (assign$ or allocat$).mp.

8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. actinic keratos$.mp. or exp Keratosis, Actinic/
15. solar keratos$.mp.
16. senile keratos$.mp.
17. hyperkeratos$.mp.
18. 14 or 15 or 16 or 17
19. 13 and 18

Appendix 4. LILACS search strategy

((Pt RANDOMIZED CONTROLLED TRIAL OR Pt CONTROLLED CLINICAL TRIAL OR Mh RANDOMIZED CONTROLLED TRIALS OR Mh RANDOM ALLOCATION OR Mh DOUBLE-BLIND METHOD OR Mh SINGLE-BLIND METHOD OR Pt MULTICENTER STUDY) OR ((tw ensaio or tw ensayo or tw trial) and (tw azar or tw acaso or tw placebo or tw control$ or tw aleat$ or tw random$ or (tw duplo and tw cego) or (tw doble and tw ciego) or (tw double and tw blind)) and tw clinic$)) AND NOT ((CT ANIMALS OR MH ANIMALS OR CT RABBITS OR CT MICE OR MH RATS OR MH PRIMATES OR MH DOGS OR MH RABBITS OR MH SWINE) AND NOT (CT HUMAN AND CT ANIMALS)) [Words] and ((actinic$ or solar or senil $) and (keratos$ or queratosis)) or hyperkeratos$ or hiperqueratos$ [Words]

WHAT'S NEW

Date	Event	Description
23 October 2019	Amended	Edited the published note about the updating of the review.

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 12, 2012

Date	Event	Description
8 June 2016	Amended	This review is going to be updated. We have written a published note to say that because the scope of the review has been reduced to make it more manageable a new protocol and then a new review will be written.
25 January 2011	Amended	Change in authors
11 June 2008	Amended	Converted to new review format.
9 January 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

We indicate below the contributions made by the reviewers.

- Link with editorial base and coordinate contributions from co-reviewers (AG)
- Draft protocol (AG, RW, with contributions from all)
- Run search (AG, WB, and MP)
- Identify relevant titles and abstracts from searches, i.e. broad screen (MP and WB)

- Obtain full text copies of studies (WB and MP)
- Select trials to include (WB, MP, and AG as arbitrator when necessary)
- Extract data from trials (WB and MP)
- Enter data into RevMan (MP)
- Carry out the analysis (MP and EV)
- Interpret the analysis (MP)
- Draft final review (MP, WB, and AG)
- Update the review (MP)

DECLARATIONS OF INTEREST

Dr Aditya Gupta, lead author of this review, participated in a clinical trial sponsored by DUSA in 2004, which was excluded from the review because it did not meet the inclusion criteria.

Dr Stephen Keohane, clinical referee for this review, states: "I have been paid for lectures and advisory boards by Galderma, Almirall, Intendis, Inc., Shire, and Bayer."

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Authorship: Since the publication of the Cochrane Protocol in 2009, the review has been updated by new authors.

Background: This was updated as the protocol was published in 2003. The 'Disease definition' section was modified to emphasise the relationship between actinic keratosis and squamous cell carcinoma, and previous information about the differential diagnosis was moved to the 'Clinical features' section. The 'Epidemiology and causes' section title was changed to 'Pathogenesis and epidemiology' to reflect better the order of the information presented. Finally, a 'How the intervention might work' section was added to follow the recommendation in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Methods:

Criteria for considering studies for this review:

Types of interventions: The sentence on the comparators accepted was slightly modified to include any variation of the treatment (duration, concentration, etc) because several studies investigated the influences of these parameters on primary and secondary outcomes.

Types of outcome measures: The rationale for selecting only per participant outcomes (i.e. randomisation per participant and not per lesion) was presented, as well as a description on the general method used to evaluate efficacy in the included studies.

Changes in the primary outcomes:

a) To make a distinction between "Global degree of improvement in symptoms and/or signs as rated by participant or medical practitioner" (subjective) and "Participant complete clearance" (objective), subjective assessment was added before the outcome description. Only global improvement indices for completely improved or cleared were considered for inclusion in meta-analysis.

b) "Lesion clearance rate of 100% and 75%" were changed for "participant complete (100%) or partial (≥ 75%) clearance" to make a distinction between "lesion complete response" expressed per lesion, which is not included in our review, and the number of participants with the percentage of lesions cleared. "Participant complete clearance" and "Participant partial (≥ 75%) clearance" were presented separately.

c) The outcomes reported in actinic keratoses studies that could be reported as "Improvement in quality of life" were cosmetic outcomes, which were reported separately as secondary outcomes. Thus, 'Improvement in quality of life' was removed from our primary outcomes.

The objective assessment, "Mean reduction in lesion counts" expressed as absolute values or percentages was included in the review because this per participant outcome was often reported, and it was the only efficacy outcome that could be analysed by meta-analysis for intraindividual studies. Thus, all primary outcomes became efficacy outcomes.

Changes in the secondary outcomes:

(a) "Severe adverse events, i.e. severe enough to require withdrawal of treatment" was changed to "Withdrawal due to adverse events" to avoid problems with the interpretation of data.

(c) "Minor patient-reported adverse events, not sufficient to require cessation of treatment, excluding skin irritation" was replaced by "Minor adverse events excluding skin irritation" because the source, reported by participant or investigator, was generally not specified.

To fulfil the requirement of a 'per participant' outcome for meta-analysis, all safety outcomes were the number of participants experiencing events in general or a specific event, and cosmetic outcomes were the number of participants with the different cosmetic measurement.

Search methods for identification of studies:

Electronic searches: We updated all searches in March 2011, and the LILACs database was added, as well as different online ongoing trial registers.

Unpublished literature: We searched additional companies, as well as the FDA website, for clinical trials in the product insert.

Conference proceedings: We searched conference proceedings from additional associations.

Data collection and analysis:

Selection of studies/Data extraction and management:

Several collaborators contributed to this review over the years, and they shared different responsibilities in the study selection, data extraction, and data analysis. During a global revision of the manuscript undertaken in March 2011, the different roles were redistributed to the current authors, and they may differ from the protocol.

Assessment of risk of bias in included studies:

Cochrane methodology was changed for assessment of methodological quality. Thus, the quality of the data was assessed with two new tools: 1) the 'Risk of bias' tables included in RevMan 5.1, and 2) the quality of evidence by the GRADEpro software.

Analysis:

The section of the protocol on planed data analysis has been divided into the following sections: measures of treatment effect, unit of analysis issues, assessment of heterogeneity, data synthesis, and subgroup analysis and investigation of heterogeneity.

In 'Measures of treatment effect', the original protocol stated that the results will be expressed as odds ratios for dichotomous outcomes. However, the results were presented as risk ratios because they are easier to interpret.

In 'Unit of analysis issues', a strategy for analysis and reporting of data from intraindividual studies and studies with multiple treatments was added.

In 'Assessment of heterogeneity', a cut-off value of the I^2 statistic as a measure of heterogeneity was added.

In 'Data synthesis', no meta-analysis method was specified in the protocol, but a random-effects model was prespecified for all analyses.

In 'Subgroup analysis and investigation of heterogeneity', subgroup analysis in the protocol was referred to the different types of interventions (i.e. topical, oral, mechanical, etc), which were analysed in separate comparisons. Subgroup analysis in the review referred to subgroup analysis within a comparison.

Because of the large number of randomised studies included in this review, non-randomised controlled studies were not listed as mentioned in the protocol.

NOTES

This review is being updated by way of a new protocol and then a review, because the scope of the review has been reduced to make it more manageable. The citation for the new protocol is as follows: Foley K, Gupta AK, Martin G, Tweed JA, Villanueva E, Carviel J. Topical treatments and photodynamic therapy for actinic keratosis of the face and scalp. Cochrane Database of Systematic Reviews 2019, Issue 10. Art. No.: CD013452. DOI: 10.1002/14651858.CD013452.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Cutaneous; Administration, Oral; Cryotherapy [methods]; Dermatologic Agents [therapeutic use]; Keratosis, Actinic [*therapy]; Photochemotherapy [methods]; Photosensitizing Agents [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans