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Topical pimecrolimus for eczema (Review)

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[Intervention Review]

Topical pimecrolimus for eczema

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ABSTRACT

Background

Pimecrolimus was developed as an alternative to topical corticosteroids for treating eczema (atopic dermatitis) but its efficacy and safety compared with existing treatments remains unclear.

Objectives

To assess the effects of topical pimecrolimus for treating eczema.

Search methods

We searched the Cochrane Skin Group Specialised Register (to October 2006), the Cochrane Central Register of Controlled Trials (*The Cochrane Library Issue* 3, 2006*)*, MEDLINE (from 2003 to October 2006), and EMBASE (from 2005 to October 2006). We also contacted researchers and manufacturers in the field.

Selection criteria

Randomised controlled trials of 1.0% topical pimecrolimus used twice daily compared against other topical comparators for treating eczema.

Data collection and analysis

Two authors independently examined each retrieved study for eligibility and extracted data for efficacy, tolerability and safety. A random-effects model was used to estimate the pooled risk ratios (RRs) and 95% confidence intervals (95% CIs).

Main results

We included 31 trials (8019 participants) in the analysis. In short-term (≤ 6 weeks) trials, pimecrolimus cream was significantly more effective and well-tolerated than vehicle (cream base, but not containing pimecrolimus). In long-term trials (≥ 6 months), pimecrolimus was significantly better than vehicle in preventing flares (9 trials, 3091 participants, RR 1.47, 95% CI 1.32 to 1.64 at six months) and in improving quality of life.

Pimecrolimus was significantly less effective than two topical corticosteroids, i.e. 0.1% triamcinolone acetonide for investigators' global assessment (1 trial, 658 participants, RR 0.75, 95% CI 0.67 to 0.83) and 0.1% betamethasone valerate for participants' global assessment (1 trial, 87 participants, RR 0.61, 95% CI 0.45 to 0.81) at three weeks. Pimecrolimus was also associated with significantly more overall withdrawals and skin burning. None of the trials reported on key adverse effects such as thinning of skin.

Pimecrolimus was significantly less effective than 0.1% tacrolimus for investigators' global assessment at 6 weeks (RR 0.58, 95% CI 0.46 to 0.74) and led to more withdrawals due to lack of efficacy (RR 2.37, 95% CI 1.10 to 5.08) based on 2 trials involving 639 participants, but there was no significant difference in proportions of participants experiencing any adverse events.

Authors' conclusions

Topical pimecrolimus is less effective than moderate and potent corticosteroids and 0.1% tacrolimus. The therapeutic role of topical pimecrolimus is uncertain due to the absence of key comparisons with mild corticosteroids.

PLAIN LANGUAGE SUMMARY

Topical pimecrolimus for eczema

This review of clinical trials aimed to find out whether topical pimecrolimus is better than topical corticosteroids or tacrolimus for treating eczema in infants, children and adults by assessing the improvement of eczema and adverse events associated with treatments.

Eczema (atopic dermatitis) is a very common and long-lasting skin disease caused by both genetic and environmental factors, and most often begins in infancy and childhood. Corticosteroid creams have been used to treat eczema but may cause unwanted side effects, including thinning of the skin. Pimecrolimus cream was developed as an alternative to topical corticosteroids, but it is much more expensive than corticosteroids. It is also not clear whether pimecrolimus is more effective or better tolerated than corticosteroids or a similar drug called tacrolimus.

This review included data from 31 clinical trials involving 8019 participants. In the short-term (less than six weeks) treatment of eczema, we found pimecrolimus was more effective and well-tolerated when compared against vehicle (cream base not containing any pimecrolimus). Likewise, pimecrolimus was better than vehicle cream in preventing deterioration in eczema based on data from 9 trials involving 3091 participants. However, we found that 3 weeks treatment with pimecrolimus was less effective than a moderate (triamcinolone acetonide, data from 1 trial with 658 participants) and a potent topical corticosteroid (betamethasone valerate, data from 1 trial with 87 participants). Furthermore, 6-weeks treatment with pimecrolimus was less effective and caused more participants to drop out of treatment due to lack of efficacy than tacrolimus based on 2 trials involving 639 participants.

Pimecrolimus caused a similar rate of adverse events to vehicle cream but had a lower overall dropout rate. In contrast, pimecrolimus had higher dropout rates and caused more skin burning than topical corticosteroids. None of the trials reported on key adverse effects, such as thinning of skin. Pimecrolimus caused a similar rate of adverse events to tacrolimus. There were no cancer-related events reported in any of the 31 clinical trials.

This review did not find evidence to support the notion that pimecrolimus was better than moderate or potent corticosteroids or tacrolimus in treating eczema. However, there is a distinct lack of trials comparing pimecrolimus against mild-potency corticosteroids.

BACKGROUND

Description of the condition

Prevalence and causes

Eczema (also known as atopic dermatitis) is a chronic, relapsing, intensely itchy, inflammatory skin disease, which typically involves the folds of the elbows or behind the knees (Williams 1994; Johansson 2004). The cause of eczema is unknown but evidence suggests a role for both genetic and environmental factors in determining disease expression. The causes of eczema are probably due to a combination of genetic and environmental factors (Cookson 2002). Eczema is often present with, or exacerbated by, food allergies, aeroallergens (e.g. house dust mites, moulds, animal danders) and skin colonisation by *Staphylococcus aureus*, which is present in 90% of eczema lesions (Leung 2003). However, up to 60% of individuals with eczema may not have specific immunoglobulin E production in response to allergens, which is associated with "atopic dermatitis", i.e. eczema with allergic reaction (Flohr 2004). To clarify the confusion on diagnosis and treatment, the world allergy association revised nomenclature for allergy and recommended using "eczema" to refer this specific disease (Johansson 2004). Symptoms of eczema may appear in infants as young as one month old, and in most cases usually appear before the age of two years. Around 60% of cases have cleared (or gone into remission) by early adolescence, although some people will experience continuing eczema into, or relapse in adult life. The prevalence of eczema varies considerably from one country to another, and also within countries (Williams 1999). In the UK there has been a steady increase in prevalence, and the condition now affects around 15% of schoolchildren (Emerson 1998; Kay 1994; Neame 1995) and 1% to 3% of adults. Most children who have eczema experience mild or moderate disease. A survey of 1760 children aged one to five years in England found that 84% of cases were mild, 14% moderate and 2% severe (Emerson 1998).

Impact of the disease

The social and economic impact of eczema is considerable, especially when the disease is severe, with sufferers experiencing significant limitations of normal social functions. It has a profound impact on the quality of life of both children (Kiebert 2002; Lewis-Jones 2001) and adults (Kiebert 2002). People with eczema experience itch, sleep loss, bleeding from the skin and interference with nearly all aspects of daily life (Herd 2000). The emotional impact of visible eczema lesions can be considerable, especially in children, and may contribute to psychological distress. The school or work time interruption caused by sleep loss and the need to take time off work for visits to health care professionals result in considerable family disturbance. (Herd 2000). In the US, the annual cost of illness for eczema has been estimated to range from $0.9 billion to $3.8 billion when projected across the total number of people younger than 65 years insured by private insurers and Medicaid (Ellis 2002). Likewise, in the UK, it has been estimated that the annual cost of eczema in children aged one to five years is £47 million, with £30 million spent by the National Health Service and £17 million spent by the families of affected children (Emerson 2001). On the basis of an estimated 1.5 million people with eczema in Germany, it has been suggested that the total annual costs to society are as high as US$325 billion (Gieler 1999).

Management of the disease

Traditionally, the treatment of mild-to-moderate eczema has included the frequent use of emollients, and intermittent use of topical corticosteroids to control acute 'flares'. Corticosteroids, though effective, may be associated with a number of local and systemic adverse events, such as skin thinning and suppression of the adrenal glands (Williams 2005). To minimise these rare but possible side effects, topical corticosteroids are generally only used to treat flares and occasionally to prevent them (Ellis 2003). Fears about the safety profile of topical corticosteroids, compounded by inconsistent advice from health professionals, have important implications for adherence to treatment. Parental knowledge on differentiating weak from strong preparations is poor (Beattie 2003; Charman (b) 2000). Systemic treatment, with immunosuppressant drugs such as ciclosporin, may be associated with potentially serious adverse effects and is generally reserved for severe cases that prove resistant to conventional treatment with topical agents.

Description of the intervention

Topical pimecrolimus

Since eczema is an immune-mediated inflammatory skin disorder, it has been considered as a good target for the immunosuppressant properties of substances called macrolides (such as cyclosporin, tacrolimus, and pimecrolimus). Pimecrolimus is a non-steroidal immunosuppressant derived from one type of the naturally occurring antimicrobial (macrolactam), called ascomycin. Laboratory experiments have shown that pimecrolimus inhibits the production of inflammatory substances in the body (such as the synthesis and release of inflammatory cytokines from T-lymphocytes, and the release of inflammatory mediators from mast cells) that are thought to be important in causing skin lesions (Stuetz 2001), and hence pimecrolimus is used in treating severe eczema.

Why it is important to do this review

In recent years, a number of clinical trials have studied the use of topical pimecrolimus in the treatment of eczema (Hoare 2000). Most studies have compared topical pimecrolimus against placebo controls. Although the placebo-controlled studies show that topical pimecrolimus clearly has a beneficial effect on eczema, it is not clear how they compare to existing treatments, and doctors and patients are sometimes confused how topical pimecrolimus should be used in relation to other existing therapies such as topical corticosteroids. It is also unclear whether topical pimecrolimus is best used as treatment of second choice after first line treatment has failed and whether it should be used for short-term or long-term control of eczema, or whether it should only be used for "sensitive sites" such as the face or armpits where skin thinning can more easily develop after using topical corticosteroids.

Recently, reports from both US and EU post-marketing surveillance signalled a potential risk of skin cancer and lymphoma associated with pimecrolimus and tacrolimus. In December 2004, the US FDA had received 10 cases (four children and six adults) of cancer-related adverse events associated with pimecrolimus, including lymphoma, basal cell carcinoma, squamous cell carcinoma and granulomatous lymphadenitis. The median exposure time of pimecrolimus in these cases was 90 days, with a range from one week and 300 days (FDA 2005). These alerts on the potential risk of rare dermatological malignancies associated with pimecrolimus

have raised concerns about the long-term safety of pimecrolimus. (FDA 2005).

OBJECTIVES

To assess the effects of topical pimecrolimus compared with other topical treatments for the treatment of eczema.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs; including cross-over trials and within-participant studies)

Types of participants

Anyone diagnosed with eczema by a medical practitioner using standardised diagnostic criteria such as the Hanifin and Rajka definition (Hanifin 1980), the UK modification (Williams 1994), or by a dermatologist using the terms 'atopic eczema' or 'eczema'. The term 'eczema' will only be acceptable when referring to children prior to the revised World Allergy nomenclature of 2003. Following the recommendations of the World Allergy Organisation Nomenclature Review Committee, we have used the term 'eczema' throughout this systematic review (Johansson 2004).

Types of interventions

Trials comparing topical pimecrolimus at a licensed therapeutic dose (1.0%) twice daily with vehicle (cream base, but not containing pimecrolimus) or another active treatment, such as topical corticosteroids or topical tacrolimus. We also included trials that allowed concomitant use of emollients.

Types of outcome measures

Primary outcomes

The primary outcome was efficacy of treatment measured as global degree of improvement in symptoms and/or signs rated by the participants (participants' global assessments; PGA) or medical practitioners (investigators' global assessment; IGA), which are defined as following:

Investigator-rated clinical response

- The proportion of participants whose eczema were rated by the investigator as clear or almost clear (IGA score 0 or 1)

Participant- or carer-rated clinical response

- The proportion of participants who rated their eczema as well-controlled or completely-controlled (PGA)
- The proportion of participants who rated their eczema as better or much better

Secondary outcomes

Safety and tolerability outcomes included:

Withdrawal from treatment

- The proportion of participants who withdraw from treatment for any reason
- The proportion of participants who withdraw from treatment due to lack of efficacy
- The proportion of participants who withdraw from treatment due to adverse events

Adverse events

- The proportions of participants experiencing any adverse events
- The proportions of participants experiencing any skin infections, bacterial skin infections, viral skin infections, skin burning and skin thinning

Tertiary outcome measures

Imrovement in pruritus

- The proportion of participants experiencing mild or absent pruritus (itch; pruritus score 0 or 1)

No flare of eczema

- The proportion of participants not experiencing flares of eczema during treatment

No rescue medication

- The proportion of participants not using topical corticosteroids as rescue medications during treatment

Improvement in quality of life (QoL)

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- Cochrane Skin Group Specialised Register (to October 2006) using the search strategy in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (*Issue* 3, 2006) using the search strategy in Appendix 2.
- MEDLINE (OVID) from 2003 to October 2006 using the search strategy in Appendix 3.
- EMBASE from 2005 to October 2006 using the search strategy in Appendix 4.

Searching other resources

References from published studies

We searched the references of the included and excluded studies in an attempt to identify any additional trials.

Unpublished literature

Unpublished and on-going trials were identified by checking the following websites:
European Agency for the Evaluation of Medicinal Products (EMEA, http://www.emea.europa.eu/, accessed 1st November 2006);
The US Food and Drug administration (FDA, http://www.fda.gov/cder/approval/index.htm, accessed 1st November 2006);
The manufacturer of pimecrolimus (Novartis) clinical trial results (http://www.novartisclinicaltrials.com/clinicaltrialrepository/public/login.jsp?target=%2Fclinicaltrialrepository%2Fpublic%2Fmain.jsp, accessed 1st November 2006);

The meta Register of Current Controlled trials (www.controlled-trials.com, www.clinicaltrials.gov, accessed October 2006);
The Cochrane Skin Group Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials/, accessed October 2006).

Language

We did not impose any language restrictions when searching for publications.

Adverse Effects

We searched for the adverse effects of pimecrolimus in MEDLINE (OVID) from 1966 to October 2006 using the search strategy in Appendix 5.

Data collection and analysis

Selection of studies

Trial eligibility was determined by two authors (LC, DMA). Any disagreement was resolved by discussion between the authors.

Data extraction and management

Two authors (LC, DMA) independently extracted dichotomous outcome data (numbers of event and intended-to-treat) and trial characteristics. The denominators related to all participants who were randomised to treatment (intention-to-treat), whereas the numerator related to the number of participants who were reported to have experienced the outcomes of interests. The authors were not blinded to the names of trialists, journal or institutions.

Assessment of risk of bias in included studies

Assessment of methodological quality

Quality assessment included an evaluation of the following components for each included study, since there is some evidence that these are associated with biased estimates of treatment effect (Juni 2001). Each component was categorised as adequate, unclear, or inadequate.

Randomisation

Methods of generation and concealment of allocation:
(a) *Allocation generation:*
adequate when the allocation sequence protects against biased allocation to the comparison groups
(b) *Allocation concealment:*
adequate in any sequence where the assignment cannot be foreseen

Blinding

Blinding of outcome assessors, participants and clinicians was adequate when they are unaware of the allocation

Loss to follow up

Presence of dropouts and withdrawals, and the analysis of these; adequate when more than 80% of participants are followed up, then analysed in the groups to which they were originally randomised (intention to treat)

In addition, the quality assessment also included:

- Degree of certainty that participants had atopic dermatitis.
- Baseline comparison of severity of disease.

Assessment of heterogeneity

Heterogeneity statistics (I^2) were calculated to test the agreement of the individual trial results with the combined meta-analytical summary (Deeks 2001; Higgins 2003). All analyses were carried out using RevMan version 4.2.6.

Data synthesis

Analysis

The primary outcome measures were investigator-rated and participant-rated efficacy, and were stratified by treatment comparators and the duration of treatment. We summarised the dichotomous results as rate ratios (relative risks) and their corresponding 95% confidence intervals (95% CIs) using a random-effects model (DerSimonian 1986) and compared topical pimecrolimus 1% against vehicle, topical corticosteroids (i.e. betamethasone valerate 0.1% and triamcinolone acetonide 0.1%) or topical tacrolimus (i.e. 0.03% or 0.1%), or different application regimens of 1.0% pimecrolimus. In addition, we separately analysed trials that allowed topical corticosteroids as rescue medication (i.e. flare-preventing trials), trials that involved participants responding or not responding to previous topical corticosteroids or pimecrolimus, and within-participant trials. We also described quality of life data from relevant studies.

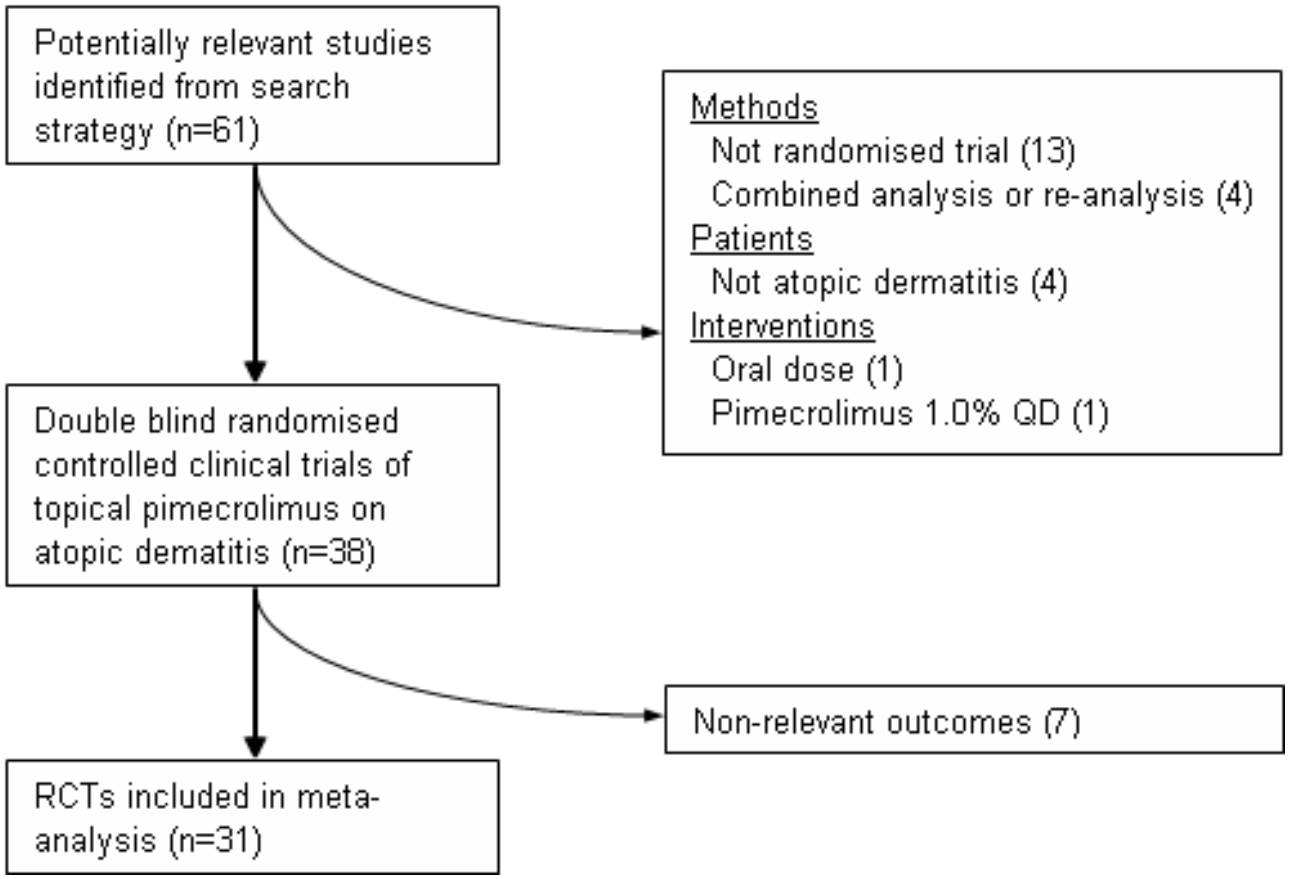
RESULTS

Description of studies

Results of the search

Sixty-one trials were identified by electronic database searches (164 publications) and supplementary searches of other data sources. Overall, we identified 31 RCTs including 8019 participants with eczema that met the inclusion criteria (Figure 1).

Figure 1. Flow diagram outlining the inclusion of studies



Included studies

(a) Design, sample sizes and participants

Of these, four trials were conducted on infants (< 24 months, n = 822), two trials on both infants and children (n = 383), 11 trials on children and adolescents (2 to 19 years, n = 3074), six trials on both children and adults (n = 1383), and eight trials on adults (> 20 years, n = 2357). Given the broad range of ages of participants included in the trials, we did not attempt to undertake subgroup analysis based on age bands.

The severity of participants' eczema varied from mild to very severe based on IGA scores in 30 trials, the majority of participants had mild to moderate (IGA 2 to 3, 15 trials, n = 3315), moderate to severe (IGA 3 to 4, 5 trials, n=1385), mild or severe (IGA 2 to 4, 3 trials, n = 807) or mild to very severe (IGA ≥ 2, 3 trials, n = 1049) eczema. In addition, two trials were conducted on participants with mild eczema (n = 1137), one trial on moderate eczema (n = 141) and one trial one severe eczema (n = 185). One trial (CASM981C2442 2006) involved 200 participants with mild to moderate facial eczema; the results from this trial are presented separately.

Four trials included participants whose response to previous treatments had been assessed prior to evaluation in the trials. One trial (CASM981C2314 2006) involved 268 participants that had already been shown to respond to 1.0% pimecrolimus twice daily. One trial (ASM981C2402 2005) involved 73 participants who had poor response to topical prednicarbate (a medium strength corticosteroid). Two trials (CASM981C2436 2006; ASM981CDE10 2005) involved 252 participants that had been shown to respond to topical corticosteroids. The results from these four trials were considered separately.

For full details, please see Characteristics of included studies.

(b) Interventions

(i) Vehicle controlled trials

Fourteen trials (2214 participants) compared 1% pimecrolimus cream applied twice daily against a vehicle control. Of these, three trials were undertaken in specific subgroups of participants, including those who had facial eczema (CASM981C2442 2006, n = 200), those who had responded to topical corticosteroids (CASM981C2436 2006, n = 67), and those who responded poorly to topical corticosteroids (ASM981C2402 2005, n = 73).

Ten trials (3364 participants) allowed the concomitant use of topical corticosteroids to control flares of eczema during treatment. Of the 10 flare-preventing trials, one trial (ASM981CDE10 2005) involved 185 children who had previously responded to topical corticosteroids.

(ii) Active controlled trials

Six of the 31 included trials compared 1% pimecrolimus cream applied twice daily against an active treatment, including 0.1% betamethasone valerate (Luger 2001), 0.1% triamcinolone acetonide (Luger 2004), 0.03% tacrolimus cream (Kempers 2004;

Paller (a) 2005) and 0.1% tacrolimus cream (Paller (b) 2005; Paller (c) 2005) applied twice daily for the treatment of eczema.

(iii) Treatment schedule trials

Three trials compared different regimens of 1% pimecrolimus cream. One trial (Ling 2005, n = 49) compared 1% pimecrolimus cream twice daily against the same strength applied four times daily, and one trial compared 1% pimecrolimus cream applied twice daily against the same strength applied once daily on participants who had previously been shown to respond to pimecrolimus (CASM981C2314 2006, n = 268).

(iv) Treatment duration

Treatment durations of the 31 included randomised controlled trials (RCTs) ranged from 1 week to 1 year; for 20 trials, the treatment durations were no more than 6 weeks, 1 trial lasted for 4 months, 8 trials lasted for 6 months and 4 trials lasted for 12 months.

Excluded studies

Thirty-three trials were excluded from this systematic review (please see 'Characteristics of excluded studies') . Three abstracts of RCTs were excluded as they duplicated data contained in full publications. We also excluded 13 (non-randomised) open-label trials which were extended from RCTs and four combined or re-analysis studies. Four excluded trials were conducted on patients with vitiligo, intertriginous psoriasis, chronic hand dermatitis and head and neck dermatitis. One trial included oral pimecrolimus and one included topical pimecrolimus 1.0% administrated once a day which were excluded. Seven trials which did not report the outcomes measures defined in this meta-analysis were also excluded.

Risk of bias in included studies

The quality of the included trials is summarised in Table 1.

Allocation

Five out of the 31 included trials (16.1%) reported an adequate allocation concealment (Kaufmann 2006; Kempers 2004; Paller (a) 2005; Paller (b) 2005; Paller (c) 2005), but the other 26 trials (83.9%) did not clearly describe the allocation generation and concealment. Most of the included RCTs did not report on the method of randomisation. Only seven trials described using a computerised system (Luger 2004; Wahn 2002) or telephoning a controlled randomisation system (Kempers 2004; Paller (a) 2005; Paller (b) 2005; Paller (c) 2005) to automate the assignment of treatment, and reported the ratio or blocks of allocation.

Blinding

Of the 31 included trials, four (Kempers 2004; Paller (a) 2005; Paller (b) 2005; Paller (c) 2005) were investigator-blind, and other 27 trials were both investigator and participant-blind (double-blind). Only nine of the 27 double-blind trials reported on the methods used to ensure the blinding of outcome assessment.

Incomplete outcome data

Follow-up and exclusions

The loss to follow up rate (attrition rate) of the included RCTs ranged from 0% to 44%. In 15 trials, the withdrawal rate was more than 20%. The attrition rate was correlated with the treatment duration (Pearson correlation coefficient = 0.38; P = 0.032). The dropouts and reasons for dropouts were recorded and analysed, with the exception of one trial which did not specify reasons for withdrawals (Whalley 2002)

Selective reporting

Only 16 trials reported the criteria used for diagnosing eczema, and 21 trials stated that the baseline severities of eczema were comparable between the different treatment groups.

Effects of interventions

1. Efficacy and quality of life

We have summarised the efficacy results for the different treatment comparisons separately. The efficacy results include Investigator-rated clinical response (IGA), participant- or carer-rated clinical response (PGA) and improvement in pruritus. Global changes in composite rating scales (e.g. Atopic Dermatitis Area Severity Index [ADASI]) or the duration of remission were not routinely reported in the included trials. Of the 31 trials only 2 trials (Eichenfield (a) 2002; Eichenfield (b) 2002) reported on the clinical signs of eczema (erythema, induration or papulation, excoriation, and lichenification) assessed by a physician as mild or absent. The impact of treatment on QoL is reported separately due to marked differences in the QoL instruments used and the timing of QoL assessments.

(a) Pimecrolimus versus vehicle

(i) Investigator-rated clinical response as clear or almost clear eczema (eight studies)

One trial (CASM981C2322 2005) involving 336 children who had mild to moderate eczema found that pimecrolimus was significantly more effective than vehicle in achieving clear or almost clear eczema following 1 and 2 weeks of therapy; the pooled rate ratios (RRs) were 2.00 (95% CI 1.06 to 3.76; Analysis 1.1) and 1.58 (95% CI 1.00 to 2.52; Analysis 1.1) respectively. Likewise, the pooled results from 5 trials (783 participants) found that pimecrolimus was significantly more effective than vehicle (RR 2.72, 95% CI 1.84 to 4.03; Analysis 1.1) on the same outcome at 3 weeks. Pimecrolimus also remained significantly more effective than vehicle following 6 weeks treatment (RR 2.03, 95% CI 1.50 to 2.74; Analysis 1.1) based on the pooled results from 3 trials involving 589 participants.

One trial (CASM981C2442 2006) that involved 200 participants with mild to moderate facial eczema found that pimecrolimus was significantly more effective than vehicle in achieving clear or almost clear facial eczema following 1, 3, and 6 weeks of treatment. The pooled RRs were 2.94 (95% CI 1.31 to 6.61; Analysis 2.1), 3.02 (95% CI 1.72 to 5.29; Analysis 2.1) and 2.88 (95% CI 1.76 to 4.72; Analysis 2.1). A further trial (ASM981C2402 2005) involving 73 children and adults with mild to moderate eczema who had not responded to a 2-week treatment of prednicarbate (a medium-strength corticosteroid) cream showed that there was no significant difference between pimecrolimus and vehicle in participants achieving clear or almost clear eczema at 6 weeks (RR 6.19, 95% CI 0.36 to 107.66; Analysis 4.1).

(ii) Participant- or carer-rated clinical response as complete or well controlled eczema (three studies)

One trial (Barba 2003) involving 106 infants and children reported that 1.0% pimecrolimus resulted in significantly more participants achieving complete or well controlled eczema than vehicle following 3 weeks of treatment (RR 1.88, 95% CI 1.33 to 2.67;Analysis 1.2). Likewise, 1 trial (Ho 2003) involving 186 participants found pimecrolimus was significantly more effective than vehicle on the same outcome at 6 weeks (RR 2.65, 95% CI 1.74 to 4.04; Analysis 1.2 comparison 01-01). However, the trial involving 73 participants who did not respond to a pre-trial treatment of prednicarbate found no significant difference in achieving complete or well controlled eczema at 6 weeks (RR 1.29, 95% CI 0.56 to 2.95; Analysis 4.2).

(iii) Mild or absent pruritus (eight studies)

Pimecrolimus resulted in significantly more participants achieving mild or absent pruritus at one week (RR 1.89, 95% CI 1.51 to 2.35; Analysis 1.3), 3 weeks (RR 2.02, 95% CI 1.69 to 2.42; Analysis 1.3) and 6 week (RR 1.82, 95% CI 1.48 to 2.25; Analysis 1.3) compared against vehicle, based on pooled results from 3 trials (472 participants), 5 trials (783 participants) and 3 trials (589 participants) respectively.

Likewise, pimecrolimus resulted in significantly more participants with facial eczema achieving mild or absent pruritus following 1, 3, and 6 weeks of treatment based on results from 200 participants, the pooled RRs were 1.81 (95% CI 1.32 to 2.50; Analysis 2.2), 1.85 (95% CI 1.39 to 2.47; Analysis 2.2) and 2.02 (95% CI 1.49 to 2.73; Analysis 2.2). However, the trial involving 73 participants who did not respond to a pre-trial of prednicarbate found no significant difference in achieving mild or absent pruritus at six weeks (RR 1.11, 95% CI 0.47 to 2.60; Analysis 4.3).

(iv) Improvement in quality of life (three studies)

Information on quality of life (QoL) was patchy, with a lack of common outcome measures (Table 2). Only six of the 31 included RCTs reported quality of life outcomes. Three trials (Leo 2004; Staab 2005; Whalley 2002) compared pimecrolimus against vehicle and the other three trials (Kapp 2002; Meurer 2002; Wahn 2002) were flare-preventing trials.

One vehicle-controlled trial (Whalley 2002) involving 403 children with mild to moderate eczema used the Parent's Index of Quality of Life in Atopic Dermatitis (PIQoL-AD) score to measure QoL. This study included a 6-week RCT period and a 20-week open-label trial period. The PIQoL-AD scores were completed by the parents of a subset of participants (children aged 2 to 8 years) at baseline (241 cases), 6 weeks (193 cases) and 6 months (161 cases) of treatment. At six weeks, those children who received pimecrolimus were judged by their parents to have a significantly improved quality of life compared with those receiving vehicle (P = 0.023). The least-square mean change was 3.20 for the pimecrolimus group and 1.63 for the vehicle group, with an estimated treatment difference of 1.57 (95% CI 0.22 to 2.92). At six months (end of open-label phase), both treatment groups showed a significant within-group improvement (P < 0.001) compared with baseline, but the mean PIQoL-AD scores were similar between the two treatment groups. A reduction of 10% or more in PIQoL-AD score between baseline and 6 months was found in 76.1% of parents of children who had been initiated with pimecrolimus and 77.1% of parents of children who had started with vehicle.

One vehicle-controlled trial (Leo 2004) involving 19 children with mild to moderate eczema reported a trend towards lower Children's Dermatology Life Quality Index (CDLQI) score (a validated measure consisting of 10 questions that inquire about the effect of eczema on a child's QoL, lower score indicates improved QoL) at 2 weeks in the pimecrolimus group, but there was no significant difference detected from baseline (P = 0.12). The mean CDLQI score changed from 7.44 to 3.8 for pimecrolimus 1.0% and from 7.72 to 5.4 for vehicle treatment.

Likewise, another trial (Staab 2005) involving 190 infants with mild to severe eczema used the Parents' Quality of Life Index Atopic Dermatitis (PQoL-AD) to measure QoL. At four weeks (end of the double-blind treatment), participants receiving pimecrolimus were judged by their parents to have a significantly improved quality of life from baseline in all five sub-scales of PQoL-AD compared against vehicle (P < 0.05); the mean percentage changes from baseline for all five sub-scales were: psychosomatic well-being 14.6% vs. 6.2%; effects on social life 6.7% vs. 2.3%; confidence in medical treatment 10.0% vs. 3.7%; emotional coping 16.1% vs. 6.5%; acceptance of disease 19.6% vs. 7.0%.

(b) Pimecrolimus versus vehicle, plus topical corticosteroids to treat flares

(i) Investigator-rated clinical response as clear or almost clear eczema (two studies)

Two trials (Kapp 2002; Siegfried 2006) involving 526 participants found that 1.0% pimecrolimus was significantly more effective than vehicle in achieving clear or almost clear eczema at 1 week (RR 3.45, 95% CI 1.66 to 7.14; Analysis 5.1). However, results from a 12-month trial (Kapp 2002) involving 251 infants found no significant difference between pimecrolimus 1% and vehicle on the same outcome at 3 weeks (RR 1.43, 95% CI 0.98 to 2.10; Analysis 5.1), 6 months (RR 1.46, 95% CI 0.98 to 2.19; Analysis 5.1) and 12 months (RR 1.15, 95% CI 0.83 to 1.60; Analysis 5.1).

(ii) Participant- or carer-rated clinical response as complete or well controlled eczema (two studies)

Kapp (et al.) (2002) found that 1.0% pimecrolimus resulted in significantly more participants achieving complete or well controlled eczema than vehicle at 6 weeks (RR 1.40, 95% CI 1.06 to 1.85; Analysis 5.2), 9 months (RR 1.33; 95% CI 1.01 to 1.74; Analysis 5.2), but not at 12 months (RR 1.15, 95% CI 0.90 to 1.47; Analysis 5.2). Pooled results from two trials (Kapp 2002; Meurer 2002) involving 443 participants also showed that pimecrolimus was significantly more effective than vehicle in achieving complete or well controlled eczema at 6 months (RR 1.62, 95% CI 1.29 to 2.04; Analysis 5.2).

(iii) Mild or absent pruritus (one study)

Similarly, Kapp (et al.) (2002) found that pimecrolimus was significantly more effective than vehicle in achieving mild or absent pruritus at 6 weeks (RR 1.33, 95% CI 1.03 to 1.72; Analysis 5.3), 6 months (RR 1.37, 95% CI 1.04 to 1.82; Analysis 5.3), 9 months (RR 1.36, 95% CI 1.04 to 1.79; Analysis 5.3), but not at 12 months (RR 1.25, 95% CI 0.98 to 1.58; Analysis 5.3).

(iv) No flare of eczema during treatment (nine studies)

Nine trials (3091 participants) reported on the proportion of participants who did not experience a flare of eczema at six months, and pimecrolimus resulted in significantly more participants without flares compared against vehicle (RR 1.47, 95% CI 1.32 to

1.64). Likewise, pimecrolimus was also significantly more effective than vehicle at preventing flares of eczema at 12 months (RR 1.69, 95% CI 1.45 to 1.96) based on data from 2 trials (Kapp 2002; Wahn 2002) involving 962 participants.

(v) No use of topical corticosteroids as rescue medication (three studies)

Data from one trial (Meurer 2002) involving 192 participants showed pimecrolimus was found to have significantly lower rates of corticosteroid use than vehicle at 6 months (RR 2.24, 95% CI 1.46 to 3.44; Analysis 5.5). In the 2 trials (Kapp 2002; Wahn 2002) which allowed the use of moderately potent topical corticosteroids as 'rescue' medication for treating flares of eczema, pimecrolimus was found to have significantly lower rates of corticosteroid use at 12 months (RR 1.76, 95% CI 1.50 to 2.08; Analysis 5.5) compared against vehicle based on results from 962 participants.

(vi) Improvement in quality of life (three studies)

Three flare prevention studies (McKenna 2006; Meurer 2002) reported on quality of life assessments. A 24-week RCT (Meurer 2002) involving 192 adults with moderate to severe eczema assessed QoL using both the Quality of Life Index AD (QoLI-AD) and the Dermatology Life Quality Index (DLQI). Participants receiving pimecrolimus had a significantly improved quality of life at 6 months compared with those receiving vehicle. The mean decreases (i.e. improvement) in the QoLI-AD score were 25.6% and 7.4% comparing pimecrolimus against vehicle (P = 0.002), and the mean decreases (i.e. improvement) in the DLQI score were 22.0% and 6.7% (P = 0.01).

McKenna 2006 reported on the QoL and health-related quality of life (HRQL) data from two 12-month flare-preventing trials, involving 251 infants with mild to very severe eczema (Kapp 2002) and 713 children with mild eczema (Wahn 2002). The Parent's Index of Quality of Life- eczema (PIQoL-AD) was used in both trials and the Children's Dermatology Life Quality Index (CDLQI) was used in the children trial to assess QoL at baseline, 6 weeks, 6 months and 12 months. Comparing change from baseline in PIQoL-AD scores, 1.0% pimecrolimus cream treatment resulted in significantly better improvement of eczema than vehicle in both trials at 6 months (P = 0.002 and 0.001 for infant and children trials) and 12 months (P = 0.016 and 0.015 for infant and children trials) of treatment, and also in the children trial at 6 weeks of treatment (P = 0.017). In the infant trial, the odds of giving an unfavourable answer to the PIQoL-AD questions were 41%, 87% and 80% higher for members of the control group at 6 weeks, 6 months and 12 months, respectively. The equivalent odds in the children trial were 34%, 59% and 46%. In addition, pimecrolimus was significantly superior to vehicle in the improvement of CDLQI score in the children trial at 6 weeks (P < 0.001), 6 months (P = 0.001) and 12 months (P = 0.10) of treatment; the mean CDLQI scores were 8.1 vs. 7.4, 4.9 vs. 7.1, 5.4 vs. 7.8 and 5.7 vs. 7.4, respectively (lower score indicates improved QoL).

(c) Pimecrolimus versus topical corticosteroids

(i) Investigator-rated clinical response as clear or almost clear eczema (one study)

A 12 month trial (Luger 2004) which compared 1.0% pimecrolimus against 0.1% triamcinolone acetonide (a mid-potency topical corticosteroid) in 658 adults with moderate to severe eczema found pimecrolimus to be significantly less effective than triamcinolone acetonide in achieving clear or almost clear of eczema after 1 week (RR: 0.52, 95%CI 0.45 to 0.61; Analysis 7.1), 3 weeks (RR 0.75, 95% CI 0.67 to 0.83; Analysis 7.1), 6 months (RR 0.89, 95%CI 0.83 to 0.96; Analysis 7.1) and 12 months (RR 0.92, 95% CI 0.86 to 0.98; Analysis 7.1) of treatment.

(ii) Participant-rated clinical response as complete or well controlled eczema (one study)

One trial (Luger 2001) compared 1% pimecrolimus against 0.1% betamethasone valerate (a potent topical corticosteroid) in 87 adults with moderate to severe eczema for 3 weeks. Pimecrolimus was found to be significantly less effective than betamethasone valerate in achieving moderately clear or better eczema (i.e. 50% improvement from baseline) at 3 weeks (RR 0.61, 95% CI 0.45 to 0.81; Analysis 8.1).

(iii) Mild or absent pruritus (*2* studies)

Luger 2001 also reported that pimecrolimus resulted in significantly fewer participants achieving mild or absent pruritus compared against 0.1% betamethasone valerate following 1 week (RR 0.51, 95% CI 0.34 to 0.75; Analysis 8.2) and 3 weeks (RR 0.58, 95% CI 0.41 to 0.81; Analysis 8.2) of treatment. Likewise, the 12-month trial (Luger 2004) found pimecrolimus resulted in significantly fewer participants achieving mild or absent pruritus than 0.1% triamcinolone acetonide at 12 months of treatment (RR 0.47, 95% CI 0.38 to 0.58; Analysis 7.2).

(iv) Improvement in quality of life (No studies)

We did not identify any quality of life assessments in trials that compared pimecrolimus against topical corticosteroids directly.

(d) Pimecrolimus versus tacrolimus

(i) Investigator-rated clinical response as clear or almost clear eczema (four studies)

Two trials (Kempers 2004; Paller (a) 2005) involving 567 children compared 1.0% pimecrolimus against 0.03% tacrolimus directly. The pooled results found no statistically significant difference between 1.0% pimecrolimus and 0.03% tacrolimus in achieving clear or almost clear of eczema following 1 week (RR 0.91, 95% CI 0.63 to 1.31; Analysis 9.1), 3 weeks (RR 0.82, 95% CI 0.58 to 1.15; Analysis 9.1) and 6 weeks (RR 0.84, 95% CI 0.69 to 1.02; Analysis 9.1) of treatment.

Paller 2005 also reported on 2 trials (Paller (b) 2005; Paller (c) 2005) involving 639 participants that compared 1% pimecrolimus against 0.1% tacrolimus directly. The pooled results found no significant difference in achieving clear or almost clear eczema following 1 week of treatment (RR 0.85, 95% CI 0.53 to 1.34; Analysis 10.1); however, 1.0% pimecrolimus was significantly less effective than 0.1% tacrolimus in achieving clear or almost clear eczema following 3 weeks (RR 0.56, 95% CI 0.41 to 0.77; Analysis 10.1) and 6 weeks (RR 0.58, 95% CI 0.46 to 0.74; Analysis 10.1) of treatment.

(ii) Mild or absent pruritus (two studies)

The results from 1 trial (Kempers 2004) involving 141 participants that compared 1.0% pimecrolimus against 0.03% tacrolimus found no statistically significant difference in achieving mild or absent pruritus following 1 week (RR 0.80, 95% CI 0.62 to 1.04; Analysis 9.2) and 6 weeks (RR 0.92, 95% CI 0.73 to 1.17; Analysis 9.2) of treatment, but 1.0% pimecrolimus was significantly less effective in achieving mild or absent pruritus at 3 weeks (RR 0.78, 95% CI 0.61 to 0.99; Analysis 9.2).

(iii) Impact on quality of life (No studies)

We did not identify any quality of life assessments in trials that compared pimecrolimus against tacrolimus directly.

(e) Different treatment schedules of pimecrolimus

(i) Investigator-rated clinical response as clear or almost clear eczema (two studies)

One trial (Ling 2005) involving 49 children and adults compared 1.0% pimecrolimus applied twice daily against 4r times daily. There were no significant differences between the 2 treatment schedules in achieving clear or almost clear eczema following 3 weeks of treatment (RR 1.04, 95% CI 0.43 to 2.52; Analysis 11.1). One trial (CASM981C2314 2006) involving 268 children who responded to a pre-trial 1% pimecrolimus twice daily treatment found no significant difference between twice daily and once daily schedules in achieving clear or almost clear eczema at 8 weeks (RR 1.07, 95% CI 0.87 to 1.31; Analysis 12.1) and 16 weeks (RR 1.05, 95% CI 0.86 to 1.28; Analysis 12.1).

(ii) Participant- or carer-rated clinical response as complete or well controlled eczema (No studies)

Ling 2005 also found that there were no significant differences between twice and four times daily regimens of pimecrolimus in achieving complete or well controlled eczema following three weeks of treatment (RR 1.33, 95% CI 0.76 to 2.31Analysis 11.1).

(iii) Mild or absent pruritus (one study)

Likewise, Ling 2005 reported no significant differences between twice and 4 times daily regimens of pimecrolimus in the proportion of participants achieving mild or absent of pruritus at 3 weeks (RR 0.96, 95% CI 0.56, 1.67; Analysis 11.3).

(iv) No flare of eczema during treatment (one study)

One trial (CASM981C2314 2006) involving 268 children who responded to a pre-trial 1% pimecrolimus twice daily treatment found no significant difference between twice daily and once daily schedules in achieving no flare of eczema at 16 weeks (RR 1.05, 95% CI 0.96 to 1.15; Analysis 12.2).

(v) Improvement in quality of life (No studies)

We did not identify any quality of life assessments in trials that compared between different treatment schedules of pimecrolimus.

2. Safety and tolerability

The tolerability results include total withdrawals, withdrawals due to lack of efficacy and withdrawals due to adverse events. The adverse events reported in the 31 included trials were generally mild. We did not identify any skin and internal cancers reported in the RCTs; likewise, there was no data on skin thinning. The most commonly reported adverse events were skin infection or application site reactions. We report the pooled results of proportions of participants experiencing any skin infections, bacterial skin infection, viral skin infections and local application site skin burning.

(a) Vehicle controlled and flare-preventing studies

(i) Withdrawal from treatment (22 studies)

Pimecrolimus was associated with significantly fewer overall withdrawals (RR 0.40, 95% CI 0.27 to 0.58; Analysis 1.4), withdrawals due to lack of efficacy (RR 0.21 95% CI 0.11 to 0.41; Analysis 1.4), and withdrawals due to adverse events (RR 0.43, 95%CI 0.19 to 0.97; Analysis 1.4) than vehicle from the pooled results of 10 (1785 participants), 8 (1657 participants) and 5 (1025 participants) vehicle-controlled trials, respectively.

One trial (CASM981C2442 2006) involving 200 participants with facial eczema found pimecrolimus resulted in fewer overall withdrawals (RR 0.44, 95%CI 0.31 to 0.63; Analysis 2.3) and withdrawals due to lack of efficacy (RR 0.27, 95%CI 0.15 to 0.48; Analysis 2.3) than vehicle, but no significant difference was detected in withdrawals due to adverse events (RR 0.82, 95%CI 0.26 to 2.59; Analysis 2.3). Similarly, results from 1 trial (CASM981C2436 2006) involving 67 participants who responded to topical corticosteroid treatment found pimecrolimus resulted in fewer overall withdrawals (RR 0.28, 95% CI 0.10 to 0.76; Analysis 3.1) and withdrawals due to lack of efficacy (RR 0.28, 95% CI 0.10 to 0.76; Analysis 3.1) than vehicle; but no withdrawals due to adverse events were reported. One further trial (ASM981C2402 2005) involving 73 participants who did not respond to topical corticosteroid treatment found no significant difference between pimecrolimus and vehicle in overall withdrawals (RR 0.62, 95% CI 0.27 to 1.42; Analysis 4.4), withdrawals due to lack of efficacy (RR 0.41, 95% CI 0.10 to 1.71; Analysis 4.4), or adverse events (RR 0.83, 95% CI 0.15 to 4.65; Analysis 4.4).

Pimecrolimus was associated with significantly fewer overall withdrawals (RR 0.64, 95% CI 0.54 to 0.76; Analysis 5.6) and withdrawals due to lack of efficacy (RR 0.42, 95% CI 0.34 to 0.51; Analysis 5.6) than vehicle from the pooled results of 9 flare-preventing trials involving 3091 participants. However, no significant difference between pimecrolimus and vehicle was detected in withdrawals due to adverse events (RR 0.60, 95% CI 0.28 to 1.27; Analysis 5.6) from the pooled results of 8 flare-preventing trials involving 2380 participants. One flare-preventing trial (ASM981CDE10 2005) involving 184 participant who responded to topical corticosteroids also found no significant difference between pimecrolimus and vehicle in overall withdrawals (RR 0.57, 95% CI 0.29 to 1.14; Analysis 6.1) and withdrawals due to lack of efficacy (RR 0.43, 95% CI 0.17 to 1.09; Analysis 6.1) than vehicle; and no withdrawals due to adverse events were reported in this trial.

(ii) Adverse events (17 studies)

We found no significant difference between pimecrolimus and vehicle in the proportions of participants experiencing any adverse events (RR 0.92, 95% CI 0.82 to 1.02; Analysis 1.5), bacterial skin infections (RR 0.13, 95% CI 0.01 to 1.12; Analysis 1.5) and skin burning (RR 1.40, 95% CI 0.90 to 2.18; Analysis 1.5) from the pooled results of four (827 participants), 1 (186 participants) and 5 (914 participants) vehicle-controlled trials, respectively.

The vehicle-controlled trial (CASM981C2442 2006) involving 200 participants with facial eczema did not report any relevant adverse event data. One trial (CASM981C2436 2006) involving 67 participants who responded to topical corticosteroids found no significant difference between pimecrolimus and vehicle in any adverse events (RR 1.70, 95% CI 0.82 to 3.51; Analysis 3.2). One trial (ASM981C2402 2005) involving 73 participants who did not respond to topical corticosteroids found no significant difference between pimecrolimus and vehicle in any adverse events (RR 1.19, 95% CI 0.76 to 1.87; Analysis 4.5), any skin infections (RR 1.66, 95% CI 0.18 to 15.16; Analysis 4.5), viral skin infections (RR 2.81, 95% CI 0.14 to

56.46; Analysis 4.5), and skin burning (RR 0.55, 95% CI 0.08 to 3.70; Analysis 4.5).

We found pimecrolimus was associated with significantly more participants experiencing any adverse events (RR 1.07, 95% CI 1.00 to 1.16; Analysis 5.7) and skin burning (RR 4.36, 95% CI 1.75 to 10.85; Analysis 5.7) than vehicle from the pooled results of four (1398 participants) and three (999 participants) flare-preventing trials. However, no significant difference between pimecrolimus and vehicle was detected in participants experiencing any skin infections (RR 1.14, 95% CI 0.75 to 1.72; Analysis 5.7), bacterial skin infections (RR 0.84, 95% CI 0.51 to 1.39; Analysis 5.7) and viral skin infections (RR 1.79, 95% CI 0.89 to 3.61; Analysis 5.7) from the pooled results of 3 (718 participants), 3 (718 participants) and 4 (982 participants) flare-preventing trials, respectively. The flare-preventing trial (ASM981CDE10 2005) involving participants who responded to topical corticosteroids did not report relevant safety outcomes.

(b) Pimecrolimus versus topical corticosteroids

(i) Withdrawal from treatment (two studies)

One 52-week trial (Luger 2004) involving 658 participants found that 1% pimecrolimus was associated with significantly more overall withdrawals (RR 2.45, 95% CI 1.98 to 3.03; Analysis 7.3), withdrawals due to lack of efficacy (RR 4.43, 95% CI 3.01 to 6.54; Analysis 7.3) and withdrawals due to adverse events (RR 5.63, 95% CI 2.20 to 14.41; Analysis 7.3) than 0.1% triamcinolone acetonide.

However, one three-week trial (Luger 2001) involving 87 participants found no significant difference between 1% pimecrolimus and 0.1% betamethasone valerate for the overall withdrawals (RR 2.18, 95% CI 0.60 to 7.88; Analysis 8.3), or withdrawals due to lack of efficacy (RR 4.67, 95% CI 0.23 to 94.61; Analysis 8.3) and withdrawals due to adverse effects (RR 2.80, 95% CI 0.30 to 25.88; Analysis 8.3).

(ii) Adverse events (two studies)

Luger 2004 found no significant difference between 1% pimecrolimus and 0.1% triamcinolone acetonide in the proportion of participants experiencing any adverse events (RR 1.07, 95% CI 0.98 to 1.17; Analysis 7.4), any skin infections (RR 0.87, 95% CI 0.65 to 1.15; Analysis 7.4), viral skin infections (RR 0.62, 95% CI 0.34 to 1.13; Analysis 7.4) or bacterial skin infections (RR 0.91, 95% CI 0.61 to 1.37; Analysis 7.4), but 1% pimecrolimus was associated with a significantly higher rate of skin burning (RR 2.38, 95% CI 1.66 to 3.40; Analysis 7.4) than 0.1% triamcinolone acetonide.

However, Luger 2001 reported that 1% pimecrolimus was associated with a significantly higher rate than 0.1% betamethasone valerate of participants experiencing any adverse events (RR 1.57, 95% CI 1.07 to 2.30) or skin burning (RR 5.13, 95% CI 1.93 to 13.66; Analysis 7.4; there was no other relevant safety outcomes reported in this trial.

None of the included trials reported on changes in skin thickness.

(c) Pimecrolimus versus tacrolimus

(i) Withdrawal from treatment (four studies)

Two trials (Kempers 2004; Paller (a) 2005) involving 567 participants found no significant difference between 1% pimecrolimus and 0.03% tacrolimus in the overall withdrawal rate (RR 1.94, 95% CI 0.54 to 6.98; Analysis 9.3), but 1% pimecrolimus was associated with significantly higher withdrawal rates due to lack of efficacy (RR 3.45, 95% CI 1.23 to 9.71; Analysis 9.3) and adverse events (RR 8.19, 95% CI 1.50 to 44.73; Analysis 9.3) than 0.03% tacrolimus.

Pooled results from 2 trials (Paller (b) 2005; Paller (c) 2005) involving 639 participants found no significant difference in the overall withdrawals (RR 1.18, 95% CI 0.91 to 1.52; Analysis 10.1) and withdrawals due to adverse events (RR 1.01, 95% CI 0.43 to 2.41; Analysis 10.2), but 1% pimecrolimus was associated with significantly a higher withdrawal rate due to lack of efficacy (RR 2.37, 95% CI 1.10 to 5.08; Analysis 10.2) than 0.1% tacrolimus.

(ii) Adverse events (four studies)

We found no significant differences between the head-to-head comparisons of 1.0% pimecrolimus against 0.03% tacrolimus in participants experiencing any adverse events (RR 1.03, 95% CI 0.90 to 1.17; Analysis 9.4), skin infections (RR 1.65, 95% CI 0.12 to 22.75; Analysis 9.4), bacterial skin infections (RR 6.90, 95% CI 0.36 to 131.23; Analysis 9.4), viral skin infections (RR 1.03, 95% CI 0.15 to 6.96; Analysis 9.4) and skin burning (RR 1.17, 95% CI 0.55 to 2.49; Analysis 9.4).

Likewise, no significant differences between 1.0% pimecrolimus and 0.1% tacrolimus in participants experiencing any adverse events (RR 1.04, 95% CI 0.47 to 2.26; Analysis 10.3), skin infections (RR 1.60, 95% CI 0.37 to 6.99; Analysis 10.3), viral skin infections (RR 1.03, 95% CI 0.07 to 16.43; Analysis 10.3) and skin burning (RR 0.76, 95% CI 0.36 to 1.62; Analysis 10.3, comparison 10-10) were detected.

(d) Different regimens of pimecrolimus

(i) Withdrawal from treatment (two studies)

We found no significant differences between 1% pimecrolimus applied twice daily compared against the same strength applied 4 times daily in overall withdrawals (RR 0.15, 95% CI 0.02 to 1.12; Analysis 11.4), withdrawals due to lack of efficacy (RR 0.09, 95% CI 0.01 to 1.62; Analysis 11.4) and withdrawals due to adverse events (RR 3.12, 95% CI 0.13 to 73.04; Analysis 11.4) based on the results of 1 trial involving 49 participants (Ling 2005).

One trial (CASM981C2314 2006) involving 268 participants who responded to a pre-trial pimecrolimus treatment compared 1% pimecrolimus twice daily against the same strength applied once daily found that the twice daily schedule was associated with significantly fewer overall withdrawals (RR 0.43, 95% CI 0.28 to 0.67; Analysis 12.3) and withdrawals due to lack of efficacy (RR 0.43, 95% CI 0.22 to 0.88; Analysis 12.3) than once daily schedule; but we found no significant difference in withdrawals due to adverse events (RR 0.67, 95% CI 0.19 to 2.31; Analysis 12.3).

(ii) Adverse events (two studies)

Ling 2005 found no significant differences between the direct comparisons of 1% pimecrolimus twice daily against the same strength applied once or 4 times daily in 49 participants experiencing any adverse events (RR 1.39, 95% CI 0.35 to 5.57; Analysis 11.5) and skin burning (RR 1.04, 95% CI 0.23 to 4.66; Analysis 11.5).

One trial (CASM981C2314 2006) found no significant differences between the direct comparisons of 1% pimecrolimus twice daily against the same strength applied once daily for 268 participants

who responded to pimecrolimus treatment in experiencing any adverse events (RR 1.02, 95% CI 0.88 to 1.19; Analysis 12.4) or skin infections (RR 2.00, 95% CI 0.18 to 21.79; Analysis 12.4).

(e) Potential serious adverse events

In our review, we found no cancer-related events reported in RCTs and a lack of long-term observational studies to examine the risk of skin cancers and lymphoma. Therefore, the risk of cancer-related events associated with pimecrolimus remains uncertain. We only found a nested case-control study that used an automated database to evaluate the association between topical immunosuppressants and lymphoma in a cohort of participants with eczema. This study identified 294 cases of lymphoma in 293253 participants, but did not find an increased risk of lymphoma in participants treated with topical corticosteroids and topical calcineurin inhibitors. The odds ratios were (1.2, 95% CI 0.8 to 1.8) for "super potent" topical steroids, (1.1, 95% CI 0.7 to 1.6) for "low potency" topical steroids, (0.8, 95% CI 0.4 to 1.6) for pimecrolimus and (0.8, 95% CI 0.4 to 1.7) for tacrolimus (Arellano 2006).

DISCUSSION

Summary of main results

Principal findings

Evidence from short-term (no more than six weeks) vehicle-controlled trials has shown that topical pimecrolimus is effective in controlling the signs and symptoms of eczema or facial eczema with acceptable tolerability and safety profiles. Evidence from long-term (more than six months) flare-preventing trials showed that pimecrolimus is effective in controlling the signs and symptoms of eczema. The long-term quality of life measures gathered from adults, carers of infants and children also suggests that pimecrolimus also improves quality of life more than vehicle alone. It is not surprising that an active treatment shows better efficacy outcomes than vehicle only in eczema. The vehicle controlled studies have been helpful in establishing that short-term efficacy and capability of preventing flares does exist and that the tolerability and short-term adverse effect profile of topical pimecrolimus is acceptable. More vehicle controlled studies are not needed (Freeman 2006) and may even be considered unethical, especially if children with severe eczema are included (Williams 2003).

Current evidence for the head-to-head comparisons of topical immunosuppressants (i.e. pimecrolimus vs. tacrolimus) are limited, yet we found some evidence in four trials that 1% pimecrolimus is as effective as 0.03% tacrolimus and less effective than 0.1% tacrolimus in treating eczema. Pimecrolimus presented similar tolerability and safety profiles to both 0.03% and 0.1% tacrolimus, but more participants withdrew from pimecrolimus treatment due to the lack of efficacy.

Strengths and limitations of the review

We comprehensively searched for randomised controlled trials from a wide range of databases in order to avoid the risk of publication bias, used clinically relevant outcome measures, and included direct comparisons with other active treatments, rather than making indirect inferences from placebo controlled trials. However, there are several limitations of this review:

(1) Participants

One limitation of our systematic review is that we failed to analyse the outcome data according to participants' age groups and the severity of eczema due to the enormous discrepancies of definitions for these subgroups within the included trials. Therefore, some caution is needed for the interpretation of results as applied to particular age groups.

We acknowledge the high drop-out (attrition) rates of included trials. Seventeen of the 31 trials have more than 20% dropouts. Although the attrition rate is related to treatment duration, 11 of the 17 trials with inadequate attrition rates are short-term trials (no more than 6 weeks). Participants' severity of eczema and efficacy of treatment may also influence the attrition rates. Therefore, we explored the reasons for attrition in terms of withdrawals due to lack of efficacy or adverse events and found the majority of participants withdrew from the trials due to lack of efficacy.

(2) Comparisons

There are very limited data available for the active comparisons (pimecrolimus vs. topical corticosteroids) and head-to-head comparisons of pimecrolimus against topical tacrolimus.

As 1.0 % pimecrolimus is licensed for acute treatment of mild to moderate eczema (including flares), in practice, 1% hydrocortisone acetate (a mild topical corticosteroid) licensed for the same indication is the most relevant comparator to pimecrolimus. However, the comparison of pimecrolimus with existing therapy for such a group is currently not available. Perhaps this is not surprising as 1% hydrocortisone is much less expensive than topical pimecrolimus and topical pimecrolimus would need to be much more effective (or have much fewer adverse effects) than 1% hydrocortisone in order to become cost-effective. Both scenarios seem unlikely given the performance of topical pimecrolimus against stronger topical corticosteroid preparations. Although we found pimecrolimus is more effective in preventing flares than vehicle, the comparative efficacy of pimecrolimus against the early use of mild topical corticosteroids is not known. In the absence of such key comparisons, the therapeutic role of pimecrolimus in treating mild to moderate eczema is unclear.

In addition, there is also a lack of crucial outcome data for other active and head-to-head comparisons. Although topical immunosuppressants (i.e. pimecrolimus and tacrolimus) were developed as an alternative to topical corticosteroids to overcome possible adverse effects of corticosteroids (such as thinning of the skin or adrenal gland suppression), we found no clear evidence that these newer, more expensive products offer better tolerability and safety profiles compared with existing standard practice. Crucially, we found no evidence to show that use of topical pimecrolimus was associated with less skin thinning than topical corticosteroids in long term studies, perhaps because such skin thinning is very rare when topical corticosteroids are used appropriately (Williams 2005). One preliminary randomised controlled trial of pimecrolimus applied to normal skin for four weeks found no thinning of the skin (Queille-Roussel 2001), however, the results are difficult to generalise to people with eczema who apply preparations over the course of a year.

One obvious area of potential use for a new and more expensive product like topical pimecrolimus is in the treatment of eczema that has become "resistant" or that has failed to respond to

topical corticosteroids. Only one small-scale study has evaluated such a use, and failed to demonstrate any greater efficacy than vehicle. Another area where topical pimecrolimus might have an important niche is in the treatment of eczema at "sensitive" sites such as the face in people who might have become dependent on inappropriate use of topical corticosteroids at such sites, and therefore at high risk of skin thinning. Although four trials have shown efficacy of topical pimecrolimus when compared with vehicle for facial eczema, we are not aware of any studies that have shown any advantage in terms of less skin thinning when compared against topical corticosteroids for such sensitive site eczema. Nor are we aware of any studies that have shown that pimecrolimus might work when topical corticosteroids have stopped working on facial eczema or in people who have developed topical corticosteroid-related skin thinning. So we have a lot of data on pimecrolimus where it is not needed, and very little to none on the clinical situations where it might be useful.

(3) Outcomes

There are various outcome measures reported relating to different timings from the included trials. No trial reported on QoL data comparing pimecrolimus against tacrolimus. We failed to analyse the global changes in composite rating scales (e.g. ADASI or eczema area and severity index [EASI]) presented in mean or median percentages of improvement from baseline. The use of investigators' global assessments of response to treatment also causes some concern. Despite the fact that these assessments of response to treatment are widely used as outcome measures in clinical trials of eczema further research is needed to fully determine their validity, reliability, and sensitivity to change (Charman (a) 2000; Charman 2003). Likewise, it is possible that blinding in placebo controlled trials may have been compromised due to relatively high proportions of participants receiving pimecrolimus experiencing skin burning.

One limitation of our systematic review is that our analyses of withdrawal rates and adverse events were based on data pooled from trials of different durations. We did not find any rare or severe adverse events reported in the included trials. However, in response to the warning from U.S. Food and Drug Administration (FDA 2006) and European Agency for the Evaluation of Medical Products (EMEA 2006) in 2006 on the potential risks of skin cancer and lymphoma associated with pimecrolimus and tacrolimus, further population-based, long-term epidemiological studies are needed to assess rare and severe adverse events of topical immunosuppressants. One study has already emerged which suggests that topical pimecrolimus is not associated with a higher risk of lymphoma, but further long term studies are needed (Arellano 2006).

AUTHORS' CONCLUSIONS

Implications for practice

Our systematic review shows that pimecrolimus is effective when compared against vehicle with short bursts of topical corticosteroids for flare-ups of eczema. However, there is limited evidence on the comparative efficacy, tolerability, and adverse events associated with pimecrolimus compared against existing optimal treatments, such as mild topical corticosteroids and tacrolimus. The clinical role of pimecrolimus is therefore uncertain owing to a lack of relevant comparative data. There is no evidence at present to suggest that pimecrolimus is effective in people who fail to respond to topical corticosteroids. Whilst topical pimecrolimus might have a useful role in treating eczema at sensitive sites such as the face where skin thinning may become a problem, no comparative studies have addressed this issue and demonstrated any advantage over existing therapy. Whilst short-term studies on drug safety are reassuring, more long term studies evaluating the possible risks associated with skin immunosuppression are needed.

Implications for research

More vehicle controlled studies are not needed and may even be considered as unethical. Pragmatic randomised controlled trials lasting at least 12 months are needed to compare topical pimecrolimus and 1% hydrocortisone acetate in children and adults with mild to moderate eczema. More trials are needed to see if topical pimecrolimus works in people who fail to respond adequately to topical corticosteroids. Trials are needed that evaluate topical pimecrolimus in sensitive sites such as the face. Outcome data should include clearing capacity, relapse, quality of life, adverse events (including skin thinning), and costs. Although several trials have been undertaken on participants who responded poorly to topical corticosteroids, current evidence is insufficient to support using pimecrolimus as a second line treatment of eczema despite recommendation by the UK National Institute of Health and Clinical Excellence (NICE 2004) and the US Food and Drug Administration to use it in such circumstances (FDA 2005). Experience of long term use of topical pimecrolimus is limited and the risk of rare but more serious adverse effects remains a concern. Further long term surveillance of these agents is needed (Williams 2002).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

ASM981C2315 2005

Methods	Parallel group, double blind, placebo control, multicentre randomised controlled trial (flare prevention study)
Participants	Inclusion criteria: children (N = 521), mild to moderate eczema, age: 2 to 17 years, requiring treatment with topical corticosteroids, pimecrolimus or tacrolimus at least twice in the six months proceeding randomisation, IGA=1. Exclusion criteria: medical history or concomitant illness and treatment could interfere with study, history of malignancy, inadequate response to tacrolimus or pimecrolimus, immunocompromised, current skin status that could interfere with study evaluation, and active infections. Wash out period: corticosteroids, immunosupressants, phototherapy: one month; topical tacrolimus or pimecrolimus: four weeks; systemic antibiotics: two weeks; topical therapy: seven days.
Interventions	pimecrolimus 1.0% BID (n=256) vs. vehicle BID (n=265) for 26 weeks. Short-term acute flares were treated with medium potency topical corticosteroids.
Outcomes	1. Efficacy: number of participants achieving no flare; mean number of flares; mean duration of not using TS (days). 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs.
Notes	Report from Novartis clinical trial results website

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ASM981C2316 2005

Methods	Parallel group, double blind, placebo control, international multicentre, randomised controlled trial (flare prevention study)
Participants	Inclusion criteria: adults (N = 543), mild to moderate eczema, age: >=18 years, IGA 2 to 3, requiring topical corticosteroid. Exclusion criteria: history of malignancy, inadequate response to tacrolimus or pimecrolimus, immunocompromised, concurrent skin disease, active viral, bacterial or fungal infections, hypersensitivity. Wash out period: pimecrolimus or tacrolimus: six months; systemic corticosteroids, immunosuppressants, cytostatics or phototherapy: one month; topical tacrolimus: four weeks, systemic antibiotics: two weeks; topical therapy: seven days.
Interventions	pimecrolimus 1.0% BID (n=277) vs. vehicle BID (n=266) for 26 weeks. Short-term acute flares were treated with medium potency topical corticosteroids.
Outcomes	1. Efficacy: number of participants achieving no flare; mean number of flares; mean duration (days) of not using TS. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs and application site skin burning.
Notes	Report from Novartis clinical trial results website

ASM981C2316 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ASM981C2402 2005

Methods	Parallel group, double blind, placebo control, international multicentre, randomised controlled trial
Participants	Inclusion criteria: children and adults (N = 73), mild to moderate eczema, age: 2 to 50 years, BSA >=5%, poor response to treatment with prednicarbate emollient cream. Exclusion criteria: concurrent skin diseases, systemic malignancy, active lymph proliferation, hypersensitivity. Wash out period: phototherapy, systemic or topical therapy: four weeks, systemic retinoid or investigational drugs: eight weeks, systemic or topical antibiotics: two weeks.
Interventions	pimecrolimus 1.0% BID (n=47) vs. vehicle BID (n=26) for 6 weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA), achieving complete or well controlled eczema (PGA) and achieving mild or absent pruritus; mean reduction in EASI from baseline; number of participants' eczema improved by at least one IGA score 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, numbers of participants experiencing any ADEs, skin infections, viral skin infections, application site skin burning.
Notes	Report from Novartis clinical trial results website. This study involved participants who had poor response to topical corticosteroid treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ASM981CDE10 2005

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial (flare prevention study)
Participants	Inclusion criteria: children (N =185), severe eczema (diagnosis criteria: Rajka & Langeland), age: 2 to 17 years, eczema score 8 or 9, responded to 21 days of treatment with prednicarbate cream 0.25%. Exclusion criteria: phototherapy, systemic or topical therapy or systemic corticosteroid prior to study entry which could have an effect on eczema.
Interventions	pimecrolimus 1.0 % BID (n=95) vs. vehicle BID (n=89) for 24 weeks. Short-term acute flares were treated with topical prednicarbate cream 0.25% BID.
Outcomes	Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs.
Notes	Report from Novartis clinical trial results website. This study involved participants who responded to topical corticosteroid treatment.

Risk of bias

ASM981CDE10 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Barba 2003

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial
Participants	Inclusion criteria: infants and children (N = 106), mild to moderate eczema, age: 3 months to 18 years, IGA score 2 to 3. Exclusion criteria: not stated. Wash out period: not stated.
Interventions	pimecrolimus 1.0% BID (n=71) vs. vehicle BID (n = 35) for three weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA), achieving complete or well controlled eczema (PGA), and achieving mild or absent pruritus; median percentage (%) of reduction in EASI from baseline 2. Safety and tolerability: total WDs; number of participants experiencing application site skin burning.
Notes	Abstract only, we did not include data for the 24-week, open-label, noncomparative trial period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

CASM981C1301 2005

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial (flare-preventing study)
Participants	Inclusion criteria: children (N = 240), mild to moderate eczema (diagnosis criteria: Williams et al.), age: 2 to 16 years, TBSA >= 5%, IGA >= 2. Exclusion criteria: history of malignant disease, active skin infections, other systemic infections, other skin conditions. Wash out period: phototherapy or systemic therapy: four weeks, antibiotics, antiviral or antifungal therapy: two weeks, topical therapy or systemic antiallergic drugs: seven days.
Interventions	pimecrolimus 1.0% BID (n = 83) vs. vehicle BID (n =7 8) for 26 weeks. Short-term acute flares were treated with hydrocortisone butyrate on body/limbs, clobetasone butyrate on face/neck, prednisolone valerate acetate lotion on scalp.
Outcomes	1. Efficacy: number of participants achieving no flare. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs.
Notes	Report from Novartis clinical trial results website.

Risk of bias

Bias	Authors' judgement	Support for judgement

CASM981C1301 2005 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

CASM981C1303 2005

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial (flare-preventing study)
Participants	Inclusion criteria: adults (N = 173), mild to moderate eczema, age: 16 to 65 years, TBSA <= 5%, IGA >= 2. Exclusion criteria: history of malignant, active skin infection, systemic infections, other skin conditions. Wash out period: phototherapy or systemic therapy: four weeks, antibiotics, antiviral or antifungal therapy: two weeks, topical therapy or systemic antiallergic therapy: seven days.
Interventions	pimecrolimus 1.0% BID (n = 86) vs. vehicle BID (n = 87) for 26 weeks. Short-term acute flares were treated with topical corticosteroids and/or tacrolimus hydrate ointment BID.
Outcomes	1. Efficacy: numbers of participants achieving no flare; median duration (days) to first flare of eczema. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs.
Notes	Report from Novartis clinical trial results website.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

CASM981C2314 2006

Methods	Parallel group, double blind, international multicentre, randomised controlled trial
Participants	Inclusion criteria: children (N = 268), mild to severe eczema, age: 2 to 17 years, TBSA >= 5%, being pretreated pimecrolimus 1% BID to remission during 6-week run-in period. Exclusion criteria: pregnant or breast-feeding women, immunocompromised, open skin infection, head lice or scabies, relapse during the run-in period, active skin infection. Wash out period: topical therapy: two weeks; phototherapy: four weeks; systemic immunosuppressant or steroids: four weeks.
Interventions	pimecrolimus 1.0% BID (n = 134) vs. pimecrolimus 1.0% QD (n = 13) for 16 weeks.
Outcomes	1. Efficacy: numbers of participants achieving no flare and achieving clear or almost clear eczema (IGA); median duration (days) to first eczema flare, EASI. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy,; WDs due to ADEs, number of participants experiencing any ADEs skin infections.
Notes	This study involved participants whose AD was treated by pimecrolimus 1.0% BID to remission.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment?	Unclear risk	B - Unclear

CASM981C2322 2005

Methods	Parallel group, double blind, placebo control, multicentre randomised controlled trial
Participants	Inclusion criteria: children (N = 336), mild to moderate eczema, age: 2 to 17 years, TBSA >= 5%. Exclusion criteria: females of childbearing potential using inadequate contraception or who were pregnant or breastfeeding, HIV, immunocompromised, skin conditions that interfere with study evaluation, investigational therapy, hypersensitivity. Wash out period: topical therapy: seven days; systemic corticosteroid or leukotriene antagonist: one month; phototherapy or immunosuppressants or cell growth inhibitors: one month.
Interventions	pimecrolimus 1.0% BID (n = 168) vs. vehicle BID (n = 168) for 4 weeks
Outcomes	1. Efficacy: number of participants achieving clear or almost clear eczema (IGA). 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs; numbers of participants experiencing any ADEs, skin infections, and application site skin burning.
Notes	Report from Novartis clinical trial results website

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

CASM981C2436 2006

Methods	Parallel group, double blind, placebo control, international multicentre, randomised controlled trial
Participants	Inclusion criteria: adults (N = 67), mild to moderate eczema (diagnosis criteria: Hanifin and Rajka, prick-test and/or elevated IgE background), age >= 20 years, >= 3 year history of AD, whole body IGA of 2 or 3, localized EASI of 1 to 8, affecting bilateral arms and/or legs >= 10 cm, after topical corticosteroids treatment for 2 weeks, localized EASI <=1. Exclusion criteria: immunocompromised, concurrent skin diseases, active skin infections, history of rheumatic fever, prosthetic constituents, poor response to study drugs, hypersensitivity, serious reactions to anaesthetics, topical therapy. Wash out period: phototherapy, systemic corticosteroids or other systemic therapy known or suspected to have an effect on AD: four weeks, antihistamines: seven days.
Interventions	pimecrolimus 1.0% BID (n = 34) vs. vehicle BID (n = 33) for 3 weeks
Outcomes	Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs.
Notes	Report from Novartis clinical trial results website. This study involved participants who responded to topical corticosteroid treatment.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

CASM981C2442 2006

Methods	Parallel group, double blind, placebo control, international multicentre, randomised controlled trial
Participants	Inclusion criteria: children and adults (N = 200), mild to moderate facial eczema (diagnosis criteria: Hanifin and Rajka), age: >= 12 years, facial IGA 2 to 3 based on assessment on the face only and excluding the ears and the neck. Exclusion criteria: <= 30% BSA, pregnant or breast-feeding women, concurrent skin disease, immunocompromised, poor response, hypersensitivity. Wash out period: phototherapy or systemic therapy: four weeks, investigational drugs: eight weeks.
Interventions	pimecrolimus 1.0% BID (n = 101) vs. vehicle BID (n = 99) for 6 weeks
Outcomes	1. Efficacy: number of participants achieving clear or almost clear facial eczema (IGA) and achieving mild or absent pruritus 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, incident rate of ADEs of different organ systems (events/days).
Notes	Report from Novartis clinical trial results website. We did not include data for the 6-week, open-label period. The numbers of participants experiencing ADEs are not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

CASM981CUS03 2005

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial (flare-preventing study)
Participants	Inclusion criteria: adults (N = 264), mild to severe eczema, age: 18 to 65 years, IGA >= 2, TBSA >= 5%. Exclusion criteria: not stated. Wash out period: not stated.
Interventions	pimecrolimus 1.0% BID (n = 176) vs. vehicle BID (n = 88) for 24 weeks. Short-term acute flares were treated with topical corticosteroids (not specified).
Outcomes	1. Efficacy: number of participants achieving no flares; mean number of flares; mean duration (days) of participants using TS. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, numbers of participants experiencing any ADEs, bacterial skin infections and application site skin burning.
Notes	Report from Novartis clinical trial results website

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Eichenfield (a) 2002

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial

Eichenfield (a) 2002 *(Continued)*

Participants	Inclusion criteria: children (N = 198), mild to moderate eczema (diagnosis criteria: Williams et al.), age: 1 to 17 years, diagnostic criteria of Williams, TBSA >5%, IGA score 2 or 3, receiving emollient for at least 7 days before baseline. Exclusion criteria: significant concurrent disease, pregnancy or breast nursing. Wash out period: phototherapy or systemic therapy within one month from baseline, topical therapy with seven days, systematic antibiotics within two weeks.
Interventions	pimecrolimus 1.0% BID (n = 130) vs. vehicle BID (n = 68) for 6 weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA) and achieving mild or absent pruritus 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs.
Notes	This is a report of two trials combined - separate data were extractable with the use of the data gathered from the FDA website regulatory submissions http://www.fda.gov/cder/foi/nda/2001/21-302_Elidel.htm (accessed 24/03/04) We could not separate the ADEs of the two studies because only the combined analysis of ADEs is available from both published results and FDA website.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Eichenfield (b) 2002

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial
Participants	Inclusion criteria: children (N = 205), mild to moderate eczema (diagnosis criteria: Williams et al.), age: 1 to 17 years,diagnostic criteria of Williams, TBSA > 5%, IGA score 2 or 3, receiving emollient for at least 7 days before baseline. Exclusion criteria: significant concurrent disease, pregnancy or breast nursing Wash out period: phototherapy or systemic therapy within one month from baseline, topical therapy with seven days, systematic antibiotics within two weeks.
Interventions	pimecrolimus 1.0% BID (n = 137) vs. vehicle BID (n = 68) or 6 weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA) and achieving mild or absent pruritus 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs.
Notes	This is a report of two trials combined - separate data were extractable with the use of the data gathered from the FDA website regulatory submissions http://www.fda.gov/cder/foi/nda/2001/21-302_Elidel.htm (accessed 24/03/04) We could not separate the ADEs of the two studies because only the combined analysis of ADEs is available from both published results and FDA website.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ho 2003

Methods	Parallel group, double blind, placebo control, international multicentre, randomised controlled trial
Participants	Inclusion criteria: infants (N = 186), mild to moderate eczema (diagnosis criteria: Seymour et al.), age: 3 to 23 months, TBSA >= 5%, IGA 2 or 3. Exclusion criteria: immunocompromised, concurrent or active skin diseases or viral skin infections, hypersensitivity. Wash out period: phototherapy or systemic treatments: one month, topical therapy: one week, sedative antihistamines to treat pruritus: one week.
Interventions	pimecrolimus 1.0% BID (n = 123) vs. vehicle BID (n = 63) for 6 weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA), achieving complete or well controlled of eczema (PGA) and achieving mild or absent pruritus; median percentage (%) of reduction in EASI from baseline 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, numbers of participants experiencing any ADEs, bacterial skin infections, and application site skin burning.
Notes	Used additional data from the FDA report to supplement data extracted from the paper. We did not included data for the 20-week, open-label, noncomparative trial period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kapp 2002

Methods	Parallel group, double blind, placebo control, international multicentre, randomised controlled trial (flare-preventing study)
Participants	Inclusion criteria: infants (N = 251), mild to very severe eczema (diagnosis criteria: Seymour et al.), age: 3 to 23 months, IGA >= 2, BSA >= 5%. Exclusion criteria: immunocompromised, malignant history, active skin infection, treated with medicines affecting eczema, skin condition could affect the evaluation of study drug. Wash out period: phototherapy or systemic therapy: one month; topical therapy: seven days; systemic antibiotics: two weeks.
Interventions	pimecrolimus 1.0% BID (n = 204) vs vehicle BID (n = 47) for 52 weeks. Short-term acute flares (IGA >= 4) were treated with moderately potent topical corticosteroids (0.02% diflupredrate, 0.1% hydrocortisone butyrate, 0.05% clobetasone butyrate, 0.02% triamcilonone acetonide, 0.2% hydrocortisone valerate).
Outcomes	1. Efficacy: number of participants achieving clear or almost clear eczema (IGA); median percentage (%) of reduction in EASI from baseline; mean percentage (%) of reduction in BSA; ; mean decrease in DLQI score; mean PIQoL-AD score. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs; numbers of participants experiencing any ADEs, skin infections, viral skin infections, and application site skin burning.
Notes	

Risk of bias

Kapp 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kaufmann 2006

Methods	Parallel group, double blind, placebo control, international multicentre, randomised controlled trial
Participants	Inclusion criteria: adults (N = 198), mild to moderate eczema, age: 18 to 81 years, IGA 2 or 3, BSA >= 5%, moderate to severe pruritus (pruritus score 2 or 3). Exclusion criteria: skin diseases, allergy, infections, poor response to topical tacrolimus, immunocompromised, malignant history, breast-feeding, pregnant, not use medically approved contraception. Wash out period: topical medication for pruritus relief or antibiotic therapy < seven days, anti-pruritus or sedatives medications < two weeks, systemic or phototherapy for eczema < one month.
Interventions	pimecrolimus 1.0%BID (n = 100) vs. emollients BID (n = 98) for 1 week
Outcomes	1. Efficacy: number of participants achieving mild or absent pruritus, number of participants improved by at least one pruritus score 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, numbers of participants experiencing any skin infections and application site skin burning.
Notes	The total duration was six weeks, but we did not include data for the five-week open-label trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kempers 2004

Methods	Parallel group, investigator blind, active control, multicentre, randomised controlled trial
Participants	Inclusion criteria: children (N = 141), moderate eczema, age: 2 to 17 years. Exclusion criteria: not stated. Wash out period: not stated.
Interventions	pimecrolimus 1.0% BID (n = 71) vs. tacrolimus 0.03% BID (n = 70) for 6 weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA) and achieving mild or absent pruritus. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs; numbers of participants experiencing any ADEs, skin infections, bacterial skin infections, viral skin infections, and application site skin burning.
Notes	We did not include data for the 20-week open-label uncontrolled extension period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Leo 2004

Methods	Parallel group, double blind, single centre, placebo control, randomised controlled trial
Participants	Inclusion criteria: children (N = 19), mild to moderate eczema, age: 7 to 17 years. Exclusion criteria: patients treated with any topical medicaiton in the previous four weeks. Wash out period: one week.
Interventions	pimecrolimus 1.0% BID (n = 9) vs. vehicle BID (n = 10) for 2 weeks
Outcomes	Efficacy: mean EASI score (95% CI); CDLQI score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Ling 2005

Methods	Parallel group, double blind, multicentre, randomised controlled trial
Participants	Inclusion criteria: children or adults (N = 49), moderate to severe eczema (diagnosis criteria: Hanifin and Raijka), age >= 11 years, >= 30% TBSA, IGA >= 2, pruritus score >= 2. Exclusion criteria: immunocompromised, concurrent skin diseased could interfere with evaluation. Wash out period: phototherapy or systemic corticosteroid therapy: one month, systemic antibiotics: two week, topical therapy: seven days.
Interventions	pimecrolimus 1.0% BID (n = 24) vs. pimecrolimus 1.0% QID (n = 25) for 3 weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA), achieving complete or well controlled eczema (PGA) and achieving mild or absent pruritus; number of participants have improved at least one IGA score; mean percentage (%) of reduction in total BSA. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, numbers of participants experiencing any ADEs and application site skin burning.
Notes	Data from poster presented at EADV 2002 conference (http://www.prous.com/webcaster/ elidel/contents/articles/Ling_ASm55b_poster.pdf and http://www.prous.com/webcaster/elidel/contents/articles/Ling_ASm55a_poster.pdf accessed 24/03/04)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Luger 2001

Methods	Parallel group, double blind, active control, international multicentre, randomised controlled trial

Luger 2001 *(Continued)*

Participants	Inclusion criteria: adults (N = 260), moderate to severe eczema (diagnosis criteria: Hanifin and Rajka, Rajka and Lengelend), age >= 18 years, TBSA 5 to 30%. Exclusion criteria: concomitant medical condition that would interfere with treatment evaluation, pregnancy, lactation, women not using medically approved contraception if child-bearing potential. Wash out period: not stated.
Interventions	pimecrolimus 1.0% BID (n = 45) vs. vehicle BID (n = 43) vs. betamethasone valerate 0.1% BID (n = 42) vs. pimecrolimus 0.05% (n = 42), 0.2% (n = 46), 0.6% (n = 42) BID for 3 weeks
Outcomes	1. Efficacy: numbers of participants achieving moderately clear or better controlled eczema (PGA >= 50% improvement) and achieving mild or absent pruritus; median percentage (%) of reduction in EASI. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, number of participants experiencing any ADEs and application site skin burning.
Notes	We did not include data from 130 participants treated on non-licensed doses of pimecrolimus.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Luger 2004

Methods	Parallel group, double blind, active control, international multicentre, randomised controlled trial
Participants	Inclusion criteria: adults (N = 658), moderate to severe eczema (diagnosis criteria: Rajka and Langeland), age >= 18 years, TBSA >= 5%. Exclusion criteria: Malignancy, acute or chronic bacterial viral or fungal diseases, child-bearing women not using approved contraception, pregnant or breast feeding, hypersensitivity, drug or alcohol abuse. Wash out period: phototherapy or systematic therapy: 1 month, topical therapy (excluding tar shampoo for scalp treatment): 24 hours.
Interventions	pimecrolimus 1.0% BID (n = 328) vs. triamcinolone acetonide 0.1% BID (n = 330) for 52 weeks
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA) and achieving mild or absent pruritus, not using topical TS; have improved by at least one IGA score; median percentage (%) of reduction in EASI; mean EASI score (95% CI). 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs; number of participants experiencing any ADEs, skin infections, bacterial skin infections, viral skin infections, and application site skin burning.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Meurer 2002

Methods	Parallel group, double blind, placebo control, multicentre randomised controlled trial (flare-preventing study)
Participants	Inclusion criteria: adults (N = 192), moderate to severe eczema (diagnosis criteria: Rajka et al.), IGA score 3 or 4, TBSA >5%. Exclusion criteria: pregnancy, lactation, women of gestational age not using reliable contraception, patient requiring potent topical corticosteroids, severe concurrent allergic disease associated to malignancies or immunocompromised states. Wash out period: phototherapy or systematic corticosteroid: three months, topical therapies or systematic antibiotics: two weeks, systematic steroids for non-AD indications: one month.
Interventions	pimecrolimus 1.0% BID (n = 96) vs. vehicle BID (n = 96) for 24 weeks
Outcomes	1. Efficacy: numbers of participants achieving complete or well controlled eczema (PGA), achieving no flare, not using TS; mean number of flares; mean duration (days) of participants not using TS; mean number of flares; median percentage (%) reduction in EASI; EASI score (95% CI); mean percentage of (%) reduction in total BSA; number of participants improved by at least one IGA score; mean decrease in QoLIAD score; mean decrease in DLQI score 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, numbers of participants experiencing any ADEs, skin infections, bacterial skin infections, viral skin infections, and application site skin burning.
Notes	This study allowed the concomitant use of cetirizine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Paller (a) 2005

Methods	Parallel group, investigator blind, active control, multicentre randomised controlled trial
Participants	Inclusion criteria: children (N = 426), mild eczema (diagnosis criteria: Hanifin and Rajka), age: 2 to 15 years, IGA = 2, TBSA >= 5%. Exclusion criteria: use of nonsteroidal immunosuppressants, light therapy, systemic and topical corticosteroids, topical H1 & H2 antihistamines, topical antimicrobials. Wash out period: four weeks.
Interventions	pimecrolimus 1.0% BID (n = 217) vs. tacrolimus 0.03% BID (n = 209) for 6 weeks
Outcomes	1. Efficacy: number of participants achieving clear or almost clear eczema (IGA); median percentage (%) of reduction in EASI from baseline; mean percentage (%) of reduction in BSA. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs; numbers of participants experiencing any ADEs, skin infections, bacterial skin infections, viral skin infections, and application site skin burning.
Notes	This paper reports separate data for three trials.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Paller (b) 2005

Methods	Parallel group, investigator blind, active control, multicentre randomised controlled trial
Participants	Inclusion criteria: children (N = 226), moderate to severe eczema (diagnosis criteria: Hanifin and Rajka), age: 2 to 15 years, IGA 3 to 4, TBSA >= 5%. Exclusion criteria: use nonsteroidal immunosuppressants, light therapy, systemic and topical corticosteroids, topical H1 & H2 antihistamines, topical antimicrobials. Wash out period: four weeks.
Interventions	pimecrolimus 1.0% BID (n = 114) vs. tacrolimus 0.1% BID (n = 112) for 6 weeks
Outcomes	1. Efficacy: number of participants achieving clear or almost clear eczema (IGA); median percentage (%) of reduction in EASI from baseline; mean percentage (%) of reduction in BSA. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs; numbers of participants experiencing any ADEs, skin infections, viral skin infections, and application site skin burning.
Notes	This paper reports separate data for three trials.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Paller (c) 2005

Methods	Parallel group, investigator blind, active control, multicentre randomised controlled trial
Participants	Inclusion criteria: adults (N = 413), mild to very severe eczema (diagnosis criteria: Hanifin and Rajka), age >= 16 years, IGA 2 to 5, TBSA >= 5%. Exclusion criteria: use nonsteroidal immunosuppressants, light therapy, systemic and topical corticosteroids, topical H1 & H2 antihistamines, topical antimicrobials. Wash out period: four weeks.
Interventions	pimecrolimus 1.0% BID (n = 203) vs. tacrolimus 0.1% BID (n = 210) for 6 weeks
Outcomes	1. Efficacy: number of participants achieving clear or almost clear eczema (IGA); median percentage (%) of reduction in EASI from baseline; mean percentage (%) of reduction in BSA 2. Safety and tolerability: total WDs; WDs due to lack of efficacy; WDs due to ADEs; numbers of participants have: any adverse event, skin infection, bacterial skin infection, viral skin infection, and skin burning
Notes	This paper reports separate data for three trials.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Siegfried 2006

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial (flare-preventing study)
Participants	Inclusion criteria: infants and children (N = 275), mild to severe eczema (diagnosis criteria: Sampson, Williams et al.), age: 3 months to 11 years. Exclusion criteria: female patients of childbearing potential if pregnant, breastfeeding or not using approval contraception up to four weeks after treatment, immunocompromised, active infection or concurrent skin condition. Wash out period: systemic therapy: one month; topical therapy: seven days.
Interventions	pimecrolimus 1.0% BID (n = 189) vs. vehicle BID (n = 92) for 24 weeks. Short-term acute flares were treated with topical corticosteroids (fluticasone propionate 0.05% cream for all participants, mometasone furate 0.1% cream for participants older than two years of age).
Outcomes	1. Efficacy: numbers of participants achieving clear or almost clear eczema (IGA), achieving complete or well controlled eczema (PGA), and achieving no flare; mean number of flares; mean duration (days) of using TS 2. Safety and tolerability: total WDs, WDs due to lack of efficacy, WDs due to ADEs, numbers of participants experiencing any ADEs, skin infections, bacterial skin infections, and viral skin infections.
Notes	Report from Novartis clinical trial results website

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Staab 2005

Methods	Parallel group, double blind, placebo control, multicentre, randomised controlled trial
Participants	Inclusion criteria: infants (N = 190), mild to very severe eczema (diagnosis criteria: Seymour et al.), age: 3 to 23 months. Exclusion criteria: immunocompromised, concomitant diseases, hypersensitivity. Wash out period: systemic corticosteroids and phototherapy: one month, antibiotics: two weeks; topical steroids or therapies: one week.
Interventions	pimecrolimus 1.0% BID (n = 130) vs. vehicle BID (n = 60) for 4 weeks.
Outcomes	1. Efficacy: number of participants achieving clear or almost clear eczema (IGA) 2. Safety and tolerability: total WDs; WDs due to lack of efficacy; number of participants have any adverse event; mean percentage (%) of reduction in EASI from baseline; mean score PIQoL-AD
Notes	Only quality of life results were presented in the publication. We did not include data for the 12-week open label noncomparative trial period.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Thaci 2003

Methods	Parallel group, double blind, placebo control, multicentre randomised controlled trial
Participants	Inclusion criteria: infants (N = 195), mild to very severe eczema, IGA >= 2, TBSA >= 5% Exclusion criteria: not stated. Wash out period: not stated.
Interventions	pimecrolimus 1.0% BID (n = 129) vs. vehicle BID (n = 66) for 4 weeks
Outcomes	Safety and tolerability: total WDs, WDs due to lack of efficacy
Notes	Abstract only

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Wahn 2002

Methods	Parallel group, double blind, placebo control, international multi-centre, randomised controlled trial (flare-preventing study)
Participants	Inclusion criteria: children (N = 711), mild eczema (diagnosis criteria: Williams et al.), age: 2 to 17 years, TBSA >= 5%, IGA >= 2. Exclusion criteria: infections that required prohibited medication or that could affect evaluation of skin. Wash out period: phototherapy or systematic therapy: one month, topical therapy: seven days, systematic antibiotics: two weeks.
Interventions	pimecrolimus 1.0% BID (n = 474) vs. emollients BID (n = 237) for 52 weeks and followed up to 53 weeks. Short-term flares were treated with moderately potent topical steroids (0.02% difluprednate, 0.25% prednicarbate, 0.1% hydrocortisone butyrate, 0.05% clobetasone butyrate, 0.02% triamcinolone acetonide, 0.1% hydrocortisone valerate).
Outcomes	1. Efficacy: numbers of participants achieving no flare and not using TS; percentage (%) of mean duration for TS use; number of participants using antihistamine; mean decrease in DLQI score; mean PIQoL-AD score. 2. Safety and tolerability: total WDs, WDs due to lack of efficacy.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Whalley 2002

Methods	Parallel group, double blind, placebo control, multi-centre, randomised controlled trial

Whalley 2002 *(Continued)*

Participants	Inclusion criteria: children (N = 241), mild to moderate eczema (diagnosis criteria: Williams et al.), IGA score 2 or 3, TBSA > 5%, age 2 to 17 years, total 430 patients, only patients over than 8 years were included, QoL score available for 241 of 278 participants. Exclusion criteria: not stated. Wash out period: not stated.
Interventions	pimecrolimus 1.0% BID (n=158) vs. vehicle BID (n=83) for six weeks
Outcomes	1. Efficacy: mean PIQoL-AD score 2. Safety and tolerability: total WDs
Notes	We did not include data for the six-month, open-label trial period. This study assessed parents of those aged two to eight years to obtain the QoL data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

AD: atopic dermatitis; IGA: investigators' global assessment; PGA: participants' global assessment; WDs: withdrawals; BID: twice daily; QID: four times daily; QD: once a day; EASI: eczema area and severity index. Eczema Area and Severity Index (EASI) scores is a method to characterize the extent of eczema. It is generally an indicator for the severity of eczema, such as IGA score, and may also be used to follow up the treatment effect. An EASI score of 15 to 20 indicates approximately a 10% to 15% body involvement of eczema (atopic dermatitis). Mild AD is defined by areas of scaling, papulation, erythema, and lichenification of 5 to 10 cm involving less than 15% total body surface area. Typical areas of involvement would include the wrists, antecubital fossa, knees, popliteal fossa, and ankles.; TS: topical corticosteroids; TBSA: total body surface area; ADSI: Atopic Dermatitis Severity Index, uses a 4-point (0-3) scale for erythema, pruritus, exudation, excoriation, and lichenification, and calculates the sum of these 5 ratings (range, 0 to 15); RCT: randomised controlled trial; ADEs: adverse drug events; flare-free days: the numbers of days on study without topical corticosteroid use; achieving clear or almost clear AD: IGA score 0-1; 95% CI: 95% confidence interval; DLQI: Dermatology Life Quality Index; QoLI-AD: Quality of Life Index- Atopic Dermatitis; CDLQI: Children's Dermatology Life Quality Index; PIQoL-AD: Parent's Index of Quality of Life- Atopic Dermatitis; PQoL-AD: Parents' Quality of Life Index- Atopic Dermatitis

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

Study	Reason for exclusion
Ball 2002	Interventions: Compared pimecrolimus 1% QD vs. vehicle QD
Belsito 2004	Participants: patients with chronic hand dermatitis
CASM9819315E1 2005	Methods: non-randomised trial
CASM981C1302 2006	Methods: non-randomised trial
CASM981C1304 2006	Methods: non-randomised trial
CASM981C2405 2005	Methods: non-randomised trial
CASM981C2405-ext.200	Methods: non-randomised trial
CASM981C2420 2005	Methods: non-randomised trial
CASM981C2421 2005	Participants: patients with vitiligo

Study	Reason for exclusion
CASM981C2434 2005	Outcomes: non-relevant outcomes
CASM981C2434E1 2005	Methods: non-randomised trial
CASM981CEG01 2005	Methods: non-randomised trial
CASM981CES01 2005	Methods: non-randomised trial
CASM981CJP01 2005	Methods: non-randomised trial
CASM981CPI01 2005	Methods: non-randomised trial
CASM981CUS05 2005	Participants: patients with intertriginous psoriasis
CASM981CUS08 2005	Outcomes: non-relevant outcomes
CASM981CZA01 2006	Methods: non-randomised trial
CASM981DE06 2005	Outcomes: non-relevant outcome measures (atopy patch test)
CASM981M2301 2006	Participants: patients with chronic hand dermatitis
McKenna 2006	Methods: combined analysis of QoL data based on Kapp A 2002 and Wahn U 2002
Meads 2005	Methods: combined analysis of QoL data based on 4 trial (trials remain unspecified)
Meurer 2004	Methods and participants: a re-analysis on patients with moderate AD (IGA=3) from Meurer 2002
Papp 2004	Methods: combined analysis based on data from Kapp A 2002 (infant) and Wahn U 2002 (children)
Papp 2005	Methods: non-randomised trial (extended from Kapp A 2002)
Queille-Roussel 2001	Outcomes: non-relevant outcome measures
Rappersberger 2002	Outcomes: non-relevant outcome measures
Van Leent 1998	Outcomes: non-relevant outcomes
Weissenbacher 2006	Participants: to investigate the effect of pre-treatment with 1% pimecrolimus cream on the atopy patch test and skin prick test
Wolff 2005	Interventions: oral pimecrolimus used

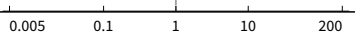
DATA AND ANALYSES

Comparison 1. Pimecrolimus 1.0% BID vs. vehicle BID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 1 week	1	336	Risk Ratio (M-H, Random, 95% CI)	2.0 [1.06, 3.76]
1.2 2 weeks	1	336	Risk Ratio (M-H, Random, 95% CI)	1.58 [1.00, 2.52]
1.3 3 weeks	5	783	Risk Ratio (M-H, Random, 95% CI)	2.72 [1.84, 4.03]
1.4 4 weeks	1	336	Risk Ratio (M-H, Random, 95% CI)	1.42 [1.00, 2.03]
1.5 6 weeks	3	589	Risk Ratio (M-H, Random, 95% CI)	2.03 [1.50, 2.74]
2 Complete or well controlled eczema (PGA)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 3 weeks	1	106	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.33, 2.67]
2.2 6 weeks	1	186	Risk Ratio (M-H, Random, 95% CI)	2.65 [1.74, 4.04]
3 Mild or absent pruritus (pruritus score 0 or 1)	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 1 week	3	472	Risk Ratio (M-H, Random, 95% CI)	1.89 [1.51, 2.35]
3.2 3 weeks	5	783	Risk Ratio (M-H, Random, 95% CI)	2.02 [1.69, 2.42]
3.3 6 weeks	3	589	Risk Ratio (M-H, Random, 95% CI)	1.82 [1.48, 2.25]
4 Withdrawals	10		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 For any reason	9	1753	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.27, 0.58]
4.2 For lack of efficacy	8	1657	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.11, 0.41]
4.3 For adverse events	5	1025	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.19, 0.97]
5 Adverse events	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Any adverse events	4	827	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.02]
5.2 Bacterial skin infections	1	186	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 1.12]
5.3 Application site skin burning	5	914	Risk Ratio (M-H, Random, 95% CI)	1.40 [0.90, 2.18]

Analysis 1.1. Comparison 1 Pimecrolimus 1.0% BID vs. vehicle BID, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

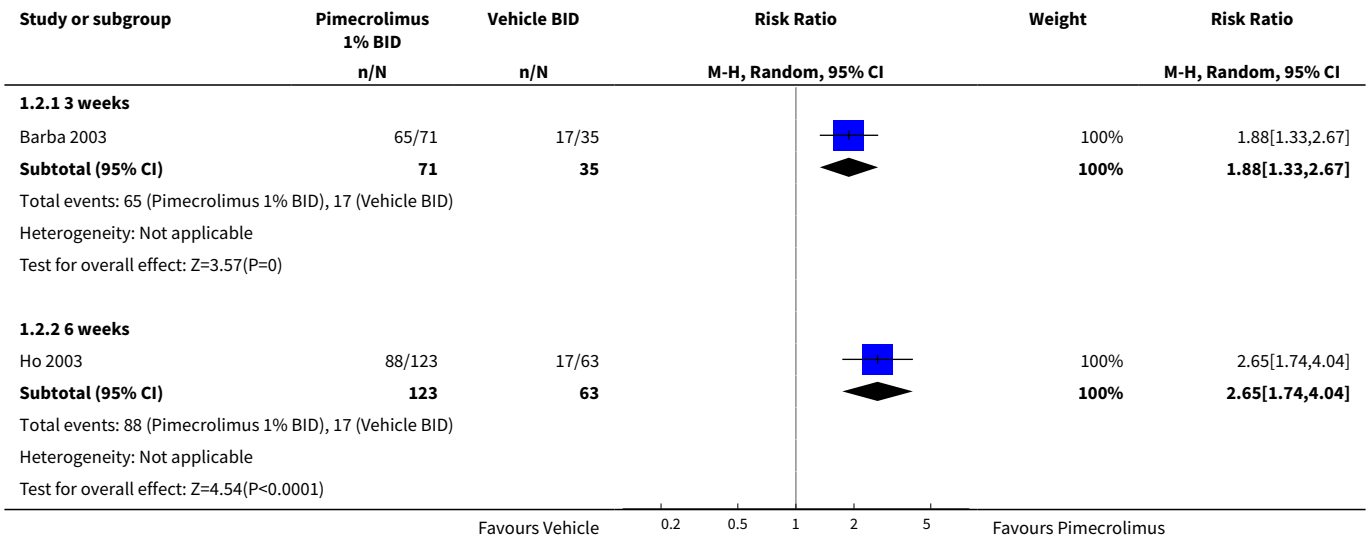
Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 1 week					
CASM981C2322 2005	26/168	13/168		100%	2[1.06,3.76]
Subtotal (95% CI)	**168**	**168**		**100%**	**2[1.06,3.76]**
Total events: 26 (Pimecrolimus 1% BID), 13 (Vehicle BID)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.15(P=0.03)					
1.1.2 2 weeks					
CASM981C2322 2005	38/168	24/168		100%	1.58[1,2.52]
Subtotal (95% CI)	**168**	**168**		**100%**	**1.58[1,2.52]**
Total events: 38 (Pimecrolimus 1% BID), 24 (Vehicle BID)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.94(P=0.05)					
1.1.3 3 weeks					
Barba 2003	38/71	8/35		29.52%	2.34[1.23,4.47]
Eichenfield (a) 2002	35/130	2/68		7.51%	9.15[2.27,36.91]
Eichenfield (b) 2002	37/137	8/68		25.5%	2.3[1.13,4.65]
Ho 2003	54/123	11/63		35.61%	2.51[1.42,4.46]
Luger 2001	5/45	0/43		1.85%	10.52[0.6,184.72]
Subtotal (95% CI)	**506**	**277**		**100%**	**2.72[1.84,4.03]**
Total events: 169 (Pimecrolimus 1% BID), 29 (Vehicle BID)					
Heterogeneity: Tau^2=0.03; Chi^2=4.58, df=4(P=0.33); I^2=12.67%					
Test for overall effect: Z=5.01(P<0.0001)					
1.1.4 4 weeks					
CASM981C2322 2005	54/168	38/168		100%	1.42[1,2.03]
Subtotal (95% CI)	**168**	**168**		**100%**	**1.42[1,2.03]**
Total events: 54 (Pimecrolimus 1% BID), 38 (Vehicle BID)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.94(P=0.05)					
1.1.5 6 weeks					
Eichenfield (a) 2002	49/130	11/68		28.26%	2.33[1.3,4.18]
Eichenfield (b) 2002	44/137	14/68		33.03%	1.56[0.92,2.64]
Ho 2003	67/123	15/63		38.71%	2.29[1.43,3.66]
Subtotal (95% CI)	**390**	**199**		**100%**	**2.03[1.5,2.74]**
Total events: 160 (Pimecrolimus 1% BID), 40 (Vehicle BID)					
Heterogeneity: Tau^2=0; Chi^2=1.43, df=2(P=0.49); I^2=0%					
Test for overall effect: Z=4.61(P<0.0001)					



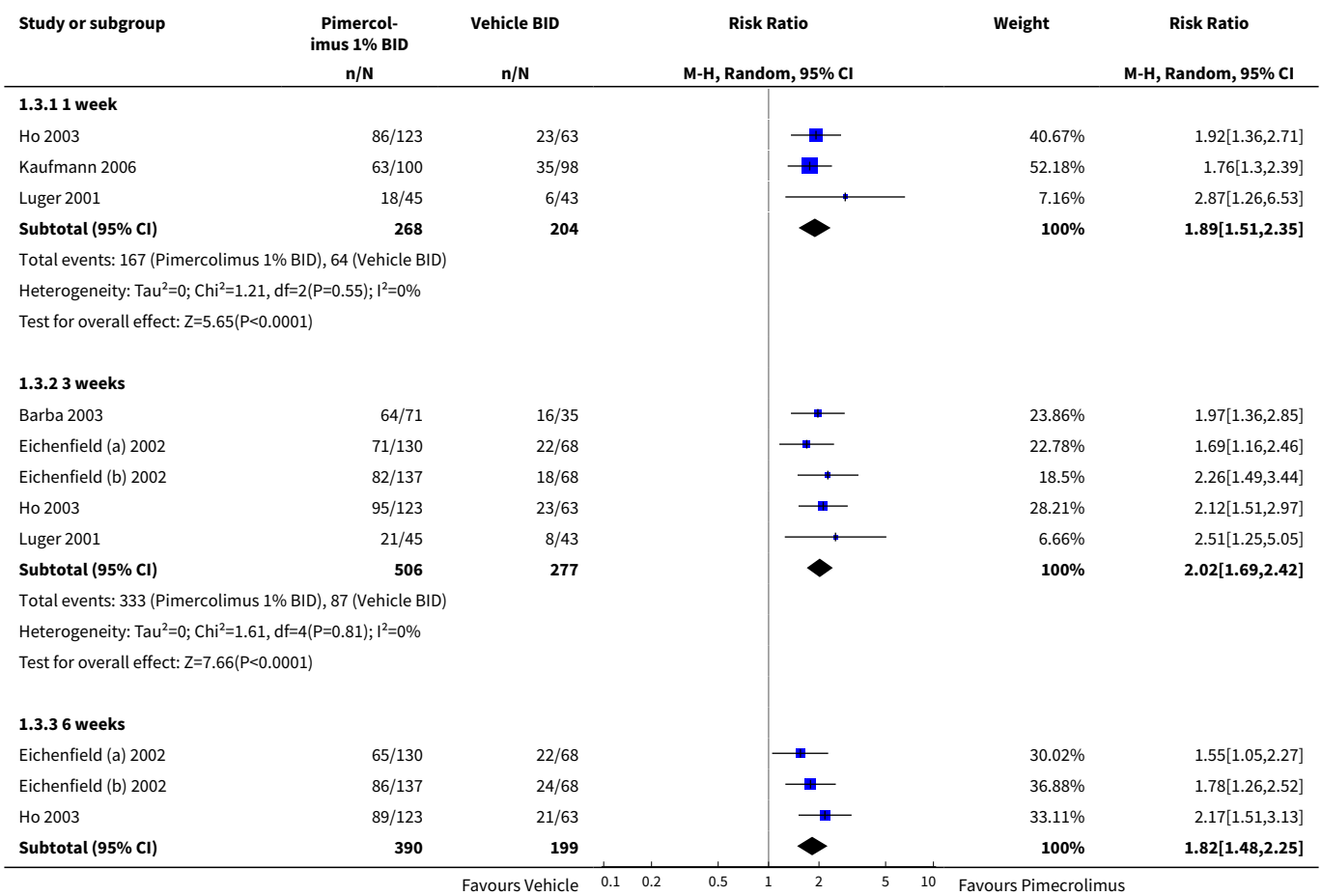
Favours Vehicle

Favours Pimecrolimus

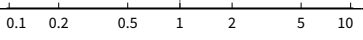
Analysis 1.2. Comparison 1 Pimecrolimus 1.0% BID vs. vehicle BID, Outcome 2 Complete or well controlled eczema (PGA).



Analysis 1.3. Comparison 1 Pimecrolimus 1.0% BID vs. vehicle BID, Outcome 3 Mild or absent pruritus (pruritus score 0 or 1).



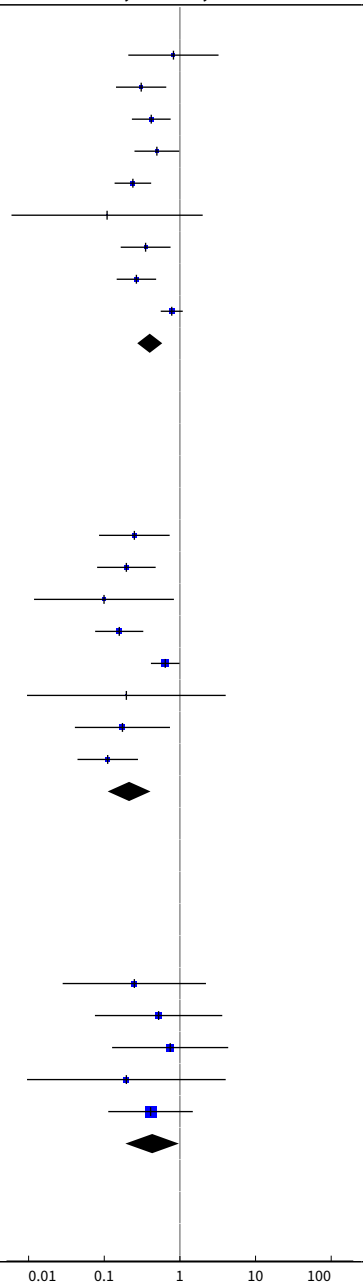
Study or subgroup	Pimercolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total events: 240 (Pimercolimus 1% BID), 67 (Vehicle BID)					
Heterogeneity: Tau²=0; Chi²=1.6, df=2(P=0.45); I²=0%					
Test for overall effect: Z=5.58(P<0.0001)					



Favours Vehicle — Favours Pimecrolimus

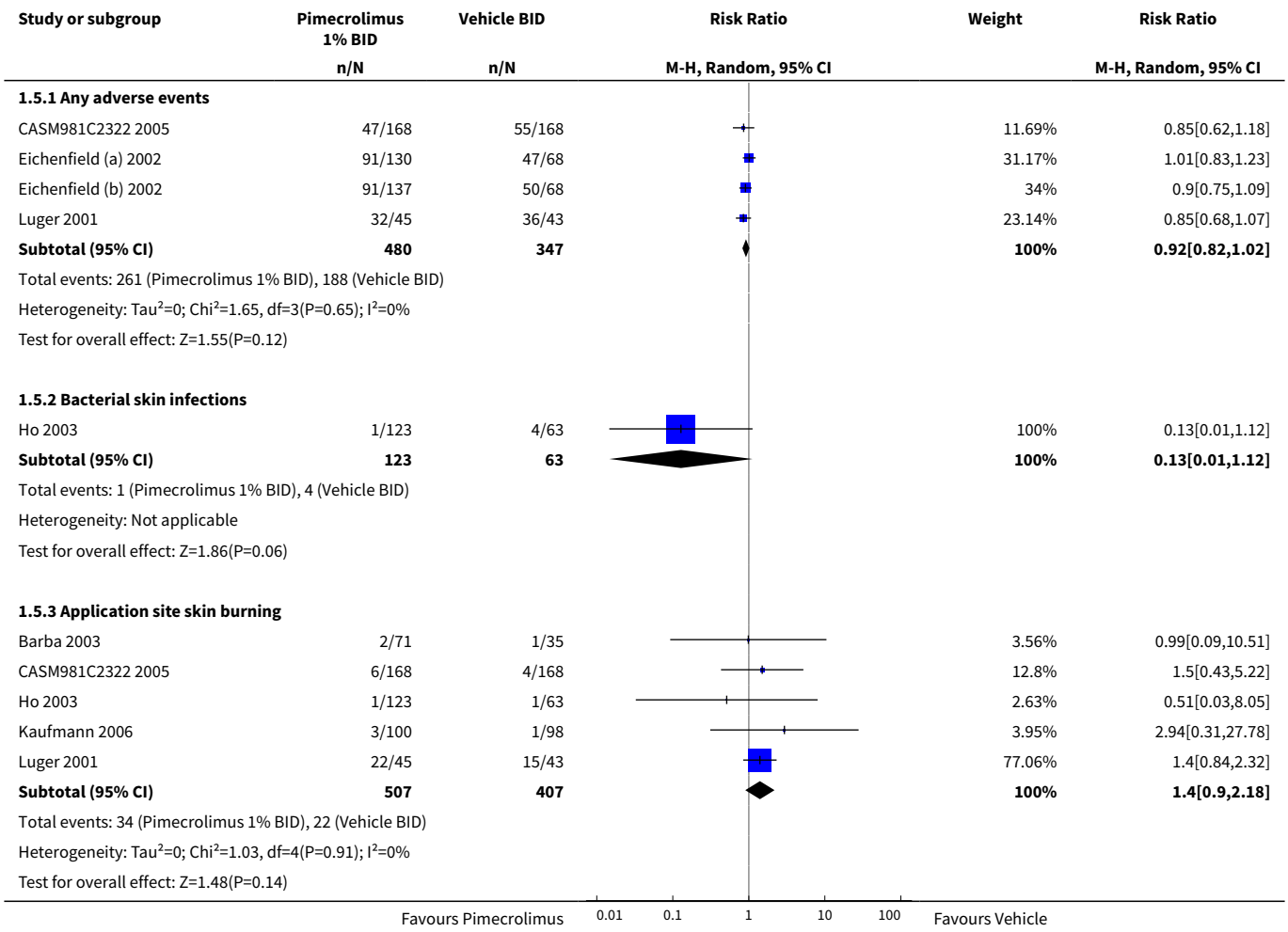
Analysis 1.4. Comparison 1 Pimecrolimus 1.0% BID vs. vehicle BID, Outcome 4 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 For any reason					
Barba 2003	5/71	3/35		6.03%	0.82[0.21,3.24]
CASM981C2322 2005	8/168	26/168		11.32%	0.31[0.14,0.66]
Eichenfield (a) 2002	16/130	20/68		13.46%	0.42[0.23,0.75]
Eichenfield (b) 2002	14/137	14/68		12.3%	0.5[0.25,0.98]
Ho 2003	14/123	30/63		13.86%	0.24[0.14,0.42]
Kaufmann 2006	0/100	4/98		1.8%	0.11[0.01,2]
Luger 2001	7/45	19/43		11.37%	0.35[0.16,0.75]
Thaci 2003	13/129	25/66		13.3%	0.27[0.15,0.49]
Whalley 2002	52/158	35/83		16.55%	0.78[0.56,1.09]
Subtotal (95% CI)	**1061**	**692**		**100%**	**0.4[0.27,0.58]**
Total events: 129 (Pimecrolimus 1% BID), 176 (Vehicle BID)					
Heterogeneity: Tau²=0.19; Chi²=21.77, df=8(P=0.01); I²=63.25%					
Test for overall effect: Z=4.74(P<0.0001)					
1.4.2 For lack of efficacy					
CASM981C2322 2005	4/168	16/168		12.54%	0.25[0.09,0.73]
Eichenfield (a) 2002	6/130	16/68		15.21%	0.2[0.08,0.48]
Eichenfield (b) 2002	1/137	5/68		4.75%	0.1[0.01,0.83]
Ho 2003	8/123	26/63		17.94%	0.16[0.08,0.33]
Kapp 2002	50/204	18/47		23.63%	0.64[0.41,0.99]
Kaufmann 2006	0/100	2/98		2.57%	0.2[0.01,4.03]
Luger 2001	2/45	11/43		8.61%	0.17[0.04,0.74]
Thaci 2003	5/129	23/66		14.75%	0.11[0.04,0.28]
Subtotal (95% CI)	**1036**	**621**		**100%**	**0.21[0.11,0.41]**
Total events: 76 (Pimecrolimus 1% BID), 117 (Vehicle BID)					
Heterogeneity: Tau²=0.52; Chi²=23.27, df=7(P=0); I²=69.91%					
Test for overall effect: Z=4.65(P<0.0001)					
1.4.3 For adverse events					
CASM981C2322 2005	1/168	4/168		15.63%	0.25[0.03,2.21]
Eichenfield (a) 2002	2/130	2/68		18.99%	0.52[0.08,3.63]
Eichenfield (b) 2002	3/137	2/68		22%	0.74[0.13,4.35]
Kaufmann 2006	0/100	2/98		8.8%	0.2[0.01,4.03]
Luger 2001	3/45	7/43		34.58%	0.41[0.11,1.48]
Subtotal (95% CI)	**580**	**445**		**100%**	**0.43[0.19,0.97]**
Total events: 9 (Pimecrolimus 1% BID), 17 (Vehicle BID)					
Heterogeneity: Tau²=0; Chi²=0.93, df=4(P=0.92); I²=0%					
Test for overall effect: Z=2.04(P=0.04)					



Favours Pimecrolimus — Favours Vehicle

Analysis 1.5. Comparison 1 Pimecrolimus 1.0% BID vs. vehicle BID, Outcome 5 Adverse events.



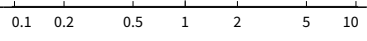
Comparison 2. Pimecrolimus 1.0% BID vs. vehicle BID, participants with facial AD

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear of facial eczema (facial IGA 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 1 week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Mild or absent pruritus (pruritus score 0 or 1)	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
2.1 1 week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawals	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 For any reason	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 For lack of efficacy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Pimecrolimus 1.0% BID vs. vehicle BID, participants with facial AD, Outcome 1 Clear or almost clear of facial eczema (facial IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.1.1 1 week				
CASM981C2442 2006	21/101	7/99		2.94[1.31,6.61]
2.1.2 3 weeks				
CASM981C2442 2006	40/101	13/99		3.02[1.72,5.29]
2.1.3 6 weeks				
CASM981C2442 2006	47/101	16/99		2.88[1.76,4.72]

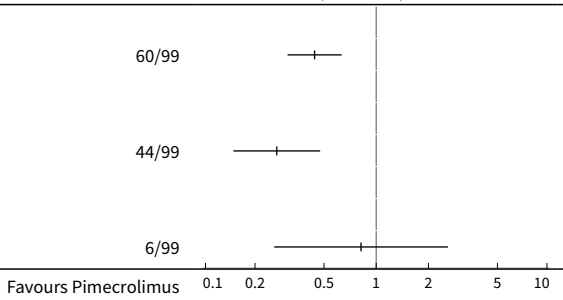


Analysis 2.2. Comparison 2 Pimecrolimus 1.0% BID vs. vehicle BID, participants with facial AD, Outcome 2 Mild or absent pruritus (pruritus score 0 or 1).

Study or subgroup	Pimercolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.2.1 1 week				
CASM981C2442 2006	61/101	33/99		1.81[1.32,2.5]
2.2.2 3 weeks				
CASM981C2442 2006	70/101	37/99		1.85[1.39,2.47]
2.2.3 6 weeks				
CASM981C2442 2006	70/101	34/99		2.02[1.49,2.73]

Analysis 2.3. Comparison 2 Pimecrolimus 1.0% BID vs. vehicle BID, participants with facial AD, Outcome 3 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
2.3.1 For any reason				
CASM981C2442 2006	27/101	60/99		0.44[0.31,0.63]
2.3.2 For lack of efficacy				
CASM981C2442 2006	12/101	44/99		0.27[0.15,0.48]
2.3.3 For adverse events				
CASM981C2442 2006	5/101	6/99		0.82[0.26,2.59]

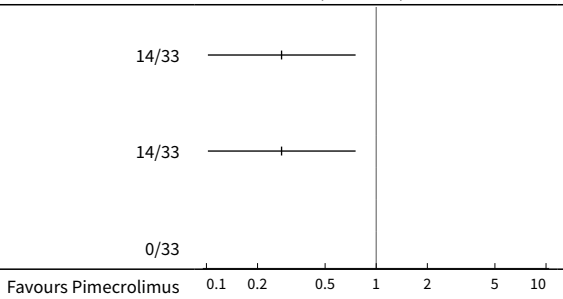


Comparison 3. Pimecrolimus 1.0% BID vs. vehicle BID, participants responded to topical steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 For any reason	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 For lack of efficacy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

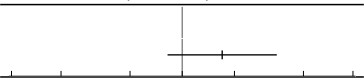
Analysis 3.1. Comparison 3 Pimecrolimus 1.0% BID vs. vehicle BID, participants responded to topical steroids, Outcome 1 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.1.1 For any reason				
CASM981C2436 2006	4/34	14/33		0.28[0.1,0.76]
3.1.2 For lack of efficacy				
CASM981C2436 2006	4/34	14/33		0.28[0.1,0.76]
3.1.3 For adverse events				
CASM981C2436 2006	0/34	0/33		Not estimable



Analysis 3.2. Comparison 3 Pimecrolimus 1.0% BID vs. vehicle BID, participants responded to topical steroids, Outcome 2 Adverse events.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.2.1 Any adverse events				
CASM981C2436 2006	14/34	8/33		1.7[0.82,3.51]



Comparison 4. Pimecrolimus 1.0% BID vs. vehicle BID, participants did not respond to topical steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete or well controlled eczema (PGA)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Mild or absent pruritus (pruritus score 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Withdrawals	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 For any reason	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 For lack of efficacy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Skin infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Viral skin infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 Application site skin burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 4.1. Comparison 4 Pimecrolimus 1.0% BID vs. vehicle BID, participants did not respond to topical steroids, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.1.1 6 weeks				
ASM981C2402 2005	5/47	0/26		6.19[0.36,107.66]

Favours Vehicle 0.001 0.1 1 10 1000 Favours Pimecrolimus

Analysis 4.2. Comparison 4 Pimecrolimus 1.0% BID vs. vehicle BID, participants did not respond to topical steroids, Outcome 2 Complete or well controlled eczema (PGA).

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.2.1 6 weeks				
ASM981C2402 2005	14/47	6/26		1.29[0.56,2.95]

Favours Vehicle 0.01 0.1 1 10 100 Favours Pimecrolimus

Analysis 4.3. Comparison 4 Pimecrolimus 1.0% BID vs. vehicle BID, participants did not respond to topical steroids, Outcome 3 Mild or absent pruritus (pruritus score 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.3.1 6 weeks				
ASM981C2402 2005	12/47	6/26		1.11[0.47,2.6]

Favours Vehicle 0.01 0.1 1 10 100 Favours Pimecrolimus

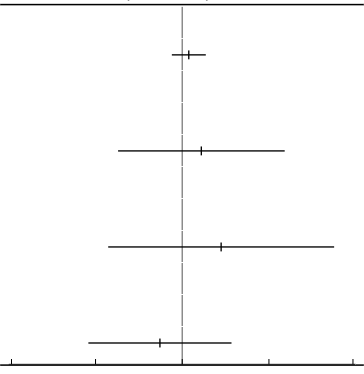
Analysis 4.4. Comparison 4 Pimecrolimus 1.0% BID vs. vehicle BID, participants did not respond to topical steroids, Outcome 4 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.4.1 For any reason				
ASM981C2402 2005	9/47	8/26		0.62[0.27,1.42]
4.4.2 For lack of efficacy				
ASM981C2402 2005	3/47	4/26		0.41[0.1,1.71]
4.4.3 For adverse events				
ASM981C2402 2005	3/47	2/26		0.83[0.15,4.65]

Favours Pimecrolimus 0.01 0.1 1 10 100 Favours Vehicle

Analysis 4.5. Comparison 4 Pimecrolimus 1.0% BID vs. vehicle BID, participants did not respond to topical steroids, Outcome 5 Adverse events.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
4.5.1 Any adverse events				
ASM981C2402 2005	28/47	13/26		1.19[0.76,1.87]
4.5.2 Skin infections				
ASM981C2402 2005	3/47	1/26		1.66[0.18,15.16]
4.5.3 Viral skin infections				
ASM981C2402 2005	2/47	0/26		2.81[0.14,56.46]
4.5.4 Application site skin burning				
ASM981C2402 2005	2/47	2/26		0.55[0.08,3.7]



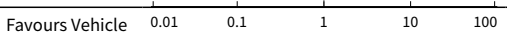
Comparison 5. Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares

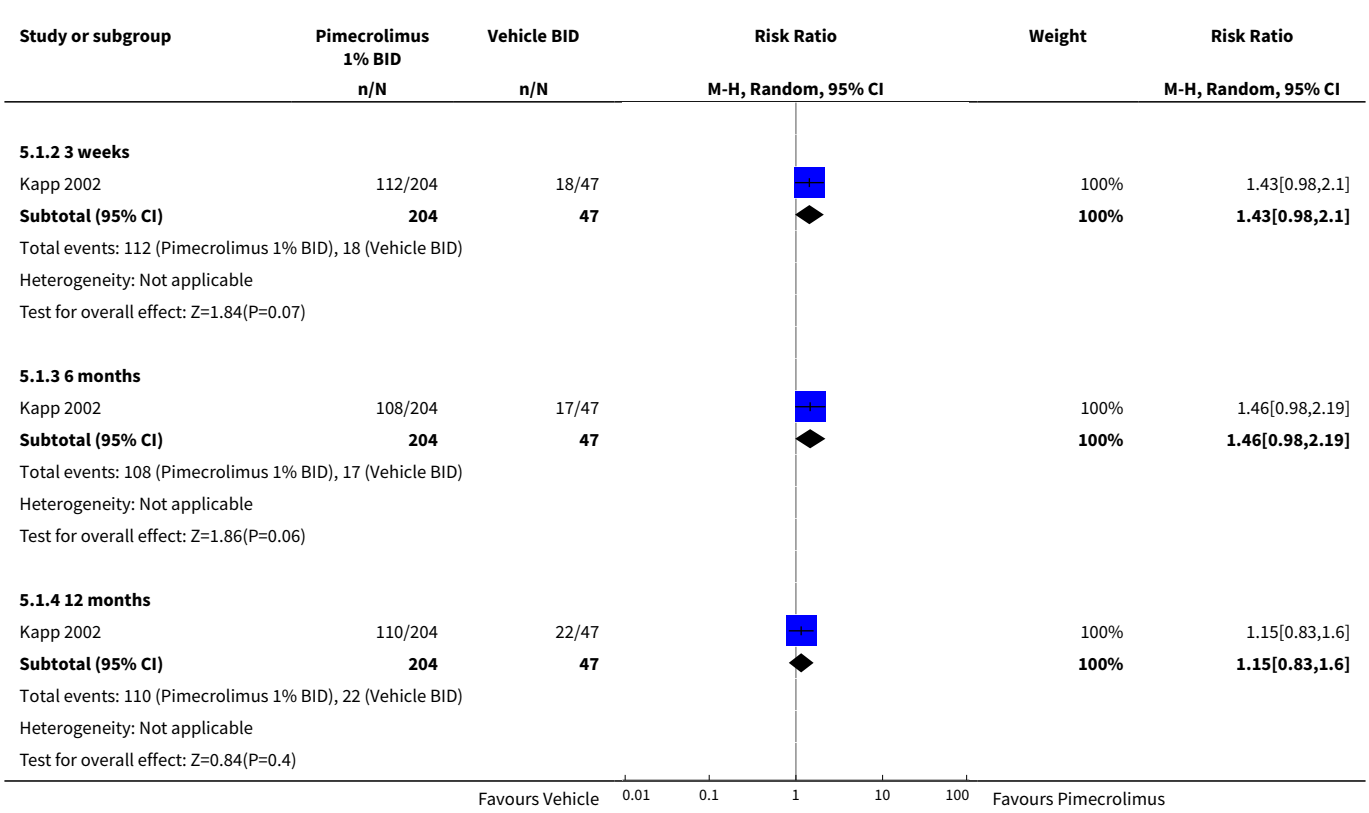
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 1 week	2	526	Risk Ratio (M-H, Random, 95% CI)	3.45 [1.66, 7.14]
1.2 3 weeks	1	251	Risk Ratio (M-H, Random, 95% CI)	1.43 [0.98, 2.10]
1.3 6 months	1	251	Risk Ratio (M-H, Random, 95% CI)	1.46 [0.98, 2.19]
1.4 12 months	1	251	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.83, 1.60]
2 Complete or well controlled eczema (PGA)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 6 weeks	1	251	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.06, 1.85]
2.2 6 months	2	443	Risk Ratio (M-H, Random, 95% CI)	1.62 [1.29, 2.04]
2.3 9 months	1	251	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.01, 1.74]
2.4 12 months	1	251	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.90, 1.47]
3 Mild or absent pruritus (pruritus score 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 9 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
3.4 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 No flare of eczema	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 6 months	9	3091	Risk Ratio (M-H, Random, 95% CI)	1.47 [1.32, 1.64]
4.2 12 months	2	962	Risk Ratio (M-H, Random, 95% CI)	1.69 [1.45, 1.96]
5 No use of rescue medication	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 6 months	1	192	Risk Ratio (M-H, Random, 95% CI)	2.24 [1.46, 3.44]
5.2 12 months	2	962	Risk Ratio (M-H, Random, 95% CI)	1.76 [1.50, 2.08]
6 Withdrawals	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 For any reason	9	3091	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.54, 0.76]
6.2 For lack of efficacy	9	3091	Risk Ratio (M-H, Random, 95% CI)	0.42 [0.34, 0.51]
6.3 For adverse events	8	2380	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.28, 1.27]
7 Adverse events	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Any adverse events	4	1398	Risk Ratio (M-H, Random, 95% CI)	1.07 [1.00, 1.16]
7.2 Skin infections	3	718	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.75, 1.72]
7.3 Viral skin infections	3	718	Risk Ratio (M-H, Random, 95% CI)	1.79 [0.89, 3.61]
7.4 Bacterial skin infections	4	982	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.39]
7.5 Application site skin burning	3	999	Risk Ratio (M-H, Random, 95% CI)	4.36 [1.75, 10.85]

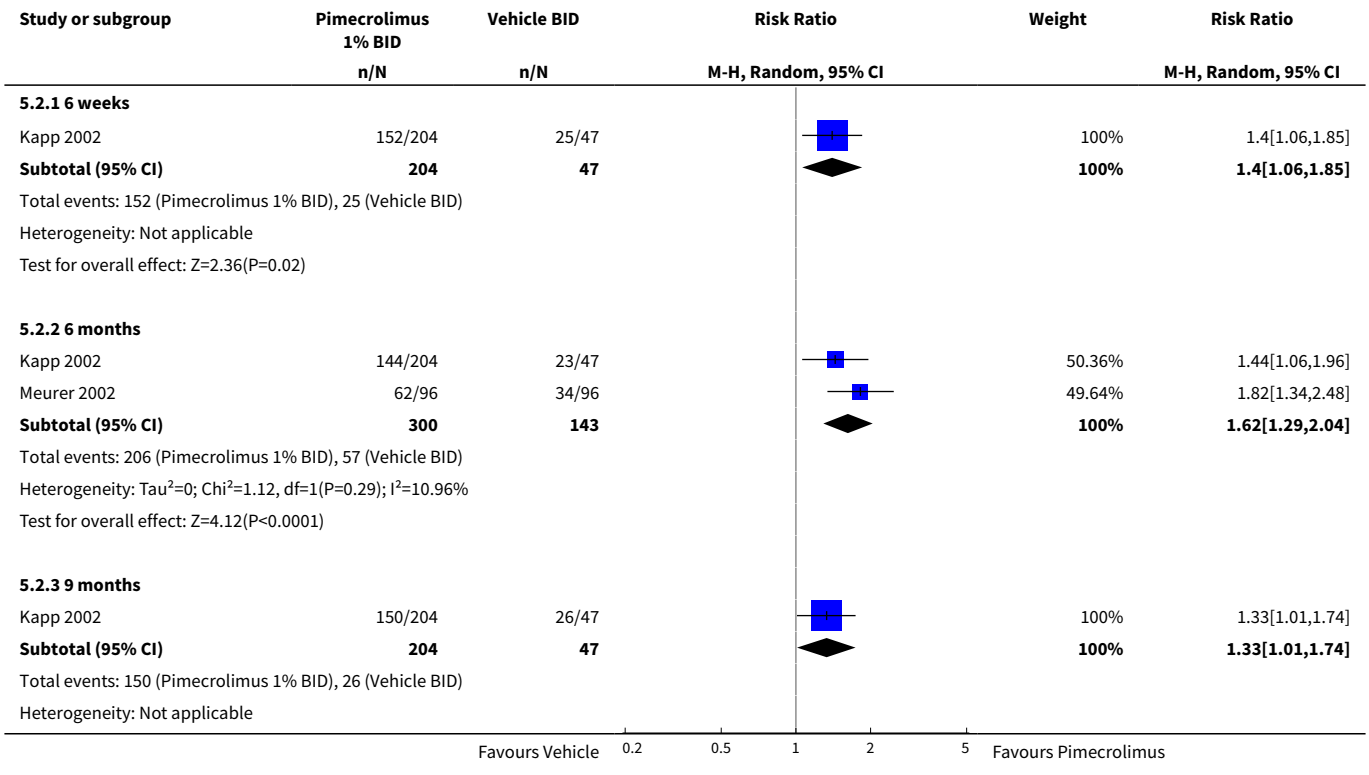
Analysis 5.1. Comparison 5 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 1 week					
Kapp 2002	91/204	4/47		43.73%	5.24[2.03,13.55]
Siegfried 2006	35/183	7/92		56.27%	2.51[1.16,5.44]
Subtotal (95% CI)	**387**	**139**		**100%**	**3.45[1.66,7.14]**
Total events: 126 (Pimecrolimus 1% BID), 11 (Vehicle BID)					
Heterogeneity: Tau^2=0.09; Chi^2=1.45, df=1(P=0.23); I^2=30.92%					
Test for overall effect: Z=3.33(P=0)					





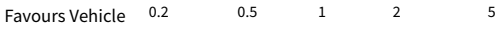
Analysis 5.2. Comparison 5 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, Outcome 2 Complete or well controlled eczema (PGA).



Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: Z=2.07(P=0.04)					
5.2.4 12 months					
Kapp 2002	145/204	29/47		100%	1.15[0.9,1.47]
Subtotal (95% CI)	**204**	**47**		**100%**	**1.15[0.9,1.47]**
Total events: 145 (Pimecrolimus 1% BID), 29 (Vehicle BID)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.15(P=0.25)					

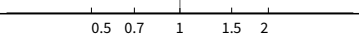
Analysis 5.3. Comparison 5 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, Outcome 3 Mild or absent pruritus (pruritus score 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.3.1 6 weeks				
Kapp 2002	156/204	27/47		1.33[1.03,1.72]
5.3.2 6 months				
Kapp 2002	149/204	25/47		1.37[1.04,1.82]
5.3.3 9 months				
Kapp 2002	154/204	26/47		1.36[1.04,1.79]
5.3.4 12 months				
Kapp 2002	157/204	29/47		1.25[0.98,1.58]



Analysis 5.4. Comparison 5 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, Outcome 4 No flare of eczema.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.4.1 6 months					
ASM981C2315 2005	159/256	107/265		17.55%	1.54[1.29,1.83]
ASM981C2316 2005	147/277	110/266		17.01%	1.28[1.07,1.54]
CASM981C1301 2005	45/83	28/78		7.31%	1.51[1.06,2.16]
CASM981C1303 2005	39/86	33/87		7.35%	1.2[0.84,1.71]
CASM981CUS03 2005	97/176	39/88		10.89%	1.24[0.95,1.63]
Kapp 2002	138/204	14/47		5.03%	2.27[1.45,3.56]
Meurer 2002	43/96	18/96		4.63%	2.39[1.49,3.83]
Siegfried 2006	94/183	31/92		8.61%	1.52[1.11,2.1]
Wahn 2002	360/474	123/237		21.63%	1.46[1.28,1.67]
Subtotal (95% CI)	**1835**	**1256**		**100%**	**1.47[1.32,1.64]**
Total events: 1122 (Pimecrolimus 1% BID), 503 (Vehicle BID)					

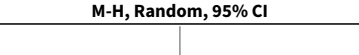


Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.01; Chi²=13, df=8(P=0.11); I²=38.47%					
Test for overall effect: Z=6.92(P<0.0001)					
5.4.2 12 months					
Kapp 2002	116/204	13/47		19.13%	2.06[1.28,3.31]
Wahn 2002	337/474	102/237		80.87%	1.65[1.41,1.93]
Subtotal (95% CI)	**678**	**284**		**100%**	**1.69[1.45,1.96]**
Total events: 453 (Pimecrolimus 1% BID), 115 (Vehicle BID)					
Heterogeneity: Tau²=0; Chi²=0.75, df=1(P=0.39); I²=0%					
Test for overall effect: Z=6.87(P<0.0001)					

Favours Vehicle — Favours Pimecrolimus

Analysis 5.5. Comparison 5 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, Outcome 5 No use of rescue medication.

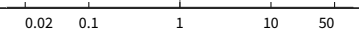
Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 6 months					
Meurer 2002	47/96	21/96		100%	2.24[1.46,3.44]
Subtotal (95% CI)	**96**	**96**		**100%**	**2.24[1.46,3.44]**
Total events: 47 (Pimecrolimus 1% BID), 21 (Vehicle BID)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.67(P=0)					
5.5.2 12 months					
Kapp 2002	130/204	16/47		15.85%	1.87[1.24,2.82]
Wahn 2002	307/474	88/237		84.15%	1.74[1.46,2.09]
Subtotal (95% CI)	**678**	**284**		**100%**	**1.76[1.5,2.08]**
Total events: 437 (Pimecrolimus 1% BID), 104 (Vehicle BID)					
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.76); I²=0%					
Test for overall effect: Z=6.79(P<0.0001)					



Favours Vehicle — Favours Pimecrolimus

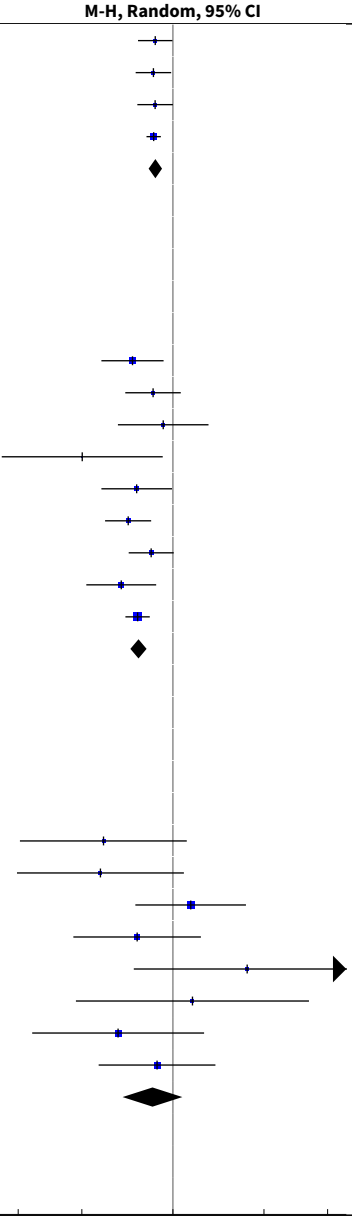
Analysis 5.6. Comparison 5 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, Outcome 6 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.6.1 For any reason					
ASM981C2315 2005	24/256	56/265		11.04%	0.44[0.28,0.69]
ASM981C2316 2005	43/277	57/266		13.5%	0.72[0.51,1.04]
CASM981C1301 2005	13/83	15/78		6.65%	0.81[0.41,1.6]
CASM981C1303 2005	6/86	21/87		4.64%	0.29[0.12,0.68]
CASM981CUS03 2005	48/176	23/88		11.57%	1.04[0.68,1.6]



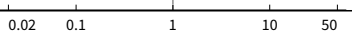
Favours Pimecrolimus — Favours Vehicle

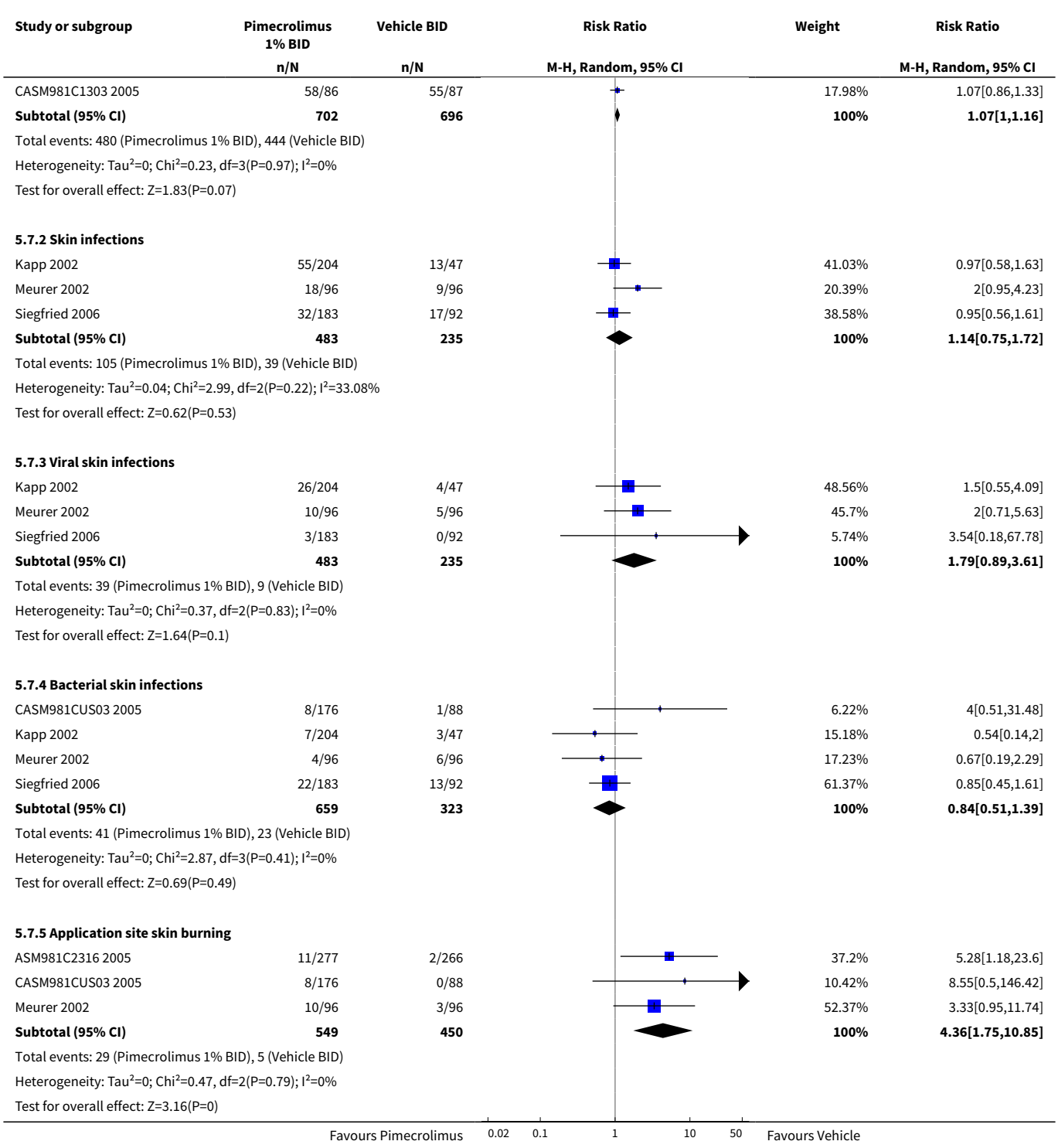
Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kapp 2002	50/204	18/47		11.32%	0.64[0.41,0.99]
Meurer 2002	22/96	36/96		10.98%	0.61[0.39,0.96]
Siegfried 2006	33/183	26/92		10.98%	0.64[0.41,1]
Wahn 2002	150/474	122/237		19.32%	0.61[0.51,0.74]
Subtotal (95% CI)	**1835**	**1256**		**100%**	**0.64[0.54,0.76]**
Total events: 389 (Pimecrolimus 1% BID), 374 (Vehicle BID)					
Heterogeneity: Tau^2=0.02; Chi^2=12.15, df=8(P=0.14); I^2=34.15%					
Test for overall effect: Z=5.12(P<0.0001)					
5.6.2 For lack of efficacy					
ASM981C2315 2005	8/256	23/265		9.52%	0.36[0.16,0.79]
ASM981C2316 2005	12/277	19/266		11.25%	0.61[0.3,1.22]
CASM981C1301 2005	5/83	6/78		5.11%	0.78[0.25,2.46]
CASM981C1303 2005	1/86	10/87		1.78%	0.1[0.01,0.77]
CASM981CUS03 2005	8/176	10/88		7.78%	0.4[0.16,0.98]
Kapp 2002	21/204	15/47		14.56%	0.32[0.18,0.58]
Meurer 2002	15/96	26/96		14.98%	0.58[0.33,1.02]
Siegfried 2006	7/183	13/92		7.91%	0.27[0.11,0.66]
Wahn 2002	59/474	72/237		27.11%	0.41[0.3,0.56]
Subtotal (95% CI)	**1835**	**1256**		**100%**	**0.42[0.34,0.51]**
Total events: 136 (Pimecrolimus 1% BID), 194 (Vehicle BID)					
Heterogeneity: Tau^2=0; Chi^2=7.19, df=8(P=0.52); I^2=0%					
Test for overall effect: Z=8.33(P<0.0001)					
5.6.3 For adverse events					
ASM981C2315 2005	1/256	6/265		10.19%	0.17[0.02,1.42]
ASM981C2316 2005	1/277	6/266		10.19%	0.16[0.02,1.32]
CASM981C1301 2005	5/83	3/78		22.08%	1.57[0.39,6.34]
CASM981C1303 2005	2/86	5/87		16.96%	0.4[0.08,2.03]
CASM981CUS03 2005	6/176	0/88		5.63%	6.54[0.37,114.73]
Kapp 2002	3/204	0/47		5.33%	1.64[0.09,31.2]
Meurer 2002	1/96	4/96		9.63%	0.25[0.03,2.2]
Siegfried 2006	4/183	3/92		19.98%	0.67[0.15,2.93]
Subtotal (95% CI)	**1361**	**1019**		**100%**	**0.6[0.28,1.27]**
Total events: 23 (Pimecrolimus 1% BID), 27 (Vehicle BID)					
Heterogeneity: Tau^2=0.23; Chi^2=8.65, df=7(P=0.28); I^2=19.04%					
Test for overall effect: Z=1.33(P=0.18)					



Analysis 5.7. Comparison 5 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, Outcome 7 Adverse events.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.7.1 Any adverse events					
ASM981C2315 2005	185/256	179/265		33.59%	1.07[0.96,1.2]
ASM981C2316 2005	180/277	158/266		30.09%	1.09[0.96,1.25]
CASM981C1301 2005	57/83	52/78		18.35%	1.03[0.83,1.28]





Comparison 6. Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, participants responded to steroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Withdrawals	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 For any reason	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 For lack of efficacy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Pimecrolimus 1.0% BID vs. vehicle BID, topical steroids for flares, participants responded to steroids, Outcome 1 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Vehicle BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
6.1.1 For any reason				
ASM981CDE10 2005	11/95	18/89		0.57[0.29,1.14]
6.1.2 For lack of efficacy				
ASM981CDE10 2005	6/95	13/89		0.43[0.17,1.09]
6.1.3 For adverse events				
ASM981CDE10 2005	0/95	0/89		Not estimable

Favours Pimecrolimus | Favours Vehicle

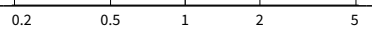
Comparison 7. Pimecrolimus 1.0% BID vs. triamcinolone acetonide 0.1% BID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 1 week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 6 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Mild or absent pruritus (pruritus score 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 12 months	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawals	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 For any reason	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 For lack of efficacy	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
3.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Skin infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 Viral skin infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.4 Bacterial skin infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.5 Application site skin burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

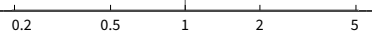
Analysis 7.1. Comparison 7 Pimecrolimus 1.0% BID vs. triamcinolone acetonide 0.1% BID, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	TAA 0.1% BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.1.1 1 week				
Luger 2004	121/328	233/330		0.52[0.45,0.61]
7.1.2 3 weeks				
Luger 2004	186/328	251/330		0.75[0.67,0.83]
7.1.3 6 months				
Luger 2004	251/328	283/330		0.89[0.83,0.96]
7.1.4 12 months				
Luger 2004	267/328	293/330		0.92[0.86,0.98]



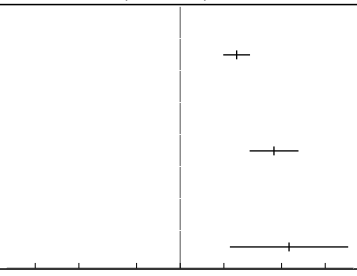
Analysis 7.2. Comparison 7 Pimecrolimus 1.0% BID vs. triamcinolone acetonide 0.1% BID, Outcome 2 Mild or absent pruritus (pruritus score 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	TAA 0.1% BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.2.1 12 months				
Luger 2004	81/328	173/330		0.47[0.38,0.58]



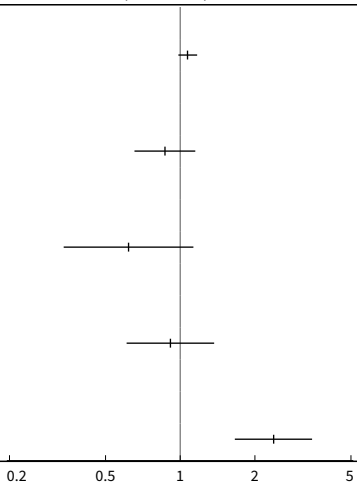
Analysis 7.3. Comparison 7 Pimecrolimus 1.0% BID vs. triamcinolone acetonide 0.1% BID, Outcome 3 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	TAA 0.1% BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.3.1 For any reason				
Luger 2004	192/328	79/330		2.45[1.98,3.03]
7.3.2 For lack of efficacy				
Luger 2004	119/328	27/330		4.43[3.01,6.54]
7.3.3 For adverse events				
Luger 2004	28/328	5/330		5.63[2.2,14.41]



Analysis 7.4. Comparison 7 Pimecrolimus 1.0% BID vs. triamcinolone acetonide 0.1% BID, Outcome 4 Adverse events.

Study or subgroup	Pimecrolimus 1% BID n/N	TAA 0.1% n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.4.1 Any adverse events				
Luger 2004	256/328	240/330		1.07[0.98,1.17]
7.4.2 Skin infections				
Luger 2004	69/328	80/330		0.87[0.65,1.15]
7.4.3 Viral skin infections				
Luger 2004	16/328	26/330		0.62[0.34,1.13]
7.4.4 Bacterial skin infections				
Luger 2004	39/328	43/330		0.91[0.61,1.37]
7.4.5 Application site skin burning				
Luger 2004	85/328	36/330		2.38[1.66,3.4]



Comparison 8. Pimecrolimus 1.0% BID vs. betamethasone valerate 0.1% BID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Moderately clear or better eczema (PGA more than 50% improvement)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Mild or absent pruritus (pruritus score 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 1 week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

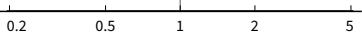
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawals	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 For any reason	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 For lack of efficacy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Application site skin burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 Pimecrolimus 1.0% BID vs. betamethasone valerate 0.1% BID, Outcome 1 Moderately clear or better eczema (PGA more than 50% improvement).

Study or subgroup	Pimecrolimus 1% BID n/N	BMV 0.1% BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.1.1 3 weeks				
Luger 2001	24/45	37/42		0.61[0.45,0.81]

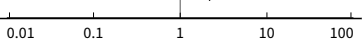
Analysis 8.2. Comparison 8 Pimecrolimus 1.0% BID vs. betamethasone valerate 0.1% BID, Outcome 2 Mild or absent pruritus (pruritus score 0 or 1).

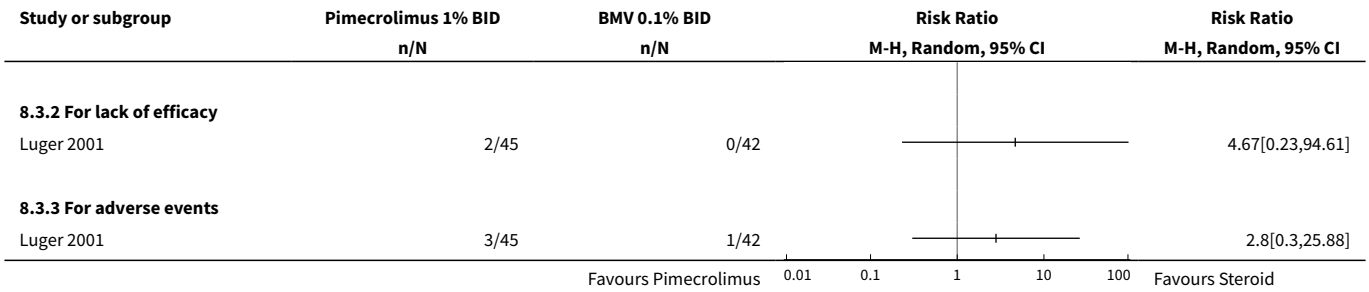
Study or subgroup	Pimecrolimus 1% BID n/N	BMV 0.1% BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.2.1 1 week				
Luger 2001	18/45	33/42		0.51[0.34,0.75]
8.2.2 3 weeks				
Luger 2001	21/45	34/42		0.58[0.41,0.81]



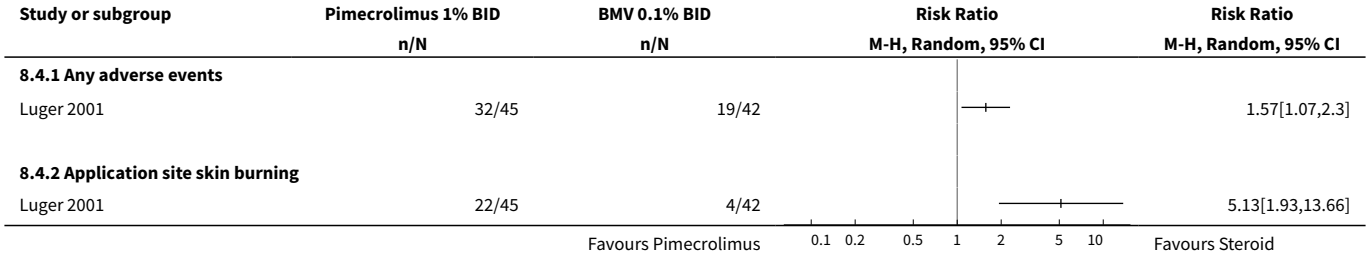
Analysis 8.3. Comparison 8 Pimecrolimus 1.0% BID vs. betamethasone valerate 0.1% BID, Outcome 3 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	BMV 0.1% BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
8.3.1 For any reason				
Luger 2001	7/45	3/42		2.18[0.6,7.88]





Analysis 8.4. Comparison 8 Pimecrolimus 1.0% BID vs. betamethasone valerate 0.1% BID, Outcome 4 Adverse events.



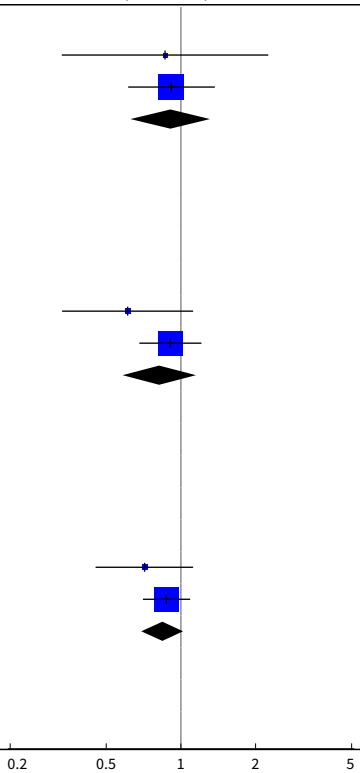
Comparison 9. Pimecrolimus 1.0% BID vs. tacrolimus 0.03% BID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 1 week	2	567	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.63, 1.31]
1.2 3 weeks	2	567	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.58, 1.15]
1.3 6 weeks	2	567	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.02]
2 Mild or absent pruritus (pruritus score 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 1 week	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 6 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawals	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 For any reason	2	567	Risk Ratio (M-H, Random, 95% CI)	1.94 [0.54, 6.98]
3.2 For lack of efficacy	2	567	Risk Ratio (M-H, Random, 95% CI)	3.45 [1.23, 9.71]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 For adverse events	2	567	Risk Ratio (M-H, Random, 95% CI)	8.19 [1.50, 44.73]
4 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Any adverse events	2	567	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.90, 1.17]
4.2 Skin infections	2	567	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.12, 22.75]
4.3 Bacterial skin infections	1	141	Risk Ratio (M-H, Random, 95% CI)	6.90 [0.36, 131.23]
4.4 Viral skin infections	2	567	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.15, 6.96]
4.5 Application site skin burning	2	567	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.55, 2.49]

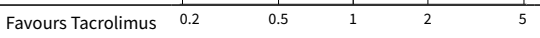
Analysis 9.1. Comparison 9 Pimecrolimus 1.0% BID vs. tacrolimus 0.03% BID, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Tacrolimus 0.03% BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 1 week					
Kempers 2004	7/71	8/70		14.9%	0.86[0.33,2.25]
Paller (a) 2005	38/217	40/209		85.1%	0.91[0.61,1.37]
Subtotal (95% CI)	**288**	**279**		**100%**	**0.91[0.63,1.31]**
Total events: 45 (Pimecrolimus 1% BID), 48 (Tacrolimus 0.03% BID)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=0.52(P=0.61)					
9.1.2 3 weeks					
Kempers 2004	13/71	21/70		18.21%	0.61[0.33,1.12]
Paller (a) 2005	63/217	67/209		81.79%	0.91[0.68,1.21]
Subtotal (95% CI)	**288**	**279**		**100%**	**0.82[0.58,1.15]**
Total events: 76 (Pimecrolimus 1% BID), 88 (Tacrolimus 0.03% BID)					
Heterogeneity: Tau^2=0.02; Chi^2=1.33, df=1(P=0.25); I^2=24.73%					
Test for overall effect: Z=1.16(P=0.24)					
9.1.3 6 weeks					
Kempers 2004	21/71	29/70		18.6%	0.71[0.45,1.12]
Paller (a) 2005	88/217	97/209		81.4%	0.87[0.7,1.09]
Subtotal (95% CI)	**288**	**279**		**100%**	**0.84[0.69,1.02]**
Total events: 109 (Pimecrolimus 1% BID), 126 (Tacrolimus 0.03% BID)					
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					



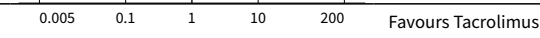
Analysis 9.2. Comparison 9 Pimecrolimus 1.0% BID vs. tacrolimus 0.03% BID, Outcome 2 Mild or absent pruritus (pruritus score 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Tacrolimus 0.03% BID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.2.1 1 week				
Kempers 2004	39/71	48/70		0.8[0.62,1.04]
9.2.2 3 weeks				
Kempers 2004	41/71	52/70		0.78[0.61,0.99]
9.2.3 6 weeks				
Kempers 2004	45/71	48/70		0.92[0.73,1.17]

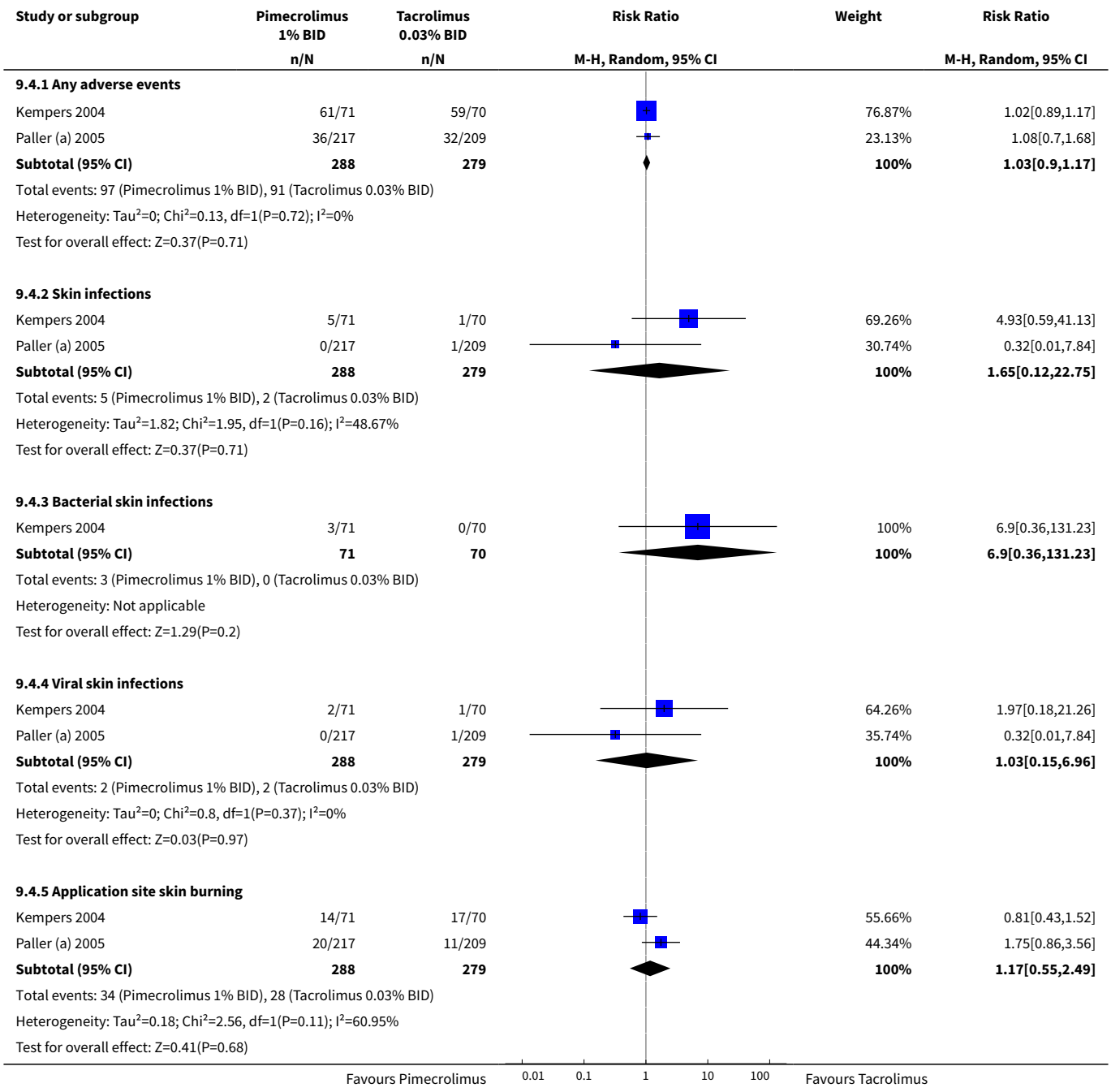


Analysis 9.3. Comparison 9 Pimecrolimus 1.0% BID vs. tacrolimus 0.03% BID, Outcome 3 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Tacrolimus 0.03% BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.3.1 For any reason					
Kempers 2004	13/71	3/70		39.78%	4.27[1.27,14.34]
Paller (a) 2005	56/217	47/209		60.22%	1.15[0.82,1.61]
Subtotal (95% CI)	**288**	**279**		**100%**	**1.94[0.54,6.98]**
Total events: 69 (Pimecrolimus 1% BID), 50 (Tacrolimus 0.03% BID)					
Heterogeneity: Tau^2=0.68; Chi^2=4.31, df=1(P=0.04); I^2=76.78%					
Test for overall effect: Z=1.02(P=0.31)					
9.3.2 For lack of efficacy					
Kempers 2004	3/71	0/70		25.04%	6.9[0.36,131.23]
Paller (a) 2005	13/217	4/209		74.96%	3.13[1.04,9.45]
Subtotal (95% CI)	**288**	**279**		**100%**	**3.45[1.23,9.71]**
Total events: 16 (Pimecrolimus 1% BID), 4 (Tacrolimus 0.03% BID)					
Heterogeneity: Tau^2=0; Chi^2=0.25, df=1(P=0.62); I^2=0%					
Test for overall effect: Z=2.35(P=0.02)					
9.3.3 For adverse events					
Kempers 2004	5/71	1/70		60%	4.93[0.59,41.13]
Paller (a) 2005	10/217	0/209		40%	20.23[1.19,343.04]
Subtotal (95% CI)	**288**	**279**		**100%**	**8.19[1.5,44.73]**
Total events: 15 (Pimecrolimus 1% BID), 1 (Tacrolimus 0.03% BID)					
Heterogeneity: Tau^2=0; Chi^2=0.67, df=1(P=0.41); I^2=0%					
Test for overall effect: Z=2.43(P=0.02)					



Analysis 9.4. Comparison 9 Pimecrolimus 1.0% BID vs. tacrolimus 0.03% BID, Outcome 4 Adverse events.



Comparison 10. Pimecrolimus 1.0% BID vs. tacrolimus 0.1% BID

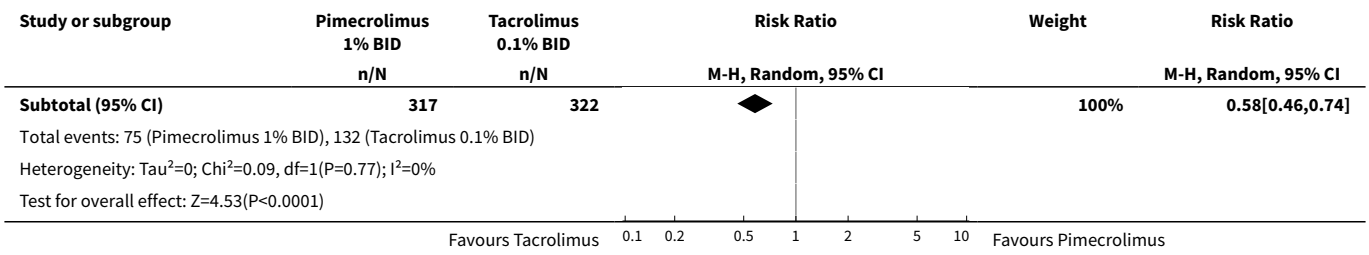
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 1 week	2	639	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.53, 1.34]
1.2 3 weeks	2	639	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.41, 0.77]
1.3 6 weeks	2	639	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.46, 0.74]
2 Withdrawals	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 For any reason	2	639	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.91, 1.52]
2.2 For lack of efficacy	2	639	Risk Ratio (M-H, Random, 95% CI)	2.37 [1.10, 5.08]
2.3 For adverse events	2	639	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.43, 2.41]
3 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Any adverse events	2	639	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.47, 2.26]
3.2 Skin infections	2	639	Risk Ratio (M-H, Random, 95% CI)	1.60 [0.37, 6.99]
3.3 Viral skin infections	1	413	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.07, 16.43]
3.4 Application site skin burning	2	639	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.36, 1.62]

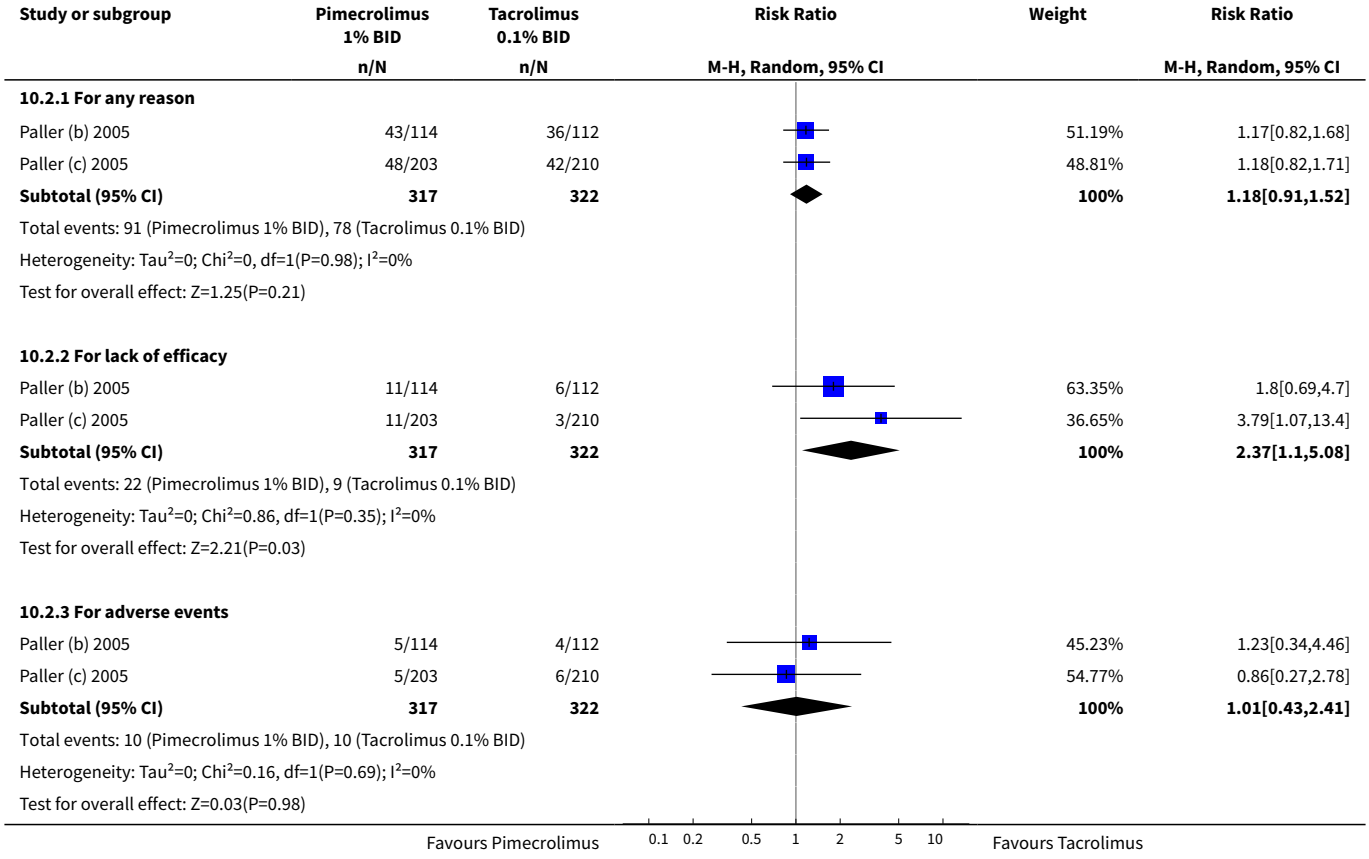
Analysis 10.1. Comparison 10 Pimecrolimus 1.0% BID vs. tacrolimus 0.1% BID, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Tacrolimus 0.1% BID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
10.1.1 1 week					
Paller (b) 2005	4/114	3/112		9.82%	1.31[0.3,5.72]
Paller (c) 2005	25/203	32/210		90.18%	0.81[0.5,1.31]
Subtotal (95% CI)	**317**	**322**		**100%**	**0.85[0.53,1.34]**
Total events: 29 (Pimecrolimus 1% BID), 35 (Tacrolimus 0.1% BID)					
Heterogeneity: Tau^2=0; Chi^2=0.37, df=1(P=0.54); I^2=0%					
Test for overall effect: Z=0.7(P=0.48)					
10.1.2 3 weeks					
Paller (b) 2005	10/114	17/112		18.4%	0.58[0.28,1.21]
Paller (c) 2005	37/203	69/210		81.6%	0.55[0.39,0.79]
Subtotal (95% CI)	**317**	**322**		**100%**	**0.56[0.41,0.77]**
Total events: 47 (Pimecrolimus 1% BID), 86 (Tacrolimus 0.1% BID)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=3.61(P=0)					
10.1.3 6 weeks					
Paller (b) 2005	20/114	36/112		23.94%	0.55[0.34,0.88]
Paller (c) 2005	55/203	96/210		76.06%	0.59[0.45,0.78]

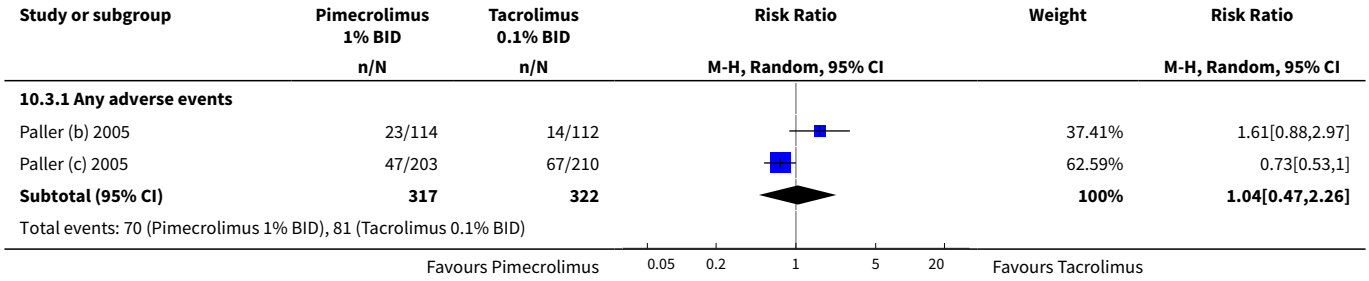
Favours Tacrolimus — Favours Pimecrolimus

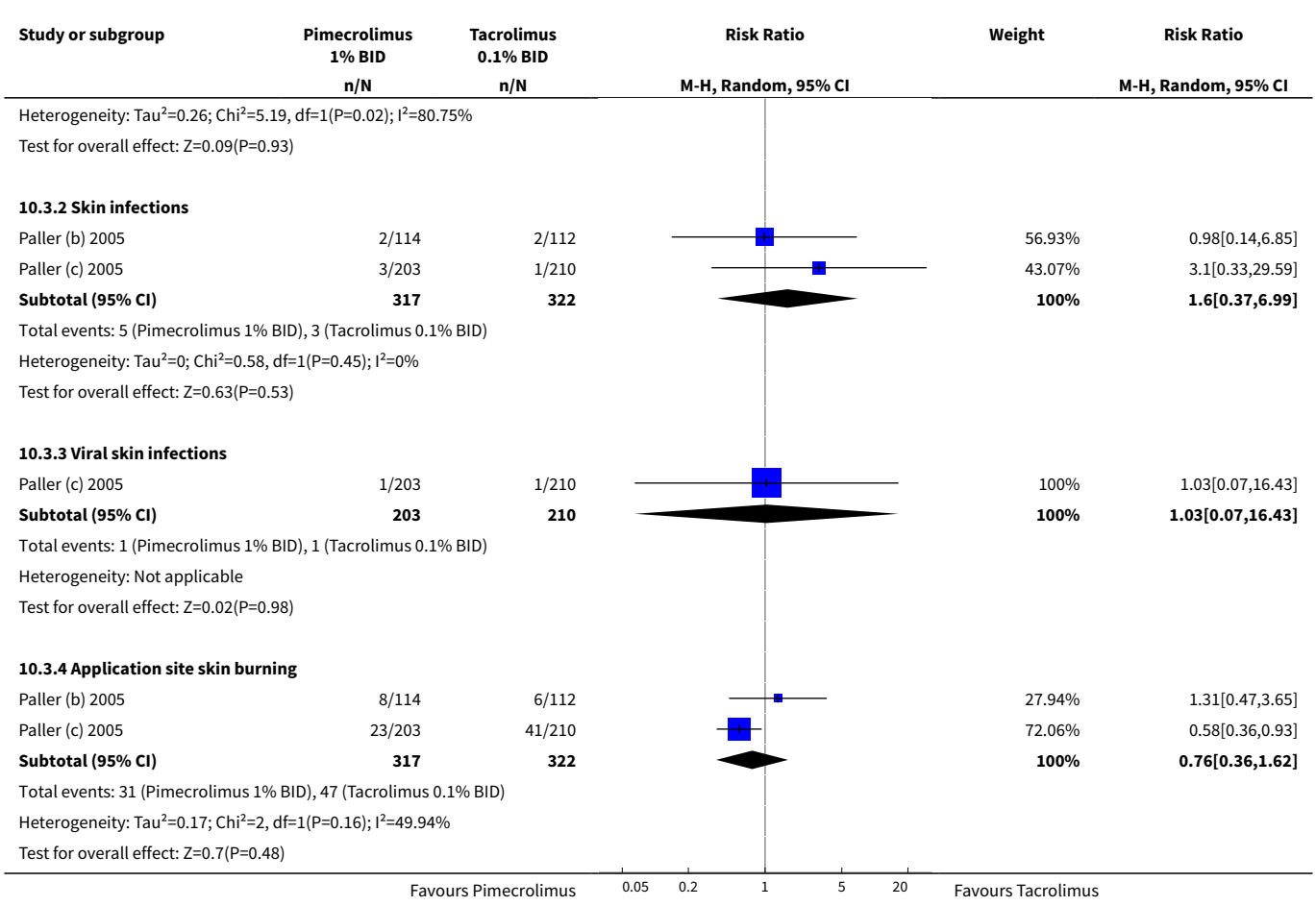


Analysis 10.2. Comparison 10 Pimecrolimus 1.0% BID vs. tacrolimus 0.1% BID, Outcome 2 Withdrawals.



Analysis 10.3. Comparison 10 Pimecrolimus 1.0% BID vs. tacrolimus 0.1% BID, Outcome 3 Adverse events.





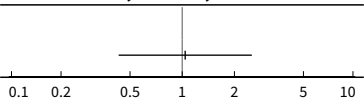
Comparison 11. Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QID

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 Complete or well controlled eczema (PGA)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Mild or absent pruritus (pruritus score 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 3 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 Withdrawals	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 For any reason	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
4.2 For lack of efficacy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Application site skin burning	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

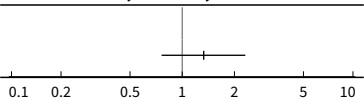
Analysis 11.1. Comparison 11 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QID, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.1.1 3 weeks				
Ling 2005	7/24	7/25		1.04[0.43,2.52]



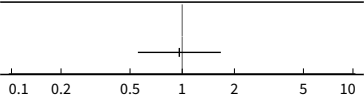
Analysis 11.2. Comparison 11 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QID, Outcome 2 Complete or well controlled eczema (PGA).

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.2.1 3 weeks				
Ling 2005	14/24	11/25		1.33[0.76,2.31]



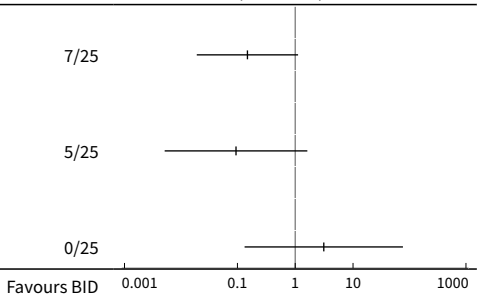
Analysis 11.3. Comparison 11 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QID, Outcome 3 Mild or absent pruritus (pruritus score 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.3.1 3 weeks				
Ling 2005	12/24	13/25		0.96[0.56,1.67]



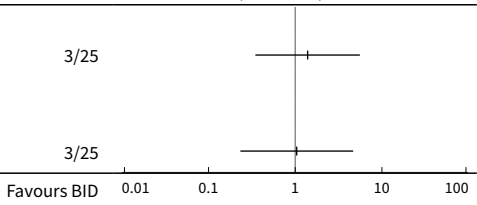
Analysis 11.4. Comparison 11 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QID, Outcome 4 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.4.1 For any reason				
Ling 2005	1/24	7/25		0.15[0.02,1.12]
11.4.2 For lack of efficacy				
Ling 2005	0/24	5/25		0.09[0.01,1.62]
11.4.3 For adverse events				
Ling 2005	1/24	0/25		3.12[0.13,73.04]



Analysis 11.5. Comparison 11 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QID, Outcome 5 Adverse events.

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
11.5.1 Any adverse events				
Ling 2005	4/24	3/25		1.39[0.35,5.57]
11.5.2 Application site skin burning				
Ling 2005	3/24	3/25		1.04[0.23,4.66]



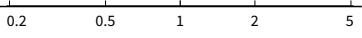
Comparison 12. Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QD, participants responding to pimecrolimus

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clear or almost clear eczema (IGA 0 or 1)	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 No flare of eczema	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 16 weeks	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Withdrawals	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 For any reason	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 For lack of efficacy	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3.3 For adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 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
4.1 Any adverse events	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Skin infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 12.1. Comparison 12 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QD, participants responding to pimecrolimus, Outcome 1 Clear or almost clear eczema (IGA 0 or 1).

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QD n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.1.1 8 weeks				
CASM981C2314 2006	79/134	74/134		1.07[0.87,1.31]
12.1.2 16 weeks				
CASM981C2314 2006	82/134	78/134		1.05[0.86,1.28]



Analysis 12.2. Comparison 12 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QD, participants responding to pimecrolimus, Outcome 2 No flare of eczema.

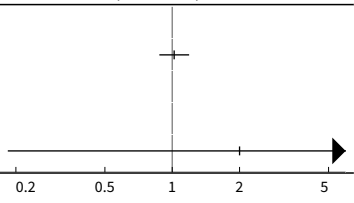
Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QD n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.2.1 16 weeks				
CASM981C2314 2006	121/134	115/134		1.05[0.96,1.15]

Analysis 12.3. Comparison 12 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QD, participants responding to pimecrolimus, Outcome 3 Withdrawals.

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QD n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.3.1 For any reason				
CASM981C2314 2006	22/134	51/134		0.43[0.28,0.67]
12.3.2 For lack of efficacy				
CASM981C2314 2006	10/134	23/134		0.43[0.22,0.88]
12.3.3 For adverse events				
CASM981C2314 2006	4/134	6/134		0.67[0.19,2.31]

Analysis 12.4. Comparison 12 Pimecrolimus 1.0% BID vs. pimecrolimus 1.0% QD, participants responding to pimecrolimus, Outcome 4 Adverse events.

Study or subgroup	Pimecrolimus 1% BID n/N	Pimecrolimus 1% QD n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
12.4.1 Any adverse events				
CASM981C2314 2006	96/134	94/134		1.02[0.88,1.19]
12.4.2 Skin infections				
CASM981C2314 2006	2/134	1/134		2[0.18,21.79]



ADDITIONAL TABLES

Table 1. Summary of methodological quality

Name of study	Allocat'n generation	Allocat'n concealed	Blinding	Loss to follow up	Attrition rate	Certainty of AD	Comparable severity
ASM981C2315 2005	Unclear	Unclear	Adequate	Adequate	15.36%	Unclear	Adequate
ASM981C2316 2005	Unclear	Unclear	Adequate	Adequate	18.42%	Unclear	Unclear
ASM981C2322 2005	Unclear	Unclear	Adequate	Adequate	10.12%	Unclear	Unclear
ASM981C2402 2005	Unclear	Unclear	Adequate	Inadequate	23.29%	Unclear	Unclear
Barba 2003	Unclear	Unclear	Adequate	Adequate	7.55%	Unclear	Unclear
CASM981C1301 2005	Unclear	Unclear	Adequate	Adequate	13.75%	Adequate	Unclear
CASM981C1303 2005	Unclear	Unclear	Adequate	Adequate	15.61%	Unclear	Unclear
CASM981C2413 2006	Unclear	Unclear	Adequate	Inadequate	27.24%	Unclear	Unclear
CASM981C2436 2006	Unclear	Unclear	Adequate	Inadequate	16.87%	Adequate	Unclear
CASM981C2442 2006	Unclear	Unclear	Adequate	Inadequate	43.5%	Adequate	Unclear
CASM981CDE10 2005	Unclear	Unclear	Adequate	Adequate	15.76%	Adequate	Unclear
CASM981CUS03 2005	Unclear	Unclear	Adequate	Adequate	26.89%	Unclear	Unclear
Eichenfield (a) 2002	Unclear	Unclear	Adequate	Adequate	18.18%	Adequate	Adequate
Eichenfield (b) 2002	Unclear	Unclear	Adequate	Adequate	13.66%	Adequate	Adequate
Ho 2003	Unclear	Unclear	Adequate	Inadequate	23.66%	Adequate	Adequate
Kapp 2002	Unclear	Unclear	Adequate	Inadequate	27.09%	Adequate	Adequate
Kaufmann 2006	Adequate	Unclear	Adequate	Adequate	5.56%	Unclear	Adequate
Kempers 2004	Adequate	Adequate	Adequate	Adequate	11.35%	Unclear	Adequate
Leo 2004	Unclear	Unclear	Adequate	Adequate	0.00%	Adequate	Unclear

Table 1. Summary of methodological quality *(Continued)*

Ling 2005	Unclear	Unclear	Adequate	Adequate	16.33%	Adequate	Unclear
Luger 2001	Unclear	Unclear	Adequate	Inadequate	22.31%	Adequate	Adequate
Luger 2004	Adequate	Unclear	Adequate	Inadequate	41.19%	Adequate	Adequate
Meurer 2002	Unclear	Unclear	Adequate	Inadequate	30.21%	Adequate	Adequate
Paller (a) 2005	Adequate	Adequate	Adequate	Adequate	24.18%	Adequate	Adequate
Paller (b) 2005	Adequate	Adequate	Adequate	Inadequate	34.96%	Adequate	Adequate
Paller (c) 2005	Adequate	Adequate	Adequate	Inadequate	21.79%	Adequate	Adequate
Staab 2005	Unclear	Unclear	Adequate	Adequate	19.39%	Adequate	Adequate
Seigfried 2006	Unclear	Unclear	Adequate	Inadequate	21.45%	Adequate	Unclear
Thaci 2003	Unclear	Unclear	Adequate	Inadequate	28.72%	Unclear	Adequate
Wahn 2002	Adequate	Unclear	Adequate	Inadequate	38.26%	Adequate	Adequate
Whalley 2002	Unclear	Unclear	Adequate	Inadequate	36.10%	Adequate	Unclear

Table 2. Quality of life measures

Population	QoL measure	Scale of measure	Study
Adults	Dermatology Life Quality Index (DLQI)	10 items, maximum score: 30 (score 0 to 3 for each item)	Meurer 2002,
	Quality of Life Index- Atopic Dermatitis (QoLI-AD)	25 items, maximum score: 25 (yes, no scored 1, 0)	Meurer 2002,
Children	Children's Dermatology Life Quality Index (CDLQI)	10 items, maximum score: 30 (score 0 to 3 for each item)	Leo 2004, Wahan 2002
Carers	Parent's Index of Quality of Life- Atopic Dermatitis (PIQoL-AD)	28 items, maximum score: 28 (yes, no scored 1, 0)	Whalley 2002, Kappa 2002, Wahn 2002
	Parents' Quality of Life Index- Atopic Dermatitis (PQoL-AD)	26 items in 5 sub-scales (each items scored 1 to 5 in 5-point Likert Scale)	Staab 2005

APPENDICES

Appendix 1. Search strategy for the Cochrane Skin Group Specialised Register

- We searched the Cochrane Skin Group Specialised Register (to October 2006) using the search terms:

(((atopic OR childhood OR infantile) AND (dermatitis OR eczema)) OR neurodermatitis OR (besniers AND prurigo)) AND (pimecrolimus OR elidel or SDZASM981)

Appendix 2. Search strategy for the Cochrane Central Register of Controlled Trials (CENTRAL)

- We searched the Cochrane Central Register of Controlled Trials (CENTRAL) in *The Cochrane Library* (*Issue* 3, 2006):

#1(atopic next dermatitis) or (atopic next eczema) or neurodermatitis in All Fields, from 1800 to 2005 in all products
#2(infantile next eczema) or (childhood next eczema) or (besniers next prurigo) in All Fields in all products
#3MeSH descriptor Dermatitis, Atopic explode all trees in MeSH products
#4MeSH descriptor Neurodermatitis explode all trees in MeSH products
#5(#1 OR #2 OR #3 OR #4)
#6(pimecrolimus):ti,ab,kw or (ELIDEL):ti,ab,kw or (SDZ ASM 981):ti,ab,kw
#7(#5 AND #6)
#8SR-SKIN
#9(#7 AND NOT #8)

Appendix 3. Search strategy for MEDLINE (OVID)

We searched MEDLINE (OVID) from 2003 to October 2006 using the following search strategy:

1. RANDOMIZED CONTROLLED TRIAL.pt.
2. CONTROLLED CLINICAL TRIAL.pt.
3. RANDOMIZED CONTROLLED TRIALS.sh.
4. RANDOM ALLOCATION.sh.
5. DOUBLE BLIND METHOD.sh.
6. SINGLE-BLIND METHOD.sh.
7. or/1-6
8. animal/ not human/
9. 7 not 8
10. CLINICAL TRIAL.pt.
11. exp CLINICAL TRIALS/
12. (clin$ adj25 trial$).ti,ab.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.

14. PLACEBOS.sh.
15. placebo$.ti,ab.
16. random$.ti,ab.
17. RESEARCH DESIGN.sh.
18. or/10-17
19. 18 not 8
20. 19 not 9
21. COMPARATIVE STUDY.sh.
22. exp EVALUATION STUDIES/
23. FOLLOW UP STUDIES.sh.
24. PROSPECTIVE STUDIES.sh.
25. (control$ or prospectiv$ or volunteer$).ti,ab.
26. or/21-25
27. 26 not 8
28. 27 not (9 or 20)
29. 9 or 20 or 28
30. exp Dermatitis, Atopic/
31. atopic dermatitis.mp.
32. atopic eczema.mp.
33. exp NEURODERMATITIS/
34. neurodermatitis.mp.
35. infantile eczema.mp.
36. childhood eczema.mp.
37. Besniers' Prurigo.mp.
38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37
39. pimecrolimus.mp.
40. ELIDEL.mp.
41. SDZ ASM 981.mp.
42. 39 or 40 or 41
43. 29 and 38 and 42
44. limit 43 to yr="2003 - 2006"1. RANDOMIZED CONTROLLED TRIAL.pt.

Appendix 4. Search strategy for EMBASE (OVID)

1. random$.mp.
2. factorial$.mp.
3. crossover$.mp.
4. placebo$.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$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign$.mp.
8. volunteer$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. atopic dermatitis.mp. or exp Atopic Dermatitis/
15. atopic eczema.mp.
16. eczema.mp. or exp ECZEMA/
17. neurodermatitis.mp. or exp NEURODERMATITIS/
18. child$ eczema.mp.
19. infant$ eczema.mp.
20. besniers prurigo.mp.
21. 14 or 15 or 16 or 17 or 18 or 19 or 20
22. pimecrolimus.mp. or exp PIMECROLIMUS/
23. ELIDEL.mp.
24. SDZ ASM 981.mp.
25. 22 or 23 or 24
26. 13 and 21 and 25

27. limit 26 to yr="2005 - 2006"

Appendix 5. Search strategy for adverse effects MEDLINE (OVID)

1. exp product surveillance, postmarketing/ or exp adverse drug reaction reporting systems/ or exp clinical trials, phase iv/
2. adverse events.mp.
3. adverse effects.mp.
4. exp hypersensitivity/ or exp drug hypersensitivity/ or exp drug eruptions/ or exp hypersensitivity, delayed/ or exp hypersensitivity, immediate/
5. exp hypersensitivity, immediate/ or exp anaphylaxis/ or exp conjunctivitis, allergic/ or exp dermatitis, atopic/ or exp food hypersensitivity/ or exp respiratory hypersensitivity/ or exp urticaria/
6. side effect$.mp.
7. exp Poisoning/
8. exp hepatitis, toxic/ or exp hepatitis, chronic, drug-induced/
9. exp Substance-Related Disorders/
10. exp Drug Toxicity/
11. exp Abnormalities, Drug-Induced/
12. exp Teratogens/
13. exp Mutagens/
14. exp Carcinogens/
15. metabolites.mp.
16. exp dermatitis, contact/ or exp dermatitis, allergic contact/ or exp dermatitis, irritant/ or exp dermatitis, phototoxic/
17. photoallergic reactions.mp.
18. exp dermatitis, allergic contact/ or exp dermatitis, photoallergic/
19. phototoxicity.mp.
20. sensitization.mp.
21. exp Burning Mouth Syndrome/
22. stinging.mp.
23. burning.mp.
24. fetal abnormalities.mp.
25. exp Drug Monitoring/
26. harm$ effects.mp.
27. (toxic effects or drug effects).mp.
28. Sleep Apnea, Obstructive/
29. ARRHYTHMIA/
30. undesirable effect$.mp.
31. (safe or safety).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
32. toxicity.mp.
33. noxious.mp.
34. serious reaction$.mp.
35. complication$.mp.
36. treatment emergent.mp.
37. tolerability.mp.
38. (adverse adj3 (effect$ or reaction$ or event$ or outcome$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word]
39. rebound.mp.
40. Hypercalcemia/ci [Chemically Induced]
41. Urinary Calculi/ci [Chemically Induced]
42. Tachyphylaxis/ci, de [Chemically Induced, Drug Effects]
43. Substance Withdrawal Syndrome/ci, de [Chemically Induced, Drug Effects]
44. ATROPHY/ci [Chemically Induced]
45. TELANGIECTASIS/ci [Chemically Induced]
46. skin thinning.mp.
47. Liver Diseases/ci [Chemically Induced]
48. Kidney Diseases/ci [Chemically Induced]
49. Disseminated Intravascular Coagulation/ci [Chemically Induced]
50. Multiple Organ Failure/ci [Chemically Induced]
51. Stevens-Johnson Syndrome/ci [Chemically Induced]
52. Epidermal Necrolysis, Toxic/ci [Chemically Induced]
53. Heart Block/ci [Chemically Induced]
54. COMA/ci [Chemically Induced]
55. PARALYSIS/ci [Chemically Induced]

56. exp Nausea/dt [Drug Therapy]
57. exp Vomiting/dt [Drug Therapy]
58. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57
59. pimecrolimus.mp.
60. elidel.mp.
61. SDZ ASM 981.mp.
62. 59 or 60 or 61
63. 58 and 62
64. mortality.mp. or MORTALITY/
65. 58 or 64
66. 62 and 65

WHAT'S NEW

Date	Event	Description
22 June 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 4, 2005
Review first published: Issue 4, 2007

Date	Event	Description
20 August 2007	New search has been performed	Minor update
13 August 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

DMA, RG and LC undertook the literature searches, identified the studies, and conducted the data extraction and quality assessment. DMA and LC also undertook the statistical analyses. DMA and LC prepared the first draft of the review. RG, KS and HCW commented and edited subsequent drafts.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- School of Pharmacy and Pharmaceutical Sciences, University of Manchester, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Topical; Adrenal Cortex Hormones [administration & dosage]; Dermatologic Agents [*administration & dosage]; Eczema [*drug therapy]; Immunosuppressive Agents [*administration & dosage]; Quality of Life; Randomized Controlled Trials as Topic; Tacrolimus [administration & dosage] [*analogs & derivatives]

MeSH check words

Adolescent; Adult; Child; Child, Preschool; Humans; Infant