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Ciclesonide versus other inhaled steroids for chronic asthma in children and adults (Review)

Manning P, Gibson PG, Lasserson TJ

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Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD007031.
DOI: 10.1002/14651858.CD007031.

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[Intervention Review]

Ciclesonide versus other inhaled steroids for chronic asthma in children and adults

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Editorial group: Cochrane Airways Group.
Publication status and date: Edited (no change to conclusions), published in Issue 1, 2010.

Citation: Manning P, Gibson PG, Lasserson TJ. Ciclesonide versus other inhaled steroids for chronic asthma in children and adults. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD007031. DOI: 10.1002/14651858.CD007031.

ABSTRACT

Background

Inhaled corticosteroids (ICS) are an integral part of asthma management, and act as an anti-inflammatory agent in the airways of the lung. These agents confer both significant benefit in terms of symptom management and improvement in lung function, but may also cause harm in terms of local and systemic side-effects. Ciclesonide is a novel steroid that is metabolised to its active component in the lung, making it a potentially useful for reducing local side effects.

Objectives

To assess the efficacy and adverse effects of ciclesonide relative to those of other inhaled corticosteroids in the management of chronic asthma.

Search methods

We searched the Cochrane Airways Group register of trials with pre-defined terms. Additional searches of PubMed and Clinicalstudyresults.org were undertaken. The literature searches for this review are current up to June 2007.

Selection criteria

Randomised parallel or crossover studies were eligible for the review. We included studies comparing ciclesonide with other steroids both at nominally equivalent dose or lower doses of ciclesonide.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Study authors were contacted for additional information. Adverse effects information was collected from the trials.

Main results

Twenty one trials involving 7243 participants were included. Equal daily doses of ciclesonide and beclomethasone (BDP) or budesonide (BUD) gave similar results for peak expiratory flow rates (PEF), although forced vital capacity (FVC) was higher with ciclesonide. Data on forced expired volume in one second (FEV1) were inconsistent. Withdrawal data and symptoms were similar between treatments. Compared with the same dose of fluticasone (FP), data on lung function parameters (FEV1, FVC and PEF) did not differ significantly. Paediatric quality of life score favoured ciclesonide. Candidiasis was less frequent with ciclesonide, although other side-effect outcomes did not give significant differences in favour of either treatment. When lower doses of ciclesonide were compared to BDP or BUD, the difference in FEV1 did not reach significance but we cannot exclude a significant effect in favour of BDP/BUD. Other lung function outcomes did not give significant differences between treatments. Paediatric quality of life scores did not differ between treatments. Adverse events

occurred with similar frequency between ciclesonide and BDP/BUD. Comparison with FP at half the nominal dose was undertaken in three studies, which indicated that FEV1 was not significantly different, but was not equivalent between the treatments (per protocol: -0.05 L 95% confidence intervals -0.11 to 0.01).

Authors' conclusions

The results of this review give some support to ciclesonide as an equivalent therapy to other ICS at similar nominal doses. The studies assessed low doses of steroids, in patients whose asthma required treatment with low doses of steroids. At half the dose of FP and BDP/BUD, the effects of ciclesonide were more inconsistent The effect on candidiasis may be of importance to people who find this to be problematic. The role of ciclesonide in the management of asthma requires further study, especially in paediatric patients. Further assessment against FP at a dose ratio of 1:2 is a priority.

PLAIN LANGUAGE SUMMARY

Ciclesonide versus other inhaled steroids for chronic asthma in children and adults

Inhaled corticosteroids, such as budesonide, beclomethasone or fluticasone, which have been available for many years, have proven to be an important therapy for controlling the inflammation caused by asthma. They are given usually twice daily, and are recommended therapy in international guidelines for most asthmatics. However, the currently available inhaled corticosteroids can be associated with significant side-effects, including local effects in the upper airways such as hoarseness and oral candida (thrush infection). Ciclesonide is a new steroid which is reported to make less of the active steroid available until the drug reaches the lung on inhalation, which could reduce the likelihood of throat symptoms. This findings of this review of 21 trials (7243 participants) do not allow certainty about the relative efficacy of ciclesonide compared to older inhaled corticosteroids, especially at higher doses. The results of the review to date do not indicate whether ciclesonide provides a significantly more useful safety profile that other inhaled corticosteroids at similar equivalent doses. However, the finding of lower oral candidiasis in patients treated with ciclesonide compared to fluticasone may be important for those patients who experience oral thrush with their current ICS. In addition, further studies in children are required to obtain data on the side-effect profile of ciclesonide in this population.

BACKGROUND

On a worldwide basis asthma is a common chronic disease in clinical practice affecting over 300 million people. It is responsible for one in 250 deaths per year and 15 million disability adjusted life years (DALYs) lost worldwide (GBA 2004). It is a condition which develops in early childhood and generally persists into adulthood (Gerritsen 1989; Martin 1982; Williams 1969). Asthma is a chronic inflammatory disease of the airways involving a complex interaction between airway structural cells and specific allergic inflammatory cells including mast cells, eosinophils and T-lymphocytes, and the release of specific cytokines and mediators of inflammation. This inflammatory response is associated with airway narrowing, especially in smaller airways, which cause patients to complain of symptoms such as cough and wheeze (GINA 1998; Tattersfield 2002). The anti-inflammatory corticosteroids have been an effective therapy for asthma for over 30 years and are now the main therapy for asthma control currently for those with persistent asthma (Adams 2005; BGAM 1997; BTS/SIGN 2003; Consensus 1999; Consensus 2005; GINA 1998; Powell 2003).

Corticosteroids deal effectively with the asthma inflammatory process through interaction with the glucocorticoid receptor, thus leading to the amelioration in asthma symptoms and control of the disease (Adams 2005; Adams 2005a; Adams 2007). The main advantage of the inhaled route is to bring the therapy directly to the disease location and at a reduced dose and hence less systemic side-effects compared to higher dose oral steroid therapy (Mash 2001). There are different types of inhaled corticosteroids available on the market given either by multi-dose dry powder or aerosol inhaler devices (e.g. beclomethasone, fluticasone, budesonide, and mometasone). Inhaled corticosteroids significantly reduce the hospitalisation rate for asthma (and hence reduce cost associated with the disease) and the mortality from the condition (Suissa 2000; Suissa 2002) when taken on a regular basis. Non-compliance is a significant problem with inhaled corticosteroid therapy due to a number of factors including increased dosing frequency and may occur due to recurrent local and also systemic side effects (Buston 2000). This has led to the development of more potent formulations with the aim of reducing daily steroid load without compromising disease control (Lasserson 2006). However, while inhaled steroids may be more effective when used four times per day, reducing dosing to twice daily or even once daily dosing can give effective control (Malo 1989; Toogood 1982). However, compliance with increased dosing frequency of inhaled steroids in asthmatics especially four times daily can be poor (Coutts 1992; Eisen 1990). The novel inhaled corticosteroid ciclesonide has recently been approved in Europe. This therapy has novel release and distribution properties, reported to result in better targeting of the anti-inflammatory effects in the airways especially to the small airways. It is inhaled as a pro-drug, which is converted to an active metabolite (des CIC) in the airways reportedly with reduced systemic and local (e.g. oropharyngeal) side effects. In addition, ciclesonide is given as a once daily therapy, and may lead to better compliance with inhaled corticosteroids.

This review considers the evidence comparing ciclesonide with other inhaled steroid therapies at nominal 1:1 and 1:2 dose ratios.

OBJECTIVES

To assess the efficacy and adverse effects of ciclesonide relative to those of other inhaled corticosteroids in the management of chronic asthma. The review assesses ciclesonide against fluticasone, beclomethasone or budesonide at equivalent dose and lower doses of ciclesonide.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) comparing the inhaled corticosteroid ciclesonide with another inhaled corticosteroid were considered for inclusion. Trials that use parallel group designs or cross-over design with a wash out period of two weeks or more were eligible. Studies published in abstract form will be included. Unpublished data, if available, will be considered.

Types of participants

Adults (aged 18 years and older) and children (less than 18 years) will be eligible for inclusion. All study participants must have a diagnosis of chronic asthma, including those with intermittent and chronic symptoms. Studies that base the diagnosis of asthma on physician opinion or on objective criteria related to symptoms, airway reversibility to an inhaled short-acting 2-agonist or airway hyper-responsiveness in keeping with international asthma guidelines such as GINA 1998 (Global Initiative for Asthma)/National Institutes of Health (NIH) or BTS/SIGN 2003) or evidenced based guidelines will be included. Studies that deliver interventions to patients in the community/family practice setting or hospital-based settings will be included. Studies with participants with pulmonary diagnosis other than asthma (for example, chronic obstructive pulmonary disease (COPD)) will be excluded.

Types of interventions

This review includes studies that have compared ciclesonide with other inhaled corticosteroids. Two comparator steroids are assessed in this review, each at dose ratios of 1:1 and 1:2: ciclesonide (CIC) versus BDP/budesonide (BDP/BUD) 1:1; CIC versus BDP/BUD 1:2 ; CIC versus fluticasone propionate (FP): 1:1; CIC versus FP 1:2. Study duration was set at a minimum of four weeks. Concomitant therapies for asthma, such as short-acting 2-agonists (rescue therapy), theophyllines, long-acting 2-agonists (Serevent or formoterol), inhaled anti-cholinergics were permitted provided that the dose and type of drug remained stable, and was not introduced at the start of the trial as part of the study protocol. Studies involving anti-leukotrienes (e.g. Singular, Accolate), combination inhalers (fluticasone-salmeterol and budesonide-formoterol) or other airway anti-inflammatory asthma therapy (e.g. cromones) were excluded. Studies were included if they were conducted in an outpatient setting.

Types of outcome measures

Primary outcomes

1. Asthma exacerbations requiring use of systemic steroids.
2. Measures of lung function, forced expired volume in one second (FEV1) and or peak expiratory flow rates (PEF)

Secondary outcomes

1. Measures of healthcare utilisation: doctor visits, emergency visits and or hospital admissions for asthma.

2. Measures of morbidity: days of school absences, days of restricted activities, nights disturbed by asthma symptoms, health-related quality of life, asthma severity, asthma-free days,
3. Measures of compliance. As a surrogate to include study withdrawal or patient preference in crossover studies.
4. Asthma symptoms
5. Rescue beta-2 agonists use
6. Measures of adverse effects including oropharyngeal (candidiasis, sore throat, hoarseness), and systemic (osteopenia, adrenal suppression, growth rate) side-effects and withdrawal rate due to side-effects will be included.

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group (CAG) Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms:

ciclesonide* or Alveso* or pregnenedione* or CIC

We searched the CAG trials register up to June 2007. Additional searches on PubMed were undertaken with the term 'ciclesonide' for articles published more recently than the last register search (October 2007).

Searching other resources

Reference lists of all primary studies and review articles were reviewed for additional references. Authors of identified trials were contacted and asked to identify other published and unpublished studies. Pharmaceutical manufacturers (Altana) was also contacted for information on any unpublished trials. We undertook additional searches of www.clinicalstudyresults.org for trial reports of ciclesonide (November 2007).

Data collection and analysis

Selection of studies

Two authors (PM and TL) screened the title and abstract of each citation identified for eligibility. Articles that appeared to fulfil the inclusion criteria were retrieved in full text. PM and TL then independently established, from the full text of the articles, whether each study met the inclusion criteria of the review. Translation into English was not necessary. Disagreement was settled by consensus.

Data extraction and management

We independently extracted data from included trials and TL entered this into RevMan 4.2. We attempted to contact study authors to identify additional papers, confirm data for accuracy and completeness.

We extracted the following characteristics of each study.
Methods
Design, randomisation method, blinding, follow-up procedures and withdrawals.
Population
Sample size, age, gender, inclusion and exclusion criteria (including asthma therapy), asthma diagnosis and severity, pulmonary function, other medical diagnoses and therapies.
Intervention
Type and dose of comparator inhaled steroid, dose of ciclesonide, timing and duration of therapy, method of delivery, co-intervention medications.
Outcomes
Reported outcomes

We extracted numerical outcome data independently.

Assessment of risk of bias in included studies

Study quality was assessed using the Jadad scale and the Cochrane approach to assessment of allocation concealment. All trials were scored and entered using the following principals.

Grade A: adequate concealment
Grade B: uncertain
Grade C: clearly inadequate concealment

Measures of treatment effect

A mean difference (MD) and 95% continuous interval (CI) was calculated for continuous variables measured on identical metrics. SMD (standardised mean difference) was used for the same continuous variables measured with different metrics. Generic inverse variance was used to pool data derived from the same scale if they were only available as mean differences with 95% CIs or standard errors.

For dichotomous outcomes, we calculated a Risk Ratio (RR) based upon the number of participants with an event versus the number of participants without an event.

Assessment of heterogeneity

We assessed statistical heterogeneity using the I square measurement, with a cut-off of 20% prompting additional analysis.

Data synthesis

Trial data was combined using RevMan 4.2. Data and pooled using a fixed-effect model. If heterogeneity was observed $I^2 \geq 20\%$ (Higgins 2003), a sensitivity analysis using a random-effects model was applied, to determine whether variation between the studies affected the pooled estimate.

The treatments compared were considered to be equivalent according to whether the 95% CI of the pooled estimates excluded a clinically meaningful benefit. We considered a difference of ≥100 ml in FEV1, ≥ 25 L/min for PEF and RR outside of 0.9 to 1.1 for exacerbations to be clinically meaningful differences. We assessed the pooled estimates for FEV1, am and pm PEF as intention to treat and per protocol populations, if these were available.

Subgroup analysis and investigation of heterogeneity

We subgrouped studies according to the age of the participants (adults versus children).

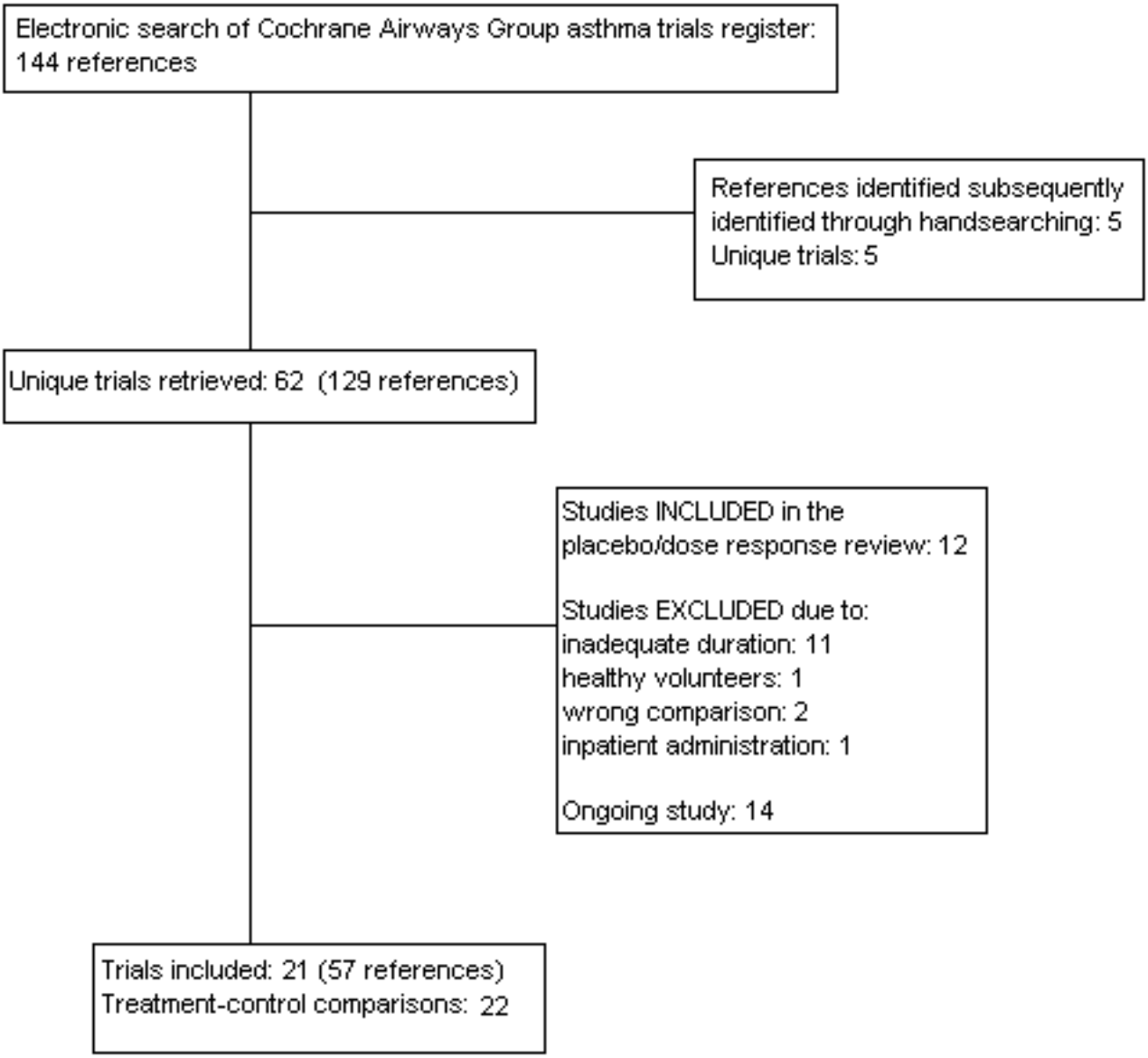
RESULTS

Description of studies

Results of the search

Literature searches identified a total of 146 citations, and following the exclusion of irrelevant studies and identification of multiple citations, 21 studies (contributing 22 treatment-control comparisons) derived from 57 citations met the review entry criteria (*see* Figure 1). For full descriptions of each study see Characteristics of included studies.

Figure 1. Flow diagram of studies in the review.



Included studies

Study design

All studies were described as randomised.

Participants

A total of 1664 children were recruited to studies with age limits up to 17 years (Pedersen 2006; Vermeulen 2007; von Berg 2007), and 5367 participants were adolescent/adult populations.

Baseline FEV1 predicted varied between the studies, as did the requirement for pre-treatment with maintenance inhaled steroids. If reported, mean FEV1 predicted suggested that the study populations had moderate airway obstruction, with three reporting FEV1 below 80% in Adachi 2007; Buhl 2006; Hansel 2006; Ukena 2006, and a number with baseline predicted FEV1 at or above 80% in Bateman 2007; Boulet 2006; Boulet 2007; Lipworth 2005; Niphadkar 2005a; Niphadkar 2005b; Pedersen 2006 In the remaining studies baseline means were not presented. In Bernstein 2004 and Vermeulen 2007, entry criteria stipulated predicted FEV1

below 80%. Pre-treatment with an inhaled steroid was an entry criterion in Boulet 2006; Buhl 2006 and Zietkowski 2006, was cited as an exclusion criterion in Lipworth 2005. In the remaining studies participants whose maintenance dose of inhaled steroids was in excess of a specified level were excluded.

Run-in periods were performed in the majority of the trials, with Buhl 2006; Hansel 2006; Magnussen 2007; Pedersen 2006; Ukena 2006; von Berg 2007 and Zietkowski 2006 performing run-in periods where participants could use only as needed rescue medication. In the remaining studies if run-in periods were reported, participants continued their usual dose of inhaled steroids, or were given a stable dose of a specific steroid.

Intervention

We assessed four comparisons represented by the following studies.
1. Ciclesonide versus BDP or BUD (nominal BDP equivalent dose ratio 1:1): Three studies (Adachi 2007; Boulet 2006; Hansel 2006; Ukena 2006).
2. Ciclesonide versus BDP or BUD (nominal BDP equivalent dose ratio 1:2): Five studies (Adachi 2007; Hansel 2006; Niphadkar 2005a; Niphadkar 2005b; Vermeulen 2007; von Berg 2007).
3. Ciclesonide versus FP (nominal FP dose ratio: 1:1): Eight studies (Bateman 2007; Bernstein 2004; ;Boulet 2006; Buhl 2006; Boulet 2007; Lipworth 2005; Magnussen 2007; Pedersen 2006; Zietkowski 2006).
4. Ciclesonide versus FP (nominal FP dose ratio: 1:2): Four studies (Bernstein 2004; Lipworth 2005; Magnussen 2007; Zietkowski 2006).

Delivery of drug, dosage & duration of studies

Ciclesonide was delivered via metered dose inhalers in all the trials. Open label assessment with budesonide was undertaken in two studies (Adachi 2007; Hansel 2006), and with fluticasone in one other study (Bateman 2007). The remaining comparisons were double-blind.

Dosing regimens varied, with ciclesonide given once daily in all studies with the exception of Bernstein 2004 and Pedersen 2006 if it was administered twice daily. Conversely the comparator inhaled steroid was administered twice daily in all studies with the exception of Boulet 2006; Ukena 2006; Vermeulen 2007 and von Berg 2007, where it was administered once daily.

One study was 12 months in duration (Adler 2006) and another was six months (Bateman 2007). The remaining studies were 12 weeks long.

Outcomes assessed

Adler 2006; Lipworth 2005 were the only two studies where lung function outcome data were not reported. Symptoms or rescue medication use were assessed in all studies except for Lipworth 2005 and Vermeulen 2007.

Excluded studies

The reasons for the exclusion of studies are listed in Characteristics of excluded studies. Fourteen studies were excluded, the most common reason for exclusion was inadequate follow-up period. A further fourteen studies were identified as ongoing. We report data from 15 parallel group trials, since these were the primary source of evidence for the review.

Risk of bias in included studies

All trials except three were described as randomised and double-blind. However, the method of blinding was available in only four studies. Methodological quality, as assessed by the Jadad scoring system, was variable. Five of the studies achieved a score of 5 (high quality), three studies a score of 4 (good quality), three a score of 3 (fair quality) and the remaining three studies a score of 2 or 1(poor quality). The studies with low (i.e. 2 or 1) Jadad scores were published in abstract form for presentation at conferences and we had only limited details about patient withdrawals from study, methods of randomisation and blinding. It is therefore possible that these scores may change upon availability of more information. Allocation concealment scores were graded A for six studies and B for the remainder.

Effects of interventions

A number of the studies identified did not provide sufficient information to contribute data to the findings of this review (Adler 2006, N = 111; Bernstein 2004, N = 531). We describe the pooled findings from 20 study comparisons recruiting 7243 participants. The data available represent 91% of participants randomised to the studies. We report data with the direction of effect indicating a difference in favour of ciclesonide.

1. Ciclesonide versus BDP or BUD (1:1 dose ratio)

Primary outcomes

Exacerbations requiring oral steroids

No studies reported data for this outcome.

Change from baseline in spirometry & clinic measured peak flow

FEV1: 0.03 L; 95% confidence interval -0.06 to 0.11 (four studies, N = 1322)
FVC: 0.06 L; 95% confidence interval 0.01 to 0.11(three studies, N = 970)

Given the different directions, and the statistical significance of two studies favouring BDP/BUD over ciclesonide, the disagreement between the study findings for change in FEV1 warrants some comment. Of the three studies Boulet 2006 administered a high dose treatment period prior to randomisation of 1280 µg/d of budesonide. This pretreatment of study participants may have led to a 'jump' in FEV1, making the comparison of ciclesonide to budesonide closer to a steroid withdrawal study. Therefore, rather than leading to an improvement in FEV1, Boulet 2006 showed that ciclesonide led to a smaller decline in FEV1 than budesonide. The high degree of statistical heterogeneity meant that our test for equivalence was not reliable.

Change in diary card peak flow

am PEF: 5.37 L/min; 95% confidence interval 0.12 to 10.61(four studies, N = 1329)
pm PEF: 3.95 L/min; 95% confidence interval -2.89 to 10.80 (two studies, N = 758)

These results exclude a clinically meaningful difference between these treatments and are suggestive of equivalence at CIC and BDP/BUD at 1:1 for this outcome..

Secondary outcomes

Symptoms, rescue medication use & non-specific exacerbations of asthma

Ukena 2006 and Hansel 2006 were the only studies reporting data for symptom scores, neither of which reported a statistically significant difference between treatments. Rescue medication use was reported as medians in Hansel 2006 with no statistically significant difference between treatments. Boulet 2006 reported no statistically significant difference in exacerbations of asthma between treatments.

Study withdrawal & adverse event data

Pooled effects did not indicate a significant difference in the frequency of withdrawals when considered as total number (relative risk 0.75; 95% confidence interval 0.47 to 1.19) or as withdrawal due to lack of efficacy (relative risk 1.33; 95% confidence interval 0.88 to 2.01). There was no statistically significant difference in the risk of any adverse event (relative risk 0.99; 95% confidence interval 0.85 to 1.15).

2. Ciclesonide versus BDP or BUD (1:2 ratio)

Primary outcomes

Exacerbations requiring oral steroids

No studies reported data for this outcome.

Change from baseline in spirometry & clinic measured peak flow

Intention to treat FEV1: -0.02 L; 95% confidence interval -0.05 to 0 (five studies, N = 1633); Per protocol FEV1: -0.03 L; 95% CI -0.06 to 0 (six studies, N = 1574)
FVC: -0.01 L; 95% confidence interval -0.04 to 0.03 (five studies, N = 1633)

Both the ITT and PP population estimates indicate that BDP/BUD is statistically superior to ciclesonide at twice the dose, although the lower limit of the 95% confidence interval is within the threshold value of 0.1 L of FEV1.

Change in diary card peak flow

am PEF: 0.07 L/min; 95% confidence interval -5.05 to 5.19 (four studies, N = 1423)
pm PEF: 3.29 L/min; 95% confidence interval -1.62 to 8.19 (four studies, N = 1423)

The ITT and PP population estimates for am PEF were similar, and the difference between ciclesonide and BDP/BUD was within the predefined limit of equivalence of 25 L/min.

Secondary outcomes

Quality of life, symptoms, rescue medication use & non-specific exacerbations of asthma

There was no significant difference between treatments in Paediatric AQLQ data (0; 95% confidence interval -0.09 to 0.09, two studies). Symptom score and rescue medication use data were only available as medians across the studies, and where available no statistically significant difference was reported.

Study withdrawal & adverse event data

There was no significant difference in the frequency of withdrawals (RR 1.31; 95% confidence interval 0.82 to 2.11) or as withdrawal due to lack of efficacy (RR 2.45; 95% confidence interval 0.84 to 7.13). There was no difference in the risk of any adverse event occurring (RR 1.04; 95% confidence interval 0.92 to 1.17), or specific events such as rhinitis (RR 0.37; 95% confidence interval 0.08 to 1.62, two studies), or upper respiratory tract infection (RR 1.05; 95% confidence interval 0.75 to 1.47).

3. Ciclesonide versus FP (1:1 dose ratio)

Primary outcomes

Exacerbations requiring oral steroids

There was no difference in the risk of an exacerbation requiring oral steroids between FP and CIC (0.88; 95% confidence interval 0.4 to 1.95, three studies, N = 1537).

Change from baseline in spirometry & clinic measured peak flow

FEV1: -0.02 L; 95% confidence interval -0.04 to 0.01(five studies, N = 2607)
FVC: 0; 95% confidence interval -0.04 to 0.04 (four studies, N = 2051)
PEF: L/min -1.59; 95% confidence interval -7.43 to 4.25 (three studies, N = 1611)

The ITT and PP population estimates for FEV1 were similar and were within predefined limits of equivalence.

Change in diary card peak flow

am PEF: 0.41 L/min; 95% confidence interval -4.71 to 5.53 (four studies, N = 2070)
pm PEF 1.3 L/min; 95% confidence interval -5.1 to 7.7 (two studies, N = 1043).

The ITT and PP population estimates for am PEF were similar and were within predefined limits of equivalence.

Secondary outcomes

Quality of life, symptoms, rescue medication use & non-specific exacerbations of asthma

Ciclesonide led to a significantly greater improvement in AQLQ scores compared with FP (0.17 units; 95% confidence interval 0.04 to 0.30, two studies). No significant differences between treatments was reported for asthma worsening when considered as total number (relative risk 1.1; 95% confidence interval 0.61 to 1.97). In Buhl 2006, both CIC and FP produced similar significant decreases in median asthma symptom scores after 12 weeks therapy. In addition, the analysis of asthma symptom scores and use of rescue medication revealed that the onset of treatment effects occurred within 24 hours for both treatments. This was associated with reduced rescue medication use for CIC and FP from baseline. In children (Pedersen 2006) both CIC and FP improved total asthma symptoms scores, nocturnal awakening days and rescue free days to a similar degree at 12 weeks. This result was seen in older and younger children alike independent of disease severity. In Zietkowski 2006, there was a reported reduction in asthma symptoms (day and night), and rescue use which was similar for CIC and FP. In Lipworth 2005, one patient each in the CIC (combined CIC 320 and CIC 640) and FP groups had a worsening of asthma. Rescue use and asthma symptoms were not reported in this study.

Study withdrawal & adverse event data

There was no significant difference in the frequency of withdrawals between treatments (RR 1.01; 95% confidence interval 0.79 to

1.28). Lack of efficacy leading to withdrawal was available for two studies which did not indicate that there was a significant difference between treatments, although the finding was of only marginal non-significance (RR 2.55; 95% CI 0.86 to 7.53). There was no difference in the risk of adverse events overall. Candidiasis occurred more frequently with FP than CIC (RR 0.24 (95% CI 0.1 to 0.58). Upper respiratory tract infection, pharyngitis or headache did not differ significantly between the treatments.

4. Ciclesonide versus FP (1:2 dose ratio)

Primary outcomes

Exacerbations requiring oral steroids

Magnussen 2007 reported a low number of events for this outcome (three participants in total).

Lung function

Pooled analysis was only possible for per protocol populations from Magnussen 2007 and BY9010/M1-142, which gave a mean difference of -0.05 L; 95% confidence interval -0.11 to 0.1).

Zietkowski 2006 reported that CIC at half the daily dose equivalent of FP improved FEV1 to a similar degree with no significant differences found between treatments as regards the end study FEV1 (WMD 0.08 L; 95% confidence interval -0.52 to 0.68) but the number of participants was low (N = 12). Other lung function parameters (FVC, am and pm PEF) were not reported. All studies reporting these data were conducted in adults (Zietkowski 2006; Lipworth 2005).

Secondary outcomes

Symptoms, rescue medications use & non-specific exacerbations of asthma

In Lipworth 2005, one patient each on CIC (combined results of CIC 320 and CIC 640 arms) and FP had a worsening of asthma but rescue use and asthma symptoms were not reported. Zietkowski 2006 reported significant clinical improvement, reduction in asthma symptoms with a reduction in rescue use were observed (P<0.05) in all treatment groups.

Study withdrawal & adverse event data

Pooled data for withdrawals due to adverse events was not significantly different (RR 0.62; 95% confidence interval 0.24 to 1.59).

DISCUSSION

This review assesses the relative efficacy and safety of ciclesonide at nominal equivalent one to one and nominal doubling doses of BDP/BUD and FP. We included 21 trials which assessed the effects of these drugs in 7243 participants.

Given the apparent similarity of effect between ciclesonide and FP/BDP/BUD at a dose ratio of 1:2, a logical expectation is that ciclesonide demonstrates superior efficacy to BDP/BUD or FP when compared at a dose ratio of 1:1. Pooled analysis of both intention to treat and per protocol populations from the studies fails to demonstrate this. However, consideration of study design may explain this phenomenon. The studies which assessed the effects of ciclesonide and FP/BDP/BUD at 1:1 ratios primarily recruited participants whose asthma was treated with a ceiling dose of steroid indicative of mild to moderate asthma. Where this criterion for study entry exceeded 500 µg BDP equivalent (Bateman 2007; Boulet 2006), FEV1 predicted indicated that their asthma was well-controlled at baseline.

When the comparator steroid doses assessed in the trials are considered, it is clear that the study populations were exposed to low doses of steroids in the 1:1 dose comparison studies. Of the 10 studies which contribute data to these analyses, only Adachi 2007 and Bateman 2007 compared ciclesonide to total daily doses of steroids higher than 500 µg/d BDP equivalent (BDP 800 µg/d and FP 660 µg/d respectively, *see* Table 1). In the remainder of the trials, ciclesonide and its comparator were given at doses of 400 µg BDP equivalent or lower. Thus, the range of doses of the comparator steroid in the 1:1 ratio analyses, combined with the stipulation for low dose maintenance steroid therapy prior to study entry, suggest that the studies may only have shown successful continuation of asthma control with ciclesonide that was evident prior to study entry. The lack of an effect between the study drugs in a population of generally mild to moderate asthma patients may reflect the requirement for low levels of anti-inflammatory preparations, and as such does not provide a reliable basis for extrapolating the findings to more severe patients, or to comparison between higher dose ranges. Studies which recruit asthma patients whose pre-study maintenance steroid regimens are high, or who exhibit the requirement for increasing steroid load during a run-in phase are required.

The limits of equivalence we have used may not be stable across the age groups assessed in the studies, and the limit of 100 ml for FEV1 was chosen conservatively since in paediatric populations where lung capacity is lower than in adults or adolescents, a clinically meaningful difference is likely to be lower. To date only two studies have been conducted in children under the age of 12 years (Pedersen 2006; von Berg 2007), and further trials in this population are a priority.

The relative effects of these drugs on safety outcomes should also be considered in assessing suitability of these therapies in chronic application. The main advantage of ciclesonide compared to other ICS such as BUD, BDP, and FP is that it is enzymatically converted in the lung to the principal active metabolite C21-des-methylpropionaql-ciclesonide (des-CIC), reducing the potential for local side effects in the mouth and throat. The pharmacology of the active compound (des-CIC) shows that it not only exhibits a high receptor binding activity (Lipworth 2005a) at a level between BUD and FP, but it has a high level of protein binding compared to FP (99% plasma protein bound compared to 90%) resulting in a lower free unbound ciclesonide steroid in the systemic circulation.

Ciclesonide should, therefore, lead to fewer systemic adverse events, but the only finding of note for adverse events was the significant reduction in oral candidiasis by 75% when compared with FP at a dose ratio of 1:1. The impact of reduced oral candidiasis may be significant for patients who find this particular side-effect an impediment to adherence with their ICS, although the way in which these data were obtained in the studies may overestimate the effect of ciclesonide. The monitoring of adverse events in studies primarily interested in efficacy can yield inconsistent results (Adams 2005b). The way in which candidiasis was measured and reported in the studies leaves the validity of this effect in doubt. Since prolonged ciclesonide use may have systemic effects, the monitoring of oral candida in a systematic way with fungal

throat cultures should be the standard way of confirming this. Gelfand 2006, a study included in the placebo/dose response review of ciclesonide (Manning 2008), took steps to provide confirmation of candida and reported a low event rate. The data on comparative tolerability and safety of ciclesonide with other ICS are imprecise (compared to BDP/BUD or FP). Data on longer term safety of ciclesonide in children, with particular consideration of the suppression of hypothalamic-pituitary-adrenal (HPA) axis and growth in children are required.

There are a number of limitations highlighted in this review. In particular, the characteristics of the studies and their populations are generally unsuitable to conclude equivalence across a range of doses of ciclesonide, and across different severities of asthma. Data on exacerbations defined by oral steroid treatment are lacking and further research in this area is necessary. Symptoms and quality of life were not reported consistently across the studies, and more data for these endpoints would be of value. These issues are important as they are the main purported advantages associated with ciclesonide in comparison to the other inhaled corticosteroids for asthma. Data on several key outcomes are incomplete in our analyses. This is primarily due to the lack of complete availability of data from the available studies, although analysis of three as yet unpublished studies has been possible (BY9010/M1-136; BY9010/M1-137; BY9010/M1-142).

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review provide evidence that ciclesonide is equivalent to BDP/BUD in terms of peak flow at dose ratios of 1:1, but the effect in terms of FEV1 was more inconsistent. When compared with FP, ciclesonide demonstrated equivalence in FEV1 and peak flow at dose ratios of 1:1. The patients recruited to the studies of this review were generally mild to moderate as measured by the stipulation for low doses of maintenance treatment and moderate airway obstruction. We could not establish that the use of ciclesonide provided equivalent or superior tolerability at the same doses since the confidence intervals indicated imprecise findings. The finding of lower oral candidiasis with ciclesonide compared to FP may be important for those who find this side effect troublesome. How confirmation of oral thrush was obtained was not reported across the studies, and future studies should provide better descriptions as to how and whether such procedures were undertaken.

Implications for research

Studies in children are required, and in particular the collection of data on side effects in this population. The findings in this review generally lack precision and more trials would help to establish the relative efficacy of ciclesonide and other ICS agents, before clinically meaningful effects can be ruled out. This is particularly the case in comparison with FP at half the dose. The updated GINA guidelines recommend the early addition of long-acting ß2-agonists therapy to ICS to gain control of asthma symptoms. It would be useful to determine whether the addition of LABAs to ciclesonide proves beneficial in future trials of this therapy.

ACKNOWLEDGEMENTS

We are grateful to the staff of the editorial base of the Cochrane Airways Group for providing assistance in running searches and obtaining papers. The contact author received a Cochrane Fellowship from the Health Research Board, for the island of Ireland.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adachi 2007

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 59 centres in Japan DURATION OF STUDY: 8 weeks (4 week run-in period CFC-BDP 800 mcg/day). CONCEALMENT OF ALLOCATION: Unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: No

Adachi 2007 *(Continued)*

	METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not stated METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Open label DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not stated JADAD SCORE (5-1): 1 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Not clear COMPLIANCE: Not reported CONFOUNDERS: Balanced groups at baseline
Participants	N SCREENED: 478 N RANDOMISED: 316 (213 to groups of interest to this review) N COMPLETED: Not clear M = 105; F = 108 MEAN AGE: 52.3 years BASELINE DETAILS: FEV1 69% predicted; FVC: 2.76 L INCLUSION CRITERIA: 16-75 years; moderate to severe asthma according to the Japanese Guidelines; treated with >800 mg/day CFC-BDP or > 400 mg/day of FP for more than four weeks; mean morning PEF during last week of run-in of <80% predicted PEF; reversibility of airflow limitation of >15%. EXCLUSION: Significant coexisting respiratory disease; hospitalization, emergency room care for asthma or treatment with systemic steroids < 4 weeks before run-in.
Interventions	1. Ciclesonide 200 mcg BID (400 mcg/d) 2. Ciclesonide 400 mcg BID (800 mcg/d) 3. Beclomethasone 400 mcg BID (800 mcg/d) DELIVERY: CIC: HFA-MDI; BDP: CFC-MDI + spacer TREATMENT PERIOD: 8 weeks RESCUE: SABA CO-INTERVENTIONS PERMITTED: Not stated % on ICS baseline: 100
Outcomes	am PEF; pm PEF; FEV1; FVC; symptoms; use of rescue medication
Notes	

Risk of bias

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

Adler 2006

Methods	STUDY DESIGN: Parallel group - pilot study LOCATION, NUMBER OF CENTRES: Multicentre DURATION OF STUDY: 12 months (2 week run-in on FP 250 mcg/d) CONCEALMENT OF ALLOCATION: Unknown COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not reported DESCRIPTION OF WITHDRAWALS/DROPOUTS: No JADAD SCORE (5-1): 2 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT (presumed as most likely) COMPLIANCE: Not reported CONFOUNDERS: Not reported

Adler 2006 *(Continued)*

Participants	N SCREENED: Unknown N RANDOMISED: 111 N COMPLETED: Unknown M = unknown; F = unknown MEDIAN AGE: Range 17-75 years BASELINE DETAILS: Not reported INCLUSION CRITERIA: Stable asthma; FEV1 >= 90% EXCLUSION: Not reported
Interventions	1. Ciclesonide 200 mcg OD (CIC 200) 2. Fluticasone 250 mcg BID (FP 500) DELIVERY: CIC: HFA-MDI; FP MDI TREATMENT PERIOD: 12 weeks RESCUE: Not reported CO-INTERVENTIONS PERMITTED: Not reported CO-INTERVENTIONS: Not reported % on ICS baseline: Not reported
Outcomes	% days without asthma symptoms; % days without asthma symptoms or rescue
Notes	Unpublished conference abstract

Risk of bias

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

Bateman 2007

Methods	STUDY DESIGN: Randomised parallel group trial LOCATION, NUMBER OF CENTRES: 100 centres in North America and Europe DURATION OF STUDY: Six months CONCEALMENT OF ALLOCATION: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: No METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Centralised, automated facsimile system (Fisher Automated Clinical Trial Service [FACTS]. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Open label DESCRIPTION OF WITHDRAWALS/DROPOUTS: Stated TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT
Participants	N SCREENED: 658 N RANDOMISED: 528 (CIC: 255; FP: 273) N COMPLETED: 447 M = 206 F = 322 MEAN AGE: 43 BASELINE DETAILS: FEV1 predicted: 93%; Baseline AQLQ score: 5.79 INCLUSION CRITERIA: 12-75 years; 6 month history of ATS defined asthma; FP 500-1000 mg/day or equivalent; FEV1 greater than 80% predicted, measured 4h post-SABA and 24 h post-other asthma medication. Post-run in: FEV1 greater than 80% predicted; reversibility of greater than 12% (and greater than 0.200 L), or diurnal PEF greater than 15% during 3 or more days within the last week of run-in. At least 1 day without any asthma symptoms during the last 7 days prior to baseline.

Bateman 2007 *(Continued)*

	EXCLUSION CRITERIA: Coexisting severe diseases; COPD and/or other relevant lung diseases other than asthma; use of systemic steroids within 4 weeks (injectable depot steroids, 6 weeks) prior study or more than three times during previous 6 months; use of non-allowed drugs, including corticosteroids other than specified in the inclusion criteria, ketotifen, inhaled anticholinergics, disodium cromoglycate and nedocromil, and bronchoconstrictive agents, including ß-blockers. Patients with more than 10 cigarette pack-years (ex-smokers or current smokers).
Interventions	1. Ciclesonide 400 mcg BID (800 mcg/d) 2. Fluticasone 330 mcg BID (660 mcg/d) DELIVERY: HFA-metered dose inhalers RUN-IN PERIOD: Two weeks on current ICS therapy (500-1000 mcg/d FP equivalent) TREATMENT PERIOD: Six months RESCUE: Salbutamol CO-INTERVENTIONS: Usual pre-study interventions permitted (LABAs, oral ß2-agonists, theophylline, leukotriene antagonists or lipoxygenase inhibitors).
Outcomes	FEV1; am PEF; symptoms; quality of life (AQLQ); exacerbations; withdrawal
Notes	

Risk of bias

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

Bernstein 2004

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Multicentre DURATION OF STUDY: 12 weeks (run-in unclear) CONCEALMENT OF ALLOCATION: Not reported COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not reported DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not reported JADAD SCORE (5-1): 2 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT(presumed) COMPLIANCE: Not reported CONFOUNDERS: Not reported.
Participants	N SCREENED: Not reported N RANDOMISED: 531 N COMPLETED: Not reported M = unknown; F = unknown MEDIAN AGE: Not reported BASELINE DETAILS: Not reported INCLUSION CRITERIA: Moderate-severe asthma for 6 months or more; FEV1 of 40-65%; age >= 12 years. EXCLUSION: unknown
Interventions	1. Ciclesonide 200 mcg BID (CIC400) 2. Ciclesonide 400 mcg BID (CIC800) 3. Fluticasone 500 mcg BID (FP1000) 4. Placebo

Bernstein 2004 *(Continued)*

	DELIVERY: CIC: MDI; FP CFC-MDI TREATMENT PERIOD: 12 weeks RESCUE: unknown CO-INTERVENTIONS PERMITTED: Not reported CO-INTERVENTIONS: Not reported % on ICS baseline: Not reported
Outcomes	FEV1; am PEF; AQLQ symptom score; adverse events
Notes	Unpublished conference abstract

Risk of bias

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

Boulet 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Europe and Canada, 64 centres. DURATION OF STUDY: 12 weeks (2 week run-in on usual dose of ICS, with high dose ICS during a post-run in baseline period prior to study entry) CONCEALMENT OF ALLOCATION: Adequate COCHRANE QUALITY SCORE: DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Yes (computer generated list) METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: yes (double dummy) DESCRIPTION OF WITHDRAWALS/DROPOUTS: Yes JADAD SCORE (5-1): 5 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported CONFOUNDERS: Baseline values showed older, more females, fewer non-smokers, higher baseline dose of ICS, lower FEV1, and greater reversibility in BUD group
Participants	N SCREENED: 688 N RANDOMISED: 359 N COMPLETED: 320 (PP) and 359 (ITT analysis) M = 148; F = 211 MEDIAN AGE (range): CIC320 39 years (12-72); BUD320 42 (12-71) BASELINE DETAILS: FEV1 (% Pred): CIC320 2.60 (81%); BUD320 2.43 (79%) INCLUSION CRITERIA: Aged 12-75 years; persistent asthma for 6 months ATS definition; FEV1 of 65-95% depending on ICS pretreatment at baseline of 320-640 ug BUD and the addition of other controller meds (LABA, LTAs or equivalent). To enter treatment period patients had to also demonstrate improvement in FEV1 during pretreatment period of >= 7% or 150 mls following the increase in their daily ICS dose of 320-640 ug BUD (or the equivalent) to 1280 mcg BUD. EXCLUSION: Concomitant severe diseases or contraindications to ICS use; abnormal lab tests suggesting disease; Use of systemic steroids within 4 weeks or injectable steroids within 6 weeks of baseline or more than 3 times within last 6 months or had an asthma exacerbation, LRTI or asthma hospitalisation within 4 weeks of baseline. Had other lung disease or COPD, or heavy smokers or ex-smokers with smoking history >= 10 cigs per day or two pipes per day; suspected noncompliance; drug abuse;or pregnancy.
Interventions	1. Ciclesonide 400 mcg OD 2. Budesonide 400 mcg OD DELIVERY: CIC: HFA-MDI (no spacer), BUD: Turbohaler in morning

Boulet 2006 *(Continued)*

	TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol MDI CO-INTERVENTIONS PERMITTED: None % on ICS baseline: not indicated (but it would appear to be all patients)
Outcomes	FEV1; FVC; am PEF; pm PEF; clinic PEF; adverse events; exacerbations; withdrawals
Notes	

Risk of bias

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

Boulet 2007

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 59 centres in North America, Europe, South Africa DURATION OF STUDY: 12 weeks (1-4 week run in on usual steroid; non-steroidal preventer medication was ceased) CONCEALMENT OF ALLOCATION: Adequate COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Centralised, automated randomisation programme. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double-dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: Stated JADAD SCORE (5-1): 5 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported CONFOUNDERS: Baseline values comparable.
Participants	N SCREENED: Not clear (637 enrolled in run-in period) N RANDOMISED: 474 (CIC: 234; FP: 240) N COMPLETED: 420 M = 182 F = 290 MEAN AGE: 39 years BASELINE DETAILS: Duration of symptoms: 15 years; allergic rhinitis: 23/35 participants INCLUSION CRITERIA: 12-75 years; ATS defined asthma (6 months); constant dose and type of asthma medication in 4 weeks prior to run-in; moderate asthma based on GINA 2002 classifications; FEV1 60-80% predicted if managed with bronchodilators or non-steroidal preventer medication; FEV1 > 80% predicted if treated with FP </= 250 mg/day or equivalent; FEV1 > 80% predicted and asthma symptoms in previous 7 days if treated with FP > 250 and <500 mg/day or equivalent; FEV1 > 85% predicted and asthma symptoms in previous 7 days if treated with FP </= 250 mg/day or equivalent in combination with LABA or theophylline treatment. Post-run in criteria: Patients previously using bronchodilators or non-steroidal preventer medication without concomitant ICS use had to have FEV1 60-80% predicted and symptoms (total and nocturnal symptoms) during last 7 days of run-in period; Patients previously using ICS had to have an FEV1 >80% predicted and nocturnal symptoms, asthma symptoms more than once but not daily, not used rescue medication daily; Reversibility demonstrated during the run-in period (if not achieved then historical reversibility accepted). EXCLUSION: Clinically relevant abnormal laboratory values; use of systemic steroids in previous 4 weeks; pregnancy, breast feeding or not using reliable contraception; current/former smoking status of 10 or more cigarette pack years.

Boulet 2007 *(Continued)*

Interventions	1. Ciclesonide OD 400 mcg in evening (+ dummy DPI) 2. Fluticasone BID 200 mcg (+ dummy MDI) DELIVERY: CIC: MDI; FP: DPI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: Not reported. CO-INTERVENTIONS: Not listed. % on ICS pre-baseline: 70
Outcomes	FEV1 L; FEV1 predicted; FVC; am PEF; pm PEF; AQLQ; symptoms; adverse events; withdrawals
Notes	

Risk of bias

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

Buhl 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Europe and South Africa, 57 centres. DURATION OF STUDY: 12 weeks (1-4 week run-in with suspension of usual ICS) CONCEALMENT OF ALLOCATION: Unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: yes appropriate (double dummy) DESCRIPTION OF WITHDRAWALS/DROPOUTS: Yes JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported CONFOUNDERS: Baseline values comparable. Note: Patients in two treatment groups were balanced with regard to prior use of ICS and other treatment medications (unclear how this was done).
Participants	N SCREENED: 644 N RANDOMISED: 529 N COMPLETED: 451 (PP) but with 529 (ITT analysis) M = 224; F = 305 MEDIAN AGE (range): CIC160 41 years (12-74); FP88 38 (12-74) BASELINE DETAILS: FEV1 (% Pred): CIC160 2.383 (75%); FP88 2.440 (75%) INCLUSION CRITERIA: Aged 12-75 years; persistent asthma for 6 months ATS definition; previous use of ICS for 6 months (constant dose up to 500 ug/day BDP or equivalent for 4 weeks and an FEV1 of 80-100% pred. At randomisation patients were required to have FEV1 50-90% after rescue was withheld for 4 hours and a decrease in FEV1 >= 10% after ICS withdrawal and a reversibility of FEV1 >= 15% after 2-4 puffs salbutamol or a diurnal variation in PEF of 15% during baseline period. EXCLUSION: Use of systemic steroids within 4 weeks of baseline or more than 3 times within last 6 months or had an asthma exacerbation, LRTI or asthma hospitalisation within 4 weeks. Had other lung disease such as COPD, or significant smoking history >= 10 pack years. "
Interventions	1. Ciclesonide 200 mcg OD in evening (double dummy placebo) 2. Fluticasone 100 mcg BID DELIVERY: CIC: MDI, FP: HFA MDI

Buhl 2006 *(Continued)*

	TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol MDI CO-INTERVENTIONS PERMITTED: None % on ICS baseline: 0
Outcomes	FEV1; am PEF; rescue medication use; adverse events; withdrawals
Notes	

Risk of bias

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

BY9010/M1-136

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Korea, 16 centres DURATION OF STUDY: 12 weeks (4 weeks run-in, prn SABA) CONCEALMENT OF ALLOCATION: unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: yes DESCRIBED AS DOUBLE BLIND: yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: not described METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: double dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: not stated JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Per protocol COMPLIANCE: not assessedCONFOUNDERS: not clear
Participants	N SCREENED: Not reported N RANDOMISED: 249 N COMPLETED: not clear M = 39%; F = 61% MEDIAN AGE: 42 years BASELINE DETAILS: FEV1 79% predicted INCLUSION CRITERIA: 18-75 years; ATS defined asthma; Korean descent; treatment with ICS (maximum FP250 mcg/d); FEV1 80-105% predicted prior to run-in (60-90% post run-in) EXCLUSION: not stated
Interventions	1. Ciclesonide 200 mcg OD 2. Budesonide 400 mcg OD DELIVERY: Ciclesonide: MDI; Budesonide: Turbohaler TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: prn SABA CO-INTERVENTIONS: Not stated % on ICS at baseline: 100
Outcomes	FEV1; am & pm PEF; safety
Notes	Unpublished data set available from http://www.clinicalstudyresults.org

Risk of bias

Bias	Authors' judgement	Support for judgement

BY9010/M1-136 *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

BY9010/M1-137

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 9 centres in Taiwan and Malaysia DURATION OF STUDY: 12 weeks (prn SABA) CONCEALMENT OF ALLOCATION: Not clear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double-dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not reported JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Per protocol and ITT COMPLIANCE: Not assessed CONFOUNDERS: Groups balanced at baseline
Participants	N SCREENED: Not reported N RANDOMISED: 125 N COMPLETED: Not reported M = not reported F = not reported MEAN AGE: 48 BASELINE DETAILS: FEV1 72% predicted INCLUSION CRITERIA: 18- 75 years; ATS defined asthma for at least 6 months; treatment with ICS for 4 weeks (maximum 250mcg fluticasone propionate or equivalent); FEV1 80-105% of predicted.
Interventions	1. Ciclesonide 200 mcg OD 2. Budesonide 400 mcg OD DELIVERY: Ciclesonide: MDI; Budesonide: Turbohaler TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: prn SABA CO-INTERVENTIONS: Not reported % on ICS at baseline: 100
Outcomes	FEV1; FVC; symptoms; adverse events
Notes	Unpublished data set available from http://www.clinicalstudyresults.org

Risk of bias

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

BY9010/M1-142

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 48 centres in Europe and Canada DURATION OF STUDY: 24 weeks

BY9010/M1-142 *(Continued)*

	CONCEALMENT OF ALLOCATION: Not clear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not clear METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not stated JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Per protocol and ITT COMPLIANCE: Not assessed CONFOUNDERS: Groups balanced at baseline
Participants	N SCREENED: Not reported N RANDOMISED: 480 N COMPLETED: Not reported M = 190 F = 290 MEDIAN AGE: 42 years BASELINE DETAILS: 76% predicted INCLUSION CRITERIA: 12-75 years; history of asthma for 6 months; treatment with ICS for 4 weeks (maximum daily dose of 250 mcg fluticasone propionate); FEV1: 80-105% predicted EXCLUSION CRITERIA: Not reported
Interventions	1. Ciclesonide 100 mcg OD 2. Fluticasone 100 mcg BID DELIVERY: Ciclesonide: MDI; TREATMENT PERIOD: 24 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: prn SABA % on ICS at baseline: 100
Outcomes	FEV1; FVC; am PEF; pm PEF; symptoms; adverse events
Notes	Unpublished data set available from http://www.clinicalstudyresults.org

Risk of bias

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

Hansel 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Europe, 62 centres. DURATION OF STUDY: 12 weeks (1-4 week run-in on prn SABA) CONCEALMENT OF ALLOCATION: Not reported COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes to ciclesonide dose but open label for BUD (no BUD placebo available) METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Yes (computer generated randomisation list) METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Appropriate for CIC arms DESCRIPTION OF WITHDRAWALS/DROPOUTS: yes JADAD SCORE (5-1): 5 (CIC v CIC); 3 (CIC v BUD)

Hansel 2006 *(Continued)*

	TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported CONFOUNDERS: Baseline values comparable
Participants	N SCREENED: 684 N RANDOMISED: 554 N COMPLETED: 490 (64 withdrawn). 49 excluded from PP analysis (protocol violations) M = 301; F = 253 MEDIAN AGE (range): CIC80 38 years (12-73); CIC320 41 (14-74); BUD 45 (13-73) BASELINE DETAILS: FEV1 (% Pred): CIC80 2.48 (73%); CIC320 2.46 (72%); BUD 2.42 (72%) INCLUSION CRITERIA: Aged 12-75 years; mild to moderate persistent asthma of over 6 months duration according to ATS criteria including asthma symptoms and spontaneous fluctuations in obstruction. EXCLUSION: Oral or systemic steroid use within 4 weeks of screening or more than 3 times during preceding 6 months; inhaled daily dose of BDP > 500 ug or equivalent steroids within 4 weeks of screening, contraindication to inhaled corticosteroids use, hypersensitivity to study meds, asthma exacerbation or LRTI within 4 weeks of screening, COPD or other relevant respiratory disease, pregnancy, breast feeding, lack of contraceptive in women of child bearing potential, inability to follow study procedures, with clinically relevant lab values suggestive of disease.
Interventions	1. Ciclesonide 100 mcg OD 2. Ciclesonide 400 mcg OD 3. BUD 200 mcg BD (open labelled) DELIVERY: HFA-MDI (CIC) and Turbohaler (BUD) TREATMENT PERIOD: 12 weeks RESCUE: SABA salbutamol or terbutaline CO-INTERVENTIONS PERMITTED: rescue only (withdrawal if asthma exacerbation needing oral or systemic steroids, other ICS) % on ICS (pre-run in): 0
Outcomes	FEV1; am PEF; asthma symptom score, rescue medication use; adverse events; 24-hour urinary cortisols (HPA-axis)
Notes	

Risk of bias

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

Lee 2004

Methods	STUDY DESIGN: Crossover LOCATION, NUMBER OF CENTRES: Single centre in Scotland DURATION OF STUDY: 4 weeks CONCEALMENT OF ALLOCATION: Not reported COCHRANE QUALITY SCORE: DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double dummy (identical devices used). DESCRIPTION OF WITHDRAWALS/DROPOUTS: 9/28 JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Bonferroni correction set at 95% CI in order to obviate pairwise comparisons. COMPLIANCE: Not reported.

Lee 2004 *(Continued)*

	CONFOUNDERS: Not reported.
Participants	N SCREENED: Not reported. N RANDOMISED: 28 N COMPLETED: 19 M = 9 F = 10 MEAN AGE: 45 years BASELINE DETAILS: FEV1 predicted 84%; am PEF: 470 L/min; rescue medication usage: 0.2 puffs/d; AQLQ: 6.15 INCLUSION CRITERIA: Non-smokers, mild-moderate asthma; stable for three months prior to study entry; BDP equivalent 2000mcg/d (half of this if used in conjunction with additional controller therapy). EXCLUSION: Oral steroids or antibiotics in 3 months prior to study entry
Interventions	1. Ciclesonide 400mcg OD 2. Fluticasone 250mcg BID DELIVERY: CIC: HAD-MDI; FP: Evohaler TREATMENT PERIOD: 2 x 4 week treatment periods RESCUE: Not clear. CO-INTERVENTIONS PERMITTED: Montelukast and Salmeterol given during washout phase to prevent withdrawals. CO-INTERVENTIONS: Montelukast and Serevent. % on ICS baseline: 100
Outcomes	Methacholine challenge; FEV1; am PEF; pm PEF; symptoms; rescue medication; AQLQ
Notes	

Risk of bias

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

Lee 2005

Methods	STUDY DESIGN: Crossover. LOCATION, NUMBER OF CENTRES: One centre in Scotland. DURATION OF STUDY: 2 x 4 week treatment periods (2 week washout). CONCEALMENT OF ALLOCATION: Unclear. COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double dummy. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 6/20 JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Bonferroni correction set at 95% CI in order to obviate pairwise comparisons. COMPLIANCE: 90% compliance required in order for data to be analysed. CONFOUNDERS: NA
Participants	N SCREENED: Not reported N RANDOMISED: 20 N COMPLETED: 14 M = 9

Lee 2005 *(Continued)*

	F = 5 MEAN AGE: 47 BASELINE DETAILS: FEV1 2.44l; FEV1 predicted: 77%. INCLUSION CRITERIA: Non-smokers with moderate persistent asthma; stable for three months prior to study entry; BDP equivalent 2000mcg/d (half of this if used in conjunction with additional controller therapy); 20% fall in FEV1 following < 0.4 mg/ml EXCLUSION: Oral steroids or antibiotics in 3 months prior to study entry
Interventions	1. Ciclesonide 800 mcg BID 2. Fluticasone 1000 mcg BID DELIVERY: CIC: HAD-MDI; FP: Evohaler TREATMENT PERIOD: 2 x 4 week treatment periods RESCUE: Not clear. CO-INTERVENTIONS PERMITTED: Montelukast and Salmeterol given during washout phase to prevent withdrawals. CO-INTERVENTIONS: Montelukast and Serevent. % on ICS baseline: 100
Outcomes	HPA axis; FEV1; methacholine challenge; am PEF; pm PEF; asthma symptoms; rescue medication puffs/d; AQLQ
Notes	

Risk of bias

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

Lipworth 2005

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA, 20 centres. DURATION OF STUDY: 12 weeks (no run-in described) CONCEALMENT OF ALLOCATION: Unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Identical inhaler devices DESCRIPTION OF WITHDRAWALS/DROPOUTS: Reported JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Similar across treatment groups (assessed by canister weight) CONFOUNDERS: Baseline characteristics comparable.
Participants	N SCREENED: Not reported. N RANDOMISED: 164 N COMPLETED: 148 M= 79; F= 85 MEAN AGE: 37 BASELINE DETAILS: FEV1: 3L; FEV1 predicted: 81% INCLUSION CRITERIA: >/-18 years; mild to moderate persistent asthma; acceptable inhaler technique; SABA only for 6 months (at least 2 x daily); FEV1 >/=70% predicted. Females taking oral contraceptives and HRT were required to have an increase in serum cortisol levels of 7mcg/dL or greater from basal to peak levels. EXCLUSION: Systemic steroid use within 6 months of screening; inhaled steroids within 2 months.

Lipworth 2005 *(Continued)*

Interventions	1. Ciclesonide 400mcg OD 2. Ciclesonide 400mcg BID 3. Fluticasone 500mcg BID 4. Placebo DELIVERY: CIC: HFA MDI without a spacer; FP: CFC MDI without a spacer. TREATMENT PERIOD: 12 weeks RESCUE: Not reported CO-INTERVENTIONS PERMITTED: None permitted % on ICS baseline: 0
Outcomes	Hypothalmic pituitary axis function; serum cortisol; safety
Notes	

Risk of bias

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

Magnussen 2007

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Europe, number of centres not reported DURATION OF STUDY: 12 weeks (1-4 weeks prn SABA) CONCEALMENT OF ALLOCATION: Unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Both treatments given via MDIs DESCRIPTION OF WITHDRAWALS/DROPOUTS: Stated JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT and PP COMPLIANCE: Not reported CONFOUNDERS: Balanced groups at baseline
Participants	N SCREENED: Not reported N RANDOMISED: 808 N COMPLETED: 764 M = 409; F = 398 MEDIAN AGE: 29-33 BASELINE DETAILS: FEV1 predicted: 79%; reversibility: 25% INCLUSION CRITERIA: ATS defined asthma; 12-75 years; 61-90% predicted (if treated with ICS), or 61-105% predicted if not treated with ICS; maximum daily dose was FP 250 mcg; post-run in participants had to demonstrate FEV1 between 60-90% predicted. EXCLUSION: Concomitant severe disease; smoking history of >10 pack years; LABA or OCS treatment in previous 4 weeks.
Interventions	1. Ciclesonide 100 mcg OD 2. Ciclesonide 200 mcg OD 3. Fluticasone 100 mcg BID DELIVERY: MDI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol

Magnussen 2007 *(Continued)*

	CO-INTERVENTIONS PERMITTED: Not reported CO-INTERVENTIONS: Not reported % on ICS: Not reported
Outcomes	FEV1; peak flow; asthma symptoms; asthma exacerbations requiring oral steroids
Notes	

Risk of bias

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

Niphadkar 2005a

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: India, 11 centres DURATION OF STUDY: 12 weeks (2 week run-in on BUD 400 mcg/d) CONCEALMENT OF ALLOCATION: Adequate. COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Computer-generated randomisation schedule. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double-dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: Reported JADAD SCORE (5-1): 5 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed CONFOUNDERS: Baseline characteristics similar.
Participants	N SCREENED: Not reported N RANDOMISED: 473 participants enrolled (405 randomised, 403 received treatment: CIC160 am: 140; CIC160 pm: 131; BUD200: 134) N COMPLETED: 370 M = 213; F = 190 MEDIAN AGE: 31 BASELINE DETAILS: FEV1: 2.2L; FEV1 predicted: 93%; PEF: 320L/min. Concomitant therapy: LABA: 105; Xanthines: 62; ICS and LABA (separate): 54; antihistamine: 37; nasal steroids: 24. INCLUSION CRITERIA: 18-69 years; diagnosis of persistent asthma (at least 6 months); maintenance ICS (BDP equivalent up to 500mcg/d); FEV1 predicted >/=70%. Post-run in phase, participants were required to have stable asthma (low variation in PEF; no more than four puffs of rescue medication on more than two consecutive days). EXCLUSION: Use of systemic steroids, asthma exacerbation or hospitalisation with asthma in 4 weeks before study entry; COPD; pregnancy/lactation.
Interventions	1. Ciclesonide 200 mcg OD (am) 2. Budesonide 200 mcg BID DELIVERY: HFA-MDI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: LABAs, oral beta-agonists, leukotriene agents, theophylline, SCG, nedocromil. CO-INTERVENTIONS: Not reported % on ICS: 100

Niphadkar 2005a *(Continued)*

Outcomes	FEV1; FVC; am PEF; pm PEF; symptoms; rescue medication use; withdrawals; adverse events
Notes	

Risk of bias

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

Niphadkar 2005b

Methods	See above.
Participants	See above.
Interventions	1. Ciclesonide 200 mcg OD (pm) 2. Budesonide 200 mcg BID See above
Outcomes	FEV1; FVC; am PEF; pm PEF; symptoms; rescue medication use; withdrawals; adverse events
Notes	Created as secondary reference to Niphadkar 2005 (am) due to additional treatment arm in this trial (pm administration of ciclesonide)

Risk of bias

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

Pedersen 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 51 centres in Europe, South Africa and Canada. DURATION OF STUDY: 12 weeks (2-4 week run in on prn SABA) CONCEALMENT OF ALLOCATION: Adequate COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Computer-generated randomisation schedule from manufacturer. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Identical inhaler devices. DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not reported JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed CONFOUNDERS: Baseline characteristics comparable.
Participants	N SCREENED: Not reported N RANDOMISED: 728 (N meeting post-run in criteria and subsequently analysed: 556. Baseline details given for per-protocol set. CIC: 277; FP279) N COMPLETED: Not reported. M = 331; F = 180

Pedersen 2006 *(Continued)*

	MEDIAN AGE: 10 BASELINE DETAILS: Add-on therapy prior to baseline: 147; ICS therapy prior to baseline: 332; mean ICS dose: 390mcg/d; FEV1: 1.7L; FEV1 predicted: 80%; am PEF: 257L; Mean FEV1 reversibility: 20% INCLUSION CRITERIA: 6-15 years; persistent asthma for at least six months (ATS criteria); clinically stable for four weeks prior to study entry; FEV1 predicted: 50-90% rescue medication only, 80-100% in patients treated with ICS only; symptom score >1 on 6 of last 10 days of run in; adequate MDI inhaler device technique without spacer. EXCLUSION: History of life-threatening asthma; two or more inpatient hospitalisations in previous year; >60 days of systemic steroids in past year >400mcg BUD or equivalent/d in 30 days prior to baseline; >8 puffs SABA/d for three consecutive days during run-in."
Interventions	1. Ciclesonide 100 mcg BID 2. Fluticasone 100 mcg BID DELIVERY: HFA-MDI TREATMENT PERIOD: 12 weeks (2-4 week run-in) RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: Not reported. CO-INTERVENTIONS: Not listed % on ICS (pre-baseline): 65%
Outcomes	FEV1; clinic PEF; am PEF; pm PEF; symptoms; rescue medication usage; adverse events
Notes	

Risk of bias

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

Ukena 2006

Methods	STUDY DESIGN: Parallel group. LOCATION, NUMBER OF CENTRES: 43 centres in three countries in Western Europe DURATION OF STUDY: 12 weeks (1-4 weeks run-in on prn SABA) CONCEALMENT OF ALLOCATION: Unclear. COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported. METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double-dummy. DESCRIPTION OF WITHDRAWALS/DROPOUTS: Reported JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed. CONFOUNDERS: Baseline characteristics comparable.
Participants	N SCREENED: Not reported. N RANDOMISED: 437 (ITT based on 399 participants: CIC: 198; BUD: 201) N COMPLETED: 371 M = 183; F = 216 MEDIAN AGE: 45 BASELINE DETAILS: FEV1 L: 2.33; FEV1 predicted: 72%; am PEF predicted: 78%; PEF variability: 12% INCLUSION CRITERIA: 12-75 years; asthma for at least six months (ATS criteria); </= 500 mcg/d BDP equivalent; stable regimen of additional anti-asthma medication if this was used; participants on prn SABA were allowed to participate. Post-run in period: FEV1: 50-90% predicted; Participants treated with ICS had to demonstrate a fall in FEV1 predicted of >/=10%; reversibility if >/= 15% FEV1 post-SABA.

Ukena 2006 *(Continued)*

	EXCLUSION: Exacerbation/lower RTI in four weeks prior to randomisation.
Interventions	1. Ciclesonide 400 mcg OD 2. Budesonide 400 mcg OD DELIVERY: CIC: HFA-MDI; BUD: DPI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: leukotriene agents, theophyllines CO-INTERVENTIONS: Not listed % on ICS: 38% pre-treated with ICS
Outcomes	FEV1; FVC; clinic PEF; am PEF; pm PEF; symptoms; rescue medication use; adverse events
Notes	

Risk of bias

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

Vermeulen 2007

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 31 centres in Europe and South Africa DURATION OF STUDY: 12 weeks (2 week baseline period – BUD 400 mcg/d) CONCEALMENT OF ALLOCATION: Adequate COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Computer-generated randomisation schedule METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: Stated JADAD SCORE (5-1): 5 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT and per protocol COMPLIANCE: Not reported CONFOUNDERS: Groups balanced at baseline
Participants	N SCREENED: 431 N RANDOMISED: 403 (CIC: 272; BUD: 131) N COMPLETED: 384 M = 272; F = 131 MEDIAN AGE: 14 BASELINE DETAILS: FEV1 73% predicted INCLUSION CRITERIA: 12-17 years old; FEV1 50-80% predicted; severe asthma (GINA 2003 definition); Not well controlled after constant treatment with fixed dose BUD 400 mg/day (or equivalent) 4 weeks prior to study entry with FEV1 45% to 80% predicted; Alternatively constant treatment with fixed dose BUD 400 to 800 mg/day (or equivalent) 4 weeks prior to study entry, with FEV1 46% to 85% predicted; Entry into treatment period at randomization (baseline), FEV1 50% to80% predicted, FEV1 reversibility > 15% salbutamol. EXCLUSION: Oral steroids within 4 weeks of study entry; concomitant severe diseases; relevant lung diseases or clinically relevant abnormal laboratory values; > 10 cigarette pack-year smoking history; females of child-bearing potential without contraception.
Interventions	1. Ciclesonide 400 mcg OD

Vermeulen 2007 *(Continued)*

	2. Budesonide 800 mcg OD DELIVERY: HFA-MDI (CIC); DPI (BUD) TREATMENT PERIOD: 12 weeks RESCUE: Not reported CO-INTERVENTIONS PERMITTED: Not reported CO-INTERVENTIONS: Not reported % on ICS: 100
Outcomes	FEV1; PEF; 24hr urinary free concentrations
Notes	

Risk of bias

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

von Berg 2007

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 59 centres in Europe and South Africa DURATION OF STUDY: 12 weeks (2-4 run in period prn SABA only) CONCEALMENT OF ALLOCATION: Unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not reported DESCRIPTION OF WITHDRAWALS/DROPOUTS: Stated JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT and per protocol. COMPLIANCE: Not reported. CONFOUNDERS: Not reported.
Participants	N SCREENED: 774 N RANDOMISED: 621 (CIC: 416; BUD: 205) N COMPLETED: M = 395; F = 226 MEAN AGE: 9 years BASELINE DETAILS: FEV1 78% predicted; ICS treatment: 51% INCLUSION CRITERIA: 6-11 years; diagnosis of persistent asthma for 6 months; FEV1 >50% to 90% predicted if rescue medication only, >50% to 100% predicted if using constant dose of controller medication other than steroids for 1 month; 80% to 105% predicted if using </=400 mcg/d BDP equivalent for 1 month before inclusion. Post-run-in: FEV1 50-90% predicted after withholding SABA for at least four hours; reversibility of FEV1 >12% of initial post-SABA; asthma symptom scores >1 on at least six of previous 10 days or use of >8 puffs of rescue medication during the previous 10 days. EXCLUSION: History of life-threatening asthma, concomitant severe diseases; two or more hospitalizations for asthma within previous 12 months; asthma exacerbation during four weeks before baseline; systemic corticosteroids during 30 days before baseline; use of systemic steroids for more than 60 days within the previous 2 years; participation in another study within 30 days before baseline. No other asthma medication permitted during study.
Interventions	1. Ciclesonide 200 mcg OD 2. Budesonide 400 mcg OD

von Berg 2007 *(Continued)*

	DELIVERY: CIC: HFA-MDI (+ Aerochamber); BUD: DPI. TREATMENT PERIOD: 12 weeks RESCUE: Not reported CO-INTERVENTIONS PERMITTED: None CO-INTERVENTIONS: NA % on ICS: Not reported. 52
Outcomes	FEV1; Peak flow; asthma symptoms; rescue medication; bone growth; 24hr urinary cortisol; adverse events.
Notes	

Risk of bias

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

Zietkowski 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: One centre in Poland. DURATION OF STUDY: 12 weeks (1-4 week run in on prn SABA) CONCEALMENT OF ALLOCATION: Unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Double-dummy DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not reported JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Assumed available case. COMPLIANCE: Not reported CONFOUNDERS: Baseline values comparable.
Participants	N SCREENED: Not clear N RANDOMISED: 35 (CIC80: 12; CIC160: 12; FP200: 11) N COMPLETED: 35 M = 19; F = 16 MEAN AGE: 45 years BASELINE DETAILS: Duration of symptoms: 15 years; allergic rhinitis: 23/35 participants INCLUSION CRITERIA: Mild allergic asthma (according to GINA guidelines); free from exacerbations in previous four weeks; non-smokers; treatment with FP equivalent 250mcg/d. EXCLUSION: Not reported.
Interventions	1. Ciclesonide 100 mcg OD 2. Ciclesonide 200 mcg OD 3. Fluticasone 100 mcg BID DELIVERY: unclear TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: Not reported. CO-INTERVENTIONS: Not listed. % on ICS pre-baseline: 100.
Outcomes	FEV1 L; FEV1 predicted; symptoms; rescue medication use

Zietkowski 2006 *(Continued)*

Notes

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

AQLQ: Asthma quality of life questionnaire; ATS: American Thoracic Society; BDP: beclomethasone dipropionate; BID: twice daily; BUD: budesonide; CFC-MDI: Chlorofluorocarbon metered dose inhaler; CIC: Ciclesonide; COPD: Chronic obstructive pulmonary disease; DPI: Dry powder inhaler device; FEV1: forced expiratory volume in one second; FP: fluticasone propionate; FVC: forced vital capacity; GINA: Global initiative for asthma; HFA-MDI: Hydro-fluoroalkane metered dose inhaler;
HPA: hypothalamic-pituitary-adrenal; ICS: inhaled corticosteroids; ITT: intention-to-treat; LABA: Long-acting beta2-agonist; MDI: metered dose inhaler; OCS: oral corticosteroids; OD: once daily; PEF: peak expiratory flow; PP: per-protocol; RTI: respiratory tract-infection; SABA: short-acting beta-agonist; SCG: sodium cromoglycate

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

Study	Reason for exclusion
Agertoft 2005	Treatment < 4 weeks
Bethke 2002	Healthy volunteers
Dahl 1998	Treatment < 4 weeks
Derom 2005	Treatment < 4 weeks
Drollman 2004	Treatment < 4 weeks
Erin 2005	Treatment < 4 weeks
Gauvreau 2005	Treatment < 4 weeks
Kanniess 2001	Treatment < 4 weeks
Larsen 2003	Treatment < 4 weeks
Postma 2001	Morning versus evening administration
Richter 2005	Treatment < 4 weeks
Subbarao 2006	Treatment < 4 weeks
Szefler 2005	Inpatient administration
Taylor 1999	Treatment < 4 weeks

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

Arshad

Trial name or title	An assessment of safety and efficacy in treating moderate to severe asthmatics with inhaled Ciclesonide vs Fluticasone
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Beck

Trial name or title	Efficacy and safety of ciclesonide administered with or without different spacers in patients with asthma (12 to 75 y). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Beckman

Trial name or title	Efficacy of ciclesonide inhaled once daily versus other corticosteroids used for treatment of mild asthma in children (4-11 ys). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	

Beckman *(Continued)*

Contact information	
Notes	

Colatruglio

Trial name or title	Effect of ciclesonide on quality of life in patients with moderate persistent asthma (21 to 65 y). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Dahl

Trial name or title	Efficacy of ciclesonide versus fluticasone propionate inpatients with mild to moderate asthma (12 to 75 y). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Derom

Trial name or title	Effect of inhaled ciclesonide versus fluticasone propionate in patients with mild to moderate asthma (18 to 65 y). Clinicaltrials.Gov. 2005
Methods	
Participants	

Derom *(Continued)*

Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Dusser

Trial name or title	Efficacy of ciclesonide and fluticasone propionate in adult patients with moderate and severe persistent asthma (18 to 75 y). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Engelstätter

Trial name or title	Efficacy of ciclesonide inhaled once daily versus fluticasone propionate inhaled twice daily in children with asthma (4 to 15 y). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Giwa

Trial name or title	Comparison of inhaled ciclesonide and fluticasone proprionate in moderate to severe asthma patients, well controlled under high doses of inhaled corticosteroids
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Hansel

Trial name or title	A 3-period double-blind, cross-over study on the onset of action of inhaled ciclesonide on airway responsiveness to adenosine monophosphate, sputum eosinophils and exhaled breath NO in patients with asthma
Methods	
Participants	Outpatients of either sex who are between 18-45 years with a history of atopic disease, who have a history of perennial bronchial asthma for at least 6 months as defined by ATS criteria (increased responsiveness to a variety of stimuli; symptoms like dyspnoe, wheezing and cough of varying degree; spontaneous fluctuations in the severity of obstruction with substantial improvements following bronchodilators or corticosteroids (American Thoracic Society, 1987)
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

O'Byrne

Trial name or title	Efficacy of ciclesonide vs fixed combination of fluticasone propionate/salmeterol vs placebo in patients with mild persistent asthma (12 to 75 y). Clinicaltrials.Gov. 2005.
Methods	
Participants	
Interventions	

O'Byrne *(Continued)*

Outcomes	
Starting date	
Contact information	
Notes	

Park

Trial name or title	Effectiveness of ciclesonide versus budesonide in patients with asthma (18 to 75 y). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Sanofi Aventis

Trial name or title	Effects of ciclesonide and beclomethasone on lens opacification in adult participants with moderate to severe persistent asthma. Clinicaltrials.Gov . 2005; Efficacy of ciclesonide vs. placebo administered as once daily or twice daily in patients not treated with inhaled corticosteroid. Clinicaltrials.Gov. 2005; Effects of ciclesonide MDI 50 mg/day and 200 mg/day (ex-value) once-daily on growth in children with mild persistent asthma. Clinicaltrials.Gov. 2005; Sanofi-Aventis. Dose response study of inhaled ciclesonide (glucocorticosteroid) to patients with persistent asthma. Clinicaltrials.Gov. 2005.
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

Stenton

Trial name or title	A double-blind randomised parallel group study comparing the efficacy and safety of 800 and 1000 mcg CIC/day in patients with asthma followed by an open long-term study to assess the safety of CIC in patients with asthma
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

ATS:
vs: versus
y: years

DATA AND ANALYSES

Comparison 1. Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline in FEV1	4	1322	L (Random, 95% CI)	0.03 [-0.06, 0.11]
1.1 Children	0	0	L (Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	4	1322	L (Random, 95% CI)	0.03 [-0.06, 0.11]
2 Change from baseline in FVC	3	970	L (Fixed, 95% CI)	0.06 [0.01, 0.11]
2.1 Children	1	399	L (Fixed, 95% CI)	0.11 [0.00, 0.22]
2.2 Adults	2	571	L (Fixed, 95% CI)	0.05 [-0.00, 0.10]
3 Change from baseline in clinic PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change from baseline in am PEF	4	1329	L/min (Fixed, 95% CI)	5.37 [0.12, 10.61]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	4	1329	L/min (Fixed, 95% CI)	5.37 [0.12, 10.61]
5 Change from baseline in pm PEF	2	758	L/min (Fixed, 95% CI)	3.95 [-2.89, 10.80]
5.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	2	758	L/min (Fixed, 95% CI)	3.95 [-2.89, 10.80]
6 Change in asthma symptom score	1		Symptom score units (Random, 95% CI)	Totals not selected
6.1 Children	0		Symptom score units (Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	1		Symptom score units (Random, 95% CI)	0.0 [0.0, 0.0]
7 Withdrawals (total)	2	771	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.47, 1.19]
7.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	2	771	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.47, 1.19]
8 Withdrawals (lack of efficacy)	3	1130	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.88, 2.01]
8.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	3	1130	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.88, 2.01]
9 Adverse events	3	1131	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.85, 1.15]
9.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	3	1131	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.85, 1.15]
10 Candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11 Pharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Exacerbations of asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Sore throat	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15 Voice alteration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Changes in cortisol levels (urinary)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Asthma (not otherwsie specified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Upper respiratory tract infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
19.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
21.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Withdrawals (adverse events)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
22.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
23.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Data not suitable for meta-analysis (medians)			Other data	No numeric data
25.1 Symptoms			Other data	No numeric data
25.2 Rescue medication use			Other data	No numeric data

Analysis 1.1. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 1 Change from baseline in FEV1.

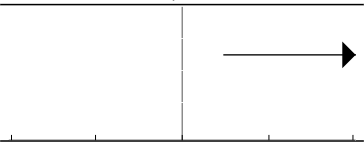
Study or subgroup	Ciclesonide N	BDP/BUD N	L (SE)	L IV, Random, 95% CI	Weight	L IV, Random, 95% CI
1.1.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.1.2 Adults						
Adachi 2007	107	106	0.1 (0.064)		19.85%	0.07[-0.05,0.19]
Boulet 2006	179	180	0.1 (0.03)		29.96%	0.05[-0.01,0.11]
Hansel 2006	184	167	-0.1 (0.046)		25.09%	-0.1[-0.19,-0.01]
Ukena 2006	198	201	0.1 (0.046)		25.09%	0.1[0.01,0.19]
Subtotal (95% CI)					**100%**	**0.03[-0.06,0.11]**
Heterogeneity: Tau^2=0.01; Chi^2=11.18, df=3(P=0.01); I^2=73.16%						
Test for overall effect: Z=0.67(P=0.5)						
Total (95% CI)					**100%**	**0.03[-0.06,0.11]**
Heterogeneity: Tau^2=0.01; Chi^2=11.18, df=3(P=0.01); I^2=73.16%						
Test for overall effect: Z=0.67(P=0.5)						
Test for subgroup differences: Not applicable						

Analysis 1.2. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 2 Change from baseline in FVC.

Study or subgroup	Ciclesonide N	BDP/BUD N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
1.2.1 Children						
Pedersen 2006	198	201	0.1 (0.056)		18.21%	0.11[0,0.22]
Subtotal (95% CI)					**18.21%**	**0.11[0,0.22]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%						
Test for overall effect: Z=1.96(P=0.05)						
1.2.2 Adults						
Adachi 2007	106	106	-0 (0.046)		27.2%	-0.01[-0.1,0.08]
Boulet 2006	179	180	0.1 (0.032)		54.59%	0.08[0.02,0.14]
Subtotal (95% CI)					**81.79%**	**0.05[-0,0.1]**
Heterogeneity: Tau^2=0; Chi^2=2.57, df=1(P=0.11); I^2=61.03%						
Test for overall effect: Z=1.89(P=0.06)						
Total (95% CI)					**100%**	**0.06[0.01,0.11]**
Heterogeneity: Tau^2=0; Chi^2=3.5, df=2(P=0.17); I^2=42.85%						
Test for overall effect: Z=2.55(P=0.01)						
Test for subgroup differences: Chi^2=0.93, df=1 (P=0.33), I^2=0%						

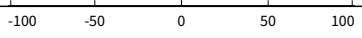
Analysis 1.3. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 3 Change from baseline in clinic PEF (L/min).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	BDP/BUD N	BDP/BUD Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.3.1 Children						
Pedersen 2006	198	80 (84.4)	201	61 (85.1)		19[2.37,35.63]
1.3.2 Adults						



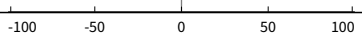
Analysis 1.4. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 4 Change from baseline in am PEF.

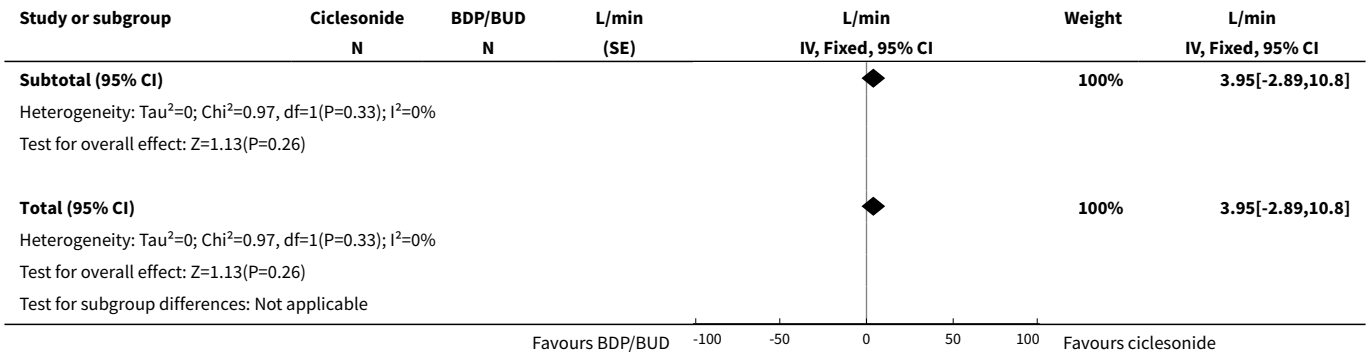
Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
1.4.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.4.2 Adults						
Adachi 2007	106	106	10.1 (5.332)		25.2%	10.09[-0.36,20.54]
Boulet 2006	179	180	6 (4.337)		38.09%	6[-2.5,14.5]
Hansel 2006	188	171	-4 (5.658)		22.38%	-4[-15.09,7.09]
Ukena 2006	198	201	10 (7.071)		14.33%	10[-3.86,23.86]
Subtotal (95% CI)					**100%**	**5.37[0.12,10.61]**
Heterogeneity: Tau²=0; Chi²=3.98, df=3(P=0.26); I²=24.55%						
Test for overall effect: Z=2(P=0.04)						
Total (95% CI)					**100%**	**5.37[0.12,10.61]**
Heterogeneity: Tau²=0; Chi²=3.98, df=3(P=0.26); I²=24.55%						
Test for overall effect: Z=2(P=0.04)						
Test for subgroup differences: Not applicable						



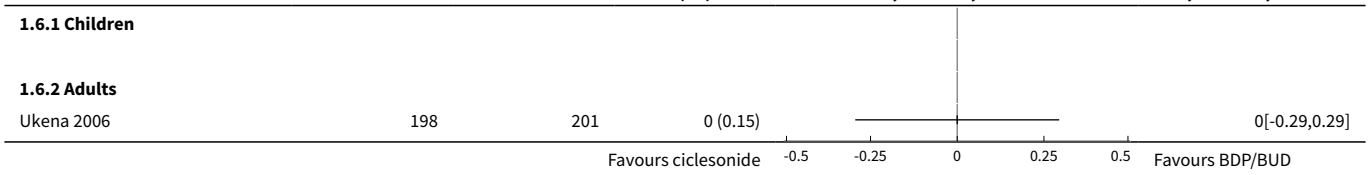
Analysis 1.5. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 5 Change from baseline in pm PEF.

Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
1.5.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.2 Adults						
Boulet 2006	179	180	2 (4.019)		75.59%	2[-5.88,9.88]
Ukena 2006	198	201	10 (7.071)		24.41%	10[-3.86,23.86]

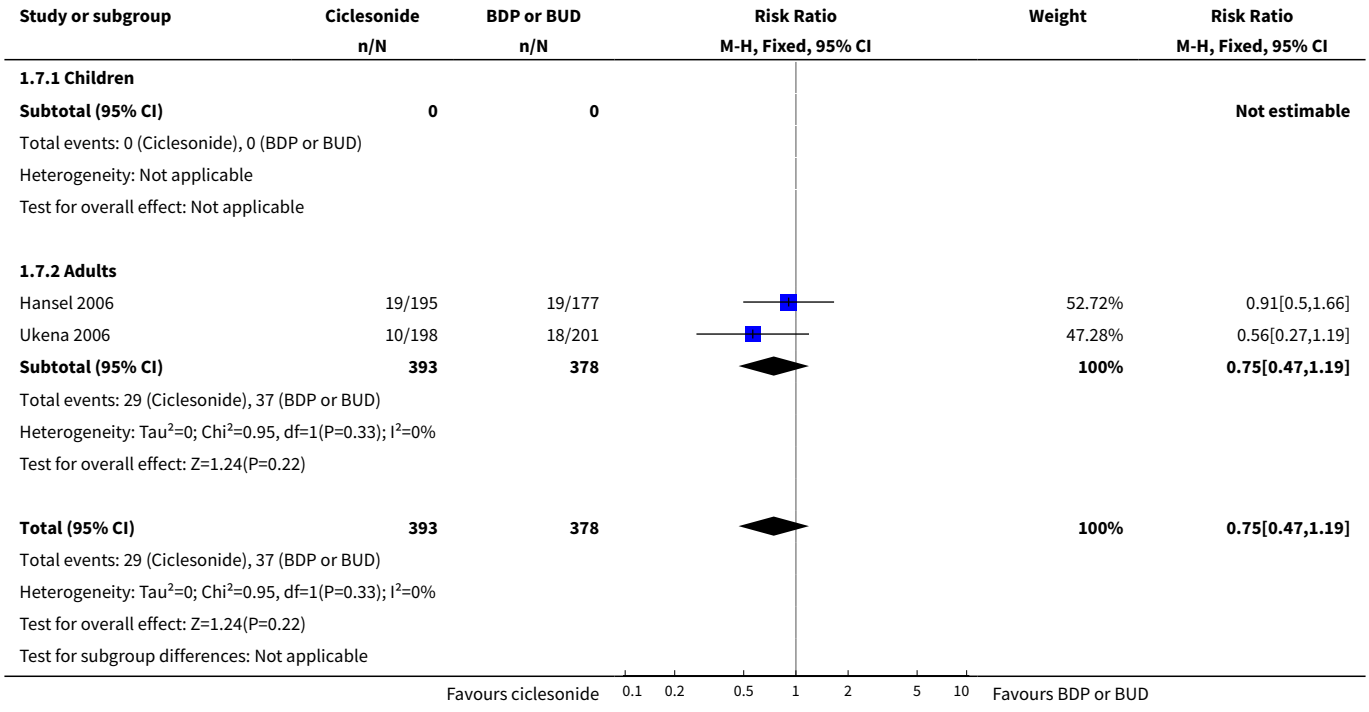




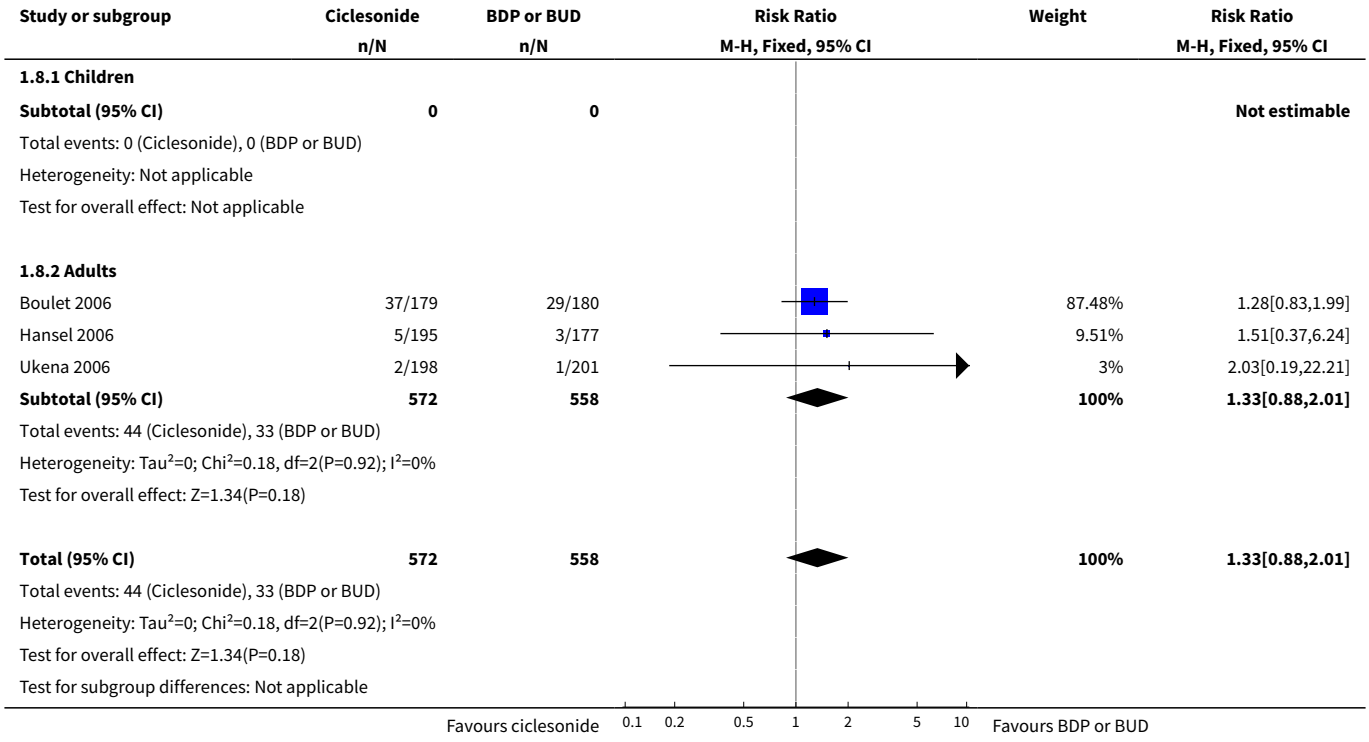
Analysis 1.6. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 6 Change in asthma symptom score.



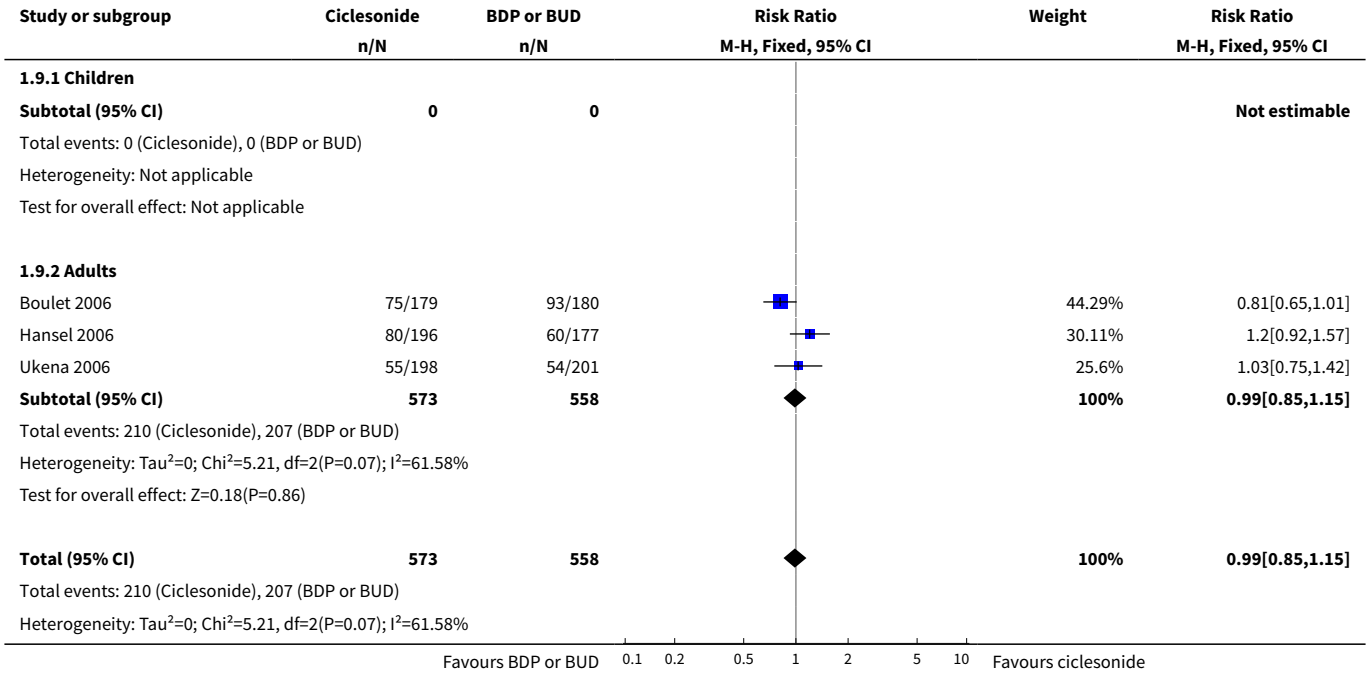
Analysis 1.7. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 7 Withdrawals (total).



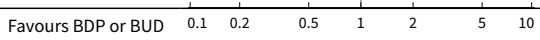
Analysis 1.8. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 8 Withdrawals (lack of efficacy).



Analysis 1.9. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 9 Adverse events.



Study or subgroup	Ciclesonide n/N	BDP or BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.18(P=0.86)					
Test for subgroup differences: Not applicable					

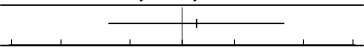


Analysis 1.10. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 10 Candidiasis.

Study or subgroup	Ciclesonide n/N	BDP or BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Boulet 2006	0/179	0/180		Not estimable

Analysis 1.11. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 11 Pharyngitis.

Study or subgroup	Ciclesonide n/N	BDP or BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Boulet 2006	6/179	5/180		1.21[0.38,3.88]

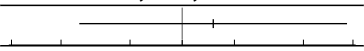


Analysis 1.13. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 13 Exacerbations of asthma.

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.13.1 Children				
1.13.2 Adults				
Boulet 2006	1/179	0/180		3.02[0.12,73.56]

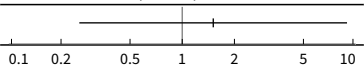
Analysis 1.14. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 14 Sore throat.

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Boulet 2006	3/179	2/180		1.51[0.26,8.92]



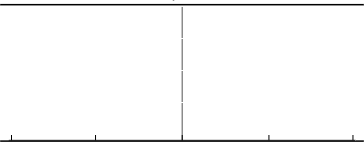
Analysis 1.15. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 15 Voice alteration.

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Boulet 2006	3/179	2/180		1.51[0.26,8.92]



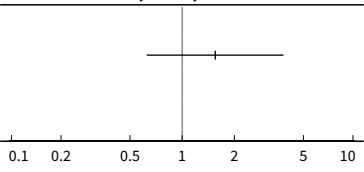
Analysis 1.16. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 16 Changes in cortisol levels (urinary).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	BDP/BUD N	BDP/BUD Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.16.1 Children						
1.16.2 Adults						
Hansel 2006	138	0.2 (0)	129	-1.4 (0)		Not estimable



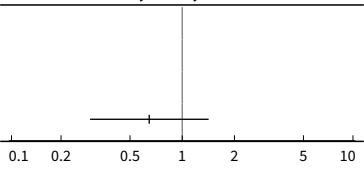
Analysis 1.17. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 17 Asthma (not otherwsie specified).

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Children				
Hansel 2006	12/196	7/177		1.55[0.62,3.84]
1.17.2 Adults				



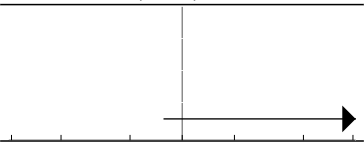
Analysis 1.18. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 18 Upper respiratory tract infection.

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Children				
1.18.2 Adults				
Hansel 2006	10/196	14/177		0.65[0.29,1.42]



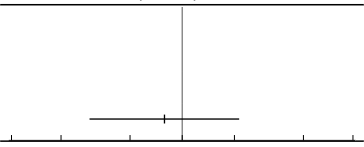
Analysis 1.19. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 19 Headache.

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.19.1 Children				
1.19.2 Adults				
Hansel 2006	7/196	0/177		13.55[0.78,235.6]



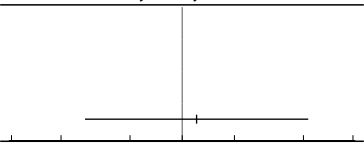
Analysis 1.21. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 21 Rhinitis.

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.21.1 Children				
1.21.2 Adults				
Hansel 2006	7/196	8/177		0.79[0.29,2.13]



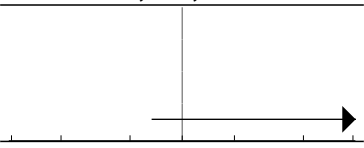
Analysis 1.22. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 22 Withdrawals (adverse events).

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.22.1 Children				
1.22.2 Adults				
Hansel 2006	4/195	3/177		1.21[0.27,5.33]



Analysis 1.23. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 23 Cough.

Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
1.23.1 Children				
1.23.2 Adults				
Hansel 2006	6/196	0/177		11.75[0.67,207.02]



Analysis 1.25. Comparison 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1), Outcome 25 Data not suitable for meta-analysis (medians).

Study	Data not suitable for meta-analysis (medians)
Symptoms	
Hansel 2006	0.05
Rescue medication use	
Hansel 2006	0.05puffs/d

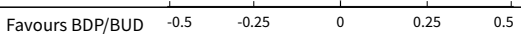
Comparison 2. Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change from baseline in FEV1	5	1633	L (Fixed, 95% CI)	-0.02 [-0.05, 0.00]
1.1 Children	1	621	L (Fixed, 95% CI)	-0.02 [-0.06, 0.02]
1.2 Adults	4	1012	L (Fixed, 95% CI)	-0.03 [-0.06, 0.01]
2 Change from baseline in FVC	5	1637	L (Fixed, 95% CI)	-0.01 [-0.04, 0.03]
2.1 Children	1	621	L (Fixed, 95% CI)	-0.02 [-0.07, 0.02]
2.2 Adults	4	1016	L (Fixed, 95% CI)	0.02 [-0.03, 0.07]
3 Change in clinic PEF	1		L/min (Fixed, 95% CI)	Totals not selected
3.1 Children	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	1		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in am PEF	4	1423	L/min (Fixed, 95% CI)	0.07 [-5.05, 5.19]
4.1 Children	1	621	L/min (Fixed, 95% CI)	-2.3 [-8.90, 4.30]
4.2 Adults	3	802	L/min (Fixed, 95% CI)	3.64 [-4.47, 11.74]
5 Change in pm PEF	4	1423	L/min (Fixed, 95% CI)	3.29 [-1.62, 8.19]
5.1 Children	1	621	L/min (Fixed, 95% CI)	3.3 [-1.00, 9.60]
5.2 Adults	3	802	L/min (Fixed, 95% CI)	3.27 [-4.54, 11.09]
6 Change in quality of life (Paediatric AQLQ)	2	1010	AQLQ (Fixed, 95% CI)	-0.00 [-0.09, 0.09]
7 Adverse events	6	1912	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.17]
7.1 Children	1	621	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.81, 1.24]
7.2 Adults	5	1291	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Worsening asthma	2	404	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.49, 1.69]
8.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	2	404	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.49, 1.69]
9 Upper respiratory tract infection	6	1802	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.75, 1.47]
9.1 Children	1	621	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.28, 1.17]
9.2 Adults	5	1181	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.86, 1.88]
10 Pharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Rhinitis	2	404	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.08, 1.62]
11.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	2	404	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.08, 1.62]
12 Oral candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
12.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Withdrawals	4	1427	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.82, 2.11]
13.1 Children	1	621	Risk Ratio (M-H, Fixed, 95% CI)	2.17 [0.83, 5.64]
13.2 Adults	3	806	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.61, 1.84]
14 Withdrawals (lack of efficacy)	3	1024	Risk Ratio (M-H, Fixed, 95% CI)	2.45 [0.84, 7.13]
14.1 Children	1	621	Risk Ratio (M-H, Fixed, 95% CI)	2.96 [0.67, 13.09]
14.2 Adults	2	403	Risk Ratio (M-H, Fixed, 95% CI)	1.95 [0.42, 9.10]
15 Withdrawals (adverse events)	4	777	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [0.96, 7.07]
15.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	4	777	Risk Ratio (M-H, Fixed, 95% CI)	2.61 [0.96, 7.07]

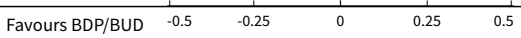
Analysis 2.1. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 1 Change from baseline in FEV1.

Study or subgroup	Ciclesonide N	BDP/BUD N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
2.1.1 Children						
von Berg 2007	416	205	-0 (0.021)		37.33%	-0.02[-0.06,0.02]
Subtotal (95% CI)					**37.33%**	**-0.02[-0.06,0.02]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.92(P=0.36)						
2.1.2 Adults						
Adachi 2007	106	106	-0 (0.036)		12.43%	-0.03[-0.1,0.04]
Niphadkar 2005a	133	67	-0 (0.051)		6.09%	-0.04[-0.14,0.06]
Niphadkar 2005b	131	66	0 (0.051)		6.09%	0.02[-0.08,0.12]
Vermeulen 2007	272	131	-0 (0.02)		38.06%	-0.03[-0.07,0.01]
Subtotal (95% CI)					**62.67%**	**-0.03[-0.06,0.01]**
Heterogeneity: Tau²=0; Chi²=0.94, df=3(P=0.82); I²=0%						
Test for overall effect: Z=1.64(P=0.1)						
Total (95% CI)					**100%**	**-0.02[-0.05,0]**
Heterogeneity: Tau²=0; Chi²=1.01, df=4(P=0.91); I²=0%						
Test for overall effect: Z=1.86(P=0.06)						
Test for subgroup differences: Chi²=0.07, df=1 (P=0.78), I²=0%						



Analysis 2.2. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 2 Change from baseline in FVC.

Study or subgroup	Ciclesonide N	BDP/BUD N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
2.2.1 Children						
von Berg 2007	416	205	-0 (0.023)		58.46%	-0.02[-0.07,0.02]
Subtotal (95% CI)					**58.46%**	**-0.02[-0.07,0.02]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.06(P=0.29)						
2.2.2 Adults						
Adachi 2007	107	106	0.1 (0.046)		14.3%	0.07[-0.02,0.16]
Niphadkar 2005a	139	67	0 (0.056)		9.57%	0.01[-0.1,0.11]
Niphadkar 2005b	131	66	0 (0.056)		9.57%	0[-0.11,0.11]
Vermeulen 2007	270	130	-0 (0.061)		8.1%	-0.04[-0.16,0.08]
Subtotal (95% CI)					**41.54%**	**0.02[-0.03,0.07]**
Heterogeneity: Tau²=0; Chi²=2.32, df=3(P=0.51); I²=0%						
Test for overall effect: Z=0.67(P=0.51)						
Total (95% CI)					**100%**	**-0.01[-0.04,0.03]**
Heterogeneity: Tau²=0; Chi²=3.74, df=4(P=0.44); I²=0%						
Test for overall effect: Z=0.38(P=0.7)						
Test for subgroup differences: Chi²=1.42, df=1 (P=0.23), I²=29.38%						



Analysis 2.3. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 3 Change in clinic PEF.

Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
2.3.1 Children					
2.3.2 Adults					
Vermeulen 2007	270	130	3 (8.8)		3[-14.25,20.25]

Favours BDP/BUD -100 -50 0 50 100 Favours ciclesonide

Analysis 2.4. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 4 Change in am PEF.

Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
2.4.1 Children						
von Berg 2007	416	205	-2.3 (3.367)		60.13%	-2.3[-8.9,4.3]
Subtotal (95% CI)					**60.13%**	**-2.3[-8.9,4.3]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.68(P=0.49)						
2.4.2 Adults						
Niphadkar 2005a	139	67	9.4 (7.913)		10.89%	9.35[-6.16,24.86]
Niphadkar 2005b	133	66	-0.8 (7.602)		11.8%	-0.85[-15.75,14.05]
Vermeulen 2007	267	130	3.1 (6.3)		17.18%	3.1[-9.25,15.45]
Subtotal (95% CI)					**39.87%**	**3.64[-4.47,11.74]**
Heterogeneity: Tau^2=0; Chi^2=0.88, df=2(P=0.65); I^2=0%						
Test for overall effect: Z=0.88(P=0.38)						
Total (95% CI)					**100%**	**0.07[-5.05,5.19]**
Heterogeneity: Tau^2=0; Chi^2=2.12, df=3(P=0.55); I^2=0%						
Test for overall effect: Z=0.03(P=0.98)						
Test for subgroup differences: Chi^2=1.24, df=1 (P=0.27), I^2=19.34%						

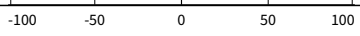
Favours BDP/BUD -100 -50 0 50 100 Favours ciclesonide

Analysis 2.5. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 5 Change in pm PEF.

Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
2.5.1 Children						
von Berg 2007	416	205	3.3 (3.214)		60.61%	3.3[-3,9.6]
Subtotal (95% CI)					**60.61%**	**3.3[-3,9.6]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.03(P=0.3)						

Favours BDP/BUD -100 -50 0 50 100 Favours ciclesonide

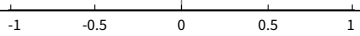
Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
2.5.2 Adults						
Niphadkar 2005a	139	67	-4.4 (7.102)		12.42%	-4.4[-18.32,9.52]
Niphadkar 2005b	133	66	4 (7.179)		12.15%	4[-10.07,18.07]
Vermeulen 2007	267	130	9.1 (6.5)		14.82%	9.1[-3.64,21.84]
Subtotal (95% CI)					**39.39%**	**3.27[-4.54,11.09]**
Heterogeneity: Tau²=0; Chi²=1.98, df=2(P=0.37); I²=0%						
Test for overall effect: Z=0.82(P=0.41)						
Total (95% CI)					**100%**	**3.29[-1.62,8.19]**
Heterogeneity: Tau²=0; Chi²=1.98, df=3(P=0.58); I²=0%						
Test for overall effect: Z=1.31(P=0.19)						
Test for subgroup differences: Chi²=0, df=1 (P=1), I²=0%						



Favours BDP/BUD — Favours ciclesonide

Analysis 2.6. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 6 Change in quality of life (Paediatric AQLQ).

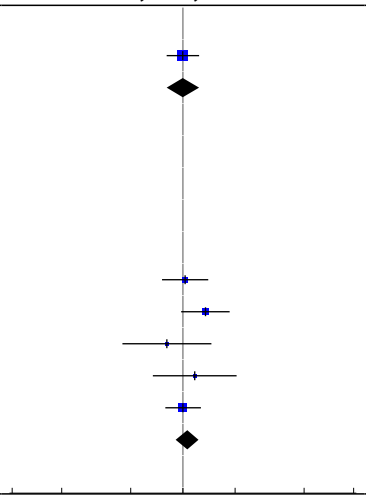
Study or subgroup	Ciclesonide N	BDP/BUD N	AQLQ (SE)	AQLQ IV, Fixed, 95% CI	Weight	AQLQ IV, Fixed, 95% CI
Vermeulen 2007	262	127	0 (0.077)		34.97%	0.01[-0.14,0.16]
von Berg 2007	416	205	-0 (0.056)		65.03%	-0.01[-0.12,0.1]
Total (95% CI)					**100%**	**-0[-0.09,0.09]**
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.83); I²=0%						
Test for overall effect: Z=0.07(P=0.95)						



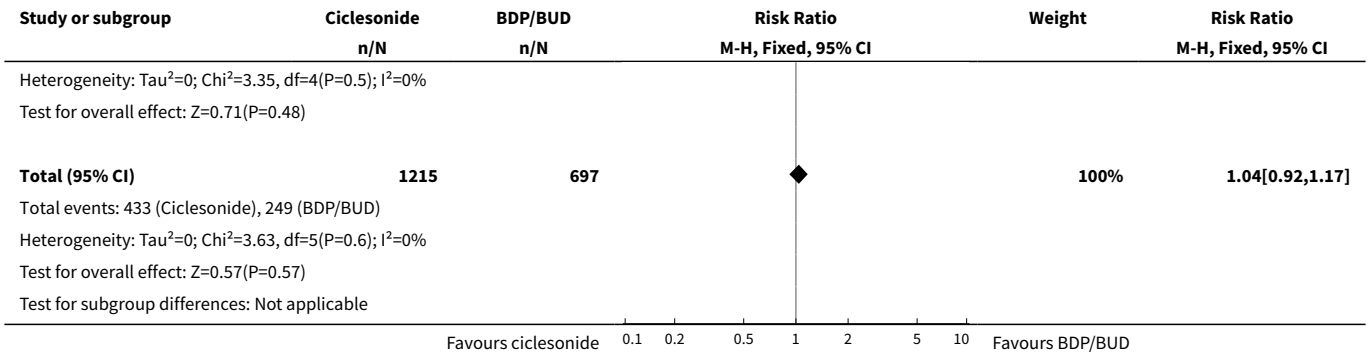
Favours BDP/BUD — Favours ciclesonide

Analysis 2.7. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 7 Adverse events.

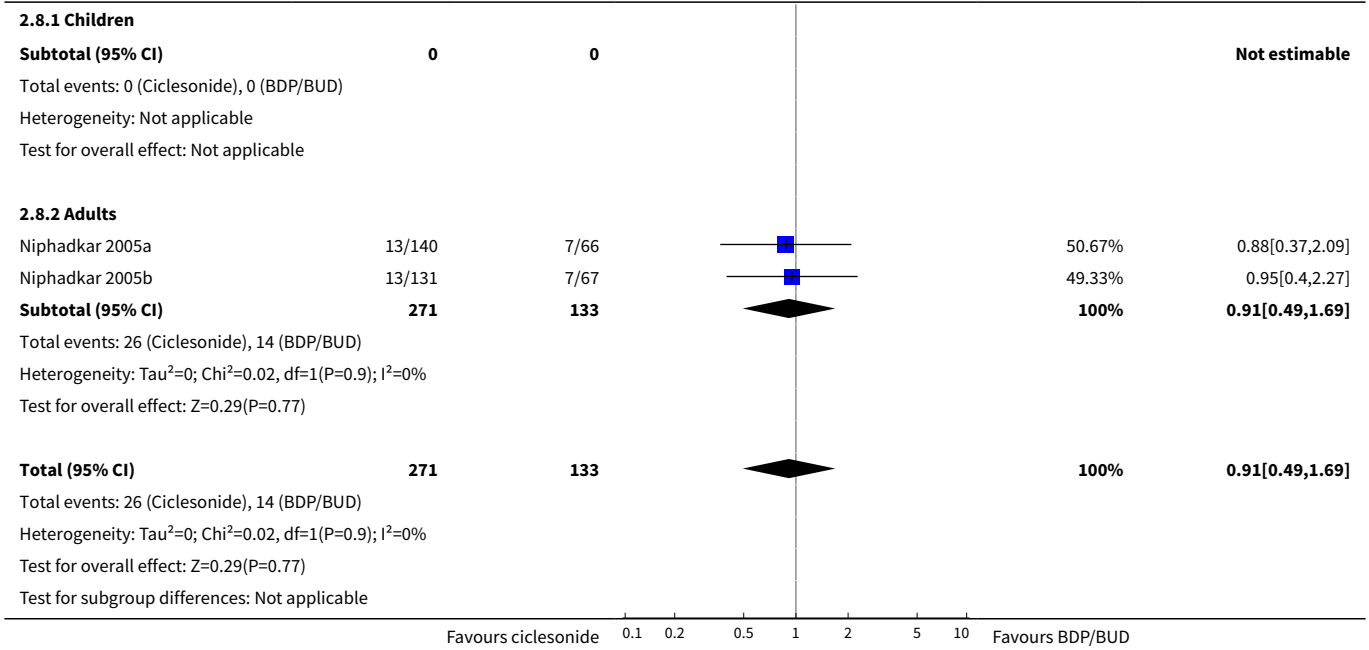
Study or subgroup	Ciclesonide n/N	BDP/BUD n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 Children					
von Berg 2007	158/416	78/205		34.07%	1[0.81,1.24]
Subtotal (95% CI)	**416**	**205**		**34.07%**	**1[0.81,1.24]**
Total events: 158 (Ciclesonide), 78 (BDP/BUD)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.02(P=0.99)					
2.7.2 Adults					
BY9010/M1-136	50/124	49/125		15.91%	1.03[0.76,1.4]
BY9010/M1-137	41/64	29/61		9.68%	1.35[0.98,1.86]
Niphadkar 2005a	24/140	14/66		6.2%	0.81[0.45,1.46]
Niphadkar 2005b	32/131	14/67		6.04%	1.17[0.67,2.04]
Vermeulen 2007	128/340	65/173		28.09%	1[0.79,1.27]
Subtotal (95% CI)	**799**	**492**		**65.93%**	**1.06[0.91,1.23]**
Total events: 275 (Ciclesonide), 171 (BDP/BUD)					



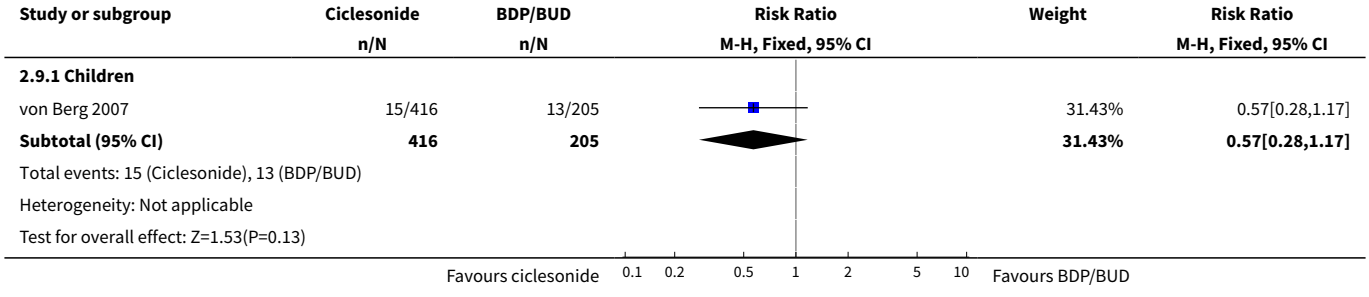
Favours ciclesonide — Favours BDP/BUD

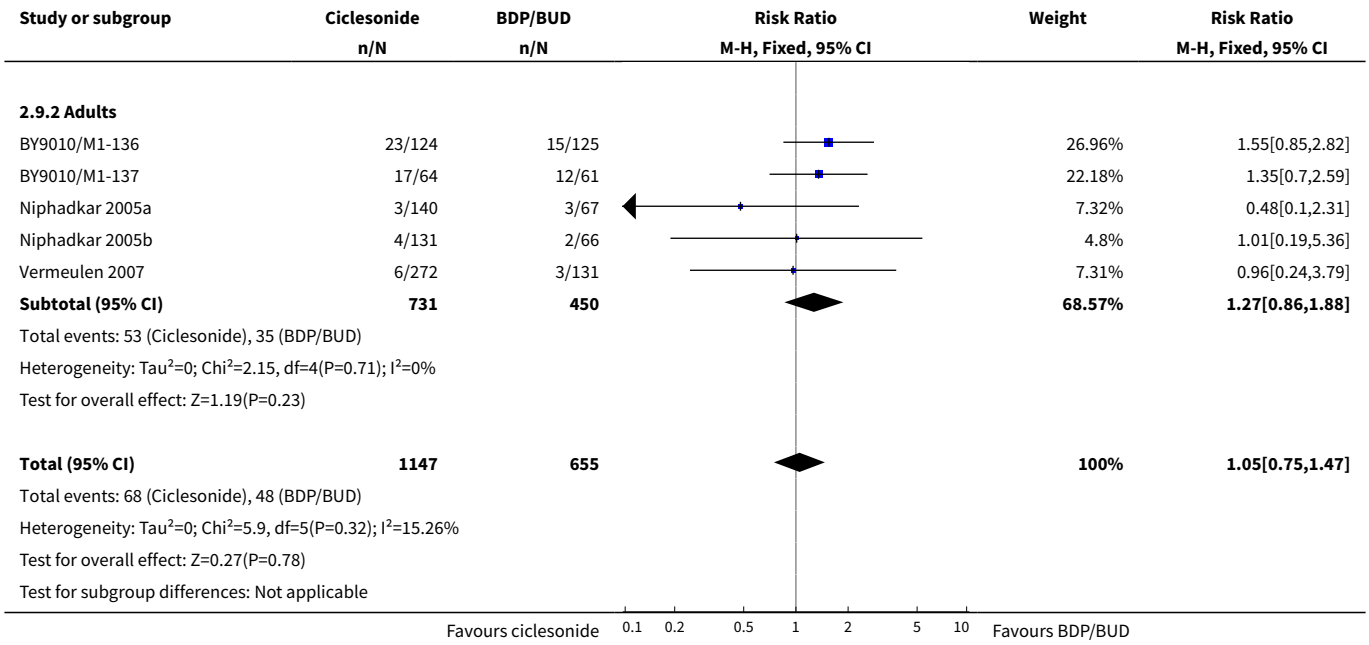


Analysis 2.8. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 8 Worsening asthma.

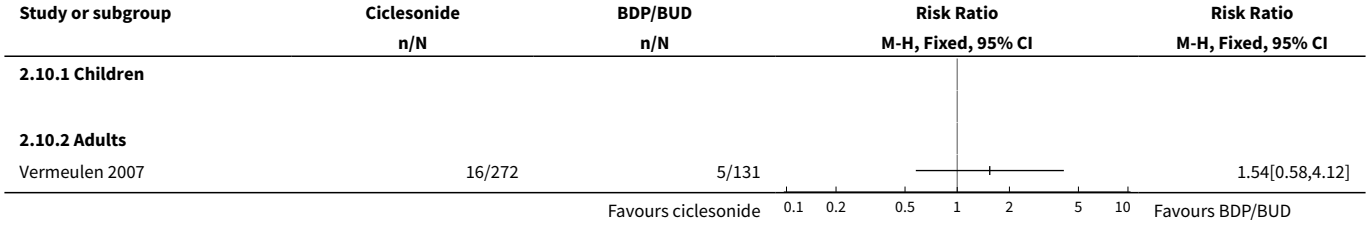


Analysis 2.9. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 9 Upper respiratory tract infection.

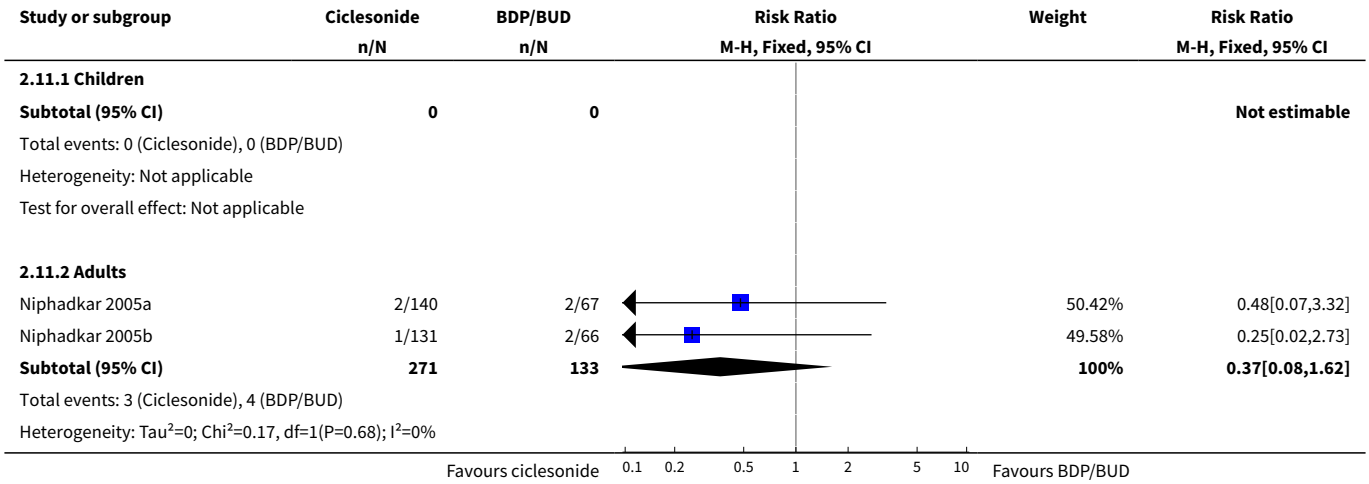


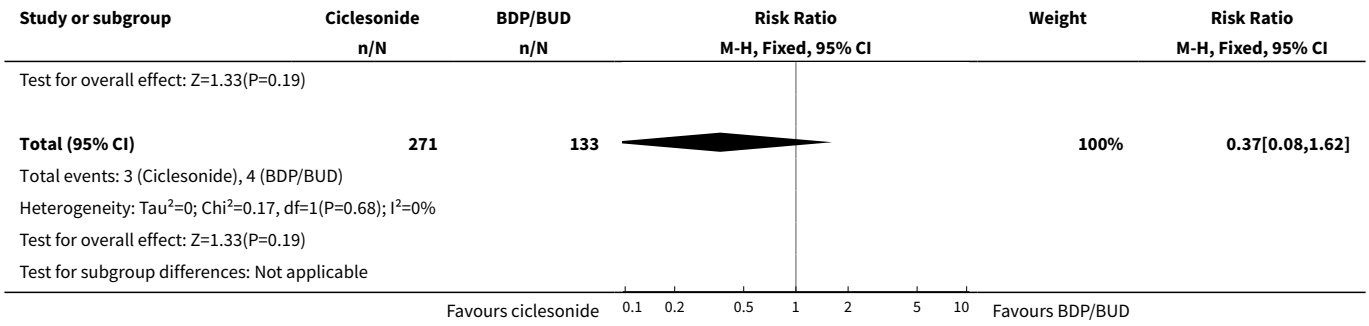


Analysis 2.10. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 10 Pharyngitis.

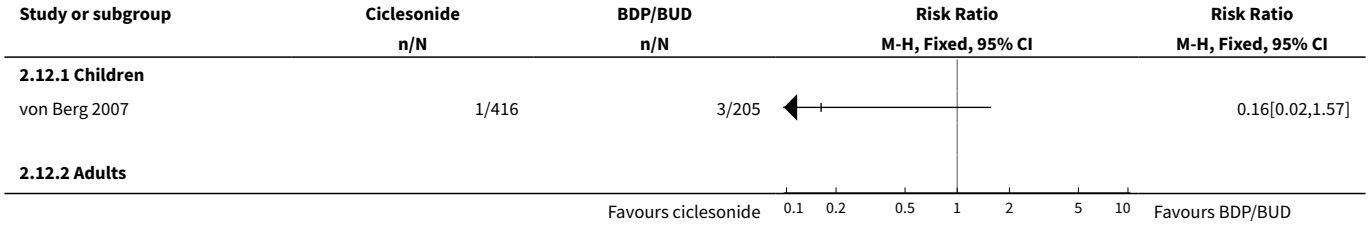


Analysis 2.11. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 11 Rhinitis.

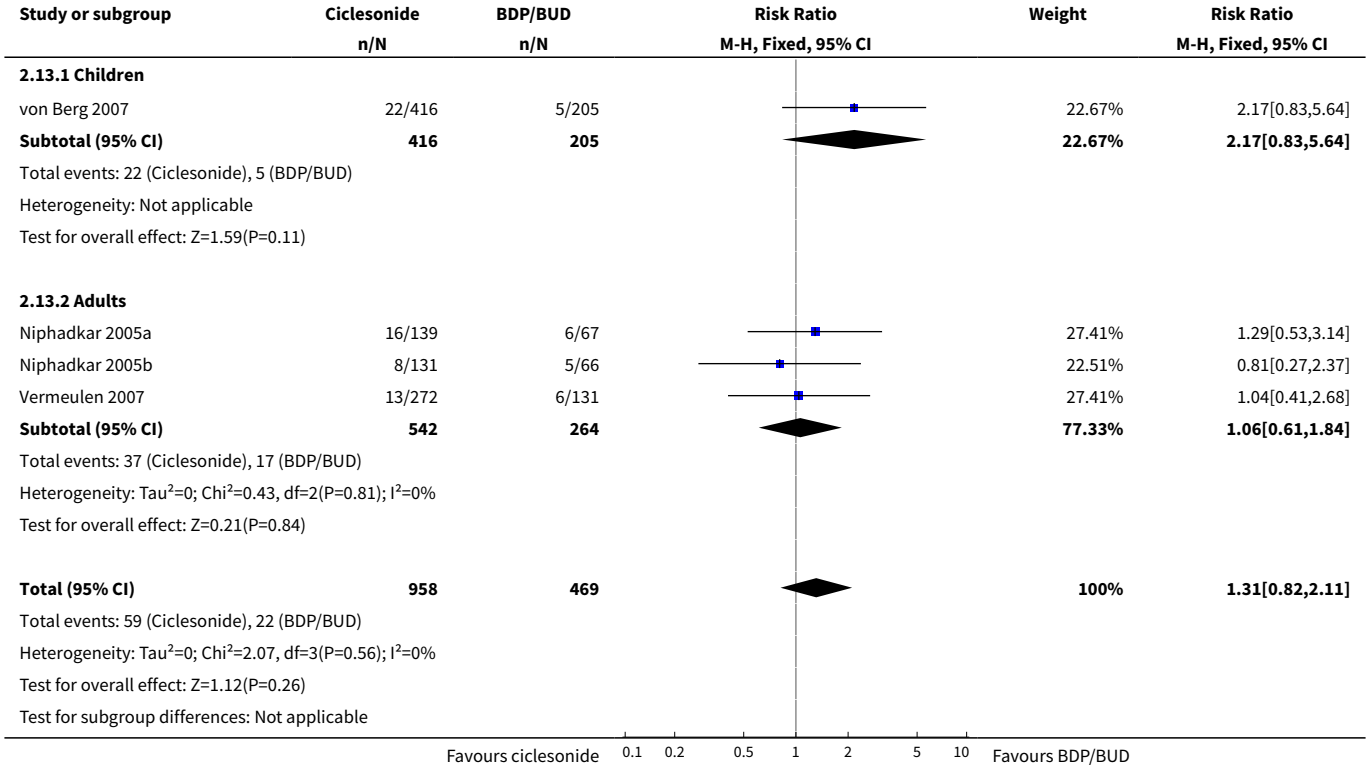




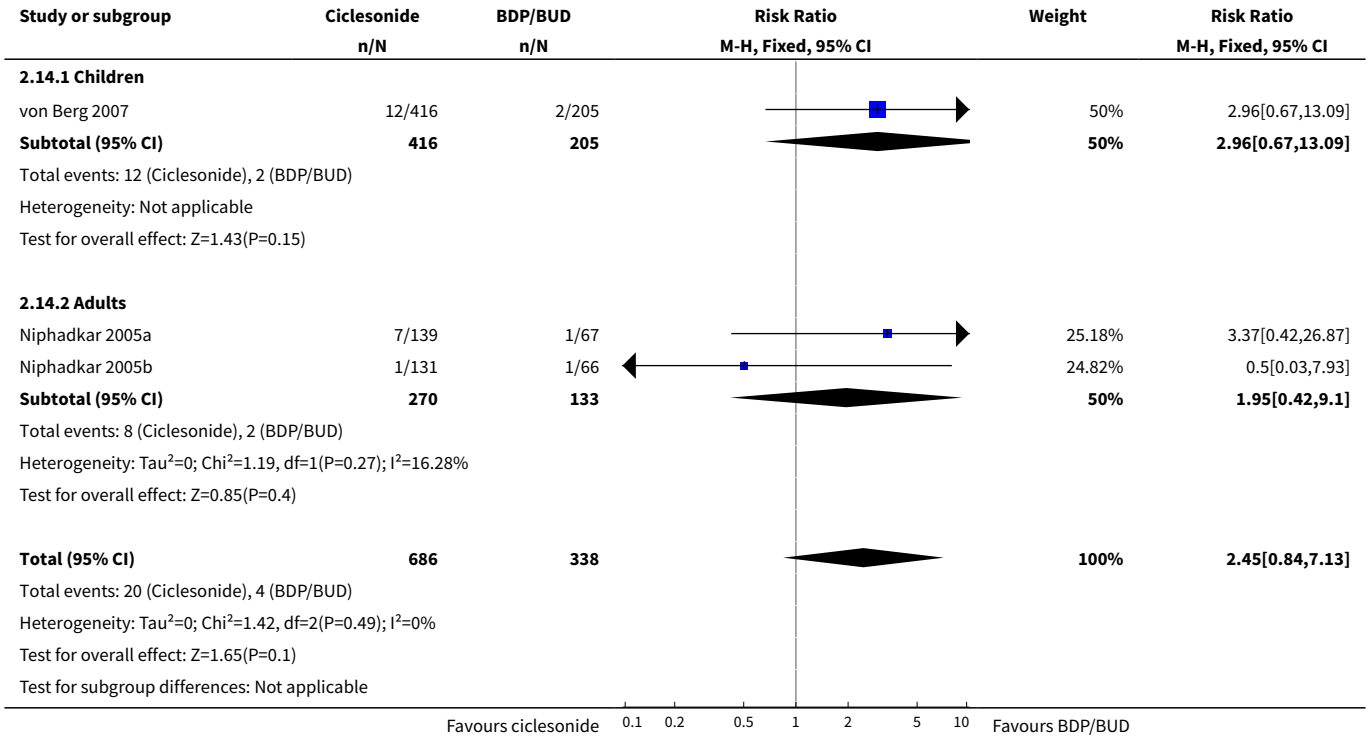
Analysis 2.12. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 12 Oral candidiasis.



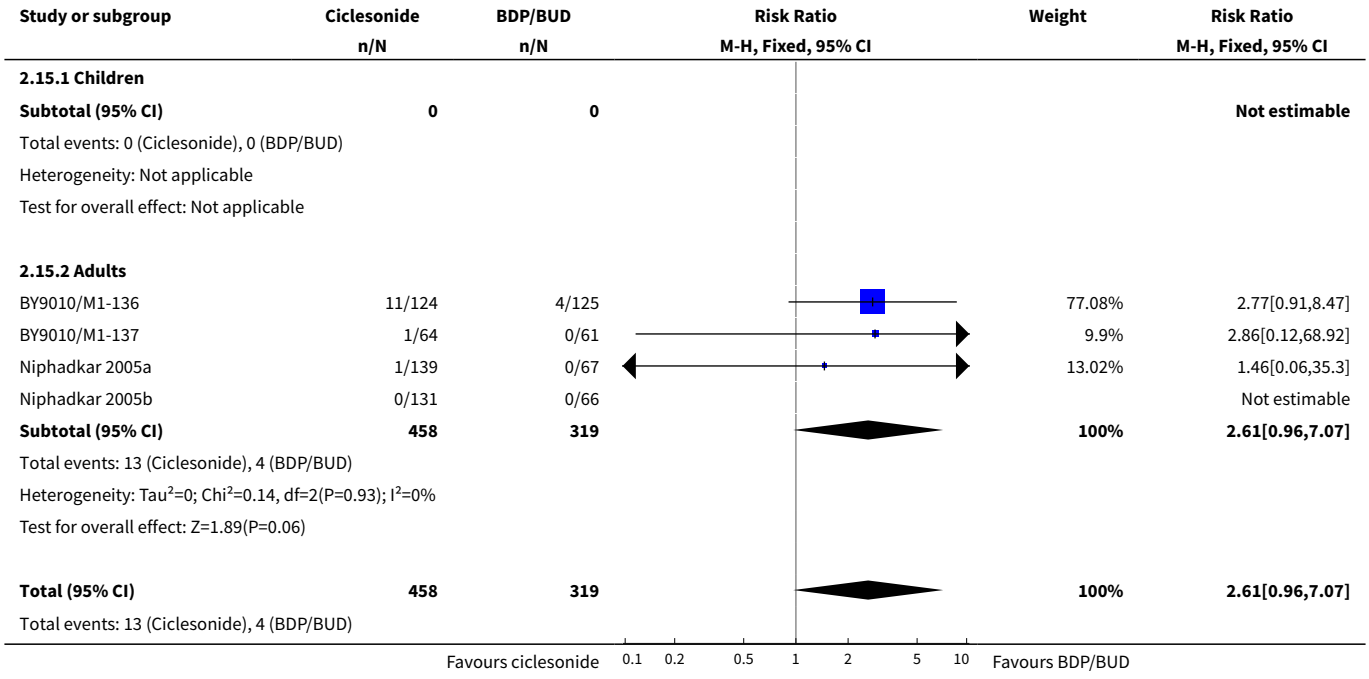
Analysis 2.13. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 13 Withdrawals.

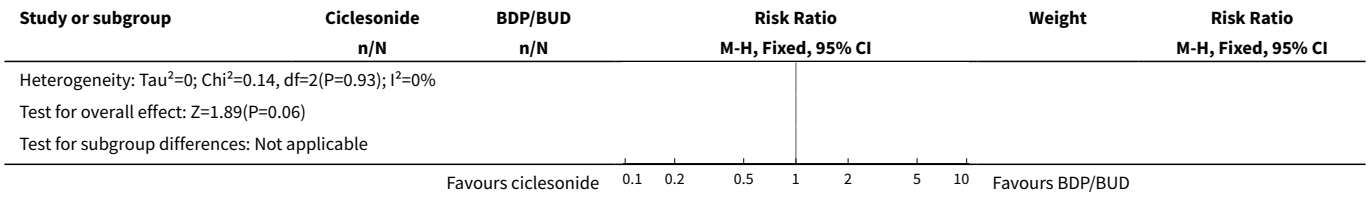


Analysis 2.14. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 14 Withdrawals (lack of efficacy).



Analysis 2.15. Comparison 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2), Outcome 15 Withdrawals (adverse events).





Comparison 3. Ciclesonide versus Fluticasone (dose ratio 1:1)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring oral steroids	3	1537	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.40, 1.95]
1.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	3	1537	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.40, 1.95]
2 Change from baseline in FEV1	5	2599	L (Fixed, 95% CI)	-0.02 [-0.04, 0.01]
2.1 Children	1	556	L (Fixed, 95% CI)	0.0 [-0.04, 0.04]
2.2 Adults	4	2043	L (Fixed, 95% CI)	-0.03 [-0.07, 0.01]
3 Change in FEV1 predicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in FVC	4	2051	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.04, 0.04]
4.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	4	2051	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.04, 0.04]
5 Change in clinic PEF	3	1611	L/min (Fixed, 95% CI)	-1.59 [-7.43, 4.25]
5.1 Children	1	556	L/min (Fixed, 95% CI)	-2.5 [-10.34, 5.34]
5.2 Adults	2	1055	L/min (Fixed, 95% CI)	-0.45 [-9.22, 8.31]
6 Change in am PEF	4	2070	L/min (Fixed, 95% CI)	0.41 [-4.71, 5.53]
6.1 Children	1	556	L/min (Fixed, 95% CI)	-2.9 [-11.33, 5.53]
6.2 Adults	3	1514	L/min (Fixed, 95% CI)	2.34 [-4.10, 8.78]
7 Change in pm PEF	2	1023	L/min (Fixed, 95% CI)	1.30 [-5.10, 7.70]
7.1 Children	1	556	L/min (Fixed, 95% CI)	-0.2 [-8.24, 7.84]

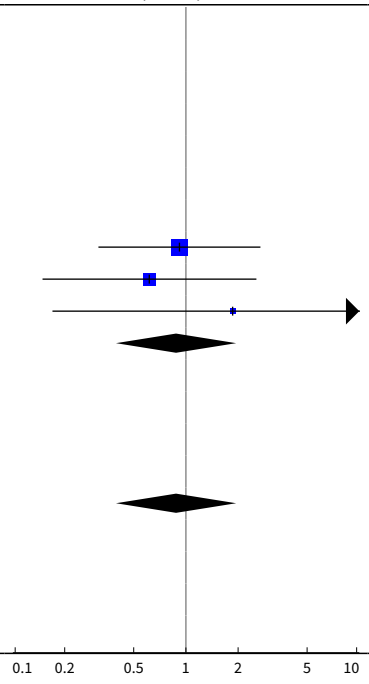
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 Adults	1	467	L/min (Fixed, 95% CI)	3.9 [-6.69, 14.49]
8 Change in rescue medication	2	1085	puffs/d (Fixed, 95% CI)	0.0 [-0.10, 0.10]
8.1 Children	1	556	puffs/d (Fixed, 95% CI)	0.0 [-0.14, 0.14]
8.2 Adults	1	529	puffs/d (Fixed, 95% CI)	0.0 [-0.14, 0.14]
9 Lack of efficacy (exacerbation requiring change in medication)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Worsening asthma	3	1552	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.61, 1.97]
10.1 Children	1	556	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.50, 3.14]
10.2 Adults	2	996	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.47, 2.14]
11 Change in asthma-symptom free days	1		% (Fixed, 95% CI)	Totals not selected
11.1 Children	1		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	0		% (Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Change in quality of life (AQLQ)	2	967	AQLQ (Fixed, 95% CI)	0.17 [0.04, 0.30]
12.1 Children	0	0	AQLQ (Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	2	967	AQLQ (Fixed, 95% CI)	0.17 [0.04, 0.30]
13 Adverse events	4	2058	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.07]
13.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	4	2058	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.07]
14 Candidiasis	3	1529	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.58]
14.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	3	1529	Risk Ratio (M-H, Fixed, 95% CI)	0.24 [0.10, 0.58]
15 Pharyngitis	5	2614	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.90, 1.74]
15.1 Children	1	556	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.49, 2.45]
15.2 Adults	4	2058	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.90, 1.85]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
16 Upper resiratory tract infection	3	1613	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.74, 1.47]
16.1 Children	1	556	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.57, 1.98]
16.2 Adults	2	1057	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.68, 1.56]
17 Headache	3	1613	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.52, 1.49]
17.1 Children	1	556	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.56, 3.73]
17.2 Adults	2	1057	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.37, 1.34]
18 Rhinitis	2	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.61, 1.61]
18.1 Children	1	556	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.55, 1.69]
18.2 Adults	1	528	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.41, 2.81]
19 Sinusitis	2	1084	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.41, 1.61]
19.1 Children	1	556	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.19, 1.65]
19.2 Adults	1	528	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.43, 2.65]
20 Withdrawals	5	2570	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.28]
20.1 Children	1	511	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.70, 3.11]
20.2 Adults	4	2059	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.74, 1.24]
21 Withdrawals (adverse events)	2	1059	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.66, 4.79]
21.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Adults	2	1059	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.66, 4.79]
22 Withdrawals (lack of efficacy)	3	1570	Risk Ratio (M-H, Fixed, 95% CI)	2.55 [0.86, 7.53]
22.1 Children	1	511	Risk Ratio (M-H, Fixed, 95% CI)	2.02 [0.51, 8.00]
22.2 Adults	2	1059	Risk Ratio (M-H, Fixed, 95% CI)	3.57 [0.59, 21.51]
23 Data not suitable for meta-analysis (medians)			Other data	No numeric data
24 Change in asthma-symptom scores	1		symptoms (Fixed, 95% CI)	Totals not selected
24.1 Children	0		symptoms (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.2 Adults	1		symptoms (Fixed, 95% CI)	0.0 [0.0, 0.0]

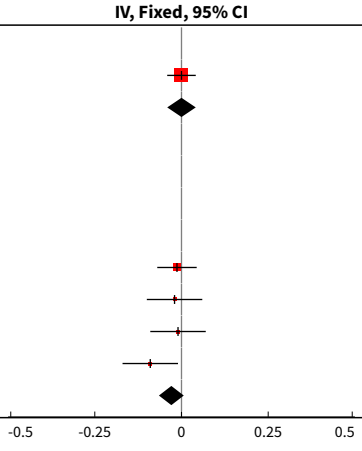
Analysis 3.1. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 1 Exacerbations requiring oral steroids.

Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ciclesonide), 0 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.1.2 Adults					
Bateman 2007	6/255	7/273		53.1%	0.92[0.31,2.69]
Boulet 2007	3/233	5/239		38.77%	0.62[0.15,2.55]
Magnussen 2007	2/278	1/259		8.13%	1.86[0.17,20.43]
Subtotal (95% CI)	**766**	**771**		**100%**	**0.88[0.4,1.95]**
Total events: 11 (Ciclesonide), 13 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=2(P=0.73); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					
Total (95% CI)	**766**	**771**		**100%**	**0.88[0.4,1.95]**
Total events: 11 (Ciclesonide), 13 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=2(P=0.73); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					
Test for subgroup differences: Not applicable					



Analysis 3.2. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 2 Change from baseline in FEV1.

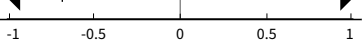
Study or subgroup	Ciclesonide N	Fluticasone N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
3.2.1 Children						
Pedersen 2006	277	279	0 (0.021)		43.12%	0[-0.04,0.04]
Subtotal (95% CI)					**43.12%**	**0[-0.04,0.04]**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.2.2 Adults						
Bateman 2007	249	269	-0 (0.029)		22.61%	-0.01[-0.07,0.04]
Boulet 2007	233	234	-0 (0.041)		11.42%	-0.02[-0.1,0.06]
Buhl 2006	266	263	-0 (0.041)		11.42%	-0.01[-0.09,0.07]
Magnussen 2007	270	259	-0.1 (0.041)		11.42%	-0.09[-0.17,-0.01]
Subtotal (95% CI)					**56.88%**	**-0.03[-0.07,0.01]**



Study or subgroup	Ciclesonide N	Fluticasone N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=2.81, df=3(P=0.42); I²=0%						
Test for overall effect: Z=1.6(P=0.11)						
Total (95% CI)					**100%**	**-0.02[-0.04,0.01]**
Heterogeneity: Tau²=0; Chi²=3.91, df=4(P=0.42); I²=0%						
Test for overall effect: Z=1.21(P=0.23)						
Test for subgroup differences: Chi²=1.1, df=1 (P=0.29), I²=9.49%						

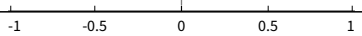
Analysis 3.3. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 3 Change in FEV1 predicted.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.3.1 Children						
3.3.2 Adults						
Boulet 2007	233	4.5 (13.4)	234	5.2 (13.3)		-0.68[-3.1,1.74]



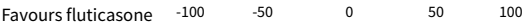
Analysis 3.4. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 4 Change in FVC.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.4.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.4.2 Adults							
Bateman 2007	249	0 (0.4)	269	0 (0.4)		39.3%	-0.04[-0.11,0.03]
Boulet 2007	233	0.2 (0.5)	234	0.2 (0.5)		21.16%	-0.01[-0.1,0.08]
Buhl 2006	266	0.5 (0.5)	263	0.5 (0.5)		22.61%	0.03[-0.06,0.12]
Magnussen 2007	278	0.3 (0.6)	259	0.2 (0.6)		16.92%	0.07[-0.03,0.17]
Subtotal ***	**1026**		**1025**			**100%**	**0[-0.04,0.04]**
Heterogeneity: Tau²=0; Chi²=3.64, df=3(P=0.3); I²=17.55%							
Test for overall effect: Z=0.04(P=0.97)							
Total ***	**1026**		**1025**			**100%**	**0[-0.04,0.04]**
Heterogeneity: Tau²=0; Chi²=3.64, df=3(P=0.3); I²=17.55%							
Test for overall effect: Z=0.04(P=0.97)							
Test for subgroup differences: Not applicable							



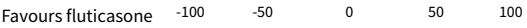
Analysis 3.5. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 5 Change in clinic PEF.

Study or subgroup	Ciclesonide N	Fluticasone N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
3.5.1 Children						
Pedersen 2006	277	279	-2.5 (4)		55.56%	-2.5[-10.34,5.34]
Subtotal (95% CI)					**55.56%**	**-2.5[-10.34,5.34]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.63(P=0.53)						
3.5.2 Adults						
Bateman 2007	249	269	0.2 (5.7)		27.36%	0.2[-10.97,11.37]
Magnussen 2007	278	259	-1.5 (7.214)		17.08%	-1.5[-15.64,12.64]
Subtotal (95% CI)					**44.44%**	**-0.45[-9.22,8.31]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.85); I²=0%						
Test for overall effect: Z=0.1(P=0.92)						
Total (95% CI)					**100%**	**-1.59[-7.43,4.25]**
Heterogeneity: Tau²=0; Chi²=0.15, df=2(P=0.93); I²=0%						
Test for overall effect: Z=0.53(P=0.59)						
Test for subgroup differences: Chi²=0.12, df=1 (P=0.73), I²=0%						



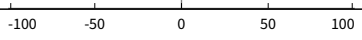
Analysis 3.6. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 6 Change in am PEF.

Study or subgroup	Ciclesonide N	Fluticasone N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
3.6.1 Children						
Pedersen 2006	277	279	-2.9 (4.3)		36.88%	-2.9[-11.33,5.53]
Subtotal (95% CI)					**36.88%**	**-2.9[-11.33,5.53]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.67(P=0.5)						
3.6.2 Adults						
Bateman 2007	249	269	5.3 (6.3)		17.18%	5.3[-7.05,17.65]
Boulet 2007	233	234	4.9 (5.26)		24.64%	4.9[-5.41,15.21]
Buhl 2006	266	263	-3 (5.658)		21.3%	-3[-14.09,8.09]
Subtotal (95% CI)					**63.12%**	**2.34[-4.1,8.78]**
Heterogeneity: Tau²=0; Chi²=1.35, df=2(P=0.51); I²=0%						
Test for overall effect: Z=0.71(P=0.48)						
Total (95% CI)					**100%**	**0.41[-4.71,5.53]**
Heterogeneity: Tau²=0; Chi²=2.29, df=3(P=0.52); I²=0%						
Test for overall effect: Z=0.16(P=0.88)						
Test for subgroup differences: Chi²=0.94, df=1 (P=0.33), I²=0%						



Analysis 3.7. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 7 Change in pm PEF.

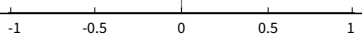
Study or subgroup	Ciclesonide N	Fluticasone N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
3.7.1 Children						
Pedersen 2006	277	279	-0.2 (4.1)		63.46%	-0.2[-8.24,7.84]
Subtotal (95% CI)					**63.46%**	**-0.2[-8.24,7.84]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.05(P=0.96)						
3.7.2 Adults						
Boulet 2007	233	234	3.9 (5.403)		36.54%	3.9[-6.69,14.49]
Subtotal (95% CI)					**36.54%**	**3.9[-6.69,14.49]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.72(P=0.47)						
Total (95% CI)					**100%**	**1.3[-5.1,7.7]**
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.55); I²=0%						
Test for overall effect: Z=0.4(P=0.69)						
Test for subgroup differences: Chi²=0.37, df=1 (P=0.55), I²=0%						



Favours fluticasone — Favours ciclesonide

Analysis 3.8. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 8 Change in rescue medication.

Study or subgroup	Ciclesonide N	Fluticasone N	puffs/d (SE)	puffs/d IV, Fixed, 95% CI	Weight	puffs/d IV, Fixed, 95% CI
3.8.1 Children						
Pedersen 2006	277	279	0 (0.071)		50.28%	0[-0.14,0.14]
Subtotal (95% CI)					**50.28%**	**0[-0.14,0.14]**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.8.2 Adults						
Magnussen 2007	270	259	0 (0.071)		49.72%	0[-0.14,0.14]
Subtotal (95% CI)					**49.72%**	**0[-0.14,0.14]**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)					**100%**	**0[-0.1,0.1]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Favours ciclesonide — Favours fluticasone

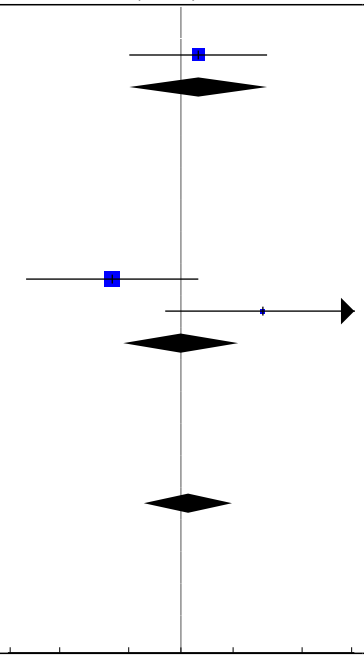
Analysis 3.9. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 9 Lack of efficacy (exacerbation requiring change in medication).

Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
3.9.1 Children				
Pedersen 2006	5/277	4/279		1.26[0.34,4.64]
3.9.2 Adults				

Favours ciclesonide — Favours fluticasone

Analysis 3.10. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 10 Worsening asthma.

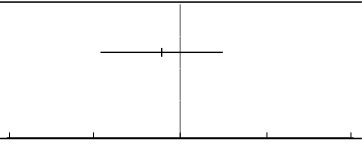
Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.10.1 Children					
Pedersen 2006	10/277	8/279		38.02%	1.26[0.5,3.14]
Subtotal (95% CI)	**277**	**279**		**38.02%**	**1.26[0.5,3.14]**
Total events: 10 (Ciclesonide), 8 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
3.10.2 Adults					
Boulet 2007	4/233	10/234		47.59%	0.4[0.13,1.26]
Buhl 2006	9/266	3/263		14.39%	2.97[0.81,10.83]
Subtotal (95% CI)	**499**	**497**		**61.98%**	**1[0.47,2.14]**
Total events: 13 (Ciclesonide), 13 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=5.14, df=1(P=0.02); I^2=80.55%					
Test for overall effect: Z=0.01(P=0.99)					
Total (95% CI)	**776**	**776**		**100%**	**1.1[0.61,1.97]**
Total events: 23 (Ciclesonide), 21 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=5.31, df=2(P=0.07); I^2=62.32%					
Test for overall effect: Z=0.31(P=0.76)					
Test for subgroup differences: Not applicable					



Favours ciclesonide — Favours fluticasone

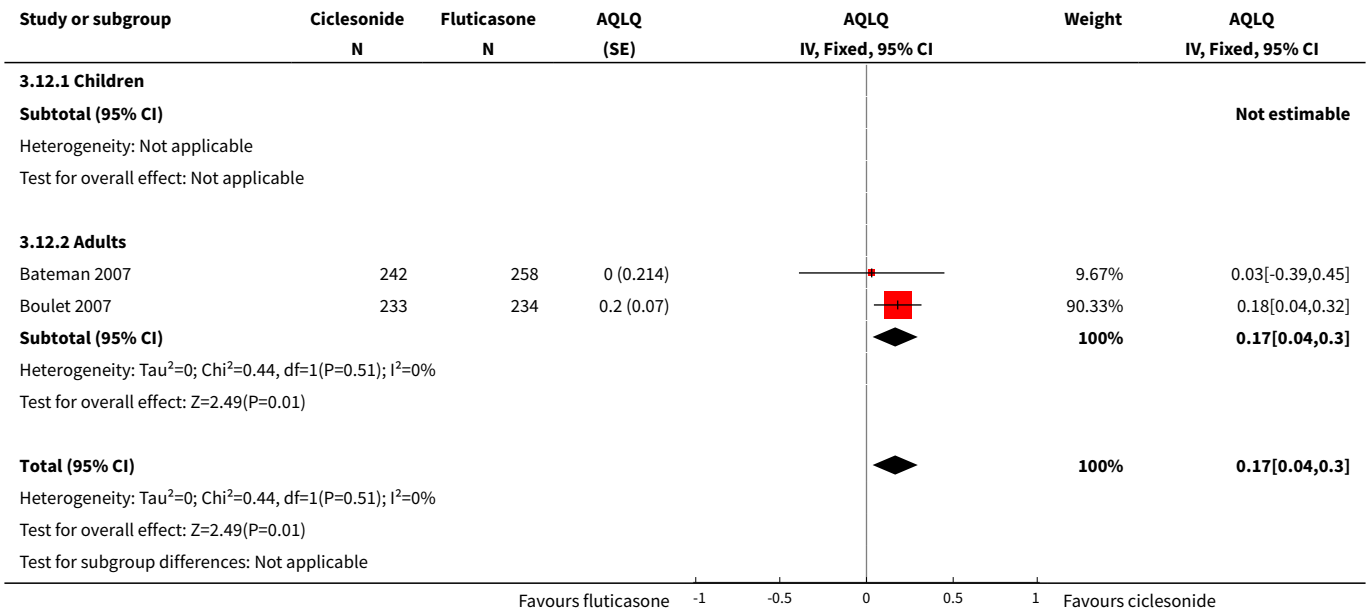
Analysis 3.11. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 11 Change in asthma-symptom free days.

Study or subgroup	Ciclesonide N	Fluticasone N	% (SE)	% IV, Fixed, 95% CI	% IV, Fixed, 95% CI
3.11.1 Children					
Pedersen 2006	277	279	-1.1 (1.8)		-1.07[-4.6,2.46]
3.11.2 Adults					

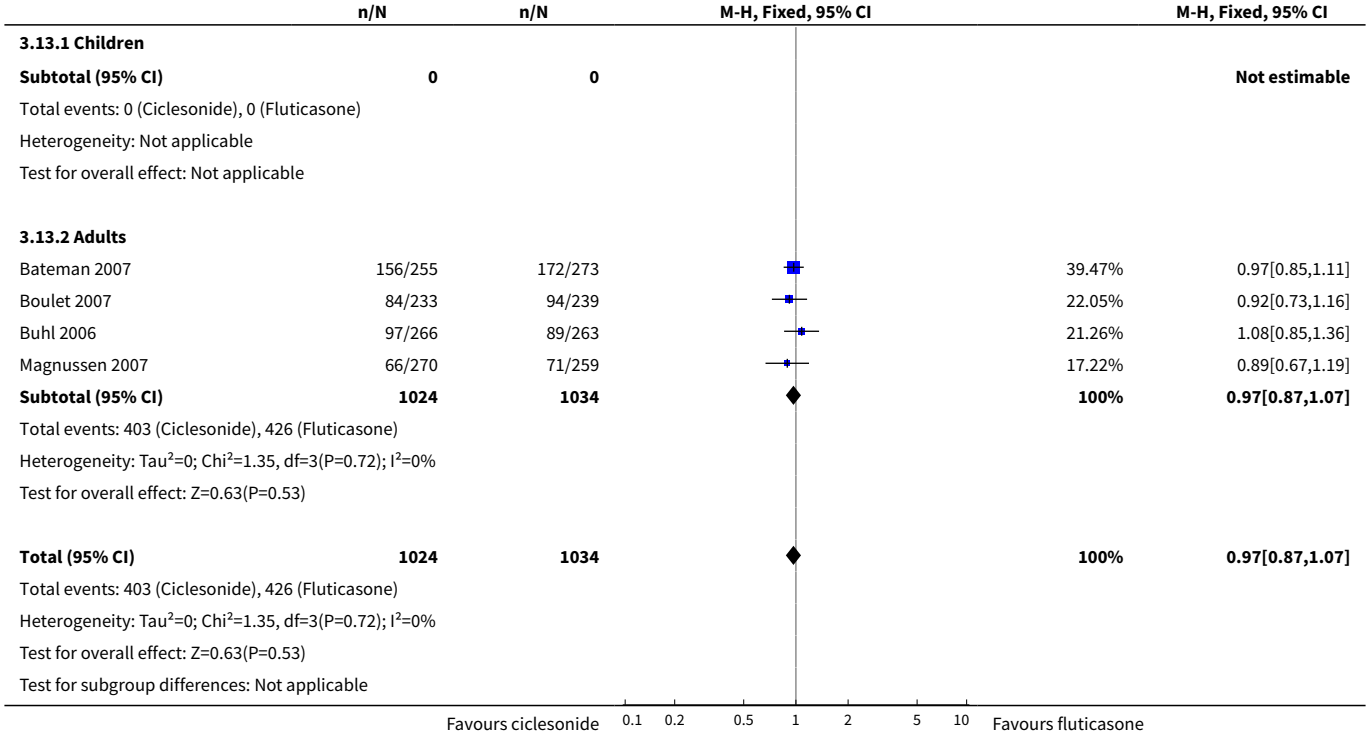


Favours ciclesonide — Favours fluticasone

Analysis 3.12. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 12 Change in quality of life (AQLQ).

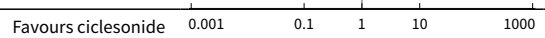


Analysis 3.13. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 13 Adverse events.



Analysis 3.14. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 14 Candidiasis.

Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.14.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ciclesonide), 0 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.14.2 Adults					
Bateman 2007	5/255	13/273		49.33%	0.41[0.15,1.14]
Boulet 2007	0/233	9/239		36.85%	0.05[0,0.92]
Buhl 2006	0/266	3/263		13.83%	0.14[0.01,2.72]
Subtotal (95% CI)	**754**	**775**		**100%**	**0.24[0.1,0.58]**
Total events: 5 (Ciclesonide), 25 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=2.25, df=2(P=0.33); I^2=10.92%					
Test for overall effect: Z=3.17(P=0)					
Total (95% CI)	**754**	**775**		**100%**	**0.24[0.1,0.58]**
Total events: 5 (Ciclesonide), 25 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=2.25, df=2(P=0.33); I^2=10.92%					
Test for overall effect: Z=3.17(P=0)					
Test for subgroup differences: Not applicable					



Analysis 3.15. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 15 Pharyngitis.

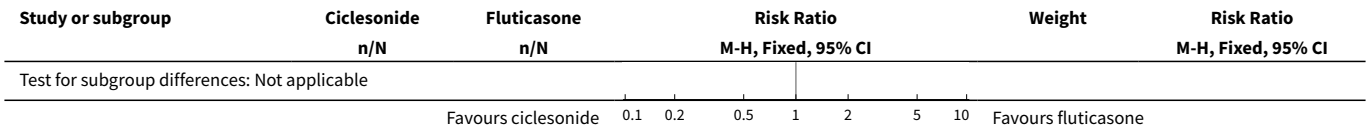
Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.15.1 Children					
Pedersen 2006	12/277	11/279		18.56%	1.1[0.49,2.45]
Subtotal (95% CI)	**277**	**279**		**18.56%**	**1.1[0.49,2.45]**
Total events: 12 (Ciclesonide), 11 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.23(P=0.82)					
3.15.2 Adults					
Bateman 2007	30/255	24/273		39.26%	1.34[0.8,2.23]
Boulet 2007	15/233	15/239		25.08%	1.03[0.51,2.05]
Buhl 2006	11/266	7/263		11.92%	1.55[0.61,3.95]
Magnussen 2007	5/270	3/259		5.19%	1.6[0.39,6.62]
Subtotal (95% CI)	**1024**	**1034**		**81.44%**	**1.29[0.9,1.85]**
Total events: 61 (Ciclesonide), 49 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=0.68, df=3(P=0.88); I^2=0%					
Test for overall effect: Z=1.38(P=0.17)					
Total (95% CI)	**1301**	**1313**		**100%**	**1.25[0.9,1.74]**
Total events: 73 (Ciclesonide), 60 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=0.81, df=4(P=0.94); I^2=0%					
Test for overall effect: Z=1.35(P=0.18)					
Test for subgroup differences: Not applicable					

Analysis 3.16. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 16 Upper resiratory tract infection.

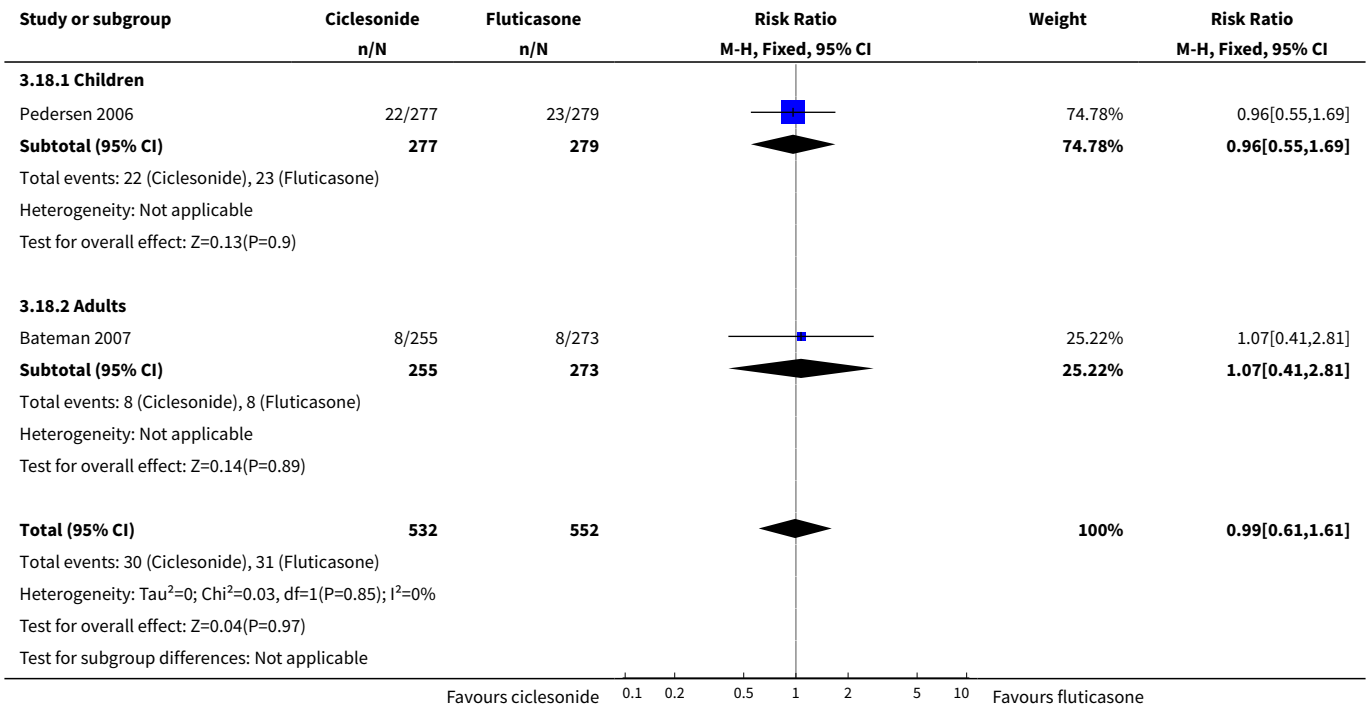
Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.16.1 Children					
Pedersen 2006	19/277	18/279		30.73%	1.06[0.57,1.98]
Subtotal (95% CI)	**277**	**279**		**30.73%**	**1.06[0.57,1.98]**
Total events: 19 (Ciclesonide), 18 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.19(P=0.85)					
3.16.2 Adults					
Bateman 2007	21/255	20/273		33.09%	1.12[0.62,2.02]
Buhl 2006	20/266	21/263		36.18%	0.94[0.52,1.7]
Subtotal (95% CI)	**521**	**536**		**69.27%**	**1.03[0.68,1.56]**
Total events: 41 (Ciclesonide), 41 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=0.17, df=1(P=0.68); I^2=0%					
Test for overall effect: Z=0.13(P=0.89)					
Total (95% CI)	**798**	**815**		**100%**	**1.04[0.74,1.47]**
Total events: 60 (Ciclesonide), 59 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=0.18, df=2(P=0.91); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
Test for subgroup differences: Not applicable					

Analysis 3.17. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 17 Headache.

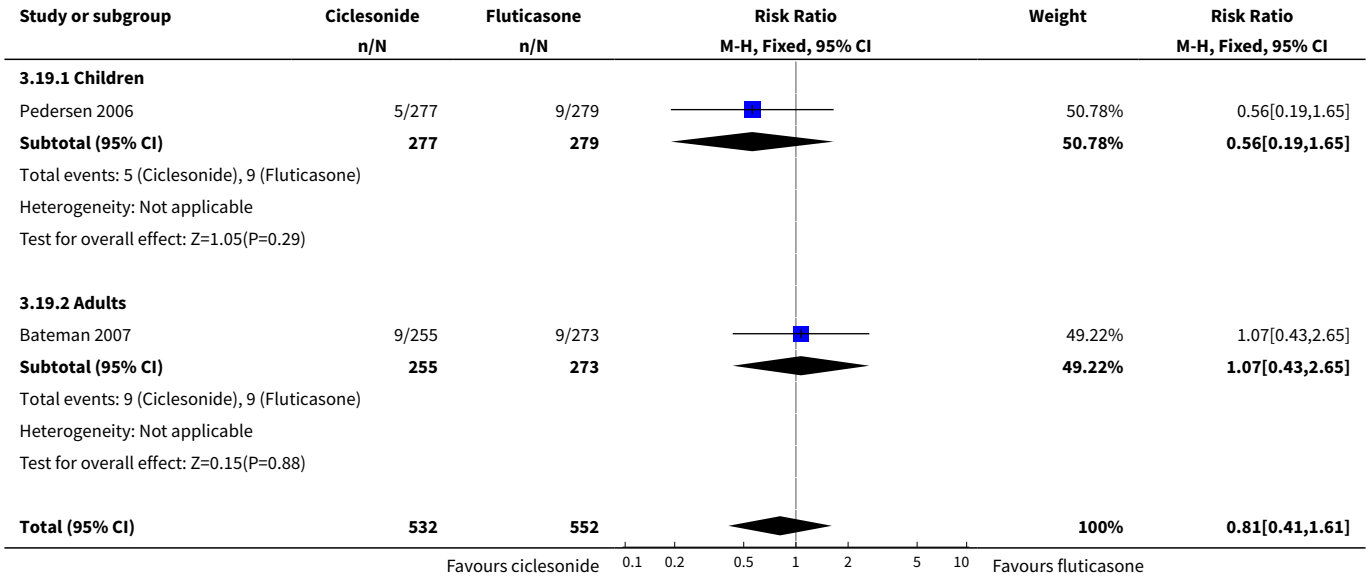
Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.17.1 Children					
Pedersen 2006	10/277	7/279		24.37%	1.44[0.56,3.73]
Subtotal (95% CI)	**277**	**279**		**24.37%**	**1.44[0.56,3.73]**
Total events: 10 (Ciclesonide), 7 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.75(P=0.45)					
3.17.2 Adults					
Bateman 2007	6/255	12/273		40.5%	0.54[0.2,1.41]
Buhl 2006	9/266	10/263		35.14%	0.89[0.37,2.15]
Subtotal (95% CI)	**521**	**536**		**75.63%**	**0.7[0.37,1.34]**
Total events: 15 (Ciclesonide), 22 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=1.08(P=0.28)					
Total (95% CI)	**798**	**815**		**100%**	**0.88[0.52,1.49]**
Total events: 25 (Ciclesonide), 29 (Fluticasone)					
Heterogeneity: Tau^2=0; Chi^2=2.05, df=2(P=0.36); I^2=2.24%					
Test for overall effect: Z=0.47(P=0.64)					

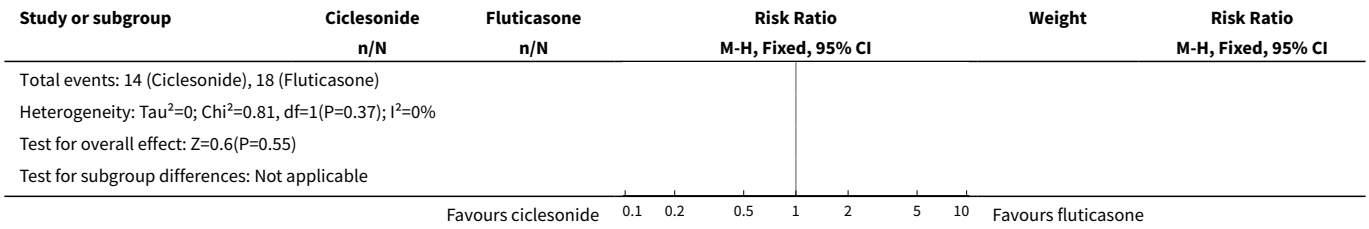


Analysis 3.18. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 18 Rhinitis.

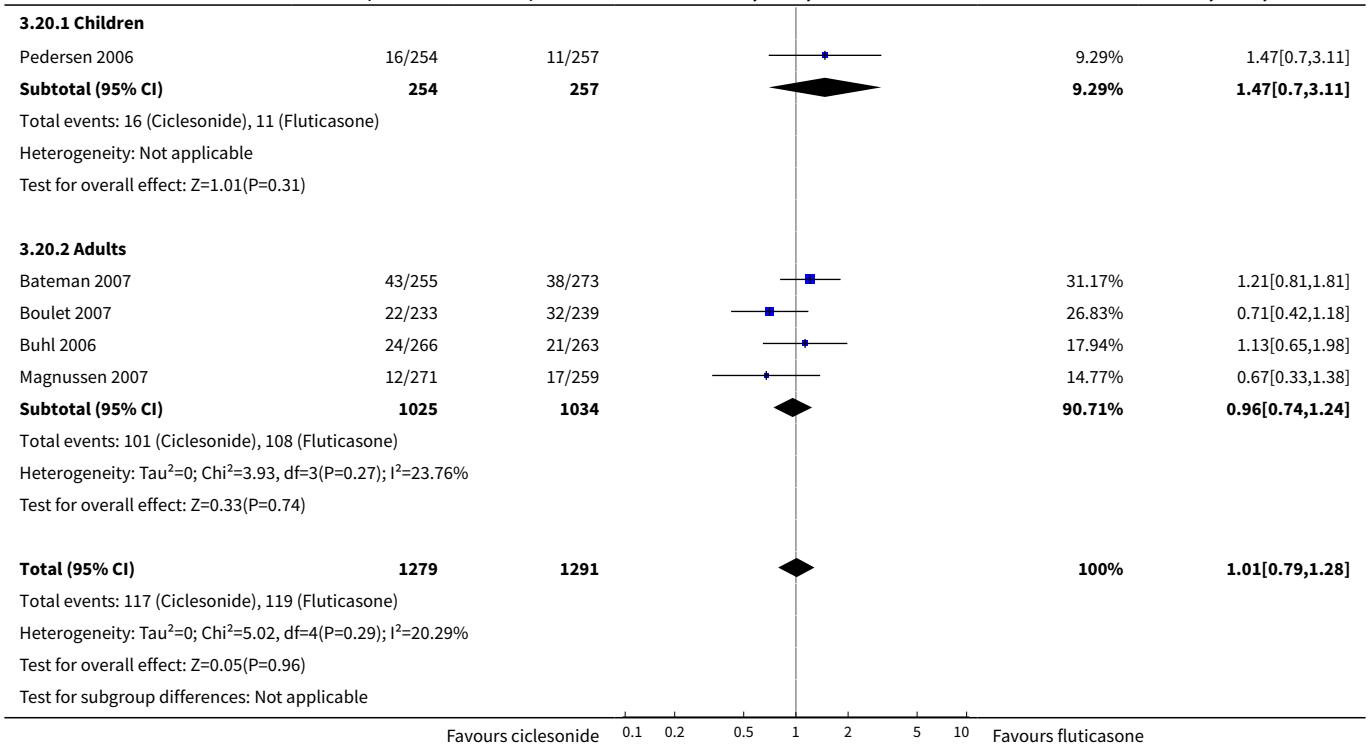


Analysis 3.19. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 19 Sinusitis.

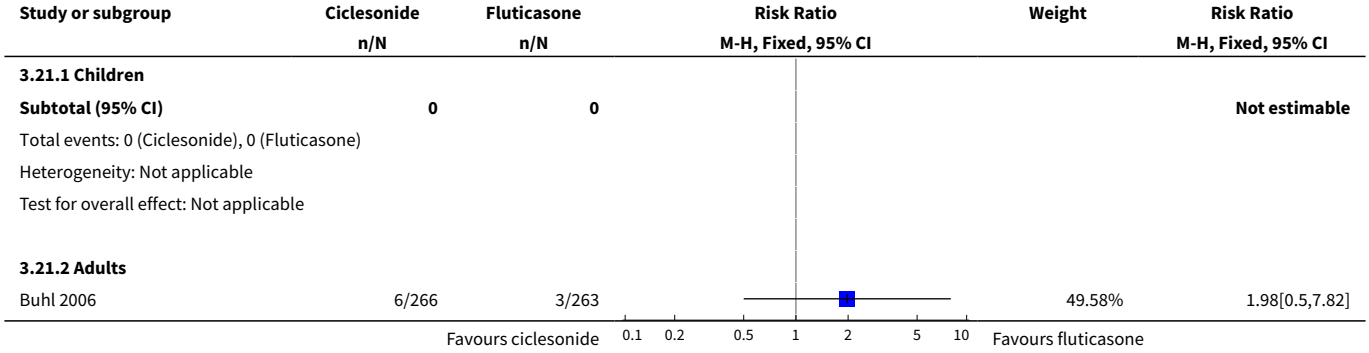


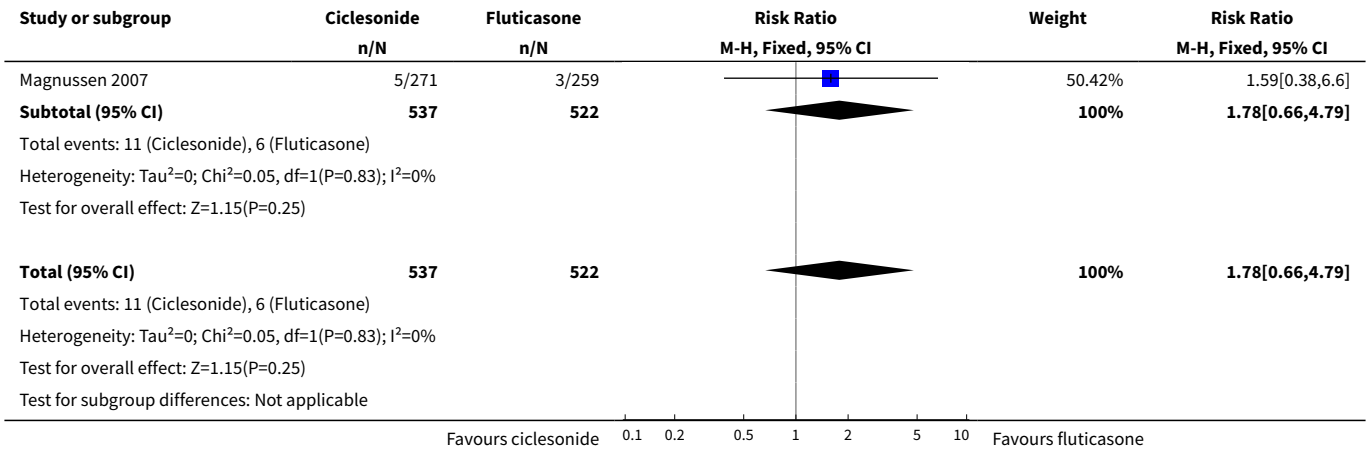


Analysis 3.20. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 20 Withdrawals.

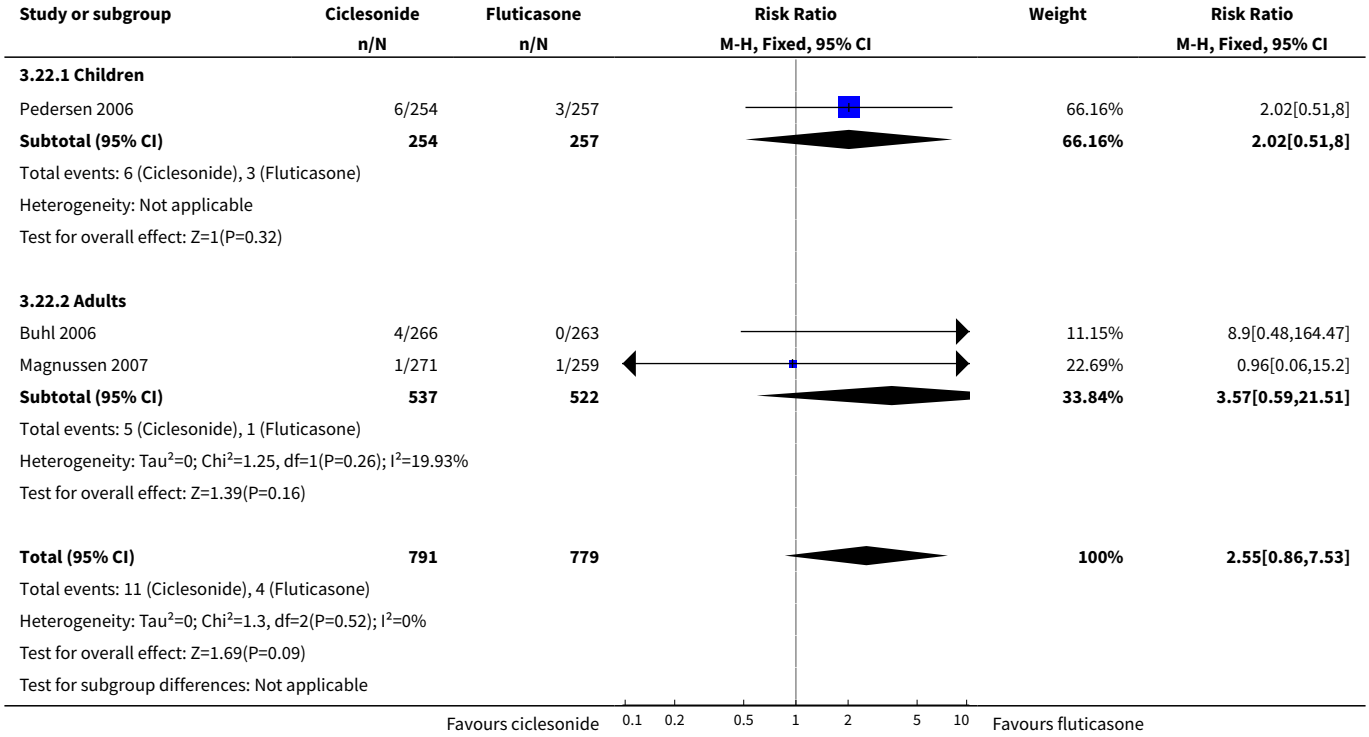


Analysis 3.21. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 21 Withdrawals (adverse events).





Analysis 3.22. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 22 Withdrawals (lack of efficacy).



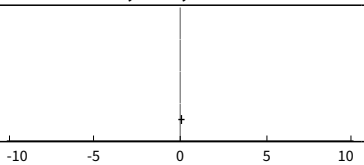
Analysis 3.23. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 23 Data not suitable for meta-analysis (medians).

Data not suitable for meta-analysis (medians)

Study	Outcome	Effect size (median)
Bateman 2007	Rescue medication use; symptoms	-0.07 puffs/d; 0
Boulet 2007	Symptoms	0
Buhl 2006	Rescue medication use	-0.21 puff/s

Analysis 3.24. Comparison 3 Ciclesonide versus Fluticasone (dose ratio 1:1), Outcome 24 Change in asthma-symptom scores.

Study or subgroup	Ciclesonide N	Fluticasone N	symptoms (SE)	symptoms IV, Fixed, 95% CI	symptoms IV, Fixed, 95% CI
3.24.1 Children					
3.24.2 Adults					
Magnussen 2007	270	259	0.1 (0.092)		0.07[-0.11,0.25]



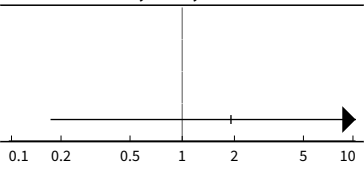
Comparison 4. Ciclesonide versus Fluticasone (dose ratio 1:2)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbations requiring oral steroids	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change from baseline in FEV1	1		L (Fixed, 95% CI)	Totals not selected
2.1 Children	0		L (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		L (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Endpoint FEV1 (Litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Endpoint FEV1 predicted (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in FVC	1		L (Fixed, 95% CI)	Totals not selected
5.1 Children	0		L (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	1		L (Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Endpoint day symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Endpoint night symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Rescue medication use (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Change in clinic PEF	1		L/min (Fixed, 95% CI)	Totals not selected
9.1 Children	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	1		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Change in rescue medication	1		puffs/d (Fixed, 95% CI)	Totals not selected
10.1 Children	0		puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	1		puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Adverse events	2	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
11.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	2	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
12 Nasopharyngitis	2	1017	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.72, 1.91]
12.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	2	1017	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.72, 1.91]
13 Withdrawals	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Withdrawal (adverse events)	2	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.24, 1.59]
14.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	2	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.24, 1.59]

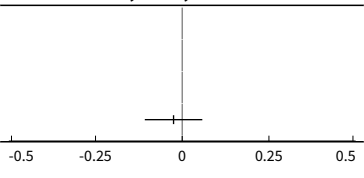
Analysis 4.1. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 1 Exacerbations requiring oral steroids.

Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Children				
4.1.2 Adults				
Magnussen 2007	2/271	1/259		1.91[0.17,20.95]



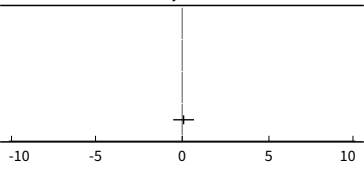
Analysis 4.2. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 2 Change from baseline in FEV1.

Study or subgroup	Ciclesonide N	Fluticasone N	L (SE)	L IV, Fixed, 95% CI	L IV, Fixed, 95% CI
4.2.1 Children					
4.2.2 Adults					
Magnussen 2007	278	259	-0 (0.042)		-0.02[-0.11,0.06]



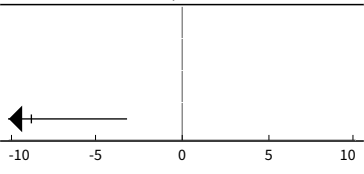
Analysis 4.3. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 3 Endpoint FEV1 (Litres).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.3.1 Children						
4.3.2 Adults						
Zietkowski 2006	12	3.2 (0.6)	11	3.1 (0.8)		0.08[-0.52,0.68]



Analysis 4.4. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 4 Endpoint FEV1 predicted (%).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.4.1 Children						
4.4.2 Adults						
Zietkowski 2006	12	93.1 (6.9)	11	101.8 (6.6)		-8.7[-14.22,-3.18]



Analysis 4.5. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 5 Change in FVC.

Study or subgroup	Ciclesonide N	Fluticasone N	L (SE)	L IV, Fixed, 95% CI	L IV, Fixed, 95% CI
4.5.1 Children					
4.5.2 Adults					
Magnussen 2007	278	259	0.1 (0.052)		0.06[-0.04,0.16]

Favours fluticasone -100 -50 0 50 100 Favours ciclesonide

Analysis 4.6. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 6 Endpoint day symptoms.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.6.1 Children						
4.6.2 Adults						
Zietkowski 2006	12	0.5 (0.5)	11	0.6 (0.6)		-0.08[-0.55,0.39]

Favours ciclesonide -10 -5 0 5 10 Favours fluticasone

Analysis 4.7. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 7 Endpoint night symptoms.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.7.1 Children						
4.7.2 Adults						
Zietkowski 2006	12	0.2 (0.3)	11	0.2 (0.2)		0.02[-0.18,0.22]

Favours ciclesonide -10 -5 0 5 10 Favours fluticasone

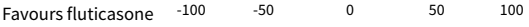
Analysis 4.8. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 8 Rescue medication use (puffs/d).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Fluticasone N	Fluticasone Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.8.1 Children						
4.8.2 Adults						
Zietkowski 2006	12	0.6 (0.6)	11	0.6 (0.5)		-0.04[-0.45,0.37]

Favours ciclesonide -10 -5 0 5 10 Favours fluticasone

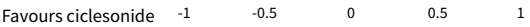
Analysis 4.9. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 9 Change in clinic PEF.

Study or subgroup	Ciclesonide N	Fluticasone N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
4.9.1 Children					
4.9.2 Adults					
Magnussen 2007	278	259	-1.4 (7.092)		-1.4[-15.3,12.5]



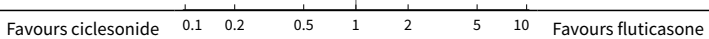
Analysis 4.10. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 10 Change in rescue medication.

Study or subgroup	Ciclesonide N	Fluticasone N	puffs/d (SE)	puffs/d IV, Fixed, 95% CI	puffs/d IV, Fixed, 95% CI
4.10.1 Children					
4.10.2 Adults					
Magnussen 2007	278	259	0 (0.071)		0[-0.14,0.14]

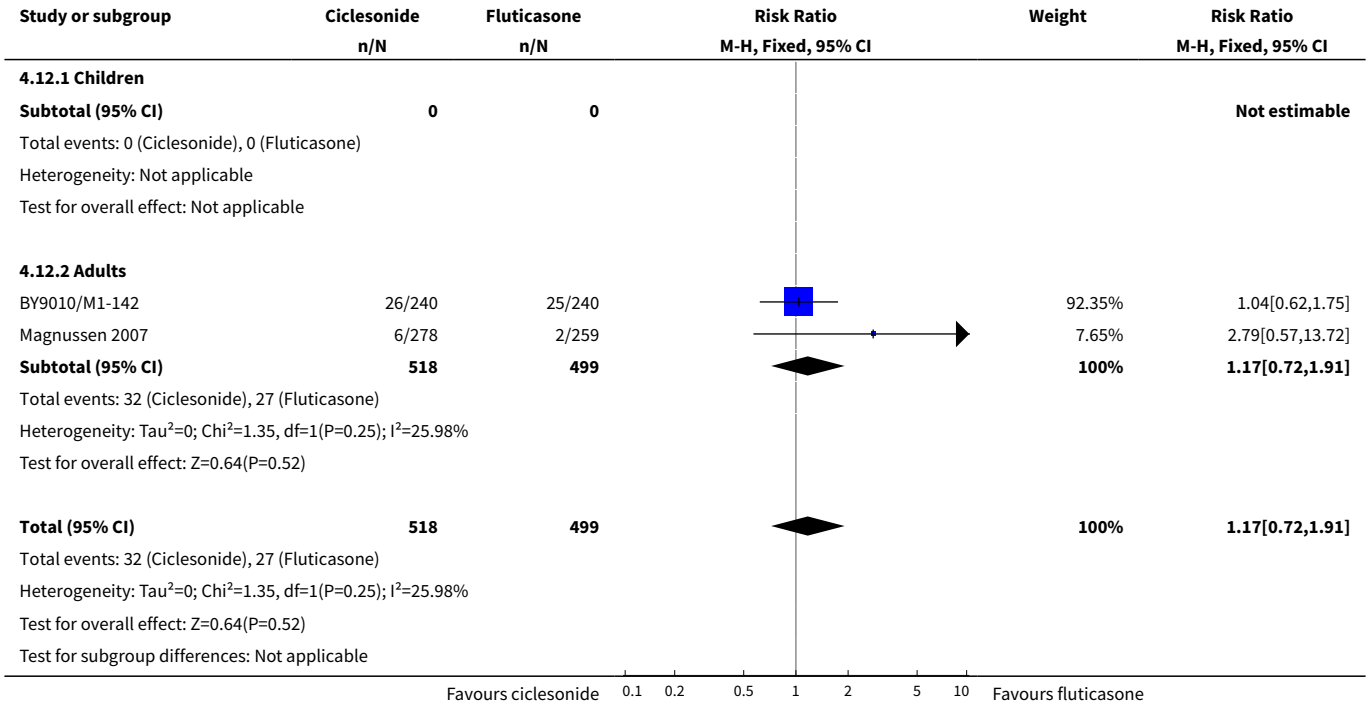


Analysis 4.11. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 11 Adverse events.

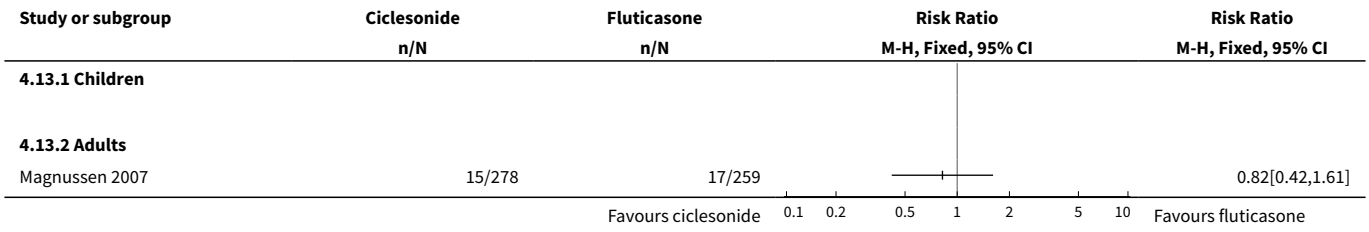
Study or subgroup	Ciclesonide n/N	Fluticasone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.11.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ciclesonide), 0 (Fluticasone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.11.2 Adults					
BY9010/M1-142	106/240	103/240		58.35%	1.03[0.84,1.26]
Magnussen 2007	70/278	71/259		41.65%	0.92[0.69,1.22]
Subtotal (95% CI)	**518**	**499**		**100%**	**0.98[0.83,1.16]**
Total events: 176 (Ciclesonide), 174 (Fluticasone)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.41$, df=1(P=0.52); $I^2=0\%$					
Test for overall effect: Z=0.2(P=0.84)					
Total (95% CI)	**518**	**499**		**100%**	**0.98[0.83,1.16]**
Total events: 176 (Ciclesonide), 174 (Fluticasone)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.41$, df=1(P=0.52); $I^2=0\%$					
Test for overall effect: Z=0.2(P=0.84)					
Test for subgroup differences: Not applicable					



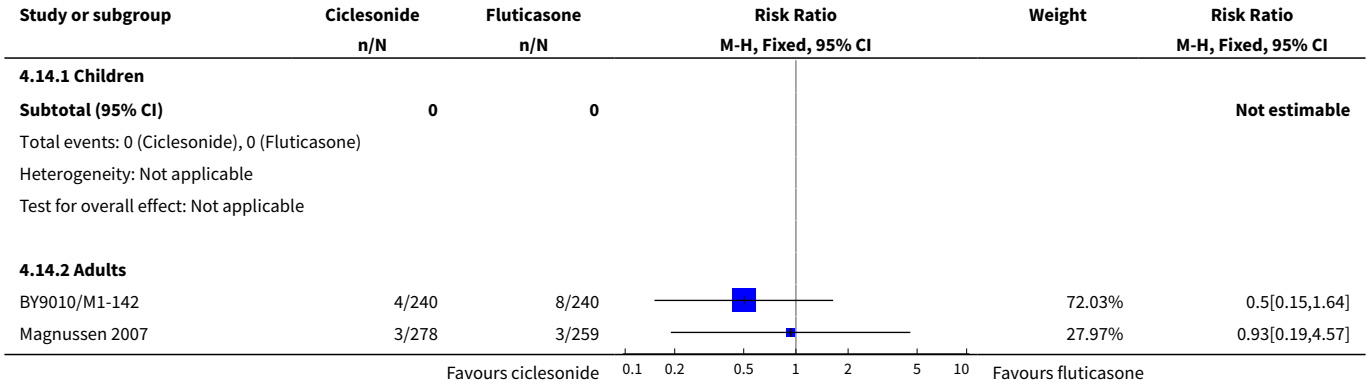
Analysis 4.12. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 12 Nasopharyngitis.

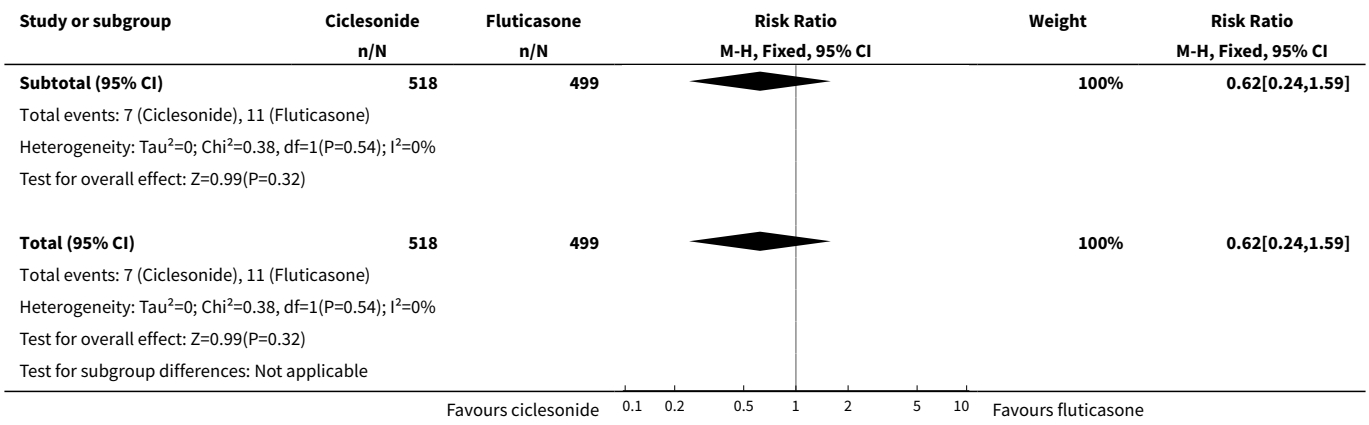


Analysis 4.13. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 13 Withdrawals.



Analysis 4.14. Comparison 4 Ciclesonide versus Fluticasone (dose ratio 1:2), Outcome 14 Withdrawal (adverse events).



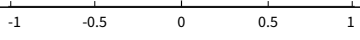


Comparison 5. Change in FEV1: Intention to treat versus per protocol analysis populations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1)	4		L (Fixed, 95% CI)	Subtotals only
1.1 ITT	4	1322	L (Fixed, 95% CI)	0.03 [-0.01, 0.07]
1.2 PP	2	618	L (Fixed, 95% CI)	0.01 [-0.05, 0.06]
2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2)	7		L (Fixed, 95% CI)	Subtotals only
2.1 ITT	5	1633	L (Fixed, 95% CI)	-0.02 [-0.05, 0.00]
2.2 PP	6	1574	L (Fixed, 95% CI)	-0.03 [-0.06, 0.00]
3 Ciclesonide versus Fluticasone (dose ratio 1:1)	5		L (Fixed, 95% CI)	Subtotals only
3.1 ITT	5	2599	L (Fixed, 95% CI)	-0.02 [-0.04, 0.01]
3.2 PP	5	2178	L (Fixed, 95% CI)	-0.01 [-0.04, 0.02]
4 Ciclesonide versus Fluticasone (dose ratio 1:2)	2		L (Fixed, 95% CI)	Subtotals only
4.1 ITT	1	537	L (Fixed, 95% CI)	-0.03 [-0.11, 0.06]
4.2 PP	2	888	L (Fixed, 95% CI)	-0.05 [-0.11, 0.01]

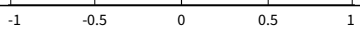
Analysis 5.1. Comparison 5 Change in FEV1: Intention to treat versus per protocol analysis populations, Outcome 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1).

Study or subgroup	Treatment N	Control N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
5.1.1 ITT						
Hansel 2006	184	167	-0.1 (0.046)		20.64%	-0.1[-0.19,-0.01]
Ukena 2006	198	201	0.1 (0.046)		20.64%	0.1[0.01,0.19]
Boulet 2006	179	180	0.1 (0.03)		48%	0.05[-0.01,0.11]
Adachi 2007	107	106	0.1 (0.064)		10.72%	0.07[-0.05,0.19]
Subtotal (95% CI)					**100%**	**0.03[-0.01,0.07]**
Heterogeneity: Tau^2=0; Chi^2=11.18, df=3(P=0.01); I^2=73.16%						
Test for overall effect: Z=1.51(P=0.13)						
5.1.2 PP						
Hansel 2006	158	140	-0.1 (0.051)		31.64%	-0.09[-0.19,0.01]
Boulet 2006	160	160	0.1 (0.035)		68.36%	0.05[-0.02,0.12]
Subtotal (95% CI)					**100%**	**0.01[-0.05,0.06]**
Heterogeneity: Tau^2=0; Chi^2=5.15, df=1(P=0.02); I^2=80.59%						
Test for overall effect: Z=0.2(P=0.84)						
Test for subgroup differences: Chi^2=0.53, df=1 (P=0.47), I^2=0%						



Analysis 5.2. Comparison 5 Change in FEV1: Intention to treat versus per protocol analysis populations, Outcome 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2).

Study or subgroup	Ciclesonide N	BDP/BUD N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
5.2.1 ITT						
Niphadkar 2005b	131	66	0 (0.051)		6.09%	0.02[-0.08,0.12]
Niphadkar 2005a	133	67	-0 (0.051)		6.09%	-0.04[-0.14,0.06]
von Berg 2007	416	205	-0 (0.021)		37.33%	-0.02[-0.06,0.02]
Adachi 2007	106	106	-0 (0.036)		12.43%	-0.03[-0.1,0.04]
Vermeulen 2007	272	131	-0 (0.02)		38.06%	-0.03[-0.07,0.01]
Subtotal (95% CI)					**100%**	**-0.02[-0.05,0]**
Heterogeneity: Tau^2=0; Chi^2=1.01, df=4(P=0.91); I^2=0%						
Test for overall effect: Z=1.86(P=0.06)						
5.2.2 PP						
Niphadkar 2005a	128	60	0 (0.051)		10.14%	0.01[-0.09,0.11]
Niphadkar 2005b	126	60	0 (0.051)		10.14%	0.04[-0.06,0.14]
Vermeulen 2007	249	122	-0 (0.054)		9.05%	-0.02[-0.12,0.09]
von Berg 2007	340	173	-0 (0.022)		56.02%	-0.03[-0.08,0.01]
BY9010/M1-136	101	114	-0.1 (0.051)		10.14%	-0.13[-0.23,-0.03]
BY9010/M1-137	51	50	-0 (0.077)		4.51%	-0.01[-0.16,0.14]
Subtotal (95% CI)					**100%**	**-0.03[-0.06,0]**
Heterogeneity: Tau^2=0; Chi^2=6.28, df=5(P=0.28); I^2=20.44%						
Test for overall effect: Z=1.78(P=0.08)						
Test for subgroup differences: Chi^2=0.07, df=1 (P=0.79), I^2=0%						



Analysis 5.3. Comparison 5 Change in FEV1: Intention to treat versus per protocol analysis populations, Outcome 3 Ciclesonide versus Fluticasone (dose ratio 1:1).

Study or subgroup	Ciclesonide N	Fluticasone N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
5.3.1 ITT						
Pedersen 2006	277	279	0 (0.021)		43.12%	0[-0.04,0.04]
Magnussen 2007	270	259	-0.1 (0.041)		11.42%	-0.09[-0.17,-0.01]
Buhl 2006	266	263	-0 (0.041)		11.42%	-0.01[-0.09,0.07]
Boulet 2007	233	234	-0 (0.041)		11.42%	-0.02[-0.1,0.06]
Bateman 2007	249	269	-0 (0.029)		22.61%	-0.01[-0.07,0.04]
Subtotal (95% CI)					**100%**	**-0.02[-0.04,0.01]**
Heterogeneity: Tau²=0; Chi²=3.91, df=4(P=0.42); I²=0%						
Test for overall effect: Z=1.21(P=0.23)						
5.3.2 PP						
Buhl 2006	230	221	-0 (0.042)		13.69%	-0.03[-0.11,0.05]
Magnussen 2007	232	219	-0 (0.051)		9.42%	-0.03[-0.13,0.07]
Pedersen 2006	254	257	0 (0.023)		46.3%	0[-0.04,0.05]
Boulet 2007	201	193	-0 (0.051)		9.42%	-0[-0.1,0.1]
Bateman 2007	171	200	-0 (0.034)		21.19%	-0.03[-0.09,0.04]
Subtotal (95% CI)					**100%**	**-0.01[-0.04,0.02]**
Heterogeneity: Tau²=0; Chi²=0.85, df=4(P=0.93); I²=0%						
Test for overall effect: Z=0.8(P=0.42)						
Test for subgroup differences: Chi²=0.04, df=1 (P=0.84), I²=0%						

Analysis 5.4. Comparison 5 Change in FEV1: Intention to treat versus per protocol analysis populations, Outcome 4 Ciclesonide versus Fluticasone (dose ratio 1:2).

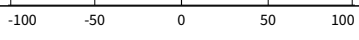
Study or subgroup	Treatment N	Control N	L (SE)	L IV, Fixed, 95% CI	Weight	L IV, Fixed, 95% CI
5.4.1 ITT						
Magnussen 2007	278	259	-0 (0.042)		100%	-0.02[-0.11,0.06]
Subtotal (95% CI)					**100%**	**-0.02[-0.11,0.06]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.59(P=0.55)						
5.4.2 PP						
Magnussen 2007	246	219	-0 (0.05)		39.31%	-0.03[-0.13,0.07]
BY9010/M1-142	216	207	-0.1 (0.04)		60.69%	-0.06[-0.14,0.02]
Subtotal (95% CI)					**100%**	**-0.05[-0.11,0.01]**
Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.63); I²=0%						
Test for overall effect: Z=1.5(P=0.13)						
Test for subgroup differences: Chi²=0.17, df=1 (P=0.68), I²=0%						

Comparison 6. Change in PEF: Intention to treat versus per protocol analysis populations

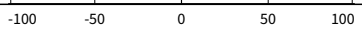
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1)	4		L/min (Fixed, 95% CI)	Subtotals only
1.1 ITT	4	1329	L/min (Fixed, 95% CI)	5.37 [0.12, 10.61]
1.2 PP	2	629	L/min (Fixed, 95% CI)	4.24 [-3.87, 12.34]
2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2)	4		L/min (Fixed, 95% CI)	Subtotals only
2.1 ITT	4	1423	L/min (Fixed, 95% CI)	0.07 [-5.05, 5.19]
2.2 PP	4	1258	L/min (Fixed, 95% CI)	-0.62 [-5.96, 4.73]
3 Ciclesonide versus Fluticasone (dose ratio 1:1)	4		L/min (Fixed, 95% CI)	Subtotals only
3.1 ITT	4	2070	L/min (Fixed, 95% CI)	0.41 [-4.71, 5.53]
3.2 PP	4	1741	L/min (Fixed, 95% CI)	-0.31 [-5.75, 5.13]
4 Ciclesonide versus Fluticasone (dose ratio 1:2)	0		L/min (Fixed, 95% CI)	Totals not selected
4.1 ITT	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 PP	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Change in PEF: Intention to treat versus per protocol analysis populations, Outcome 1 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1).

Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
6.1.1 ITT						
Adachi 2007	106	106	10.1 (5.332)		25.2%	10.09[-0.36,20.54]
Boulet 2006	179	180	6 (4.337)		38.09%	6[-2.5,14.5]
Hansel 2006	188	171	-4 (5.658)		22.38%	-4[-15.09,7.09]
Ukena 2006	198	201	10 (7.071)		14.33%	10[-3.86,23.86]
Subtotal (95% CI)					**100%**	**5.37[0.12,10.61]**
Heterogeneity: Tau²=0; Chi²=3.98, df=3(P=0.26); I²=24.55%						
Test for overall effect: Z=2(P=0.04)						
6.1.2 PP						
Boulet 2006	160	160	8 (5.1)		65.78%	8[-2,18]
Hansel 2006	164	145	-3 (7.071)		34.22%	-3[-16.86,10.86]
Subtotal (95% CI)					**100%**	**4.24[-3.87,12.34]**

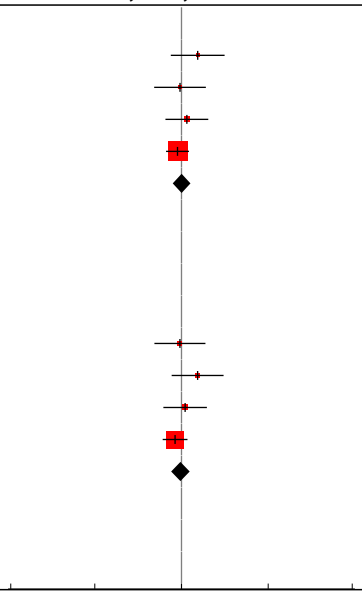


Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=1.59, df=1(P=0.21); I²=37.18%						
Test for overall effect: Z=1.02(P=0.31)						
Test for subgroup differences: Chi²=0.05, df=1 (P=0.82), I²=0%						



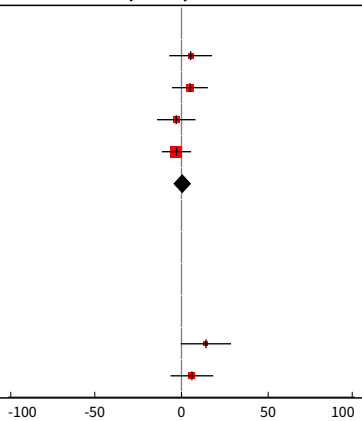
Analysis 6.2. Comparison 6 Change in PEF: Intention to treat versus per protocol analysis populations, Outcome 2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2).

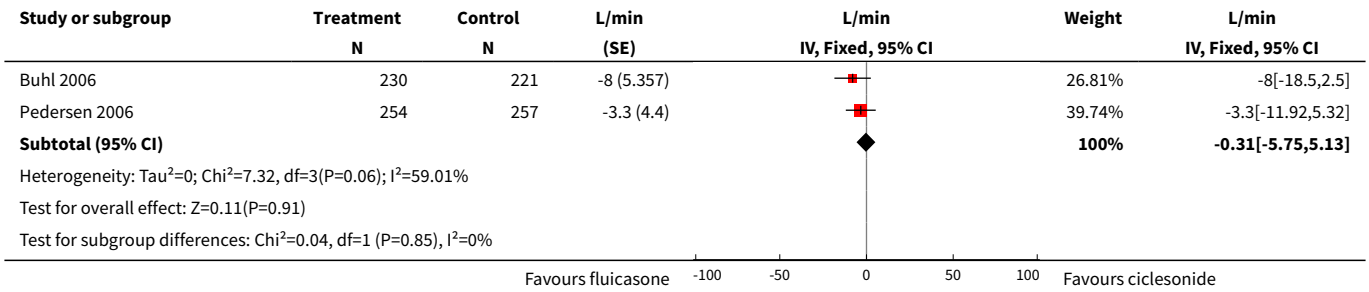
Study or subgroup	Ciclesonide N	BDP/BUD N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
6.2.1 ITT						
Niphadkar 2005a	139	67	9.4 (7.913)		10.89%	9.35[-6.16,24.86]
Niphadkar 2005b	133	66	-0.8 (7.602)		11.8%	-0.85[-15.75,14.05]
Vermeulen 2007	267	130	3.1 (6.3)		17.18%	3.1[-9.25,15.45]
von Berg 2007	416	205	-2.3 (3.367)		60.13%	-2.3[-8.9,4.3]
Subtotal (95% CI)					**100%**	**0.07[-5.05,5.19]**
Heterogeneity: Tau²=0; Chi²=2.12, df=3(P=0.55); I²=0%						
Test for overall effect: Z=0.03(P=0.98)						
6.2.2 PP						
Niphadkar 2005a	128	60	-0.9 (7.505)		13.2%	-0.9[-15.61,13.81]
Niphadkar 2005b	126	60	9.3 (7.635)		12.76%	9.3[-5.66,24.26]
Vermeulen 2007	249	122	2.1 (6.4)		18.16%	2.1[-10.44,14.64]
von Berg 2007	340	173	-3.7 (3.648)		55.88%	-3.7[-10.85,3.45]
Subtotal (95% CI)					**100%**	**-0.62[-5.96,4.73]**
Heterogeneity: Tau²=0; Chi²=2.58, df=3(P=0.46); I²=0%						
Test for overall effect: Z=0.23(P=0.82)						
Test for subgroup differences: Chi²=0.03, df=1 (P=0.86), I²=0%						



Analysis 6.3. Comparison 6 Change in PEF: Intention to treat versus per protocol analysis populations, Outcome 3 Ciclesonide versus Fluticasone (dose ratio 1:1).

Study or subgroup	Treatment N	Control N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
6.3.1 ITT						
Bateman 2007	249	269	5.3 (6.3)		17.18%	5.3[-7.05,17.65]
Boulet 2007	233	234	4.9 (5.26)		24.64%	4.9[-5.41,15.21]
Buhl 2006	266	263	-3 (5.658)		21.3%	-3[-14.09,8.09]
Pedersen 2006	277	279	-2.9 (4.3)		36.88%	-2.9[-11.33,5.53]
Subtotal (95% CI)					**100%**	**0.41[-4.71,5.53]**
Heterogeneity: Tau²=0; Chi²=2.29, df=3(P=0.52); I²=0%						
Test for overall effect: Z=0.16(P=0.88)						
6.3.2 PP						
Bateman 2007	177	208	14.1 (7.4)		14.05%	14.1[-0.4,28.6]
Boulet 2007	201	193	6 (6.296)		19.41%	6[-6.34,18.34]





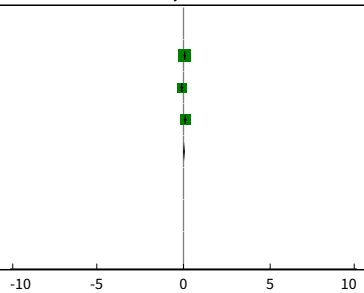
Comparison 8. WMD archive

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	11		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Ciclesonide versus BDP or BUD	3	963	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.02, 0.08]
1.2 Ciclesonide versus BDP or BUD per protocol	1	298	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.19, 0.01]
1.3 Ciclesonide versus BDP or BUD (dose ratio 1:2)	4	1130	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.05, 0.01]
1.4 Ciclesonide versus BDP or BUD pre protocol (dose ratio 1:2)	4	702	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.08, 0.03]
1.5 Ciclesonide versus fluticasone (dose ratio 1:1)	3	1530	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.09, 0.01]
1.6 Ciclesonide versus fluticasone per protocol (dose ratio 1:1)	2	845	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.08, 0.05]
2 Change in am PEF (L/min)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Ciclesonide versus BDP or BUD	3	970	Mean Difference (IV, Fixed, 95% CI)	4.98 [-1.69, 11.64]
2.2 Ciclesonide versus BDP or BUD per protocol	1	309	Mean Difference (IV, Fixed, 95% CI)	-3.0 [-16.86, 10.86]
2.3 Ciclesonide versus BDP or BUD (1:2)	3	616	Mean Difference (IV, Fixed, 95% CI)	7.17 [-0.29, 14.64]
2.4 Ciclesonide versus BDP or BUD (1:2)	2	374	Mean Difference (IV, Fixed, 95% CI)	4.10 [-6.40, 14.61]
2.5 Ciclesonide versus fluticasine (dose ratio 1:1)	3	1525	Mean Difference (IV, Fixed, 95% CI)	0.64 [-6.03, 7.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.6 Ciclesonide versus fluticasine per protocol (dose ratio 1:1)	1	394	Mean Difference (IV, Fixed, 95% CI)	6.00 [-6.34, 18.34]
3 Change in pm PEF (L/min)	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Ciclesonide versus fluticasine (dose ratio 1:1)	1	467	Mean Difference (IV, Fixed, 95% CI)	3.90 [-6.69, 14.49]
3.2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2)	3	918	Mean Difference (IV, Fixed, 95% CI)	-0.99 [-6.63, 4.65]
3.3 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1)	1	399	Mean Difference (IV, Fixed, 95% CI)	10.0 [-3.86, 23.86]
4 Change in quality of life (AQLQ)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Ciclesonide versus fluticasone (dose ratio 1:1)	1	500	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.39, 0.45]
4.2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:2)	1	389	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.14, 0.16]
5 Change in FVC	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Ciclesonide versus BDP/BUD (1:2 dose ratio)	3	615	Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.06, 0.06]
5.2 Ciclesonide versus Beclomethasone or Budesonide (dose ratio 1:1)	2	612	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.02, 0.16]
6 Change in rescue medication	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Ciclesonide versus fluticasone (dose ratio 1:1)	1	504	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 WMD archive, Outcome 1 Change in FEV1.

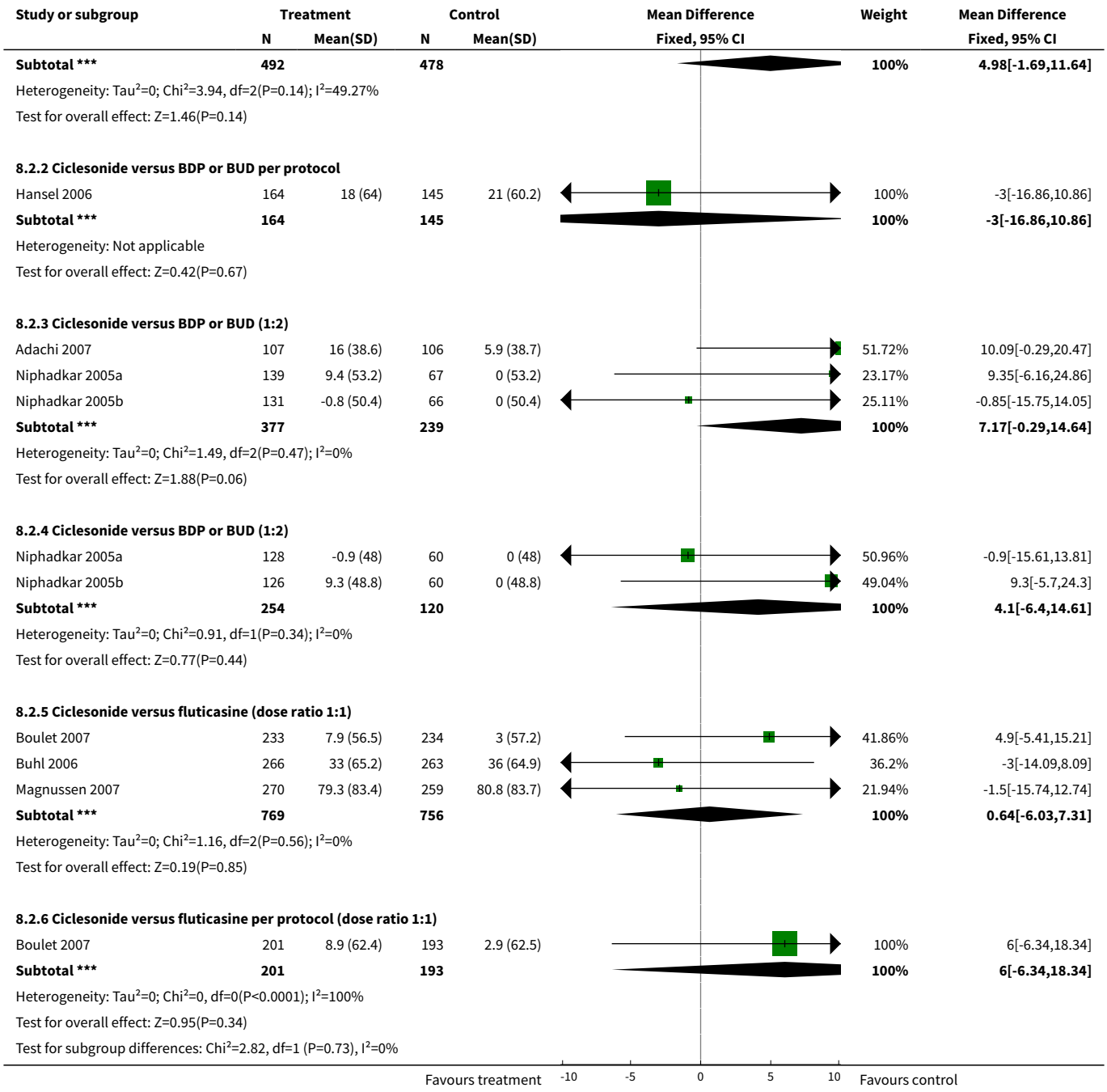
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.1.1 Ciclesonide versus BDP or BUD							
Adachi 2007	107	0.1 (0.3)	106	0 (0.3)		40.14%	0.07[-0.01,0.15]
Hansel 2006	184	0.3 (0.5)	167	0.4 (0.4)		28.33%	-0.1[-0.19,-0.01]
Ukena 2006	198	0.4 (0.5)	201	0.3 (0.5)		31.53%	0.1[0.01,0.19]
Subtotal * **	**489**		**474**			**100%**	**0.03[-0.02,0.08]**
Heterogeneity: Tau²=0; Chi²=10.89, df=2(P=0); I²=81.64%							
Test for overall effect: Z=1.24(P=0.22)							



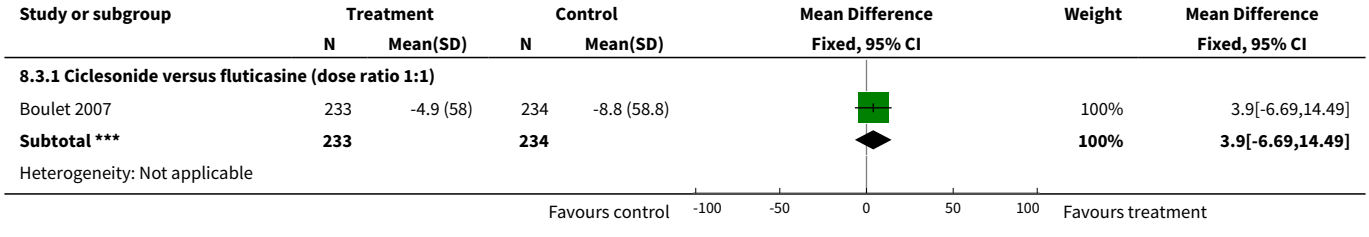
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.1.2 Ciclesonide versus BDP or BUD per protocol							
Hansel 2006	158	0.3 (0.5)	140	0.4 (0.5)		100%	-0.09[-0.19,0.01]
Subtotal ***	**158**		**140**			**100%**	**-0.09[-0.19,0.01]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.72(P=0.08)							
8.1.3 Ciclesonide versus BDP or BUD (dose ratio 1:2)							
Adachi 2007	106	-0 (0.2)	106	0 (0.3)		20.17%	-0.03[-0.1,0.04]
Niphadkar 2005a	139	0 (0.4)	67	0 (0.4)		8.79%	0.04[-0.06,0.14]
Niphadkar 2005b	133	0 (0.3)	66	0 (0.3)		9.09%	0.02[-0.08,0.12]
von Berg 2007	340	0.2 (0.2)	173	0.3 (0.2)		61.94%	-0.03[-0.07,0.01]
Subtotal ***	**718**		**412**			**100%**	**-0.02[-0.05,0.01]**
Heterogeneity: Tau^2=0; Chi^2=2.28, df=3(P=0.52); I^2=0%							
Test for overall effect: Z=1.25(P=0.21)							
8.1.4 Ciclesonide versus BDP or BUD pre protocol (dose ratio 1:2)							
BY9010/M1-136	107	0.4 (0.4)	114	0.5 (0.4)		28.68%	-0.13[-0.23,-0.03]
BY9010/M1-137	51	0.4 (0.4)	50	0.4 (0.4)		14.05%	-0.01[-0.16,0.14]
Niphadkar 2005a	128	0 (0.3)	60	0 (0.3)		28.63%	0.01[-0.09,0.11]
Niphadkar 2005b	126	0 (0.4)	66	0 (0.4)		28.64%	0.04[-0.06,0.14]
Subtotal ***	**412**		**290**			**100%**	**-0.02[-0.08,0.03]**
Heterogeneity: Tau^2=0; Chi^2=5.87, df=3(P=0.12); I^2=48.87%							
Test for overall effect: Z=0.86(P=0.39)							
8.1.5 Ciclesonide versus fluticasone (dose ratio 1:1)							
Boulet 2007	233	0.2 (0.5)	239	0.2 (0.5)		32.23%	-0.02[-0.1,0.06]
Buhl 2006	266	0.5 (0.5)	263	0.5 (0.5)		34.61%	-0.01[-0.09,0.07]
Magnussen 2007	270	0.4 (0.5)	259	0.5 (0.5)		33.17%	-0.09[-0.17,-0.01]
Subtotal ***	**769**		**761**			**100%**	**-0.04[-0.09,0.01]**
Heterogeneity: Tau^2=0; Chi^2=2.2, df=2(P=0.33); I^2=8.93%							
Test for overall effect: Z=1.65(P=0.1)							
8.1.6 Ciclesonide versus fluticasone per protocol (dose ratio 1:1)							
Boulet 2007	201	0 (0.5)	193	0 (0.5)		51.1%	0[-0.09,0.09]
Magnussen 2007	232	0.4 (0.5)	219	0.5 (0.5)		48.9%	-0.03[-0.13,0.07]
Subtotal ***	**433**		**412**			**100%**	**-0.01[-0.08,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.66); I^2=0%							
Test for overall effect: Z=0.42(P=0.67)							
Test for subgroup differences: Chi^2=6.58, df=1 (P=0.25), I^2=24.03%							

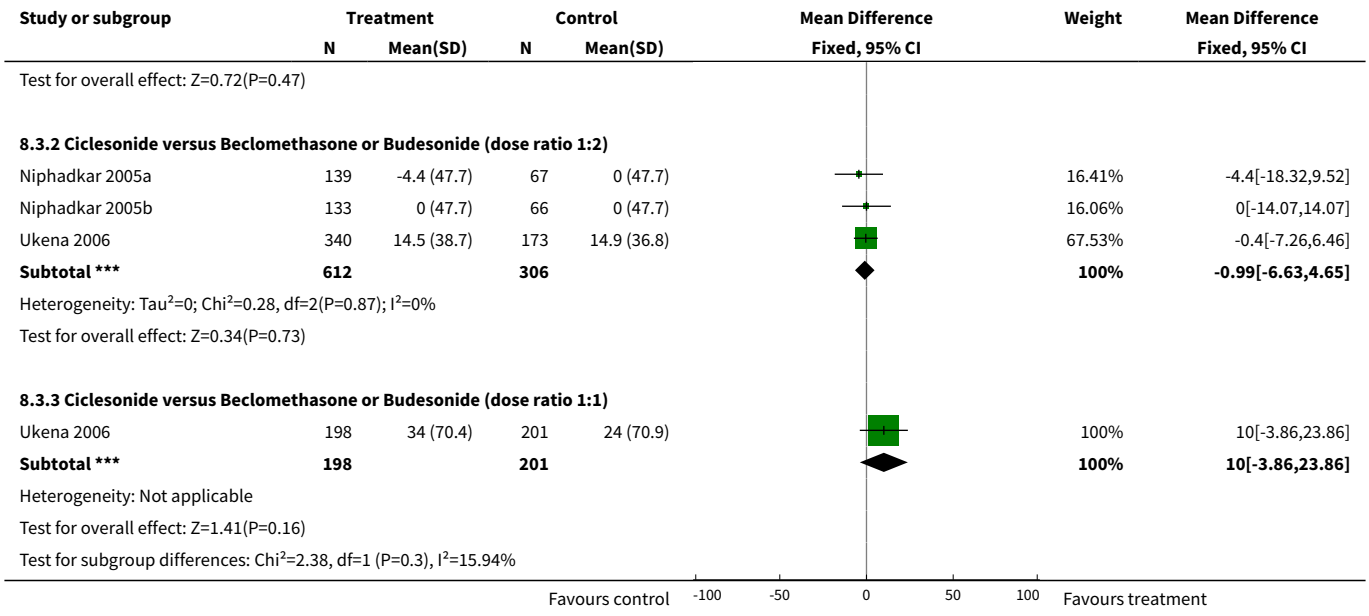
Analysis 8.2. Comparison 8 WMD archive, Outcome 2 Change in am PEF (L/min).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.2.1 Ciclesonide versus BDP or BUD							
Adachi 2007	106	16 (38.9)	106	5.9 (38.7)		40.72%	10.09[-0.36,20.54]
Hansel 2006	188	17 (54.9)	171	21 (52.3)		36.15%	-4[-15.09,7.09]
Ukena 2006	198	46 (70.4)	201	36 (70.9)		23.14%	10[-3.86,23.86]

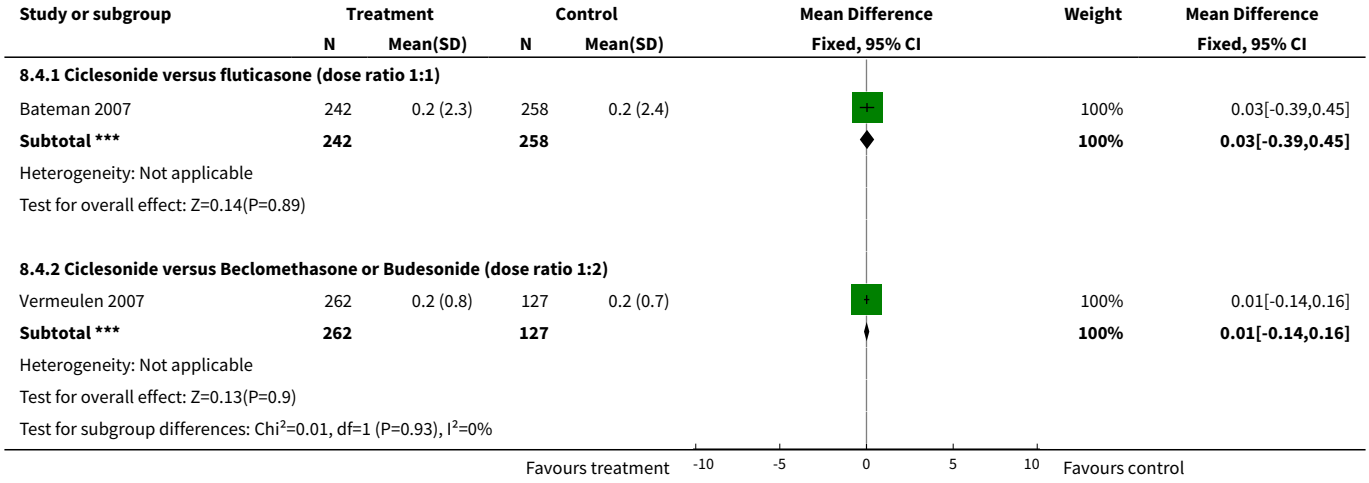


Analysis 8.3. Comparison 8 WMD archive, Outcome 3 Change in pm PEF (L/min).

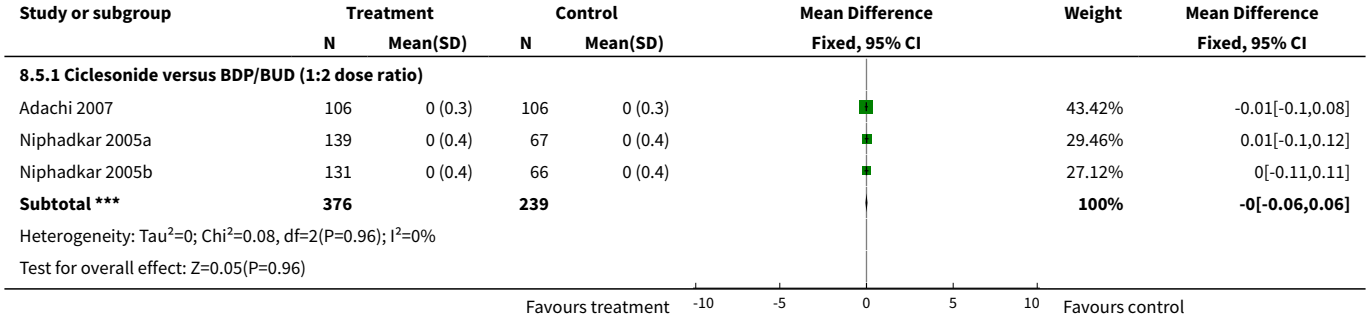


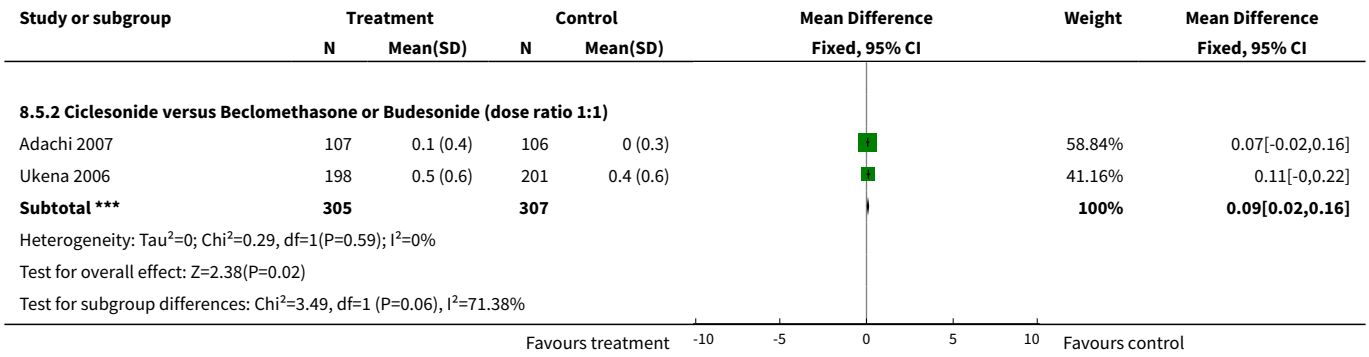


Analysis 8.4. Comparison 8 WMD archive, Outcome 4 Change in quality of life (AQLQ).

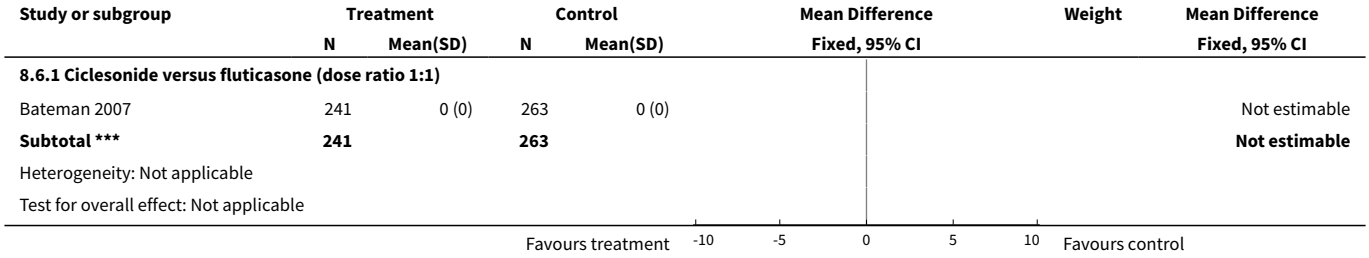


Analysis 8.5. Comparison 8 WMD archive, Outcome 5 Change in FVC.





Analysis 8.6. Comparison 8 WMD archive, Outcome 6 Change in rescue medication.



ADDITIONAL TABLES

Table 1. Ciclesonide & comparator dose

Study ID	ICS criterion (BDP)	Dose of CIC	Comparator
Adachi 2007	>800mcg	i) 400 ii) 800	BDP800
Adler 2006	Not reported	200	FP500
Bateman 2007	1000-2000	800	FP660
Bernstein 2004	Not reported	i) 400 ii) 800	FP1000
Boulet 2006	320-640	400	BUD400
Boulet 2007	<1000	400	FP400
Buhl 2006	<500	200	FP200
BY9010/M1-136	<500	200	BUD400
BY9010/M1-137	<500	200	BUD400
BY9010/M1-142	<500	100	FP200

Table 1. Ciclesonide & comparator dose *(Continued)*

Hansel 2006	<500	i) 100 ii) 200	BUD200
Lipworth 2005	0	i) 400 ii) 800	FP1000
Magnussen 2007	<500	i) 100 ii) 200	FP200
Niphadkar 2005	<500	200	BUD200
Pedersen 2006	<400	200	FP200
Ukena 2006	<500	400	BUD400
Vermeulen 2007	400-800	400	BUD800
von Berg 2007	<400	200	BUD400
Zietkowski 2006	500	i) 100 ii) 200	FP200

WHAT'S NEW

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

HISTORY

Protocol first published: Issue 4, 2006
Review first published: Issue 2, 2008

Date	Event	Description
17 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

PM: initiation of protocol; assessment of studies, data extraction, write-up
TL: Assessment of studies, data extraction, data entry & analysis, write-up
PG: Protocol development, write-up, contact editor

DECLARATIONS OF INTEREST

None declared.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Cochrane Fellowship from the Health Research Board, Ireland.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Androstadienes [therapeutic use]; Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Beclomethasone [therapeutic use]; Budesonide [therapeutic use]; Chronic Disease; Fluticasone; Pregnenediones [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans