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Ciclesonide versus placebo for chronic asthma in adults and children (Review)

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[Intervention Review]

Ciclesonide versus placebo for chronic asthma in adults and children

Pat Manning [1], Peter G Gibson[2], Toby J Lasserson[3]

[1]Consultants Clinic, Bon Secours Hospital, Dublin , Ireland. [2]Department of Respiratory and Sleep Medicine, John Hunter Hospital, Hunter Mail Centre, Australia. [3]Community Health Sciences, St George's, University of London, London, UK

Contact: Pat Manning , Consultants Clinic, Bon Secours Hospital, Glasnevin, Dublin , 9, Ireland. pjmanning@eircom.net.

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ABSTRACT

Background

Inhaled corticosteroids are an integral part of asthma management, and act as an anti-inflammatory agent in the airways of the lung. These agents confer 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 has efficient distribution and release properties that mean it can be taken once daily, making it potentially useful in ongoing asthma management.

Objectives

To assess the efficacy of inhaled ciclesonide in adults and children with chronic asthma.

Search methods

We searched the Cochrane Airways Group register of trials with pre-defined terms. Additional searches of CENTRAL and PubMed 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 placebo, and we also included studies comparing ciclesonide at different doses.

Data collection and analysis

Two authors assessed studies for inclusion in the review, extracted data independently and checked each others' work. We contacted study investigators in order to obtain additional data. Extracted data were entered into RevMan 4.2 and analysed as fixed effect mean differences for continuous data, and fixed effect risk ratios for dichotomous data.

Main results

Eighteen trials (reporting 20 study comparisons) met the review entry criteria. We report findings from 18 group comparisons where data were available (6343 participants, of whom 1692 were children).

Ciclesonide versus placebo: The short duration of the included studies means that there is a lack of data with respect to the impact of ciclesonide on asthma exacerbations. At doses of 100 mcg/d or less up to 400 mcg/d in mild to moderate asthma, ciclesonide improved lung function, asthma symptoms and rescue inhaler use, compared with placebo.

Dose response outcomes: Comparisons of 100 versus 200 mcg/d, 100 versus 400 mcg/d and 400 versus 800 mcg/d did not yield significant differences in lung function outcomes.
Adverse event data were not available in sufficient detail to permit assessment of the safety profile of this drug.

Authors' conclusions

Ciclesonide was more effective than placebo, in the short term, in improving lung function in patients with mild to moderate asthma previously treated with inhaled corticosteroids. There remain questions as to dose response, and the lack of data on the longer term impact on exacerbations and safety profile should be addressed in future studies.

PLAIN LANGUAGE SUMMARY

Ciclesonide versus placebo for chronic asthma in adults and children

In asthma, inflammation (swelling in the wall) narrows the airway and is the main factor giving rise to asthmatic symptoms of cough, wheeze, shortness of breath and chest tightness. Inhaled corticosteroids (ICS) which are given usually more than once daily are now recommended as first line therapy for most people with asthma. The currently available ICS, such as budesonide (BUD), beclomethasone (BDP) or fluticasone (FP), have been available for many years and have proven to be an important therapy for controlling inflammation and symptoms. However, these drugs can be associated with significant side-effects, especially local effects in the upper airways such as hoarseness and oral candida (thrush infection). The main reputed advantage of ciclesonide (CIC, a new generation of ICS), is its ability not only (as with other ICS) to be delivered locally by inhalation but specifically to the lower airways of the lung in a form which potentially minimises local side-effects. Overall this advantage of CIC could lead to a reduction of local airway side-effects with once daily therapy and thereby improving adherence to therapy. The results from this review indicate that CIC at low to moderate doses improves lung function and reduces asthma symptoms compared to placebo, but the short duration of the studies means that there is a lack of information about the impact on asthma exacerbations. Thus the currently recommended doses of CIC of 100-200 mcg daily would seem appropriate. However, the number of studies in the higher dose range are low and further studies are therefore required in adults and children to determine whether higher CIC doses will give significant benefit without increasing adverse events. It will also be important to determine in clinical studies how CIC compares to the other currently available ICS in terms of efficacy and safety in asthmatic adults and children in order to determine the precise role of CIC therapy in asthma. The published data are insufficient to assess the reputed safety advantage of ciclesonide, and better assessment and reporting in studies is required to address this important question.

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. It is a condition which can develop 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 (Tattersfield 2002; GINA 1998). 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 2000; Adams 2007; Powell 2003; BGAM 1997; BTS/SIGN 2003; Consensus 1999; Consensus 2005; GINA 1998).

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. 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 when taken on a regular basis (Suissa 2000; Suissa 2002). Non-compliance is a significant problem with inhaled corticosteroid therapy due to a number of factors including increased dosing frequency and local or systemic side effects (Buston 2000). However, while inhaled steroids may be effective when used morning and evening, reducing dosing to a once daily dosing regimen can give also effective control (Malo 1989; Toogood 1982). 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 (CIC) has recently been approved in Europe. Research from clinical trials has shown the drug to be an effective therapy in persistent asthma in improving lung function, and in reducing asthma symptoms. 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 can also be given once daily, and may lead to better compliance with inhaled corticosteroids.

OBJECTIVES

The objectives of this review were to compare the efficacy and safety of ciclesonide in adults (aged 18 years and older) and children (less than 18 years) who have persistent asthma of any severity compared with placebo therapy, and with ciclesonide at alternative doses.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCT) comparing the inhaled ciclesonide with placebo were considered for inclusion. Trials that use parallel group designs or cross-over design with a washout period of two weeks or more were eligible. Studies published in abstract form and unpublished data were also eligible for inclusion.

Types of participants

Adults (aged 18 years and older) and children (less than 18 years) were eligible for inclusion. All study subjects had 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 On Asthma) / National Institutes of Health (NIH) or BTS/SIGN 2003) or evidenced based guidelines were included. Studies that delivered interventions to patients in the community/family practice setting or hospital-based settings were included. Studies with subjects with pulmonary diagnosis other than asthma (e.g. COPD) were excluded.

Types of interventions

Studies that included inhaled ciclesonide at any dose versus placebo, or compared different doses of ciclesonide were considered. A second review of ciclesonide in comparison with other inhaled corticosteroids, such as budesonide, beclomethasone, fluticasone, triamcinolone, flunisolide has been undertaken separately. Therapy should be for at least 4 weeks. Concomitant therapies for asthma, such as short-acting beta2-agonists (rescue therapy), theophyllines, long-acting 2-agonists (Serevent or formoterol), inhaled anti-cholinergics were allowed provided that patient's asthma is stable.

Types of outcome measures

The primary outcomes were:
1.

4.

Primary outcomes

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

Secondary outcomes

1. Mild asthma exacerbations not requiring systemic steroids or severe exacerbations requiring hospital admissions.
2. Rescue medication use
3. Symptoms
4. 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.

5. Measures of healthcare utilisation: doctor visits, emergency visits and or hospital admissions for asthma.
6. 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. Measures of compliance. As a surrogate to include study withdrawal or patient preference in crossover studies.

We have given a narrative overview of the following metrics, creating an additional table and re-expressing their effects as standardised mean differences:

- am PEF
- FEV1
- Symptoms
- Rescue medication usage

Search methods for identification of studies

Electronic searches

Trials were identified using the Cochrane Airways Group 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

Additional searches of CENTRAL and PubMed were carried out (see Table 1 for the full CENTRAL search strategy). Abstracts from the American Thoracic Society annual conference 2006-2007 were searched online with the keyword 'ciclesonide'. Searches are current to June 2007.

Searching other resources

Reference lists of all primary studies and review articles were reviewed for additional references. We consulted www.clinicalstudyresults.org for unpublished studies.

Data collection and analysis

Selection of studies

The title and abstract of each citation identified using the search strategy identified was screened independently by PM and TL for eligibility. Articles that appear to fulfil the inclusion criteria were retrieved in full text. From the full text of the articles, PM and TL independently established whether each study met the inclusion criteria as a RCT with the above interventions. Disagreement was resolved by consensus. Translation into English was not necessary.

Data extraction and management

Data from included trials were extracted independently and checked before TL entered the data into RevMan 4.2. We attempted to obtain additional outcome data from investigators where possible.

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

Assessment of risk of bias in included studies

Study quality was assessed using 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

Jadad scores were also calculated for each study (Jadad 1996).

Data synthesis

Trial data were combined using RevMan 4.2. Data were pooled using a fixed effect model.

A mean difference (MD) and 95% CI were 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 are only available as mean differences with 95% CIs or standard errors.

For dichotomous outcomes, a Risk Ratio (RR) was calculated based upon the number of participants with an event versus the number of participants without an event. Fixed Effect modelling was used to pool data for RRs unless heterogeneity was observed (I square >/=20%; Higgins 2003), in which case a sensitivity analysis with Random Effects modelling was used.

Studies were grouped according to whether they were conducted in adults or children.

RESULTS

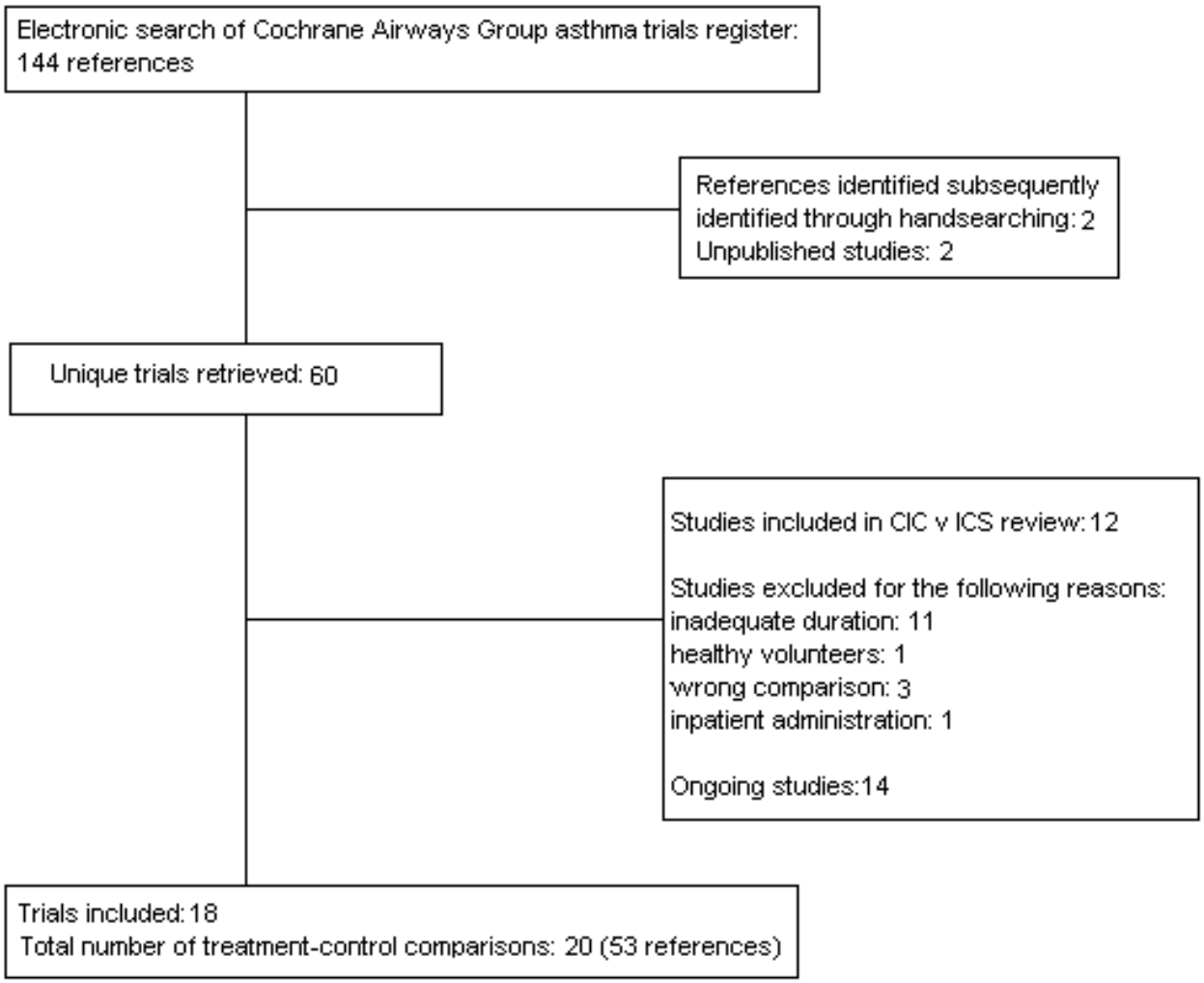
Description of studies

Results of the search

Literature searches current up to June 2007 identified a total of 148 citations and 18 trials representing 53 of these citations, and reporting 20 study comparisons, met the review entry criteria (see Figure 1). For details of each included study see table 'Characteristics of included studies'. Reasons for the exclusion of 16 studies are detailed in the table 'Characteristics of excluded studies'. Of the 18 trials which met the review entry criteria, two yielded additional group comparisons. Gelfand 2006a; Gelfand 2006b assessed similar doses of ciclesonide (50 and 100 mcg/d of ciclesonide), and EFC6163a; EFC6163b assessed once daily and twice daily inhalation of the same dose of ciclesonide. One

of the 18 trials was a crossover study (Wilson 2006). Two studies do not contribute data to the analysis of the review as we have not been able to obtain effect estimates: Baena Cagnani 2006 (N=661); Bernstein 2004 (N=531). The following description of study characteristics pertains to the 18 parallel group study comparisons which yielded data, since these were the primary source of evidence for the review.

Figure 1. Flow diagram of studies in this review



Included studies

Study design

Three studies reported integrated analyses of more than one trial (Pearlman 2005; Gelfand 2006a; Gelfand 2006b). Two dose comparison trials were open label; the remainder were double-blind.

Participants

The studies randomised 6343, of whom 1692 were children. The remainder of the study participants were either adults or their age could not be determined.

Baseline FEV1 predicted and requirement for maintenance treatment varied between the studies. One study recruited participants on oral steroid therapy (Bateman 2006), with a mean FEV1 predicted of 55%. Mean FEV1 predicted at baseline was above 80% in one study (Lipworth 2005), in five studies it was between 70 and 80% (Adachi 2007a; Chapman 2005; Hansel 2006; Langdon 2005; Magnussen 2007), and in two studies it was below 70% (Adachi 2007b; Gelfand 2006a). In the remaining studies, maximum allowable baseline FEV1 was 85% in Pearlman 2005, 80% in DFI6153, 70% in Bateman 2006a and 65% in Bernstein 2004.

Requirement for pre-study maintenance ICS treatment featured in Adachi 2007a; Adachi 2007b; Chapman 2005; DFI6153; Langdon 2005; O'Connor 2002 and Zietkowski 2006 as a criterion of study entry, and in Gelfand 2006a and Pearlman 2005 use of ICS prior to baseline was permitted. Lipworth 2005 only included participants whose asthma was controlled with as needed short-acting beta-agonist. In the remaining studies no mention of inhaled steroid treatment was made in study entry or exclusion criteria.

Intervention

We assessed three comparisons represented by the following studies (all doses quoted are ex-valve):

1. Ciclesonide versus placebo (non-OCS) analysing doses separately (100 mcg/d or less (Adachi 2007a; Gelfand 2006a; Gelfand 2006b); 200 mcg/d (Adachi 2007a; Chapman 2005; DFI6153; EFC6163a; EFC6163b; Gelfand 2006a); 400 mcg/d (Adachi 2007a; DFI6153; Pearlman 2005); 800 mcg/d (Chapman 2005; DFI6153) and greater than 800 mcg/d (DFI6153)
2. Ciclesonide versus placebo (OCS users) analysing doses separately (<800 and >800 mcg/d): Bateman 2006.
3. Ciclesonide at different doses (50 versus 100 mcg/d (Gelfand 2006a); 100 versus 200 mcg/d (Adachi 2007a; Gelfand 2006a; Magnussen 2007; Pearlman 2005; Zietkowski 2006); 100 versus 400 mcg/d (Hansel 2006; Langdon 2005) 200 versus 400 mcg/d (Bernstein 2004; DFI6153; Pearlman 2005); 200 versus 800 mcg/d (Bateman 2006a; Chapman 2005; DFI6153); 400 versus 800 mcg/d (Adachi 2007b; Lipworth 2005; DFI6153); 800 versus 1600 mcg/d (O'Connor 2002).

Delivery of drug and duration of studies

Ciclesonide was delivered via metered dose inhalers in all the trials with the exception of DFI6153 where it was delivered via dry powder inhaler.

Dosing regimens varied, with ciclesonide given once daily in all studies with the exception of Bateman 2006; Bernstein 2004; DFI6153 where it was administered twice daily.

One study was 12 months (Baena Cagnani 2006) and another six weeks in duration (DFI6153). The remaining studies were 12 weeks long, but some included a run in period of up to 4 weeks

Outcomes assessed

Baena Cagnani 2006 and 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.

Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

Thirteen studies were described as randomised and double-blinded. The method of blinding was known in two studies. One dose-comparison study was open label (Adachi 2007b). Methodological quality, as assessed by the Jadad scoring system, was variable. Only one of the studies achieved a score of 5 (high quality), three studies a score of 4 (good quality), six a score of 3 (fair quality) and the remaining four studies a score of 2 (poor quality). Three of the low quality studies were published in abstract form for presentation at international respiratory or allergy conferences and we had only limited details about patient withdrawals from study, methods of randomisation and blinding. It is therefore possible that these scores represent an underestimation of the true methodological quality.

Effects of interventions

1. Ciclesonide versus placebo (non-OCS users)

Primary outcomes

No data were found in relation to asthma exacerbations.

Change in FEV1 (Litres):

100 mcg/d or less: 0.08; 95% confidence interval 0.05 to 0.11 (five studies, N = 1677). The subgroup estimates for this outcome were significantly different from each other (children versus adults: 0.05 versus 0.13 (P = 0.019).
200 mcg/d 0.12; 95% confidence interval 0.08 to 0.15 (four studies, N = 1543). One paediatric study contributed to this outcome.
400 mcg/d: 0.17 L; 95% confidence interval 0.14 to 0.21 (six studies, N = 1717). All of these studies were conducted in adults.
800 mcg/d: One unpublished study reported a significant difference in favour of ciclesonide (DFI6153, N = 374). Chapman 2005 reported a significant difference in favour of ciclesonide for end of treatment FEV1.
1600 mcg/d: One unpublished study reported a significant difference in favour of ciclesonide (DFI6153, N = 372).

Change in FEV1 percent predicted:

100 mcg/d or less: 2.96%; 95% confidence interval 1.80 to 4.12 (four studies, N = 1432).
200 mcg/d: 3.06%; 95% confidence interval 1.85 to 4.26 (three studies, N = 1171).
400 mcg/d: 3.10%; 95% confidence interval 1.66 to 4.53 (two studies, N = 666).

Change in am PEF:

100 mcg/d or less: 14 L/min; 95% confidence interval 10 to 18 (five studies, N = 1677).
200 mcg/d: 19 L/min; 95% confidence interval 15 to 23 (five studies, N = 1768).
400 mcg/d: 18 L/min; 95% confidence interval 14 to 22 (six studies, N = 1722).
800 mcg/d: 28 L/min; 95% confidence interval 21 to 35 (two studies, N = 594).
1600 mcg/d: One unpublished study reported a significant difference in favour of ciclesonide (DFI6153, N = 372)

Change in pm PEF:

100 mcg/d or less: 12 L/min; 95% confidence interval 8 to 16 (five studies, N = 1677).
200 mcg/d: 14 L/min; 95% confidence interval 10 to 18 (three studies, N = 1166).
400 mcg/d: 15 L/min; 95% confidence interval 10 to 21 (three studies, N = 906).

Secondary outcomes

Quality of life & asthma symptoms

Change in asthma symptoms favoured ciclesonide in studies conducted in adults, across three dose ranges where data could be pooled as standardised mean differences (100 mcg/d or less: -0.39; 95% confidence interval -0.52 to - 0.34; 200 mcg/d: -0.51; 95% confidence interval -0.65 to -0.38; 400 mcg/d: -0.48; 95% confidence interval -0.59 to -0.38).

Rescue medication use

There was a significant reduction in the frequency of rescue medication use in favour of low dose CIC compared with placebo (CIC 100 mcg or less: -0.87 puffs/d (-1.36 to -0.37, three studies); 200 mcg/d: -1.1 puffs/d; 95% confidence interval -1.32 to -0.89; three studies). One unpublished study found a significant reduction in rescue medication use in favour of ciclesonide (DFI6153, N = 372)

Study withdrawal & adverse event data

Study withdrawal occurred less frequently in the low dose CIC groups compared with placebo in adults and children (100 mcg/d or less: RR 0.67; 95% confidence intervals 0.55 to 0.83, four studies N =1174). Withdrawals were primarily due to a loss of efficacy or adverse events. Similar results were seen with CIC 200 mcg (RR 0.55; 95% confidence intervals 0.43 to 0.7, three studies, N = 877). Specific adverse events did not differ between treatment groups (pharyngitis, nasopharyngitis, headache, URTI and rhinitis). Very little data were available to indicate the frequency of oral candidiasis (confirmed by culture) in each treatment group.

2. Ciclesonide versus Placebo (OCS users)

No data were identified for OCS-treated exacerbations.

Lung function

A single parallel study (Bateman 2006) of good methodological quality (Jadad score 4) was conducted in 141 asthmatic patients age range 12-75 years with severe persistent oral steroid dependant asthma. There was no significant changes from baseline in FEV1 for CIC but it was reduced in the placebo group. Improvement in morning PEF occurred in CIC versus placebo (MD 16.67; 95% confidence interval -1.85 to 35.59) this was only significant in the CIC1280 group.

Oral steroid reduction

In the single study (Bateman 2006) the prednisolone dose was significantly reduced in the CIC group by 58.26% compared to placebo MD (95% confidence interval -86.13 to -30.39). Discontinuation of maintenance of oral steroids was more common in CIC compared to placebo RR 2.81 (95% confidence intervals 1.11 to 7.11).

3. Ciclesonide at different doses

Results are presented in favour of the lower dose of CIC, and significant differences were not shown in the between dose comparisons.

Primary outcomes

Exacerbations requiring oral corticosteroids were only reported in one study (Magnussen 2007) and the numbers were too small to draw any conclusions (there were 2 patients with exacerbations in each arm given 100 mcg and 200 mcg of ciclesonide).

Change in FEV1 (Litres):

100 versus 200 mcg/d: 0.02; 95% confidence interval -0.01 to 0.06 (four studies, N = 1726)
100 versus 400 mcg/d: 0.00; 95% confidence interval -0.05 to 0.05 (three studies, N = 747)
200 versus 400 mcg/d: 0.03; 95% confidence interval -0.02 to 0.09 (two studies, N = 537)
400 versus 800 mcg/d: -0.06; 95% confidence interval -0.12 to 0.00 (two studies, N = 583)

One paediatric study compared CIC 50 and 100 mcg/d and did not detect a significant difference between treatments in change from baseline in FEV1 (0.03 L; 95% confidence interval -0.02 to 0.08).

Change in FEV1 (predicted):

100 versus 200 mcg/d: 0.31; 95% confidence interval -0.74 to 1.35 (three studies, N = 1176).

Change in am PEF L/min:

100 versus 200 mcg/d: 3.80; 95% confidence interval -0.78 to 8.37 (three studies, N = 1176)
100 versus 400 mcg/d: -0.48; 95% confidence interval -7.59 to 6.64 (three studies, N = 749)
200 versus 400 mcg/d: 2.17; 95% confidence interval -5.04 to 9.38 (two studies, N = 537)
200 versus 800 mcg/d: -4.78; 95% confidence interval -11.65 to 2.09 (two studies, N = 594)

Change in pm PEF L/min:

100 versus 200 mcg/d: 2.28; 95% confidence interval -2.04 to 6.60 (three studies, N = 1176)
100 versus 400 mcg/d: 1.36; 95% confidence interval -6.05 to 8.78 (two studies, N = 396)

Secondary outcomes

Quality of life and asthma symptoms

800 mcg and 1600 mcg/d: standardised mean difference -0.06; 95% confidence interval -0.20 to 0.08 (two studies, N = 737).

There were no significant differences in the change from baseline found in terms of quality of life (AQLQ questionnaire) between 100 and 200 mcg/d with -0.08 (95% confidence intervals -0.25 to 0.09; P=0.35) in adults (Hansel 2006).

Change in rescue medication use (puffs/d)

400 versus 800 mcg/d: 0.12; 95% confidence interval -0.13 to 0.37 (two studies, N = 583)
800 versus 1600 mcg/d: 0.15; 95% confidence interval -0.07 to 0.37 (two studies, N = 735)

Study withdrawal & adverse event data

There was no difference in the likelihood of study withdrawal due to lack of efficacy between 100 and 200 mcg and between 100 and 400 mcg/d. There was a high level of statistical heterogeneity between studies assessing 100 and 200 in adverse events. Specific adverse events from individual studies were too imprecise to derive meaningful results from our analyses.

DISCUSSION

From the 20 study comparisons included in this review, data from 18 contribute to the analyses. The two parallel group studies which did not yield any data remain unpublished in full text form as of August 2007 (Baena Cagnani 2006; Bernstein 2004). The studies did not provide information on asthma exacerbations, but in comparison with placebo, lung function assessments favoured ciclesonide in studies of up to 12 weeks duration. The evidence available on adverse events is insufficient to draw reliable inferences regarding its safety and tolerability.

Placebo comparison

Although the doses assessed indicated favourable effects of ciclesonide, the effect sizes were somewhat smaller than those established by similar reviews of beclomethasone, budesonide and

fluticasone (Adams 1999; Adams 2005a; Adams 2005b). However, indirect comparison between these preparations may not be reliable, since it assumes that the populations recruited to the efficacy studies of the respective preparations were pre-treated with similar doses of inhaled steroids. Nevertheless it is noteworthy that ciclesonide studies conducted in adults and adolescents yielded a difference in FEV1 of between 0.13 to 0.17 against placebo in the ranges from 100 to 400 mcg/d. Studies conducted in pre-trial maintenance inhaled steroid users from meta-analysis of fluticasone studies gave a larger effect size of 0.33 L (personal communication). The eligibility criteria of the trials stipulated a requirement for maintenance inhaled corticosteroid treatment as a maximum BDP equivalent of 800-1000 mcg/d (Adachi 2007a; Chapman 2005; EFC6163a; EFC6163b; Langdon 2005; Pearlman 2005), and group mean airway obstruction was lower than 80% in the studies. Thus, requirement for pre-baseline steroid treatment was indicative of a more severe patient population in the ciclesonide studies than those of fluticasone trials.

In OCS users, (i.e. subjects on lowest maintenance oral steroids for 12 months), a single study found that ciclesonide permitted a reduction in the oral maintenance steroid dosage and prevented falls in FEV1 while improving morning PEF (daily dose of 800 and 1600 mcg). This was also associated with a greater likelihood of oral candidiasis in the combined ciclesonide group, but the increase was not statistically significant. Pharyngitis was not a problem in these high doses of ciclesonide. A similar finding was reported for high dose FP 1000-1500 in Adams 2005b, whereby FP was associated not only with a greater likelihood of oral candidiasis, but also sore throat and symptoms of hoarseness.

Adverse event data did not yield findings that provide firm guidance on the effects of ciclesonide. The studies available may not been conducted over a sufficient period of time in order to provide useful data to this end. The reputed benefits of ciclesonide in terms of fewer local side-effects remain to be shown by additional trials of longer duration, that assess for oral candida using microbiological confirmation of infection.

Dose response analysis

The analyses of the dose ranging studies was limited, with inconclusive effects on FEV1 found in adults between 100 and 200 mcg/d, and also between doses of 100 and 400 mcg/d. In terms of am and pm PEF no significant changes were found between low and higher doses of ciclesonide. This highlights some uncertainty in the lower dose ranges of ciclesonide, and reinforces the requirement for more work in this area. Currently the effect estimates do not provide evidence that increasing the dose of ciclesonide confers significant benefit, but the confidence intervals are too wide to draw any conclusions.

Since the number of studies and participants is low, the evidence base may be underpowered to identify a dose response curve in ciclesonide. The confidence limits do not exclude the possibility of a meaningful effect in favour of higher doses. The data from placebo groups are also noteworthy with baseline details of Gelfand 2006a indicating that participants had moderate airway obstruction (around 69% predicted of FEV1), and placebo-treated children saw FEV1 improve by 0.22 L over baseline values.

Quality of Life, exacerbations and asthma symptoms

Data from studies conducted in adults indicated that ciclesonide led to significant improvements in both quality of life (QoL) and asthma symptoms at low doses compared with placebo. Currently the effect estimates do not provide evidence that increasing the dose of ciclesonide confers significant benefit; as with the lung function endpoints in the confidence limits do not exclude the possibility of a meaningful effect in favour of higher doses.

There is a lack of evidence regarding the impact of ciclesonide on the prevention of exacerbations of asthma which prompt additional treatment with steroids or presentation in acute care settings. Studies reporting outcome data which are defined adequately in terms of the required treatment strategy would help to establish the role of ciclesonide in the management of asthma better.

Effect size overview (Table 1)

Since the number of studies in the medium and high dose ranges were low, we tabulated effect sizes (given as standard deviation units) for FEV1, am PEF, symptoms and rescue medication use for the low dose comparison with placebo. This indicated that the effect size was stronger for symptoms and rescue medication use than for lung function outcomes.

Limitations of the review

One large parallel group trial only available as a conference abstract has not contributed data to this review, which is a safety study conducted over 12 months (Baena Cagnani 2006). Given the relatively low numbers of studies contributing data to primary outcomes analysed in this review, the absence of published data could leave the effect estimates open to the threat of publication bias. We could not reliably detect this since the most number of studies available for analysis was for any one outcome was six, meaning that funnel plot asymmetry may not be a sensitive instrument for assessing this.

In summary, the evidence from this review indicates that in short term studies at low and moderate doses (50-800 mcg/d), ciclesonide is effective in improving lung function, and reducing symptoms compared with placebo in patients previously treated with regular inhaled steroids. There is a lack of evidence regarding the impact of ciclesonide on exacerbations. Effects from dose response studies have been conflicting and do not yet show how the dose response curve of ciclesonide compares with that of other steroid preparations such as fluticasone or beclomethasone. It is feasible that differing characteristics of the participants recruited to the studies in this review may have affected the behaviour of outcomes in the dose response comparisons, since placebo controlled trials with low attrition rates likely reflect a response to inhaled therapy in people with mild asthma (Adams 2006). In view of the limited evidence available on the effects of increasing the dose of ciclesonide this review cannot make firm recommendations regarding the dose response curve of ciclesonide.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this review clearly show a short-term benefit of ciclesonide compared to placebo, in terms of lung function,

symptoms and rescue inhaler use. The results have not identified an apparent dose-response effect of ciclesonide across a wide range of doses.

Implications for research

The included studies are of short duration and the number of studies in the medium and high dose range are low; thus further longer term studies in adults and children at higher doses are required to determine the impact of ciclesonide on exacerbations and to assess whether increasing the doses of ciclesonide confers significant benefit and to evaluate, as yet, unidentified safety issues with this strategy. In Bateman 2006, CIC at higher doses allowed a reduction in oral steroid doses in steroid dependant asthmatics . Further studies are needed to identify the usefulness and safety of recommending this strategy on a wider basis for such patients. Finally, it will be important to evaluate and compare the efficacy and safety of ciclesonide with currently available inhaled corticosteroids.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Adachi 2007a

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: 50 centres in Japan DURATION OF STUDY: 8 weeks (4 week run-in period reported with BDP 400mcg/d) 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: Not stated JADAD SCORE (5-1): 2

Adachi 2007a *(Continued)*

	TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Available case (assumed) COMPLIANCE: Not reported CONFOUNDERS: Slight imbalance between groups in terms of PEF% predicted at baseline
Participants	N SCREENED: 435 N RANDOMISED: 311 N COMPLETED: 311 (assumed) M= 171, F= 140 MEAN AGE: 51 years BASELINE DETAILS: FEV1 % predicted: 71% INCLUSION CRITERIA: 16-75 years; mild to moderate asthma according to the Japanese guidelines; treatment with 400-800 mcg/day BDP/200-400 mcg/d FP >4 weeks; mean morning PEF during the last week of run-in 60% to 90% predicted PEF. EXCLUSION: Significant coexisting respiratory disease; hospitalisation, emergency room care for asthma or treatment with systemic steroids <4 weeks before run-in.
Interventions	1. Ciclesonide 100mcg OD 2. Ciclesonide 200mcg OD 3. Ciclesonide 400mcg OD 4. Placebo DELIVERY: MDI TREATMENT PERIOD: 8 weeks RESCUE: SABA CO-INTERVENTIONS PERMITTED: Not stated CO-INTERVENTIONS: Not reported % on ICS baseline: 100
Outcomes	am PEF; pm PEF; FEV1; FVC; symptoms; use of rescue medication; adverse events
Notes	

Risk of bias

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

Adachi 2007b

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 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)

Adachi 2007b *(Continued)*

	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; hospitalisation, emergency room care for asthma or treatment with systemic steroids <4 weeks before run-in.
Interventions	1. Ciclesonide 200mcg BID (400mcg/d) 2. Ciclesonide 400mcg BID (800mcg/d) 3. Beclomethasone 400mcg BID (800mcg/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

Baena Cagnani 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Multicentre, USA, South America DURATION OF STUDY: 12 months (6 month run-in period reported, unclear treatment regime) 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 as most likely) COMPLIANCE: Not reported CONFOUNDERS: Not reported
Participants	N SCREENED: Unknown N RANDOMISED: 661 (eligible patients) N COMPLETED: Unknown M= unknown F= unknown MEDIAN AGE: Range - males 5-8.5 years; females 5-7.5 years BASELINE DETAILS: Unknown INCLUSION CRITERIA: Mild persistent asthma; children EXCLUSION: Not reported
Interventions	1. Ciclesonide 50mcg OD 2. Ciclesonide 100cg OD

Baena Cagnani 2006 *(Continued)*

	3. Placebo DELIVERY: MDI TREATMENT PERIOD: 12 months RESCUE: Not reported CO-INTERVENTIONS PERMITTED: Not reported CO-INTERVENTIONS: Not reported % on ICS baseline: Not reported
Outcomes	Growth velocity; adverse events; withdrawals
Notes	Unpublished conference abstract

Risk of bias

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

Bateman 2006

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA and South Africa, 60 centres. DURATION OF STUDY: 12 weeks (lowest effective oral steroid dose achieved for each patient during screening period) 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: YesJADAD SCORE (5-1): 4TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITTCOMPLIANCE: yesCONFOUNDERS: Baseline values comparable "
Participants	N SCREENED: 241 N RANDOMISED: 141 N COMPLETED: 114 (PP) and 140 (ITT analysis - 1 patient excluded CIC1280 group because no post baseline measurements) M= 44F= 96 MEDIAN AGE (range):CIC640 48.3 years (13-74); CIC1280 48.2 (17-70); Placebo 48.3 (12-73) BASELINE DETAILS: FEV1 (% Pred): CIC640 1.583 (52.07%); CIC1280 1.713 (57.21%); Placebo 1.621 (56.36%) INCLUSION CRITERIA: Male and females; Aged >= 12 years; oral corticosteroid-dependant (OCS) asthma for 12 months GINA definition; oral steroids daily or alternate days 5 of 6 months and ICS daily for 6 months, using inhaled beta2 agonists for rescue for 2 weeks; lowest effective OCS according to criteria at randomisation; FEV1 40-80% (pred) on withholding beta2-agnoists for 6 hours, and >= 12% reversibility following inhaled medication with an absolute increase >=200mls within the 12 months. EXCLUSION: Smokers or ex-smokers with smoking history >= 10 pack year of cigs and who quit less than 6 months.
Interventions	1. Ciclesonide 400mcg BD 2. Ciclesonide 800mcg BD 3. Placebo DELIVERY: HFA-MDI TREATMENT PERIOD: 12 weeks RESCUE: Albuterol HFA-MDI

Bateman 2006 *(Continued)*

	CO-INTERVENTIONS PERMITTED: To continue on intranasal steroids for rhinitis, cromolyn, antihistamines, hydrocortisone creams or ointments, < 1% at stable dose, montelukast, anti-cholinergics, oral beta2-agonists, LABAs, SABA or nebulised SABA CO-INTERVENTIONS: reduction in OCS% on ICS baseline: all patients
Outcomes	Am PEF; rescue medication use; reduction in maintenance OCS use; asthma symptoms; HPA function; adverse events; withdrawals
Notes	

Risk of bias

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

Bateman 2006a

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Multicentre DURATION OF STUDY: 12 weeks (2-4 weeks on FP250mcg/d) 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 as most likely) COMPLIANCE: Not reported CONFOUNDERS: Not reported
Participants	N SCREENED: Unknown N RANDOMISED: 680 (eligible patients) N COMPLETED: Not reported M= unknown F= unknown MEDIAN AGE Not reported BASELINE DETAILS: Not reported INCLUSION CRITERIA: Severe asthma; FEV1 < 70% predicted age 12-75 years EXCLUSION: Not reported
Interventions	1. Ciclesonide 200mcg OD 2. Ciclesonide 400mcg BD DELIVERY: HFA-MDI TREATMENT PERIOD: 12 weeks RESCUE: Not reported CO-INTERVENTIONS PERMITTED: Not reported CO-INTERVENTIONS: Not reported % on ICS baseline: 100 (FP 250mcg BD)
Outcomes	FEV1, am PEF; symptoms; asthma exacerbations
Notes	Unpublished conference abstract

Risk of bias

Bateman 2006a *(Continued)*

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

Bernstein 2004

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Multicentre 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 200mcg BD 2. Ciclesonide 400mcg BD 3. Fluticasone 1000mcg BD 4. Placebo 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

Chapman 2005

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: Canada, 25 centres. DURATION OF STUDY: 12 weeks (2 week run-in on current 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: Identical devices 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
Participants	N SCREENED: 440 N RANDOMISED: 329 N COMPLETED: 185 M=166; F= 163 MEDIAN AGE (range):CIC160 41 years (18-68); CIC640 39 (18-69); Placebo 41 (19-69) BASELINE DETAILS: FEV1 (% Pred): CIC160 2.70 (78%); CIC640 2.66 78; 2.61 (77%) INCLUSION CRITERIA: Aged 18-70 years; either sex; persistent asthma ATS definition; previous use of ICS for 4 weeks (400-800 ug/day BDP, Tri, BUD or Fluisolide or 200-500 ug/day Fluticasone; at randomisation FEV1 (% pred) between >= 60% - <=90% pred bronchodilator and have 1 of the following ; 12% variability in FEV1 or >= 200 mls after two-4 puffs salbutamol at randomisation or methacholine tests 8 mg/ml or less, or diurnal variation in PEF >= 15% at least 3 of 7 days before randomisation. EXCLUSION: asthma exacerbation of asthma or RTI within 6 weeks of the study, hospitalisation for asthma within 6 months, COPD or current or former smokers > 10 pack years, pregnant or lactating females or premenopausal women not using effective contraception, Lack of efficacy (LOC) criteria before randomisation, use of oral steroids, or more than 8 puffs of salbutamol on two successive days during baseline.
Interventions	1. Ciclesonide 200mcg OD 2. Ciclesonide 800mcg OD 3. Placebo DELIVERY: CIC: HFA MDI without a spacer, Placebo MDI without spacer TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol MDI CO-INTERVENTIONS PERMITTED: Theophylline. % on ICS baseline: 100
Outcomes	Am PEF; rescue medication use; cortisol levels; adverse events; withdrawals
Notes	

Risk of bias

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

DFI6153

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA, 66 centres DURATION OF STUDY: 6 weeks (2 week run-in on FP 100mcg) CONCEALMENT OF ALLOCATION: Unclear COCHRANE QUALITY SCORE: B DESCRIBED AS RANDOMISED: Yes

DFI6153 *(Continued)*

	DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not reported METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not clear DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not clear JADAD SCORE (5-1): 2 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported CONFOUNDERS: Not clear
Participants	N SCREENED: Not clear N RANDOMISED: 1145 N COMPLETED: Not clear M=not clear ; F= not clear MEDIAN AGE (range): Not clear BASELINE DETAILS: Not available INCLUSION CRITERIA: >12 years; history of persistent asthma (>6 months before screening); treatment with ICS for >1 month before screening; FEV1 >40% and <80% predicted. EXCLUSION: Not reported.
Interventions	1. Ciclesonide 100mcg BD 2. Ciclesonide 200mcg BD 3. Ciclesonide 400mcg BD 4. CIcliesonide 400mcg BD 5. Ciclesonide 800mcg BD 6. Placebo DELIVERY: CIC: DPI (CIC group 3 given via MDI) TREATMENT PERIOD: 6 weeks RESCUE: Salbutamol MDI CO-INTERVENTIONS PERMITTED: % on ICS baseline: 100
Outcomes	FEV1; am PEF; rescue medication use; symptoms; nocturnal awakenings; safety
Notes	

Risk of bias

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

EFC6163a

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA, 38 centres DURATION OF STUDY: 6 weeks (1 week run-in on FP <440mcg) 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 devices DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not clear JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported

EFC6163a *(Continued)*

	CONFOUNDERS: Not clear
Participants	N SCREENED: Not clear N RANDOMISED: 456 N COMPLETED: Not clear M=not clear ; F= not clear MEDIAN AGE (range): Not clear BASELINE DETAILS: Not available INCLUSION CRITERIA: >12 years; history of persistent asthma (6 months); ICS monotherapy for >1 month or use of ICS/LABA combination therapy for >1 month; FEV1 60-90% predicted (ICS monotherapy)/FEV1 70-95% (ICS/LABA combination therapy); </=440mcg/d FP or equivalent or </=200/100 FP/SAL equivalent. EXCLUSION: Not reported.
Interventions	1. Ciclesonide 100mcg BD 2. Ciclesonide 200mcg OD 3. Placebo DELIVERY: CIC: MDI TREATMENT PERIOD: weeks RESCUE: Not reported CO-INTERVENTIONS PERMITTED: % on ICS baseline: 100
Outcomes	FEV1; am PEF; rescue medication use; symptoms; nocturnal awakenings; safety
Notes	

Risk of bias

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

EFC6163b

Methods	See above
Participants	See above
Interventions	See above
Outcomes	See above
Notes	

Risk of bias

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

Gelfand 2006a

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: USA (100 ctrs), Mexico (21), Poland (10); 131 centres. DURATION OF STUDY: 12 weeks (4 week run-in period, stable maintenance medications) 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: Yes JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not reported CONFOUNDERS: Baseline values comparable
Participants	N SCREENED: Not stated N RANDOMISED: 1031 (ITT population 1018) N COMPLETED: 870 M= 652; F= 366 MEDIAN AGE (range): CIC40 8.14 years; CIC80 8.20; CIC160 8.33; Placebo 8.2 (all ranges 4-11 years) BASELINE DETAILS: FEV1 (% Pred): CIC40 1.29 (68.5); CIC80 1.29 (68.3); CIC160 1.30 (68.2); Placebo 1.32 (68.5%) INCLUSION CRITERIA: 4-11 years; persistent asthma (all severities - 1997 NIH criteria); FEV1 (% predicted between 40% and 90%; 12% variability in FEV1 after two puffs albuterol at randomisation or within 12 months of screening; if on controller therapy must have had a 10% drop in FEV1 (between screening and randomisation after maintenance treatment stopped); patients using only beta2agonist at screening had to have at least 1 of 3: 24 hour asthma symptom score >= 3, PEF variability > 20%, albuterol use >= 2 puffs daily; effective use of MDI inhaler and ability to perform spirometry EXCLUSION: Oral or systemic steroid use within 4 weeks of screening; life-threatening asthma, two or more hospitalizations for asthma exacerbation with 1 year before study, urinary cortisol level < 10 ug/dL at screening
Interventions	1. Ciclesonide 50mcg OD 2. Ciclesonide 100mcg OD 3. Ciclesonide 200mcg OD 4. Placebo DELIVERY: HFA MDI without a spacer TREATMENT PERIOD: 12 weeks RESCUE: Albuterol HRA-MDI CO-INTERVENTIONS PERMITTED: steroid creams (<1%), nasal and eye cromoglycate, anti-histamines, decongestants and regular immunotherapy % on ICS baseline: 0
Outcomes	FEV1; pm PEF; Quality of life (AQLQ); adverse events; withdrawals
Notes	

Risk of bias

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

Gelfand 2006b

Methods	As above
Participants	As above. Second study ID created for estimates involving lower dose range of study (i.e. 40 & 80mcg/d)
Interventions	As above
Outcomes	FEV1; pm PEF; Quality of life (AQLQ); adverse events; withdrawals
Notes	

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: Appropiate for CIC arms DESCRIPTION OF WITHDRAWALS/DROPOUTS: yes JADAD SCORE (5-1): 5 (CIC v CIC); 3 (CIC v BUD) 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= 301F= 253 MEDIAN AGE (range): CIC80 38 years (12-73); CIC320 41 (14-74); BUD 45 (13-73) BASELINE DETAILS: FEV1 % predicted 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 100mcg OD 2. Ciclesonide 400mcg OD 3. BUD 200 mcg BD (open labelled) DELIVERY: HFA-MDI (CIC) and Turbohaler (BUD)

Hansel 2006 *(Continued)*

	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

Langdon 2005

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: UK and Canada, 51 centres. DURATION OF STUDY: 12 weeks (2 week run-in on maintenance 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: Identical devices DESCRIPTION OF WITHDRAWALS/DROPOUTS: Reported JADAD SCORE (5-1): 4 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed CONFOUNDERS: Baseline values comparable.
Participants	N SCREENED: Unclear N RANDOMISED: 360 (488 entered run-in phase) N COMPLETED: 215 M= 161 F= 299 MEAN AGE: 40.56 years BASELINE DETAILS: FEV1: 2.54L; FEV1 % predicted: 78; am PEF: 412L/min; PEF variability: 7.2L INCLUSION CRITERIA: 18-70 years old; history of asthma; FEV1 60-95% predicted; inhaled corticosteroid maintenance therapy (BDP equivalent 4-800mcg/d; stable dosage regimen for four weeks); post-run in FEV1 60-90% predicted; FEV1 reversibility >/=15% EXCLUSION: COPD; exacerbation of asthma within 6 weeks of study entry; >10 cigarettes/day; nasal/topical corticosteroids and LABA therapy before 4 weeks of study entry
Interventions	1. Ciclesonide 100mcg OD 2. Ciclesonide 400mcg OD 3. Placebo DELIVERY: HFA-metered dose inhaler TREATMENT PERIOD: 12 weeks RESCUE: salbutamol CO-INTERVENTIONS PERMITTED: Medications not listed under exclusion criteria % on ICS (pre-run in): 100

Langdon 2005 *(Continued)*

Outcomes	FEV1; FVC; Clinic PEF; am PEF; pm PEF; Symptoms (total, day, night, rescue medication use); adverse events; withdrawals
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= 79F= 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.
Interventions	1. Ciclesonide 400mcg OD 2. Ciclesonide 400mcg BD 3. Fluticasone 500mcg BD 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

Lipworth 2005 *(Continued)*

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 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

O'Connor 2002

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: DURATION OF STUDY: 12 weeks (2 week run-in on 1600mcg/d BDP) 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): Not clear COMPLIANCE: Not reported CONFOUNDERS: Not reported.
Participants	N SCREENED: Not reported N RANDOMISED: 365 N COMPLETED: 275 M= Not reported; F= Not reported MEAN AGE: Not reported BASELINE DETAILS: Not reported INCLUSION CRITERIA: Moderate to severe asthma; treatment with BDP equivalent 800-2000mcg/d; symptom score >4 over last week of run in; sum of rescue medication >14 puffs over run in. EXCLUSION: Not reported.
Interventions	1. Ciclesonide 400mcg BD 2. Ciclesonide 800mcg BD DELIVERY: MDI TREATMENT PERIOD: 12 weeks (2 week run in on high dose BDP) RESCUE: Not reported CO-INTERVENTIONS PERMITTED: Not reported % on ICS: 100
Outcomes	FEV1; rescue medication usage; symptoms; withdrawal due to lack of efficacy.
Notes	Reported as unpublished conference abstract

Risk of bias

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

Pearlman 2005

Methods	STUDY DESIGN: Parallel group LOCATION, NUMBER OF CENTRES: United States, number of centres: not clear. DURATION OF STUDY: 12 weeks (1-4 weeks on single-blind placebo) 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 described METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not described DESCRIPTION OF WITHDRAWALS/DROPOUTS: Not reported JADAD SCORE (5-1): 2 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): ITT COMPLIANCE: Not assessed

Pearlman 2005 *(Continued)*

	CONFOUNDERS: Similar characteristics at baseline.
Participants	N SCREENED: 2512 N RANDOMISED: 1015 (study i: 526; study ii: 489) N COMPLETED: Not reported (only withdrawals due to lack of efficacy reported) M= 413F= 598 MEAN AGE: 36.6 BASELINE DETAILS: FEV1: 2.44L; am PEF: 364L/min; pm PEF: 380L/min; symptom score: 2.63; saba use: 3.16 puffs/d; AQLQ: 4.6 INCLUSION CRITERIA: >12 years; mild-moderate asthma; not using more than 400mcg/d FP, 250/50 FP/SAL combination, 1000mcg/d BUD or equivalent, leukotrienes, SABA or LABA for ess than 30 days before study entry; FEV1 60-85% predicted; greater than 12% reversibility to SABA; symptomatic over last 7 days prior to randomisation (score >3; PEF variability >20%; SABA usage 2 or more puffs/d over 3 of last 7 days). EXCLUSION: Continual asthma; frequent night symptoms; history of life threatening asthma; two or more hospitalisations with asthma in past year; COPD; systemic steroids in 3 months prior to randomisation.
Interventions	1. Ciclesonide 100mcg OD 2. Ciclesonide 200mcg OD 3. Ciclesonide 400mcg OD 4. Placebo DELIVERY: HFA-MDI TREATMENT PERIOD: 12 weeks RESCUE: Salbutamol CO-INTERVENTIONS PERMITTED: None CO-INTERVENTIONS: Not reported % on ICS: Not reported.
Outcomes	FEV1; FEV1 predicted; am PEF L/min; pm PEF L/min; symptoms; rescue medication use; quality of life; night awakenings; serum cortisol; adverse events
Notes	

Risk of bias

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

Wilson 2006

Methods	STUDY DESIGN: Crossover LOCATION, NUMBER OF CENTRES: Single centre in Canada. DURATION OF STUDY: 2 x 4 week treatment periods (1 week run-in and 2 week washout) CONCEALMENT OF ALLOCATION: Performed by a pharmacist and coded in a sealed envelope COCHRANE QUALITY SCORE: A DESCRIBED AS RANDOMISED: Yes DESCRIBED AS DOUBLE BLIND: Yes METHOD OF RANDOMISATION WELL DESCRIBED/APPROPRIATE: Not clear METHOD OF BLINDING WELL DESCRIBED/APPROPRIATE: Not clear. DESCRIPTION OF WITHDRAWALS/DROPOUTS: 3/20 JADAD SCORE (5-1): 3 TYPE OF ANALYSIS (AVAILABLE CASE/TREATMENT RECEIVED/ ITT): Available case. COMPLIANCE: Participants asked to fill in a chart when medication was taken. CONFOUNDERS: NA

Wilson 2006 *(Continued)*

Participants	N SCREENED: Not reported. N RANDOMISED: 20 N COMPLETED: 17 M= 8 F= 9 MEAN AGE: 30 years BASELINE DETAILS: FEV1: 3.35 INCLUSION CRITERIA: History of mild-moderate asthma; 18-71 years of age; atopic; non-smokers; stable for 4 weeks prior to study entry; bronchial hyperresponsiveness to methacholine challenge; prn SABA only. EXCLUSION: Cardiac or pulmonary disease beside asthma.
Interventions	1. Ciclesonide 200mcg QD 2. Placebo DELIVERY: HFA-MDI TREATMENT PERIOD: 4 weeks RESCUE: Salbutamol. CO-INTERVENTIONS PERMITTED: SABA CO-INTERVENTIONS: SABA only. % on ICS baseline: 0
Outcomes	Methacholine challenge; exhaled nitric oxide; FEV1; PEF; symptoms; 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 reportedJADAD 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 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.

Zietkowski 2006 *(Continued)*

	EXCLUSION: Not reported.
Interventions	1. Ciclesonide OD 100mcg 2. Ciclesonide OD 200mcg 3. Fluticasone BD 100mcg 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
Notes	

Risk of bias

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

BD: twice daily; BDP: beclomethasone dipropionate; DPI: dry powder inhaler; FP: fluticasone propionate; ICS: inhaled corticosteroid; MDI: metered dose inhaler; OD: once daily; SABA: short-acting beta-agonist

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

Study	Reason for exclusion
Agertoft 2005	Treatment <4 weeks
Bethke 2002	Healthy volunteers
Dahl 1998	Treatment <4weeks
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
Lee 2004	Wrong comparison
Lee 2005	Wrong comparison
Postma 2001	Morning versus evening administration
Richter 2005	Treatment <4 weeks

Study	Reason for exclusion
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 (4-11yrs). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
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 in patients with mild to moderate asthma (12 to 75 y). Clinicaltrials.Gov. 2005
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	

Dahl *(Continued)*

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	
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	

Engelstätter *(Continued)*

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	
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 subjects 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 50mg/day and 200mg/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	

Sanofi Aventis *(Continued)*

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 1000mcg 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	

DATA AND ANALYSES

Comparison 1. Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	5	1673	Litres (Fixed, 95% CI)	0.08 [0.05, 0.11]
1.1 Children	2	765	Litres (Fixed, 95% CI)	0.05 [0.00, 0.09]
1.2 Adults	3	908	Litres (Fixed, 95% CI)	0.13 [0.08, 0.18]
2 Change in FEV1 predicted	4	1428	Mean Difference (IV, Fixed, 95% CI)	2.97 [1.80, 4.13]
2.1 Children	2	765	Mean Difference (IV, Fixed, 95% CI)	2.09 [-0.19, 4.36]
2.2 Adults	2	663	Mean Difference (IV, Fixed, 95% CI)	3.27 [1.92, 4.63]

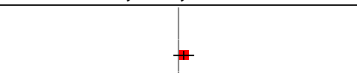
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Change in FVC	2	402	Litres (Fixed, 95% CI)	0.11 [0.03, 0.19]
3.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	2	402	Litres (Fixed, 95% CI)	0.11 [0.03, 0.19]
4 Change in clinic PEF	1		L/min (Fixed, 95% CI)	Totals not selected
4.1 Children	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	1		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in am PEF	5	1673	L/min (Fixed, 95% CI)	13.94 [9.74, 18.14]
5.1 Children	2	765	L/min (Fixed, 95% CI)	9.5 [3.26, 15.74]
5.2 Adults	3	908	L/min (Fixed, 95% CI)	17.62 [11.94, 23.30]
6 Change in pm PEF	5	1677	L/min (Fixed, 95% CI)	10.70 [6.91, 14.49]
6.1 Children	2	769	L/min (Fixed, 95% CI)	8.25 [2.80, 13.71]
6.2 Adults	3	908	L/min (Fixed, 95% CI)	12.98 [7.72, 18.24]
7 Change in rescue beta-agonist use	3	908	Puffs/d (Random, 95% CI)	-0.87 [-1.36, -0.37]
7.1 Children	0	0	Puffs/d (Random, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	3	908	Puffs/d (Random, 95% CI)	-0.87 [-1.36, -0.37]
8 Change in total symptoms	2	741	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.53, -0.24]
8.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	2	741	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.53, -0.24]
9 Change in daytime symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Change in nighttime symptoms	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	1		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
11 Change in nighttime awakenings (n/night)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Change in quality of life score (paediatric AQLQ)	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Change from baseline in quality of life score (AQLQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Adverse event	4	1174	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.81, 0.99]
14.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.80, 0.99]
14.2 Adults	2	402	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.70, 1.22]
15 Candidiasis	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 Children	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Pharyngitis	2	772	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.53, 2.28]
16.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.53, 2.28]
16.2 Adults	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Nasopharyngitis	3	929	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.74, 1.42]
17.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.62, 1.53]
17.2 Adults	1	157	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.69, 1.73]
18 Headache	4	1174	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.34]
18.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.56, 1.39]
18.2 Adults	2	402	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.33, 2.44]
19 Upper respiratory tract infection	4	1174	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.65, 1.36]
19.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.44, 1.12]

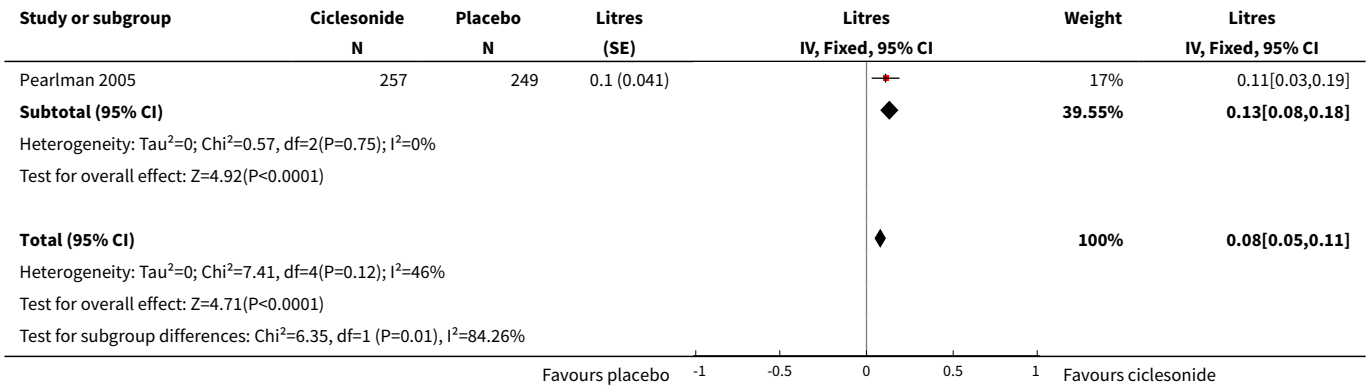
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
19.2 Adults	2	402	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.83, 2.93]
20 Withdrawals	4	1174	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.55, 0.83]
20.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.56, 1.06]
20.2 Adults	2	402	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.46, 0.78]
21 Withdrawals (lack of efficacy)	5	1680	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.38, 0.60]
21.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.37, 0.90]
21.2 Adults	3	908	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.34, 0.59]
22 Withdrawals (adverse events)	4	1174	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.43, 0.99]
22.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.39, 0.92]
22.2 Adults	2	402	Risk Ratio (M-H, Fixed, 95% CI)	3.08 [0.32, 29.36]
23 Rhinitis	3	1017	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.72, 1.96]
23.1 Children	2	772	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.63, 2.04]
23.2 Adults	1	245	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.52, 3.48]
24 Asthma (not otherwise specified)	3	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.40, 0.75]
24.1 Children	2	768	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.46, 0.92]
24.2 Adults	1	245	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.13, 0.62]

Analysis 1.1. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

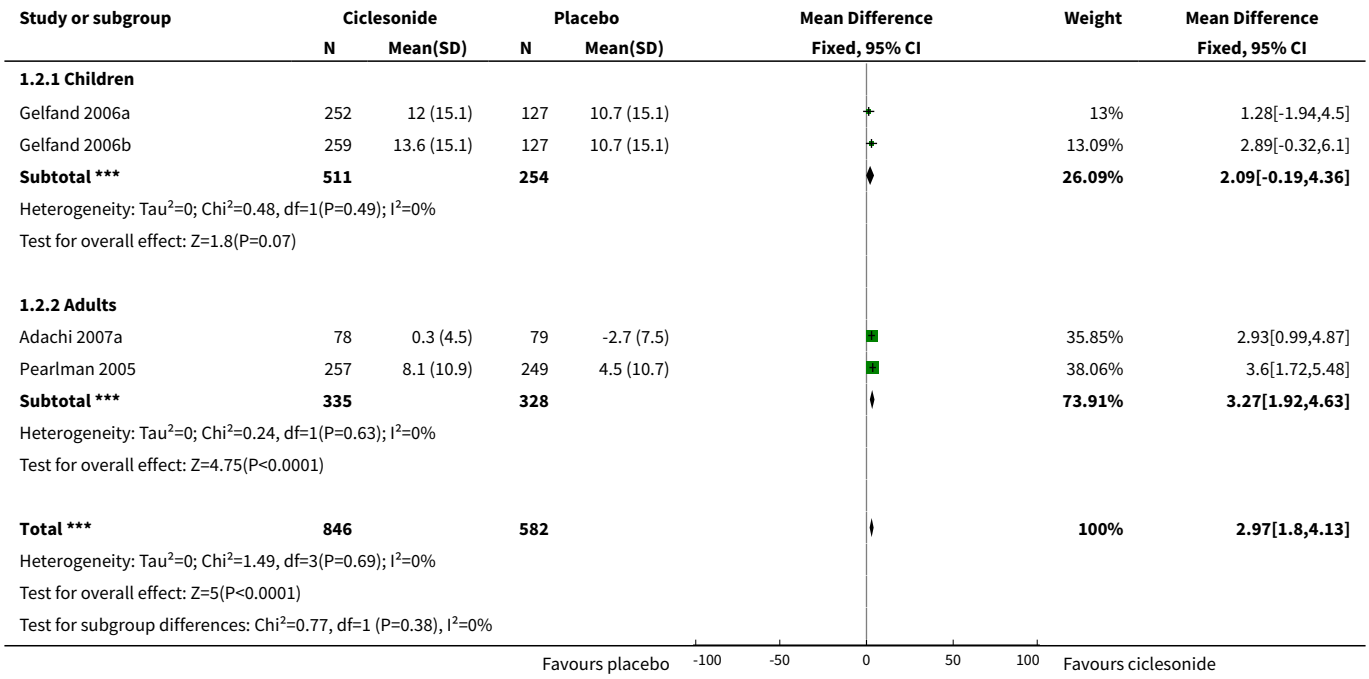
Study or subgroup	Ciclesonide N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
1.1.1 Children						
Gelfand 2006a	252	127	0 (0.031)		30.22%	0.03[-0.03,0.09]
Gelfand 2006b	259	127	0.1 (0.031)		30.22%	0.06[0,0.12]
Subtotal (95% CI)					**60.45%**	**0.05[0,0.09]**
Heterogeneity: Tau^2=0; Chi^2=0.48, df=1(P=0.49); I^2=0%						
Test for overall effect: Z=2.08(P=0.04)						
1.1.2 Adults						
Adachi 2007a	78	79	0.1 (0.046)		13.43%	0.14[0.05,0.23]
Langdon 2005	120	125	0.2 (0.056)		9.12%	0.16[0.05,0.27]



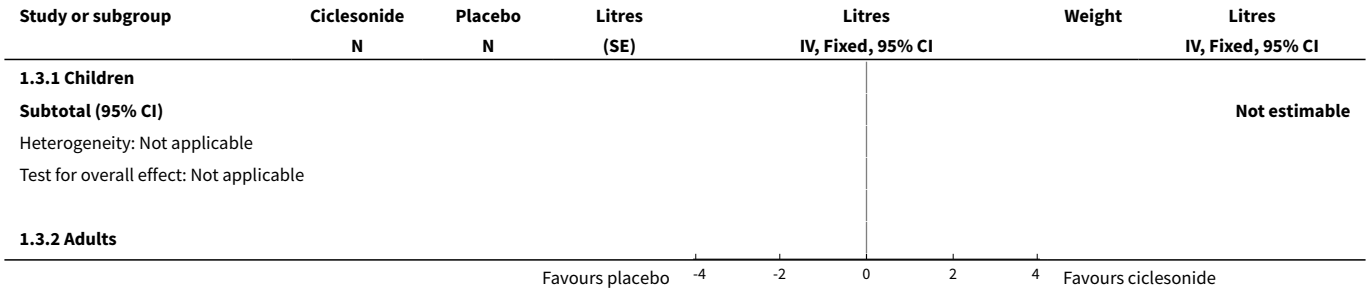
Favours placebo — Favours ciclesonide



Analysis 1.2. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 2 Change in FEV1 predicted.



Analysis 1.3. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 3 Change in FVC.



Study or subgroup	Ciclesonide N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
Adachi 2007a	78	79	0.1 (0.051)		61.31%	0.08[-0.02,0.18]
Langdon 2005	120	125	0.2 (0.064)		38.69%	0.15[0.02,0.28]
Subtotal (95% CI)					**100%**	**0.11[0.03,0.19]**
Heterogeneity: Tau²=0; Chi²=0.73, df=1(P=0.39); I²=0%						
Test for overall effect: Z=2.68(P=0.01)						
Total (95% CI)					**100%**	**0.11[0.03,0.19]**
Heterogeneity: Tau²=0; Chi²=0.73, df=1(P=0.39); I²=0%						
Test for overall effect: Z=2.68(P=0.01)						
Test for subgroup differences: Not applicable						

Favours placebo -4 -2 0 2 4 Favours ciclesonide

Analysis 1.4. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 4 Change in clinic PEF.

Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
1.4.1 Children					
1.4.2 Adults					
Langdon 2005	120	125	21.5 (9.787)		21.47[2.29,40.65]

Favours placebo -1 -0.5 0 0.5 1 Favours ciclesonide

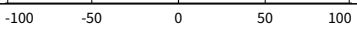
Analysis 1.5. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 5 Change in am PEF.

Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
1.5.1 Children						
Gelfand 2006a	252	127	7 (4.505)		22.64%	7[-1.83,15.83]
Gelfand 2006b	259	127	12 (4.505)		22.64%	12[3.17,20.83]
Subtotal (95% CI)					**45.28%**	**9.5[3.26,15.74]**
Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%						
Test for overall effect: Z=2.98(P=0)						
1.5.2 Adults						
Adachi 2007a	78	79	29.2 (6.464)		11%	29.18[16.51,41.85]
Langdon 2005	120	125	20 (6.1)		12.35%	20[8.04,31.96]
Pearlman 2005	257	249	12.6 (3.827)		31.38%	12.63[5.13,20.13]
Subtotal (95% CI)					**54.72%**	**17.62[11.94,23.3]**
Heterogeneity: Tau²=0; Chi²=5.05, df=2(P=0.08); I²=60.4%						
Test for overall effect: Z=6.08(P<0.0001)						
Total (95% CI)					**100%**	**13.94[9.74,18.14]**
Heterogeneity: Tau²=0; Chi²=9.22, df=4(P=0.06); I²=56.62%						
Test for overall effect: Z=6.5(P<0.0001)						
Test for subgroup differences: Chi²=3.55, df=1 (P=0.06), I²=71.87%						

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 1.6. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 6 Change in pm PEF.

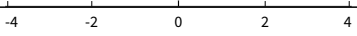
Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
1.6.1 Children						
Gelfand 2006a	252	129	5.2 (3.934)		24.12%	5.22[-2.49,12.93]
Gelfand 2006b	259	129	11.3 (3.934)		24.12%	11.29[3.58,19]
Subtotal (95% CI)					**48.23%**	**8.25[2.8,13.71]**
Heterogeneity: Tau^2=0; Chi^2=1.19, df=1(P=0.28); I^2=15.99%						
Test for overall effect: Z=2.97(P=0)						
1.6.2 Adults						
Adachi 2007a	78	79	24.9 (6.036)		10.25%	24.86[13.03,36.69]
Langdon 2005	120	125	14 (5.537)		12.17%	14[3.15,24.85]
Pearlman 2005	257	249	8.4 (3.566)		29.35%	8.41[1.42,15.4]
Subtotal (95% CI)					**51.77%**	**12.98[7.72,18.24]**
Heterogeneity: Tau^2=0; Chi^2=5.55, df=2(P=0.06); I^2=63.97%						
Test for overall effect: Z=4.83(P<0.0001)						
Total (95% CI)					**100%**	**10.7[6.91,14.49]**
Heterogeneity: Tau^2=0; Chi^2=8.23, df=4(P=0.08); I^2=51.42%						
Test for overall effect: Z=5.54(P<0.0001)						
Test for subgroup differences: Chi^2=1.49, df=1 (P=0.22), I^2=33.06%						



Favours placebo — Favours ciclesonide

Analysis 1.7. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 7 Change in rescue beta-agonist use.

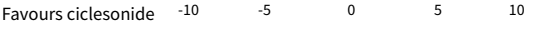
Study or subgroup	Ciclesonide N	Placebo N	Puffs/d (SE)	Puffs/d IV, Random, 95% CI	Weight	Puffs/d IV, Random, 95% CI
1.7.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.7.2 Adults						
Adachi 2007a	78	79	-0.8 (0.25)		29.9%	-0.84[-1.33,-0.35]
Langdon 2005	120	125	-0.5 (0.16)		36.21%	-0.5[-0.81,-0.19]
Pearlman 2005	257	249	-1.3 (0.194)		33.89%	-1.28[-1.66,-0.9]
Subtotal (95% CI)					**100%**	**-0.87[-1.36,-0.37]**
Heterogeneity: Tau^2=0.15; Chi^2=9.64, df=2(P=0.01); I^2=79.25%						
Test for overall effect: Z=3.44(P=0)						
Total (95% CI)					**100%**	**-0.87[-1.36,-0.37]**
Heterogeneity: Tau^2=0.15; Chi^2=9.64, df=2(P=0.01); I^2=79.25%						
Test for overall effect: Z=3.44(P=0)						
Test for subgroup differences: Not applicable						



Favours ciclesonide — Favours placebo

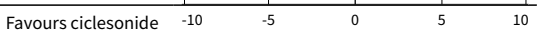
Analysis 1.8. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 8 Change in total symptoms.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
1.8.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
1.8.2 Adults							
Langdon 2005	120	0 (2)	115	1 (2)		31.35%	-0.5[-0.76,-0.24]
Pearlman 2005	257	-0.6 (1.3)	249	-0.1 (1.3)		68.65%	-0.34[-0.51,-0.16]
Subtotal ***	**377**		**364**			**100%**	**-0.39[-0.53,-0.24]**
Heterogeneity: Tau^2=0; Chi^2=1.01, df=1(P=0.32); I^2=0.5%							
Test for overall effect: Z=5.23(P<0.0001)							
Total ***	**377**		**364**			**100%**	**-0.39[-0.53,-0.24]**
Heterogeneity: Tau^2=0; Chi^2=1.01, df=1(P=0.32); I^2=0.5%							
Test for overall effect: Z=5.23(P<0.0001)							
Test for subgroup differences: Not applicable							



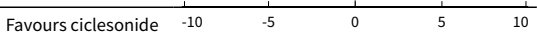
Analysis 1.9. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 9 Change in daytime symptoms.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.9.1 Children						
1.9.2 Adults						
Langdon 2005	120	0 (0.9)	115	0.4 (0.9)		-0.43[-0.65,-0.21]



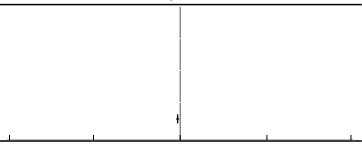
Analysis 1.10. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 10 Change in nighttime symptoms.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.10.1 Children						
1.10.2 Adults						
Langdon 2005	120	0 (0.9)	115	0.4 (0.9)		-0.43[-0.65,-0.21]



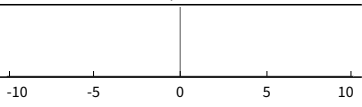
Analysis 1.11. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 11 Change in nighttime awakenings (n/night).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.11.1 Children						
1.11.2 Adults						
Pearlman 2005	257	-0.1 (0.5)	249	0.1 (0.5)		-0.15[-0.23,-0.07]



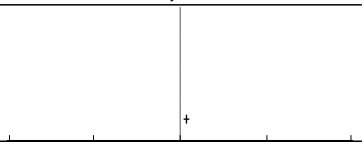
Analysis 1.12. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 12 Change in quality of life score (paediatric AQLQ).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Gelfand 2006a	252	0.5 (0)	129	0.3 (0)		Not estimable
Gelfand 2006b	259	0.5 (0)	129	0.3 (0)		Not estimable



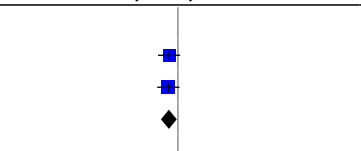
Analysis 1.13. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 13 Change from baseline in quality of life score (AQLQ).

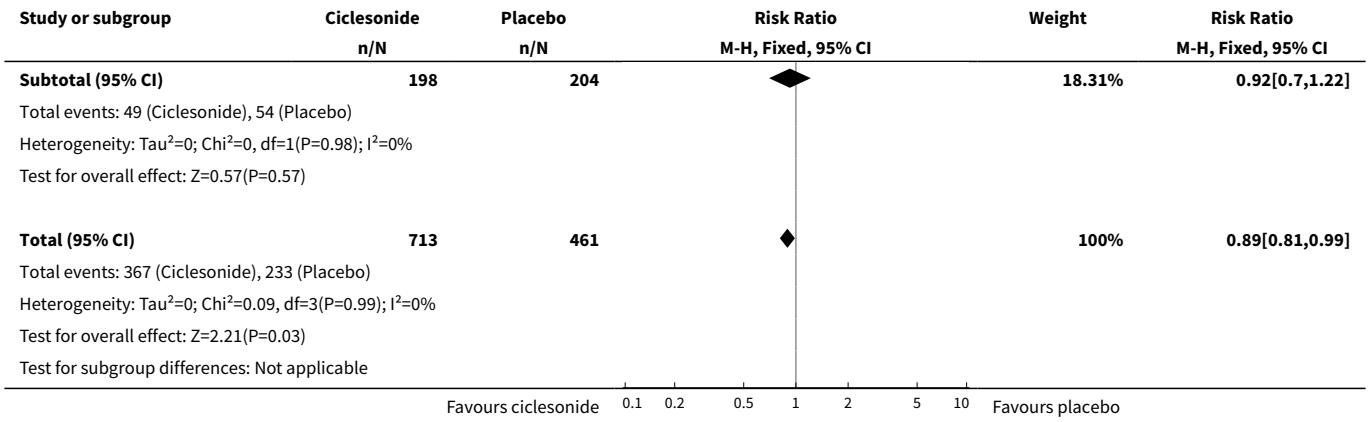
Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.13.1 Children						
1.13.2 Adults						
Pearlman 2005	257	0.5 (1)	249	0.1 (1)		0.36[0.19,0.53]



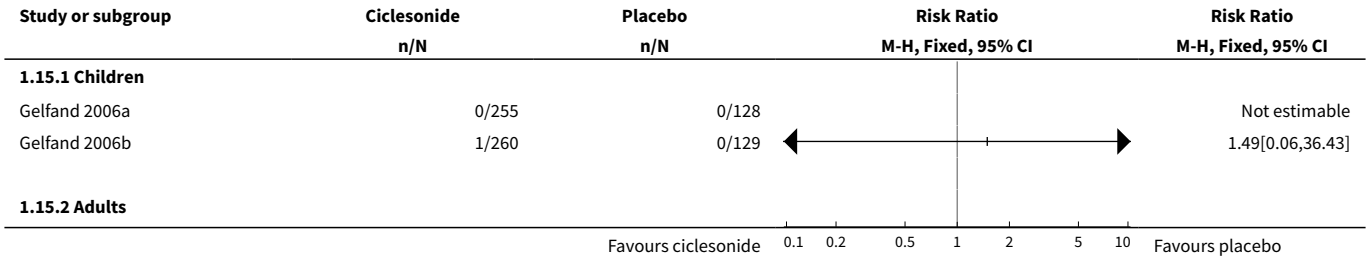
Analysis 1.14. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 14 Adverse event.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.14.1 Children					
Gelfand 2006a	158/255	89/128		40.54%	0.89[0.77,1.03]
Gelfand 2006b	160/260	90/129		41.15%	0.88[0.76,1.02]
Subtotal (95% CI)	**515**	**257**		**81.69%**	**0.89[0.8,0.99]**
Total events: 318 (Ciclesonide), 179 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=2.24(P=0.03)					
1.14.2 Adults					
Adachi 2007a	42/78	46/79		15.63%	0.92[0.7,1.22]
Langdon 2005	7/120	8/125		2.68%	0.91[0.34,2.44]

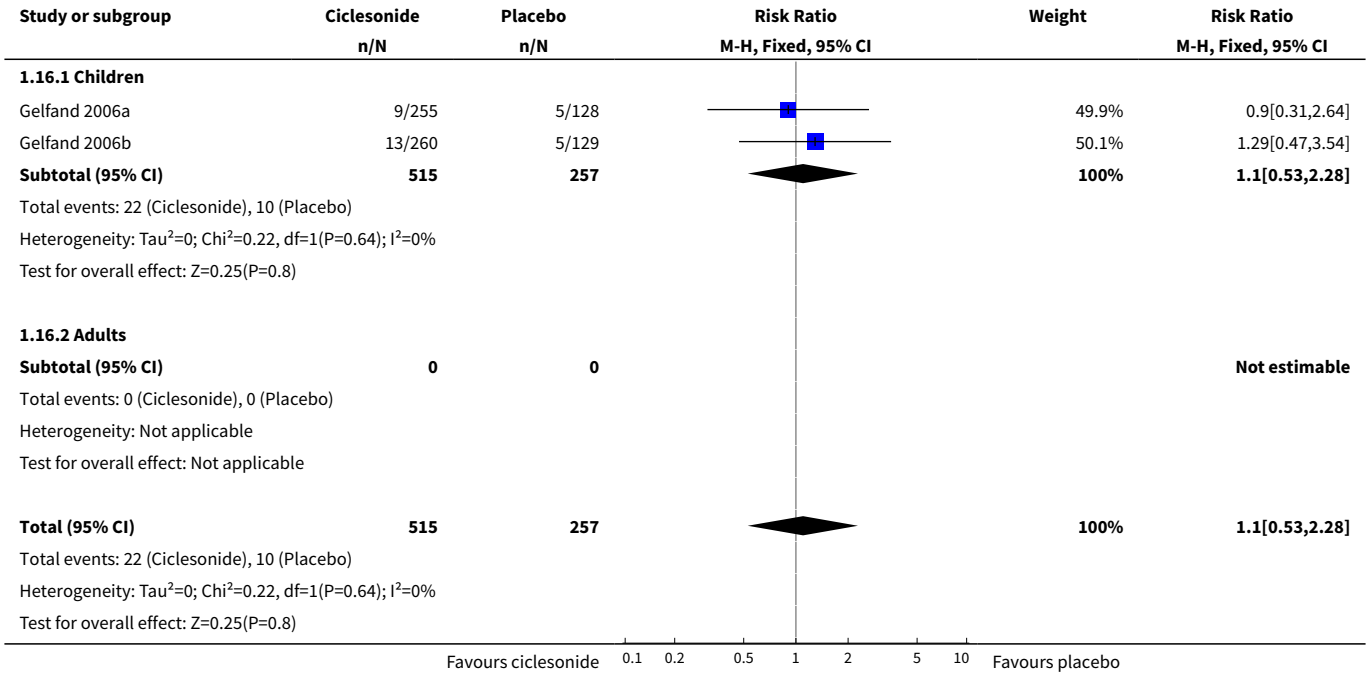




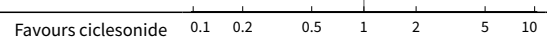
Analysis 1.15. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 15 Candidiasis.



Analysis 1.16. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 16 Pharyngitis.

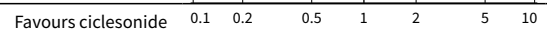


Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for subgroup differences: Not applicable					



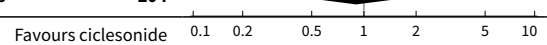
Analysis 1.17. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 17 Nasopharyngitis.

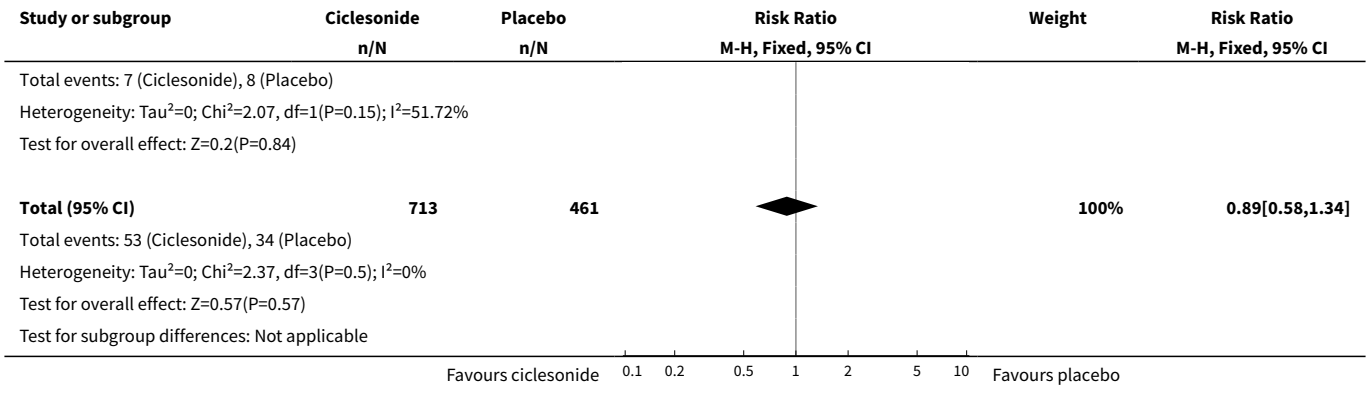
Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 Children					
Gelfand 2006a	18/255	13/128		29.57%	0.7[0.35,1.37]
Gelfand 2006b	33/260	13/129		29.69%	1.26[0.69,2.31]
Subtotal (95% CI)	**515**	**257**		**59.26%**	**0.98[0.62,1.53]**
Total events: 51 (Ciclesonide), 26 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.64, df=1(P=0.2); I^2=38.84%					
Test for overall effect: Z=0.1(P=0.92)					
1.17.2 Adults					
Adachi 2007a	26/78	24/79		40.74%	1.1[0.69,1.73]
Subtotal (95% CI)	**78**	**79**		**40.74%**	**1.1[0.69,1.73]**
Total events: 26 (Ciclesonide), 24 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.4(P=0.69)					
Total (95% CI)	**593**	**336**		**100%**	**1.03[0.74,1.42]**
Total events: 77 (Ciclesonide), 50 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.78, df=2(P=0.41); I^2=0%					
Test for overall effect: Z=0.16(P=0.87)					
Test for subgroup differences: Not applicable					



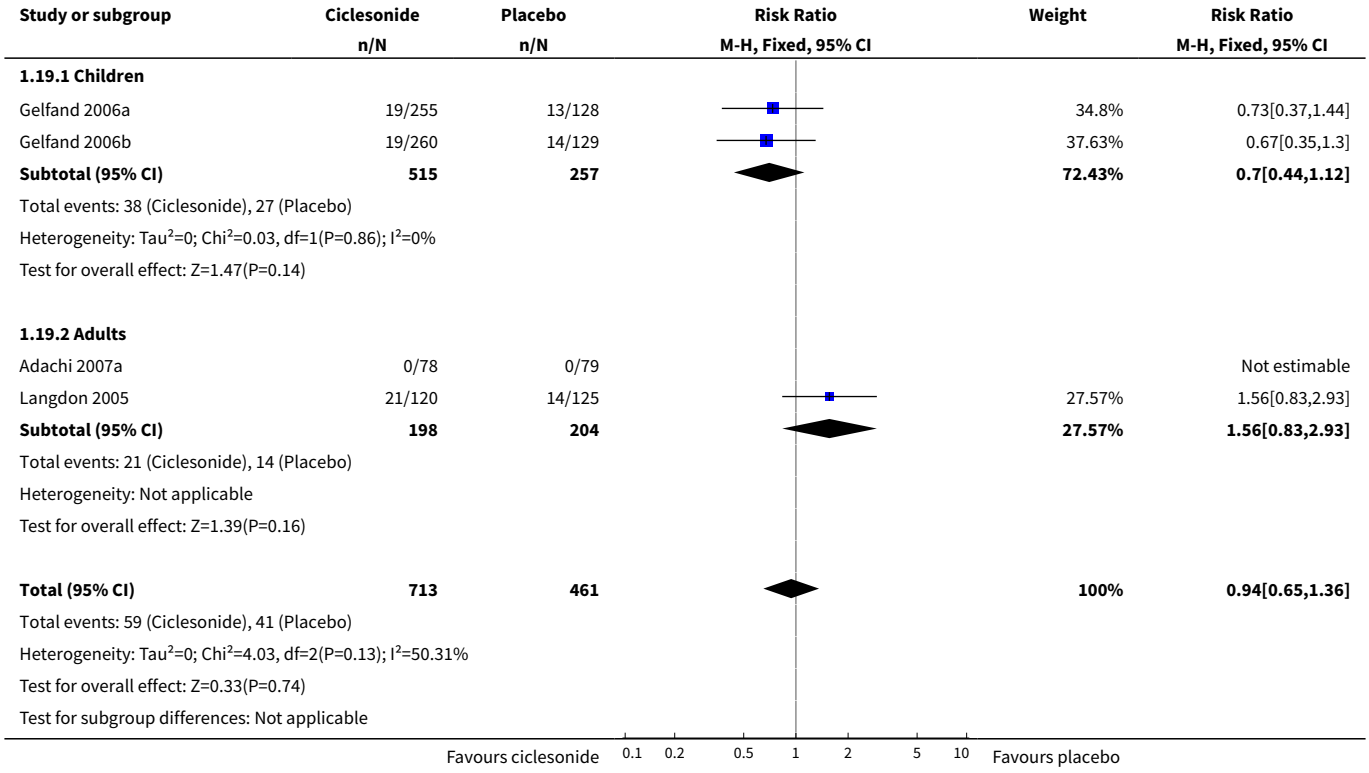
Analysis 1.18. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 18 Headache.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 Children					
Gelfand 2006a	20/255	13/128		40.65%	0.77[0.4,1.5]
Gelfand 2006b	26/260	13/129		40.81%	0.99[0.53,1.87]
Subtotal (95% CI)	**515**	**257**		**81.46%**	**0.88[0.56,1.39]**
Total events: 46 (Ciclesonide), 26 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=0.54(P=0.59)					
1.18.2 Adults					
Adachi 2007a	1/78	4/79		9.33%	0.25[0.03,2.22]
Langdon 2005	6/120	4/125		9.2%	1.56[0.45,5.4]
Subtotal (95% CI)	**198**	**204**		**18.54%**	**0.9[0.33,2.44]**

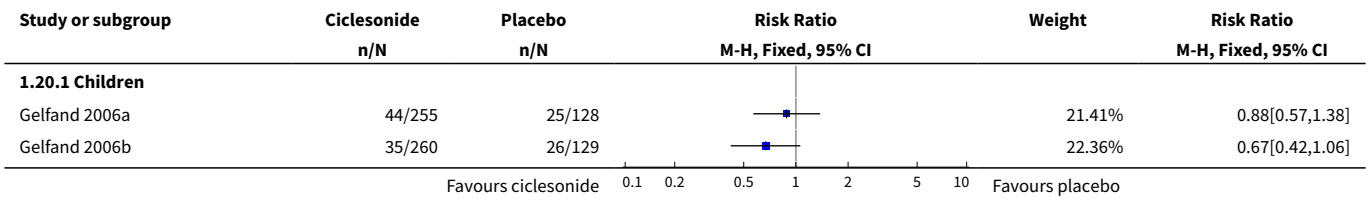


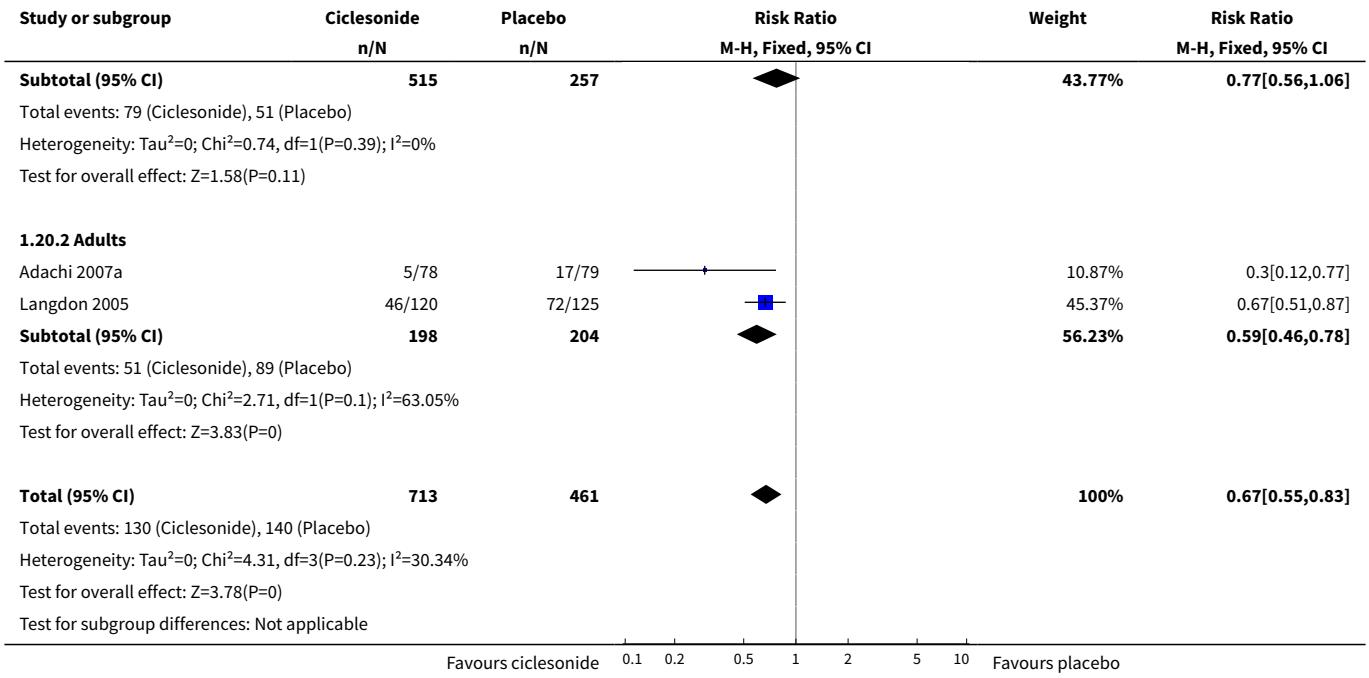


Analysis 1.19. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 19 Upper respiratory tract infection.

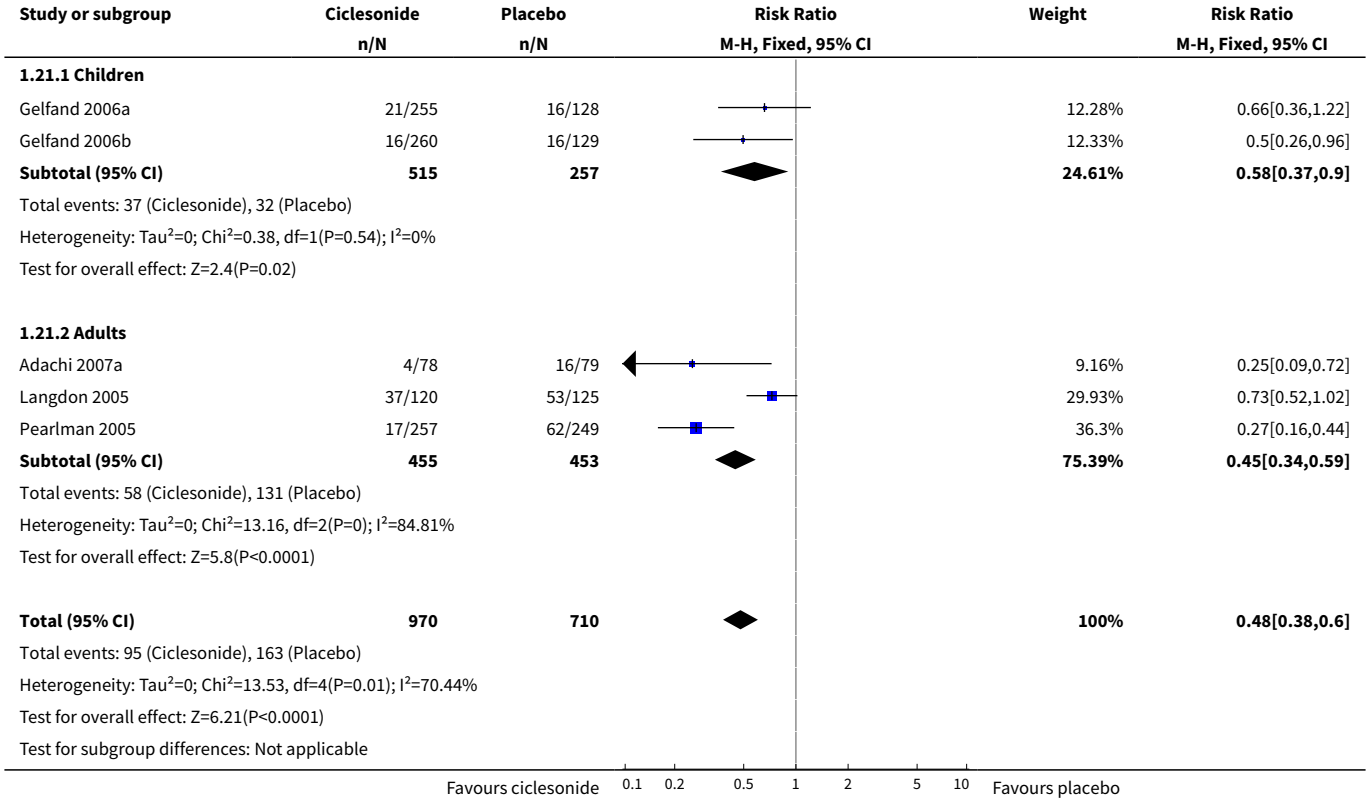


Analysis 1.20. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 20 Withdrawals.

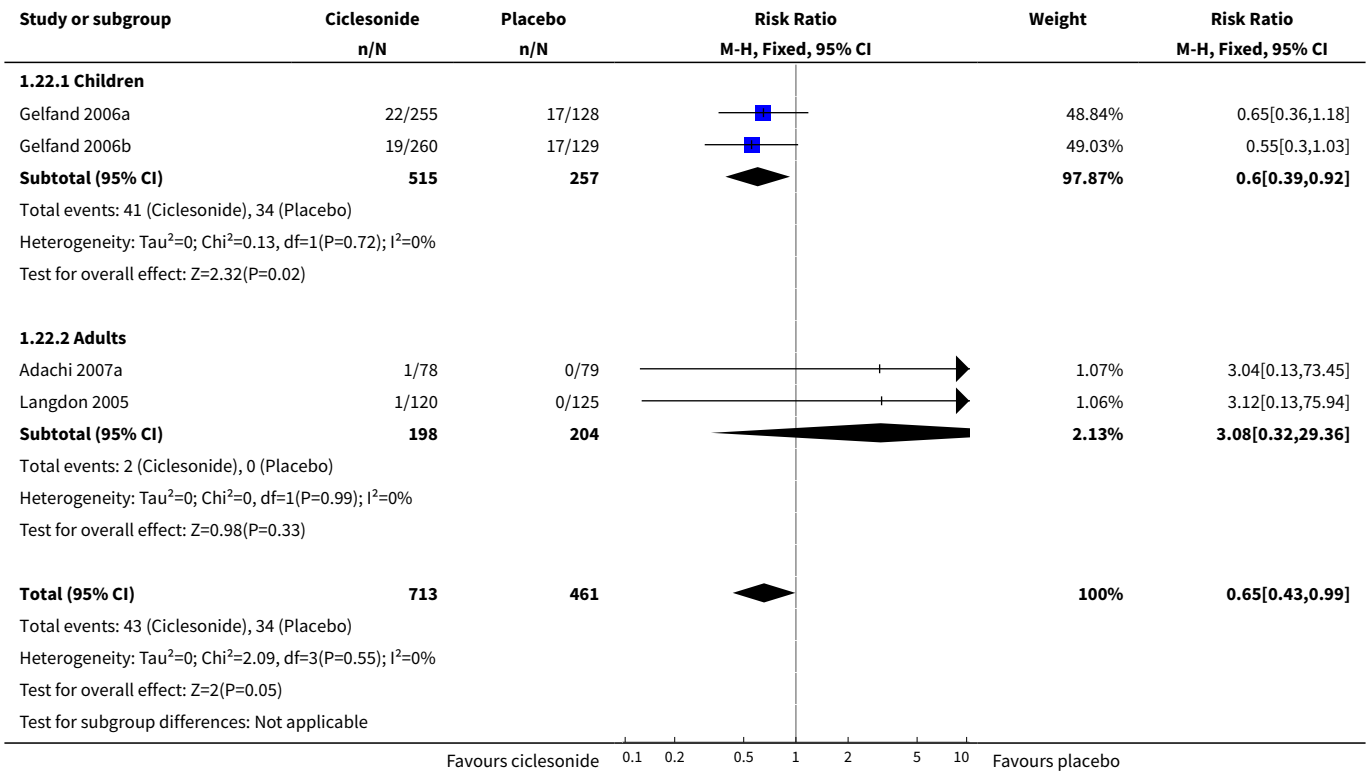




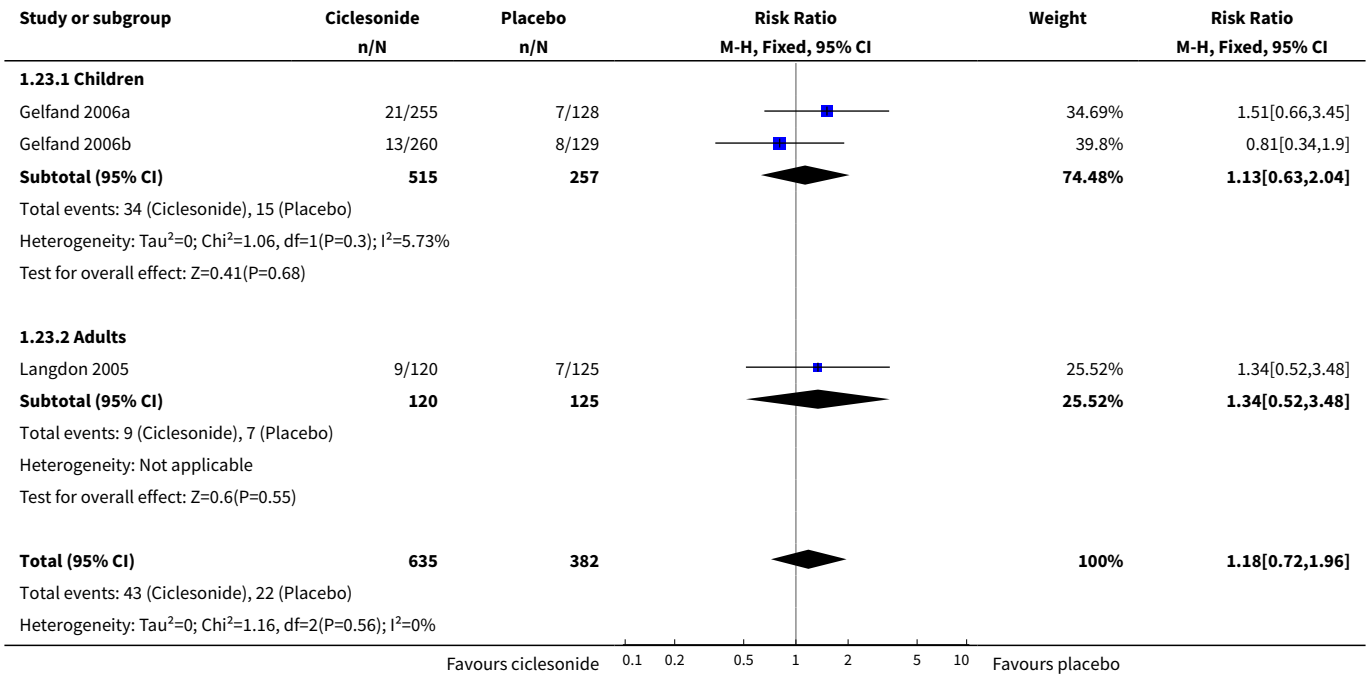
Analysis 1.21. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 21 Withdrawals (lack of efficacy).

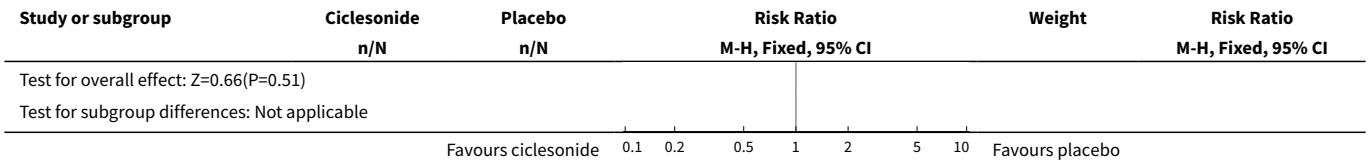


Analysis 1.22. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 22 Withdrawals (adverse events).

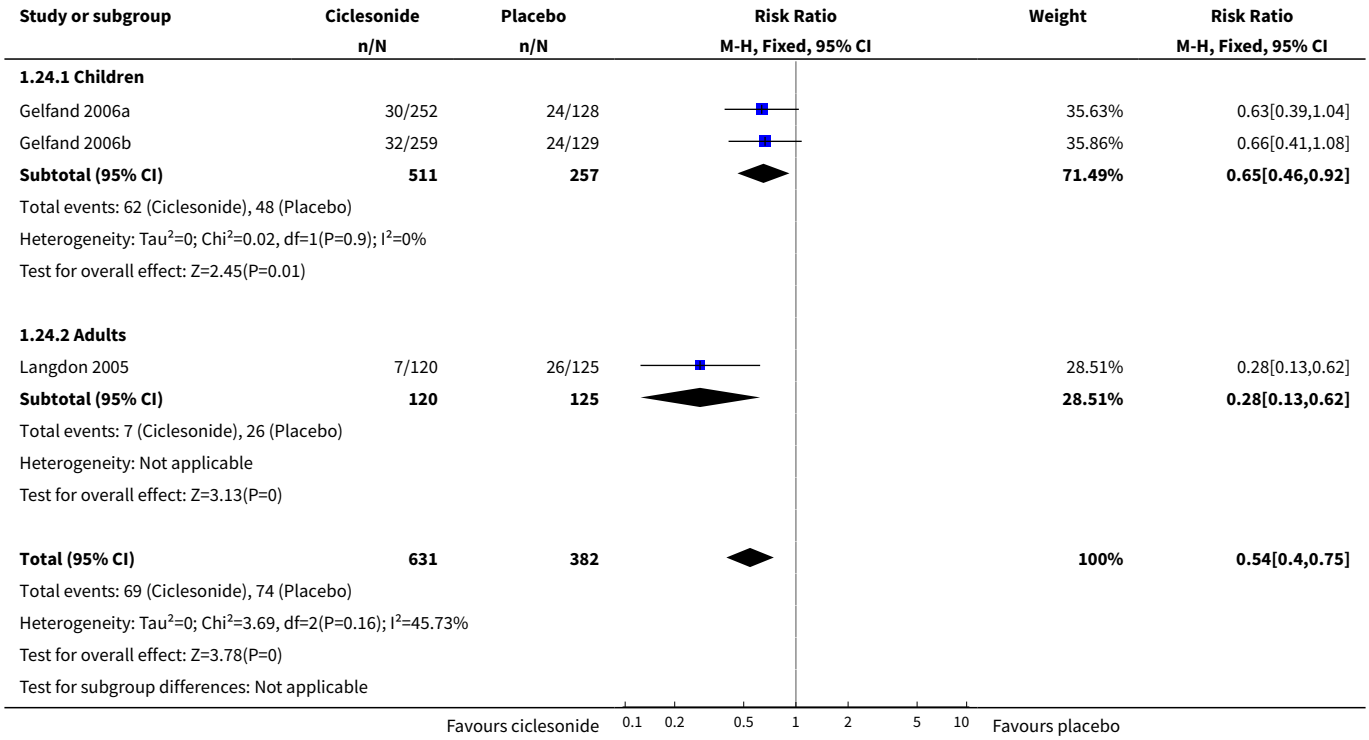


Analysis 1.23. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 23 Rhinitis.





Analysis 1.24. Comparison 1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies), Outcome 24 Asthma (not otherwise specified).



Comparison 2. Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 at endpoint	1		L (Fixed, 95% CI)	Totals not selected
1.1 Children	0		L (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		L (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in FEV1	4	1543	L (Fixed, 95% CI)	0.12 [0.08, 0.15]
2.1 Children	1	507	L (Fixed, 95% CI)	0.07 [0.02, 0.12]
2.2 Adults	3	1036	L (Fixed, 95% CI)	0.17 [0.12, 0.22]

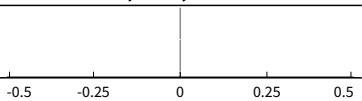
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Change in FEV1 predicted	3	1171	Mean Difference (IV, Fixed, 95% CI)	3.06 [1.85, 4.26]
3.1 Children	1	507	Mean Difference (IV, Fixed, 95% CI)	3.48 [0.86, 6.10]
3.2 Adults	2	664	Mean Difference (IV, Fixed, 95% CI)	2.94 [1.58, 4.30]
4 Change in FVC	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 clinic PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in am PEF	5	1768	L/min (Fixed, 95% CI)	18.66 [14.74, 22.57]
6.1 Children	1	507	L/min (Fixed, 95% CI)	7.53 [0.49, 14.57]
6.2 Adults	4	1261	L/min (Fixed, 95% CI)	23.64 [18.93, 28.35]
7 Change in pm PEF (L/min)	4	1383	Mean Difference (IV, Fixed, 95% CI)	13.93 [9.52, 18.35]
7.1 Children	1	507	Mean Difference (IV, Fixed, 95% CI)	8.7 [2.40, 15.00]
7.2 Adults	3	876	Mean Difference (IV, Fixed, 95% CI)	18.97 [12.78, 25.15]
8 Change in rescue 2-agonists use	3	1034	Puffs/d (Fixed, 95% CI)	-1.11 [-1.32, -0.89]
8.1 Children	0	0	Puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	3	1034	Puffs/d (Fixed, 95% CI)	-1.11 [-1.32, -0.89]
9 Change in asthma symptom scores	3	1091	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.65, -0.38]
9.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	3	1091	Std. Mean Difference (IV, Fixed, 95% CI)	-0.51 [-0.65, -0.38]
10 Change in nighttime awakenings (SMD)	2	874	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.47, -0.20]
10.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

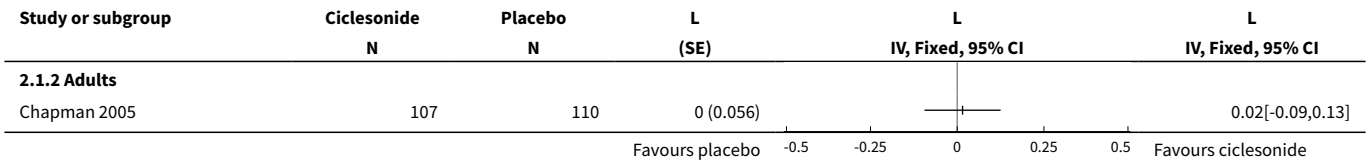
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Adults	2	874	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.47, -0.20]
11 Change in quality of life score (paediatric AQLQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Change from baseline in quality of life score (AQLQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Loss of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Withdrawals	3	877	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.43, 0.70]
14.1 Children	1	510	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.41, 0.93]
14.2 Adults	2	367	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.38, 0.69]
15 Withdrawals (lack of efficacy)	3	1159	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.22, 0.45]
15.1 Children	1	510	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.24, 0.81]
15.2 Adults	2	649	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.16, 0.41]
16 Withdrawals (adverse events)	3	1159	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.27, 0.56]
16.1 Children	1	510	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.27, 0.84]
16.2 Adults	2	649	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.22, 0.55]
17 Changes in cortisol levels (serum)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18 Changes in cortisol levels (urinary)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19 Asthma (not otherwise specified)	2	724	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.83]
19.1 Children	1	507	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.44, 1.01]
19.2 Adults	1	217	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.28, 0.84]
20 Candidiasis	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
20.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
21 Sore throat	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
22 Voice alteration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
23 Headache	3	877	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.66, 1.41]
23.1 Children	1	510	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.87]
23.2 Adults	2	367	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.41, 1.38]
24 Upper respiratory tract infection	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
24.2 Adults	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Symptoms of asthma (wheeze, dsypnea or cough)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
26 Rhinitis	2	727	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.33, 1.00]
26.1 Children	1	510	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.23, 1.26]
26.2 Adults	1	217	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.29, 1.26]
27 Adverse event	2	670	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.84, 1.05]
27.1 Children	1	510	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.89, 1.11]
27.2 Adults	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.54, 1.01]
28 Pharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
28.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Nasopharyngitis	2	660	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.81, 1.61]
29.1 Children	1	510	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.79, 2.09]
29.2 Adults	1	150	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.60, 1.59]

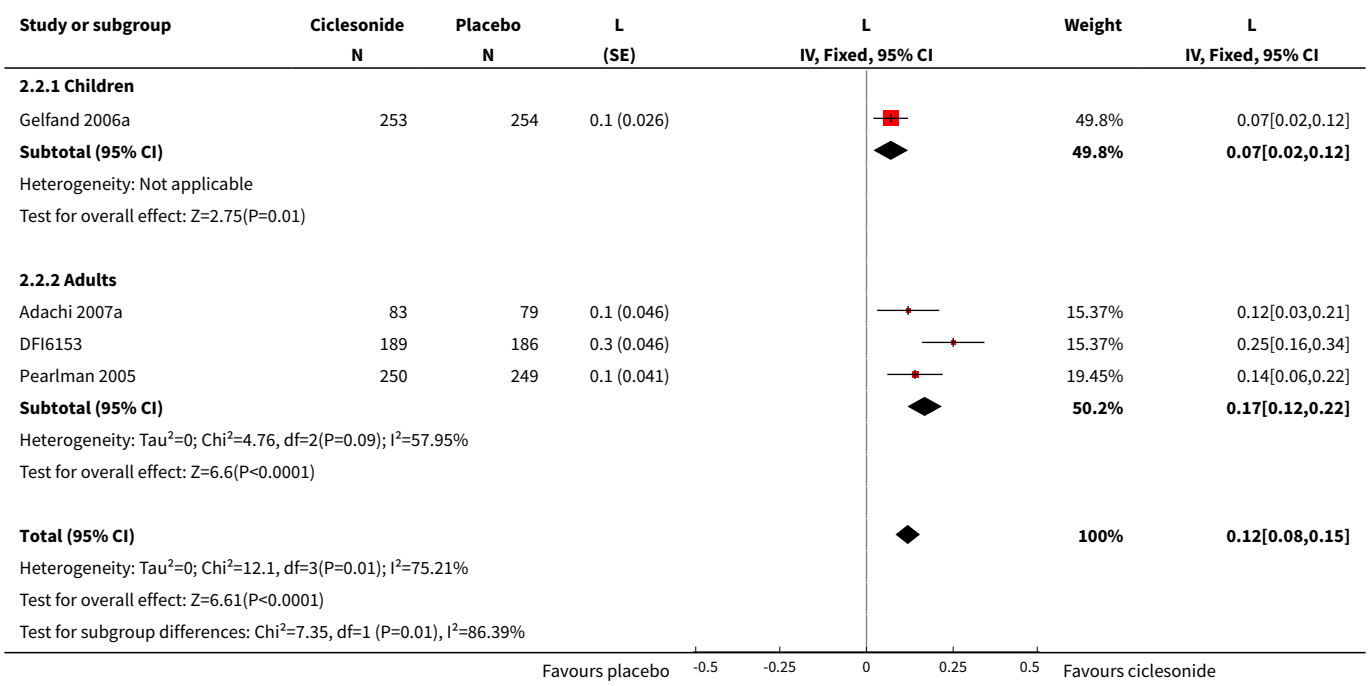
Analysis 2.1. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 1 FEV1 at endpoint.

Study or subgroup	Ciclesonide N	Placebo N	L (SE)	L IV, Fixed, 95% CI	L IV, Fixed, 95% CI
2.1.1 Children					

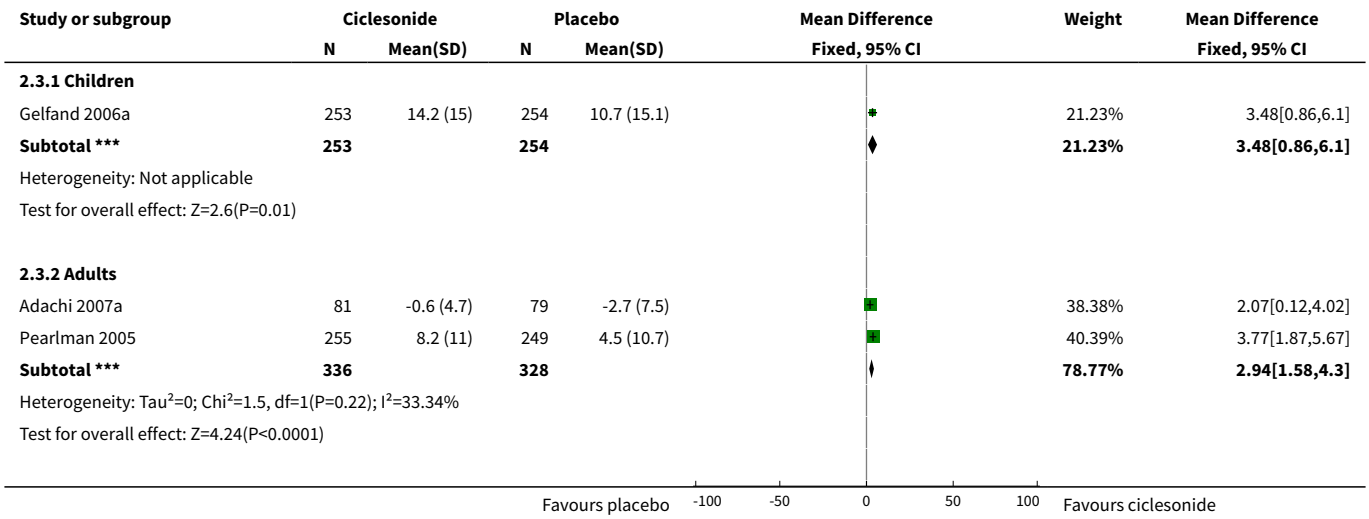




Analysis 2.2. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 2 Change in FEV1.



Analysis 2.3. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 3 Change in FEV1 predicted.



Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Total ***	**589**		**582**			**100%**	**3.06[1.85,4.26]**
Heterogeneity: Tau²=0; Chi²=1.63, df=2(P=0.44); I²=0%							
Test for overall effect: Z=4.96(P<0.0001)							
Test for subgroup differences: Chi²=0.13, df=1 (P=0.72), I²=0%							

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 2.4. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 4 Change in FVC.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.4.1 Children						
2.4.2 Adults						
Adachi 2007a	81	0.1 (0.2)	79	-0.1 (0.4)		0.18[0.08,0.28]

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 2.5. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 5 Change in clinic PEF (L/min).

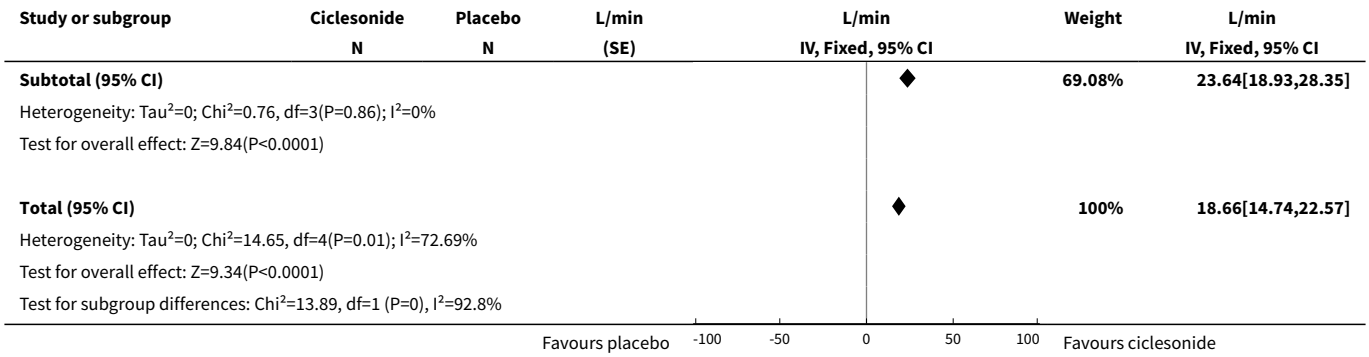
Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.5.1 Children						
2.5.2 Adults						
Chapman 2005	107	4.6 (0)	110	-21.6 (0)		Not estimable

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 2.6. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 6 Change in am PEF.

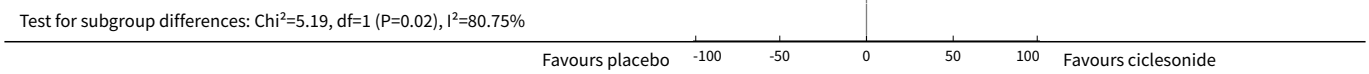
Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
2.6.1 Children						
Gelfand 2006a	253	254	7.5 (3.592)		30.92%	7.53[0.49,14.57]
Subtotal (95% CI)					**30.92%**	**7.53[0.49,14.57]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.1(P=0.04)						
2.6.2 Adults						
Adachi 2007a	81	79	28.7 (6.469)		9.53%	28.7[16.02,41.38]
Chapman 2005	117	110	23.5 (5.566)		12.87%	23.5[12.59,34.41]
DFI6153	189	186	23.2 (4.49)		19.79%	23.2[14.4,32]
Pearlman 2005	250	249	22.2 (3.852)		26.88%	22.23[14.68,29.78]

Favours placebo -100 -50 0 50 100 Favours ciclesonide



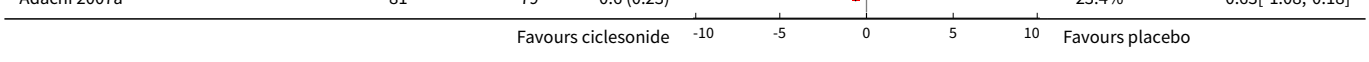
Analysis 2.7. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 7 Change in pm PEF (L/min).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.7.1 Children							
Gelfand 2006a	253	15.8 (36.2)	254	7.1 (36.2)		49.02%	8.7[2.4,15]
Subtotal ***	**253**		**254**			**49.02%**	**8.7[2.4,15]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.7(P=0.01)							
2.7.2 Adults							
Adachi 2007a	81	3.4 (39.5)	79	-23.3 (42.4)		12.07%	26.66[13.95,39.37]
Chapman 2005	107	-3.5 (0)	110	-17 (0)			Not estimable
Pearlman 2005	250	18.1 (40.6)	249	1.5 (40.1)		38.91%	16.58[9.5,23.66]
Subtotal ***	**438**		**438**			**50.98%**	**18.97[12.78,25.15]**
Heterogeneity: Tau²=0; Chi²=1.85, df=1(P=0.17); I²=45.81%							
Test for overall effect: Z=6.01(P<0.0001)							
Total ***	**691**		**692**			**100%**	**13.93[9.52,18.35]**
Heterogeneity: Tau²=0; Chi²=7.04, df=2(P=0.03); I²=71.59%							
Test for overall effect: Z=6.19(P<0.0001)							
Test for subgroup differences: Chi²=5.19, df=1 (P=0.02), I²=80.75%							



Analysis 2.8. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 8 Change in rescue 2-agonists use.

Study or subgroup	Ciclesonide N	Placebo N	Puffs/d (SE)	Puffs/d IV, Fixed, 95% CI	Weight	Puffs/d IV, Fixed, 95% CI
2.8.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.8.2 Adults						
Adachi 2007a	81	79	-0.6 (0.23)		23.4%	-0.63[-1.08,-0.18]



Study or subgroup	Ciclesonide N	Placebo N	Puffs/d (SE)	Puffs/d IV, Fixed, 95% CI	Weight	Puffs/d IV, Fixed, 95% CI
DFI6153	189	186	-1.1 (0.168)		43.65%	-1.11[-1.44,-0.78]
Pearlman 2005	250	249	-1.4 (0.194)		32.96%	-1.44[-1.82,-1.06]
Subtotal (95% CI)					**100%**	**-1.11[-1.32,-0.89]**
Heterogeneity: Tau²=0; Chi²=7.25, df=2(P=0.03); I²=72.43%						
Test for overall effect: Z=9.95(P<0.0001)						
Total (95% CI)					**100%**	**-1.11[-1.32,-0.89]**
Heterogeneity: Tau²=0; Chi²=7.25, df=2(P=0.03); I²=72.43%						
Test for overall effect: Z=9.95(P<0.0001)						
Test for subgroup differences: Not applicable						

Favours ciclesonide -10 -5 0 5 10 Favours placebo

Analysis 2.9. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 9 Change in asthma symptom scores.

Study or subgroup	Ciclesonide N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.9.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.9.2 Adults							
Chapman 2005	107	0 (0)	110	0.4 (0)			Not estimable
DFI6153	189	-0.6 (1)	186	0 (1)		42.3%	-0.63[-0.83,-0.42]
Pearlman 2005	250	-0.7 (1.3)	249	-0.1 (1.3)		57.7%	-0.43[-0.61,-0.25]
Subtotal ***	**546**		**545**			**100%**	**-0.51[-0.65,-0.38]**
Heterogeneity: Tau²=0; Chi²=1.91, df=1(P=0.17); I²=47.71%							
Test for overall effect: Z=7.47(P<0.0001)							
Total ***	**546**		**545**			**100%**	**-0.51[-0.65,-0.38]**
Heterogeneity: Tau²=0; Chi²=1.91, df=1(P=0.17); I²=47.71%							
Test for overall effect: Z=7.47(P<0.0001)							
Test for subgroup differences: Not applicable							

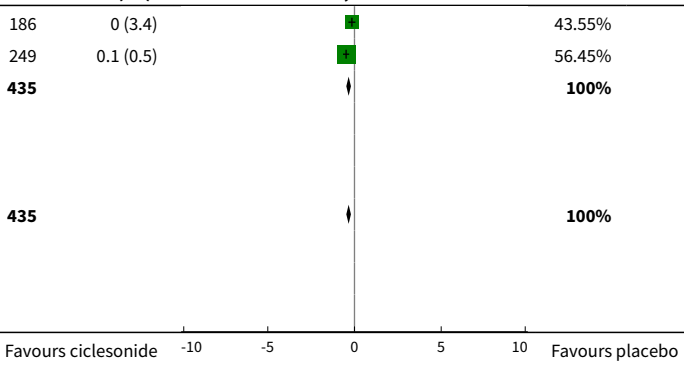
Favours ciclesonide -10 -5 0 5 10 Favours placebo

Analysis 2.10. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 10 Change in nighttime awakenings (SMD).

Study or subgroup	Ciclesonide N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.10.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.10.2 Adults							

Favours ciclesonide -10 -5 0 5 10 Favours placebo

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
DFI6153	189	-0.5 (3.4)	186	0 (3.4)		43.55%	-0.15[-0.35,0.05]
Pearlman 2005	250	-0.2 (0.5)	249	0.1 (0.5)		56.45%	-0.48[-0.66,-0.31]
Subtotal * **	**439**		**435**			**100%**	**-0.34[-0.47,-0.2]**
Heterogeneity: Tau²=0; Chi²=5.89, df=1(P=0.02); I²=83.03%							
Test for overall effect: Z=4.95(P<0.0001)							
Total * **	**439**		**435**			**100%**	**-0.34[-0.47,-0.2]**
Heterogeneity: Tau²=0; Chi²=5.89, df=1(P=0.02); I²=83.03%							
Test for overall effect: Z=4.95(P<0.0001)							
Test for subgroup differences: Not applicable							

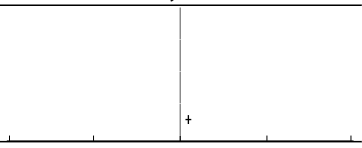


Analysis 2.11. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 11 Change in quality of life score (paediatric AQLQ).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Gelfand 2006a	253	0.6 (0)	254	0.3 (0)		Not estimable

Analysis 2.12. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 12 Change from baseline in quality of life score (AQLQ).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.12.1 Children						
2.12.2 Adults						
Pearlman 2005	250	0.6 (1)	249	0.1 (1)		0.47[0.3,0.64]

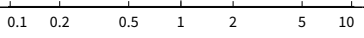


Analysis 2.13. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 13 Loss of efficacy.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	32/107	70/110		0.47[0.34,0.65]

Analysis 2.14. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 14 Withdrawals.

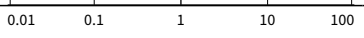
Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.14.1 Children					
Gelfand 2006a	31/253	51/257		38.69%	0.62[0.41,0.93]
Subtotal (95% CI)	**253**	**257**		**38.69%**	**0.62[0.41,0.93]**
Total events: 31 (Ciclesonide), 51 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.3(P=0.02)					
2.14.2 Adults					
Adachi 2007a	4/71	17/79		12.3%	0.26[0.09,0.74]
Chapman 2005	36/107	65/110		49.01%	0.57[0.42,0.77]
Subtotal (95% CI)	**178**	**189**		**61.31%**	**0.51[0.38,0.69]**
Total events: 40 (Ciclesonide), 82 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.09, df=1(P=0.15); I^2=52.08%					
Test for overall effect: Z=4.42(P<0.0001)					
Total (95% CI)	**431**	**446**		**100%**	**0.55[0.43,0.7]**
Total events: 71 (Ciclesonide), 133 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.31, df=2(P=0.32); I^2=13.24%					
Test for overall effect: Z=4.79(P<0.0001)					
Test for subgroup differences: Not applicable					



Favours ciclesonide — Favours placebo

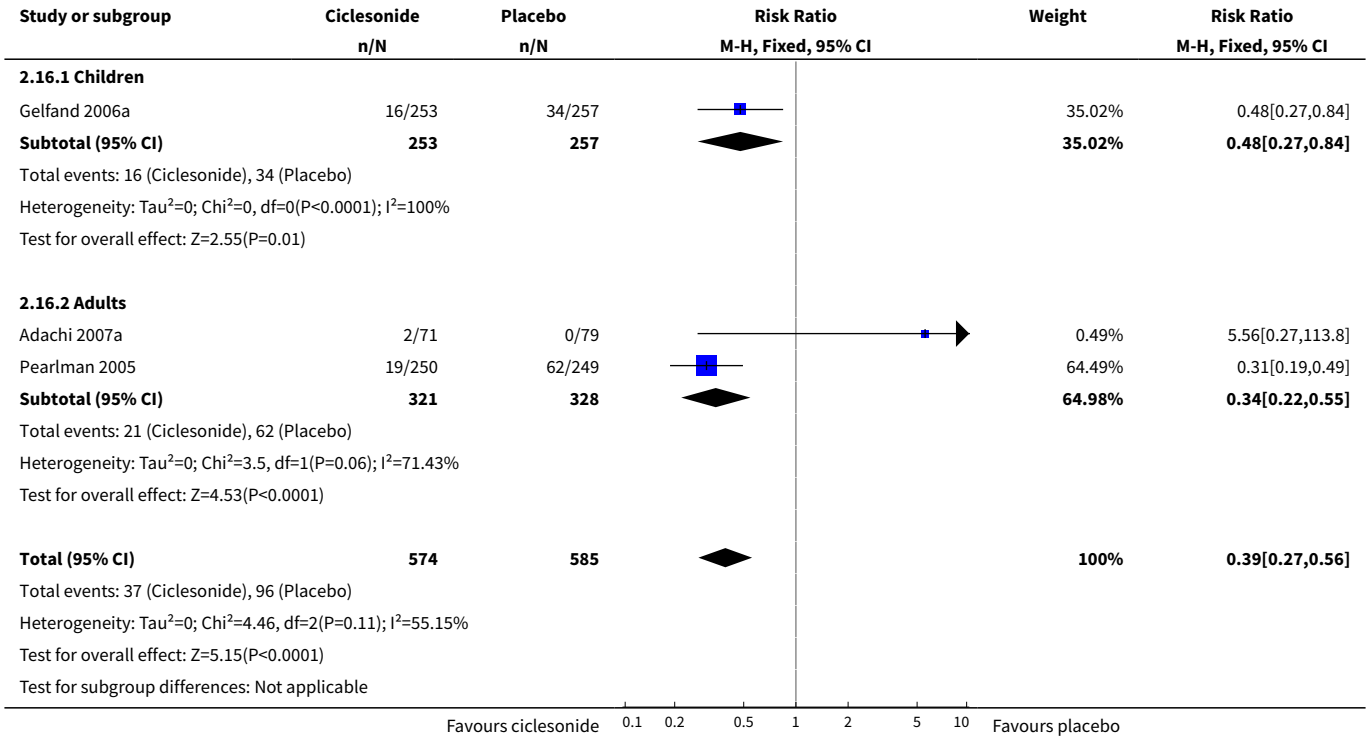
Analysis 2.15. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 15 Withdrawals (lack of efficacy).

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.15.1 Children					
Gelfand 2006a	14/253	32/257		29.12%	0.44[0.24,0.81]
Subtotal (95% CI)	**253**	**257**		**29.12%**	**0.44[0.24,0.81]**
Total events: 14 (Ciclesonide), 32 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.63(P=0.01)					
2.15.2 Adults					
Adachi 2007a	1/71	16/79		13.89%	0.07[0.01,0.51]
Pearlman 2005	19/250	62/249		56.98%	0.31[0.19,0.49]
Subtotal (95% CI)	**321**	**328**		**70.88%**	**0.26[0.16,0.41]**
Total events: 20 (Ciclesonide), 78 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.11, df=1(P=0.15); I^2=52.67%					
Test for overall effect: Z=5.66(P<0.0001)					
Total (95% CI)	**574**	**585**		**100%**	**0.31[0.22,0.45]**
Total events: 34 (Ciclesonide), 110 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.49, df=2(P=0.17); I^2=42.71%					
Test for overall effect: Z=6.2(P<0.0001)					
Test for subgroup differences: Not applicable					

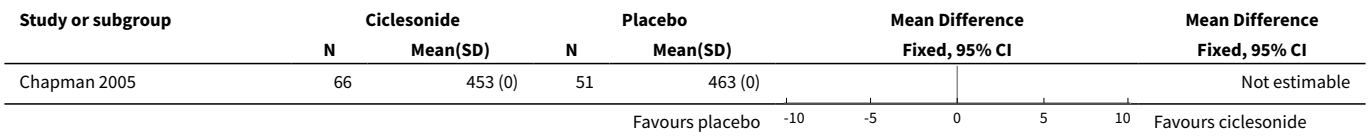


Favours ciclesonide — Favours placebo

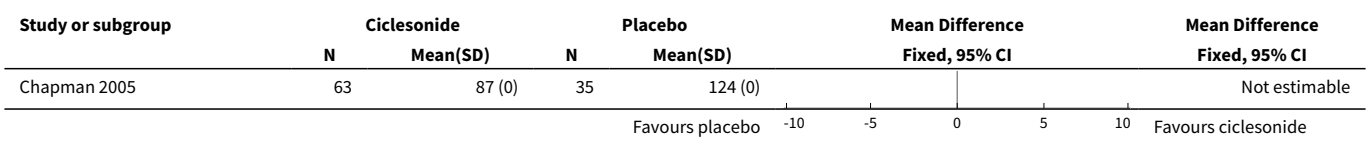
Analysis 2.16. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 16 Withdrawals (adverse events).



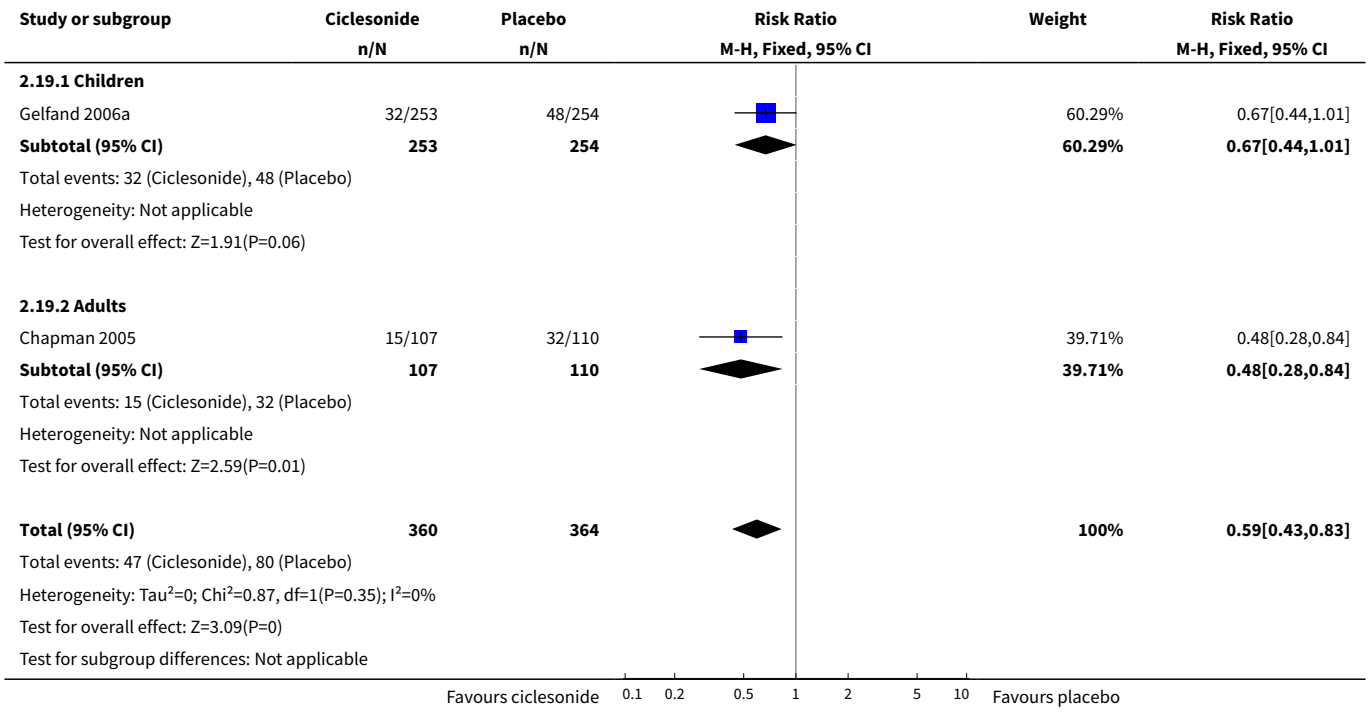
Analysis 2.17. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 17 Changes in cortisol levels (serum).



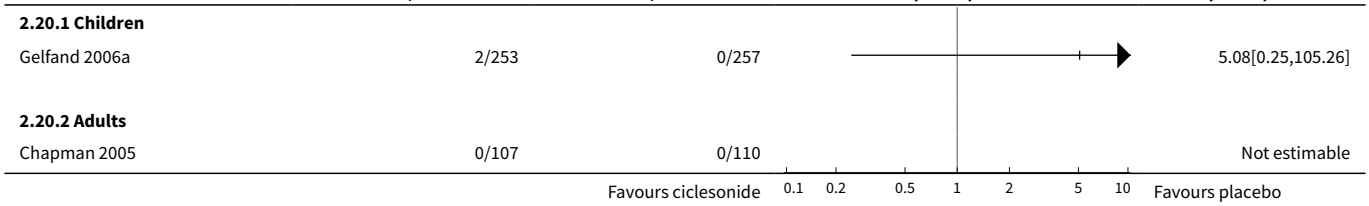
Analysis 2.18. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 18 Changes in cortisol levels (urinary).



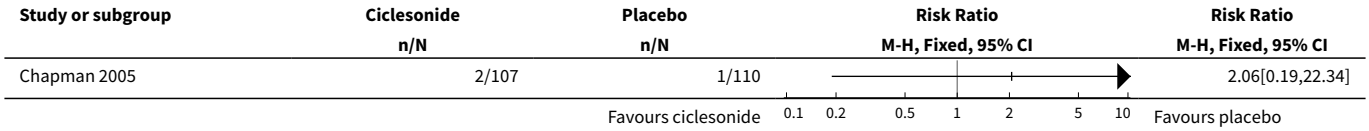
Analysis 2.19. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 19 Asthma (not otherwise specified).



Analysis 2.20. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 20 Candidiasis.

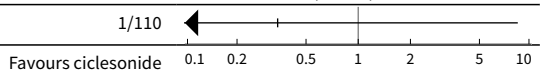


Analysis 2.21. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 21 Sore throat.



Analysis 2.22. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 22 Voice alteration.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	0/107	1/110		0.34[0.01,8.32]

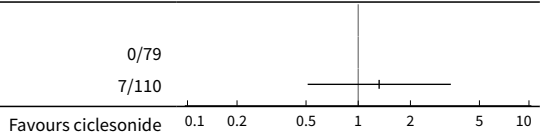


Analysis 2.23. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 23 Headache.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.23.1 Children					
Gelfand 2006a	29/253	26/257		54.5%	1.13[0.69,1.87]
Subtotal (95% CI)	**253**	**257**		**54.5%**	**1.13[0.69,1.87]**
Total events: 29 (Ciclesonide), 26 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.49(P=0.62)					
2.23.2 Adults					
Adachi 2007a	2/71	4/79		8%	0.56[0.11,2.95]
Chapman 2005	14/107	18/110		37.5%	0.8[0.42,1.53]
Subtotal (95% CI)	**178**	**189**		**45.5%**	**0.76[0.41,1.38]**
Total events: 16 (Ciclesonide), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.16, df=1(P=0.69); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					
Total (95% CI)	**431**	**446**		**100%**	**0.96[0.66,1.41]**
Total events: 45 (Ciclesonide), 48 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=2(P=0.57); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					
Test for subgroup differences: Not applicable					

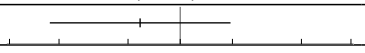
Analysis 2.24. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 24 Upper respiratory tract infection.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
2.24.2 Adults				
Adachi 2007a	0/71	0/79		Not estimable
Chapman 2005	9/107	7/110		1.32[0.51,3.42]



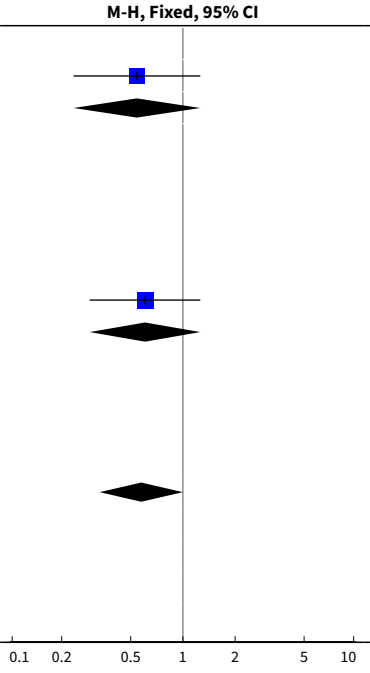
Analysis 2.25. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 25 Symptoms of asthma (wheeze, dsypnea or cough).

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	4/107	7/110		0.59[0.18,1.95]



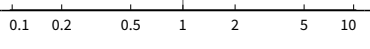
Analysis 2.26. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 26 Rhinitis.

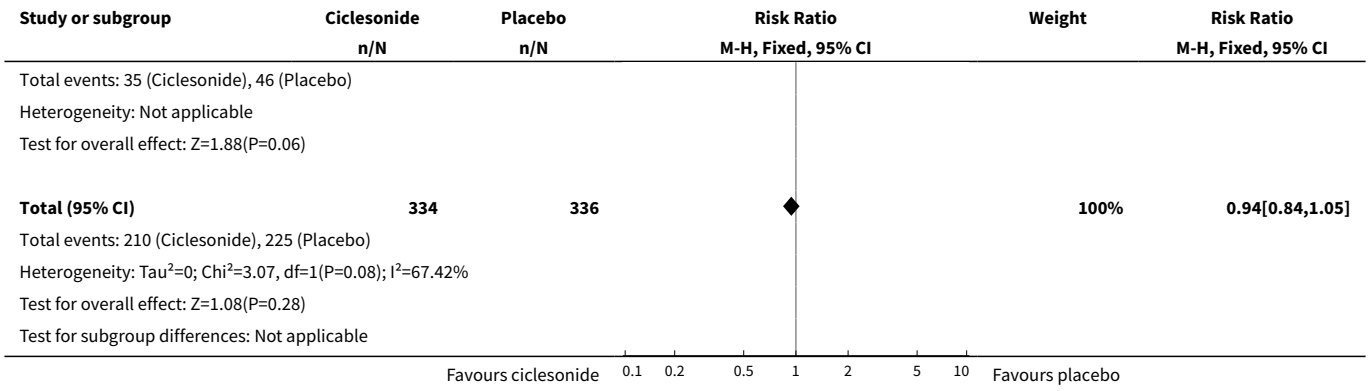
Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.26.1 Children					
Gelfand 2006a	8/253	15/257		47.03%	0.54[0.23,1.26]
Subtotal (95% CI)	**253**	**257**		**47.03%**	**0.54[0.23,1.26]**
Total events: 8 (Ciclesonide), 15 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.43(P=0.15)					
2.26.2 Adults					
Chapman 2005	10/107	17/110		52.97%	0.6[0.29,1.26]
Subtotal (95% CI)	**107**	**110**		**52.97%**	**0.6[0.29,1.26]**
Total events: 10 (Ciclesonide), 17 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.34(P=0.18)					
Total (95% CI)	**360**	**367**		**100%**	**0.58[0.33,1]**
Total events: 18 (Ciclesonide), 32 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=0.04$, df=1(P=0.85); $I^2=0\%$					
Test for overall effect: Z=1.96(P=0.05)					
Test for subgroup differences: Not applicable					



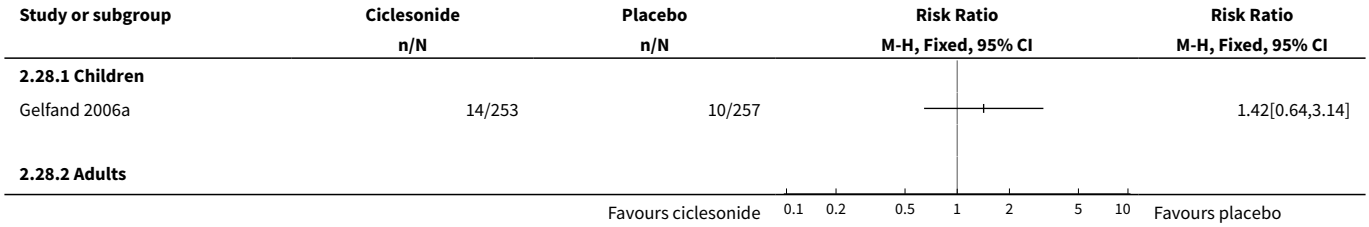
Analysis 2.27. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 27 Adverse event.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.27.1 Children					
Gelfand 2006a	175/253	179/257		79.22%	0.99[0.89,1.11]
Subtotal (95% CI)	**253**	**257**		**79.22%**	**0.99[0.89,1.11]**
Total events: 175 (Ciclesonide), 179 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.12(P=0.91)					
2.27.2 Adults					
Adachi 2007a	35/81	46/79		20.78%	0.74[0.54,1.01]
Subtotal (95% CI)	**81**	**79**		**20.78%**	**0.74[0.54,1.01]**

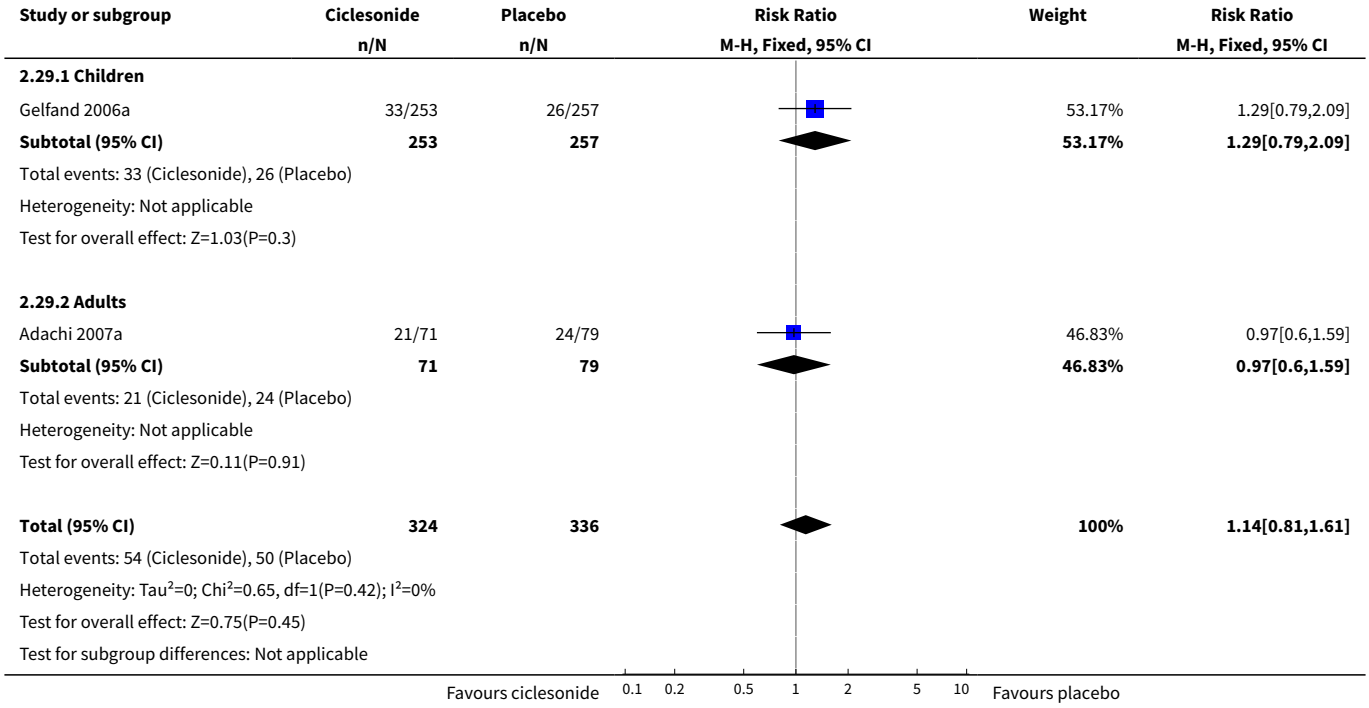




Analysis 2.28. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 28 Pharyngitis.



Analysis 2.29. Comparison 2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies), Outcome 29 Nasopharyngitis.



Comparison 3. Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies)

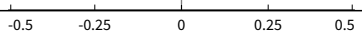
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change in FEV1	6	1717	Litres (Fixed, 95% CI)	0.17 [0.14, 0.21]
1.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	6	1717	Litres (Fixed, 95% CI)	0.17 [0.14, 0.21]
2 Change from base-line in FEV1% predict-ed	2	666	Mean Difference (IV, Fixed, 95% CI)	3.10 [1.66, 4.53]
2.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	2	666	Mean Difference (IV, Fixed, 95% CI)	3.10 [1.66, 4.53]
3 Change in FVC	2	402	Litres (Fixed, 95% CI)	0.12 [0.03, 0.20]
3.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	2	402	Litres (Fixed, 95% CI)	0.12 [0.03, 0.20]
4 Change in am PEF	6	1722	L/min (Fixed, 95% CI)	18.19 [14.31, 22.07]
4.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	6	1722	L/min (Fixed, 95% CI)	18.19 [14.31, 22.07]
5 Change in pm PEF	3	906	L/min (Fixed, 95% CI)	15.30 [10.04, 20.55]
5.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	3	906	L/min (Fixed, 95% CI)	15.30 [10.04, 20.55]
6 Change in asthma symptom scores	5	1560	Std. Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.59, -0.38]
6.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	5	1560	Std. Mean Difference (IV, Fixed, 95% CI)	-0.48 [-0.59, -0.38]
7 Change in rescue 2-agonists use	6	1722	Puffs/d (Fixed, 95% CI)	-0.78 [-0.94, -0.62]
7.1 Children	0	0	Puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	6	1722	Puffs/d (Fixed, 95% CI)	-0.78 [-0.94, -0.62]
8 Change in nighttime awakenings (SMD)	2	874	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.47, -0.20]
8.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8.2 Adults	2	874	Std. Mean Difference (IV, Fixed, 95% CI)	-0.34 [-0.47, -0.20]
9 Change from base-line in quality of life score (AQLQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
9.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Withdrawals	2	402	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.29, 0.56]
10.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	2	402	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.29, 0.56]
11 Withdrawals (lack of efficacy)	3	906	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.23, 0.44]
11.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	3	906	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.23, 0.44]
12 Adverse events	4	858	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.13]
12.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	4	858	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.13]
13 Upper respiratory tract infection	2		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	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Headache	2	402	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.65, 3.68]
14.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	2	402	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.65, 3.68]
15 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Nasopharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17 Change in high dose peak serum cortisol levels	2	157	mcg/dL (Fixed, 95% CI)	-0.75 [-2.24, 0.75]
17.1 Children	0	0	mcg/dL (Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Adults	2	157	mcg/dL (Fixed, 95% CI)	-0.75 [-2.24, 0.75]

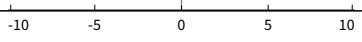
Analysis 3.1. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

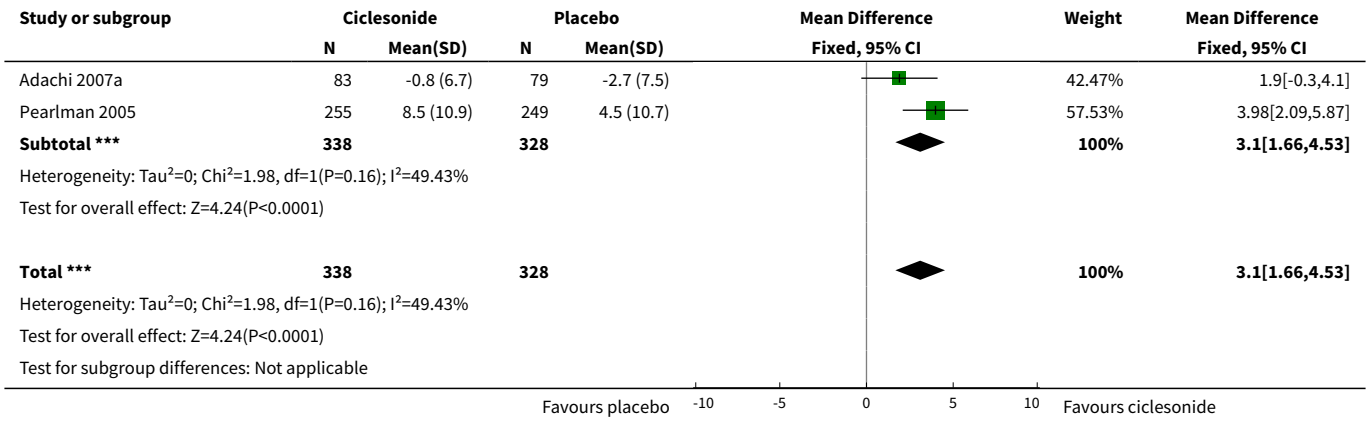
Study or subgroup	Ciclesonide N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
3.1.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.1.2 Adults						
Adachi 2007a	83	79	0.1 (0.046)		17.96%	0.12[0.03,0.21]
DFI6153	184	186	0.3 (0.046)		17.96%	0.25[0.16,0.34]
EFC6163a	150	74	0.1 (0.051)		14.55%	0.14[0.04,0.24]
EFC6163b	149	73	0.2 (0.051)		14.55%	0.19[0.09,0.29]
Langdon 2005	115	125	0.2 (0.056)		12.24%	0.22[0.11,0.33]
Pearlman 2005	250	249	0.1 (0.041)		22.73%	0.14[0.06,0.22]
Subtotal (95% CI)					**100%**	**0.17[0.14,0.21]**
Heterogeneity: Tau²=0; Chi²=6.05, df=5(P=0.3); I²=17.3%						
Test for overall effect: Z=8.91(P<0.0001)						
Total (95% CI)					**100%**	**0.17[0.14,0.21]**
Heterogeneity: Tau²=0; Chi²=6.05, df=5(P=0.3); I²=17.3%						
Test for overall effect: Z=8.91(P<0.0001)						
Test for subgroup differences: Not applicable						



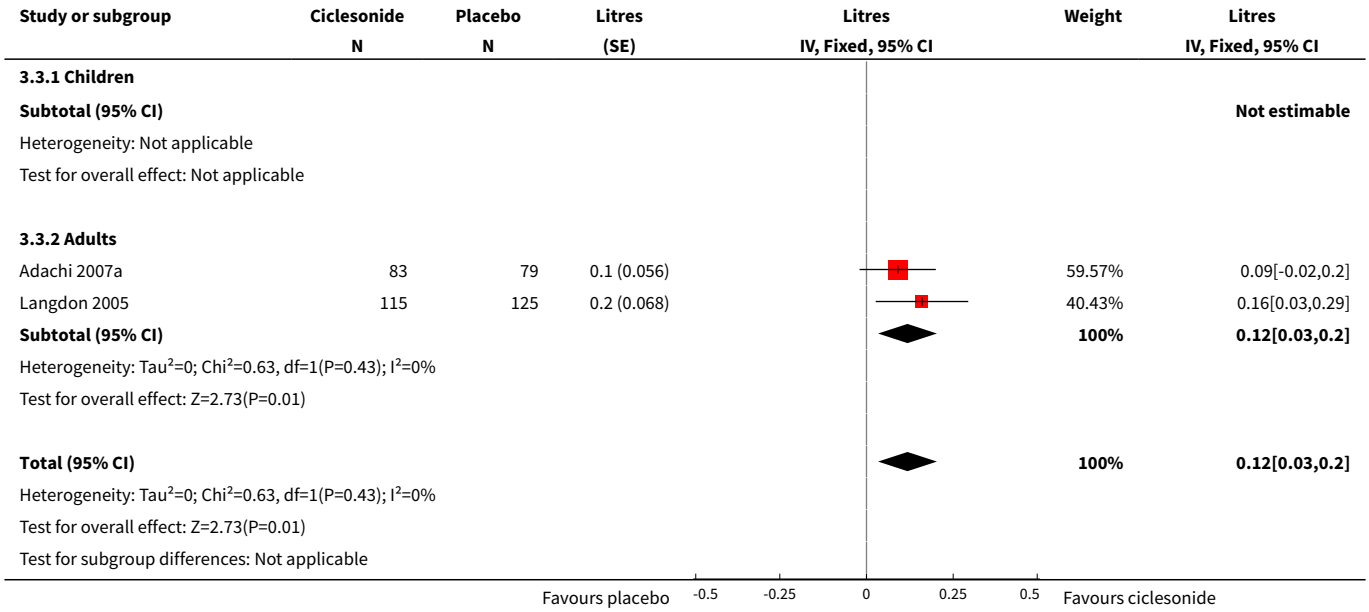
Analysis 3.2. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 2 Change from baseline in FEV1% predicted.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.2.1 Children							
Subtotal * **	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.2.2 Adults							

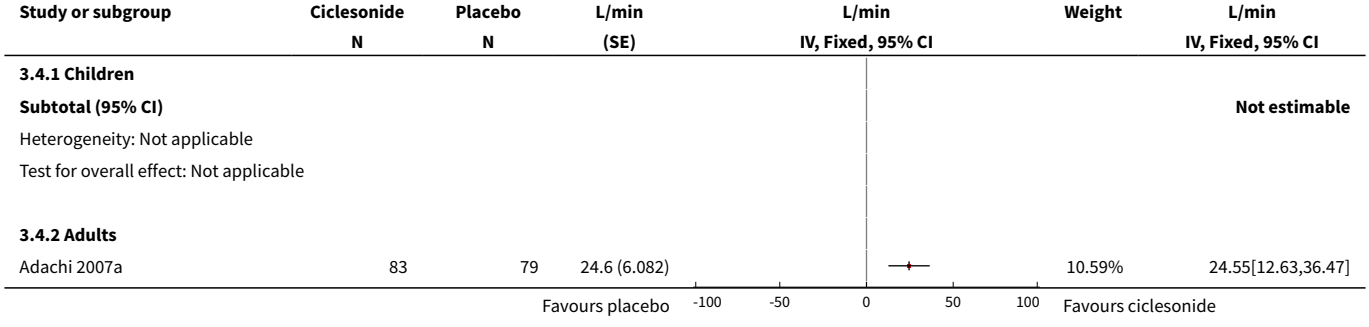


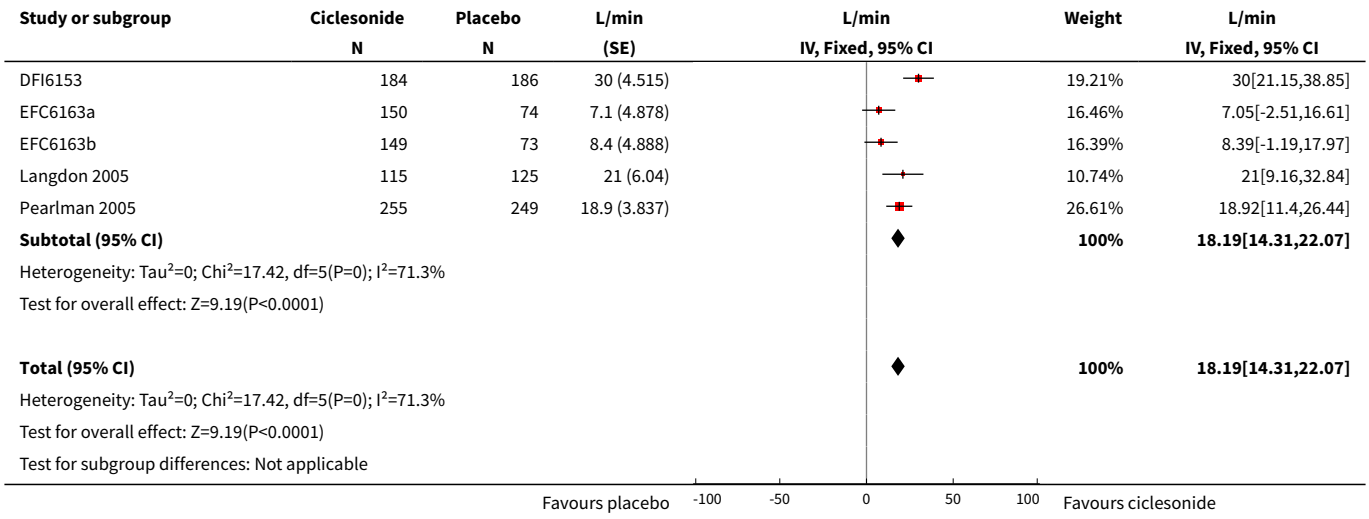


Analysis 3.3. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 3 Change in FVC.

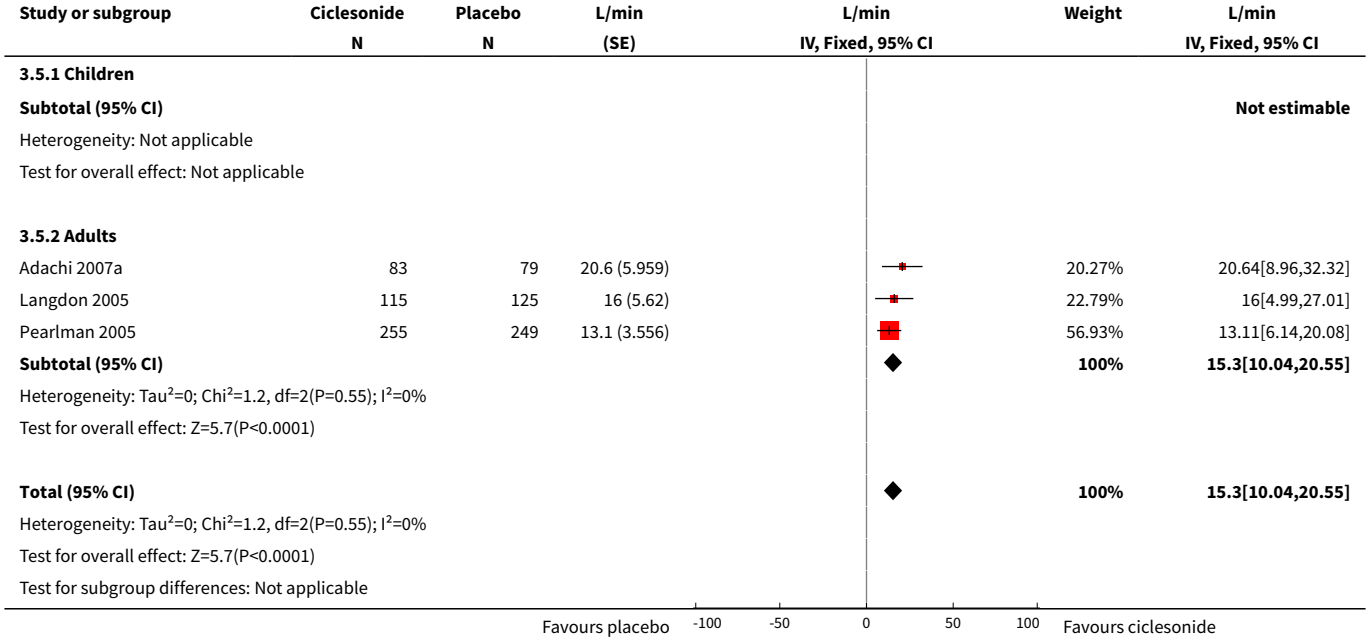


Analysis 3.4. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 4 Change in am PEF.

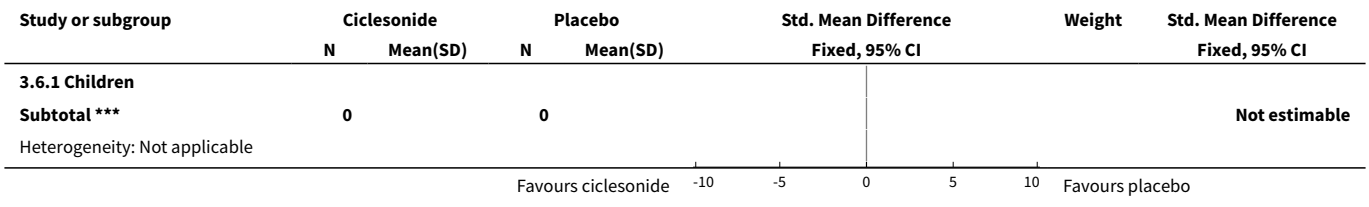




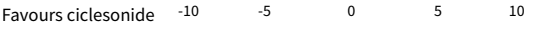
Analysis 3.5. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 5 Change in pm PEF.



Analysis 3.6. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 6 Change in asthma symptom scores.

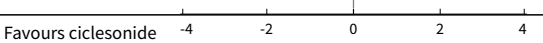


Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Test for overall effect: Not applicable							
3.6.2 Adults							
DFI6153	184	-0.8 (1)	186	0 (1)		23.64%	-0.75[-0.96,-0.54]
EFC6163a	150	-0.4 (1)	74	0 (1)		13.35%	-0.38[-0.66,-0.1]
EFC6163b	149	-0.4 (1)	73	0 (1)		13.21%	-0.37[-0.65,-0.09]
Langdon 2005	115	-1 (1.9)	125	0 (1.9)		15.86%	-0.52[-0.77,-0.26]
Pearlman 2005	255	-0.6 (1.3)	249	-0.1 (1.3)		33.93%	-0.36[-0.54,-0.19]
Subtotal ***	**853**		**707**			**100%**	**-0.48[-0.59,-0.38]**
Heterogeneity: Tau^2=0; Chi^2=9.08, df=4(P=0.06); I^2=55.97%							
Test for overall effect: Z=9.24(P<0.0001)							
Total ***	**853**		**707**			**100%**	**-0.48[-0.59,-0.38]**
Heterogeneity: Tau^2=0; Chi^2=9.08, df=4(P=0.06); I^2=55.97%							
Test for overall effect: Z=9.24(P<0.0001)							
Test for subgroup differences: Not applicable							



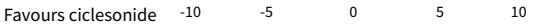
Analysis 3.7. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 7 Change in rescue 2-agonists use.

Study or subgroup	Ciclesonide N	Placebo N	Puffs/d (SE)	Puffs/d IV, Fixed, 95% CI	Weight	Puffs/d IV, Fixed, 95% CI
3.7.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.7.2 Adults						
Adachi 2007a	83	79	-0.6 (0.2)		16.38%	-0.65[-1.04,-0.26]
DFI6153	184	186	-1.3 (0.171)		22.41%	-1.3[-1.63,-0.97]
EFC6163a	150	74	-0.6 (0.194)		17.41%	-0.6[-0.98,-0.22]
EFC6163b	149	73	-0.6 (0.194)		17.41%	-0.64[-1.02,-0.26]
Langdon 2005	115	125	-0.5 (0.17)		22.65%	-0.5[-0.83,-0.17]
Pearlman 2005	255	249	-1.5 (0.418)		3.75%	-1.46[-2.28,-0.64]
Subtotal (95% CI)					**100%**	**-0.78[-0.94,-0.62]**
Heterogeneity: Tau^2=0; Chi^2=16.42, df=5(P=0.01); I^2=69.55%						
Test for overall effect: Z=9.66(P<0.0001)						
Total (95% CI)					**100%**	**-0.78[-0.94,-0.62]**
Heterogeneity: Tau^2=0; Chi^2=16.42, df=5(P=0.01); I^2=69.55%						
Test for overall effect: Z=9.66(P<0.0001)						
Test for subgroup differences: Not applicable						



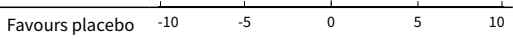
Analysis 3.8. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 8 Change in nighttime awakenings (SMD).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
3.8.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
3.8.2 Adults							
DFI6153	184	-0.7 (3.3)	186	0 (3.3)		42.74%	-0.22[-0.42,-0.01]
Pearlman 2005	255	-0.1 (0.5)	249	0.1 (0.5)		57.26%	-0.42[-0.6,-0.25]
Subtotal ***	**439**		**435**			**100%**	**-0.34[-0.47,-0.2]**
Heterogeneity: Tau^2=0; Chi^2=2.32, df=1(P=0.13); I^2=56.84%							
Test for overall effect: Z=4.92(P<0.0001)							
Total ***	**439**		**435**			**100%**	**-0.34[-0.47,-0.2]**
Heterogeneity: Tau^2=0; Chi^2=2.32, df=1(P=0.13); I^2=56.84%							
Test for overall effect: Z=4.92(P<0.0001)							
Test for subgroup differences: Not applicable							



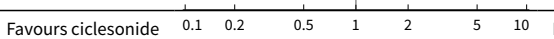
Analysis 3.9. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 9 Change from baseline in quality of life score (AQLQ).

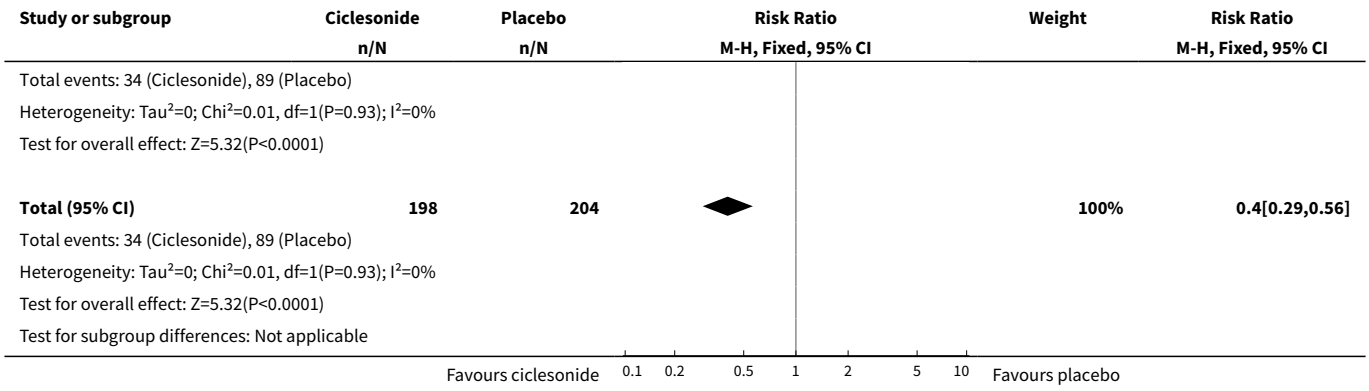
Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.9.1 Children						
3.9.2 Adults						
Pearlman 2005	255	0.7 (1)	249	0.1 (1)		0.55[0.38,0.72]



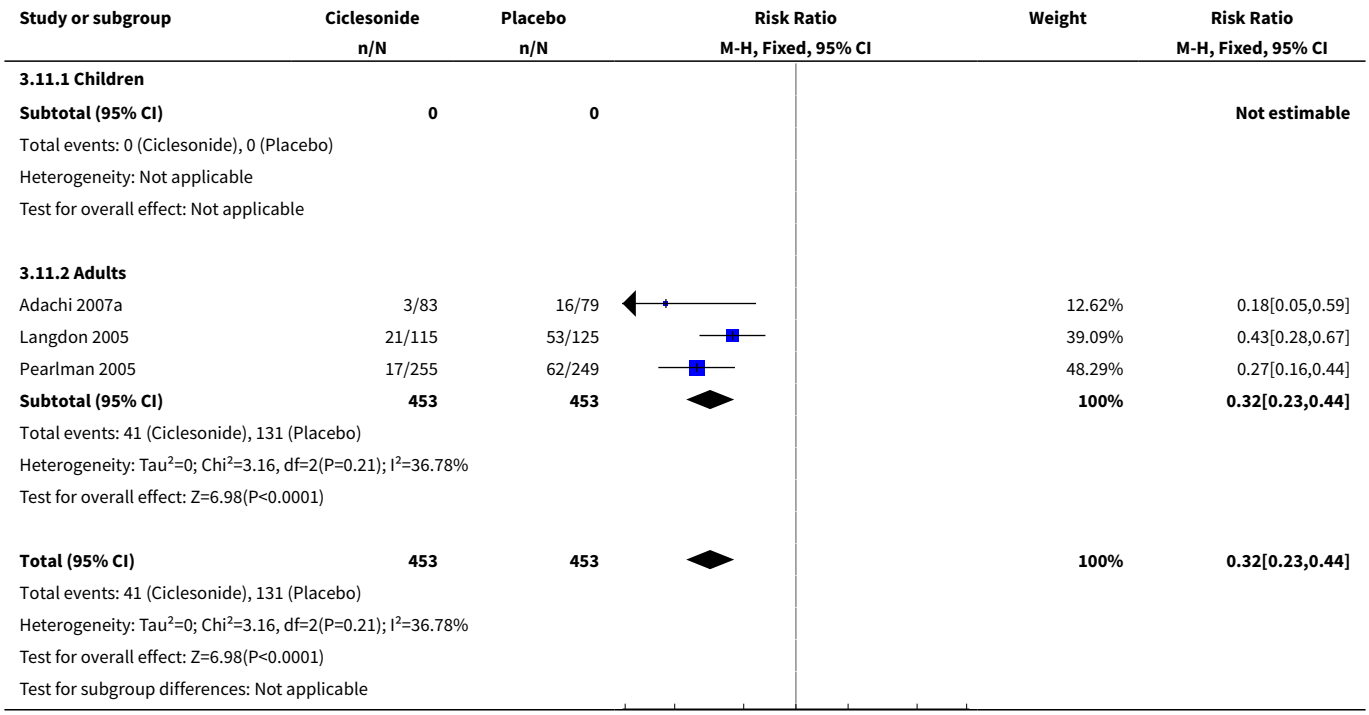
Analysis 3.10. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 10 Withdrawals.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.10.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ciclesonide), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.10.2 Adults					
Adachi 2007a	7/83	17/79		20.16%	0.39[0.17,0.89]
Langdon 2005	27/115	72/125		79.84%	0.41[0.28,0.59]
Subtotal (95% CI)	**198**	**204**		**100%**	**0.4[0.29,0.56]**

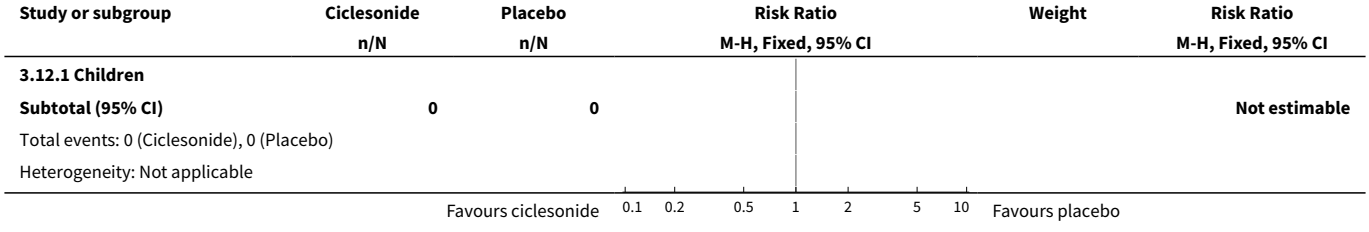


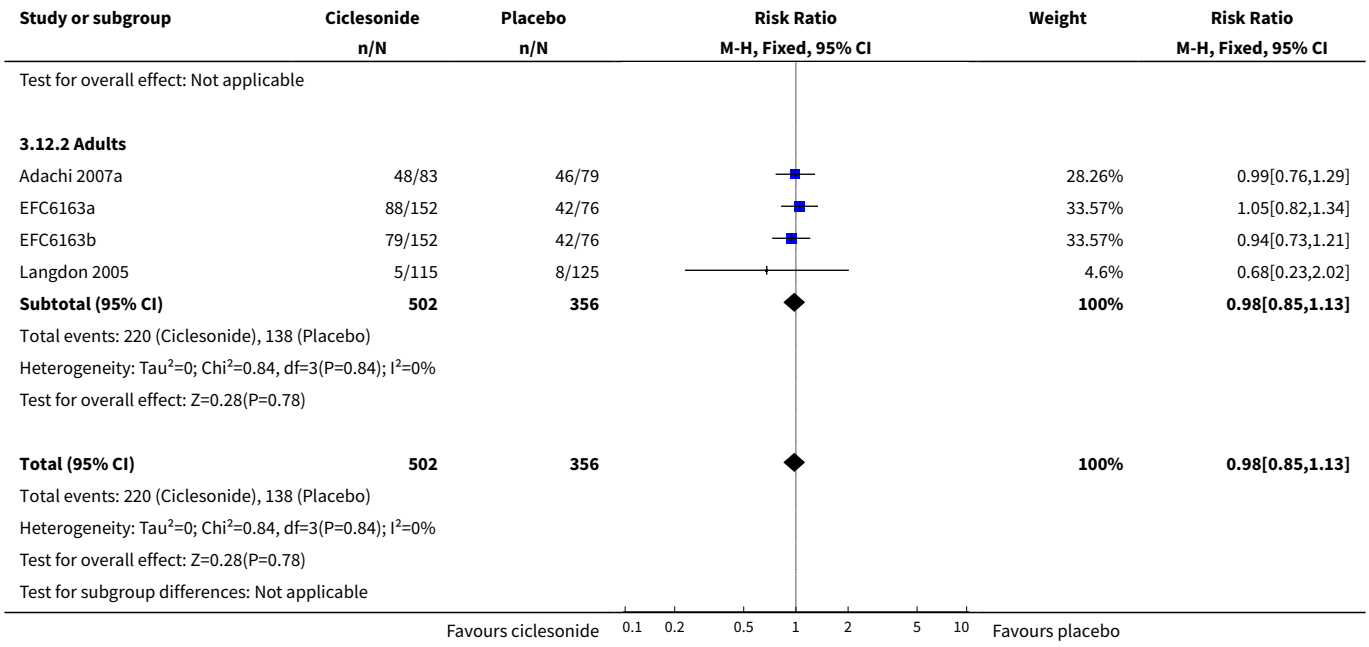


Analysis 3.11. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 11 Withdrawals (lack of efficacy).

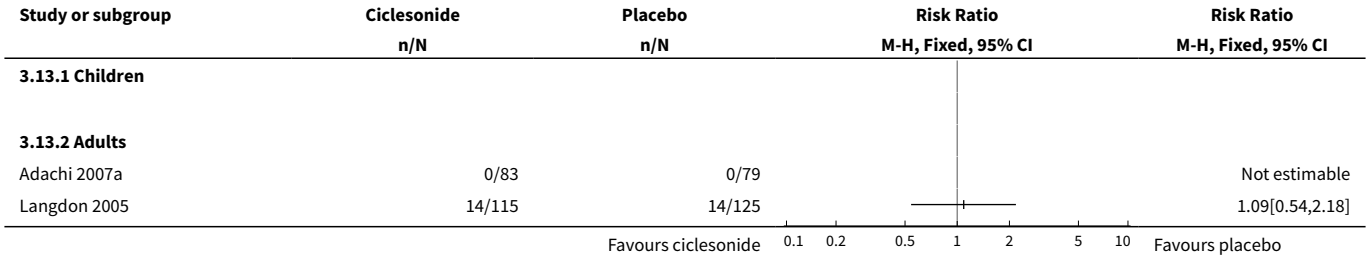


Analysis 3.12. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 12 Adverse events.

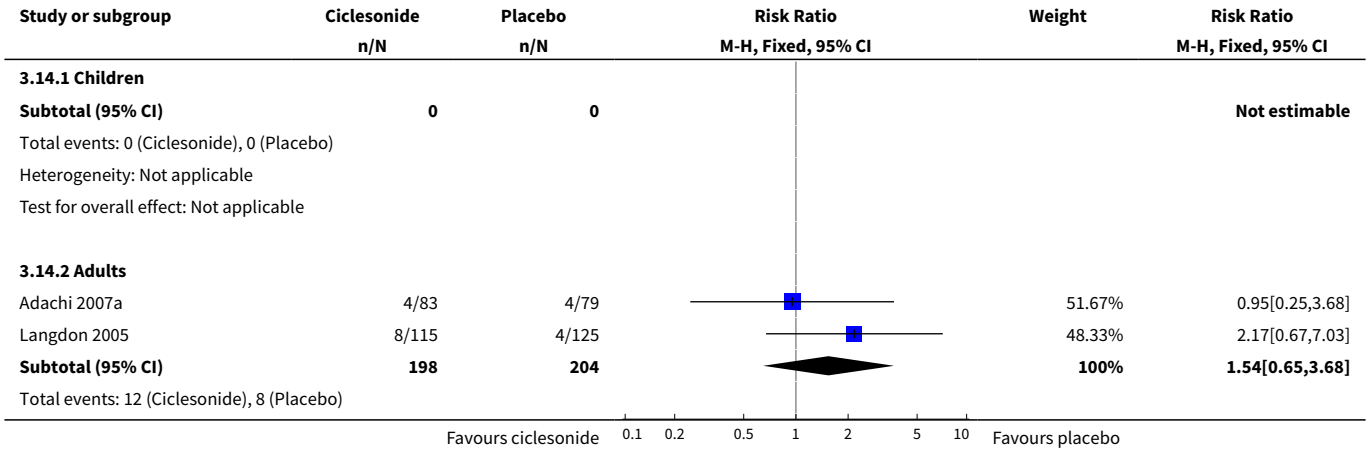


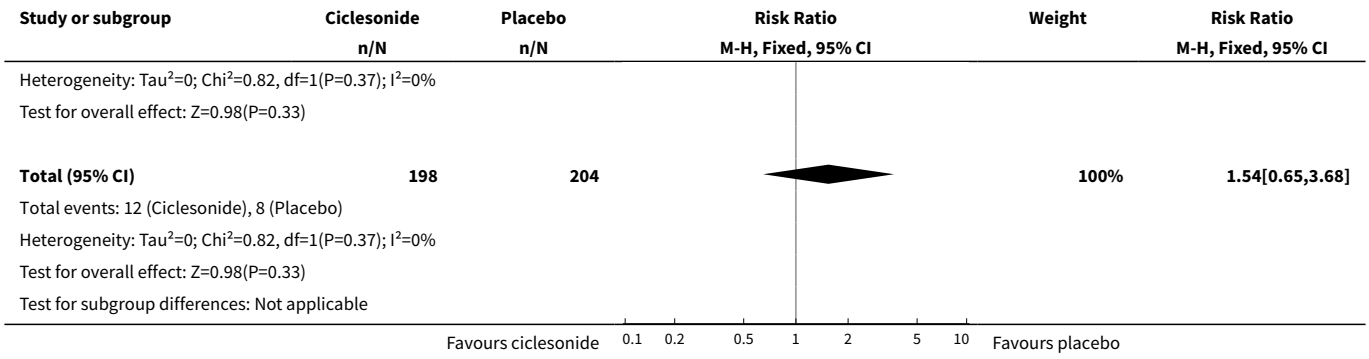


Analysis 3.13. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 13 Upper respiratory tract infection.

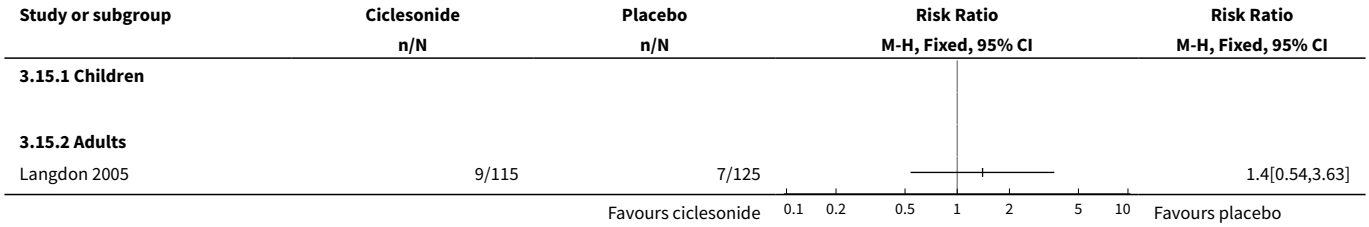


Analysis 3.14. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 14 Headache.

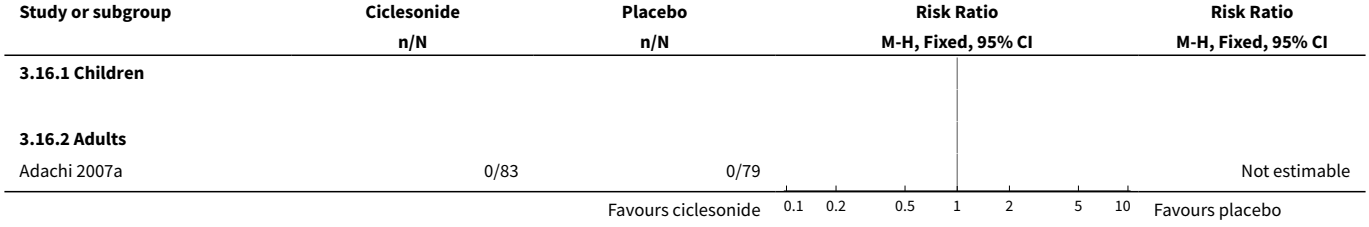




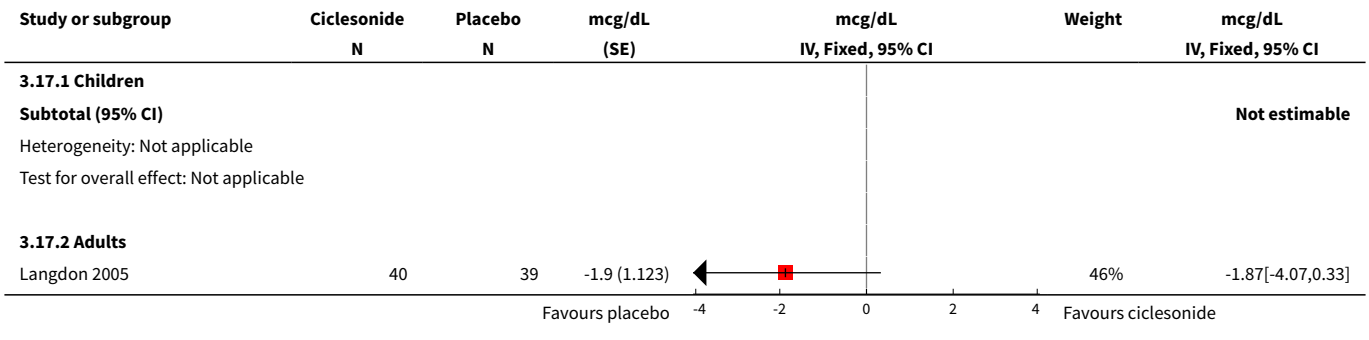
Analysis 3.15. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 15 Rhinitis.

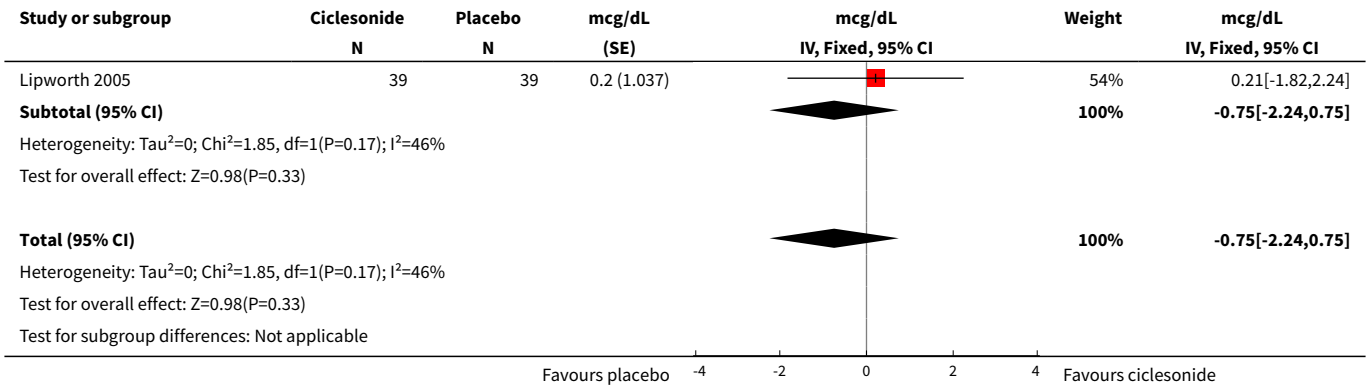


Analysis 3.16. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 16 Nasopharyngitis.



Analysis 3.17. Comparison 3 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies), Outcome 17 Change in high dose peak serum cortisol levels.





Comparison 4. Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies)

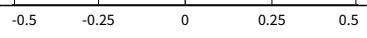
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
1.1 Children	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FEV1 at endpoint	1		L (Fixed, 95% CI)	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 Change in FEV1 predicted	0		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	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in FVC	0		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	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in am PEF	2	594	L/min (Fixed, 95% CI)	28.09 [21.24, 34.94]
5.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	2	594	L/min (Fixed, 95% CI)	28.09 [21.24, 34.94]
6 Change in pm PEF (L/min)	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 Change in clinic PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Change in asthma symptom scores	2	594	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-1.08, -0.66]
8.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	2	594	Mean Difference (IV, Fixed, 95% CI)	-0.87 [-1.08, -0.66]
9 Change in rescue beta2-agonists use	2	594	Puffs/d (Fixed, 95% CI)	-1.19 [-1.52, -0.86]
9.1 Children	0	0	Puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	2	594	Puffs/d (Fixed, 95% CI)	-1.19 [-1.52, -0.86]
10 Change in high dose peak serum cortisol levels	1		mcg/dL (Fixed, 95% CI)	Totals not selected
10.1 Children	0		mcg/dL (Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	1		mcg/dL (Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Changes in cortisol levels (urinary)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Worsening asthma	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Loss of efficacy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Withdrawals	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15 Candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
16 Sore throat	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
17 Voice alteration	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
18 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
19 Upper respiratory tract infection	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
20 Symptoms of asthma (wheeze, dsypnea or cough)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
21 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
22 Adverse events	0		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

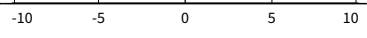
Analysis 4.1. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Ciclesonide N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
4.1.1 Children					
4.1.2 Adults					
DFI6153	186	186	0.3 (0.046)		0.25[0.16,0.34]



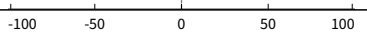
Analysis 4.2. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 2 FEV1 at endpoint.

Study or subgroup	Ciclesonide N	Placebo N	L (SE)	L IV, Fixed, 95% CI	L IV, Fixed, 95% CI
4.2.1 Children					
4.2.2 Adults					
Chapman 2005	112	110	0.1 (0.058)		0.15[0.04,0.26]



Analysis 4.5. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 5 Change in am PEF.

Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
4.5.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.2 Adults						
Chapman 2005	112	110	27 (5.571)		39.37%	27[16.08,37.92]
DFI6153	186	186	28.8 (4.49)		60.63%	28.8[20,37.6]
Subtotal (95% CI)					**100%**	**28.09[21.24,34.94]**
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.8); I^2=0%						
Test for overall effect: Z=8.04(P<0.0001)						



Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
Total (95% CI)				◆	**100%**	**28.09[21.24,34.94]**
Heterogeneity: Tau²=0; Chi²=0.06, df=1(P=0.8); I²=0%						
Test for overall effect: Z=8.04(P<0.0001)						
Test for subgroup differences: Not applicable						

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 4.6. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 6 Change in pm PEF (L/min).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
4.6.1 Children						
4.6.2 Adults						
Chapman 2005	112	-0.7 (0)	110	-17 (0)		Not estimable

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 4.7. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 7 Change in clinic PEF (L/min).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Chapman 2005	112	5.2 (0)	110	-21.6 (0)		Not estimable

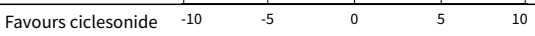
Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 4.8. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 8 Change in asthma symptom scores.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.8.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
4.8.2 Adults							
Chapman 2005	112	0 (0)	110	0.4 (0)			Not estimable
DFI6153	186	-0.9 (1)	186	0 (1)	+	100%	-0.87[-1.08,-0.66]
Subtotal ***	**298**		**296**		◆	**100%**	**-0.87[-1.08,-0.66]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=8.31(P<0.0001)							
Total ***	**298**		**296**		◆	**100%**	**-0.87[-1.08,-0.66]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							

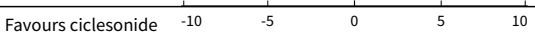
Favours ciclesonide -10 -5 0 5 10 Favours placebo

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for overall effect: Z=8.31(P<0.0001)							
Test for subgroup differences: Not applicable							



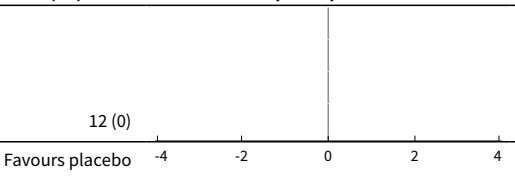
Analysis 4.9. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 9 Change in rescue beta2-agonists use.

Study or subgroup	Ciclesonide N	Placebo N	Puffs/d (SE)	Puffs/d IV, Fixed, 95% CI	Weight	Puffs/d IV, Fixed, 95% CI
4.9.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.9.2 Adults						
Chapman 2005	112	110	0 (0)			Not estimable
DFI6153	186	186	-1.2 (0.168)		100%	-1.19[-1.52,-0.86]
Subtotal (95% CI)					**100%**	**-1.19[-1.52,-0.86]**
Heterogeneity: Not applicable						
Test for overall effect: Z=7.07(P<0.0001)						
Total (95% CI)					**100%**	**-1.19[-1.52,-0.86]**
Heterogeneity: Not applicable						
Test for overall effect: Z=7.07(P<0.0001)						
Test for subgroup differences: Not applicable						



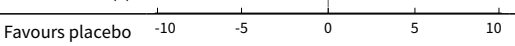
Analysis 4.10. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 10 Change in high dose peak serum cortisol levels.

Study or subgroup	Ciclesonide N	Placebo N	mcg/dL (SE)	mcg/dL IV, Fixed, 95% CI	mcg/dL IV, Fixed, 95% CI
4.10.1 Children					
4.10.2 Adults					
Chapman 2005	61	51	12 (0)		Not estimable



Analysis 4.11. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 11 Changes in cortisol levels (urinary).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Chapman 2005	58	106 (0)	35	124 (0)		Not estimable



Analysis 4.12. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 12 Worsening asthma.

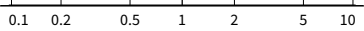
Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	15/112	32/110		0.46[0.26,0.8]

Analysis 4.13. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 13 Loss of efficacy.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	35/112	70/110		0.49[0.36,0.67]

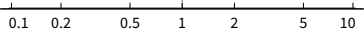
Analysis 4.14. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 14 Withdrawals.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	43/112	65/110		0.65[0.49,0.86]



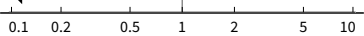
Analysis 4.15. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 15 Candidiasis.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	0/112	0/110		Not estimable



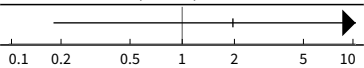
Analysis 4.16. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 16 Sore throat.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	0/112	1/110		0.33[0.01,7.95]



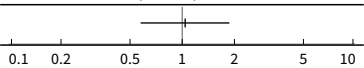
Analysis 4.17. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 17 Voice alteration.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	2/112	1/110		1.96[0.18,21.35]



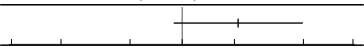
Analysis 4.18. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 18 Headache.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	19/112	18/110		1.04[0.58,1.87]



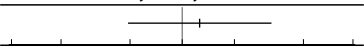
Analysis 4.19. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 19 Upper respiratory tract infection.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	15/112	7/110		2.1[0.89,4.96]



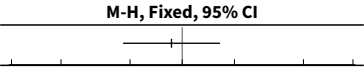
Analysis 4.20. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 20 Symptoms of asthma (wheeze, dsypnea or cough).

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	9/112	7/110		1.26[0.49,3.27]



Analysis 4.21. Comparison 4 Ciclesonide versus placebo 800mcg/d (ex-valve, parallel group studies), Outcome 21 Rhinitis.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Chapman 2005	15/112	17/110		0.87[0.46,1.65]



Comparison 5. Ciclesonide versus placebo 1600mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
1.1 Children	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in am PEF	1		L/min (Fixed, 95% CI)	Totals not selected
2.1 Children	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in rescue beta2-agonists use	1		Puffs/d (Fixed, 95% CI)	Totals not selected
3.1 Children	0		Puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	1		Puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in asthma symptom scores	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]

Analysis 5.1. Comparison 5 Ciclesonide versus placebo 1600mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Ciclesonide N	Placebo N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
5.1.1 Children					
5.1.2 Adults					
DFI6153	184	186	0.3 (0.043)		0.3[0.21,0.39]

Favours placebo -0.5 -0.25 0 0.25 0.5 Favours ciclesonide

Analysis 5.2. Comparison 5 Ciclesonide versus placebo 1600mcg/d (ex-valve, parallel group studies), Outcome 2 Change in am PEF.

Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
5.2.1 Children					
5.2.2 Adults					

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Study or subgroup	Ciclesonide N	Placebo N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
DFI6153	184	186	25.1 (4.541)		25.1[16.2,34]

Favours placebo -100 -50 0 50 100 Favours ciclesonide

Analysis 5.3. Comparison 5 Ciclesonide versus placebo 1600mcg/d (ex-valve, parallel group studies), Outcome 3 Change in rescue beta2-agonists use.

Study or subgroup	Ciclesonide N	Placebo N	Puffs/d (SE)	Puffs/d IV, Fixed, 95% CI	Puffs/d IV, Fixed, 95% CI
5.3.1 Children					
5.3.2 Adults					
DFI6153	184	186	-1.4 (0.171)		-1.42[-1.75,-1.09]

Favours ciclesonide -10 -5 0 5 10 Favours placebo

Analysis 5.4. Comparison 5 Ciclesonide versus placebo 1600mcg/d (ex-valve, parallel group studies), Outcome 4 Change in asthma symptom scores.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.4.1 Children						
5.4.2 Adults						
DFI6153	184	-0.9 (1)	186	0 (1)		-0.87[-1.08,-0.66]

Favours ciclesonide -10 -5 0 5 10 Favours placebo

Comparison 6. Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in maintenance oral steroid dose (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Discontinuation of maintenance oral steroid	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Change in FEV1	1		L (Fixed, 95% CI)	Totals not selected
4 Change in rescue medication use (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Change in 24hr symptom scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Change in am PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Withdrawals (total)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Withdrawals (lack of efficacy)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
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
12 Hoarseness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Suppression of HPA axis function (end point)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Withdrawals (adverse events)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 1 Change in maintenance oral steroid dose (%).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Bateman 2006	47	-47.4 (69.2)	45	-4.2 (69.1)		-43.19[-71.46,-14.92]

Favours ciclesonide -100 -50 0 50 100 Favours placebo

Analysis 6.2. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 2 Discontinuation of maintenance oral steroid.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006	14/47	5/45		2.68[1.05,6.83]

Favours treatment 0.1 0.2 0.5 1 2 5 10 Favours control

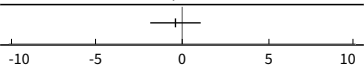
Analysis 6.3. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 3 Change in FEV1.

Study or subgroup	Ciclesonide N	Placebo N	L (SE)	L IV, Fixed, 95% CI	L IV, Fixed, 95% CI
Bateman 2006	47	48	0.2 (0.074)		0.17[0.02,0.31]

Favours placebo -10 -5 0 5 10 Favours ciclesonide

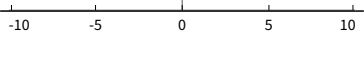
Analysis 6.4. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 4 Change in rescue medication use (puffs/d).

Study or subgroup	Ciclesonide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bateman 2006	47	-0.1 (3.5)	45	0.3 (3.6)		-0.39[-1.85,1.07]



Analysis 6.5. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 5 Change in 24hr symptom scores.

Study or subgroup	Ciclesonide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bateman 2006	47	0.1 (1.5)	45	-0.2 (1.5)		0.34[-0.28,0.96]



Analysis 6.6. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 6 Change in am PEF (L/min).

Study or subgroup	Ciclesonide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bateman 2006	47	4.3 (44.9)	45	-0.7 (46)		5.02[-13.57,23.61]

Analysis 6.7. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 7 Withdrawals (total).

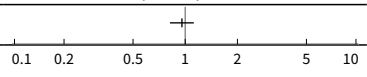
Study or subgroup	Ciclesonide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bateman 2006	8/47	14/45		0.55[0.25,1.18]

Analysis 6.8. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 8 Withdrawals (lack of efficacy).

Study or subgroup	Ciclesonide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bateman 2006	6/47	13/45		0.44[0.18,1.06]

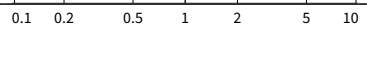
Analysis 6.9. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 9 Adverse events.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006	40/47	40/45		0.96[0.82,1.12]



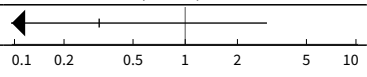
Analysis 6.10. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 10 Candidiasis.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006	3/47	0/45		6.71[0.36,126.32]



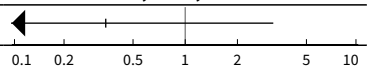
Analysis 6.11. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 11 Pharyngitis.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	1/47	3/45		0.32[0.03,2.96]



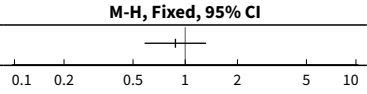
Analysis 6.12. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 12 Hoarseness.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	1/45	3/47		0.35[0.04,3.22]



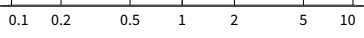
Analysis 6.13. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 13 Suppression of HPA axis function (end point).

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	22/47	24/45		0.88[0.58,1.32]



Analysis 6.14. Comparison 6 Ciclesonide versus placebo plus OCS 800mcg/d (ex-valve, parallel group studies), Outcome 14 Withdrawals (adverse events).

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	4/47	13/45		0.29[0.1,0.84]



Comparison 7. Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in maintenance oral steroid dose (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2 Discontinuation of maintenance oral steroid	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3 Change in FEV1	1		L (Fixed, 95% CI)	Totals not selected
4 Change in rescue medication use (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5 Change in 24hr symptom scores	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6 Change in am PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Withdrawals (total)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8 Withdrawals (lack of efficacy)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
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
12 Hoarseness	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13 Suppression of HPA axis function (end point)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14 Withdrawals (adverse events)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 1 Change in maintenance oral steroid dose (%).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Bateman 2006	48	-62.5 (67.9)	45	-4.2 (69.1)		-58.26[-86.13,-30.39]

Favours ciclesonide -100 -50 0 50 100 Favours placebo

Analysis 7.2. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 2 Discontinuation of maintenance oral steroid.

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006	15/48	5/45		2.81[1.11,7.11]

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours ciclesonide

Analysis 7.3. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 3 Change in FEV1.

Study or subgroup	Ciclesonide N	Placebo N	L (SE)	L IV, Fixed, 95% CI	L IV, Fixed, 95% CI
Bateman 2006	47	48	0.2 (0.074)		0.17[0.02,0.31]

Favours placebo -10 -5 0 5 10 Favours ciclesonide

Analysis 7.4. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 4 Change in rescue medication use (puffs/d).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Bateman 2006	48	-0.1 (3.5)	45	0.3 (3.6)		-0.4[-1.85,1.05]

Favours ciclesonide -1 -0.5 0 0.5 1 Favours placebo

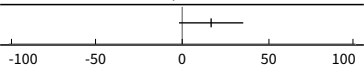
Analysis 7.5. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 5 Change in 24hr symptom scores.

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Bateman 2006	48	-0.3 (1.5)	45	-0.2 (1.5)		-0.07[-0.68,0.54]

Favours ciclesonide -10 -5 0 5 10 Favours placebo

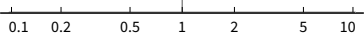
Analysis 7.6. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 6 Change in am PEF (L/min).

Study or subgroup	Ciclesonide		Placebo		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Bateman 2006	48	16 (45)	45	-0.7 (46)		16.67[-1.85,35.19]



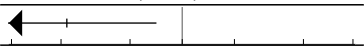
Analysis 7.7. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 7 Withdrawals (total).

Study or subgroup	Ciclesonide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bateman 2006a	5/48	14/45		0.33[0.13,0.85]



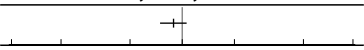
Analysis 7.8. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 8 Withdrawals (lack of efficacy).

Study or subgroup	Ciclesonide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bateman 2006	3/48	13/45		0.22[0.07,0.71]



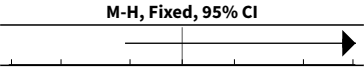
Analysis 7.9. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 9 Adverse events.

Study or subgroup	Ciclesonide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bateman 2006a	38/48	40/45		0.89[0.75,1.06]



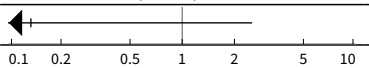
Analysis 7.10. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 10 Candidiasis.

Study or subgroup	Ciclesonide	Placebo	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Bateman 2006a	4/48	0/45		8.45[0.47,152.62]



Analysis 7.11. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 11 Pharyngitis.

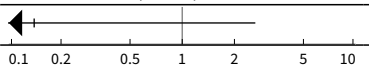
Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	0/48	3/45		0.13[0.01,2.53]



Favours ciclesonide — Favours placebo

Analysis 7.12. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 12 Hoarseness.

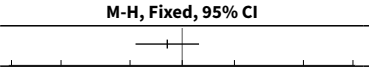
Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	0/48	3/47		0.14[0.01,2.64]



Favours ciclesonide — Favours placebo

Analysis 7.13. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 13 Suppression of HPA axis function (end point).

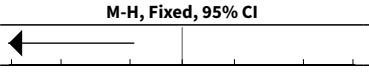
Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	21/48	24/45		0.82[0.54,1.25]



Favours ciclesonide — Favours placebo

Analysis 7.14. Comparison 7 Ciclesonide versus placebo plus OCS greater than 800mcg/d (ex-valve, parallel group studies), Outcome 14 Withdrawals (adverse events).

Study or subgroup	Ciclesonide n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Bateman 2006a	1/48	13/45		0.07[0.01,0.53]



Favours treatment — Favours control

Comparison 8. Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies)

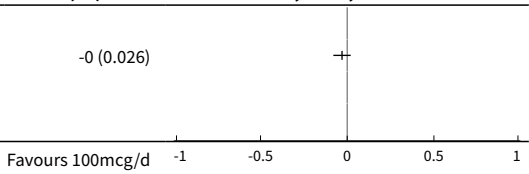
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
1.1 Children	1		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in FEV1 predicted (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in am 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 in pm PEF (L/min)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in quality of life score (paediatric AQLQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Pharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Nasopharyngitis	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 Asthma (not other-wise specified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Headache	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Upper respiratory tract infection	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 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Withdrawals	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Withdrawals (lack of efficacy)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Withdrawals (adverse events)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
16.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

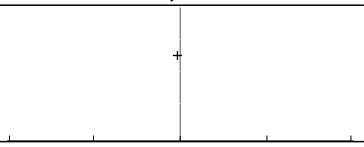
Analysis 8.1. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	50mcg/d N	100mcg/d N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
8.1.1 Children					
Gelfand 2006a	252	259	-0 (0.026)		-0.03[-0.08,0.02]
8.1.2 Adults					



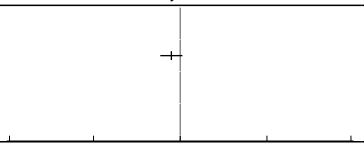
Analysis 8.2. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 2 Change in FEV1 predicted (%).

Study or subgroup	Ciclesonide 50mcg/d N	Mean(SD)	Ciclesonide 100mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.2.1 Children						
Gelfand 2006a	252	12 (15.1)	259	13.6 (15.1)		-1.61[-4.23,1.01]
8.2.2 Adults						



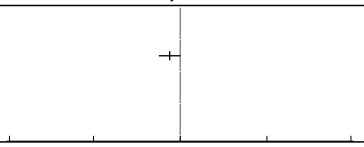
Analysis 8.3. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 3 Change in am PEF (L/min).

Study or subgroup	Ciclesonide 50mcg/d N	Mean(SD)	Ciclesonide 100mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.3.1 Children						
Gelfand 2006a	252	15 (36.5)	259	20.1 (37)		-5.11[-11.48,1.26]
8.3.2 Adults						



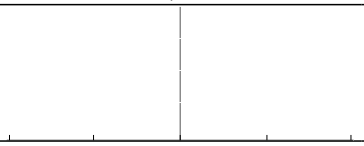
Analysis 8.4. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 4 Change in pm PEF (L/min).

Study or subgroup	Ciclesonide 50mcg/d N	Mean(SD)	Ciclesonide 100mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.4.1 Children						
Gelfand 2006a	252	12.3 (36.1)	259	18.3 (36.4)		-6.07[-12.36,0.22]
8.4.2 Adults						

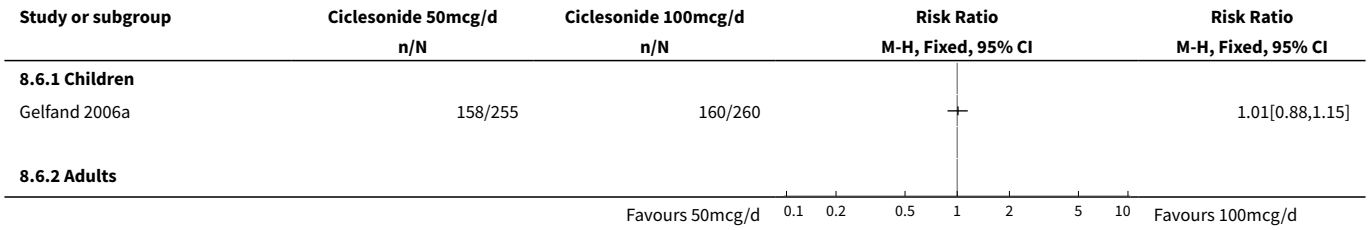


Analysis 8.5. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 5 Change in quality of life score (paediatric AQLQ).

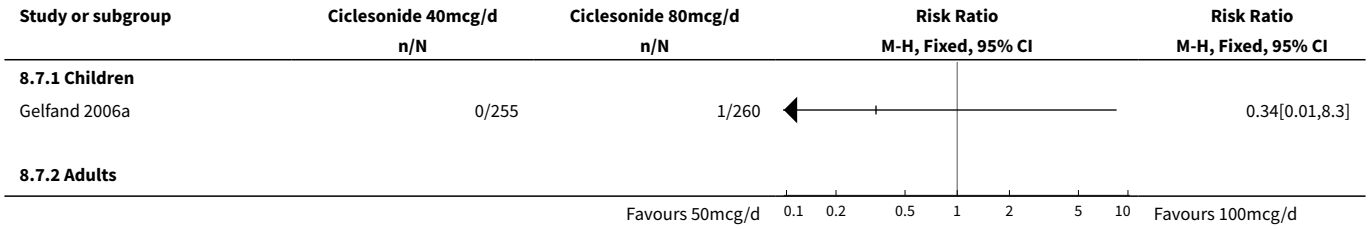
Study or subgroup	Ciclesonide 50mcg/d N	Mean(SD)	Ciclesonide 100mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
8.5.1 Children						
Gelfand 2006a	252	0.5 (0)	259	0.5 (0)		Not estimable
8.5.2 Adults						



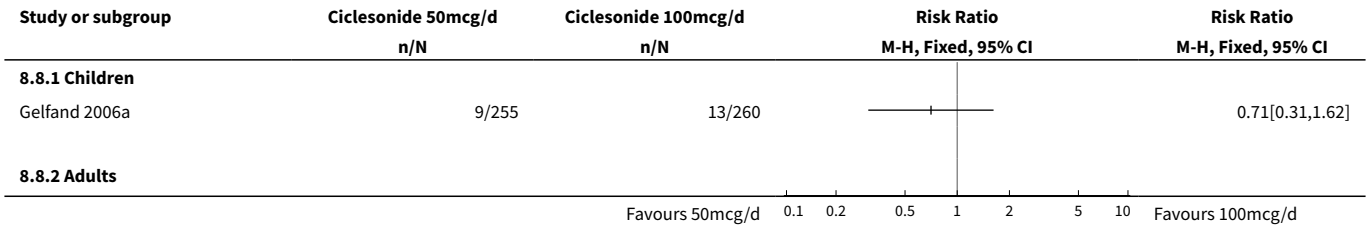
Analysis 8.6. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 6 Adverse event.



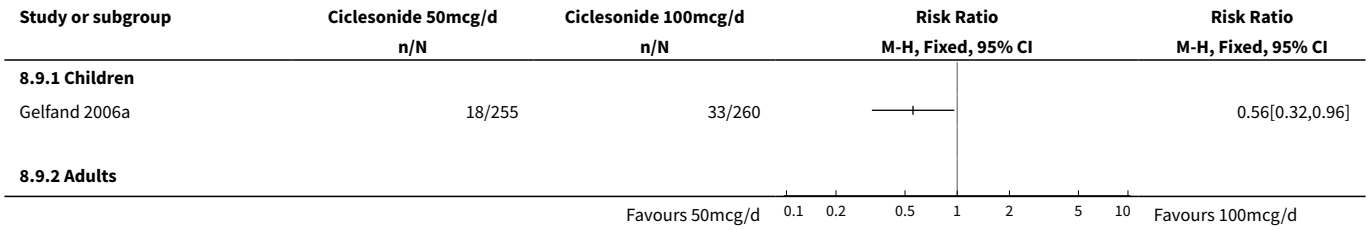
Analysis 8.7. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 7 Candidiasis.



Analysis 8.8. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 8 Pharyngitis.

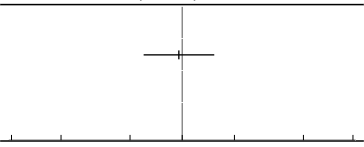


Analysis 8.9. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 9 Nasopharyngitis.



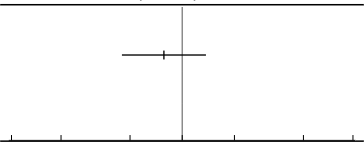
Analysis 8.10. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 10 Asthma (not otherwise specified).

Study or subgroup	Ciclesonide 50mcg/d n/N	Ciclesonide 100mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.10.1 Children				
Gelfand 2006a	30/255	32/260		0.96[0.6,1.53]
8.10.2 Adults				



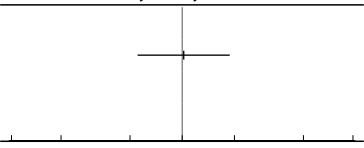
Analysis 8.11. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 11 Headache.

Study or subgroup	Ciclesonide 50mcg/d n/N	Ciclesonide 100mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.11.1 Children				
Gelfand 2006a	20/255	26/260		0.78[0.45,1.37]
8.11.2 Adults				



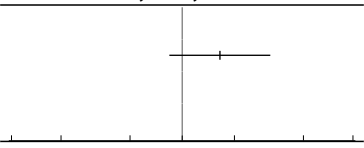
Analysis 8.12. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 12 Upper respiratory tract infection.

Study or subgroup	Ciclesonide 50mcg/d n/N	Ciclesonide 100mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.12.1 Children				
Gelfand 2006a	19/255	19/260		1.02[0.55,1.88]
8.12.2 Adults				

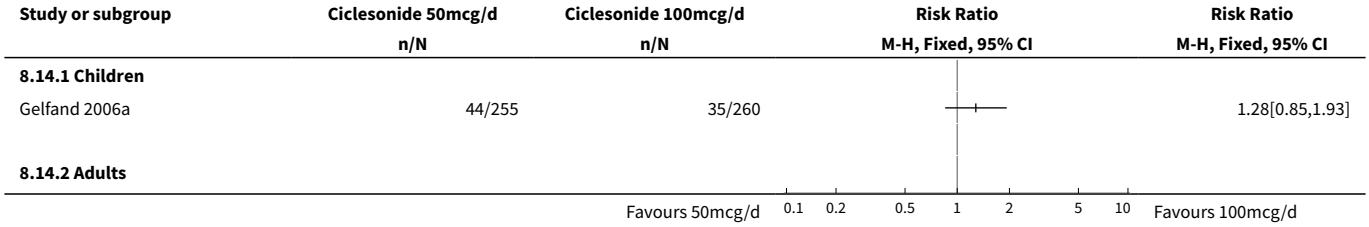


Analysis 8.13. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 13 Rhinitis.

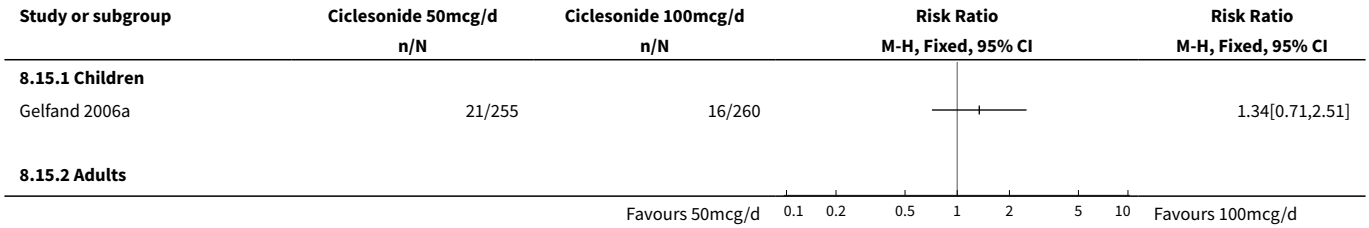
Study or subgroup	Ciclesonide 50mcg/d n/N	Ciclesonide 100mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
8.13.1 Children				
Gelfand 2006a	21/255	13/260		1.65[0.84,3.22]
8.13.2 Adults				



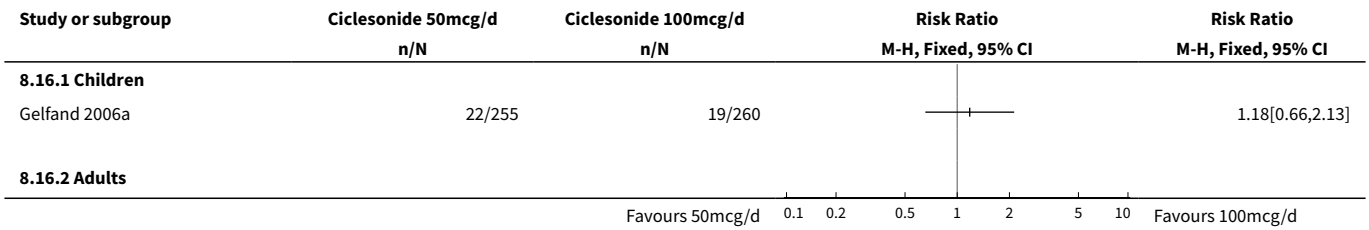
Analysis 8.14. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 14 Withdrawals.



Analysis 8.15. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 15 Withdrawals (lack of efficacy).



Analysis 8.16. Comparison 8 Ciclesonide 50 versus 100mcg/d (ex-valve, parallel group studies), Outcome 16 Withdrawals (adverse events).



Comparison 9. Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	4	1726	Litres (Fixed, 95% CI)	-0.01 [-0.04, 0.03]
1.1 Children	1	512	Litres (Fixed, 95% CI)	-0.01 [-0.06, 0.04]
1.2 Adults	3	1214	Litres (Fixed, 95% CI)	-0.00 [-0.05, 0.04]
2 Change in FEV1 predicted (%)	3	1176	Mean Difference (IV, Fixed, 95% CI)	0.31 [-0.74, 1.35]
2.1 Children	1	512	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-3.20, 2.02]

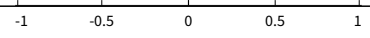
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Adults	2	664	Mean Difference (IV, Fixed, 95% CI)	0.48 [-0.67, 1.62]
3 Change in am PEF (L/min)	3	1176	Mean Difference (IV, Fixed, 95% CI)	4.04 [-0.53, 8.61]
3.1 Children	1	512	Mean Difference (IV, Fixed, 95% CI)	5.0 [-1.37, 11.37]
3.2 Adults	2	664	Mean Difference (IV, Fixed, 95% CI)	3.02 [-3.55, 9.59]
4 Change in pm PEF (L/min)	3	1176	Mean Difference (IV, Fixed, 95% CI)	2.26 [-2.05, 6.58]
4.1 Children	1	512	Mean Difference (IV, Fixed, 95% CI)	2.56 [-3.73, 8.85]
4.2 Adults	2	664	Mean Difference (IV, Fixed, 95% CI)	2.00 [-3.94, 7.94]
5 Change in quality of life score (paediatric AQLQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Adverse event	2	672	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
6.1 Children	1	513	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.78, 1.01]
6.2 Adults	1	159	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.90, 1.72]
7 Candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Pharyngitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Nasopharyngitis	2	672	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.75, 1.47]
9.1 Children	1	513	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.62, 1.53]
9.2 Adults	1	159	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.72, 1.95]
10 Asthma (not other-wise specified)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
11 Headache	2	672	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.52, 1.39]
11.1 Children	1	513	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.53, 1.44]
11.2 Adults	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.61]
12 Upper respiratory tract infection	2		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	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 Children	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Withdrawals	2	672	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
14.1 Children	1	513	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.70, 1.73]
14.2 Adults	1	159	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.36, 4.66]
15 Withdrawals (lack of efficacy)	3	1177	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.78, 1.92]
15.1 Children	1	513	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.55, 2.23]
15.2 Adults	2	664	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.72, 2.37]
16 Withdrawals (ad-verse events)	2	672	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.59, 2.01]
16.1 Children	1	513	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.61, 2.20]
16.2 Adults	1	159	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.05, 5.61]
17 Change in symp-toms	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Change in rescue medication usage (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
19 Change from base-line in quality of life score (AQLQ)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Change from base-line in nocturnal awakenings (n/night)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 FEV1 (L) (end of treatment)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 FEV1 predicted (%) (end of treatment)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Day symptoms (end of treatment)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
23.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Night symptoms (end of treatment)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
24.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Rescue medication usage (puffs/d) (end of treatment)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

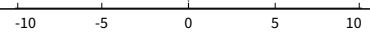
Analysis 9.1. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	100mcg/d N	200mcg/d N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
9.1.1 Children						
Gelfand 2006a	259	253	-0 (0.026)		46.04%	-0.01[-0.06,0.04]
Subtotal (95% CI)					**46.04%**	**-0.01[-0.06,0.04]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.39(P=0.69)						
9.1.2 Adults						
Adachi 2007a	78	81	-0 (0.041)		17.99%	-0.03[-0.11,0.05]
Magnussen 2007	278	270	0 (0.041)		17.99%	0.03[-0.05,0.11]
Pearlman 2005	257	250	-0 (0.041)		17.99%	-0.01[-0.09,0.07]
Subtotal (95% CI)					**53.96%**	**-0[-0.05,0.04]**
Heterogeneity: Tau^2=0; Chi^2=1.12, df=2(P=0.57); I^2=0%						
Test for overall effect: Z=0.14(P=0.89)						
Total (95% CI)					**100%**	**-0.01[-0.04,0.03]**
Heterogeneity: Tau^2=0; Chi^2=1.16, df=3(P=0.76); I^2=0%						
Test for overall effect: Z=0.37(P=0.71)						
Test for subgroup differences: Chi^2=0.04, df=1 (P=0.85), I^2=0%						



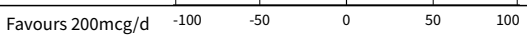
Analysis 9.2. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 2 Change in FEV1 predicted (%).

Study or subgroup	Ciclesonide 100mcg/ N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.2.1 Children							
Gelfand 2006a	259	13.6 (15.1)	253	14.2 (15)		16.16%	-0.59[-3.2,2.02]
Subtotal ***	**259**		**253**			**16.16%**	**-0.59[-3.2,2.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.44(P=0.66)							
9.2.2 Adults							
Adachi 2007a	78	0.3 (4.5)	81	-0.6 (4.7)		53.87%	0.86[-0.57,2.29]
Pearlman 2005	250	8.2 (11)	255	8.5 (10.9)		29.97%	-0.21[-2.12,1.7]
Subtotal ***	**328**		**336**			**83.84%**	**0.48[-0.67,1.62]**
Heterogeneity: Tau^2=0; Chi^2=0.77, df=1(P=0.38); I^2=0%							
Test for overall effect: Z=0.82(P=0.41)							
Total ***	**587**		**589**			**100%**	**0.31[-0.74,1.35]**
Heterogeneity: Tau^2=0; Chi^2=1.31, df=2(P=0.52); I^2=0%							
Test for overall effect: Z=0.57(P=0.57)							
Test for subgroup differences: Chi^2=0.54, df=1 (P=0.46), I^2=0%							



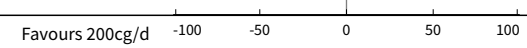
Analysis 9.3. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 3 Change in am PEF (L/min).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.3.1 Children							
Gelfand 2006a	259	20 (37)	253	15 (36.6)		51.49%	5[-1.37,11.37]
Subtotal ***	**259**		**253**			**51.49%**	**5[-1.37,11.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.54(P=0.12)							
9.3.2 Adults							
Adachi 2007a	78	4.2 (42.3)	81	3.8 (43.2)		11.84%	0.48[-12.81,13.77]
Pearlman 2005	250	21.1 (43.3)	255	17.2 (43.3)		36.67%	3.84[-3.71,11.39]
Subtotal ***	**328**		**336**			**48.51%**	**3.02[-3.55,9.59]**
Heterogeneity: Tau^2=0; Chi^2=0.19, df=1(P=0.67); I^2=0%							
Test for overall effect: Z=0.9(P=0.37)							
Total ***	**587**		**589**			**100%**	**4.04[-0.53,8.61]**
Heterogeneity: Tau^2=0; Chi^2=0.37, df=2(P=0.83); I^2=0%							
Test for overall effect: Z=1.73(P=0.08)							
Test for subgroup differences: Chi^2=0.18, df=1 (P=0.67), I^2=0%							



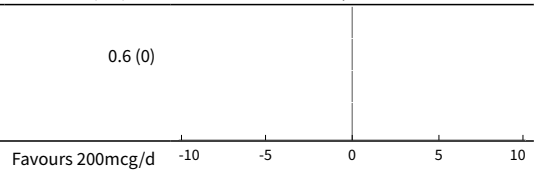
Analysis 9.4. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 4 Change in pm PEF (L/min).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.4.1 Children							
Gelfand 2006a	259	18.3 (36.4)	253	15.8 (36.2)		47.21%	2.56[-3.73,8.85]
Subtotal ***	**259**		**253**			**47.21%**	**2.56[-3.73,8.85]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.8(P=0.42)							
9.4.2 Adults							
Adachi 2007a	78	1.6 (32.7)	81	3.4 (39.5)		14.73%	-1.8[-13.05,9.45]
Pearlman 2005	250	18.1 (40.6)	255	14.6 (39.7)		38.06%	3.47[-3.53,10.47]
Subtotal ***	**328**		**336**			**52.79%**	**2[-3.94,7.94]**
Heterogeneity: Tau^2=0; Chi^2=0.61, df=1(P=0.44); I^2=0%							
Test for overall effect: Z=0.66(P=0.51)							
Total ***	**587**		**589**			**100%**	**2.26[-2.05,6.58]**
Heterogeneity: Tau^2=0; Chi^2=0.62, df=2(P=0.73); I^2=0%							
Test for overall effect: Z=1.03(P=0.3)							
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.9), I^2=0%							



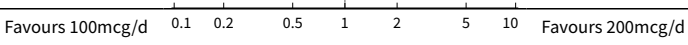
Analysis 9.5. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 5 Change in quality of life score (paediatric AQLQ).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
9.5.1 Children						
Gelfand 2006a	259	0.5 (0)	253	0.6 (0)		Not estimable
9.5.2 Adults						



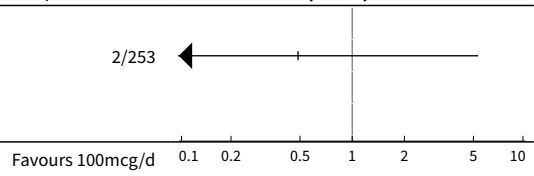
Analysis 9.6. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 6 Adverse event.

Study or subgroup	Ciclesonide 100mcg/d n/N	Ciclesonide 200mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.6.1 Children					
Gelfand 2006a	160/260	175/253		83.78%	0.89[0.78,1.01]
Subtotal (95% CI)	**260**	**253**		**83.78%**	**0.89[0.78,1.01]**
Total events: 160 (Ciclesonide 100mcg/d), 175 (Ciclesonide 200mcg/d)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.81(P=0.07)					
9.6.2 Adults					
Adachi 2007a	42/78	35/81		16.22%	1.25[0.9,1.72]
Subtotal (95% CI)	**78**	**81**		**16.22%**	**1.25[0.9,1.72]**
Total events: 42 (Ciclesonide 100mcg/d), 35 (Ciclesonide 200mcg/d)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.33(P=0.18)					
Total (95% CI)	**338**	**334**		**100%**	**0.95[0.84,1.07]**
Total events: 202 (Ciclesonide 100mcg/d), 210 (Ciclesonide 200mcg/d)					
Heterogeneity: Tau^2=0; Chi^2=3.71, df=1(P=0.05); I^2=73.05%					
Test for overall effect: Z=0.89(P=0.37)					
Test for subgroup differences: Not applicable					



Analysis 9.7. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 7 Candidiasis.

Study or subgroup	Ciclesonide 100mcg/d n/N	Ciclesonide 200mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
9.7.1 Children				
Gelfand 2006a	1/260	2/253		0.49[0.04,5.33]
9.7.2 Adults				

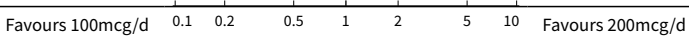


Analysis 9.8. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 8 Pharyngitis.

Study or subgroup	Ciclesonide 100mcg/d n/N	Ciclesonide 200mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
9.8.1 Children				
Gelfand 2006a	13/260	14/253		0.9[0.43,1.88]
9.8.2 Adults				

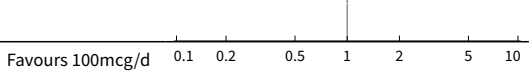
Analysis 9.9. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 9 Nasopharyngitis.

Study or subgroup	Ciclesonide 100mcg/d n/N	Ciclesonide 200mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
9.9.1 Children					
Gelfand 2006a	33/260	33/253		61.88%	0.97[0.62,1.53]
Subtotal (95% CI)	**260**	**253**		**61.88%**	**0.97[0.62,1.53]**
Total events: 33 (Ciclesonide 100mcg/d), 33 (Ciclesonide 200mcg/d)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=0.12(P=0.91)					
9.9.2 Adults					
Adachi 2007a	24/78	21/81		38.12%	1.19[0.72,1.95]
Subtotal (95% CI)	**78**	**81**		**38.12%**	**1.19[0.72,1.95]**
Total events: 24 (Ciclesonide 100mcg/d), 21 (Ciclesonide 200mcg/d)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
Total (95% CI)	**338**	**334**		**100%**	**1.05[0.75,1.47]**
Total events: 57 (Ciclesonide 100mcg/d), 54 (Ciclesonide 200mcg/d)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%					
Test for overall effect: Z=0.31(P=0.76)					
Test for subgroup differences: Not applicable					

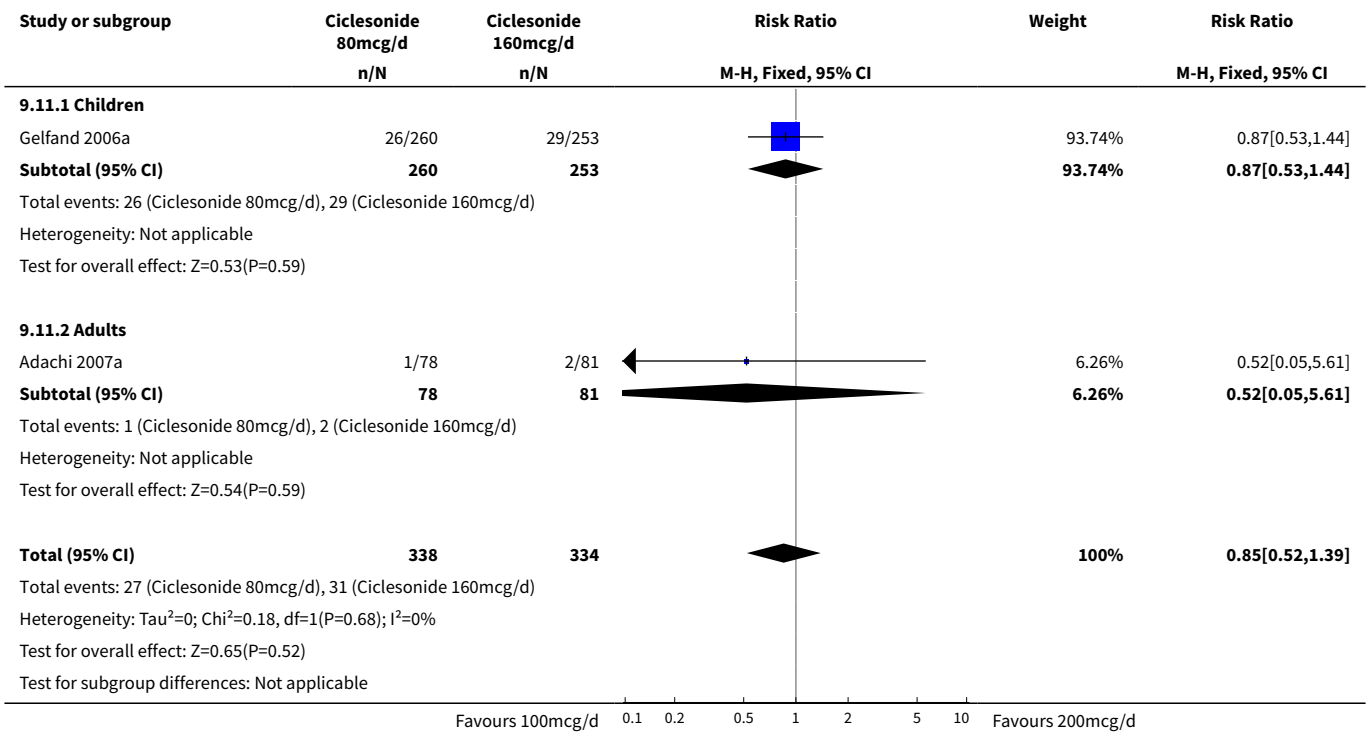


Analysis 9.10. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 10 Asthma (not otherwise specified).

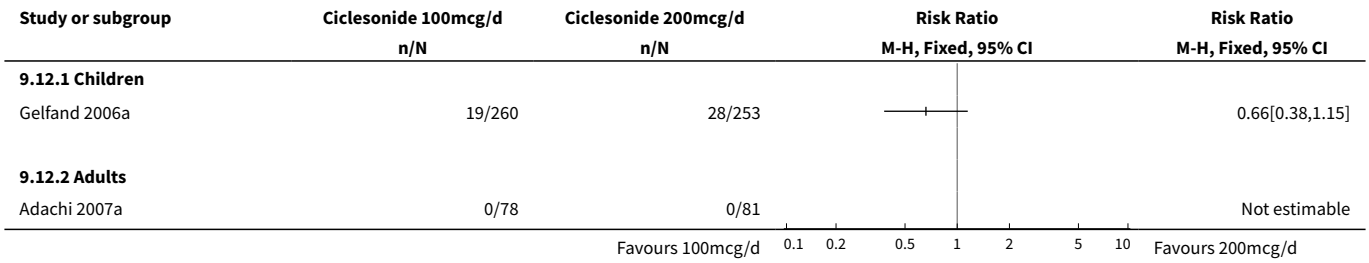
Study or subgroup	Ciclesonide 100mcg/d n/N	Ciclesonide 200mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
9.10.1 Children				
Gelfand 2006a	32/260	32/253		0.97[0.62,1.54]
9.10.2 Adults				



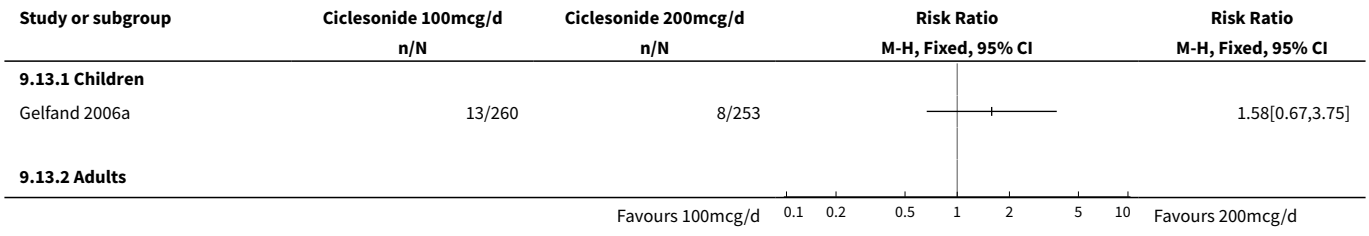
Analysis 9.11. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 11 Headache.



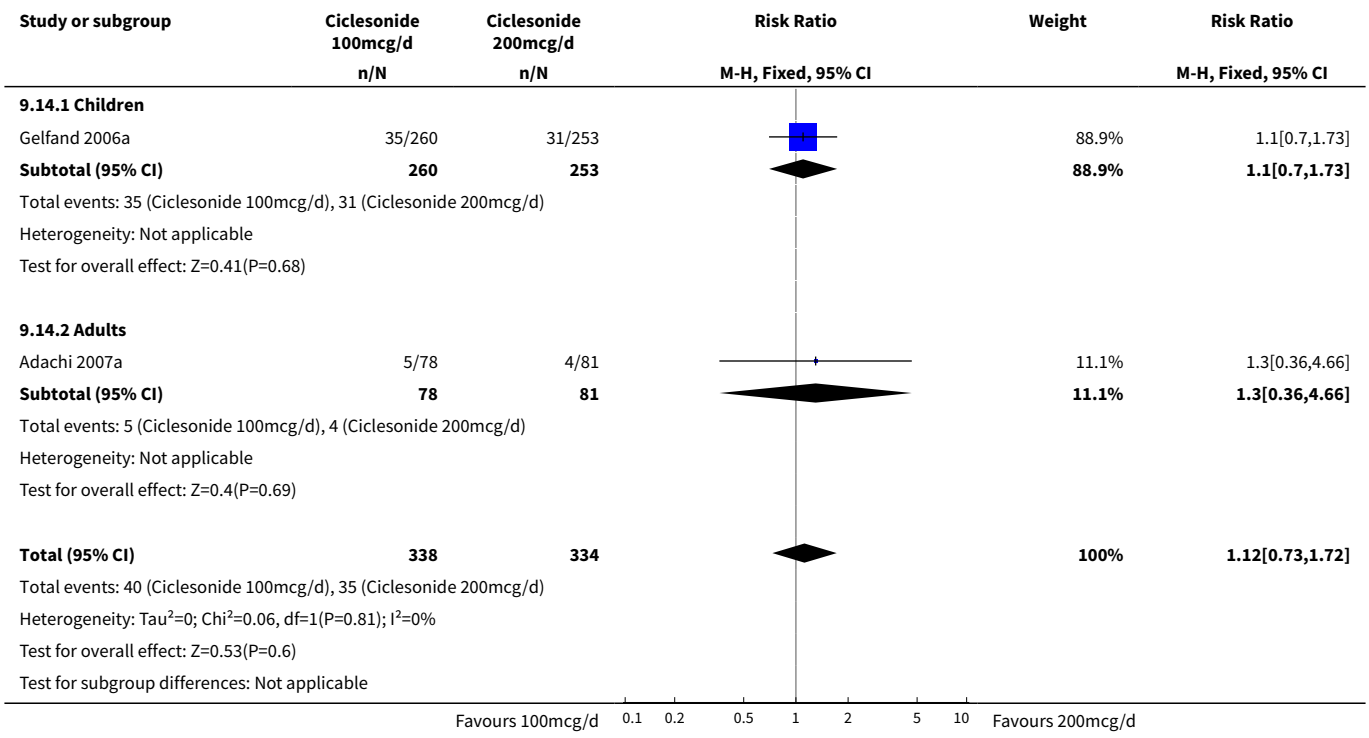
Analysis 9.12. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 12 Upper respiratory tract infection.



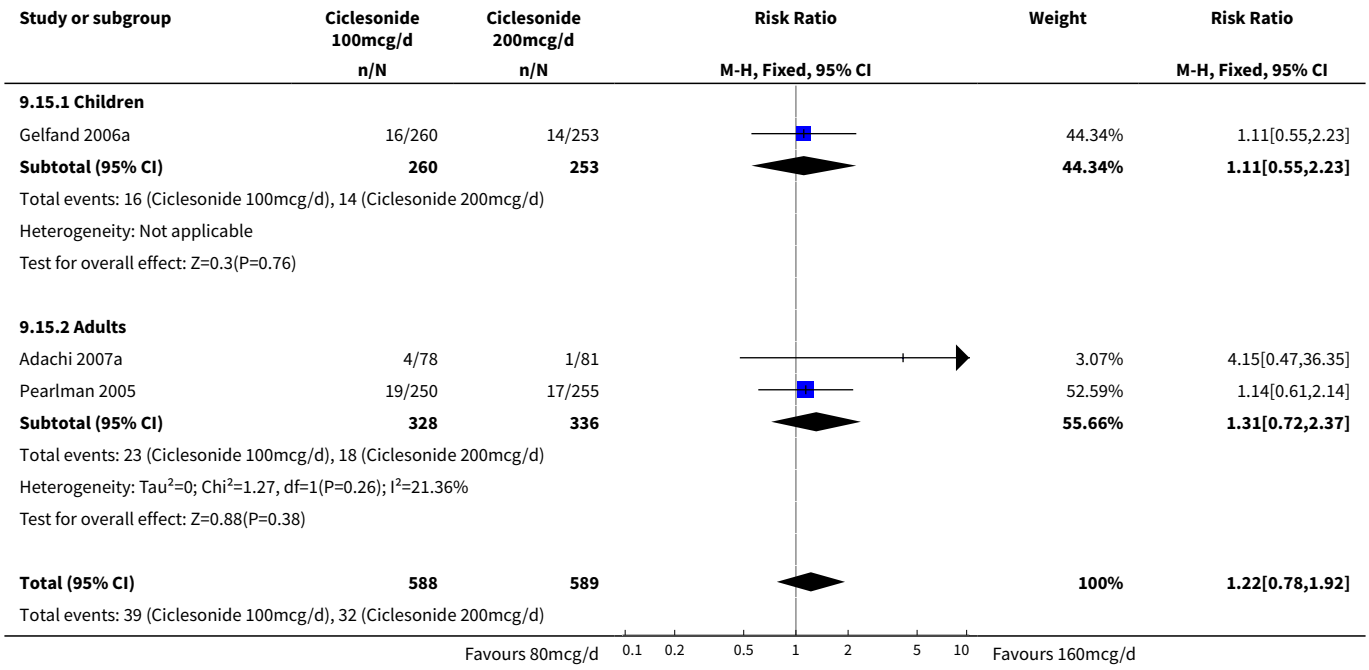
Analysis 9.13. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 13 Rhinitis.

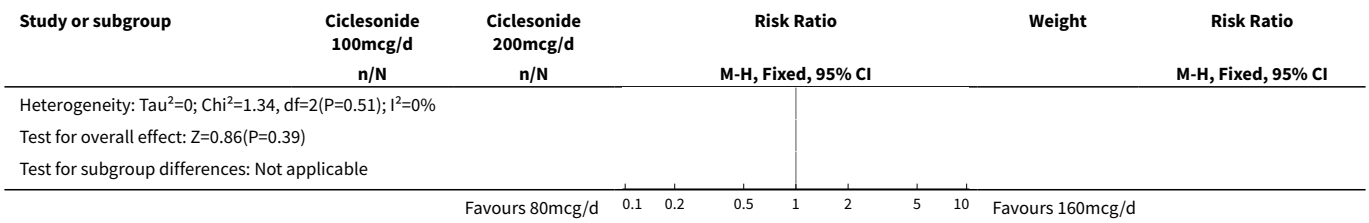


Analysis 9.14. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 14 Withdrawals.

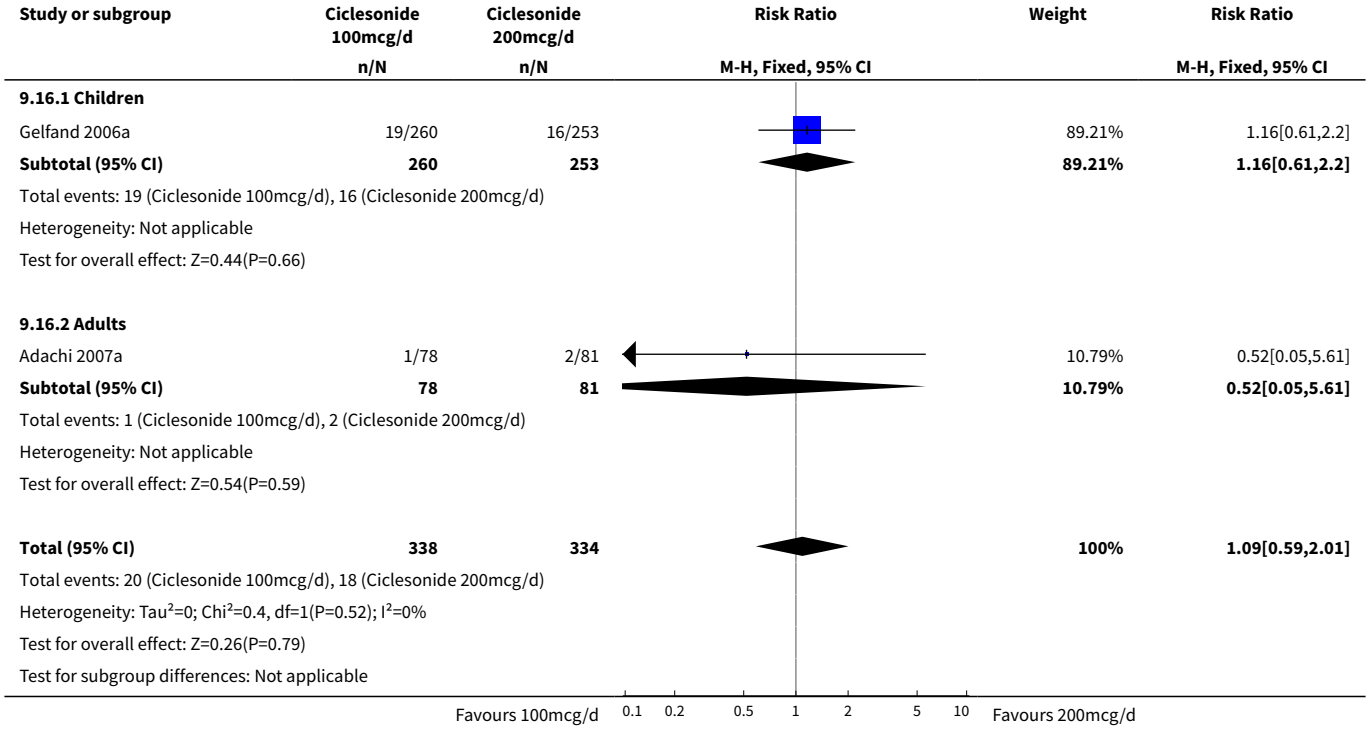


Analysis 9.15. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 15 Withdrawals (lack of efficacy).

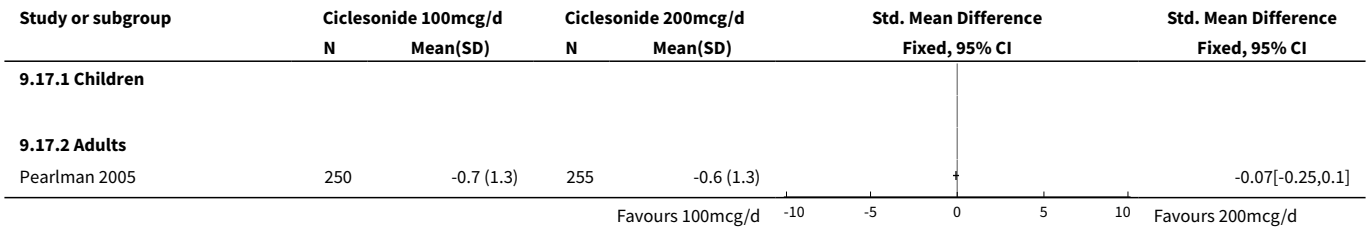




Analysis 9.16. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 16 Withdrawals (adverse events).

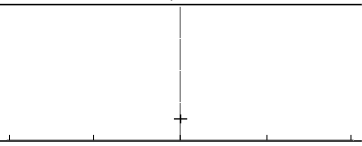


Analysis 9.17. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 17 Change in symptoms.



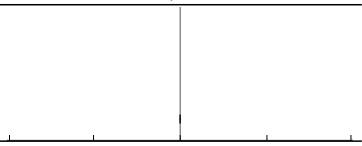
Analysis 9.18. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 18 Change in rescue medication usage (puffs/d).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
9.18.1 Children						
9.18.2 Adults						
Pearlman 2005	250	-1 (2.2)	255	-1 (2.1)		0.02[-0.36,0.4]



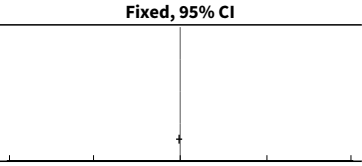
Analysis 9.19. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 19 Change from baseline in quality of life score (AQLQ).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
9.19.1 Children						
9.19.2 Adults						
Pearlman 2005	250	0.6 (1)	255	0.7 (1)		-0.08[-0.25,0.09]



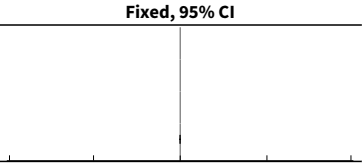
Analysis 9.20. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 20 Change from baseline in nocturnal awakenings (n/night).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
9.20.1 Children						
9.20.2 Adults						
Pearlman 2005	250	-0.2 (0.5)	255	-0.1 (0.5)		-0.06[-0.24,0.11]



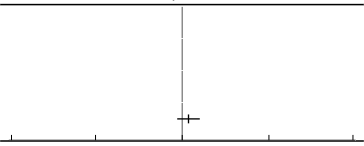
Analysis 9.21. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 21 FEV1 (L) (end of treatment).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
9.21.1 Children						
9.21.2 Adults						
Zietkowski 2006	12	3.1 (0.6)	12	3.2 (0.6)		-0.09[-0.59,0.41]



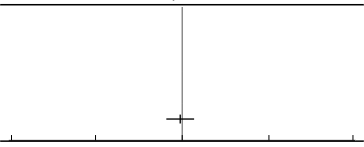
Analysis 9.22. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 22 FEV1 predicted (%) (end of treatment).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
9.22.1 Children						
9.22.2 Adults						
Zietkowski 2006	12	96.7 (9.2)	12	93.1 (6.9)		3.62[-2.89,10.13]



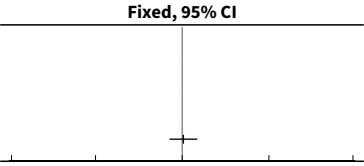
Analysis 9.23. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 23 Day symptoms (end of treatment).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
9.23.1 Children						
9.23.2 Adults						
Zietkowski 2006	12	0.4 (0.5)	12	0.5 (0.5)		-0.12[-0.92,0.69]



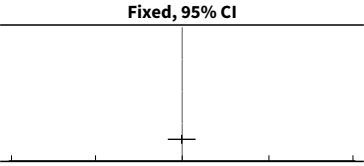
Analysis 9.24. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 24 Night symptoms (end of treatment).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
9.24.1 Children						
9.24.2 Adults						
Zietkowski 2006	12	0.2 (0.3)	12	0.2 (0.3)		0.07[-0.73,0.87]



Analysis 9.25. Comparison 9 Ciclesonide 100 versus 200mcg/d (ex-valve, parallel group studies), Outcome 25 Rescue medication usage (puffs/d) (end of treatment).

Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 200mcg/d N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
9.25.1 Children						
9.25.2 Adults						
Zietkowski 2006	12	0.6 (0.7)	12	0.6 (0.6)		-0.03[-0.83,0.77]



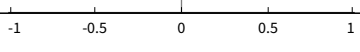
Comparison 10. Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies)

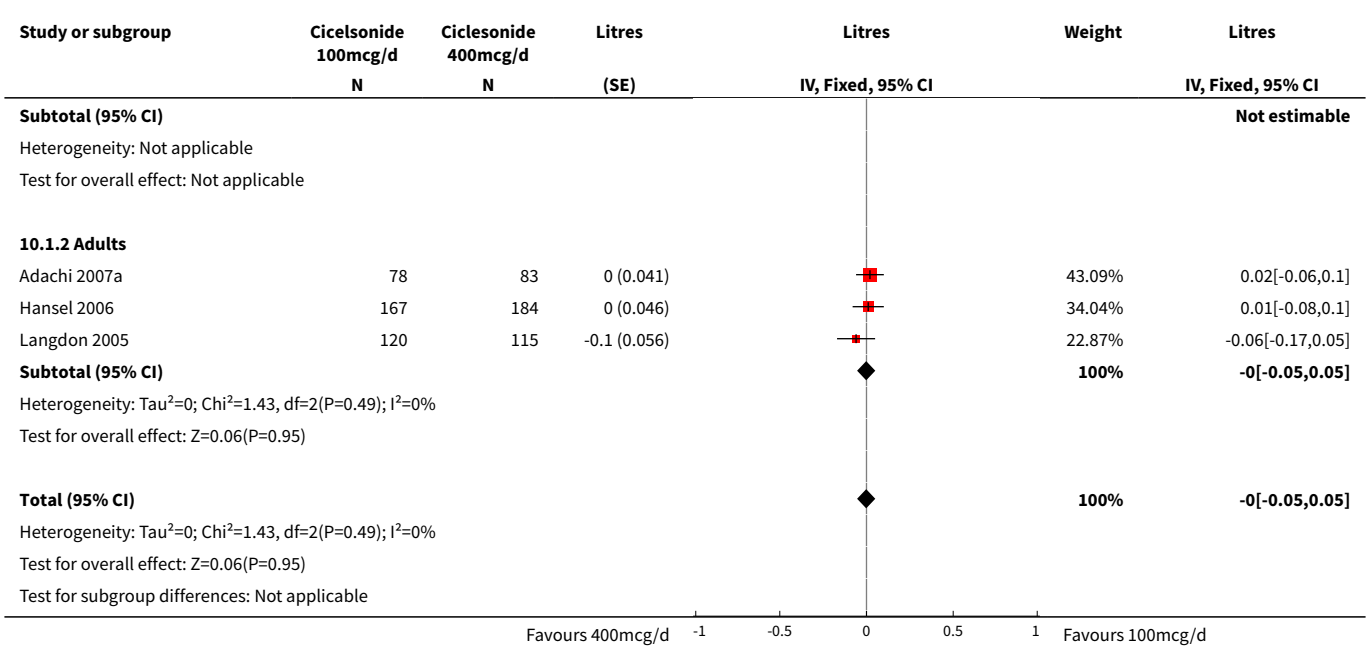
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change in FEV1	3	747	Litres (Fixed, 95% CI)	-0.00 [-0.05, 0.05]
1.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	3	747	Litres (Fixed, 95% CI)	-0.00 [-0.05, 0.05]
2 Change in FEV1 pre-dicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in am PEF	3	749	L/min (Fixed, 95% CI)	-0.48 [-7.59, 6.64]
3.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	3	749	L/min (Fixed, 95% CI)	-0.48 [-7.59, 6.64]
4 Change in pm PEF	2	396	L/min (Fixed, 95% CI)	1.36 [-6.05, 8.78]
4.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	2	396	L/min (Fixed, 95% CI)	1.36 [-6.05, 8.78]
5 Change clinic PEF	1		L/min (Fixed, 95% CI)	Totals not selected
5.1 Children	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	1		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in FVC	2	396	Litres (Fixed, 95% CI)	-0.01 [-0.08, 0.06]
6.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	2	396	Litres (Fixed, 95% CI)	-0.01 [-0.08, 0.06]
7 Change from base-line in quality of life score (AQLQ)	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 Adverse event	2	539	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.10]
8.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	2	539	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.10]
9 Headache	2	539	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.32, 2.21]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
9.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	2	539	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.32, 2.21]
10 Upper respiratory tract infection	2		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	2		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Rhinitis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
11.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Withdrawals	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.87, 2.40]
12.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [0.87, 2.40]
13 Withdrawals (lack of efficacy)	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.50, 4.06]
13.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.50, 4.06]
14 Withdrawals (adverse events)	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.58, 4.45]
14.1 Children	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	2	538	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.58, 4.45]
15 Increased cough	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
15.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

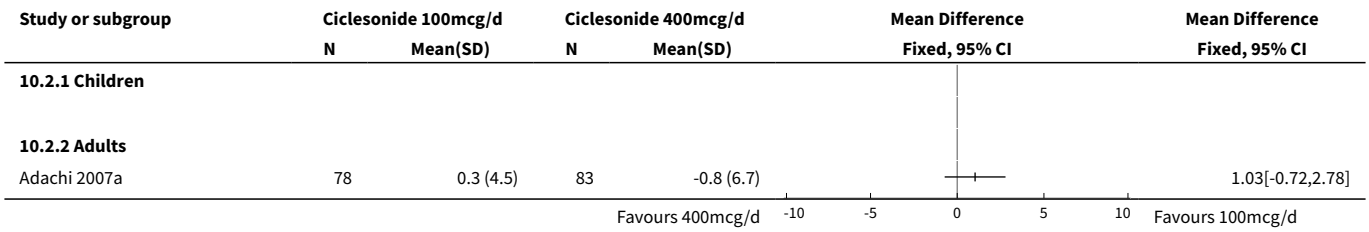
Analysis 10.1. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Cicelsonide 100mcg/d N	Ciclesonide 400mcg/d N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
10.1.1 Children						

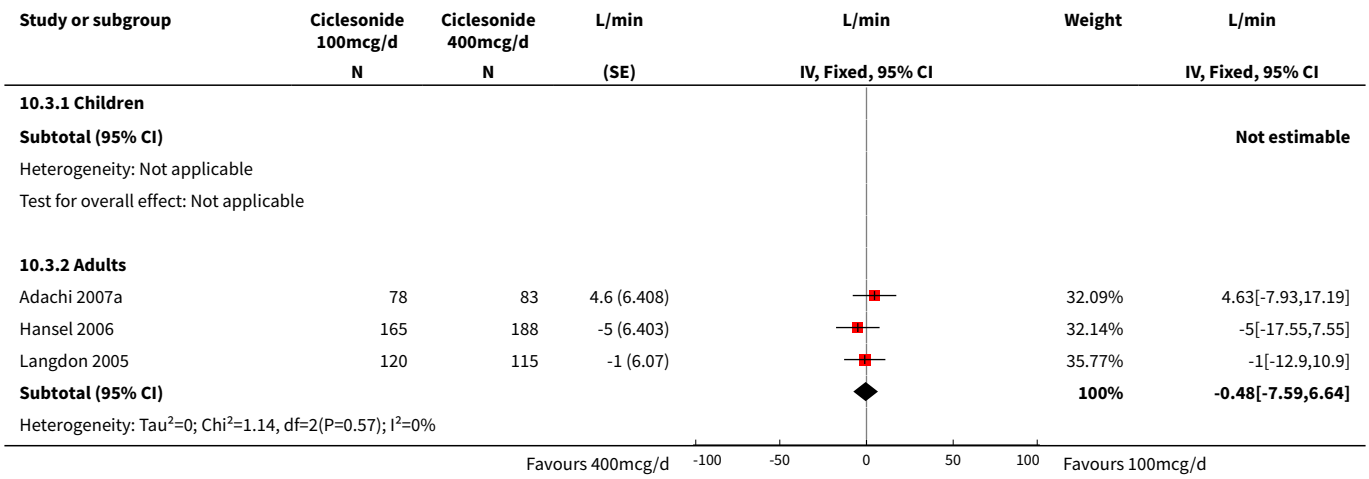


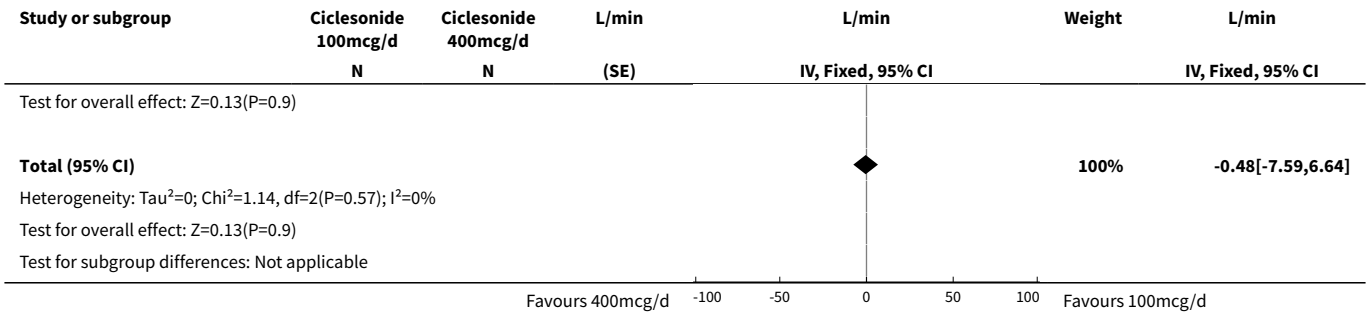


Analysis 10.2. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 2 Change in FEV1 predicted.

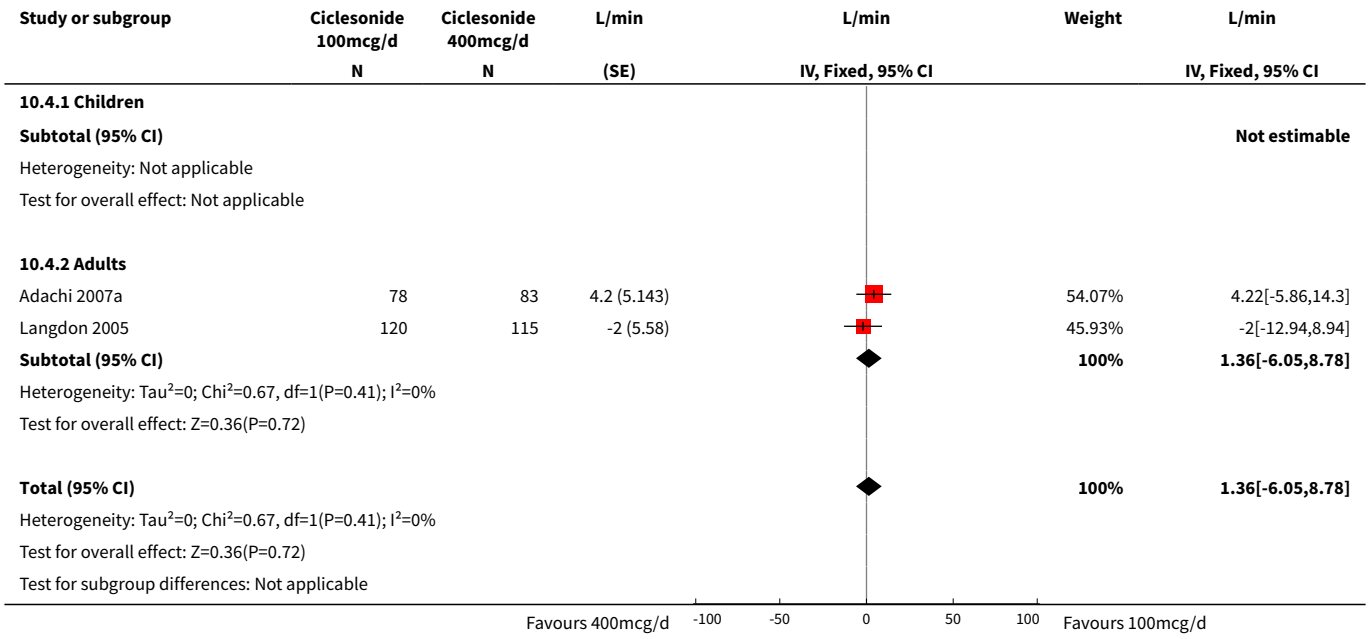


Analysis 10.3. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 3 Change in am PEF.

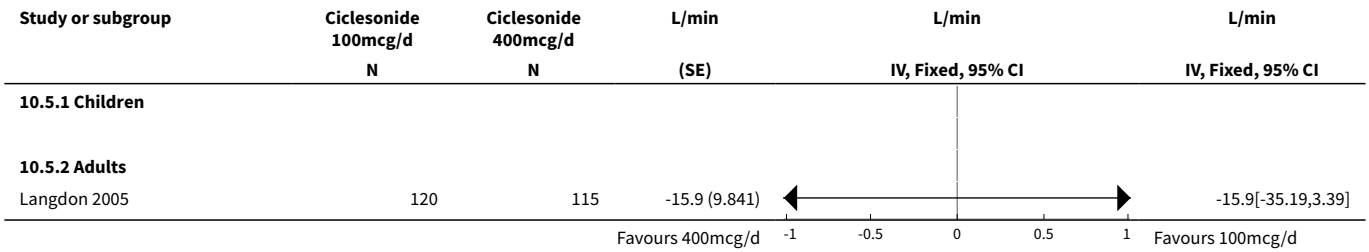




Analysis 10.4. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 4 Change in pm PEF.

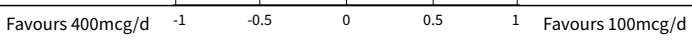


Analysis 10.5. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 5 Change clinic PEF.



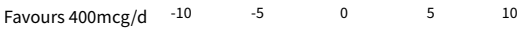
Analysis 10.6. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 6 Change in FVC.

Study or subgroup	Ciclesonide 100mcg/d N	Ciclesonide 400mcg/d N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
10.6.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
10.6.2 Adults						
Adachi 2007a	78	83	-0 (0.04)		73.14%	-0.01[-0.09,0.07]
Langdon 2005	120	115	-0 (0.066)		26.86%	-0.01[-0.14,0.12]
Subtotal (95% CI)					**100%**	**-0.01[-0.08,0.06]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%						
Test for overall effect: Z=0.29(P=0.77)						
Total (95% CI)					**100%**	**-0.01[-0.08,0.06]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%						
Test for overall effect: Z=0.29(P=0.77)						
Test for subgroup differences: Not applicable						



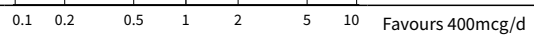
Analysis 10.7. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 7 Change from baseline in quality of life score (AQLQ).

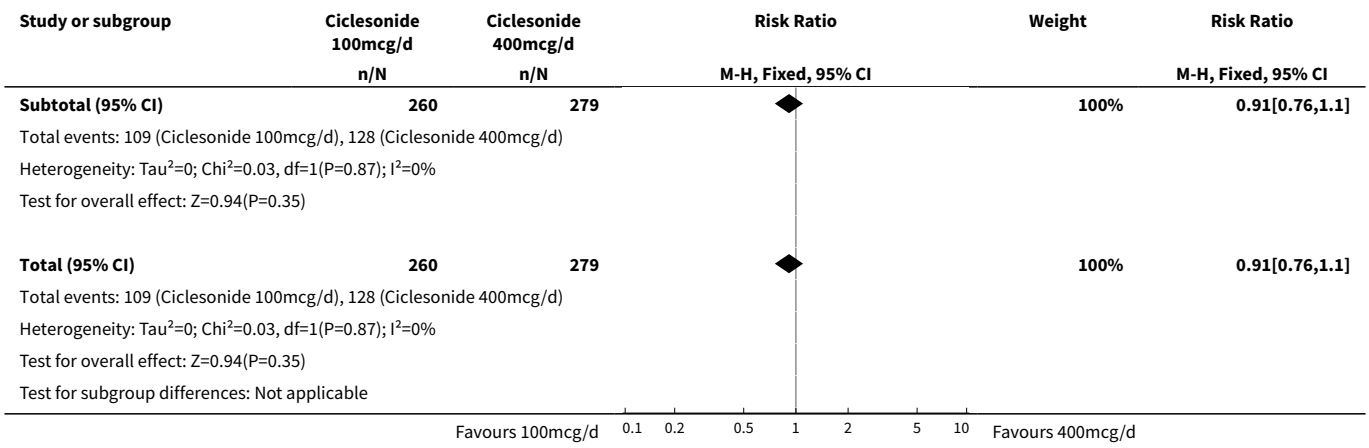
Study or subgroup	Ciclesonide 100mcg/d N	Mean(SD)	Ciclesonide 400mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.7.1 Children						
10.7.2 Adults						
Pearlman 2005	257	0.5 (1)	255	0.7 (1)		-0.19[-0.36,-0.02]



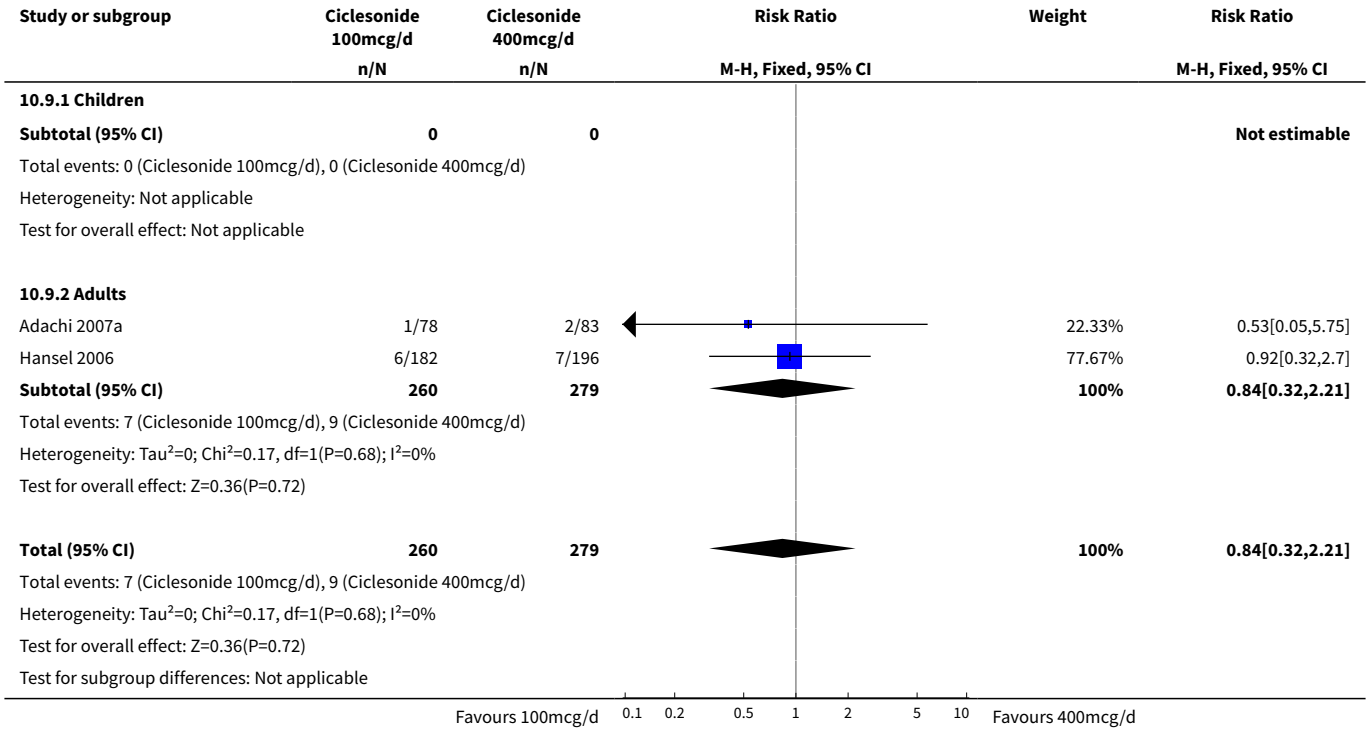
Analysis 10.8. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 8 Adverse event.

Study or subgroup	Ciclesonide 100mcg/d n/N	Ciclesonide 400mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
10.8.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Ciclesonide 100mcg/d), 0 (Ciclesonide 400mcg/d)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
10.8.2 Adults					
Adachi 2007a	42/78	48/83		37.65%	0.93[0.71,1.23]
Hansel 2006	67/182	80/196		62.35%	0.9[0.7,1.16]

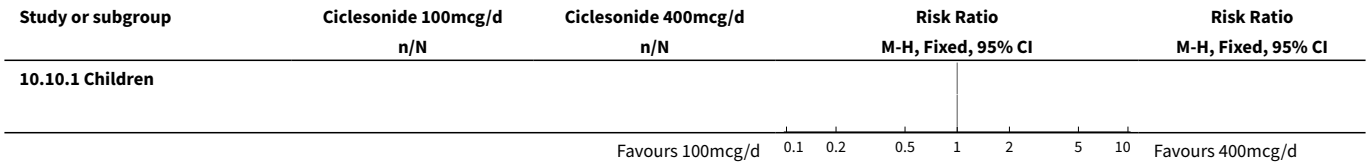


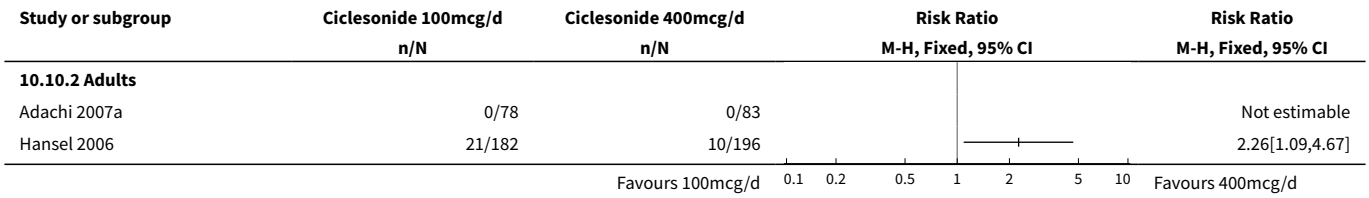


Analysis 10.9. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 9 Headache.

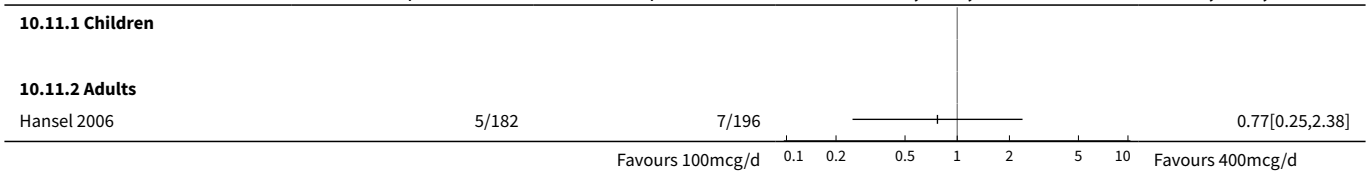


Analysis 10.10. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 10 Upper respiratory tract infection.

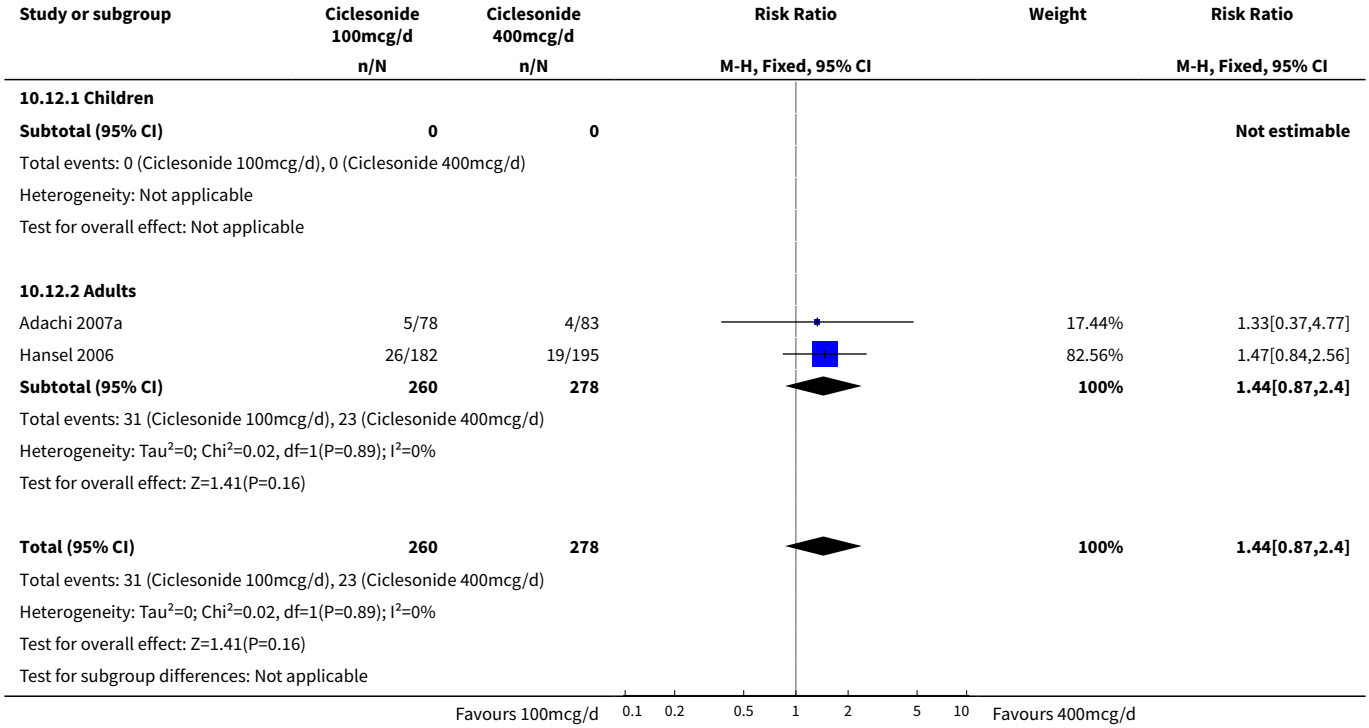




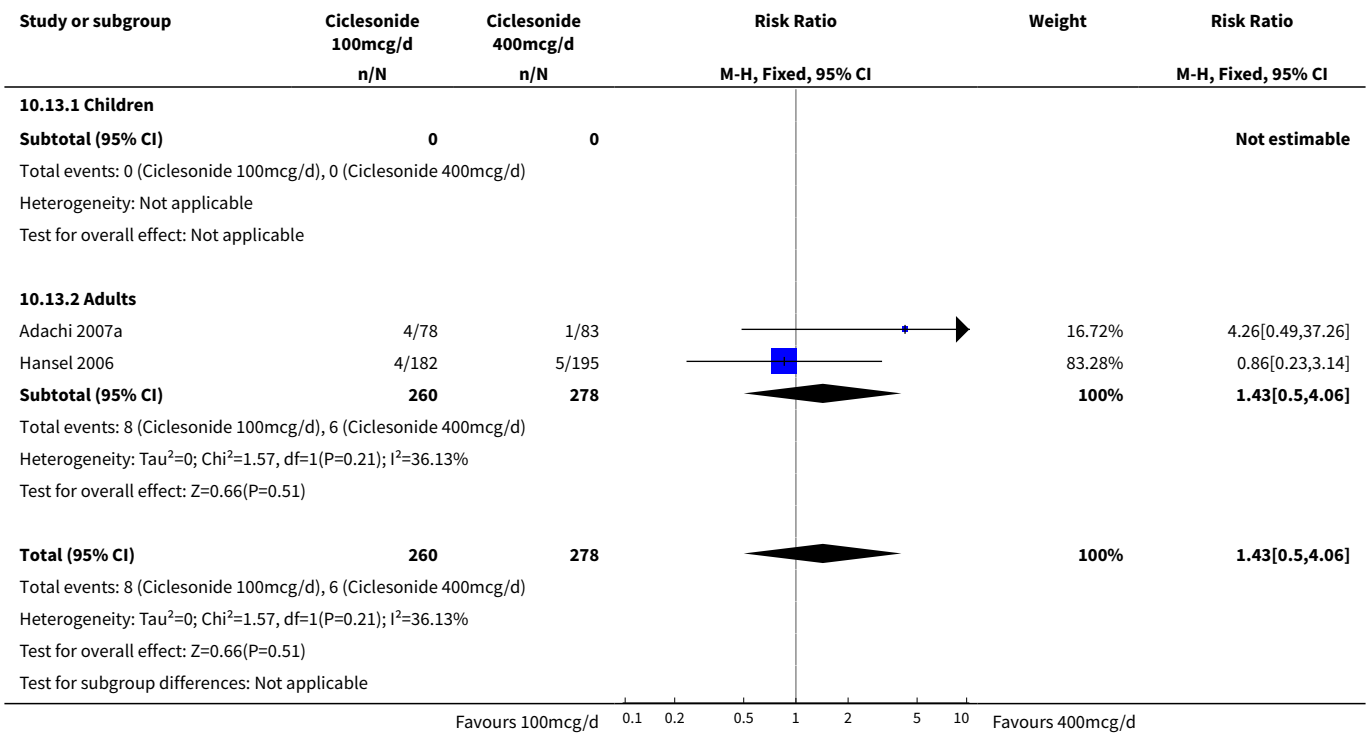
Analysis 10.11. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 11 Rhinitis.



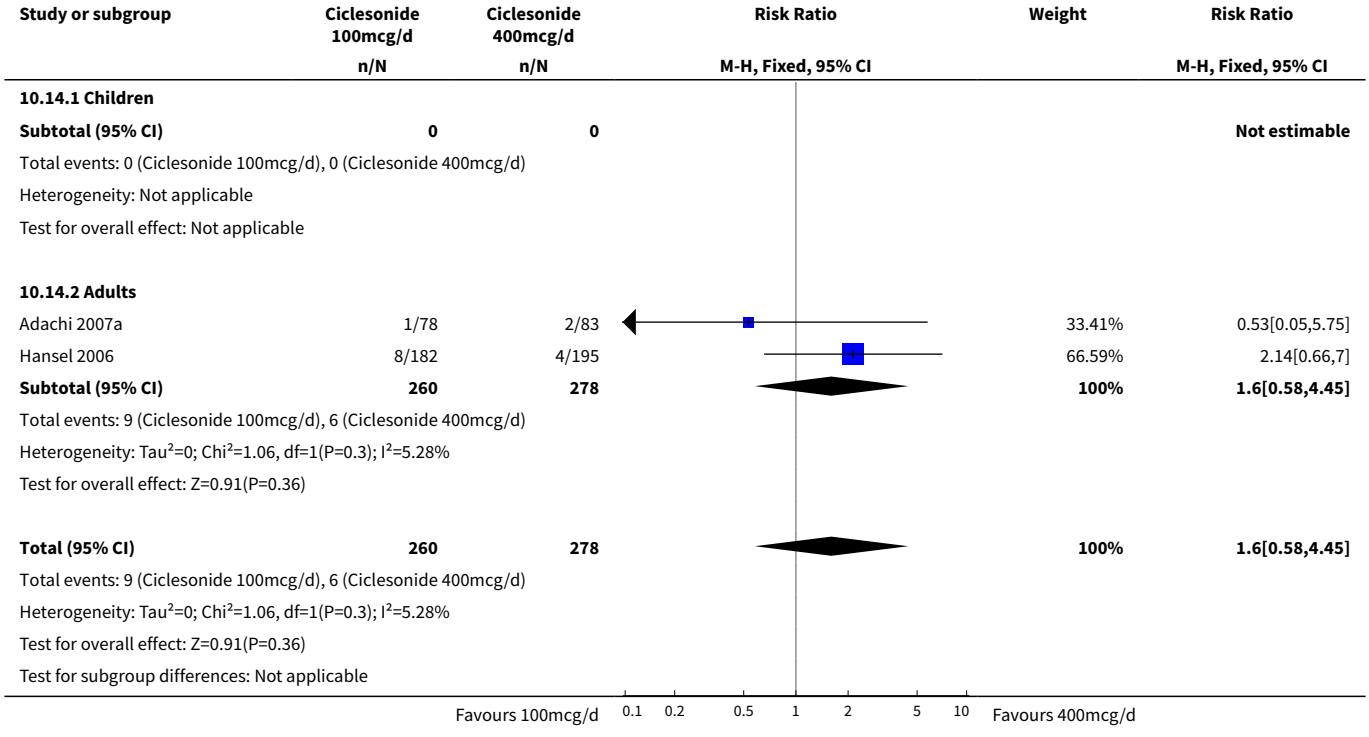
Analysis 10.12. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 12 Withdrawals.



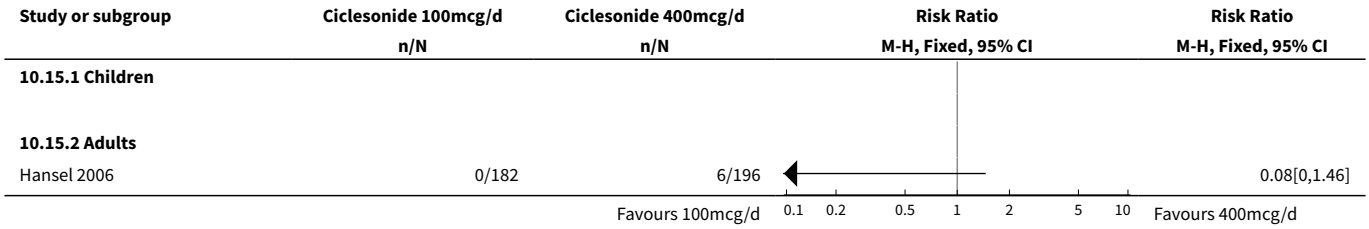
Analysis 10.13. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 13 Withdrawals (lack of efficacy).



Analysis 10.14. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 14 Withdrawals (adverse events).



Analysis 10.15. Comparison 10 Ciclesonide 100 versus 400mcg/d (ex-valve, parallel group studies), Outcome 15 Increased cough.

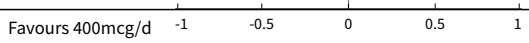


Comparison 11. Ciclesonide 200 versus 400mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	2	537	Litres (Fixed, 95% CI)	0.03 [-0.02, 0.09]
1.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	2	537	Litres (Fixed, 95% CI)	0.03 [-0.02, 0.09]
2 Change in FEV1 predicted (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in am PEF (L/min)	2	537	Litres (Fixed, 95% CI)	2.17 [-5.04, 9.38]
3.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	2	537	Litres (Fixed, 95% CI)	2.17 [-5.04, 9.38]
4 Change in FVC (L)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse events	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

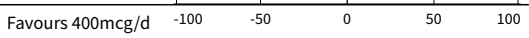
Analysis 11.1. Comparison 11 Ciclesonide 200 versus 400mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Ciclesonide 200mcg/d N	Ciclesonide 400mcg/d N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
11.1.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.1.2 Adults						
Adachi 2007a	81	83	0.1 (0.036)		62.31%	0.05[-0.02,0.12]
DFI6153	189	184	0 (0.046)		37.69%	0[-0.09,0.09]
Subtotal (95% CI)					**100%**	**0.03[-0.02,0.09]**
Heterogeneity: Tau²=0; Chi²=0.74, df=1(P=0.39); I²=0%						
Test for overall effect: Z=1.11(P=0.27)						
Total (95% CI)					**100%**	**0.03[-0.02,0.09]**
Heterogeneity: Tau²=0; Chi²=0.74, df=1(P=0.39); I²=0%						
Test for overall effect: Z=1.11(P=0.27)						
Test for subgroup differences: Not applicable						



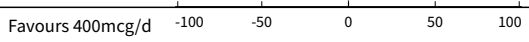
Analysis 11.2. Comparison 11 Ciclesonide 200 versus 400mcg/d (ex-valve, parallel group studies), Outcome 2 Change in FEV1 predicted (%).

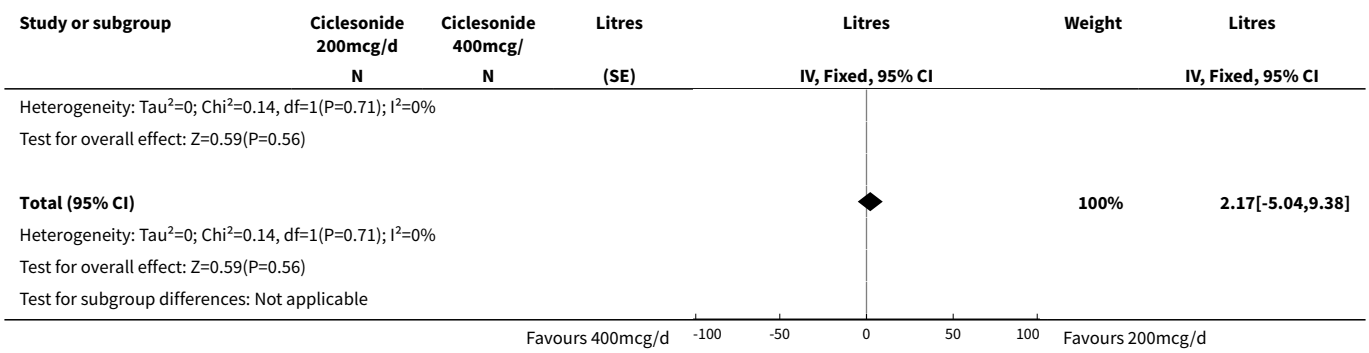
Study or subgroup	Ciclesonide 200mcg/d N	Mean(SD)	Ciclesonide 400mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.2.1 Children						
11.2.2 Adults						
Adachi 2007a	81	-0.6 (4.7)	83	-0.8 (6.7)		0.17[-1.59,1.93]



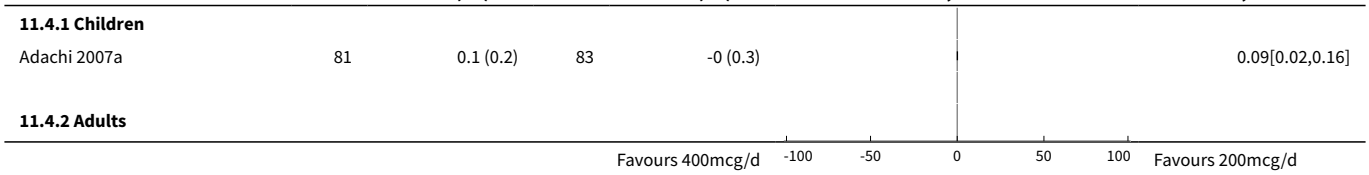
Analysis 11.3. Comparison 11 Ciclesonide 200 versus 400mcg/d (ex-valve, parallel group studies), Outcome 3 Change in am PEF (L/min).

Study or subgroup	Ciclesonide 200mcg/d N	Ciclesonide 400mcg/ N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
11.3.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
11.3.2 Adults						
Adachi 2007a	81	83	4.2 (6.418)		32.86%	4.15[-8.43,16.73]
DFI6153	189	184	1.2 (4.49)		67.14%	1.2[-7.6,10]
Subtotal (95% CI)					**100%**	**2.17[-5.04,9.38]**

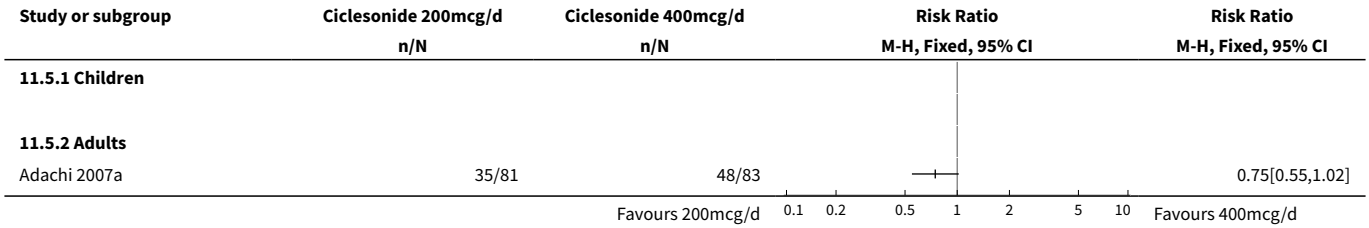




Analysis 11.4. Comparison 11 Ciclesonide 200 versus 400mcg/d (ex-valve, parallel group studies), Outcome 4 Change in FVC (L).



Analysis 11.5. Comparison 11 Ciclesonide 200 versus 400mcg/d (ex-valve, parallel group studies), Outcome 5 Adverse events.



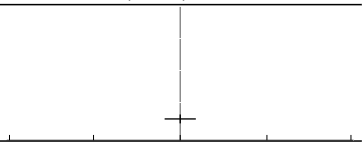
Comparison 12. Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies)

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change in FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
1.1 Children	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in am PEF	2	594	L/min (Fixed, 95% CI)	-4.78 [-11.65, 2.09]
2.1 Children	0	0	L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.2 Adults	2	594	L/min (Fixed, 95% CI)	-4.78 [-11.65, 2.09]
3 Change in pm PEF	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 clinic PEF	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 rescue medication usage (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in symp-toms	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Adverse event	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Candidiasis	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Withdrawals	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
9.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Sore throat	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]

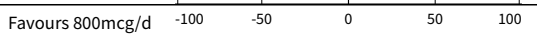
Analysis 12.1. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Ciclesonide 200mcg/d N	Ciclesonide 800mcg/d N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
12.1.1 Children					
12.1.2 Adults					
DFI6153	189	186	0 (0.046)		0[-0.09,0.09]



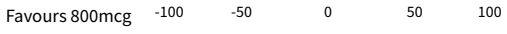
Analysis 12.2. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 2 Change in am PEF.

Study or subgroup	Ciclesonide 200mcg/d N	Ciclesonide 800mcg/d N	L/min (SE)	L/min IV, Fixed, 95% CI	Weight	L/min IV, Fixed, 95% CI
12.2.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.2.2 Adults						
Chapman 2005	107	112	-3.5 (5.607)		39.07%	-3.5[-14.49,7.49]
DFI6153	189	186	-5.6 (4.49)		60.93%	-5.6[-14.4,3.2]
Subtotal (95% CI)					**100%**	**-4.78[-11.65,2.09]**
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.77); I^2=0%						
Test for overall effect: Z=1.36(P=0.17)						
Total (95% CI)					**100%**	**-4.78[-11.65,2.09]**
Heterogeneity: Tau^2=0; Chi^2=0.09, df=1(P=0.77); I^2=0%						
Test for overall effect: Z=1.36(P=0.17)						
Test for subgroup differences: Not applicable						



Analysis 12.3. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 3 Change in pm PEF.

Study or subgroup	Ciclesonide 200mcg/d N	Mean(SD)	Ciclesonide 800mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
12.3.1 Children						
12.3.2 Adults						
Chapman 2005	107	-3.5 (0)	112	-0.7 (0)		Not estimable



Analysis 12.4. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 4 Change in clinic PEF.

Study or subgroup	Ciclesonide 200mcg/d N	Mean(SD)	Ciclesonide 800mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
12.4.1 Children						
12.4.2 Adults						
Chapman 2005	107	4.6 (0)	112	5.2 (0)		Not estimable

Favours 800mcg -100 -50 0 50 100 Favours 200mcg

Analysis 12.5. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 5 Change in rescue medication usage (puffs/d).

Study or subgroup	Ciclesonide 200mcg/d N	Mean(SD)	Ciclesonide 800mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
12.5.1 Children						
12.5.2 Adults						
DFI6153	189	0.1 (1.6)	186	0 (1.6)		0.08[-0.25,0.41]

Favours 200mcg/d -10 -5 0 5 10 Favours 800mcg/d

Analysis 12.6. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 6 Change in symptoms.

Study or subgroup	Ciclesonide 200mcg/d N	Mean(SD)	Ciclesonide 800mcg/d N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
12.6.1 Children						
12.6.2 Adults						
DFI6153	189	0.2 (1)	186	0 (1)		0.15[-0.05,0.35]

Favours low dose -10 -5 0 5 10 Favours high dose

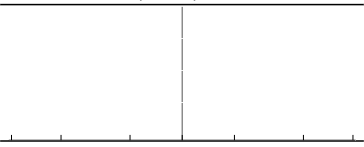
Analysis 12.7. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 7 Adverse event.

Study or subgroup	Ciclesonide 200mcg/d n/N	Ciclesonide 800mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
12.7.1 Children				
12.7.2 Adults				
Chapman 2005	0/1	0/1		Not estimable

Favours 200mcg/d 0.1 0.2 0.5 1 2 5 10 Favours 800mcg/d

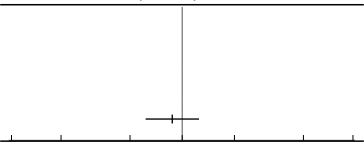
Analysis 12.8. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 8 Candidiasis.

Study or subgroup	Ciclesonide 200mcg/d n/N	Ciclesonide 800mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
12.8.1 Children				
12.8.2 Adults				
Chapman 2005	0/107	0/112		Not estimable



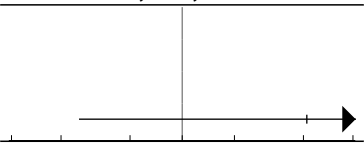
Analysis 12.9. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 9 Withdrawals.

Study or subgroup	Ciclesonide 200mcg/d n/N	Ciclesonide 800mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
12.9.1 Children				
12.9.2 Adults				
Chapman 2005	36/107	43/112		0.88[0.61,1.25]



Analysis 12.10. Comparison 12 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies), Outcome 10 Sore throat.

Study or subgroup	Ciclesonide 200mcg/d n/N	Ciclesonide 800mcg/d n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
12.10.1 Children				
12.10.2 Adults				
Chapman 2005	2/107	0/112		5.23[0.25,107.72]



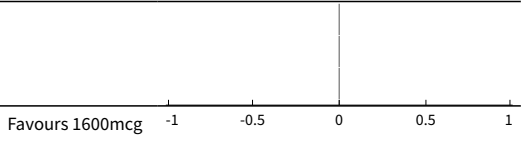
Comparison 13. Ciclesonide 200 versus 1600mcg/d (ex-valve, parallel group studies)

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change in FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
1.1 Children	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in am PEF	1		L/min (Fixed, 95% CI)	Totals not selected
2.1 Children	0		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Adults	1		L/min (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in rescue medication usage (puffs/d)	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 symptoms	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Adverse event	0		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Candidiasis	0		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Withdrawals	0		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
7.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Sore throat	0		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
8.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 13.1. Comparison 13 Ciclesonide 200 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Ciclesonide 200mcg/d N	Ciclesonide 1600mcg N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
13.1.1 Children					
13.1.2 Adults					



Study or subgroup	Ciclesonide 200mcg/d N	Ciclesonide 1600mcg N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
DFI6153	189	184	-0 (0.045)		-0.05[-0.14,0.04]

Favours 1600mcg -1 -0.5 0 0.5 1 Favours 200mcg

Analysis 13.2. Comparison 13 Ciclesonide 200 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 2 Change in am PEF.

Study or subgroup	Ciclesonide 200mcg N	Ciclesonide 1600mcg N	L/min (SE)	L/min IV, Fixed, 95% CI	L/min IV, Fixed, 95% CI
13.2.1 Children					
13.2.2 Adults					
DFI6153	189	184	-1.9 (4.515)		-1.9[-10.75,6.95]

Favours 1600mcg -100 -50 0 50 100 Favours 200mcg

Analysis 13.3. Comparison 13 Ciclesonide 200 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 3 Change in rescue medication usage (puffs/d).

Study or subgroup	Ciclesonide 200mcg N	Ciclesonide 200mcg Mean(SD)	Ciclesonide 1600mcg N	Ciclesonide 1600mcg Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
13.3.1 Children						
13.3.2 Adults						
DFI6153	189	0.3 (1.6)	186	0 (1.6)		0.31[-0.02,0.64]

Favours 200mcg -10 -5 0 5 10 Favours 1600mcg

Analysis 13.4. Comparison 13 Ciclesonide 200 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 4 Change in symptoms.

Study or subgroup	Ciclesonide 200mcg N	Ciclesonide 200mcg Mean(SD)	Ciclesonide 1600mcg N	Ciclesonide 1600mcg Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
13.4.1 Children						
13.4.2 Adults						
DFI6153	189	0.3 (1)	186	0 (1)		0.25[0.05,0.45]

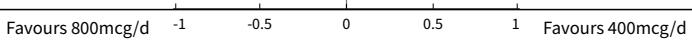
Favours 200mcg -10 -5 0 5 10 Favours 1600mcg

Comparison 14. Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	2	583	Litres (Fixed, 95% CI)	-0.06 [-0.12, 0.00]
1.1 Children	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	2	583	Litres (Fixed, 95% CI)	-0.06 [-0.12, 0.00]
2 Change in FEV1 predicted (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in FVC (L)	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 am PEF	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 pm PEF	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in rescue beta2-agonists use	2	583	Puffs/d (Fixed, 95% CI)	0.12 [-0.13, 0.37]
6.1 Children	0	0	Puffs/d (Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	2	583	Puffs/d (Fixed, 95% CI)	0.12 [-0.13, 0.37]
7 Change in high dose peak serum cortisol levels	0		mcg/dL (Fixed, 95% CI)	Totals not selected
7.1 Children	0		mcg/dL (Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	0		mcg/dL (Fixed, 95% CI)	0.0 [0.0, 0.0]

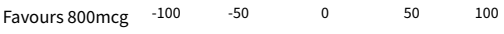
Analysis 14.1. Comparison 14 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Ciclesonide 400mcg/d N	Ciclesonide 800mcg/d N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
14.1.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
14.1.2 Adults						
Adachi 2007b	106	107	-0.1 (0.041)		55.86%	-0.1[-0.18,-0.02]
DFI6153	186	184	0 (0.046)		44.14%	0[-0.09,0.09]
Subtotal (95% CI)					**100%**	**-0.06[-0.12,0]**
Heterogeneity: $Tau^2=0$; $Chi^2=2.65$, df=1(P=0.1); $I^2=62.29\%$						
Test for overall effect: Z=1.83(P=0.07)						
Total (95% CI)					**100%**	**-0.06[-0.12,0]**
Heterogeneity: $Tau^2=0$; $Chi^2=2.65$, df=1(P=0.1); $I^2=62.29\%$						
Test for overall effect: Z=1.83(P=0.07)						
Test for subgroup differences: Not applicable						



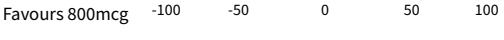
Analysis 14.2. Comparison 14 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies), Outcome 2 Change in FEV1 predicted (%).

Study or subgroup	Ciclesonide 400mcg/d N	Mean(SD)	Ciclesonide 800mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.2.1 Children						
14.2.2 Adults						
Adachi 2007b	106	-1.2 (7.1)	107	1 (5.9)		-2.21[-3.95,-0.47]



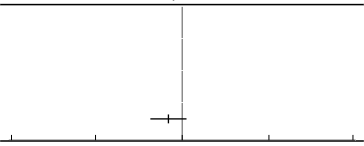
Analysis 14.3. Comparison 14 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies), Outcome 3 Change in FVC (L).

Study or subgroup	Ciclesonide 400mcg/d N	Mean(SD)	Ciclesonide 800mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.3.1 Children						
14.3.2 Adults						
Adachi 2007b	106	0 (0.3)	107	0 (0.3)		-0.01[-0.1,0.08]



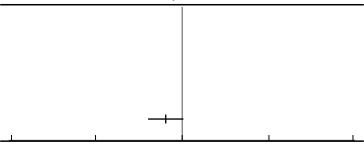
Analysis 14.4. Comparison 14 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies), Outcome 4 Change in am PEF.

Study or subgroup	Ciclesonide 400mcg/d N	Mean(SD)	Ciclesonide 800mcg/d N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.4.1 Children						
14.4.2 Adults						
Adachi 2007b	106	16 (38.9)	107	24 (38.7)		-7.96[-18.38,2.46]



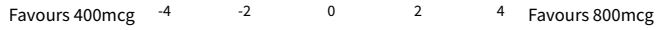
Analysis 14.5. Comparison 14 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies), Outcome 5 Change in pm PEF.

Study or subgroup	Ciclesonide 400mcg N	Mean(SD)	Ciclesonide 800mcg N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.5.1 Children						
14.5.2 Adults						
Adachi 2007b	106	9.2 (37.9)	107	18.7 (38)		-9.52[-19.71,0.67]



Analysis 14.6. Comparison 14 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies), Outcome 6 Change in rescue beta2-agonists use.

Study or subgroup	Ciclesonide 400mcg N	Ciclesonide 800mcg N	Puffs/d (SE)	Puffs/d IV, Fixed, 95% CI	Weight	Puffs/d IV, Fixed, 95% CI
14.6.1 Children						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
14.6.2 Adults						
Adachi 2007b	106	107	0.4 (0.196)		42.59%	0.43[0.05,0.81]
DFI6153	186	184	-0.1 (0.168)		57.41%	-0.11[-0.44,0.22]
Subtotal (95% CI)					**100%**	**0.12[-0.13,0.37]**
Heterogeneity: Tau^2=0; Chi^2=4.38, df=1(P=0.04); I^2=77.17%						
Test for overall effect: Z=0.94(P=0.35)						
Total (95% CI)					**100%**	**0.12[-0.13,0.37]**
Heterogeneity: Tau^2=0; Chi^2=4.38, df=1(P=0.04); I^2=77.17%						
Test for overall effect: Z=0.94(P=0.35)						
Test for subgroup differences: Not applicable						

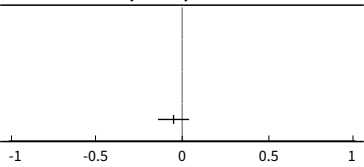


Comparison 15. Ciclesonide 800 versus 1600mcg/d (ex-valve, parallel group studies)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
1.1 Children	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in clinic PEF (%)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in symptoms	2	737	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.20, 0.08]
3.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	2	737	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.20, 0.08]
4 Change in rescue medication usage (puffs/d)	2	735	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.07, 0.37]
4.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	2	735	Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.07, 0.37]
5 Withdrawals (lack of efficacy)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5.1 Children	0		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	1		Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

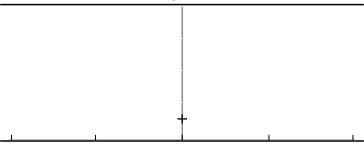
Analysis 15.1. Comparison 15 Ciclesonide 800 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 1 Change in FEV1.

Study or subgroup	Ciclesonide 800mcg N	Ciclesonide 1600mcg N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
15.1.1 Children					
15.1.2 Adults					
DFI6153	186	184	-0 (0.046)		-0.05[-0.14,0.04]



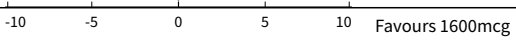
Analysis 15.2. Comparison 15 Ciclesonide 800 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 2 Change in clinic PEF (%).

Study or subgroup	Ciclesonide 800mcg N	Ciclesonide 800mcg Mean(SD)	Ciclesonide 1600mcg N	Ciclesonide 1600mcg Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
15.2.1 Children						
15.2.2 Adults						
O'Connor 2002	177	5 (12.5)	188	5 (14.6)		0[-2.78,2.78]



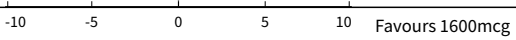
Analysis 15.3. Comparison 15 Ciclesonide 800 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 3 Change in symptoms.

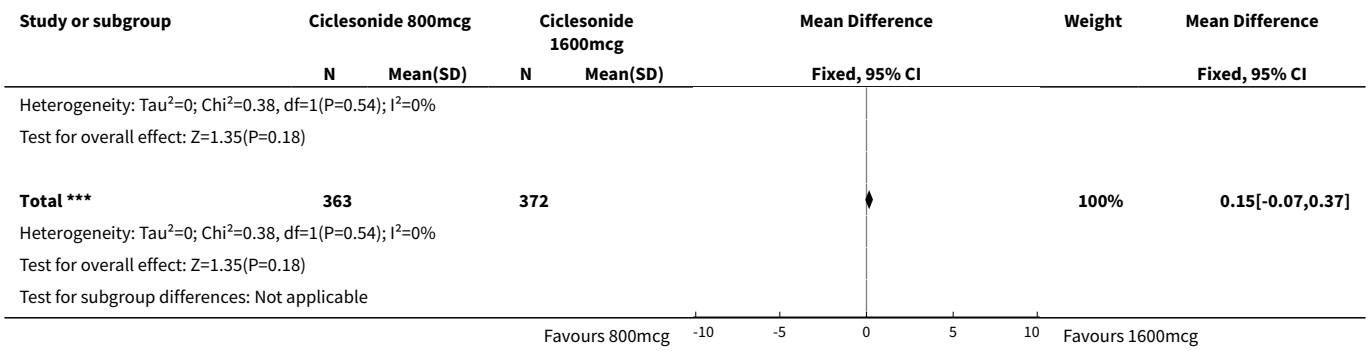
Study or subgroup	Ciclesonide 800mcg N	Ciclesonide 800mcg Mean(SD)	Ciclesonide 1600mcg N	Ciclesonide 1600mcg Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
15.3.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
15.3.2 Adults							
DFI6153	186	-0.1 (1)	186	0 (1)		50.47%	-0.1[-0.3,0.1]
O'Connor 2002	177	-0.4 (1)	188	-0.4 (1)		49.53%	-0.02[-0.23,0.18]
Subtotal ***	**363**		**374**			**100%**	**-0.06[-0.2,0.08]**
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%							
Test for overall effect: Z=0.81(P=0.42)							
Total ***	**363**		**374**			**100%**	**-0.06[-0.2,0.08]**
Heterogeneity: Tau^2=0; Chi^2=0.28, df=1(P=0.6); I^2=0%							
Test for overall effect: Z=0.81(P=0.42)							
Test for subgroup differences: Not applicable							



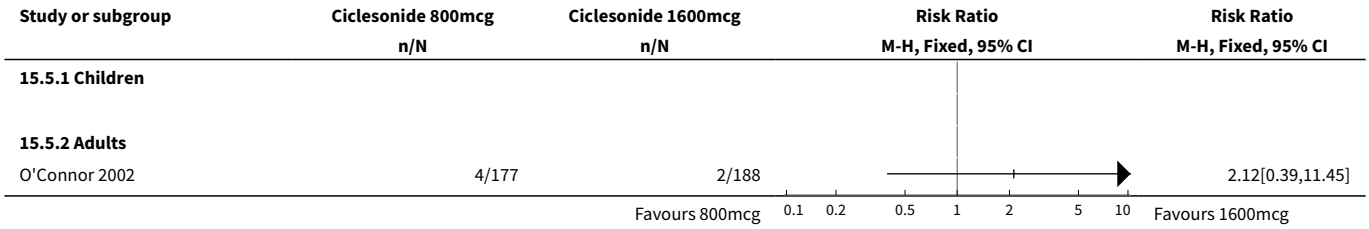
Analysis 15.4. Comparison 15 Ciclesonide 800 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 4 Change in rescue medication usage (puffs/d).

Study or subgroup	Ciclesonide 800mcg N	Ciclesonide 800mcg Mean(SD)	Ciclesonide 1600mcg N	Ciclesonide 1600mcg Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
15.4.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
15.4.2 Adults							
DFI6153	186	0.2 (1.6)	184	0 (1.6)		44.77%	0.23[-0.1,0.56]
O'Connor 2002	177	-0.3 (0.9)	188	-0.3 (1.9)		55.23%	0.09[-0.21,0.39]
Subtotal ***	**363**		**372**			**100%**	**0.15[-0.07,0.37]**





Analysis 15.5. Comparison 15 Ciclesonide 800 versus 1600mcg/d (ex-valve, parallel group studies), Outcome 5 Withdrawals (lack of efficacy).



Comparison 16. WMD archive

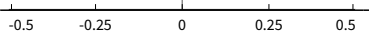
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1	9		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group trials)	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 Ciclesonide 400mcg (ex-valve, parallel group trials)	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 Ciclesonide 50 versus 100mcg/d	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 Ciclesonide 100 versus 200mcg/d	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 Ciclesonide 100 versus 400mcg/d	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 Ciclesonide 200 versus 400mcg/d	1		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
1.8 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in am PEF (L/min)	9		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)	5		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group trials)	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 Ciclesonide 400mcg (ex-valve, parallel group trials)	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 Ciclesonide 800mcg (ex-valve, parallel group trials)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Ciclesonide 100 versus 400mcg/d	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 Ciclesonide 200 versus 400mcg/d	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in pm PEF (L/min)	4		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)	4		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Ciclesonide 400mcg (ex-valve, parallel group trials)	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Ciclesonide 100 versus 400mcg/d	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Changes in cortisol levels (serum)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Ciclesonide versus placebo greater than 600mcg/d (parallel group studies)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in FVC	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

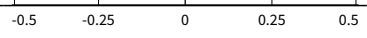
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.2 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 Ciclesonide 100 versus 400mcg/d	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in rescue 2-agonists use	5		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve parallel group studies)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group trials)	2		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 Ciclesonide 400mcg (ex-valve, parallel group trials)	3		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.4 Ciclesonide 800mcg (ex-valve, parallel group trials)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.5 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Change in asthma symptom scores	2		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies)	2		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 16.1. Comparison 16 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	Mean Difference Fixed, 95% CI
16.1.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)						
Adachi 2007a	78	-0 (0.2)	79	-0.1 (0.3)		0.14[0.05,0.23]
Gelfand 2006a	252	0.3 (0.3)	129	0.2 (0.3)		0.03[-0.03,0.09]
Gelfand 2006b	259	0.3 (0.3)	129	0.2 (0.3)		0.06[-0,0.12]
Pearlman 2005	257	0.3 (0.5)	249	0.2 (0.5)		0.11[0.03,0.19]
16.1.2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group trials)						
Adachi 2007a	81	0 (0.2)	79	-0.1 (0.3)		0.17[0.09,0.25]
Gelfand 2006a	253	0.3 (0.3)	254	0.2 (0.3)		0.07[0.02,0.12]
Pearlman 2005	250	0.3 (0.5)	249	0.2 (0.5)		0.12[0.04,0.2]
16.1.3 Ciclesonide 400mcg (ex-valve, parallel group trials)						
Adachi 2007a	83	-0 (0.3)	79	-0.1 (0.3)		0.12[0.03,0.21]
EFC6163a	150	0.1 (0.4)	74	0 (0.4)		0.14[0.04,0.24]
EFC6163b	149	0.2 (0.4)	73	0 (0.4)		0.19[0.09,0.29]

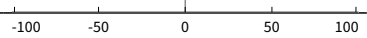


Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Pearlman 2005	250	0.3 (0.5)	249	0.2 (0.5)		0.14[0.06,0.22]
16.1.4 Ciclesonide 50 versus 100mcg/d						
Gelfand 2006a	252	0.3 (0.3)	259	0.3 (0.3)		-0.03[-0.08,0.02]
16.1.5 Ciclesonide 100 versus 200mcg/d						
Adachi 2007a	78	-0 (0.2)	81	0 (0.2)		-0.03[-0.1,0.04]
Gelfand 2006a	259	0.3 (0.3)	253	0.3 (0.3)		-0.01[-0.06,0.04]
Magnussen 2007	278	0.4 (0.5)	270	0.4 (0.5)		0.03[-0.05,0.11]
Pearlman 2005	257	0.3 (0.5)	250	0.3 (0.5)		-0.01[-0.09,0.07]
16.1.6 Ciclesonide 100 versus 400mcg/d						
Adachi 2007a	78	-0 (0.2)	83	-0 (0.3)		0.02[-0.06,0.1]
Hansel 2006	167	0.3 (0.5)	184	0.3 (0.5)		0.01[-0.08,0.1]
16.1.7 Ciclesonide 200 versus 400mcg/d						
Adachi 2007a	81	0 (0.2)	83	-0 (0.3)		0.05[-0.02,0.12]
16.1.8 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies)						
Adachi 2007b	106	-0 (0.2)	107	0.1 (0.3)		-0.1[-0.18,-0.02]

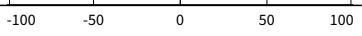


Analysis 16.2. Comparison 16 WMD archive, Outcome 2 Change in am PEF (L/min).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
16.2.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)						
Adachi 2007a	78	4.2 (42.3)	79	-24.9 (38.6)		29.18[16.51,41.85]
Gelfand 2006a	252	15 (36.5)	127	8 (44)		7[-1.88,15.88]
Gelfand 2006b	259	20 (37)	127	8 (44)		12[3.12,20.88]
Langdon 2005	120	20 (47.8)	125	0 (47.8)		20[8.04,31.96]
Pearlman 2005	257	10.9 (43.3)	249	-1.7 (42.8)		12.63[5.13,20.13]
16.2.2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group trials)						
Adachi 2007a	81	3.8 (43.2)	79	-24.9 (38.6)		28.7[16.02,41.38]
Chapman 2005	107	-4.5 (41)	110	-28 (41)		23.5[12.59,34.41]
Gelfand 2006a	253	15 (36.6)	254	8 (44)		7[-0.04,14.04]
Pearlman 2005	250	21.1 (43.3)	249	-1.2 (42.8)		22.23[14.68,29.78]
16.2.3 Ciclesonide 400mcg (ex-valve, parallel group trials)						
Adachi 2007a	83	-0.4 (38.8)	79	-24.9 (38.6)		24.55[12.63,36.47]
EFC6163a	150	7.1 (34.3)	74	0 (34.3)		7.05[-2.51,16.61]
EFC6163b	149	8.4 (34.2)	73	0 (34.2)		8.39[-1.19,17.97]
Pearlman 2005	255	17.2 (43.3)	249	-1.7 (42.8)		18.92[11.4,26.44]
16.2.4 Ciclesonide 800mcg (ex-valve, parallel group trials)						
Chapman 2005	112	-1 (42)	110	-28 (41)		27[16.08,37.92]
16.2.5 Ciclesonide 100 versus 400mcg/d						



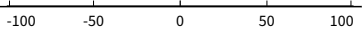
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Adachi 2007a	78	4.2 (42.3)	83	-0.4 (38.8)		4.63[-7.93,17.19]
Hansel 2006	165	12 (64.2)	188	17 (54.9)		-5[-17.55,7.55]
16.2.6 Ciclesonide 200 versus 400mcg/d						
Adachi 2007a	81	3.8 (43.2)	83	-0.4 (38.8)		4.15[-8.43,16.73]
16.2.7 Ciclesonide 200 versus 800mcg/d (ex-valve, parallel group studies)						
Chapman 2005	107	-4.5 (41)	112	-1 (42)		-3.5[-14.49,7.49]



Favours treatment — Favours control

Analysis 16.3. Comparison 16 WMD archive, Outcome 3 Change in pm PEF (L/min).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
16.3.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)						
Adachi 2007a	78	1.6 (32.7)	79	-23.3 (42.4)		24.86[13.03,36.69]
Gelfand 2006a	252	12.3 (36.1)	127	7.1 (36.2)		5.22[-2.5,12.94]
Gelfand 2006b	259	18.3 (36.4)	127	7.1 (36.2)		11.29[3.59,18.99]
Pearlman 2005	257	9.9 (40.1)	249	1.5 (40.1)		8.41[1.42,15.4]
16.3.2 Ciclesonide 400mcg (ex-valve, parallel group trials)						
Adachi 2007a	83	-2.6 (32.5)	79	-23.3 (42.4)		20.64[8.96,32.32]
Pearlman 2005	255	14.6 (39.7)	249	1.5 (40.1)		13.11[6.14,20.08]
16.3.3 Ciclesonide 100 versus 400mcg/d						
Adachi 2007a	78	1.6 (32.7)	83	-2.6 (32.5)		4.22[-5.86,14.3]



Favours placebo — Favours ciclesonide

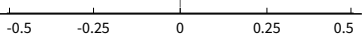
Analysis 16.4. Comparison 16 WMD archive, Outcome 4 Changes in cortisol levels (serum).

Study or subgroup	Ciclesonide N	Ciclesonide Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
16.4.1 Ciclesonide versus placebo greater than 600mcg/d (parallel group studies)						
Chapman 2005	61	475 (0)	51	463 (0)		Not estimable

Favours control — Favours ciclesonide

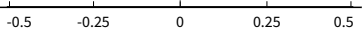
Analysis 16.5. Comparison 16 WMD archive, Outcome 5 Change in FVC.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
16.5.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve, parallel group studies)						
Adachi 2007a	78	-0 (0.2)	79	-0.1 (0.4)		0.08[-0.02,0.18]
16.5.2 Ciclesonide versus placebo 400mcg/d (ex-valve, parallel group studies)						



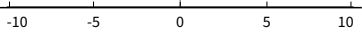
Favours control — Favours treatment

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Adachi 2007a	83	-0 (0.3)	79	-0.1 (0.4)		0.09[-0.02,0.2]
16.5.3 Ciclesonide 100 versus 400mcg/d						
Adachi 2007a	78	-0 (0.2)	83	-0 (0.3)		-0.01[-0.09,0.07]



Analysis 16.6. Comparison 16 WMD archive, Outcome 6 Change in rescue 2-agonists use.

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
16.6.1 Ciclesonide versus placebo 100mcg/d or less (ex-valve parallel group studies)						
Pearlman 2005	257	-0.9 (2.2)	249	0.4 (2.1)		-1.28[-1.66,-0.9]
16.6.2 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group trials)						
Chapman 2005	107	0 (0)	110	0.6 (0)		Not estimable
Pearlman 2005	250	-1 (2.2)	249	0.4 (2.1)		-1.44[-1.82,-1.06]
16.6.3 Ciclesonide 400mcg (ex-valve, parallel group trials)						
EFC6163a	150	-0.6 (1.4)	74	0 (1.4)		-0.6[-0.98,-0.22]
EFC6163b	149	-0.6 (1.4)	73	0 (1.4)		-0.64[-1.02,-0.26]
Pearlman 2005	255	-1 (2.1)	249	0.4 (2.1)		-1.46[-1.83,-1.09]
16.6.4 Ciclesonide 800mcg (ex-valve, parallel group trials)						
Chapman 2005	112	0 (0)	110	0.6 (0)		Not estimable
16.6.5 Ciclesonide 400 versus 800mcg/d (ex-valve, parallel group studies)						
DFI6153	184	-0.1 (1.6)	186	0 (1.6)		-0.11[-0.44,0.22]



Analysis 16.7. Comparison 16 WMD archive, Outcome 7 Change in asthma symptom scores.

Study or subgroup	Ciclesonide N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
16.7.1 Ciclesonide versus placebo 200mcg/d (ex-valve, parallel group studies)						
Chapman 2005	107	0 (0)	110	0.4 (0)		Not estimable
Pearlman 2005	250	-0.7 (1.3)	249	-0.1 (1.3)		-0.43[-0.61,-0.25]

ADDITIONAL TABLES

Table 1. CENTRAL Search Strategy

Search strategy
#1 MeSH descriptor Asthma, explode all trees in MeSH products
#2 asthma*

Table 1. CENTRAL Search Strategy *(Continued)*

#3 wheez*
#4 MeSH descriptor Bronchial Spasm, explode all trees in MeSH products
#5 bronch* near spas*
#6 bronchospas*
#7 bronchoconstrict*
#8 bronch* near constrict*
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 ciclesonide*
#11 alvesco
#12 CIC
#13 (#10 OR #11 OR #12)
#15 (#9 AND #13)

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
11 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

PM: Protocol initiation & development; study assessment & data extraction; write-up.
PG: Protocol development; review development; contact editor
TL: Protocol development; study assessment & data extraction; data entry & analysis; write-up

DECLARATIONS OF INTEREST

None known.

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)

Anti-Asthmatic Agents [*therapeutic use]; Asthma [*drug therapy]; Chronic Disease; Placebo Effect; Pregnenediones [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans