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Fluticasone at different doses for chronic asthma in adults and children (Review)

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[Intervention Review]

Fluticasone at different doses for chronic asthma in adults and children

Nick P Adams[1], Janine C Bestall[2], Paul Jones[3], Toby J Lasserson[4], Benedict Griffiths[5], Christopher J Cates[4]

[1]Respiratory Medicine, Worthing & Southlands NHS Trust, Worthing, UK. [2]Division of Physiological Medicine, St George's Hospital Medical School, London, UK. [3]Cardiovascular Medicine, St George's Hospital Medical School, London, UK. [4]Community Health Sciences, St George's, University of London, London, UK. [5]Mayday Hospital, London, UK

Contact address: Nick P Adams, Respiratory Medicine, Worthing & Southlands NHS Trust, Worthing, UK. Nick.Adams@wash.nhs.uk, nadams2002@btinternet.com.

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ABSTRACT

Background

Inhaled fluticasone propionate (FP) is a high-potency inhaled corticosteroid used in the treatment of asthma.

Objectives

1. To assess the efficacy and safety outcomes of inhaled fluticasone at different nominal daily doses in the treatment of chronic asthma.
2. To test for the presence of a dose-response effect.

Search methods

We searched the Cochrane Airways Group Trials Register (January 2008).

Selection criteria

Randomised trials in children and adults comparing fluticasone at different nominal daily doses in the treatment of chronic asthma. Two reviewers independently assessed articles for inclusion and methodological quality.

Data collection and analysis

One review author extracted data. These were checked and verified by a second reviewer. Quantitative analyses where undertaken using Review Manager.

Main results

Fifty-one published and unpublished trials (representing 55 group comparisons, 10,797 participants) met the inclusion criteria. In asthmatics with mild to moderate disease who were not on oral steroids, FP did not exhibit a dose-response effect in the lower dose comparisons in FEV1 (50mcg, 100mcg, 200mcg and 4-500mcg daily). There were no statistically significant differences between 4-500mcg and 800-1000mcg, and between 50-100 and 800-1000mcg of FP. When 200mcg was compared with 800-1000mcg daily FEV1 favoured the four/five fold increase. For PEF, a dose response was present with FP when low and moderate, and low and high doses of FP were compared. There was no evidence of a dose-response effect on symptoms or rescue beta-2 agonist use. The likelihood of hoarseness and oral candidiasis was significantly greater for the higher doses (800 to 1000 µg/day). People with oral steroid-dependent asthma treated with FP (2000 µg/day) were significantly more likely to reduce oral prednisolone than those on 1000 to 1500 µg/day (Peto odds Ratio 2.8, 95% CI 1.3 to 6.3). The highest dose also allowed a significant reduction in daily oral prednisolone dose compared to 1000 to 1500 µg/day (WMD 2.0 mg/day, 95% CI 0.1 to 4.0 mg/day).

Authors' conclusions

We have not found evidence of a pronounced dose response in FEV1 with increasing doses of fluticasone. The number of studies contributing to our primary outcomes was low. At dose ratios of 1:2, there are statistically significant differences in favour of the higher dose in morning peak flow across the low dose range. The clinical impact of these differences is open to interpretation. Patients with moderate disease achieve similar levels of asthma control on medium doses of fluticasone (400 to 500 µg/day) as they do on high doses (800 to 1000 µg/day). More work in severe asthma would help to confirm that doses of FP above 500 µg/day confer greater benefit in this subgroup than doses of around 200 µg/day. In oral corticosteroid-dependent asthmatics, reductions in prednisolone requirement may be gained with FP 2000 µg/day.

PLAIN LANGUAGE SUMMARY

Fluticasone at different doses for chronic asthma in adults and children

Fluticasone (FP) is an inhaled corticosteroid commonly used to treat inflammation of the airways (passages to the lungs) and improve breathing in people with asthma. This review examined the effectiveness of FP when given at different doses for treating asthma in children and adults. High doses (800 to 1000 microgram per day) led to small improvements in measures of airway opening compared to low doses (50 to 100 microgram per day) in people with mild to moderate asthma. High dose FP did not lead to clear improvements in symptoms over the lower dose and increased the risk of a hoarse voice and fungal mouth infections. In people with severe asthma, very high doses FP (2000 microgram per day) appeared to allow more people on oral steroids to stop or reduce their dose of oral steroid tablets compared to lower doses of FP (1000 to 1500 microgram per day).

BACKGROUND

Fluticasone propionate (FP) is an anti-inflammatory inhaled corticosteroid (ICS) used for the treatment of childhood and adult asthma. It is licensed for use over a range of nominal daily doses and is widely used in the UK, Europe, Northern America and other areas of the world. Current asthma management guidelines produced by leading respiratory societies and organisations recommend a dose titration approach to the use of all ICSs, including FP (BTS 1997; GINA 1995; NHLBI 1997). For patients with persistent evidence of sub-optimal control as judged by frequency of symptoms, rescue bronchodilator requirement and measures of airway calibre (forced expiratory volume in one minute (FEV1), peak expiratory flow (PEF)) consideration should be given to increasing the daily dose of FP in the hope of achieving improved control. This recommendation is borne out of assuming a dose-response effect, in other words, that larger doses lead to improved measures of control. The best way of determining whether such an approach has a sound foundation is to undertake a trial in which patients are randomised to different doses of FP. The purpose of this review was, therefore, to evaluate all the available evidence from randomised trials that have compared FP at different nominal daily doses in order to assess whether a clinically relevant dose-response effect is present.

OBJECTIVES

1. To assess the efficacy and safety outcomes in studies that compared inhaled FP at different nominal daily doses for the treatment of chronic asthma in adults and children.

2. To test for the presence of a dose-response effect.

METHODS

Criteria for considering studies for this review

Types of studies

Only prospective, randomised studies were considered. Double, single and unblinded studies were eligible for inclusion. Both parallel-group design and crossover studies were considered.

Types of participants

Studies including children and/or adults with a clinical diagnosis of chronic asthma were reviewed. Participants needed to be at least two years of age or older and have a diagnosis of chronic asthma. Diagnosis based on the physician opinion alone was acceptable, as well as asthma diagnosed using objective criteria related to asthma symptoms, airway reversibility, and all bronchial hyper-responsiveness. Treatment in the setting of primary care, hospital outpatients clinics, or institutional care was considered.

Types of interventions

Inhaled fluticasone at one nominal daily dose versus fluticasone (FP) at a second nominal daily dose. Treatment periods had to be for at least one week. Delivery of FP by a metered dose inhaler (MDI) or an MDI with a chamber or dry powder inhaler (DPI) was acceptable. Studies using nebulisers were specifically excluded. Patients receiving any two interventions were acceptable, including the use of oral corticosteroids (OCS).

Types of outcome measures

Primary outcomes

The primary outcome for this review is FEV1. We have subgrouped only on this outcome, and done so for the measurement of FEV1 with the highest number of effect estimates available (mostly change from baseline in Litres).

Secondary outcomes

1. Measurements of lung function other than FEV1 (i.e. PEFR, FVC)
2. Symptoms
3. Rescue medication use
4. Health status/health related quality of life (HRQOL);
5. Exacerbations (primary care physician visits, emergency room visits, hospital admission and days loss from work or school)
6. Adverse events

Growth and measurements of bone turnover are considered in other Cochrane reviews and we do not summarise evidence for these effects of therapy here.

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, CINAHL, AMED and PsycINFO, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms:

steroid* OR glucocorticoid* OR corticosteroid* OR fluticasone OR Flixotide OR Flovent

Searches are current to January 2008

Searching other resources

1. Reference lists of all included studies and relevant narrative reviews were searched for additional RCTs.
2. The UK headquarters of GSK (manufacturers of Becotide, Becloforte and Flixotide) and the Swedish headquarters of Astra Zeneca (manufacturers of Pulmicort) were asked if they were aware of further missed trials.
3. We handsearched the GSK clinical trials register (http://ctr.gsk.co.uk) for unpublished data
4. Authors of studies were asked if they were aware of further missed trials.
5. The British Journal of Clinical Research and the European Journal of Clinical Research (journals not electronically indexed on MEDLINE or EMBASE) were hand-searched.
6. Proceedings of the British Thoracic Society (1997 to 2003), European Respiratory Society (1997 to 2003) and the American Thoracic Society (1997 to 2003) were searched for relevant trials.

Data collection and analysis

Selection of studies

The decision to exclude studies prior to full paper retrieval was made independently by two reviewers (NPA and JB). In cases of disagreement, the full text article was retrieved. Papers retrieved in full text were assessed by two reviewers independently (NPA and JB), any disagreement regarding eligibility was resolved by consensus. Two reviewers (NPA and JB) who were blinded to the author's names, institution and funding sources, independently assessed included studies for methodological quality. Data that were not available for inclusion in the meta-analysis has been listed in Table 2.

Data extraction and management

Two authors (NPA and TL) extracted data for each outcome from the published results of included trials. In the case of continuous outcomes (such as FEV1), only data from the last evaluable time point was used. Where data had to be extracted from graphical plots, an attempt was made to verify the data by contacting authors.

Assessment of risk of bias in included studies

We assessed the risk of bias for each included study according to recommendations described in the Cochrane Handbook. We have assessed the risk of bias for the generation and concealment of allocation schedules for the eligible studies, and blinding of treatment preparations. We have judged the degree of bias for each domain to be of high risk (No), low risk (Yes) or unclear risk (Unclear). Our previous approach is described in Appendix 1.

Dealing with missing data

Authors were written to (by mail, fax and/or electronic mail) in an attempt to clarify details of methods, and to request missing or incomplete outcome data. Attempts were made to send requests to correct current addresses by searching MEDLINE, EMBASE and hospital web sites for up to date contact details. Glaxo Wellcome (UK) was also approached for data concerning trials in which contact authors did not initially reply, or when authors suggested doing so. Data that were not available for inclusion in the meta-analysis have been listed in Table 2

We have imputed a number of missing standard deviations for a number of studies. Our methods for doing so are described in Table 3. We have maintained an approach consistent with the recommendations regarding imputation in the Cochrane Handbook, whereby these studies represent a small proportion of the studies included in a given outcome. We report the findings of outcomes that contain imputed estimates, but outcomes with unimputed data are also available.

Assessment of heterogeneity

We assessed heterogeneity with I square measurement. Sensitivity analysis with random effects modelling was used where this value exceeded 20%.

Data synthesis

A weighted treatment effect across trials was calculated using the Cochrane statistical package RevMan 5. For continuous outcomes, a weighted mean difference (WMD) or standardised mean difference (SMD) was calculated, as appropriate. For binary or dichotomous outcomes odds ratios (OR) were calculated. Pooled treatment effects were expressed with their 95% confidence intervals (95% CI).

A number of conditions were established a priori regarding the comparisons to be made, as follows:

1. Adult and paediatric lung function data reported as litres (i.e. FEV1 and PEF) were not combined due to the different lung volumes in these populations. Where data were presented on a % predicted scale which takes account of age, we combined paediatric and adult data.
2. Parallel and crossover trials were not pooled together.
3. Studies were categorised based on the presence or absence of regular oral corticosteroid (OCS) use at participant enrolment. It was expected that most trials with patients on regular oral steroids would use a steroid-sparing design in which daily dose of OCS was progressively reduced. In such studies the principal outcome variable is the dose of oral steroid needed to maintain asthma control. Conversely, studies in which patients were not treated with regular OCS would be more likely to have designs aimed at detecting improvements in asthma control. It would be inappropriate to combine trials with these different designs and aims

Subgroup analysis and investigation of heterogeneity

For each reported outcome, subgroup analyses have been undertaken. These are based on patient age (children or adults); treatment duration (one to four weeks, one to five months, six months or longer); delivery device (MDI or DPI); asthma severity (mild, mild-to-moderate, moderate). These analyses have been used to explore variations in treatment response according to these factors. In particular, for outcomes where heterogeneity exists between studies, subgroup analyses have been used to try to identify factors that may account for heterogeneity. These are discussed as appropriate in the following section.

RESULTS

Description of studies

Results of the search

For details of the search history see Table 4. From searches conducted in January 2008, six new studies met the inclusion criteria FLIP01; FLIP01a; FLIP39; FLTA3014; FLTA3022/FLTA3022a; Pinnas 2005. Additional unpublished data were identified from the GSK online repository of trial data for the following studies: Agertoft 1997; Allen 1998; Boner 1999; Chervinsky 1994; Dahl 1993; Kemp 2004; Katz 1998; Nathan 2000; Nelson 1999; Pearlman 1999; Lumry 2006; Peden 1998; Verona 2003.

Included studies

A total of 55 randomised group comparisons (derived from 51 studies, represented by 89 published and unpublished references) are now included in the review.

Populations

The majority of studies were multicentre trials that recruited patients from the USA, Europe and Canada. One study (Katz 1998) also included patients from Asia. Two single centre studies were conducted in Denmark (Agertoft 1997) and The Netherlands

(Hofstra 2000). Only one study (Raphael 1999) recruited patients from primary as well as a secondary care/hospital outpatient clinic setting. All other studies were conducted in secondary care. The majority of studies assessed adults, with only seven studies recruiting children.

Study Design

Two studies (Agertoft 1997; Derom 1999) were of crossover design, all others were parallel group studies. The parallel studies were of varying length. The majority were of six to 12 weeks duration. One study (Dahl 1993) lasted four weeks, two studies (Nelson 1999, Noonan 1995) were of 16 weeks, and three studies (Ind 2003; SAM40012; Verona 2003) were of six months duration. Two studies (Allen 1998; Verona 2003) lasted a year.

Interventions

A range of daily doses of FP were compared. These included less than 2-fold dose comparisons (e.g. 1000 versus 1500 mcg/d), two-fold comparisons, (e.g. 50 versus 100, 200 versus 400, 1000 versus 2000 mcg/d), four-fold dose comparisons (e.g. 200 versus 800 mcg/d) and greater than five-fold dose comparisons (e.g. 50 versus 1000 mcg/d). Ten studies (Casale 2001; Chervinsky 1994, Dahl 1993, Nathan 2000; O'Sullivan 2002; Pearlman 1997, Lumry 2006; Sheffer 1996, Wasserman 1996, Wolfe 1996) assessed three or more doses as randomised treatment arms within the same trial. One study (Peden 1998) compared two doses of FP (100 versus 200 mcg/d) administered using two different delivery devices (Diskhaler DPI and Diskus/Accuhaler DPI). Patients were randomised to receive either FP 100 or 200 mcg/d delivered via either delivery device. A number of studies also included treatment arms with either a placebo or other inhaled corticosteroid. These interventions have not been assessed in this review. Details of these interventions are provided in the notes section of the included studies table.

Delivery device

Eighteen studies used a dry powder inhaler (either Diskhaler or Diskus/Accuhaler) and 19 used a metered dose inhaler. In one study (Ayres 1995), patients were given the option of using an MDI, with or without an additional spacer/chamber device provided that this was consistently throughout the trial. In six studies (Boner 1999; Bukovskis 2002; Derom 2005; Giannini 2003; Nieto 2001; Pauwels 2002) the delivery device used was not stated.

Prior treatment with oral corticosteroids (OCS)

Three studies (FLTA3022/FLTA3022a; Noonan 1995; Nelson 1999) recruited oral steroid dependent asthmatics. Use of oral prednisolone was an inclusion criterion for all studies.

Prior treatment with inhaled corticosteroids (ICS)

In 48 studies, patients were not receiving oral steroids at enrolment. In 16 of these (Allen 1998; Ayres 1995; Chervinsky 1994; Dahl 1993; Ind 2003; Lawrence 1997; Meijer 1999; Nathan 2000; Pearlman 1997; Lumry 2006; Peden 1998, Raphael 1999; SAM40012; Verona 2003; Wallin 2003; Wolfe 1996) patients were receiving a regular ICS, however in all cases this was discontinued at the point of randomisation. In six studies, recent use of ICS was a specific exclusion criterion (Galant 1996; Hofstra 2000; Katz 1998; Kemp 2004; Noonan 1998; Sheffer 1996; Wasserman 1996). In two studies (Agertoft 1997; Boner 1999) it was unclear if any patients were receiving an ICS at the time of enrolment.

Asthma severity

Patients with a range of asthma severity were studied. Table 5 provides a breakdown of included studies according to baseline FEV_1 (% predicted), symptom frequency reported at baseline and the stated opinion of investigators regarding asthma severity. An overall approximation of severity based on these features is given, related to the current GINA 1995/NHLBI 1997 classification. In summary, six studies recruited patients with mild asthma, 11 studies recruited patients with mild to moderate asthma and 17 studies assessed moderately severe asthmatics. Three studies (Ayres 1995; Ind 2003; Verona 2003) assessed patients with moderate to severe asthma, one study (Raphael 1999) included patients with a spectrum of disease from mild to severe whilst three studies (Allen 2000; Nelson 1999, Noonan 1995) assessed severe, oral steroid dependent asthmatics. In the case of 10 studies not enough details were available to make an estimation.

Outcomes

A range of efficacy and safety outcomes was assessed. Those that have not been considered include growth assessment (Agertoft 1997, Allen 1998) and biochemical markers of bone turnover (Ayres 1995). All other outcomes were considered. A significant amount of data could not be included in the meta-analysis. This is listed in Table 2. This was requested from the authors who either did not respond or were unwilling/unable to provide it.

Excluded studies

See Characteristics of excluded studies.

Risk of bias in included studies

An overview of our judgements (high, low or unclear risk of bias) for each of three domains relating to allocation (generation and concealment), and blinding is given in Figure 1.

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

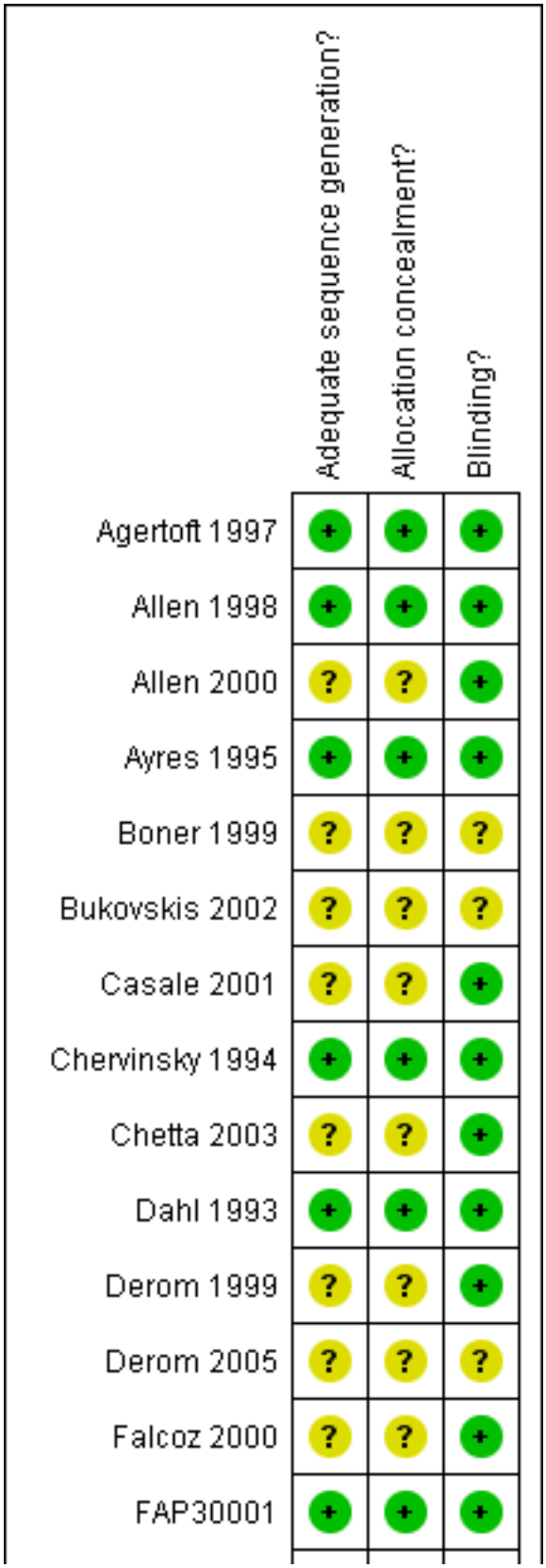


Figure 1. (Continued)

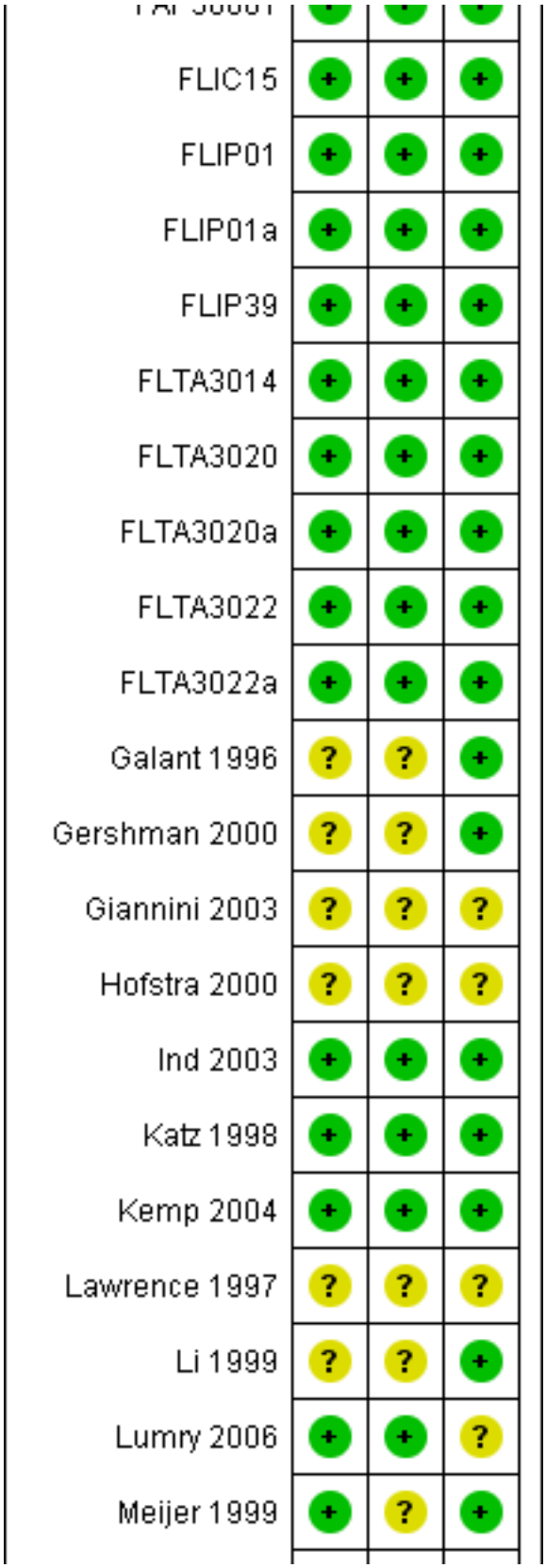
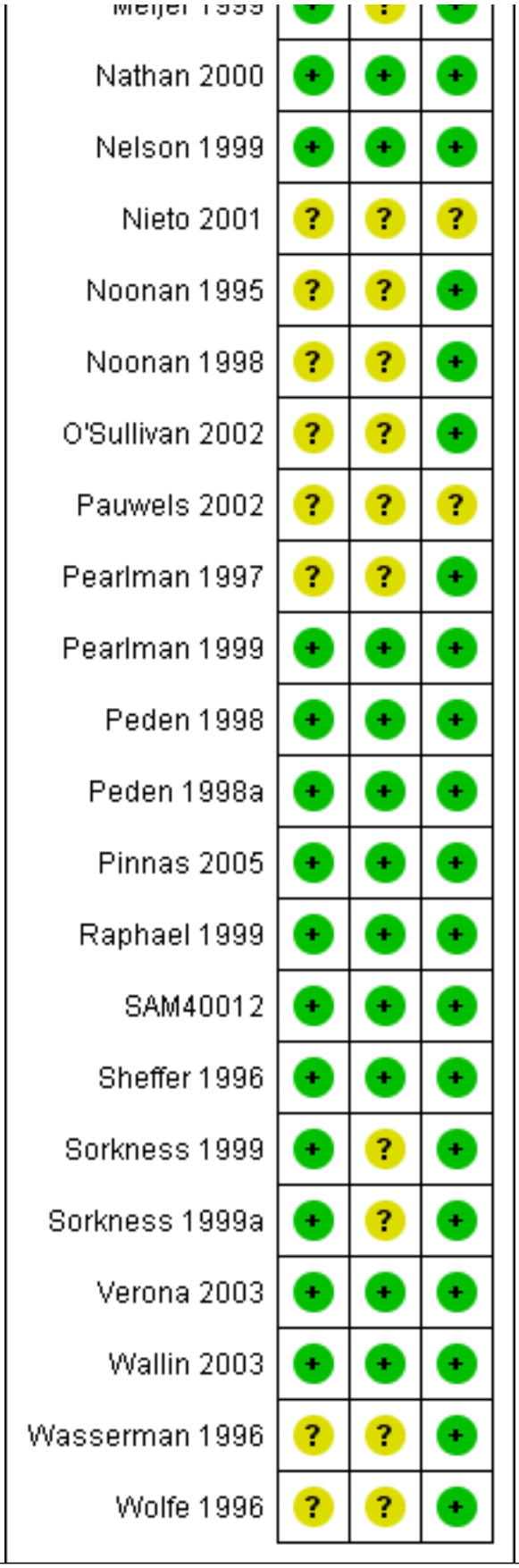


Figure 1. (Continued)



The procedures for allocating participants randomly were satisfactory, although we could not ascertain the risk of bias for this aspect of study design in 23 of 55 studies. Similarly in 25 studies we could not determine how well concealed the allocation procedures were.

Adequate masking of treatment group assignment with blinding was a common feature of the studies, as might be anticipated for trials of different doses: 46 out of 55 studies assessed different doses of FP through identical inhaler devices.

Effects of interventions

The results were grouped by the dose comparisons used. We report data for outcomes with the lower dose of FP taken to be the active treatment group, and the higher dose of FP the control group.

Efficacy measures: lower dose range comparisons

FP 50 versus 100 µg/day

A single study (Sheffer 1996) reported the results of a comparison of FP 50 versus 100 µg/day. This study assessed the effects of treatment over a 12-week period in adults with moderately severe asthma. A number of outcomes were reported including FEV1, morning PEF, asthma symptoms, night-time awakenings, rescue beta-2 agonist use and the number of patients withdrawn due to lack of efficacy. No significant differences between the two doses were apparent for any outcome.

FP 50 versus 200 µg/day

Two studies included a comparison of FP 50 versus 200 µg/day. One study (Chervinsky 1994) included adults with mild to moderate asthma who were treated for eight weeks. Sheffer 1996 recruited adults with moderate asthma who were treated over a 12-week period. A number of common outcomes were reported, all were expressed as a change compared to baseline. No significant differences between doses were apparent for FEV1, morning PEF, evening PEF, daily use of rescue beta-2 agonist or trial withdrawal due to lack of efficacy. However, there were significantly greater reductions in asthma symptom score (SMD 0.32, 95% CI 0.10 to 0.54) and number of night-time awakenings per week (WMD 0.09, 95% CI 0.02 to 0.16) with the higher dose. No heterogeneity was apparent when studies were pooled.

FP 100 versus 200 µg/day

Primary outcome

There was no statistically significant change between the lower and higher doses of FP in FEV1 in paediatric (-0.04 Litres, 95% CI -0.09 to 0.01, three studies: Analysis 3.1), or adult (0.03 Litres, 95% CI -0.02 to 0.07, six studies: Analysis 3.1) studies. The level of I square measurements were 0 for both of these outcomes.

The remaining outcomes are reported below:

Secondary outcomes

Children

The higher doses were more effective than lower doses for peak flow measurements (change in am PEF from baseline: -3.67 Litres/min, 95% CI -9.81 to 2.46, four studies: Analysis 3.8; change in pm PEF from baseline: -4.50 Litres/min, 95% CI -11.77 to 2.77, two studies: Analysis 3.9)

Adults

For adult studies, the higher doses were more effective than lower doses in improving peak flow (change in am PEF from baseline: -7.04 Litres/min, 95% CI -11.87 to -2.20, six studies: Analysis 3.8; change in pm PEF from baseline: -7.04 Litres/min, 95% CI -12.66 to -1.43, four studies: Analysis 3.9)

Outcomes pooled for adults and children

Daily symptom score: SMD 0.04 (95% CI -0.07 to 0.15), eight studies: Analysis 3.13.

Daily use of beta-2 agonist: WMD 0.14 puffs per day (95% CI -0.09 to 0.37), nine studies: Analysis 3.11

Number of night-time awakenings per week): WMD 0.05 (95% CI 0.01 to 0.1), four studies: Analysis 3.14

Night-time awakening score: SMD 0.17 (95% CI 0.04 to 0.30), 5 studies, n=921: Analysis 3.16

The number of people withdrawn due to lack of efficacy criteria (see Table 6 for studies reporting a priori defined criteria) was reported in eight studies. No significant difference between treatments was apparent (Peto OR 1.01, 95% CI 0.76 to 1.36).

Allen 1998 reported health status in 205 children with mild to moderate asthma who were randomised to receive FP 100 or 200 µg/day over a 12-month treatment period. The health status of the children was assessed using: the Functional Status IIR (FSIIR) and the Sleep-scale Children Questionnaire (SLP-C). The effect of the children having asthma on their parents' lives was evaluated using the Quality of Life of Parents of Asthmatic Children Questionnaire (QOL-PAC). No significant differences between FP doses were apparent at the 12-month time point for the FSIIR, SLP-C or any domain of the QOL-PAC.

Pearlman 1997 assessed these doses of FP over a 12-week period in adults. This study reported health status using a general instrument, the Medical Outcomes Short Form 36 (SF-36), and an asthma-specific instrument, the Living with Asthma Questionnaire (LWA-20). No significant differences between treatment groups were apparent.

FP 200 versus 400 to 500 µg/day

Primary outcome

There was no statistically significant difference between lower and higher doses of FP from 11 studies in adults (0.01 litres, 95% CI -0.04 to 0.05; Analysis 5.3). Two paediatric and two adult studies assessed FEV1 as percent predicted, with no significant difference observed between the doses (FEV1 predicted: MD -0.96% (95% CI -3.45 to 1.53), Analysis 5.1).

Secondary outcomes

Children

The lower doses were significantly less effective than higher doses for improving peak flow measurements (change in am PEF: -7.92 L/

min, 95% CI -12.93 to -2.91, two studies: Analysis 5.6; change in pm PEF: -9.36 L/min, 95% CI -14.37 to -4.35, two studies: Analysis 5.8).

Adults

For adult participants, there was no statistically significant differences between the doses compared (change in am PEF: -1.97 L/min, 95% CI -5.77 to 1.82, 11 studies: Analysis 5.6; change in pm PEF: -3.76 L/min, 95% CI -9.18 to 1.66, five studies: Analysis 5.8)

Outcomes pooled for adults and children

The 95% confidence intervals for the pooled estimates included no difference for the following outcomes:

Daily symptom score: 0.11 SMD, 95% CI -0.02 to 0.24, seven studies: Analysis 5.14

Daily use of rescue beta-2 agonist: WMD 0.18 puffs/day, 95% CI -0.08 to 0.43, seven studies: Analysis 5.11

Number of night-time awakenings per week: WMD -0.01 awakenings (95% CI -0.05 to 0.04), two studies: Analysis 5.12

Exacerbations requiring OCS: Peto OR: 1.21 (95% CI 0.72 to 2.05), two studies: Analysis 5.18

No significant differences were present when comparing doses for FVC and FEF 25 to 75 (Raphael 1999).

For the following outcomes the confidence intervals excluded no statistically significant difference in favour of the higher dose of FP:

Number of patients withdrawn due to lack of efficacy: Peto OR 1.40 (95% CI 1.01 to 2.13), seven studies: Analysis 5.17

FP 100 versus 400 to 500 µg/day

Primary outcome

No significant difference between doses was apparent for the change in FEV1 from baseline (0.01 litres (95% CI -0.09 to 0.1), three studies: Analysis 7.1. These studies were conducted in adults with moderate and mild asthma.

Secondary outcomes

The lower dose of FP was significantly less effective than the higher dose in improving morning PEF (-8 litres/min (95% CI -15 to -1), three studies: Analysis 7.3. Symptom scores also favoured higher doses (SMD 0.31 (95% CI 0.03 to 0.6), two studies: Analysis 7.6.

Middle versus higher dose range comparisons

FP 400 to 500 versus 800 to 1000 µg/day

Primary outcome

There was no significant difference between moderate and high doses of FP in the change in FEV1 (-0.01 litres, 95% CI -0.06 to 0.04), five studies: Analysis 9.1). These five studies were conducted in adults with predominantly moderate and severe asthma.

Secondary outcomes

Change in morning PEF: -2.3 litres/min (95% CI -7.94 to 3.35), four studies: Analysis 9.2

Change in evening PEF: 5.83 litres/min (95% CI -2.94 to 14.60), two studies: Analysis 9.3

Exacerbations requiring treatment with oral steroids: Peto OR 1.24 (95% CI 0.77 to 1.98), two studies: Analysis 9.9

Withdrawals due to any reason: Peto OR 1.27 (95% CI 0.88 to 1.83), five studies: Analysis 9.10

Withdrawals due to adverse events: Peto OR 0.44 (95% CI 0.17 to 1.25), four studies: Analysis 9.11

Lower versus higher dose-range comparisons

FP 50 to 100 versus 800 to 1000 µg/day

Primary outcome

There was no significant difference in the change in FEV1 predicted (WMD 0.43% predicted, 95% CI -4.87 to 5.72; 2 studies: Analysis 11.2).

Secondary outcomes

The lower doses of FP were significantly less effective than the higher doses in improving morning PEF: WMD -22 litres/min (95% CI -29 to -15, two studies: Analysis 11.8), and evening PEF: WMD -13 litres/min (95% CI -19 to -6, two studies: Analysis 11.9).

Withdrawals due to lack of efficacy: Peto OR 5.31, 95% CI 2.18 to 12.96: Analysis 11.20.

Withdrawals (any reason): Peto OR 5.29, 95% CI 1.59, 17.60: Analysis 11.19.

FP 200 versus 800 to 1000 µg/day

Primary outcome

Change from baseline in FEV1 was significantly lower with 200mcg of FP than at higher dose (-0.11 litres, 95% CI -0.19 to -0.04, three studies: Analysis 12.1).

Secondary outcomes

The higher doses of FP led to greater improvements in morning and evening PEF (8.07 litres/min (95% CI 1.61 to 14.53, four studies: Analysis 12.5*; and 8 litres/min (95% CI 1 to 15), two studies: Analysis 12.6).

No significant difference between treatment groups was apparent for the following measures; when expressed as a change compared to baseline and reported in favour of the higher dose:

Daily asthma symptom score: SMD 0.22 (95% CI -0.09 to 0.54), two studies: Analysis 12.10

Rescue beta-2 agonist use: WMD 0.11 puffs/day (95% CI -0.29 to 0.50), two studies: Analysis 12.13

Physician-rated efficacy and responses judged to be ineffective: Peto OR 1.3 (95% CI 0.9 to 2.0), two studies: Analysis 12.12.

Number of patients withdrawn due to lack of efficacy: Peto OR 1.32 (95% CI 0.73 to 2.4), four studies: Analysis 12.14

*Denotes significant heterogeneity (I2 54.5%). Random-effects modelling for this outcome resulted in a non-significant difference (WMD 8.32 litres/min, 95% CI -1.37 to 18.02). When the study

conducted in more mild participants was removed from the analysis (Chervinsky 1994), the heterogeneity resolved completely and the pooled-effect estimate was non-significant (WMD -4 litres/min, 95% CI -11.04 to 3.24). This may not be the sole reason for variation between the studies. Indeed, one area of uncertainty is the relative potency of FP using older propellants compared with the more recently developed CFC-free propellants. Lumry 2006 compared CFC-free (HFA) preparations of FP. While questions pertaining to the relative efficacy with CFC and HFA are not fully answered, there is a theoretical possibility that better deposition of the steroid particles in the small airways of the lungs enhances the potency of the drug. This would make FP more effective when propelled with HFA than older preparations of FP, especially in lower dose ranges.

Safety measures

Results were reported as the number of patients experiencing at least one of the following events during the treatment period. The following table summarises the findings for the dose comparisons that were assessed. A Peto odds ratio below one indicated fewer people with side effects at the lower FP dose.

Oropharyngeal side effects

Sore throat or pharyngitis
FP 100 versus 200 µg/day: Peto OR 1.87 (95% CI 0.71 to 4.93)
FP 200 versus 400 to 500 µg/day: Peto OR 0.98 (95% CI 0.6 to 1.63)
FP 100 versus 400 to 500 µg/day: Peto OR 1.02 (95% CI 0.29 to 3.56)
FP 200 versus 800 to 1000 µg/day: Peto OR 0.51 (95% CI 0.18 to 1.39)

Hoarseness and dysphonia
FP 100 versus 200 µg/day: Peto OR 0.65 (95% CI 0.27 to 1.57)
FP 200 versus 400 to 500 µg/day: Peto OR 0.76 (95% CI 0.4 to 1.46)
FP 100 versus 400 to 500 µg/day: Peto OR 0.28 (95% CI 0.08 to 0.92)
FP 200 versus 800 to 1000 µg/day: Peto OR 0.51 (95% CI 0.24 to 1.08)
FP 50 to 100 versus 800 to 1000 µg/day: Peto OR 0.18 (95% CI 0.05 to 0.59)

Oral candidiasis
FP 100 versus 200 µg/day: Peto OR 0.98 (95% CI 0.46 to 2.08)
FP 200 versus 400 to 500 µg/day: Peto OR 0.87 (95% CI 0.47 to 1.61)
FP 100 versus 400 to 500 µg/day: Peto OR 0.89 (95% CI 0.32 to 2.49)
FP 200 versus 800 to 1000 µg/day: Peto OR 0.33 (95% CI 0.16 to 0.70)
FP 50 to 100 versus 800 to 1000 µg/day: Peto OR 0.32 (95% CI 0.11 to 0.97)

No heterogeneity was present for any comparison. With regard to the likelihood of sore throat, there were no significant differences between FP daily doses over a wide dose range. However, higher doses were associated with a significantly greater risk of hoarseness and dysphonia. The studies comparing FP 50 to 100 versus 800 to 1000 µg/day (Chervinsky 1994; Dahl 1993) were of four and eight-weeks duration respectively. A significantly greater likelihood of hoarseness and oral candidiasis was apparent for patients treated with FP at the higher dose.

Hypothalamo-pituitary adrenal (HPA) function
Basal adrenocortical activity, as assessed by morning plasma cortisol, was reported in a number of studies (Chervinsky 1994; Dahl 1993; Lawrence 1997; Li 1999; Pearlman 1997; Peden 1998/Peden 1998a; Sorkness 1999; Sorkness 1999a; Wolfe 1996). Data were rarely presented in a form suitable for inclusion in a meta-analysis. However, no significant differences were seen in any study.

Two studies reported plasma cortisol levels following the standard short ACTH stimulation test (cortisol levels measured 30 to 60 minutes after intravenous injection of cosyntropin, 250 µg). No significant differences in levels were apparent when comparing four daily doses of FP (100, 200, 400, 800 µg/day) (Dahl 1993), or three daily doses of FP (100, 200, 500 µg/day) (Pearlman 1997).

Non-oral steroid treated asthmatics: crossover studies

Two studies (Agertoft 1997; Derom 1999) were conducted using a crossover design. No significant differences between FP doses were apparent for FEV1 or morning PEF in either study. Agertoft 1997 also reported no significant differences in evening PEF, asthma symptoms and 24-hour urinary free cortisol excretion.

Oral steroid-treated asthmatics

Oral steroid-sparing design

Two parallel group studies (Nelson 1999; Noonan 1995) were conducted in oral steroid-treated patients using an oral steroid-sparing design. Both were large, high quality (Jadad score 3 or 4) multicentre trials in adults with severe asthma and conducted in the USA. An inclusion criterion for both studies was that participants were treated with, and dependent on, oral prednisolone for asthma control at the time of enrolment. Two nominal daily doses of FP were compared in each trial: FP 1000 µg/day or 2000 µg/day (Nelson 1999) delivered via the Accuhaler DPI; and FP 1500 µg/day or 2000 µg/day delivered via MDI (Noonan 1995). The mean daily baseline dose of oral prednisolone for the two studies was 13.0 to 13.6 mg/day and 9.5 to 10.2 mg/day respectively. In both studies a high proportion of patients (> 80%) were also receiving treatment with regular inhaled corticosteroids (beclomethasone, triamcinolone or flunisolide) at enrolment, although this was not an inclusion criterion in either case. Reduction in daily dose of oral prednisolone was the primary outcome measure and both trials were of 16-weeks duration. Criteria for prednisolone dose reduction were established a priori and were based on maintenance of stable asthma control determined in relation to baseline control. This was assessed using changes in FEV1, PEF, rescue beta-2 agonist use and frequency of symptoms at clinic visits. Pooled with unpublished data (FLTA3022; FLTA3022a) there was no significant difference between the higher and lower dose of FP (FP 2000 µg/day compared with FP 1000 to 1500 µg/day) in terms of the number of participants who were able to stop OCS therapy (Peto OR 1.53, 95% CI 0.88 to 2.68). There was also no significant difference in the change in daily oral prednisolone requirement (MD 1 mg/day, 95% CI -0.45 to 2.45).

The studies were designed to maintain stable asthma control and this may explain the non-significant effects observed with random effects with moderate levels of heterogeneity for the outcomes (four studies, N = 274):
Change in FEV1 (-0.14 L (95% CI -0.32 to 0.04), I square 54.5%)
Change in am PEF (-21.17 L/min (95% CI -51 to 8.87), I square 74%)
Change in pm PEF (-21.73 L/min (95% CI -47.87 to 4.41), I square 72.1%)
Change in symptom scores (SMD 0.15 (95% CI -0.09 to 0.39), I square 34%)
Change in daily rescue medication use (-0.14 puffs/d (95% CI -1.05 to 0.78), I square 36%)

There was a low level of heterogeneity present in the analysis change in asthma quality of life questionnaire (-0.12 AQLQ units (95% CI -0.48 to 0.23), I square 5.7%).

Health status was assessed in both studies. Nelson 1999 reported the results of the Asthma Quality of Life Questionnaire (AQLQ). No significant difference between FP doses was apparent for overall score. A significant improvement in the symptoms domain that favoured the higher dose was apparent (mean difference 0.74, 95% CI 0.15 to 1.33); no significant differences between doses were seen for other domains. Significantly greater improvements in a number of domains of the Medical Outcomes Short Study Form (SF-36), a general health status questionnaire, were found for FP 2000 µg/day compared to FP 1500 µg/day by Noonan 1995. These included physical functioning and role limitations because of physical health problems. Other domains did not show any significant dose-dependent differences.

Trials not using an oral steroid-sparing design

A single study (Ayres 1995) compared FP 1000 versus 2000 µg/day over a six-week treatment period. This was a large multicentre trial in 671 adults with moderate to severe asthma and was of fair methodological quality (Jadad score 3). One in eight patients randomised to receive FP treatment were receiving oral prednisolone (< 10 mg/day) at the time or enrolment. A number of outcome measures were reported. Only the evening PEF showed a significantly greater improvement favouring higher dose FP (mean difference 7 litre/min, 95% CI 0 to 15). No significant differences between the two doses were apparent for FEV1, morning PEF, improvement in symptom-free days, or daytime/night-time rescue beta-2 agonist use. There were no significant differences between treatment groups with regard to the incidence of oropharyngeal side effects, including oral candidiasis.

DISCUSSION

We analysed data from 51 studies (yielding 55 randomised comparisons) with participants. The overall risk of bias from these trials was low. The purpose of the review was to test whether a dose-response effect is evident for fluticasone (FP), i.e. whether significantly greater improvements were present with higher as opposed to lower doses of FP. When asking such a question an important distinction needs to be made between statistically significant dose-dependent changes and those that are also of clinical significance. In a previous systematic review (Adams 2008) we assessed the efficacy and safety of FP when compared with placebo. That review was a quantitative synthesis of all the available randomised clinical trial evidence. Comparisons between active drug and placebo have the greatest likelihood of detecting clinically worthwhile improvements in asthma control and treatment-associated side effects. A significant proportion of the studies included in the current review included a placebo treatment arm and were also analysed in the previous review. As a result, the findings from that review can be considered as a benchmark whereby present findings can be better put into context. They are referred to in the following discussion, which considers dose response by outcome.

FEV1

For dose comparisons over the lower-to-middle part of the dose range (FP 50 and 400 to 500 µg/day) no dose-response effect was apparent in people who had asthma and were not receiving oral steroids. In such people, these doses of FP have been shown to produce clinically significant improvements in FEV1 compared to placebo (0.31 to 0.41 litres) (Adams 2008). A statistically significant dose-response effect was apparent when comparing high doses (800 to 1000 µg/day) to the lower dose range (200 µg/day), although additional benefit with the high dose FP was relatively small (110 mls).

Diary card peak expiratory flow (PEF)

For diary card PEF, a statistically significant dose-response effect was seen over most parts of the dose range. This was apparent when comparing the lower and middle part of the dose range. In comparison with FP 100 µg/day, FP 200 µg/day led to small improvements in morning and evening PEF. Curiously, FP 400 to 500 µg/day was not superior to 100mcg/day but was when compared with 200 µg/day in adults. Given that the difference in both comparisons was not likely to be noticeable (2 and 8 litres for 100 and 200mcg respectively), this apparent discordant finding may be attributable to differential statistical power, or may be artefactual.

When moderate doses of FP were compared with higher doses the dose-response effect was less apparent overall. There was no significant difference between FP (400 to 500 µg/day) and FP (800 to 1000 µg/day) in morning PEF. These data suggest that there is a consistent dose response when doses of FP are increased in the lower dose ranges but at higher doses of FP (400 to 500 µg/day) the dose-dependent response became less apparent.

With a four to five-fold dose increase (200 and 800 to 1000 µg/day) a greater difference favouring the higher dose was seen for both morning and evening PEF. Similarly with a ten-fold plus increase in dose of FP (50 to 100 versus 800 to 1000 µg/day).

Symptoms and rescue beta-2 agonist use

Although all daily doses of FP led to significant improvements in symptoms scores when compared with placebo (Adams 2008), no dose response effect was apparent when making comparisons of individual doses across any part of the dose range. The same pattern of response was present for rescue beta-2 agonist requirement. All daily doses of FP led to significantly greater reductions in use compared to placebo (Adams 2008) but the dose relationship for FP was flat and there was no significant difference in benefit between high (1000 µg/day) and low dose (200 µg/day).

Health status

Measures of health status were reported infrequently and did not cover the whole of the FP dose range. Where reported, however, no dose response was apparent. This included measures of child and parent well-being at doses over the lower part of the dose range, using disease specific instruments (Allen 1998) and comparisons over the lower and mid-dose range using general and disease specific instruments (Lumry 2006; Pearlman 1997).

Oropharyngeal side effects

A significant dose-response effect was apparent for the likelihood of participants experiencing oral candidiasis. This was apparent when comparing high dose FP (1000 µg/day) with low dose FP (50 to 100 µg/day): the higher the dose the greater the risk. No significant difference in likelihood was seen when comparing doses in the

lower part of the dose range. A similar picture was seen for risk of experiencing hoarseness. No dose-response effect was seen for likelihood of sore throat. This is consistent with the finding that an increased likelihood of sore throat was only apparent when the highest dose of FP was compared to placebo. Doses of 500 µg/day or less did not lead to an increased incidence of this side effect (Adams 2008).

Hypothalamo-pituitary-adrenal axis function

Measures of basal adrenal function (using morning plasma cortisol levels and 24-hour urinary cortisol excretion) and dynamic tests of adrenal reserve (post ACTH plasma cortisol levels) were reported in a number of studies. These studies covered most of the FP dose range and no differences were seen. However, non-randomised evidence does suggest that adrenal suppression has been documented as a serious side-effect of fluticasone (Tattersfield 2004).

Clinical significance and generalisability of findings

Children and adults treated with FP using a variety of dry powder and aerosol delivery devices were included in this review. Participants were treated for varying lengths of time, from four weeks up to one year. A notable feature of this analysis is that the addition of new studies increased heterogeneity in outcomes that had previously been homogeneous. This enabled us to revisit our a priori-defined subgroup analyses. Where sufficient data have been assembled, overall subgroup analyses have failed to identify groups who appeared to respond to treatment in a consistently different way. The findings appear to apply to children (over two years of age) and adults treated with all delivery devices (keeping in mind the use of nebulisers was excluded) for periods of one month up to a year. An important feature of the participants included in this analysis is that most appeared to have mild-to-moderate or moderate asthma, based on the current GINA 1995/NHLBI 1997 criteria (using the baseline characteristics of the patients, listed in Table 5). It appears that, as a population, people with mild to moderate asthma who are not receiving oral corticosteroids do not experience any further gains in terms of symptom relief or needs for rescue beta-2 agonists when doses of FP are increased above 100 µg/day. However, people can be expected to gain some incremental improvements in measures of airway function on higher rather than lower daily doses. However, these additional improvements are small and it is difficult to judge whether they are clinically worthwhile.

Current UK guidelines recommend that adults and children with asthma should be prescribed low-dose steroids if their symptoms are severe enough to warrant initiation of preventative therapy. Subsequently, if they are inadequately controlled on low-dose steroids, a trial of additive therapy, such as long-acting beta agonists, is recommended (BTS 2003), although use of LABA as a monotherapy does carry risks (Cates 2008). This is based on the assumption that dose-dependent improvements in asthma control (symptoms, exacerbations, rescue beta-2 agonist use, PEF variability) can be achieved. The findings of this review provided evidence to support this approach. However, it also suggests that most people with mild to moderate asthma achieve similar levels of control, certainly in terms of symptom relief and bronchodilator requirements, in the lower part of the dose range for fluticasone as they do when up to five-fold increases in daily doses are prescribed. The use of high-dose FP was accompanied by an increased risk of oral side effects. This needs to be borne in mind when advising patients about possible side effects and when choosing a prescribed dose.

Oral steroid-treated asthma

High-dose FP was effective in allowing people who were dependent on oral steroids and receiving inhaled steroids to reduce or stop the use of prednisolone (Adams 2008). In this group of patients, a dose-response effect was apparent for likelihood of both stopping prednisolone completely and reducing the daily dose. Very high dose FP (2000 µg/day) led to significantly greater improvements in these outcomes compared to FP (1000 to 1500 µg/day). A NNT of 6 (95% CI 3 to 25) implied that only six patients needed to be treated at the higher daily dose over 16 weeks to allow an extra patient to stop prednisolone completely compared to those treated with FP 1000 to 1500 µg/day. The highest dose of FP also allowed an additional 2 mg/day (95% CI 0.1 to 4.0 mg/day) reduction in prednisolone dose compared to FP 1000 to 1500 µg/day, in people with a baseline prednisolone use of between 9 and 14 mg/day. Such improvements may be beneficial. An interesting finding of this analysis was that a clear dose-response effect over this range was also apparent in terms of improvement in FEV1, morning PEF, evening PEF and daily asthma symptom score. In fact, the additional improvements seen for the highest dose of FP, compared to 1000 to 1500 µg/day, for these patients were substantially greater than those seen in mild to moderately severe asthmatics over a 10-fold plus increase in dose (FP 100 and FP 800 to 1000 µg/day). The explanation for this difference may lie in the fact that people with severe asthma had a greater scope for improvement in these measures, as judged by their significantly impaired baseline lung function (Table 5).

Methodological limitations

The search for trials covered a large volume of literature but it is possible that relevant, published trials were missed. However, Glaxo Smith Kline (GSK) who have the sole licence for the manufacture of fluticasone (Flixotide) and who have sponsored many of the trials included in this review only alerted us to one further study, published after the date of the last electronic search. This provided a degree of reassurance that the search strategy was effective and that no further studies were missed.

Many trials included in this review were conducted with the objective of assessing whether FP exhibits a dose-response effect. In this context, failure to detect dose differences could be interpreted as a negative finding. It is possible that relevant, negative trials exist but have not been published. Failure to include such studies could lead to a biased over-estimate of dose differences. However, this possibility seems unlikely as authors who are experts in the area and GSK did not alert us to such studies.

This review does not include data on bone turnover. Given the concerns raised about the short and long-term side-effect profile of steroids (BTS 2003), maintaining patients on the lowest possible dose is recommended in order to minimise the risk of potential adverse events without compromising asthma control.

Studies including infants under the age of two years were specifically excluded. The diagnosis of asthma and administration of inhaled medication are especially difficult in this group of

patients, so the findings of this review should not be extrapolated to this group.

FP has been licensed for use in the UK in the form of a nebulised solution. Trials using nebulisers were specifically excluded from this review and the findings from this review should not be extrapolated to the use of fluticasone using a nebuliser.

AUTHORS' CONCLUSIONS

Implications for practice

Inhaled fluticasone (FP) is an effective treatment for chronic asthma when administered over a wide range of daily doses. Although a shallow dose-response effect is evident for a number of measures of asthma control where oral steroids are not given, the findings of this review would suggest that most children and adults with mild to moderate asthma do not achieve clinically worthwhile improvements in FEV1 with higher doses (more than 500 µg/day) as compared to lower doses (up to 200 µg/day). Small increases in peak flow have been shown with higher doses of FP, but although these are statistically significant they may not be large enough to be clinically important. Severe, oral steroid-dependent asthmatics gain clinically worthwhile benefit in terms of oral steroid cessation and reduction in daily dose of prednisolone on very high doses of FP (2000 µg/day). People who cannot be weaned off oral steroids using lower doses should have a trial of FP 2000 µg/day.

Implications for research

A large number of people have been studied in the assessment of the relative efficacy of fluticasone (FP) at different doses. Clinically-relevant outcome measures related to airway calibre and symptoms have been assessed in both children and adults. However, a number of possible avenues of further research can be identified. Heath status (patient-centred evaluation of the impact of asthma on functional state) has been reported infrequently and has not been assessed over the whole of the available dose range. There is a place for further studies over the available dose range using disease-specific instruments and where clinically meaningful change scores can be established. Other important outcomes have not been assessed. These include those that have health economic significance, including hospital and primary care physician attendance rates due to clinical asthma exacerbations that necessitate additional treatment or hospital admission. Longer-term studies (six months or greater) would be needed to reliably assess these outcomes. Such trials are likely to be difficult to set up and very expensive.

The identified upper limits of the dose-response effect require some confirmatory work. In particular, the assessment of FP at doses between 400 to 500 µg/day compared with a two-fold increase in children and in more severe asthma would help to extend the validity of the evidence. In the present review the trial populations were predominantly adult populations with moderately severe asthma.

The long-term effects of different doses of FP on HPA axis and any associated risk of adrenal insufficiency are unknown. Studies that assess these risks will need to include patients treated for a number of years and will need to include many patients in order to have adequate power of detecting differences because such events are likely to be rare. Prospective RCTs will almost certainly be unable to answer these questions due to limitations of cost. Well-conducted retrospective cohort studies will probably be the only way to evaluate the differential risk, if any, of different doses of FP in terms of clinically meaningful disturbances to HPA function.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Agertoft 1997

Methods	Setting: Denmark, paediatric outpatient clinic Design: crossover, 2 week washout Length of intervention period: 2 weeks Randomisation: yes, computer generated random sequence with balanced blocks Masking: double-blind Excluded: stated (none) Withdrawals: stated (one child from low dose group due to sore throat) Baseline characteristics: comparable between groups Jadad score: 5
Participants	48 children: 27M 21F Age range: 6-12 years Inclusion criteria: Pre-pubertal children 'Mild' asthma requiring treatment with as needed beta2 agonists only Exclusion criteria: Inhaled or oral steroid use in last 2 months
Interventions	1. FP 200mcg/d 2. FP 400mcg/d Delivery device: Accuhaler DPI
Outcomes	FEV1 Morning PEFR Evening PEFR Daily asthma symptom score Daily use of beta2agonist 24 hour urinary cortisol excretion Growth by lower leg knemometry
Notes	Patients also received BUD and placebo in a randomised fashion: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated random sequence with balanced blocks
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Allen 1998

Methods	Setting: multicentre study USA, paediatric outpatient clinic Length of intervention period: 12 months Randomisation: yes, method not stated Allocation concealment: yes (randomisation code generated off site and concealed using sealed envelopes) Design: parallel group Masking: double blind

Allen 1998 *(Continued)*

	Excluded: stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	344 children enrolled, 325 randomised: 81M 244F Age range: M 4-11 years, F 4-9 years) Inclusion criteria: Pre-pubescent children with mild to moderate asthma (ATS criteria 1987) for at least 3 months FEV1 60 (% predicted) or greater Exclusion criteria: Systemic, intra-nasal or opthalmic corticosteroids in last month More than 60 days of systemic corticosteroid use in last 2 years
Interventions	1. FP 50 mcg 2xdaily (100 mcg/d) 2. FP 100 mcg 2xdaily (200 mcg/d) Delivery device: Diskhaler DPI
Outcomes	Height assessment HRQOL: Functional Status IIR (FSII) questionnaire, Sleep Scale Children (SLP-C) questionnaire, Quality of Life of Parents of Asthmatic Children Questionniare (QOL-PAC) Oral corticosteroids for asthma exacerbation (No. of courses or prednisolone) Withdrawal due to asthma exacerbation Oro-pharyngeal side effects
Notes	Authors confirmed use of allocation concealment Criteria for withdrawal due to lack of efficacy: requirement for more than two seven day courses of oral corticosteroid Placebo treatment arm also included: results not considered in this review Data available from www.clinicalstudyresults.org

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	Randomisation code generated off site and concealed using sealed envelopes
Blinding? All outcomes	Low risk	Double blind; identical inhaler devices

Allen 2000

Methods	Randomised, double-blind parallel group trial. Withdrawals: not stated. Jadad score: 2
Participants	N = 111. Distribution between groups not clear. Mean FEV1: 61% Inclusion criteria: adolescent/adult asthmatics; OCS dependent Exclusion criteria: not clear

Allen 2000 *(Continued)*

Interventions	i) FP 1000mcg BiD (2000); ii) FP500mcg BiD (1000); iii) Placebo. Inhaler device: Diskus. Study duration: 52 weeks.
Outcomes	Steroid consumption; lung function; adverse events
Notes	Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double blind; identical inhaler devices

Ayres 1995

Methods	Setting: multicentre study worldwide, hospital outpatient clinics Design: parallel group Length of intervention period: 6 weeks Randomisation: computer generated random sequence Allocation concealment: yes (central coding by pharmaceutical company sponsor) Masking: double blind Withdrawals: adverse event rates reported, unclear if any led to patient withdrawal Baseline characteristics: comparable between groups Jadad score: 3
Participants	862 adults enrolled, 671 randomised Age range: 18-70 years Inclusion criteria: Adults with a clinical history of severe asthma Requiring BDP 1-2 mg/d or BUD 0.8-1.6 mg/d BUD for asthma control During run-in period: Asthma symptom scores of 1 or more on 4 out of last 7 days and either: 1. At least 15% reversibility FEV1 post beta2 agonist or: 2. Diurnal variation in PEFR 15% or greater on 4 out of last 7 days or: 3. Need for 2 or more doses beta2 agonist each of last 7 days with either a). % predicted FEV1 80% or greater b) Mean morning PEFR 80% or greater in last 7 days Exclusion criteria: Alteration of normal asthma medication during run-in period Hospital admission due to asthma exacerbation in last month Systemic corticosteroids > 10mg daily Suspected of being steroid hypersensitive Concomitant disease likely to complicate evaluation of drug Current smokers
Interventions	1. FP 125 mcg 4 puffs 2xdaily (1000 mcg/d) 2. FP 250 mcg 4 puffs 2xdaily (2000 mcg/d) Delivery device: MDI +/- spacer
Outcomes	Outcomes reported as change compared to baseline:

Ayres 1995 *(Continued)*

	FEV1 FVC Clinic PEFR Morning PEFR Evening PEFR Diurnal variation in PEFR Symptom free days Symptom free nights Rescue beta2 agonist free days Asthma exacerbations Morning plasma cortisol Biochemical markers of bone turnover
Notes	Details concerning randomisation method provided by Glaxo Wellcome 12.5% of patients randomised to FP treatment arms receiving oral prednisolone (< 10mg/d) at the time of enrolment. No attempt was made to reduce dose in these patients Patients were given the option of using spacer device BUD treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated random sequence
Allocation concealment?	Low risk	Central coding by pharmaceutical company sponsor)
Blinding? All outcomes	Low risk	Double blind; identical inhaler devices

Boner 1999

Methods	Setting: multicentre study Europe and New Zealand Length of intervention period: 6 weeks Randomisation: yes, method not stated Allocation concealment: not stated Design: parallel group Masking: no details Excluded: no details Withdrawals: no details Baseline characteristics: no details Jadad score: 1
Participants	89 children Age range: 5-16 years Inclusion criteria: Children with asthma, no further details Exclusion criteria: No details
Interventions	1. FP 200 mcg/d 2. FP 400 mcg/d

Boner 1999 *(Continued)*

	Delivery device: no details
Outcomes	Methacholine BHR (PC20 FEV1) FEV1
Notes	Study presented in abstract form only

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Bukovskis 2002

Methods	Randomised, double-blind parallel group trial. Method of randomisation: not reported Withdrawals: not stated Jadad score: 2
Participants	N=19 (FP500: N: 10; FP100: N: 9)
Interventions	FP100 v FP500. Inhaler device not specified. Study duration: 24 weeks. Inhaler device: unclear.
Outcomes	FEV1; PD20; am/pm PEF; ß-2 agonist use; symptoms; blood eosinophils; sputum cell count;
Notes	Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Casale 2001

Methods	Multicentre, single-blind, randomised open label controlled trial. Method of randomisation not reported. Open label study with exception of flunisolide and placebo treatment groups. Withdrawals not described. Jadad score: 1

Casale 2001 *(Continued)*

Participants	N=78 (PLA: 15; FP110: 14; FP220: 12; FP330: 20; FP440: 17); Mean age (SD): PLA: 31.5 (10.09); FP110: 36.1 (8.70); FP220: 32.2 (8.66); FP330: 29.1 (8.66); FP440: 29.4 (10.20); M/F (%): PLA: 47/53; FP110: 57/43; FP220: 50/50; FP330: 40/60; FP440: 35/65; Mean FEV1 (SD): PLA: 3.0 (0.66); FP110: 3.3 (0.86); FP220: 3.2 (0.67); FP330: 3.0 (0.69); FP440: 3.2 (0.77) Inclusion criteria: non-smokers; 18-50 years; diagnosis of persistent mild to moderate asthma confirmed within previous 12 months by response to SABA (increase in FEV1 >/= 12%)/methacholine challenge <8mg/mL); FEV1 >/=65% predicted; no OCS/nasal/ICS use in previous 6 months Exclusion criteria: significant pulmonary disease (e.g. COPD); exacerbation within 6 weeks; URTI within 30 days screening; oestrogen usage; current condition that might confound data interpretation
Interventions	PLA versus FP220 versus FP440 versus FP660 versus FP880 . Study duration: 3 weeks. Inhaler device: pMDI
Outcomes	HPA function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Chervinsky 1994

Methods	Setting: multicentre study USA, hospital outpatient clinic Length of intervention period: 8 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	331 adults Mean age: 48-59 years Inclusion criteria: Mild to moderate asthma (as defined by the Committee on Diagnositic standards for Non-Tuberculous Respiratory Diseases 1962) Treatment with BDP for at least 1 month prior to study and daily beta2 agonist, or daily theophylline for at least 2 weeks prior to study FEV1 60-90 (% predicted) Exclusion criteria: Not stated
Interventions	1. FP 50 mcg 2xdaily (100 mcg/d) 2. FP 100 mcg 2xdaily (200mcg/d) 3. FP 500 mcg 2xdaily (1000 mcg/d) Delivery device: MDI

Chervinsky 1994 *(Continued)*

Outcomes	Probability of remaining in study All outcomes expressed as change compared to baseline: FEV1 FVC FEF25-75 Morning PEFR Evening PEFR Daily symptom score Daily beta2 agonist use Night awakenings Morning plasma cortisol Urinary free cortisol Plasma cortisol 60 min post ACTH Physician-rated global assessment of efficacy Oropharyngeal side-effects
Notes	No reply from author to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, morning PEFR, night-time awakenings or clinical exacerbation requiring emergency hospital treatment Placebo treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Chetta 2003

Methods	Randomised, double-blind, parallel group trial. Method of randomisation: not reported. Withdrawals: 12. Non-ITT Jadad score: 3
Participants	N=30 randomised. Data only presented on those completing the study. FP100: N=8; FP1000: N=8. Mean age (SD): FP100: 28 (8); FP1000: 26 (8); Atopic (%): 100/100; Mean duration of asthma (years): FP100: 11 (7); FP1000: 13 (9); Mean FEV1 (% predicted): FP100: 100 (SD 18); FP1000: 110 (22); Asthma severity score: FP100: 7 (2); FP1000: 6 (2). Inclusion criteria: mild to moderate asthma; well-documented history of asthma; baseline FEV1>70% predicted Exclusion criteria: exacerbations within 2 months; CS within 6 months of study; free from respiratory infections in 4 weeks prior to study

Chetta 2003 *(Continued)*

Interventions	FP100 (BID) versus FP500 (BID). Inhaler device: pMDI + spacer. Study duration: 6 weeks
Outcomes	PD20; FEV1; Mast cells; eosinophils; vessels; membrane thickness; vascular area
Notes	High attrition rate

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Dahl 1993

Methods	Setting: world-wide multicentre study, hospital outpatient clinic Design: parallel group Length of intervention period: 4 weeks Randomisation: yes, computer generated sequence Allocation concealment: yes (central coding by pharmaceutical company sponsors) Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 4
Participants	825 adults: 297M 528F Age range: 17-74 years Inclusion criteria: Adults with moderately severe chronic asthma requiring BDP 1000 mcg/d or less. During run-in period: Daytime or night-time symptoms during at least 4 days or: Diurnal variation in PEFR of 20% or more Exclusion criteria: Systemic steroids within the last month Serious concurrent disease Baseline asthma control: See inclusion criteria
Interventions	1. FP 100 mcg/d 2. FP 200 mcg/d 3. FP 400 mcg/d 4. FP 800 mcg/d Delivery device: MDI
Outcomes	Change in morning PEFR compared to baseline Change in evening PEFR compared to baseline Diurnal variation in PEFR FEV1 (% predicted) FVC % symptom free days Rescue beta2 agonist use (puffs/day) Plasma cortisol Plasma cortisol 30 mins after 250 mcg ACTH Incidence of oral candidiasis Incidence of oropharyngeal side effects
Notes	Details of randomisation method and SD values for FEV1 (% predicted) provided by Glaxo Wellcome A BDP treatment arm also included: results not considered in this review

Risk of bias

Dahl 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Derom 1999

Methods	Randomised, crossover double-blind, placebo controlled trial. Withdrawals stated. Non-ITT. Jadad score: 3
Participants	N = 23. 8F; Mean age: 33 (19-57); FEV1: 2.95 (SD 0.83) (FEV1 % predicted: 80.0 (SD 21.4)); Mean FVC: 4.42 L (SD 0.94). Inclusion criteria: either sex; 18-60 years of age; ATS defined asthma; >/=40% predicted value; Either post-BD increase in FEV1 of at least 200ml or >/=12% of baseline, OR diurnal variation of PEF >/=15% on at least 2 days/week during run-in. Exclusion criteria: Exacerbation 4 weeks before inclusion; use of oral steroids within 4 weeks; use of ICS within 6 months; other systemic steroids within 4 weeks.
Interventions	FP 200mcg; FP 1000mcg; BUD: 200mcg; BUD 800mcg; Placebo administered over 1 week. Inhaler device: DPI Concomitant therapy: IP, xanthines, sodium cromoglycate permitted provided doses kept at constant level 4 weeks prior to inclusion
Outcomes	FEV1; PEFR; Serum cortisol; White blood cell count; Neutrophils; Basophils
Notes	Data reported for effects after 24hours @ 1 week

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Derom 2005

Methods	Randomised double-blind placebo-controlled double dummy crossover trial. Jadad score: 2
Participants	N=25

Derom 2005 *(Continued)*

Interventions	FP500 versus FP1000 versus PLA; washout period: 3 weeks. Study duration: 6 treatment periods unclear duration . Inhaler device: unclear
Outcomes	Cortisol suppression; PC20
Notes	Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Falcoz 2000

Methods	Randomised, double-blind, parallel group study, Non-ITT. Jadad score 3.
Participants	N randomised = 232 (230 evaluable: FP 100mcg: 78; FP 500mcg: 79; Placebo: 73); Mean age 38 years; Participants suffered from mild-to-moderate asthma Inclusion criteria: Mild-to-moderate asthma (defined as FEV1 50-80%) Exclusion criteria: Not stated
Interventions	1) FP 100mcg 2) FP 500mcg 3) Placebo. Duration 6 weeks. Inhaler device: DPI.
Outcomes	Plasma concentrations
Notes	Data taken only for study 1. Study 2 assessed equal dose of FP given via different inhalers

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

FAP30001

Methods	Setting: multicentre study in USA Design: parallel group

FAP30001 *(Continued)*

	Length of intervention period: 26 weeks Randomisation: yes, method unclear Allocation concealment: unclear Masking: double-blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	N = 182. Mean age: 37-39. Inclusion criteria: >12 years; ATS-defined asthma; FEV1 >/=45% predicted; able to use MDI Exclusion criteria: History of life threatening asthma; systemic steroids within 6 months of study entry; immunosuppressive agents prior to study entry
Interventions	Run-in period: 1-2 weeks 1) FP HFA 220mcg bid (440mcg/d) 2) FPHFA 440mcg bid (880mcg/d) Inhaler device: MDI
Outcomes	Withdrawals Change in FEV1 % predicted Change in FEV1 Litres Change in am PEF L/min Change in pm PEF L/min Change in symptom scores Change in symptom free days Change in number of awakenings/nt Adverse events
Notes	Unpublished study downloaded from www.clinicalstudyresults.org

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

FLIC15

Methods	Setting: multicentre study in Italy Design: parallel group Length of intervention period: 4 weeks Randomisation: yes, method unclear Allocation concealment: unclear Masking: double-blind Excluded: not stated Withdrawals: stated

FLIC15 *(Continued)*

	Baseline characteristics: comparable Jadad score: 3
Participants	33 participants. Mean age 37-44 years. Inclusion criteria: M/F participants; age 18-60 years; persistent mild-moderate asthma (ATS). Exclusion criteria: Preventer medication 4 weeks prior to study entry.
Interventions	Run-in period: 2 weeks i) FP100mcg bid (200mcg/d) ii) FP500mcg bid (1000mcg/d) iii) Placebo Inhaler device: DPI
Outcomes	Withdrawals; FEV1; PEFR; FVC
Notes	Unpublished study downloaded from www.clinicalstudyresults.org

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

FLIP01

Methods	Setting: multicentre study in Belgium, Netherlands, Germany, Switzerland Design: parallel group Length of intervention period: 5 weeks Randomisation: yes, method unclear Allocation concealment: unclear Masking: double-blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	110 participants - age not reported Inclusion criteria: Moderate asthma (no steroids)
Interventions	i) FP 50mcg/d ii) FP 100mcg/d iii) FP 200mcg/d iv) BDP 100mcg/d

FLIP01 *(Continued)*

	v) BDP 200mcg/d Inhaler device: MDI
Outcomes	Withdrawals; am & pm PEF; symptoms; adverse events
Notes	Unpublished study

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

FLIP01a

Methods	As Above
Participants	As above
Interventions	As above
Outcomes	As above
Notes	Unpublished study

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	As for FLIP01
Allocation concealment?	Low risk	As for FLIP01
Blinding? All outcomes	Low risk	As for FLIP01

FLIP39

Methods	Setting: multicentre study in Europe Length of intervention period: 12 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated

FLIP39 *(Continued)*

	Baseline characteristics: comparable Jadad score: 3
Participants	196 children. Median age: 10 (6-17) Inclusion criteria: 6-16 years of age; established history of childhood asthma; perennial symptoms requiring treatment with up to 400mcg/d ICS; history of recurrent episode of bronchoconstriction or cough; and >/=10% reversibility in FEV1 post-SABA; Prior to randomisation, participants were required to show two fo the following in last 12 days of run-in period: mean of 4 lowest PEFR </=85% predicted or mean PEFR </=95% predicted; ii) diurnal variation in PEFR at least 20% on >/=4 days; iii) asthma symptoms on >/=4 days; iv) bronchodilator use on at least 2 of 4 days. Exclusion criteria: systemic CS in previous 4 weeks/run-in or on >3 times in last 6 months; acute lower RTI in last 14 days that would affect baseline lung function/symptoms
Interventions	2 week run-in period (200mcg/d BDP) followed by randomisation to: 1. FP 50mcg BID (100mcg/d) 2. FP 100mcg BID (200mcg/d) Inhaler device: DPI
Outcomes	am PEF pm PEF clinic PEF FEV1 Assessment of efficacy Symptoms Rescue medication usage Adverse events Withdrawal
Notes	Sourced from http://ctr.gsk.co.uk

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

FLTA3014

Methods	Setting: 21 centres in USA Length of intervention period: 26 weeks Randomisation: yes, method not described Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable

FLTA3014 *(Continued)*

	Jadad score: 3
Participants	379 adults and adolescents. Mean age: 37-39 Inclusion criteria: >/=12 years; 6 month history of asthma requiring pharmacotherapy; FEV1 50-85%; use of SABA and/or ICS
Interventions	1. FP 100mcg BID (without spacer) 2. FP250mcg BID (with spacer) 3. FP250mcg BID (without spacer) 4. Placebo (with or without spacer) Inhaler device: MDI
Outcomes	FEV1; am PEF; pm PEF; withdrawals; SABA usage; symptoms; adverse events; withdrawals
Notes	Sourced from http://ctr.gsk.co.uk

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

FLTA3020

Methods	Setting: 25 centres in USA Length of intervention period: 12 weeks Randomisation: yes, method not described Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	191 adults and adolescents Mean age: 31-36 years. Inclusion criteria: >/=12 years; 6 month history of asthma requiring pharmacotherapy; FEV1 50-85%; use of SABA and/or ICS; pre-BD FEV1% predicted 60-90%; SABA prn or regular use only; effective use of MDI. Exclusion criteria: ICS within 30 days of screening; hospitalisation due to asthma on 2+ occasions in 12 months prior to screening; significant other medication within 30 days of screening
Interventions	1. HFA-FP 110mcg BID

FLTA3020 *(Continued)*

	2. HFA-FP 220mcg BID 3. CFC-FP 110mcg BID 4. CFC-FP 220mcg BID 5. Placebo Inhaler device: MDI
Outcomes	FEV1; am PEF; pm PEF; withdrawals; symptoms; rescue medication usage; adverse events
Notes	Sourced from www.clinicalstudyresults.org

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

FLTA3020a

Methods	As above
Participants	As above
Interventions	As above
Outcomes	As above
Notes	As above

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	As for FLTA3020
Allocation concealment?	Low risk	As for FLTA3020
Blinding? All outcomes	Low risk	As for FLTA3020

FLTA3022

Methods	Setting: 39 centres in USA Design: parallel group Length of intervention period: 16 weeks (plus 2 week run-in)

FLTA3022 *(Continued)*

	Randomisation: yes, method not described Masking: double-blind (identical devices) Excluded: not stated Withdrawals: stated (placebo: 22; FP440hfa bid: 6; FP880hfa bid: 13; FP440cfc bid: 6; FP880cfc bid: 8) Baseline characteristics: comparable between groups Jadad score: 4
Participants	168 adolescents/adults: 78M/90F Age range: >12 (mean age: 50 years) Inclusion criteria: 12 years of age or older FEV1 40-85 (% predicted); oral steroid dependent asthma Exclusion criteria: History of life-threatening asthma; 3 or more hospitalisations in past year; therapy with antileukotrienes, nedocromil and/or ipratropium bromide within 4 weeks of randomisation
Interventions	1. FP440mcg CFC bid 2. FP880mcg CFC bid 3. FP440mcg HFA bid 4. FP880mcg HFA bid 5. Placebo Inhaler device: MDI
Outcomes	Oral steroid reduction FEV1 am PEF pm PEF Symptoms Rescue medication usage AQLQ Withdrawals Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

FLTA3022a

Methods	As above
Participants	As above
Interventions	As above
Outcomes	As above

FLTA3022a *(Continued)*

Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	As for FLTA3022
Allocation concealment?	Low risk	As for FLTA3022
Blinding? All outcomes	Low risk	As for FLTA3022

Galant 1996

Methods	Setting: multicentre study USA, hospital outpatient clinic Length of intervention period: 12 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 4
Participants	353 adolescents/adults: 236M 117F Age range: 12-75 years Inclusion criteria: 12 years of age or older FEV1 45-75 (% predicted) 15% or greater reversibility in FEV1 after inhaled beta2 agonist Significant asthma symptoms during run-in period: e.g. daily asthma symptoms with > 8 puffs beta2 agonist/day or 2- 4 weekly nighttime awakenings due to asthma Exclusion criteria: History of life-threatening asthma Smokers of 10 pack years or greater Previous use of inhaled, oral, injectable or intra-nasal corticosteroids Pregnancy
Interventions	1. FP 25 mcg 2 puffs 2xdaily (100 mcg/d) 2. FP 50 mcg 2 puffs 2xdaily (200 mcg/d) Delivery device: MDI
Outcomes	Probability of remaining in study All outcomes expressed as change compared to baseline: FEV1 Morning PEFR Daily use of beta2 agonist Daily asthma symptom score Night-time awakenings per week 'Effective or very effective' Physician rated global assessment of efficacy (No. of patients) Oropharyngeal side effects
Notes	No reply from author to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported

Galant 1996 *(Continued)*

	A priori criteria for withdrawal due to lack of efficacy were established based on diurnal variability in PEFR, night-time awakenings, rescue beta2 agonist use and FEV1 Placebo treatment arm also included: results not considered in this review Study also included an oral theophylline treatment arm: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Gershman 2000

Methods	Randomised, double-blind, single dummy, parallel group study. Participants randomised according to their entry in to the treatment phase. 2 participants withdrew from the low dose FP. ITT population Jadad score: 3
Participants	N = 24 (FP1000mcg group: 12; FP100mcg group: N = 12. FP1000: 3F/9M; FP100: 12M). 23/24 atopic asthma. Mean FEV1 (% pred): FP1000 group: 69; FP100 group: 66; FEF25-75%: FP1000 group: 1.87 (SEM 0.17); FP100 group: 2.18 (SEM 0.22); PC20: FP1000 group: 0.95 (0.1 to 11.2); FP 100 group: 0.63 (0.3 to 2.5); ECP ng/mL: FP 1000 group: 84 (24 to 165); FP 100 group: 154 (24 to 282)
Interventions	FP100mcg daily versus FP1000mcg daily. Duration: 6 weeks. Inhaler device: MDI+spacer
Outcomes	Lung function (FEV1; PEF; FEF); PC20; ECP; Symptoms
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Giannini 2003

Methods	Randomised, double-blind parallel group study. Method of randomisation: Not reported. Withdrawals: No withdrawals occurred. Jadad score: 3

Giannini 2003 *(Continued)*

Participants	N=27. Mean age: 38.67 (SD 16.97). M/F: 15/12; history of atopy: 18/6; FEV1: 3.23 (SD 0.91); FEV1 % predicted (median (range)): 96 (76-122); PD20: 0.220 Inclusion criteria: diurnal/nocturnal symptoms=0, low PEF variability [maximal amplitude(-MA) <10%). Exclusion criteria: no use of ß-agonists throughout run-in
Interventions	FP100 versus FP250 versus PLA. Inhaler device: unclear
Outcomes	FEV1; PD20; Sputum eosinophils; max amplitude; PEF; Symptoms; Rescue medication use
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Hofstra 2000

Methods	Randomised, double-blind, placebo-controlled, 3-arm parallel group trial. Methods of randomisation: not reported. ITT population Jadad score: 2
Participants	N = 37 (PLA: 12; FP100: 11; FP250: 14); Age: PLA: 9.8 (SD 2.4); FP100: 9.9 (SD 1.6); FP250: 11.1 (SD 2.4); FEV1 (% predicted): PLA: 92.1 (SD 12.5); FP100: 96.6 (SD 6.9); FP250: 93.2 (SD 13.3) Exclusion criteria: ICS use in last 4 months
Interventions	Inhaled FP100 BID (200mcg/d)versus inhaled FP250 BID (500mcg/d) versus placebo, via MDI with a volumatic spacer Duration: 6 weeks (FP100 versus FP250 versus PLA); subsequent 12 weeks, PLA group re-allocated at random to FP100 or FP250 group. Data extracted up until 6 weeks (subsequent time points have data from participants who had been treated with PLA for preceding 6 weeks)
Outcomes	FEV1 (% predicted); EIB; PD20
Notes	Patients were randomised to receive FP or placebo and treated for 6 weeks. After 6 weeks patients receiving placebo were re-randomised to either dose of FP for a further 18 weeks. Placebo treatment arm also included: results not considered in this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available

Hofstra 2000 *(Continued)*

Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Ind 2003

Methods	Setting: multicentre study Canada, Denmark, Iceland, Italy, UK Length of intervention period: 24 weeks Randomisation: yes, not reported Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	496 adults 266 F; 230M Age range: 16-75 years Inclusion criteria: 16-75 years Requirement for high dose BDP Poor control Two exacerbations in past year requiring a change of therapy Symptomatic (assessed during run-in)
Interventions	i) FSC (not covered in this review) ii) FP 500mcg/d iii) FP 1000mcg/d Inhaler device: MDI
Outcomes	Withdrawals (n) am PEF pm PEF Exacerbations Symptoms Relief medication usage Clinic FEV1 Clinic FVC Physician assessment of effectiveness (n) Subjects assessment of effectiveness (n) Adverse events (n)
Notes	Unpublished trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices used

Katz 1998

Methods	Setting: multicentre study, Europe, Middle East and Asia, hospital outpatient clinics Length of intervention period: 12 weeks Randomisation: yes, method not stated Allocation concealment: unclear

Katz 1998 *(Continued)*

	Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	263 children: 166M 97F Age range: 4-11 years Inclusion criteria: Diagnosis of asthma (not otherwise defined) Recurrent episodes of bronchoconstriction and cough Able to use delivery device and peak flow meter satisfactorily PEFR 75 (% predicted)or less, or PEFR 75-90 (% predicted) with asthma symptoms during run-in period Exclusion criteria: Treatment with inhaled corticosteroids within last 3 months Oral steroids in last month Continuous treatment with oral steroids over 2 months or more in past Hospital admission due to asthma in last 3 months
Interventions	1. FP 50 mcg 2 x daily (100 mcg/d) 2. FP 100 mcg 2 x daily (200 mcg/d) Delivery device: Diskhaler DPI
Outcomes	Outcomes expressed as change compared to baseline: FEV1 FVC FEF 25-75 Morning PEFR Evening PEFR Daily asthma symptom score Night-time wakening score Daily use of beta2 agonists Probability of remaining in study
Notes	Reply from author but unable to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, PEFR, sleep disturbance or rescue beta2 agonist use Placebo treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices used

Kemp 2004

Methods	Setting: multicentre study, USA Length of intervention period: 2 years Randomisation: yes (randomisation code generated off-site) Allocation concealment: adequate Design: parallel group Masking: double blind (identical) Excluded: yes Withdrawals: stated Jadad score: 5

Kemp 2004 *(Continued)*

Participants	190 adults and adolescents screened, 160 randomised (three arm study; PLA: N = 54; FP400: N = 55; FP1000: 51), Age range: 18-50; Mean baseline FEV1 (% predicted): PLA: 83; FP100: 82; FP500: 85 Inclusion criteria: 18-50 years (F: 18-40); mild asthma (6 months); FEV1: 50-100% predicted Exclusion criteria: Significant co-morbidity of bone; alterations in body weight; reversal of nocturnal sleeping hours; substance abuse
Interventions	FP200 BID (400) versus FP1000 BID (1000) versus PLA. Inhaler device: MDI
Outcomes	Bome mineral density; withdrawals; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	Randomisation code generated off-site
Blinding? All outcomes	Low risk	Idenitcal inhaler devices

Lawrence 1997

Methods	Setting: multicentre study USA, hospital outpatient clinics Length of intervention period: 6 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind, double dummy Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 4
Participants	261 adults Age range: 18-71 years Inclusion criteria: Diagnosis of asthma (ATS criteria 1987) Treatment with ICS for 3 months or longer Treatment with BDP 336 mcg/d or TA 800 mcg/d at stable dose for 2 weeks FEV1 50-80 (% predicted) 15% or greater reversibility in FEV1 after inhaled beta2 agonist Exclusion criteria: Systemic, intra-nasal or opthalmic corticosteroids in last 2 months Oral corticosteroids for > 2 months in last 6 months Pregnancy
Interventions	1. FP100 mcg 2xdaily (200 mcg/d) 2. FP 500 mcg 2xdaily (1000 mcg/d) Delivery device: Diskhaler DPI
Outcomes	Probability of remaining in study Outcomes expressed as change compared to baseline: FEV1 Morning PEFR Daily asthma symptom score Daily use of beta2 agonist Morning plasma cortisol Oro-pharyngeal side effects
Notes	No reply from author to clarify details of randomisation method

Lawrence 1997 *(Continued)*

	Results for continuous outcomes expressed as change to endpoint (point of withdrawal) A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, morning PEFR, night-time awakenings or clinical exacerbation requiring emergency hospital treatment Placebo treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Li 1999

Methods	Randomised, double-blind, triple dummy, placebo-controlled trial. Methods of randomisation not reported. Withdrawals: Placebo: 0; FP88: 1; FP220: 1. Non-ITT. Jadad score: 4
Participants	N = 128 (N for treatments considered by this review: 63; Placebo: 17; FP88: 22; FP220: 24). M/F ratio (%): PLA: 82/18; FP88: 68/32; FP220: 58/42; Mean age (range): PLA: 31 (19-41); FP88: 30 (19-42); FP220: 33 (18-53); Ethnic origin (%) (White/Other): PLA: 94/6; FP88: 95/5; FP220: 88/13; FEV1 % Predicted: PLA: 89.1; FP88: 82.5; FP220: 88.2; Concurrent medication: Salmeterol: PLA: 0; FP88: 0; FP220: 1; Theophylline: PLA: 2; FP88: 0; FP220: 3; Cromolyn: PLA: 0; FP88: 1; FP220: 1; Nedocromil: PLA: 0; FP88: 0; FP220: 1 Inclusion criteria: Non-smokers; asthma according to ATS criteria; duration of disease >6 months; FEV1 >/=50% predicted Exclusion criteria: Pregnancy/lactation; use of methotrexate/gold salts; use of inhaled cromolyn/nedocromil; use of oral, intranasal, inhaled or injectable steroids <4 weeks of study commencement; use of >/= 140mg prednisone or equivalent dosage in past year; significant concomitant illness; immunotherapy requiring change in dosage regimen within 12 weeks; reversal of nocturnal sleeping hours; concurrent use of over-the-counter medication that might affect course of asthma or interact with sympathomimetic amines or confound cortisol assay
Interventions	FP88 versus FP220 versus Placebo. Inhaler device: pMDI + spacer. Duration: 28 days.
Outcomes	HPA axis function; plasma concentration; area under the curve; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available

Li 1999 *(Continued)*

Blinding? All outcomes	Low risk	Identical inhaler devices

Lumry 2006

Methods	Randomised, double-blind, parallel group study. Method of randomisation: not reported; blinding: not reported. Withdrawals - Last observation carried forward. Missing: PLA: 2; FP88 BID: 3; FP220 BID: 1; FP440 BID: 2 Jadad score: 3
Participants	N=415 (PLA: 104; FP172: 103; FP440: 106; FP880: 102); Mean FEV1 % predicted: PLA: 65.6; FP172: 65.3; FP440: 65.5; FP880: 66.2; mean am PEF (l/min): PLA: 346; FP172: 334; FP440: 329; FP880: 333.1 Inclusion criteria: >/=12 years; asthma for >6 months requiring tx with ICS for >/=3 months; FEV1: 45-80% predicted; >/=12% reversibility Exclusion criteria: not reported
Interventions	HFA FP88 BID (172 mcg/d) versus HFA FP220 BID (440) versus HFA FP440 BID (880). Study duration: 12 weeks. Inhaler device: MDI
Outcomes	am PEF; FEV1 (% predicted)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Unclear risk	Identical inhaler devices used

Meijer 1999

Methods	Randomised, double-blind, double-dummy parallel group trial. Method of randomisation: computerised minimisation method. Participants stratified according to age, previous dose of ICS, FEV % pred, reversibility to 200mcg sal, smoking status, serum IgE and PC20 methacholine. ITT population (all participants who contributed one reading). ICS tapered down at least 3 weeks prior to randomisation. If symptoms deteriorated during tapering phase thy were asked to present earlier for randomisation. Jadad score: 4
Participants	N = 120 (Prednisolone: 40; FP2000: 40; FP500: 40;); Median age: Prednisolone: 28 (18-53); FP2000: 27 (18-48); FP500: 27 (18-56); M/F: Prednisolone: 14/26; FP2000: 14/26; FP500: 13/27; Smokers (%) (Current:Ex-smoker:Non-smoker): Prednisolone: 28:23:49; FP2000: 31:15:54; FP500: 28:23:49; FEV1 (% predicted): Prednisolone: 80 (65 to 91); FP2000: 79 (67 to 91); FP500: 81 (70 to 96); Reversibility (% pred): Prednisolone: 12 (9.2 to 17.8); FP2000: 11.4 (9 to 17.2); FP500: 12.3 (9.2 to 14.4); Log2 PC20 methacholine (mg/ml): Prednisolone: -0.86 (0.36); FP2000: -0.83 (0.37); FP500: -0.83 (0.36); Log2 PC20 AMP (mg/ml): Prednisolone: 1.89 (0.56); FP2000: 3.02 (0.54); FP500: 2.59 (0.67); IgE (IU/ml): Prednisolone: 251 (157 to

Meijer 1999 *(Continued)*

	615); FP2000: 251 (85 to 550); FP500: 181 (97 to 631); Blood eosinophils (%): Prednisolone: 5.8 (3.6 to 8.0); FP2000: 5.0 (4.0 to 6.8); FP500: 5.1 (2.8 to 7.9); Sputum eosinophils (%): Prednisolone: 5.5 (2.0 to 14.7); FP2000: 5.0 (1.0 to 8.0); FP500: 5.0 (1.67 to 12); Serum ECP (mcg/l): Prednisolone: 19.5 (10.4 to 26.8); FP2000: 13.3 (9.9 to 22); FP500: 17.1 (9.3 to 24.9); Serum ECP Prednisolone (mcg/l): 78.4 (28 to 292); FP2000: 73.6 (33 to 250); FP500: 95.8 (46 to 233); Serum cortisol (nmol/l): Prednisolone: 420 (302 to 563); FP2000: 425 (320 to 725); FP500: 445 (265 to 740). Inclusion criteria: 18-56 years; diagnosis of asthma; concentration of methacholine causing 20% fall in FEV1 (PC20) of 8mg/ml; 1 +ve skin prick test to 17 most common aeroallergens; reversibility to ß2 agonist (>/= 9% of predicted FEV1); ability to expectorate after hypertonic saline. Exclusion criteria: Participants who experienced exacerbation during run-in phase which required course of oral steroids.
Interventions	Inhaled FP 500mcg versus Inhaled FP 2000mcg versus oral prednisolone. Duration: 2 weeks. Inhaler device: DPI.
Outcomes	FEV (% predicted); PC20 methacholine (DC); PC20 AMP (DC); PEF (L/min); Daytime symptoms; rescue medication (puffs/day); Sputum eosinophils (%); Serum ECP (mcg/l); Sputum ECP (mcg/l); Serum cortisol
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computerised minimisation method. Participants stratified according to age, previous dose of ICS, FEV % predicted, reversibility to 200mcg SABA, smoking status, serum IgE and PC20 methacholine
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Double dummy design

Nathan 2000

Methods	Randomised, double-blind, placebo controlled multi-centre trial. Method of randomisation not reported. Participants randomised according to baseline therapy: ICS or ß-2. Withdrawals: PLA: 43; FP100: 34; FP200: 28; FP500: 20. Jadad score: 3
Participants	N = 330. (PLA: 84; FP100mcg: 79; FP200mcg: 81; FP500mcg: 86); Gender (% M:F): PLA: 56:44; FP100: 65:35; FP200: 56:44; FP500: 55:45; Age range: 12-75; Mean age: PLA: 38; FP100: 34; FP200: 38; FP500: 37; FEV1 L: PLA: 2.22 (SEM 0.06); FP100: 2.40 (0.07); FP200: 2.21 (SEM 0.07); FP500: 2.26 (SEM 0.05); FEV1 % predicted: PLA: 62.6 (SEM 1.07); FP100: 64.3 (SEM 0.89); FP200: 63.3 (SEM 1.03); FP500: 63.7 (SEM 0.96); am PEF (L/min): PLA: 394 (SEM 10); FP100: 397 (SEM 10); FP200: 395 (SEM 10); FP500: 379 (SEM 10); pm PEF (L/min): PLA: 412 (SEM 10); FP100: 420 (SEM 10); FP200: 414 (SEM 10); FP500: 404 (SEM 10); Asthma symptom scores: PLA: 1.10 (SEM 0.07); FP100: 1.18 (SEM 0.06); FP200: 1.03 (SEM 0.07); FP500: 1.08 (SEM 0.07); Albuterol use (puffs/d): PLA: 3.05 (SEM 0.26); FP100: 3.43 (SEM 0.26); FP200: 2.62 (SEM 0.24); FP500: 3.18 (SEM 0.26); Nighttime awakenings, No. (%): PLA: 0.09 (SEM 0.02); FP100: 0.08 (SEM 0.02); FP200: 0.12 (SEM 0.02); FP500: 0.10 (SEM 0.02) .
Interventions	Inhaled FP100mcg QD versus FP200mcg QD versus FP500mcg QD versus placebo. Diskus inhaler. Duration: 12 weeks (plus open label extension)

Nathan 2000 *(Continued)*

Outcomes	Lung function (FEV1; am PEF; pm PEF); asthma symptoms; albuterol use; nighttime awakenings; withdrawals; safety; HPA axis function
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Nelson 1999

Methods	Setting: multicentre study USA, hospital outpatient clinics Length of intervention period: 16 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	111 adults: 44M 67F Age range: 12-77 years Inclusion criteria: 12 years of age or older Diagnosis of asthma (ATS criteria 1987) Dependent on oral corticosteroids for asthma control for 6 months or longer Requiring 5-40 mg/day oral prednisolone FEV1 40-80 (% predicted) 15% or greater reversibility in FEV1 after inhaled beta2 agonist Exclusion criteria: Life-threatening asthma or other severe concurrent disease Use of intra-nasal, injectable, topical corticosteroids Methotrexate, cyclosporin, azathioprine, troleandomycin within last 3 months
Interventions	1. FP 500 mcg 2xdaily (1000 mcg/d) 2. FP 1000 mcg 2xdaily (2000 mcg/d) Delivery device: Accuhaler DPI
Outcomes	100% reduction in daily dose oral prednisolone (No. of patients) 1-49% reduction in daily dose oral prednisolone (No. of patients) 0% reduction or increase in daily dose oral prednisolone (No. of patients) Outcomes reported as a change compared to baseline: Daily dose oral prednisolone FEV1 Morning PEFR Evening PEFR Daily asthma symptom score Daily beta2 agonist use Night-time awakenings Health status: asthma Quality of Life Questionnaire (AQLQ) Plasma cortisol < 5mcg/L (No. of patients) Peak plasma cortisol < 18 mcg/dL during 6 hour iv infusion with 250 mcg co-syntropin (No. of patients) Change in plasma cortisol < 7 mcg/dL following co-syntropin infusion (No. of patients) Change in morning plasma cortisol compared to baseline
Notes	No reply from author to clarify details of randomisation method Usual ICS discontinued at randomisation

Nelson 1999 *(Continued)*

	A priori criteria for prednisolone dose reduction based on FEV1 (% predicted), PEFR (% predicted), number of night-time awakenings, beta-2 agonist use compared to run in period values Patients were withdrawn from the study if they experienced asthma exacerbation requiring hospital admission, or 3 bursts of oral prednisolone due to exacerbation Placebo treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Nieto 2001

Methods	Randomised controlled trial. Method of randomisation not reported; blinding not reported. Withdrawals not reported. Jadad score: 1
Participants	N=18 (distribution between groups unclear). M/F: 9/9; mean age: 30 (SD 8); PC20: 1.14 (1.38). Inclusion criteria: not reported. Exclusion criteria: not reported.
Interventions	FP100 BID (200) versus FP250 BID (500). Inhaler device: unclear
Outcomes	PC20; exhaled nitric oxide
Notes	Unpublised conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Noonan 1995

Methods	Setting: multicentre study USA, hospital outpatient clinics Length of intervention period: 16 weeks

Noonan 1995 *(Continued)*

	Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: stated Withdrawals: Baseline characteristics: comparable Jadad score: 4
Participants	96 adults: 46M 50F Mean age: 50-52 years Inclusion criteria: 12 years of age or older Diagnosis of asthma (ATS criteria 1987) Dependent on oral corticosteroids for asthma control for 6 months or longer FEV1 40-80 (% predicted) Documented evidence of previous attempts to reduce oral steroid dose Exclusion criteria: Use of methotrexate, gold salts or troleandomycin in last 3 months Nasal corticosteroid use 10 pack year history of smoking or greater Pregnancy or lactation
Interventions	1. FP 750 mcg 2xdaily (1500 mcg/d) 2. FP 1000 mcg 2xdaily (2000 mcg/d) Delivery device: MDI
Outcomes	100% reduction in daily oral steroid use (% patients) 1-49% reduction in daily oral steroid use (% patients) 0% or increase in daily oral steroid use (% patients) Outcomes expressed as change compared to baseline: Daily oral FEV1 Morning PEFR Evening PEFR Daily use of beta2 agonists Daily asthma symptom score Quailty of life: Medical Outcomes Study Short Form (SF-36)
Notes	No reply from author to clarify details of randomisation method Usual ICS discontinued at randomisation Daily dose oral prednisolone reduced according to pre-defined criteria An uncontrolled one year open label study was undertaken following the randomised 16 week trial, when all patients received FP 2000 mcg/d. Results not considered in this review Placebo treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Noonan 1998

Methods	Setting: multicentre study USA, hospital outpatient clinic Length of intervention period: 8 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated

Noonan 1998 *(Continued)*

	Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	138 adults: 84M 54F Age range: 12-59 years Inclusion criteria: 12 years of age or older Diagnosis of asthma (ATS criteria 1987) 6 months or longer FEV1 60 (% predicted) or greater 15% or greater reversibility in FEV1 after inhaled beta2 agonist Methacholine BHR (PD20 FEV1) < 18 mg Asthma stability during run in period based on a priori defined criteria related to PEFR, medication requirement and symptoms Exclusion criteria: Recent hospitalisation due to asthma exacerbation Treatment with corticosteroids, theophylline, sodium cromoglycate, nedocromil Pregnancy
Interventions	1. FP 50 mcg 2xdaily (100 mcg/d) 2. FP 100 mcg 2xdaily (200 mcg/d) Delivery device: MDI
Outcomes	Outcomes expressed as change compared to baseline: FEV1 Morning PEFR Evening PEFR Methacholine BHR (log e PD20 FEV1) Daily asthma symptom score Daily use of beta2 agonist Night-time awakenings Probability of remaining in study Oro-pharyngeal side effects
Notes	No reply from author to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, morning PEFR, night-time awakenings or clinical exacerbation requiring emergency hospital treatment MDI's used for all interventions. Formulations of FP with 1% lecithin and 10% lecithin used. Only data for 1% formulation included in meta-analysis Placebo treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

O'Sullivan 2002

Methods	Randomised, double-blind, parallel group trial. Method of randomisation not reported; blinding not reported. Withdrawals: N = 1. nonITT population Jadad score: 3
Participants	N=36. Mean age: FP100: 32 (SEM 2.8); FP500: 32 (SEM 2.1); FP2000: 34 (SEM 2.8); FEV1% predicted: FP100: 81 (SEM 4.2); FP500: 86 (SEM 2.7); FP2000: 79 (SEM 3.3); Mean PC20: FP100: 1.11 (0.41); FP500: 0.55 (SEM 0.18); FP2000: 0.86 (SEM 0.51). Inclusion criteria: Atopic asthma as determined by skin prick test; fev1 >/=60% predicted; change in FEV1 >/=12% post SABA; PC20 fall of 4mg/mL; all participants were steroid naive; SABA prn

O'Sullivan 2002 *(Continued)*

	Exclusion criteria: RTI in previous 6 months; steroid (I/O) use in 6 weeks prior to enrolment
Interventions	FP100 versus FP500 versus FP2000. Study duration: 2 weeks. 2 week run-in period with placebo inhalers. Inhaler device: MDI
Outcomes	FEV1; FEF; FEV1/FVC; PEF L/min; Symptoms; bronchial biopsy; PC20; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Pauwels 2002

Methods	Randomised, double-blind, double-dummy crossover study. Method of randomisation: not reported; blinding: not reported. Jadad score: 2
Participants	N=26, Other details not reported
Interventions	Ciclesonide (400mcg QID; 800mcg QID; 800mcg QID), FP500 BID & FP1000 BID or PLA. Study duration: 6 x 1 week treatment period. Inhaler device: unclear
Outcomes	% Cortisol suppression; PC20
Notes	Unpublished conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Unclear risk	Information not available

Pearlman 1997

Methods	Setting: multicentre study USA, hospital outpatient clinic Length of intervention period: 12 weeks Randomisation: yes, method not stated

Pearlman 1997 *(Continued)*

	Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	342 subjects randomised Age range: 12-72 years Inclusion criteria: Diagnosis of asthma (ATS criteria 1987) Required maintenance inhaled corticosteroids for at least 3 months FEV! 50-80 (%predicted) 15% or greater reversibility in FEV1 after inhaled beta2 agonist During last 7 days of run-in period: No more than 12 puffs per day of albuterol No more than 4 morning PEFR 20% less than previous evenings No more than 2 nights wakening due to asthma requiring inhaled albuterol adequate compliance with study medication Exclusion criteria: Previous use of gold or methotrexate for control of asthma Inhaled cromoglycate or oral steroids in the last 4 weeks Significant co-existent illness Pregnancy or lactation
Interventions	1. FP 50 mcg 1 actuation 2xdaily (100 mcg/d) 2. FP 100mcg 1 actuation 2xdaily (200 mcg/d) 3. FP 250 mcg 1 actuation 2xdaily (500 mcg/d) Delivery device: Diskhaler DPI
Outcomes	Outcomes expressed as change compared to baseline: FEV1 Morning PEFR Evening PEFR Daily asthma symptom score Night-time awakenings Daily use of beta2 agonist Medical Outcomes Study Short Form (SF-36A) Living with Asthma Questionnaire (LWA) Validated sleep scale Probability of remaining in study Physician global assessment of efficacy Serum cortisol Oro-pharyngeal side effects
Notes	No reply from author to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, morning PEFR, night-time awakenings or clinical exacerbation requiring emergency hospital treatment Placebo treatment arm also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices used

Pearlman 1999

Methods	Randomised, double-blind, double-dummy, parallel group multi-centre trial. Method of randomisation not reported. ITT population. Withdrawals: PLA 1; SAL42mcg: 2; FP88mcg: 1; FP220mcg: 1; SL42mcg/FP88mcg: 2; SAL42mcg/FP220mcg: 21 Jadad score: 3

Pearlman 1999 *(Continued)*

Participants	N = 136 (PLA: 23; FP88: 23; FP220: 23; SAL: 21; SAL/FP88: 25; SAL/FP220: 21).Mean age (range): PLA: 35 (12-62); SAL: 29 (15-57); FP88: 27 (13-50); FP220: 32 (14-61); SAL/FP88: 33 (14-60); SAL/FP220: 26 (13-52); Gender (M:F %): PLA: 43:57; SAL42: 67:33; FP88: 74:26; FP220: 57:43; SAL/FP88: 40:60; SAL/FP220: 67:33; Mean FEV1 (% predicted): PLA: 68; SAL: 70; FP88: 69; FP220: 65; SAL/FP88: 67; SAL/FP220: 69; Reversibility: PLA: 32; SAL: 27; FP88: Inclusion criteria: >/=12 years of age; ATS defined asthma (at least 6 months), requiring medical treatment; FEV1 between 50-80% predicted; >/=15% increase in FEV1 post-SABA; treatment with prn SABA; female participants had -ve pregnancy tests and either surgically sterile, postmenopausal at 1 year or using acceptable birth control for 1 month prior to participation Exclusion criteria: History of life-threatening asthma; hypersensitivity reaction to beta-agonists/corticosteroids; smoking within previous year/history >10 pack years; use of OCS/ICS or parenteral steroids (except for Flonase); use of steroid therapy in previous month; OCS treatment in previous 6 months; use of OTC medication that may affect the course of asthma; abnormal CXR; clinically significant abnormal 12-lead ECG; history of concurrent disease (glaucoma, diabetes + hypertension)
Interventions	PLA versus FP88mcg BID versus FP220mcg BID versus SAL42mcg/FP88mcg BID versus SAL42mcg/FP220mcg BID daily. Inhaler device: MDI. Duration: 4 weeks
Outcomes	FEV1; Am PEF; Symptoms; % days without asthma; % nights awakening due to asthma; rescue medication use; adverse effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Peden 1998

Methods	Setting: multicentre study USA, paediatric outpatient clinic Length of intervention period: 12 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind, double dummy Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	177 children: 112M 65F Age range: 4-11 years Inclusion criteria: History of chronic asthma (ATS criteria 1987) Symptoms requiring maintenance therapy for 3 months or more PEFR 85 (% predicted) or greater FEV1 50-85 (% predicted)

Peden 1998 *(Continued)*

	15% or greater improvement in FEV1 after inhaled beta2 agonist Asthma stability during run-in period, based on a priori beta2 agonist use and morning PEFR Exclusion criteria: Life-threatening asthma Severe concurrent disease Systemic steroids in last month Previous treatment with methotrexate or gold
Interventions	1. FP 50mcg 2xdaily (100 mcg/d) via Accuhaler DPI 2. FP 100mcg 2xdaily (200mcg/d) via Accuhaler DPI
Outcomes	Outcomes expressed as change compared to baseline: FEV1 FEV1 (% predicted) Morning PEFR Morning PEFR (% predicted) Evening PEFR Daily asthma symptom score Daily use of beta2 agonist Night-time awakening score Morning plasma cortisol Total urinary free cortisol excretion (mcg/24 hours) Probability of remaining in study
Notes	No reply from author to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A placebo treatment arm was also included: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Double dummy design

Peden 1998a

Methods	See Peden 1998
Participants	174 children: 100M 74F See Peden 1998a for inclusion and exclusion criteria
Interventions	1. FP 50 mcg 2xdaily (100 mcg/d) via Diskhaler DPI 2. 100 mcg 2xdaily (200 mcg/d) via Diskhaler DPI
Outcomes	See Peden 1998
Notes	See Peden 1998

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Peden 1998

Peden 1998a *(Continued)*

Allocation concealment?	Low risk	See Peden 1998
Blinding? All outcomes	Low risk	See Peden 1998

Pinnas 2005

Methods	Setting: multicentre study USA. Length of intervention period: 12 weeks. Randomisation: yes, method not stated. Allocation concealment: unclear. Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	397 adults randomised, 312 completed: 212F Age range: >/=12 years Inclusion criteria: treatment with SABA only for 6 months previously; am pre-SABA FEV1 of 45-80% predicted; >/=12% reversibility. No run-in period described.
Interventions	FP: 1. 88mcg 2 x daily 2. 110mcg 2 x daily 2. 220mcg 2 x daily 3. Placebo Inhaler device: MDI
Outcomes	Change in FEV1; am PEF; rescue medication usage; symptoms; quality of life; adverse events
Notes	Conference abstract Sourced from www.clinicalstudyresults.org

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Raphael 1999

Methods	Setting: multicentre study USA, primary care and hospital outpatient clinics Design: parallel group Length of intervention period: 12 weeks Randomisation: yes, computer generated sequence Allocation concealment: yes (central coding by pharmaceutical company sponsors) Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 5
Participants	399 adolescents and adults: 167M 232F Age range: 12-83 years Inclusion criteria: 12 years of age or older with established diagnosis of asthma (no further details) At end of run-in period: FEV1 of 45-65 (% predicted), or if FEV1 65-80 (% predicted) additional evidence of sub-optimal control (> 8 puffs rescue beta2 agonist/week, diurnal PEFR variability > 20%, any night-time wakening due to asthma symptoms requiring beta2 agonist) 12% or greater increase in FEV1 after inhaled beta2 agonist Regular treatment with BDP or TA 8-12 puffs/day for one month or longer Exclusion criteria: Use of systemic steroids, leukotriene modifiers, sodium cromoglycate or nedocromil within last month Smokers Asthma exacerbation during run-in period Baseline asthma control: Reduced FEV1 of 45-65 (% predicted) or significant symptoms (see above)
Interventions	1. FP 44 mcg 2 puffs 2xdaily (176 mcg/d) 2. FP 110 mcg 2 puffs 2xdaily (440 mcg/d) Delivery device: MDI
Outcomes	Change in FEV1 compared to baseline Change in FEF25-75 compared to baseline Change in FVC compared to baseline Change in morning PEFR compared to baseline Change in evening PEFR compared to baseline Change in rescue beta2 agonist use compared to baseline (puffs/day) Change in daily asthma symptom score compared to baseline Change % days with no rescue beta2 agonist use compared to baseline Change in % days with no symptoms compared to baseline Withdrawal due to asthma exacerbation (No. of patients) Oropharyngeal side effects Oropharyngeal Candidiasis
Notes	Study also included two further treatment arms with BDP: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated sequence
Allocation concealment?	Low risk	Central coding by pharmaceutical company sponsors
Blinding? All outcomes	Low risk	Identical inhaler devices

SAM40012

Methods	Setting: multicentre study Europe and Israel Design: parallel group Length of intervention period: 24 weeks Randomisation: yes Allocation concealment: not reported Masking: double blind, double dummy Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	367 children (ITT population: 355); 245M 110F

SAM40012 *(Continued)*

	Age range: 4-11 years Inclusion criteria: 4-11 years of age; participants symptomatic despite moderate dose of ICS for at least 4 weeks; symptom score during run-in >/=2 on at least 3 of last 7 days; mean am PEF during run-in of >50 to <85% of post SABA at randomisation
Interventions	1. FP100 BD (200mcg/d) 2. FP200 BD (400mcg/d) Inhaler device: DPI
Outcomes	% symptom free days and nights; use of reliever medication; am PEF (L/min); pm PEF (L/min); Clinic PEF; exacerbations; adverse events
Notes	Unpublished study - data retrieved and extracted from study detailed online

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Sheffer 1996

Methods	Setting: multicentre study USA, hospital outpatient clinics Length of intervention period: 12 weeks Randomisation: yes, computer generated sequence Allocation concealment: yes Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 5
Participants	307 patients: 185M 122F Age range: 12-72 years Inclusion criteria: Diagnosis of asthma requiring at least 3 months of regular therapy FEV1 45-75 (% predicted) 15% or greater reversibility in FEV1 after inhaled beta2 agonist Exclusion criteria: More than 1 month's use of oral steroids in the past Any oral, topical or inhaled steroid or cromoglycate in last month Previous history of life threatening asthma Pregnancy or lactation
Interventions	1. FP 25 mcg 1 puff 2xdaily (50 mcg/d) 2. FP 50 mcg 1 puff 2xdaily (100 mcg/d) 3. FP 50 mcg 2 puffs 2xdaily (200 mcg/d)

Sheffer 1996 *(Continued)*

	Delivery device: MDI
Outcomes	Outcomes expressed as change compared to baseline: FEV1; Morning PEFR; Evening PEFR; Night-time awakenings; Daily wheeze score; Daily cough score; Daily breathlessness score; Daily use of beta2 agonists; Probability of remaining in study
Notes	Randomisation details confirmed by author For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, morning and evening PEFR, diurnal variability in PEFR, night-time awakenings or clinical exacerbation requiring emergency hospital treatment

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	Computer generated sequence
Allocation concealment?	Low risk	Off site by third party
Blinding? All outcomes	Low risk	Identical inhaler devices

Sorkness 1999

Methods	Randomised, double-blind, triple dummy, placebo controlled, parallel group study. Method of randomisation: computer-generated randomisation. Blinding: matching inhalers. Withdrawals: Placebo: 0; FP100: 1; FP500: 1. ITT population. Jadad score: 5
Participants	N = 168 (N for treatment groups considered by the review: Placebo: 30; FP100: 27; FP500: 30); Mean age (SE): PLA: 27.9 (1.6); FP100: 27.7 (1.7); FP500: 28.2 (1.6); Gender (M/F): PLA: 26/4; FP100: 26/1; FP500: 24/6; Race (White/other %): PLA: 67/33; FP100: 81/19; FP500: 77/23; FEV1 % predicted (SE): PLA: 87 (2.5); FP100: 88 (3.1); FP500: 83 (3.9) Inclusion criteria: 18-51 years of age; documented diagnosis of asthma (>/=6 months according to ATS criteria; FEV1 at least 50% predicted Exclusion criteria: Pregnancy or lactation; corticosteroid/immunosuppressive therapy for 3 months prior to study entry; use of 140mg prednisone or equivalent in any dosage or form in previous year; current/prior use of antiasthma medication other than beta-agonists, theophylline or cromolyn sodium; historical or current evidence of significant concomitant disease; use of oral contraceptives or other hormonal therapy; current use of prescription or over the counter medication known to interact with corticosteroids or to cause an abnormal response to exogenous glucocorticoids or reversal of normal nocturnal sleeping hours
Interventions	FP200 versus FP1000 versus Placebo. Delivery device: Rotadisk. Duration of study: 4 weeks
Outcomes	AUC; Plasma cortisol; withdrawals; adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Sorkness 1999 *(Continued)*

Adequate sequence generation?	Low risk	Computer-generated randomisation.
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Triple dummy design

Sorkness 1999a

Methods	Randomised, double-blind, triple dummy, placebo controlled, parallel group study. Method of randomisation: computer-generated randomisation. Blinding: matching inhalers. Withdrawals: PLA: 1; FP100: 3; FP500: 2. ITT population. Jadad score: 5
Participants	N = 119 (N for treatment groups considered by the review: PLA: 31; FP200: 29; FP500: 30); Mean age (SE): PLA: 32.1 (1.7); FP200: 31.4 (1.8); FP500: 33 (1.6); Gender (M/F): PLA: 25/6; FP200: 26/3; FP500: 26/4; Race (White/other %): PLA: 94/6; FP200: 93/7; FP500: 90/10; FEV1 % predicted (SE): PLA: 87 (2.7); FP200: 86 (2.7); FP500: 88 (3) Inclusion criteria: 18-51 years of age; documented diagnosis of asthma (>/=6 months according to ATS criteria; FEV1 at least 50% predicted Exclusion criteria: Pregnancy or lactation; corticosteroid/immunosuppressive therapy for 3 months prior to study entry; use of 140mg prednisone or equivalent in any dosage or form in previous year; current/prior use of antiasthma medication other than beta-agonists, theophylline or cromolyn sodium; historical or current evidence of significant concomitant disease; use of oral contraceptives or other hormonal therapy; current use of prescription or over the counter medication known to interact with corticosteroids or to cause an abnormal response to exogenous glucocorticoids or reversal of normal nocturnal sleeping hours
Interventions	FP200 versus FP500 versus Placebo. Delivery device: Rotadisk. Duration of study: 4 weeks
Outcomes	AUC; Plasma cortisol; withdrawals; adverse events
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	Computer-generated randomisation.
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Verona 2003

Methods	Randomised, double-blind parallel group, multi-centre (Eastern Europe) study. Method of randomisation: computer-generated randomisation schedule; Blinding - both FP doses administered via Diskus.

Verona 2003 *(Continued)*

	Withdrawals: FP200: 97/267; FP400: 83/261 - High withdrawal rate as some trial centres did not participate in extension beyond 16 weeks. Ns used based on correspondence with GSK. Jadad score: 5
Participants	N = 528 (FP200: 267; FP400: 261); Mean age: FP200: 7.8 (SD 2.1); FP400: 7.9 (SD 2); M/F (%): FP200: 72/28; FP400: 72/28; Ethnicity: White/non-white (%): FP200: >99/<1; FP400: 100/0; mean duration of asthma symptoms (years): FP200: 3.82 (SD 2.2); FP400: 4.05 (SD 2.37); Treatment with BUD/FP/BDP/FLUN (%): FP200: 38/26/25/1; FP400: 41/33/24/<1; mean clinic PEF (% predicted): FP200: 105.1 (21.7); FP400: 101.6 (22.4); mean am PEF (L/min): FP200: 256.9 (SD 75); FP400: 255.4 (SD 72.2); pm PEF (L/min): 265.9 (SD 73.1); FP400: 261.3 (SD 72.2)
Interventions	FP200 versus FP400 via Diskus inhaler. Study duration 52 weeks (2 week run-in). Participants were allowed to take: oral theophylline, SABAs, DSCG or nedocromil sodium
Outcomes	Asthma exacerbations; clinic PEF; diary PEF (am& pm); symptoms; adverse events
Notes	GSK responded with data on Ns and means/SEMs 060904

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Wallin 2003

Methods	Randomised, double-blind, parallel group trial. Method of randomisation: not reported. Blinding: identical inhalers. Withdrawals: FP400: N = 3; FP1000: N = 3. Unclear population for analysis - assumed non-ITT Jadad score: 4
Participants	N = 56 (FP400: 19; FP1000: 19; FP+SAL: 18 - baseline characteristics reported only for FP groups); M/F: FP400: 8/11; FP1000: 9/10; Mean age: FP400: 42 (SEM 12); FP1000: 40 (SEM 15); Asthma duration (months): FP400: 206 (SEM 130); FP1000: 176 (SEM 169); FEV1 L: FP400: 3.0 (SEM 0.9); FP1000: 3.3 (SEM 0.9); FEV1 % predicted: FP400: 91 (SEM 20); FP1000: 92 (SEM 12); PC20 mg/mL: FP400: 1.86 (SEM 2.33); FP1000: 6.22 (SEM 7.54); Reversibility (%): FP400: FEV1: 12 (SEM 11); PEF: 24 (SEM 19); FP1000: FEV1: 12 (SEM 11); PEF: 20 (SEM 17). Run-in treatment: FP400: BUD: 2; BDP: 2; FP: 5; FP1000: BUD: 14; BDP: 2; FP: 3 Inclusion criteria: Symptomatic asthma during run-in period in spite of normal medication (frequent asthma symptoms, need for SABAs, >/=20% variation between am and pm PEF); Lung function: 15% increase in FEV1 post-SABA; PC20 methacholine <4mg/mL Exclusion criteria: RTI in previous four weeks
Interventions	FP200 BID (400mcg/d) versus FP500 BID (1000 mcg/d) via Diskus inhaler. SABA prn concomitant therapy. Study duration: 12 weeks (2 week run-in period)
Outcomes	PEF; FEV1; Bronchial lavage; immunohistochemistry

Wallin 2003 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	See Appendix 2
Allocation concealment?	Low risk	See Appendix 2
Blinding? All outcomes	Low risk	Identical inhaler devices

Wasserman 1996

Methods	Setting: multicentre study USA, primary care and hospital outpatient clinics Length of intervention period: 12 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	331 adults randomised, 265 completed: 265M 66F Age range 12-74 years Inclusion criteria: Diagnosis of asthma (ATS criteria 1987) for at least 6 months FEV1 50-80 (% predicted) 15% or greater reversibility in FEV1 after inhaled beta2 agonist During run-in: 12 or less puffs/day albuterol 4 or less mornings when PEFR decreased 20% or less than previous night PEFR 2 or less nights wakening requiring albuterol Good compliance Exclusion criteria: Smoking Use of any oral, inhaled or topical steroid within last month of study Oral steroids for 2 months or longer within last 6 month
Interventions	1. FP 50 mcg 1 actuation 2xdaily (100 mcg/d) 2. FP 100 mcg 1 actuation 2xdaily (200 mcg/d) 3. FP 250 mcg 1 actuation 2xdaily (500 mcg/d) Delivery device: Diskhaler DPI
Outcomes	Outcomes expressed as change compared to baseline: FEV1 FVC FEF 25-75% Morning PEFR Evening PEFR Daily asthma score Change in night time awakenings Daily use of beta2 agonist Probability of remaining in study Physician global assessment of efficacy Oro-pharyngeal side effects
Notes	No reply from author to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, morning PEFR, night-time awakenings or clinical exacerbation requiring emergency hospital treatment Study also included a placebo treatment arm: results not considered in this review

Risk of bias

Wasserman 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Described as randomised; other information not available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

Wolfe 1996

Methods	Setting: multicentre study USA, hospital outpatient clinics Length of intervention period: 12 weeks Randomisation: yes, method not stated Allocation concealment: unclear Design: parallel group Masking: double blind Excluded: not stated Withdrawals: stated Baseline characteristics: comparable Jadad score: 3
Participants	304 adults: 169M 135F Age range: 12-87 years Inclusion criteria: 12 years of age or older Diagnosis of moderate asthma, for at least 6 months Current treatment with inhaled corticosteroids and regular/as needed beta2 agonists Exclusion criteria: During run-in period: More than 12 puffs albuterol daily for 3 or more days Diurnal variation in PEFR > 20% for 4 or more days Awakening more than 2 nights due to asthma symptoms And: Systemic steroids in last month Significant concurrent disease Pregnancy or lactation
Interventions	1. FP 100 mcg 2xdaily (200 mcg/d) 2. FP 250 mcg 2xdaily (500 mcg/d) 3. FP 500 mcg 2xdaily (1000 mcg/d) Delivery device: MDI
Outcomes	Outcomes expressed as change compared to baseline: FEV1 Morning PEFR Evening PEFR Daily use of beta2 agonist Daily cough score Daily wheezing score Daily breathlessness score Daily asthma symptom score Probability of remaining in the study Physician related global assessment of efficacy Oropharyngeal side effects Morning plasma cortisol
Notes	No reply from author to clarify details of randomisation method For continuous outcomes change scores from baseline to endpoint (i.e. point of withdrawal) were reported A priori criteria for withdrawal due to lack of efficacy were established based on FEV1, morning PEFR, night-time awakenings or clinical exacerbation requiring emergency hospital treatment Study also included a placebo treatment arm: results not considered in this review

Risk of bias

Bias	Authors' judgement	Support for judgement

Wolfe 1996 *(Continued)*

Adequate sequence generation?	Unclear risk	Described as randomised; no other information available
Allocation concealment?	Unclear risk	Information not available
Blinding? All outcomes	Low risk	Identical inhaler devices

ACTH: adrenocorticotropic hormone; ATS: American Thoracic Society; BDP: beclomethasone dipropionate; BHR: bronchial hyperresponsiveness; BUD: budesonide; DPI: dry powder inhaler; FEF25-75: forced expiratory flow at 25 to 75% of FVC; FEV1: forced expired volume in one second; FP: fluticasone propionate; FSC: fluticasone/salmeterol combination; FVC: forced vital capacity; ICS: inhaled corticosteroid; ITT: intension-to-treat; mcg/d: micrograms per day; MDI: metered dose inhaler; PC20 FEV1: provocative concentration of inhalant required to produce a 20% fall in FEV1; PD20 FEV1: provocative dose of inhalant required to produce a 20% fall in FEV1; PEFR: peak expiratory flow rate; TA: triamcinolone acetonide

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

Study	Reason for exclusion
Ayres 2000	Delivery device comparison
Bisgaard 1999	This study assessed a group of young children including infants under the age of two years
Dorini 2001	Outcomes not relevant
FLTA2007	Placebo controlled study
Fowler 2002	Wrong comparison
Harrison 2001	Wrong comparison
Kelly 2001	Varying dose of FP
Laforce 2000	Wrong comparison
Lipworth 1997	Crossover study with intervention periods of only 4 days
Lundback 1993	Delivery device comparison
Lundback 1994	Delivery device comparison
Medici 2000	Outcomes not relevant
Murray 1998	Wrong comparison
Pieters 1998	Delivery device comparison
Visser 2001	Wrong comparison
Wittmann 1999	Wrong comparison
Wolfe 2000	Comparison of QID versus BID administration of 200mcg FP
ZuWallack 2000	Once versus twice daily administration of FP (same dosage with different dosing strategy compared)

DATA AND ANALYSES

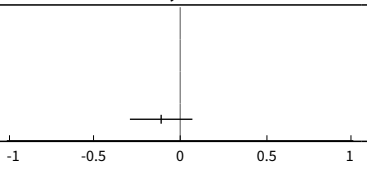
Comparison 1. Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in morning PEFR compared to baseline (L/min)	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 morning PEFR compared to baseline (L/min)	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 daily asthma symptom score compared to baseline	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 number of night-time awakenings/week compared to baseline	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 daily use of beta2 agonist compared to baseline (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Number of patients withdrawn due to lack of efficacy	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
7.1 Children	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

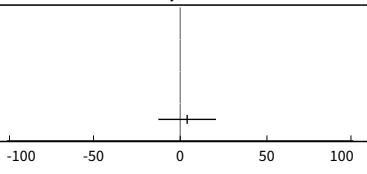
Analysis 1.1. Comparison 1 Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages), Outcome 1 Change in FEV1 compared to baseline (litres).

Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 100 N	FP 100 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.1.1 Children						
1.1.2 Adults						
Sheffer 1996	76	0.4 (0.6)	79	0.5 (0.5)		-0.11[-0.29,0.07]



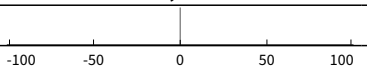
Analysis 1.2. Comparison 1 Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages), Outcome 2 Change in morning PEFR compared to baseline (L/min).

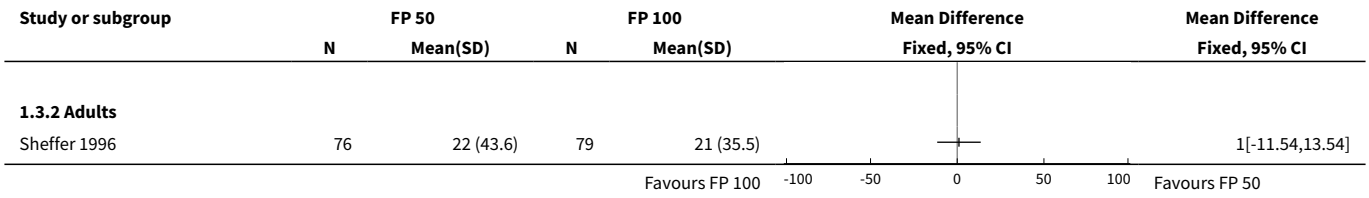
Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 100 N	FP 100 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.2.1 Children						
1.2.2 Adults						
Sheffer 1996	76	31 (52.3)	79	27 (53.3)		4[-12.63,20.63]



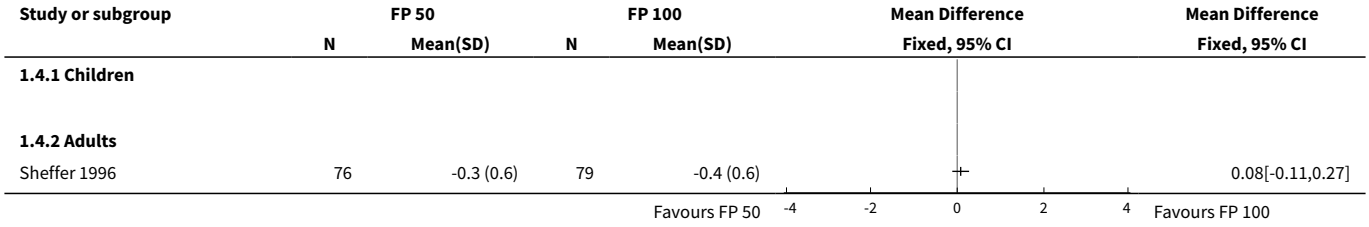
Analysis 1.3. Comparison 1 Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages), Outcome 3 Change in morning PEFR compared to baseline (L/min).

Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 100 N	FP 100 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.3.1 Children						

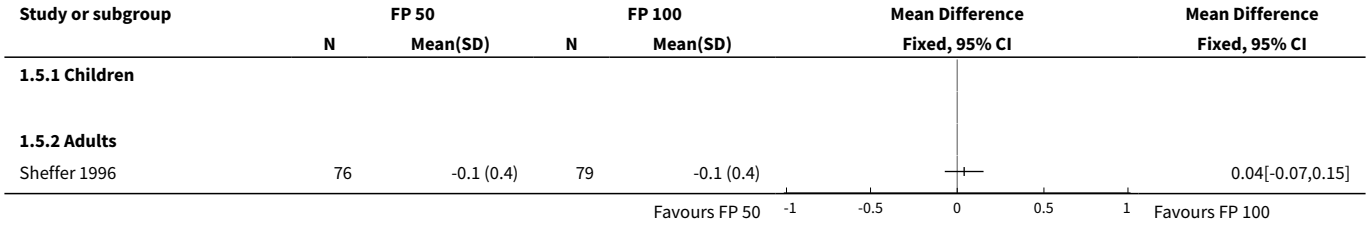




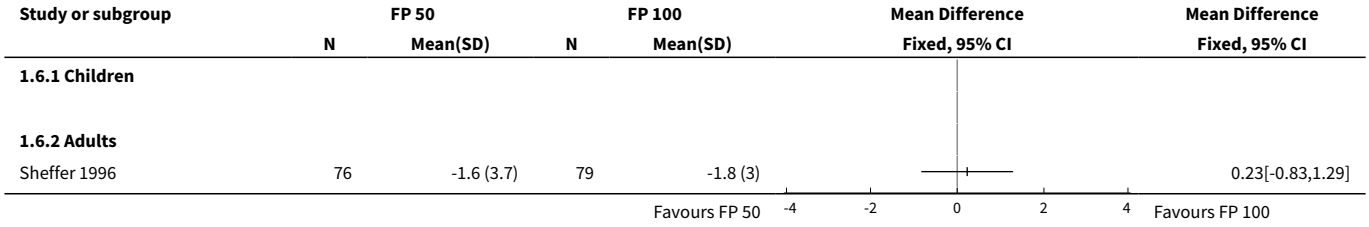
Analysis 1.4. Comparison 1 Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages), Outcome 4 Change in daily asthma symptom score compared to baseline.



Analysis 1.5. Comparison 1 Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages), Outcome 5 Change in number of night-time awakenings/week compared to baseline.

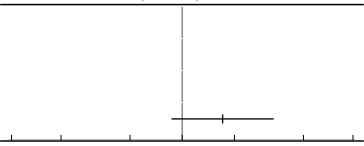


Analysis 1.6. Comparison 1 Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages), Outcome 6 Change in daily use of beta2 agonist compared to baseline (puffs/d).



Analysis 1.7. Comparison 1 Parallel group studies, no oral steroids: 50 versus 100 mcg/d (all ages), Outcome 7 Number of patients withdrawn due to lack of efficacy.

Study or subgroup	FP 50 n/N	FP 100 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
1.7.1 Children				
1.7.2 Adults				
Sheffer 1996	28/76	20/79		1.71[0.87,3.37]



Comparison 2. Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages)

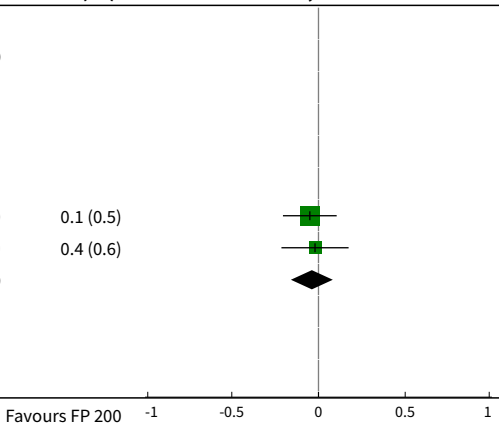
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change in FEV1 compared to base-line (litres)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	2	313	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.16, 0.08]
2 Change in FVC compared to baseline (litres)	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 FEF25-75 compared to baseline (L/second)	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 morning PEFR compared to baseline (L/min)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	2	313	Mean Difference (IV, Fixed, 95% CI)	-7.49 [-17.31, 2.33]
5 Change in evening PEFR compared to baseline (L/min)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	2	313	Mean Difference (IV, Fixed, 95% CI)	-7.95 [-17.24, 1.34]
6 Change in daily asthma symptom score compared to baseline	2	313	Std. Mean Difference (IV, Fixed, 95% CI)	0.32 [0.10, 0.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	2	313	Std. Mean Difference (IV, Fixed, 95% CI)	0.32 [0.10, 0.54]
7 Change in number of night-time awakenings/week compared to baseline	2	313	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.02, 0.16]
7.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 Adults	2	313	Mean Difference (IV, Fixed, 95% CI)	0.09 [0.02, 0.16]
8 Change in daily use of beta2 agonist compared to baseline (puffs/d)	2	313	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.37, 0.51]
8.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	2	313	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.37, 0.51]
9 Number of patients withdrawn due to lack of efficacy	2	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.88, 2.46]
9.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	2	313	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.48 [0.88, 2.46]
10 Hoarseness or dysphonia (No. of patients)	2	322	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.14, 1.97]
10.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	2	322	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.52 [0.14, 1.97]
11 Oral Candidiasis (No. of patients)	2	322	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.05, 1.35]
11.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	2	322	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.27 [0.05, 1.35]
12 Physician global rated efficacy: ineffective	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
12.1 Children	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
12.2 Adults	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

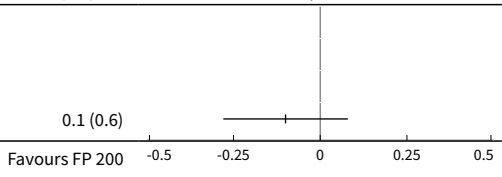
Analysis 2.1. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 1 Change in FEV1 compared to baseline (litres).

Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.1.2 Adults							
Chervinsky 1994	78	0.1 (0.5)	80	0.1 (0.5)		60.98%	-0.05[-0.2,0.1]
Sheffer 1996	76	0.4 (0.6)	79	0.4 (0.6)		39.02%	-0.02[-0.21,0.17]
Subtotal ***	**154**		**159**			**100%**	**-0.04[-0.16,0.08]**
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%							
Test for overall effect: Z=0.62(P=0.53)							
Test for subgroup differences: Not applicable							



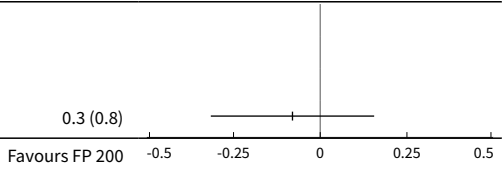
Analysis 2.2. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 2 Change in FVC compared to baseline (litres).

Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.2.1 Children						
2.2.2 Adults						
Chervinsky 1994	78	-0 (0.6)	80	0.1 (0.6)		-0.1[-0.28,0.08]



Analysis 2.3. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 3 Change in FEF25-75 compared to baseline (L/second).

Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.3.1 Children						
2.3.2 Adults						
Chervinsky 1994	78	0.2 (0.7)	80	0.3 (0.8)		-0.08[-0.32,0.16]



Analysis 2.4. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 4 Change in morning PEFR compared to baseline (L/min).

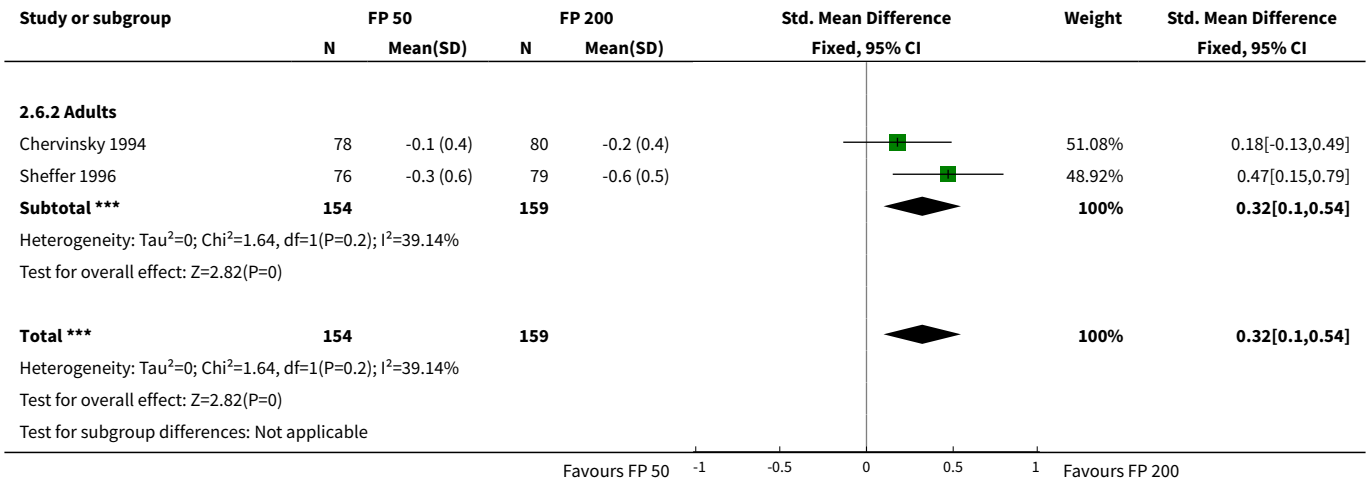
Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.4.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.4.2 Adults							
Chervinsky 1994	78	11 (40)	80	15 (38)		65.11%	-4[-16.17,8.17]
Sheffer 1996	76	31 (52.3)	79	45 (53.3)		34.89%	-14[-30.63,2.63]
Subtotal ***	**154**		**159**			**100%**	**-7.49[-17.31,2.33]**
Heterogeneity: Tau^2=0; Chi^2=0.9, df=1(P=0.34); I^2=0%							
Test for overall effect: Z=1.49(P=0.13)							
Test for subgroup differences: Not applicable							

Analysis 2.5. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 5 Change in evening PEFR compared to baseline (L/min).

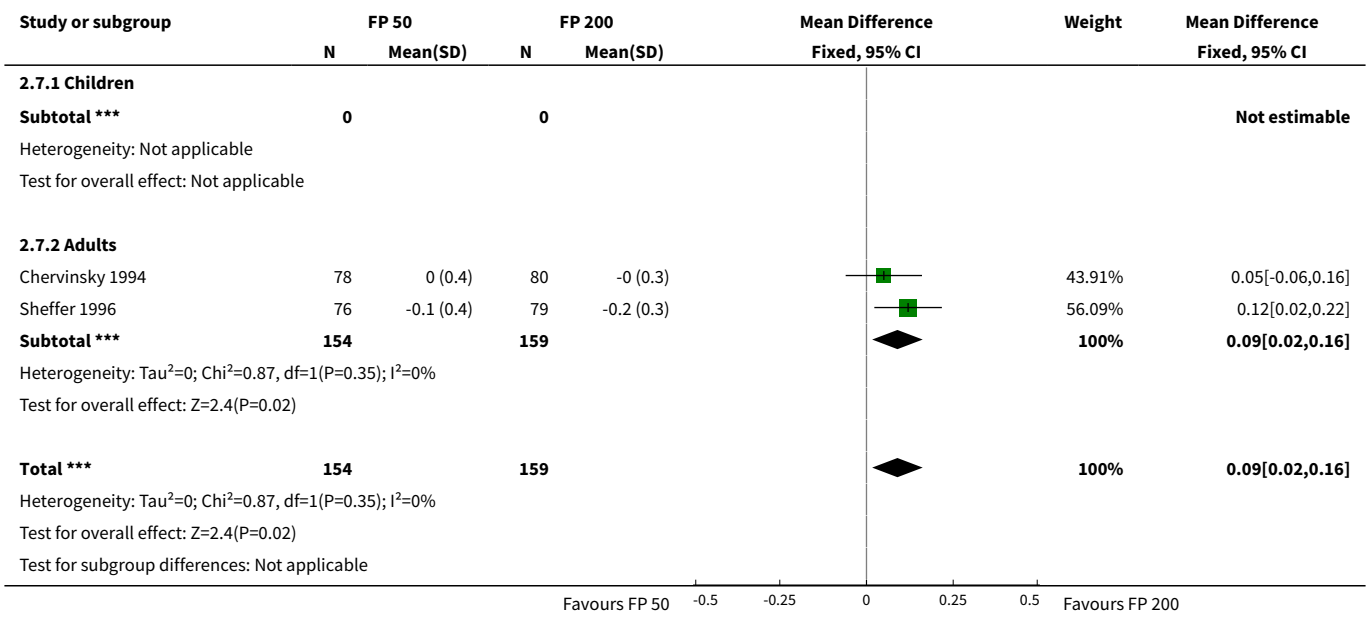
Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.5.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.5.2 Adults							
Chervinsky 1994	78	7 (38)	80	12 (37)		63.12%	-5[-16.7,6.7]
Sheffer 1996	76	22 (43.6)	79	35 (53.3)		36.88%	-13[-28.3,2.3]
Subtotal ***	**154**		**159**			**100%**	**-7.95[-17.24,1.34]**
Heterogeneity: Tau^2=0; Chi^2=0.66, df=1(P=0.42); I^2=0%							
Test for overall effect: Z=1.68(P=0.09)							
Test for subgroup differences: Not applicable							

Analysis 2.6. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 6 Change in daily asthma symptom score compared to baseline.

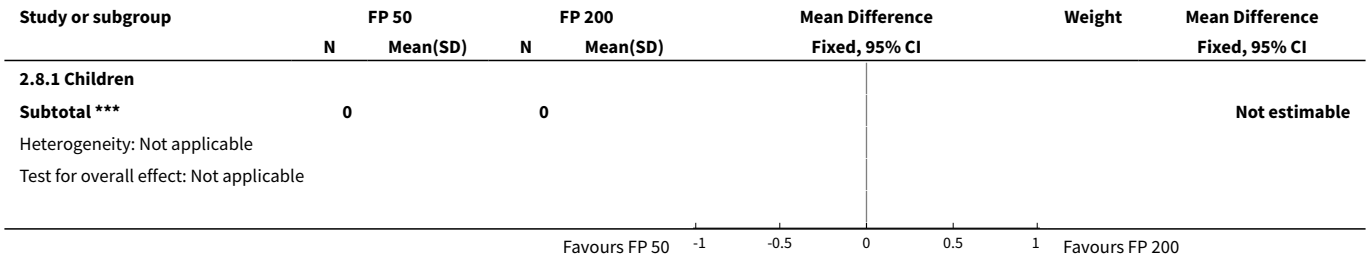
Study or subgroup	FP 50 N	FP 50 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.6.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

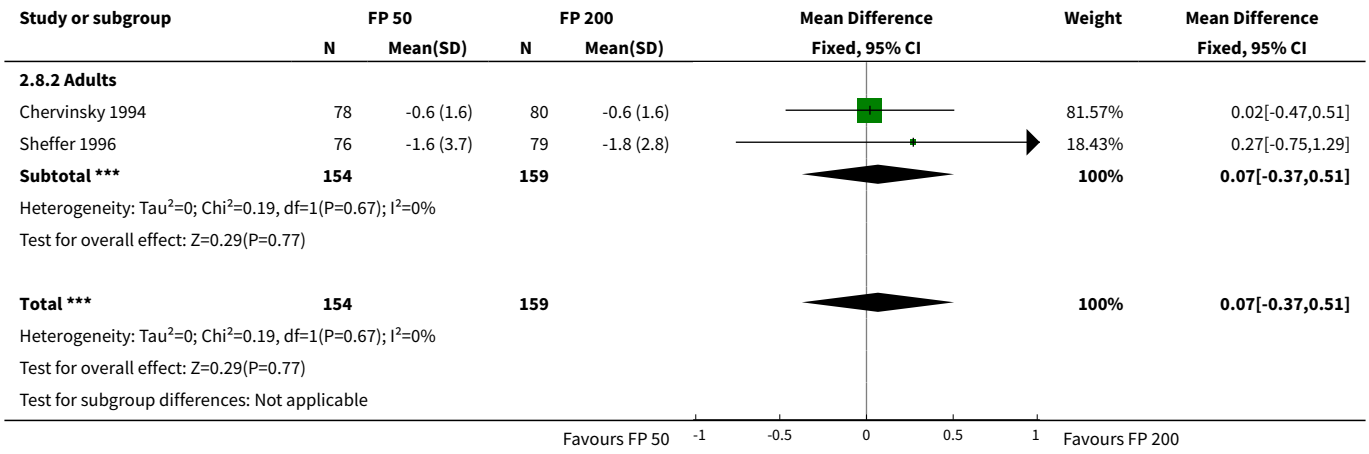


Analysis 2.7. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 7 Change in number of night-time awakenings/week compared to baseline.

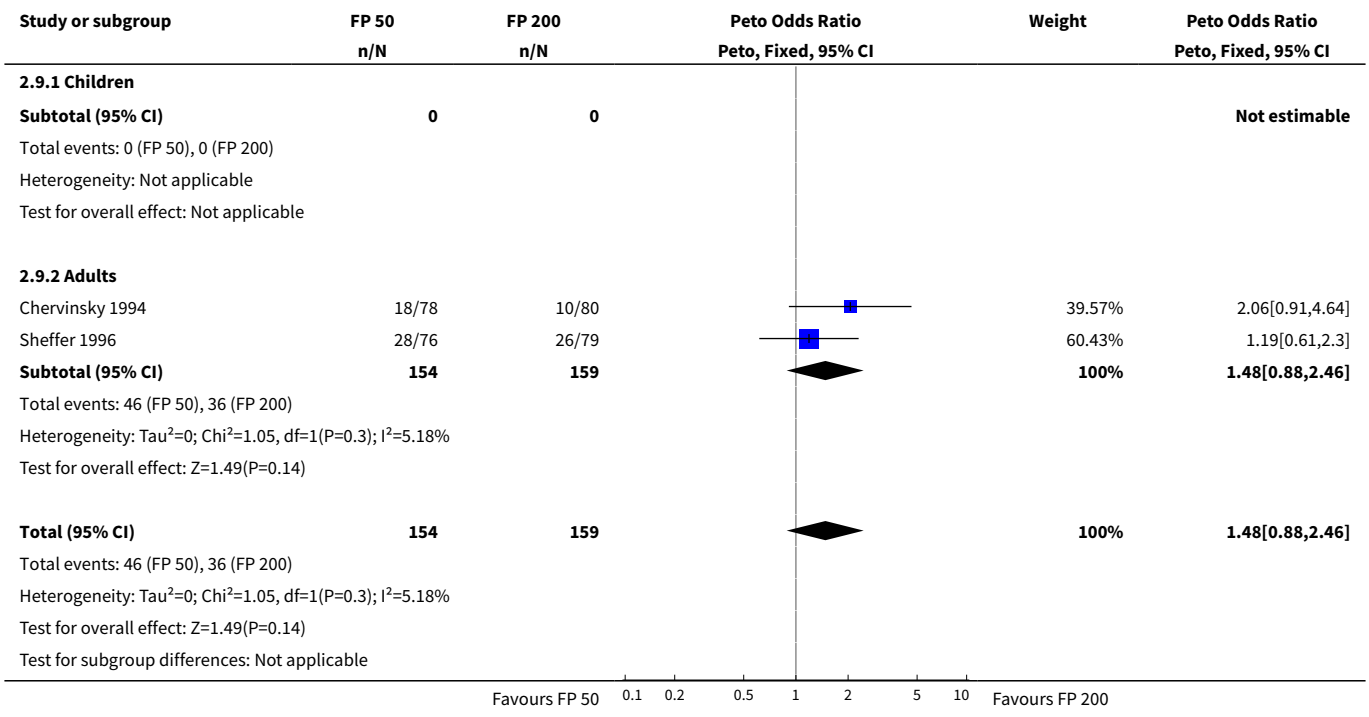


Analysis 2.8. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 8 Change in daily use of beta2 agonist compared to baseline (puffs/d).

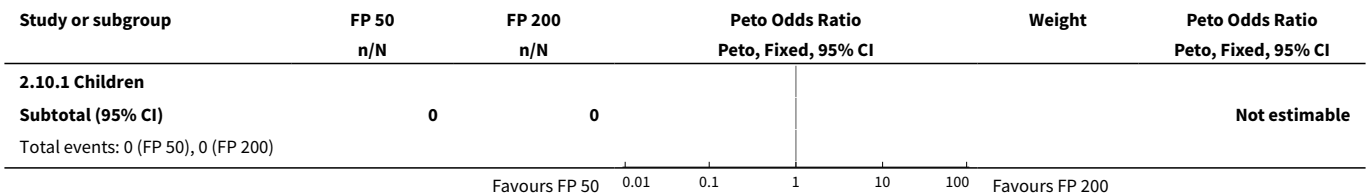


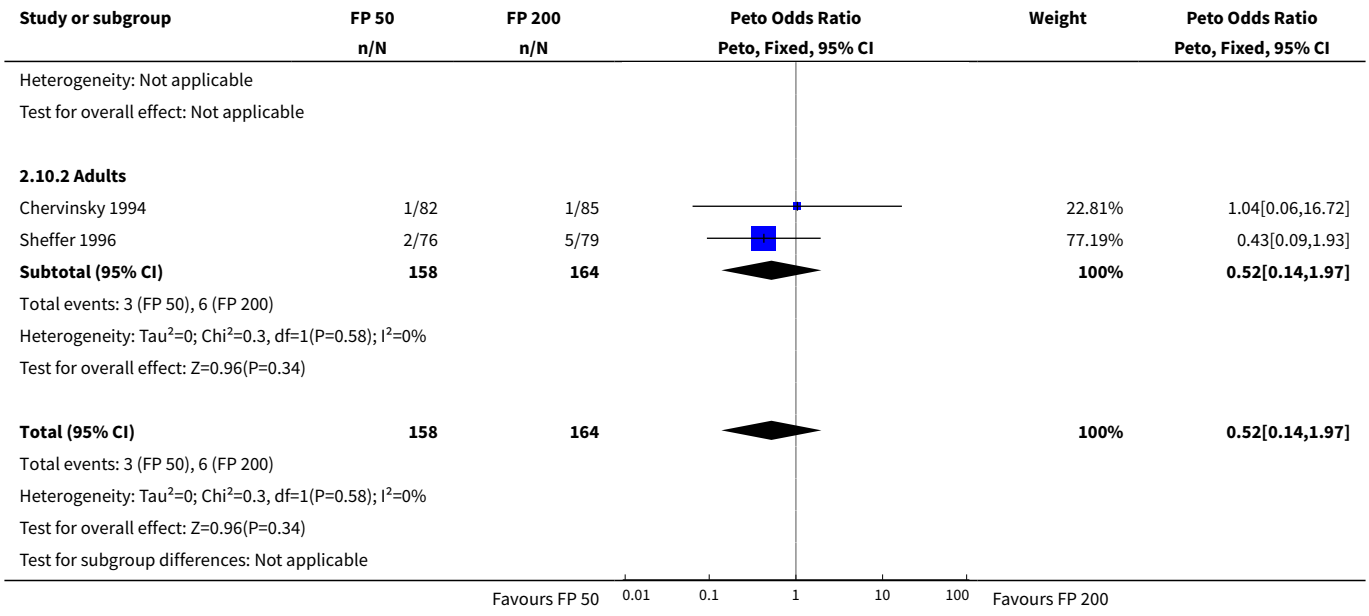


Analysis 2.9. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 9 Number of patients withdrawn due to lack of efficacy.

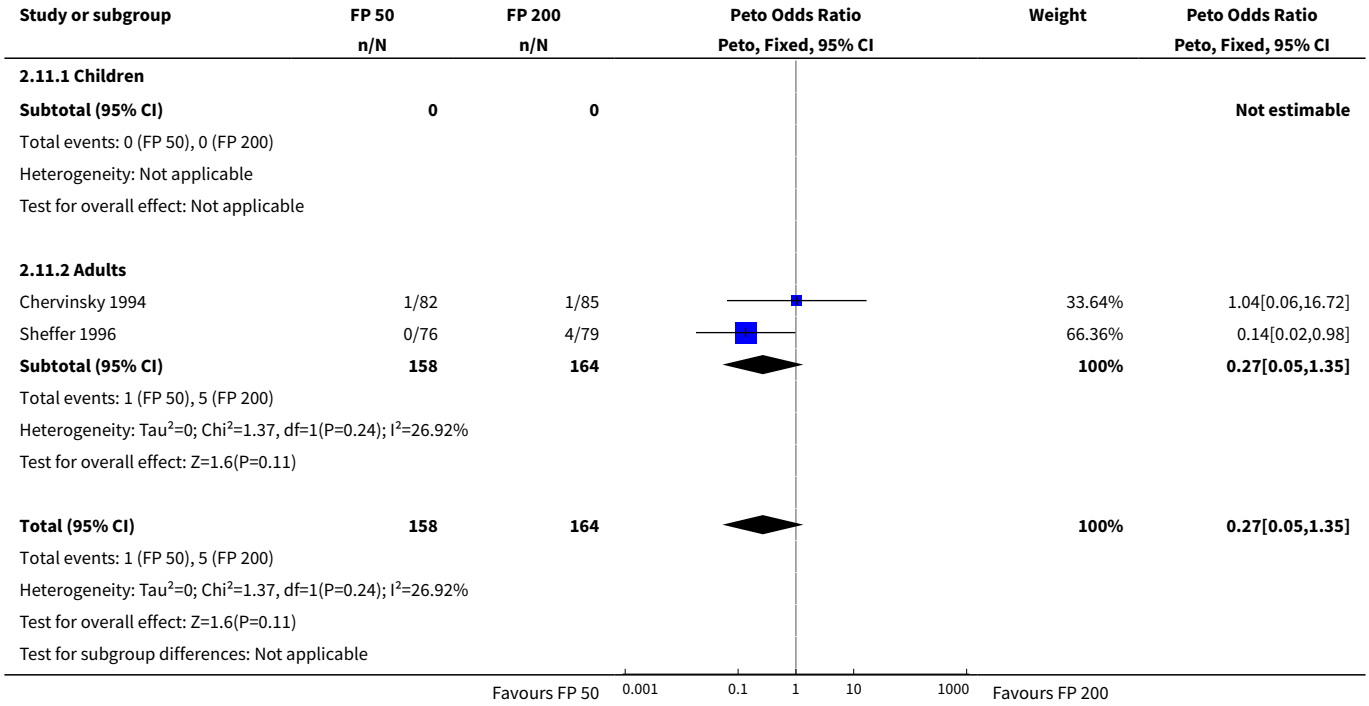


Analysis 2.10. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 10 Hoarseness or dysphonia (No. of patients).



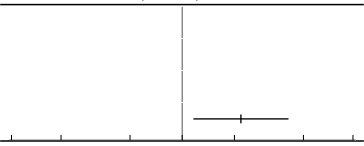


Analysis 2.11. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 11 Oral Candidiasis (No. of patients).



Analysis 2.12. Comparison 2 Parallel group studies, no oral steroids: 50 versus 200 mcg/d (all ages), Outcome 12 Physician global rated efficacy: ineffective.

Study or subgroup	FP 50 n/N	FP 200 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
2.12.1 Children				
2.12.2 Adults				
Chervinsky 1994	37/82	23/85		2.18[1.16,4.1]



Comparison 3. Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change in FEV1 compared to base-line (litres)	10		Litres (Fixed, 95% CI)	Subtotals only
1.1 Children	4	656	Litres (Fixed, 95% CI)	-0.04 [-0.09, 0.01]
1.2 Adults	6	887	Litres (Fixed, 95% CI)	0.03 [-0.02, 0.07]
2 Change in FEV1 compared to base-line (litres)	10		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 Children	4	656	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.08, 0.02]
2.2 Adults	6	887	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.05, 0.07]
3 FEV1 (% predicted)	2		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	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 FEV1 (% predicted)	2	432	% (Fixed, 95% CI)	-0.52 [-3.83, 2.79]
4.1 Children	1	179	% (Fixed, 95% CI)	-2.0 [-6.00, 2.00]
4.2 Adults	1	253	% (Fixed, 95% CI)	2.70 [-3.19, 8.59]
5 FEV1 Litres	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 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]
6.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
7 Change in clinic PEFR compared to baseline (L/min)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Children	2	351	Mean Difference (IV, Fixed, 95% CI)	3.00 [-6.84, 12.84]
7.2 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Change in morning PEFR compared to baseline (L/min)	11		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Children	4	710	Mean Difference (IV, Fixed, 95% CI)	-3.67 [-9.81, 2.46]
8.2 Adults	7	1148	Mean Difference (IV, Fixed, 95% CI)	-7.04 [-11.87, -2.20]
9 Change in evening PEFR compared to baseline (L/min)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 Children	2	351	Mean Difference (IV, Fixed, 95% CI)	-4.50 [-11.77, 2.77]
9.2 Adults	4	648	Mean Difference (IV, Fixed, 95% CI)	-7.04 [-12.66, -1.43]
10 Rescue medication usage	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]
11 Change in daily use of beta2 agonist compared to baseline (puffs/d)	9	1409	Mean Difference (IV, Fixed, 95% CI)	0.14 [-0.09, 0.37]
11.1 Children	3	522	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.14, 0.49]
11.2 Adults	6	887	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.21, 0.42]
12 Symptom scores	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 Change in daily asthma symptom score compared to baseline	8	1252	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.07, 0.15]
13.1 Children	3	522	Std. Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.17, 0.18]
13.2 Adults	5	730	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.08, 0.21]
14 Change in number of night-time awakenings/week compared to base-line	4	661	Mean Difference (IV, Fixed, 95% CI)	0.05 [0.01, 0.09]
14.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

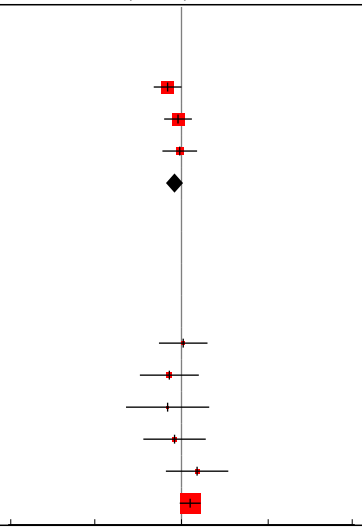
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 Adults	4	661	Mean Difference (IV, Fixed, 95% CI)	0.05 [0.01, 0.09]
15 Percentage of symptom-free days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Change in night-time awakening score compared to baseline	6	921	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [0.04, 0.30]
16.1 Children	2	351	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.04, 0.38]
16.2 Adults	4	570	Std. Mean Difference (IV, Fixed, 95% CI)	0.17 [0.01, 0.34]
17 HRQOL: Functional Status IIR questionaire (short version)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 HRQOL: Sleep Scale Children questionnaire	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
18.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 HRQOL: Quality of Life of Parents of Asthmatic Children questionnaire, burden dimension	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 HRQOL: Quality of Life of Parents of Asthmatic Children questionnaire, subjective norms dimension	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 HRQOL: Quality of Life of Parents of Asthmatic Children questionnaire, subjective norms dimension	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
21.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21.2 Adults	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
22 Physician global rated efficacy: ineffective	2	357	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.77, 2.44]
22.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.2 Adults	2	357	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [0.77, 2.44]
23 Withdrawal due to asthma exacerbation (No. of patients)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
23.1 Children	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 Adults	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
24 Withdrawals due to adverse events	3	627	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.54, 2.47]
24.1 Children	0	0	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Adults	3	627	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.54, 2.47]
25 Number of patients withdrawn due to lack of efficacy	9	1657	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.76, 1.35]
25.1 Children	3	522	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.79, 1.97]
25.2 Adults	6	1135	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.61, 1.28]
26 Oral Candidiasis (No. of patients)	6	1150	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.46, 2.08]
26.1 Children	2	391	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.33 [0.30, 5.90]
26.2 Adults	4	759	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.88 [0.37, 2.11]
27 Headaches	3	511	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.15, 2.60]
27.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
27.2 Adults	3	511	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.62 [0.15, 2.60]
28 Sore throat or pharyngitis (No. of patients)	5	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.71, 4.93]

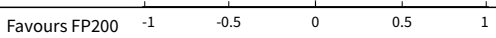
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
28.2 Adults	5	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.87 [0.71, 4.93]
29 Hoarseness or dysphonia (No. of patients)	7	1365	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.27, 1.57]
29.1 Children	2	391	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.20, 4.99]
29.2 Adults	5	974	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.54 [0.19, 1.55]
30 Urinary free cortisol excretion (mcg/24 hours)	2	228	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-3.73, 2.32]
30.1 Children	2	228	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-3.73, 2.32]
30.2 Adults	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Morning plasma cortisol (mcg/dL)	3	377	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-1.01, 0.89]
31.1 Children	2	333	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-1.14, 0.99]
31.2 Adults	1	44	Mean Difference (IV, Fixed, 95% CI)	0.0 [-2.09, 2.09]

Analysis 3.1. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 1 Change in FEV1 compared to baseline (litres).

Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
3.1.1 Children						
FLIP39	86	80	-0.2 (0)			Not estimable
Katz 1998	69	70	-0.1 (0.041)		37.88%	-0.08[-0.16,-0]
Peden 1998	90	87	-0 (0.041)		37.88%	-0.02[-0.1,0.06]
Peden 1998a	91	83	-0 (0.051)		24.24%	-0.01[-0.11,0.09]
Subtotal (95% CI)					**100%**	**-0.04[-0.09,0.01]**
Heterogeneity: Tau^2=0; Chi^2=1.55, df=2(P=0.46); I^2=0%						
Test for overall effect: Z=1.61(P=0.11)						
3.1.2 Adults						
Galant 1996	91	86	0 (0.071)		11.53%	0.01[-0.13,0.15]
Nathan 2000	79	81	-0.1 (0.087)		7.82%	-0.07[-0.24,0.1]
Noonan 1998	35	34	-0.1 (0.122)		3.92%	-0.08[-0.32,0.16]
Pearlman 1997	85	81	-0 (0.092)		6.98%	-0.04[-0.22,0.14]
Sheffer 1996	79	79	0.1 (0.092)		6.98%	0.09[-0.09,0.27]
Wasserman 1996	79	78	0.1 (0.031)		62.78%	0.05[-0.01,0.11]

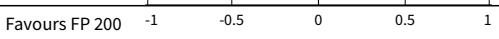


Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
Subtotal (95% CI)					**100%**	**0.03[-0.02,0.07]**
Heterogeneity: Tau²=0; Chi²=3.64, df=5(P=0.6); I²=0%						
Test for overall effect: Z=1.13(P=0.26)						
Test for subgroup differences: Chi²=3.76, df=1 (P=0.05), I²=73.43%						



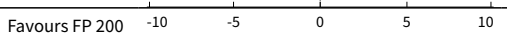
Analysis 3.2. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 2 Change in FEV1 compared to baseline (litres).

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.2.1 Children							
FLIP39	86	0 (0)	80	0.2 (0)			Not estimable
Katz 1998	69	0.2 (0.3)	70	0.3 (0.3)		36.27%	-0.08[-0.16,0]
Peden 1998	90	0.2 (0.3)	87	0.2 (0.3)		36.81%	-0.02[-0.1,0.06]
Peden 1998a	91	0.2 (0.3)	83	0.2 (0.4)		26.92%	0.01[-0.09,0.11]
Subtotal ***	**336**		**320**			**100%**	**-0.03[-0.08,0.02]**
Heterogeneity: Tau²=0; Chi²=2.09, df=2(P=0.35); I²=4.12%							
Test for overall effect: Z=1.32(P=0.19)							
3.2.2 Adults							
Galant 1996	91	0.7 (0.5)	86	0.7 (0.5)		20.28%	0.01[-0.13,0.15]
Nathan 2000	79	0.2 (0.5)	81	0.3 (0.5)		14.77%	-0.07[-0.24,0.1]
Noonan 1998	35	0.3 (0.4)	34	0.4 (0.6)		7.19%	-0.08[-0.32,0.16]
Pearlman 1997	85	0.4 (0.6)	81	0.5 (0.6)		12.3%	-0.04[-0.22,0.14]
Sheffer 1996	79	0.5 (0.5)	79	0.4 (0.6)		12.55%	0.09[-0.09,0.27]
Wasserman 1996	79	0.6 (0.4)	78	0.5 (0.4)		32.9%	0.05[-0.06,0.16]
Subtotal ***	**448**		**439**			**100%**	**0.01[-0.05,0.07]**
Heterogeneity: Tau²=0; Chi²=2.99, df=5(P=0.7); I²=0%							
Test for overall effect: Z=0.27(P=0.79)							
Test for subgroup differences: Chi²=1.05, df=1 (P=0.3), I²=5.12%							

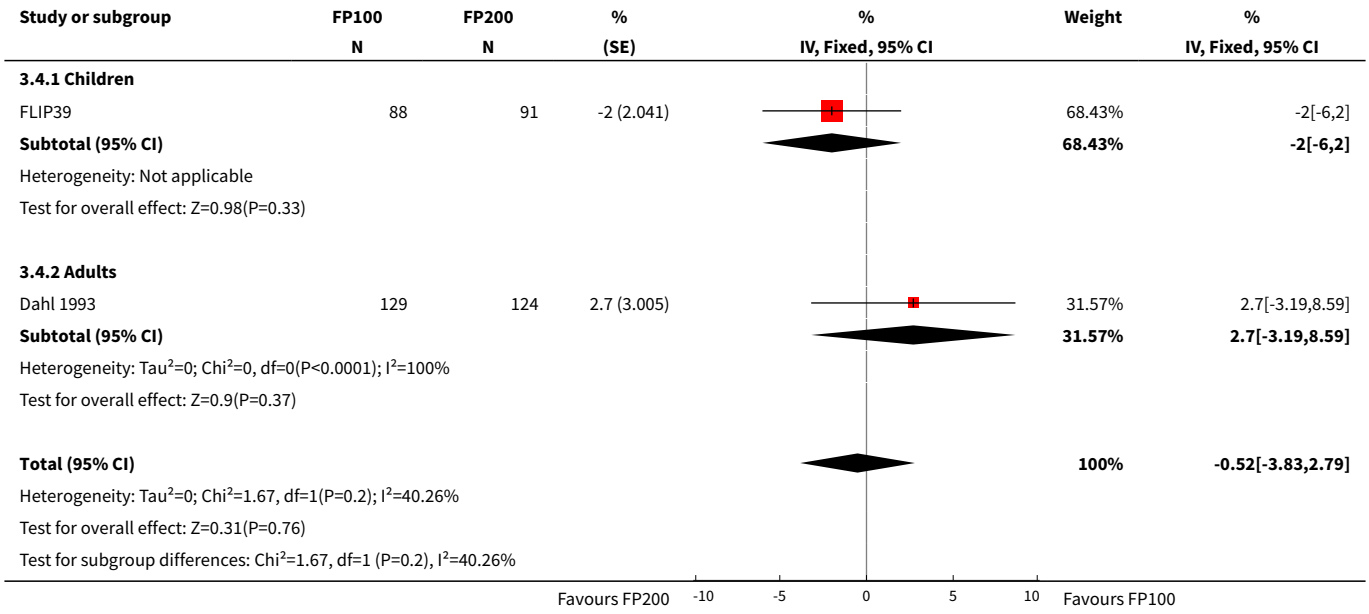


Analysis 3.3. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 3 FEV1 (% predicted).

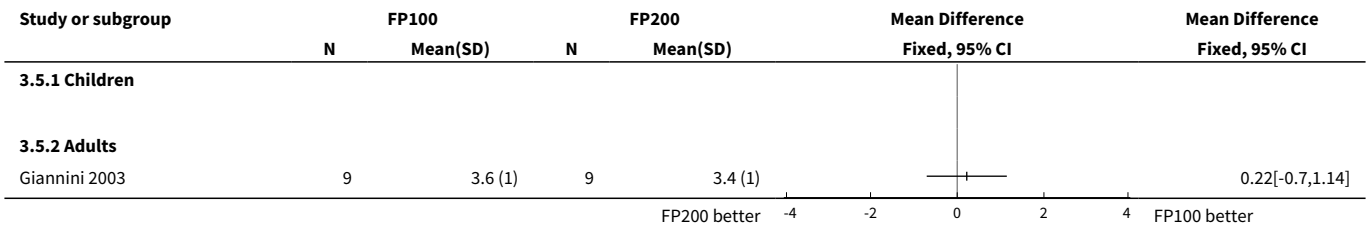
Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.3.1 Children						
FLIP39	88	85 (0)	91	87 (0)		Not estimable
3.3.2 Adults						
Dahl 1993	129	76.2 (22.1)	124	73.5 (25.5)		2.7[-3.19,8.59]



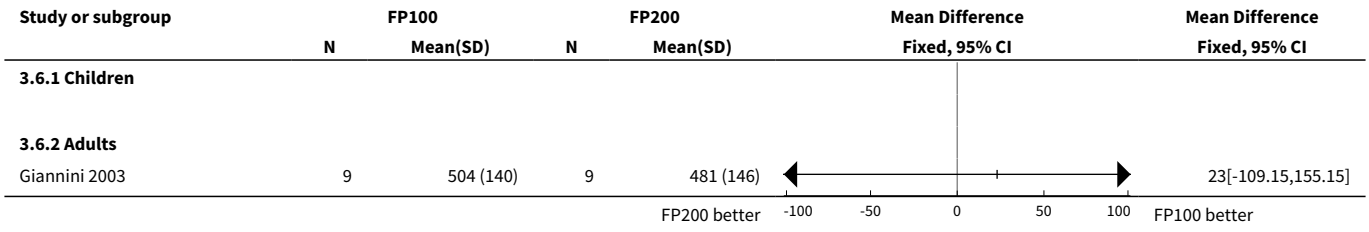
Analysis 3.4. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 4 FEV1 (% predicted).



Analysis 3.5. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 5 FEV1 Litres.

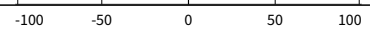


Analysis 3.6. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 6 PEF (L/min).



Analysis 3.7. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 7 Change in clinic PEFR compared to baseline (L/min).

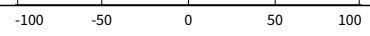
Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP200 N	FP200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.7.1 Children							
Peden 1998	90	51 (47)	87	48 (47)		50.44%	3[-10.85,16.85]
Peden 1998a	91	55 (48)	83	52 (46)		49.56%	3[-10.97,16.97]
Subtotal ***	**181**		**170**			**100%**	**3[-6.84,12.84]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Z=0.6(P=0.55)							
3.7.2 Adults							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Favours FP 200 Favours FP 100

Analysis 3.8. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 8 Change in morning PEFR compared to baseline (L/min).

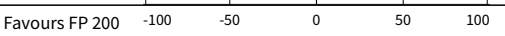
Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.8.1 Children							
FLIP39	91	19 (40.6)	97	20 (42.8)		26.54%	-1[-12.91,10.91]
Katz 1998	85	50 (46)	86	57 (46)		19.81%	-7[-20.79,6.79]
Peden 1998	90	34 (28)	87	40 (46)		29.69%	-6[-17.26,5.26]
Peden 1998a	91	41 (48)	83	42 (36)		23.96%	-1[-13.54,11.54]
Subtotal ***	**357**		**353**			**100%**	**-3.67[-9.81,2.46]**
Heterogeneity: Tau²=0; Chi²=0.76, df=3(P=0.86); I²=0%							
Test for overall effect: Z=1.17(P=0.24)							
3.8.2 Adults							
Dahl 1993	129	5 (32)	132	13 (37)		33.26%	-8[-16.39,0.39]
Galant 1996	91	54 (57)	86	49 (57)		8.29%	5[-11.8,21.8]
Nathan 2000	79	1 (35.6)	81	11 (36)		19.03%	-10[-21.09,1.09]
Noonan 1998	35	29 (65)	34	34 (52)		3.04%	-5[-32.73,22.73]
Pearlman 1997	85	20 (46)	81	16 (54)		10%	4[-11.29,19.29]
Sheffer 1996	79	27 (53.3)	79	45 (53.3)		8.47%	-18[-34.62,-1.38]
Wasserman 1996	79	33 (26.6)	78	42 (44.2)		17.91%	-9[-20.43,2.43]
Subtotal ***	**577**		**571**			**100%**	**-7.04[-11.87,-2.2]**
Heterogeneity: Tau²=0; Chi²=6.1, df=6(P=0.41); I²=1.68%							
Test for overall effect: Z=2.85(P=0)							
Test for subgroup differences: Chi²=0.71, df=1 (P=0.4), I²=0%							



Favours FP 200 Favours FP 100

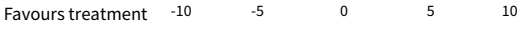
Analysis 3.9. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 9 Change in evening PEFR compared to baseline (L/min).

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.9.1 Children							
Peden 1998	90	26 (28)	87	34 (37)		56.29%	-8[-17.69,1.69]
Peden 1998a	91	36 (38)	83	36 (36)		43.71%	0[-11,11]
Subtotal ***	**181**		**170**			**100%**	**-4.5[-11.77,2.77]**
Heterogeneity: Tau^2=0; Chi^2=1.14, df=1(P=0.28); I^2=12.61%							
Test for overall effect: Z=1.21(P=0.22)							
3.9.2 Adults							
Dahl 1993	129	2 (32)	132	7 (31)		53.93%	-5[-12.65,2.65]
Nathan 2000	79	7 (44.4)	81	11 (36)		20.02%	-4[-16.55,8.55]
Noonan 1998	35	16 (23)	34	29 (47)		10.25%	-13[-30.54,4.54]
Sheffer 1996	79	21 (35.5)	79	35 (53.3)		15.81%	-14[-28.12,0.12]
Subtotal ***	**322**		**326**			**100%**	**-7.04[-12.66,-1.43]**
Heterogeneity: Tau^2=0; Chi^2=1.88, df=3(P=0.6); I^2=0%							
Test for overall effect: Z=2.46(P=0.01)							
Test for subgroup differences: Chi^2=0.29, df=1 (P=0.59), I^2=0%							



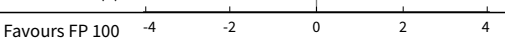
Analysis 3.10. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 10 Rescue medication usage.

Study or subgroup	FP100 N	FP100 Mean(SD)	FP200 N	FP200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.10.1 Children						
3.10.2 Adults						
Giannini 2003	9	0 (0)	9	0.1 (0.4)		Not estimable

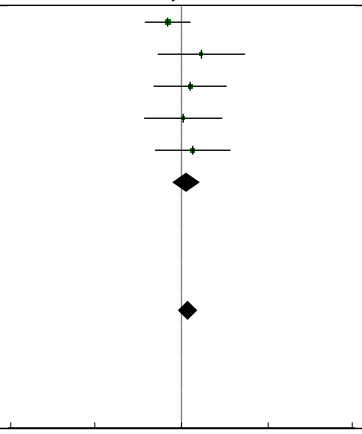


Analysis 3.11. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 11 Change in daily use of beta2 agonist compared to baseline (puffs/d).

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.11.1 Children							
Katz 1998	85	-0.7 (1.7)	86	-1 (1.7)		20.36%	0.32[-0.18,0.82]
Peden 1998	90	-0.7 (2.2)	87	-1 (1.9)		14.2%	0.29[-0.31,0.89]
Peden 1998a	91	-1 (1.7)	83	-0.9 (2.1)		15.42%	-0.12[-0.69,0.45]
Subtotal ***	**266**		**256**			**49.98%**	**0.18[-0.14,0.49]**
Heterogeneity: Tau^2=0; Chi^2=1.48, df=2(P=0.48); I^2=0%							
Test for overall effect: Z=1.08(P=0.28)							
3.11.2 Adults							
Galant 1996	91	-1.7 (2.9)	86	-2.5 (3)		6.7%	0.8[-0.07,1.67]

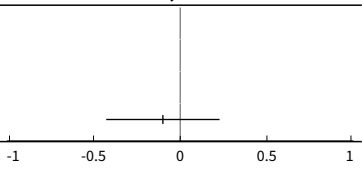


Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nathan 2000	79	-0.5 (1.7)	81	-0.2 (1.7)		18.27%	-0.32[-0.85,0.21]
Noonan 1998	35	-0.9 (2)	34	-1.4 (2.3)		5%	0.46[-0.55,1.47]
Pearlman 1997	85	-0.9 (2.8)	81	-1.1 (2.8)		7.11%	0.2[-0.64,1.04]
Sheffer 1996	79	-1.8 (3)	79	-1.8 (2.8)		6.23%	0.04[-0.86,0.94]
Wasserman 1996	79	-1.3 (2.8)	78	-1.6 (2.8)		6.71%	0.26[-0.61,1.13]
Subtotal ***	**448**		**439**			**50.02%**	**0.1[-0.21,0.42]**
Heterogeneity: Tau²=0; Chi²=5.62, df=5(P=0.35); I²=11.01%							
Test for overall effect: Z=0.64(P=0.52)							
Total ***	**714**		**695**			**100%**	**0.14[-0.09,0.37]**
Heterogeneity: Tau²=0; Chi²=7.2, df=8(P=0.52); I²=0%							
Test for overall effect: Z=1.22(P=0.22)							
Test for subgroup differences: Chi²=0.1, df=1 (P=0.76), I²=0%							



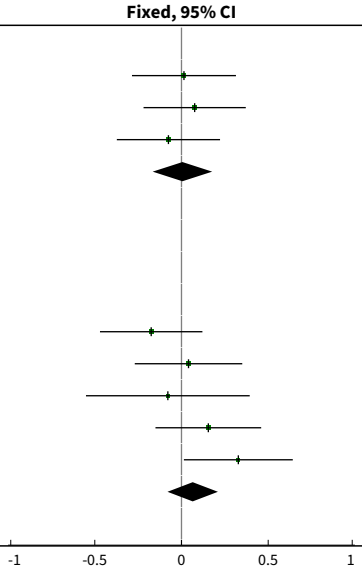
Analysis 3.12. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 12 Symptom scores.

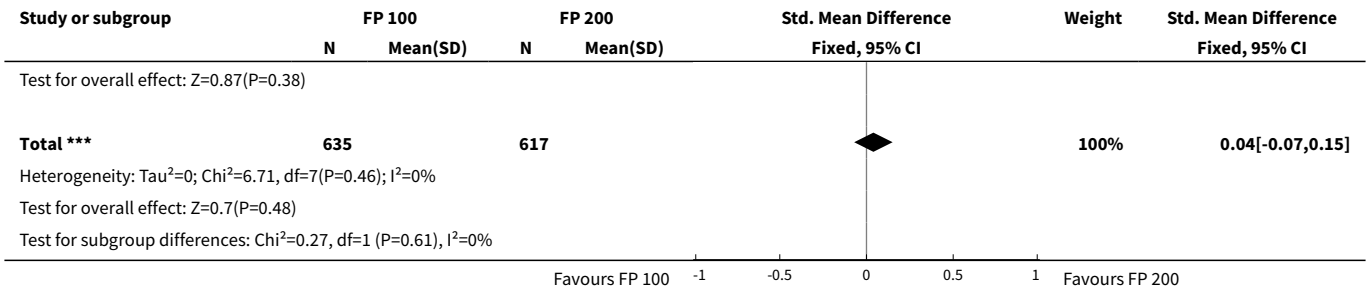
Study or subgroup	FP100 N	FP100 Mean(SD)	FP200 N	FP200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.12.1 Children						
3.12.2 Adults						
Giannini 2003	9	0.1 (0.3)	9	0.2 (0.4)		-0.1[-0.43,0.23]



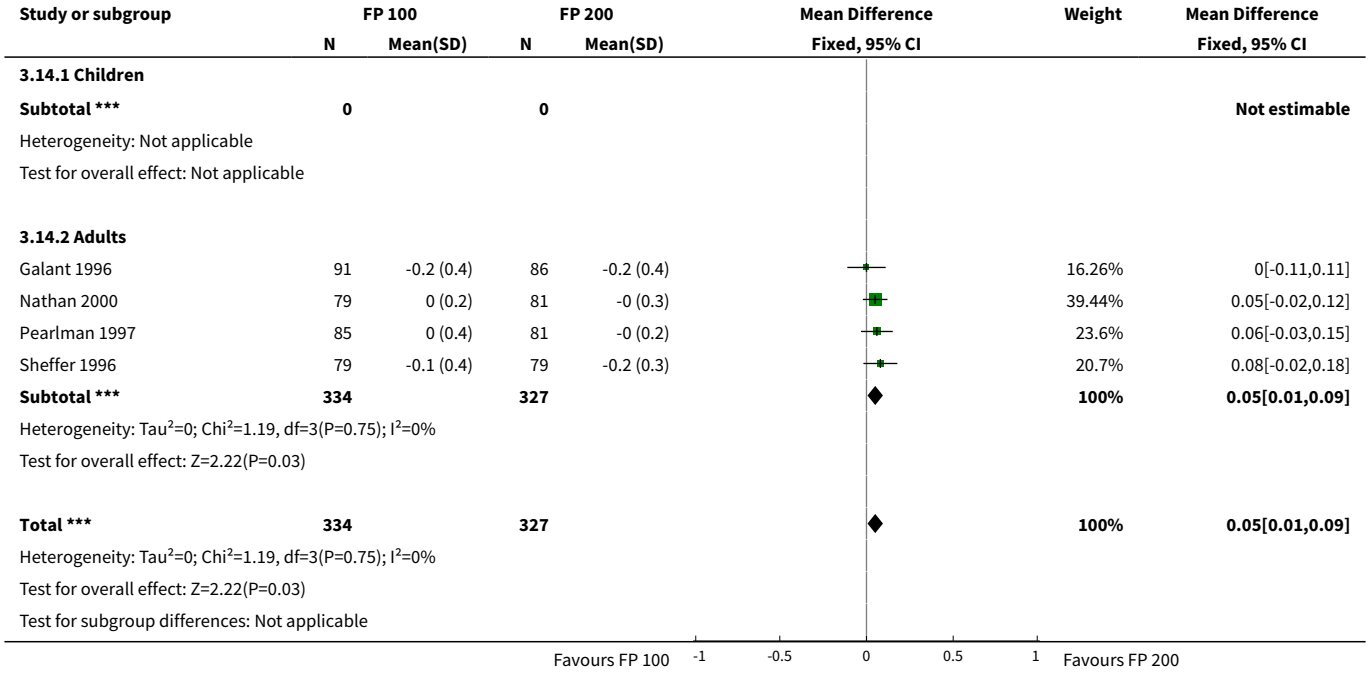
Analysis 3.13. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 13 Change in daily asthma symptom score compared to baseline.

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
3.13.1 Children							
Katz 1998	85	-0.4 (0.7)	86	-0.4 (0.7)		13.71%	0.01[-0.29,0.31]
Peden 1998	90	-0.4 (0.7)	87	-0.4 (0.7)		14.17%	0.08[-0.22,0.37]
Peden 1998a	91	-0.4 (0.7)	83	-0.4 (0.6)		13.91%	-0.08[-0.37,0.22]
Subtotal ***	**266**		**256**			**41.79%**	**0.01[-0.17,0.18]**
Heterogeneity: Tau²=0; Chi²=0.51, df=2(P=0.78); I²=0%							
Test for overall effect: Z=0.06(P=0.95)							
3.13.2 Adults							
Galant 1996	91	-0.6 (0.6)	86	-0.5 (0.6)		14.12%	-0.17[-0.47,0.12]
Nathan 2000	79	-0.2 (0.5)	81	-0.2 (0.5)		12.82%	0.04[-0.27,0.35]
Noonan 1998	35	-0.2 (0.4)	34	-0.2 (0.3)		5.52%	-0.08[-0.55,0.39]
Pearlman 1997	85	-0.1 (0.3)	81	-0.2 (0.4)		13.26%	0.15[-0.15,0.46]
Sheffer 1996	79	-0.4 (0.6)	79	-0.6 (0.5)		12.49%	0.33[0.01,0.64]
Subtotal ***	**369**		**361**			**58.21%**	**0.06[-0.08,0.21]**
Heterogeneity: Tau²=0; Chi²=5.93, df=4(P=0.2); I²=32.6%							

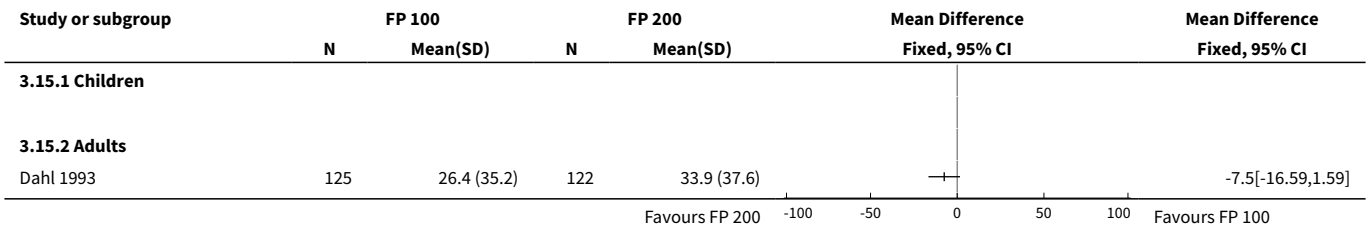




Analysis 3.14. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 14 Change in number of night-time awakenings/week compared to baseline.

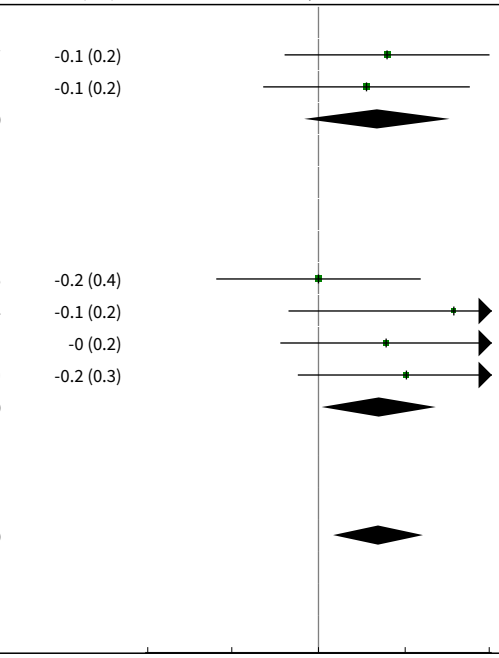


Analysis 3.15. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 15 Percentage of symptom-free days.



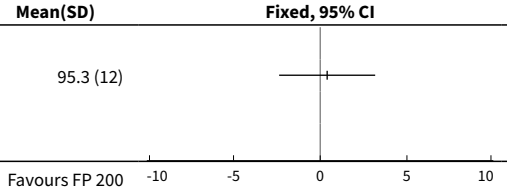
Analysis 3.16. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 16 Change in night-time awakening score compared to baseline.

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
3.16.1 Children							
Peden 1998	90	-0 (0.1)	87	-0.1 (0.2)		19.23%	0.2[-0.1,0.49]
Peden 1998a	91	-0 (0.1)	83	-0.1 (0.2)		18.92%	0.14[-0.16,0.44]
Subtotal ***	**181**		**170**			**38.15%**	**0.17[-0.04,0.38]**
Heterogeneity: Tau^2=0; Chi^2=0.08, df=1(P=0.78); I^2=0%							
Test for overall effect: Z=1.57(P=0.12)							
3.16.2 Adults							
Galant 1996	91	-0.2 (0.4)	86	-0.2 (0.4)		19.32%	0[-0.29,0.29]
Noonan 1998	35	-0 (0.2)	34	-0.1 (0.2)		7.39%	0.39[-0.09,0.87]
Pearlman 1997	85	0 (0.4)	81	-0 (0.2)		18.03%	0.2[-0.11,0.5]
Sheffer 1996	79	-0.1 (0.4)	79	-0.2 (0.3)		17.12%	0.25[-0.06,0.57]
Subtotal ***	**290**		**280**			**61.85%**	**0.17[0.01,0.34]**
Heterogeneity: Tau^2=0; Chi^2=2.4, df=3(P=0.49); I^2=0%							
Test for overall effect: Z=2.07(P=0.04)							
Total ***	**471**		**450**			**100%**	**0.17[0.04,0.3]**
Heterogeneity: Tau^2=0; Chi^2=2.47, df=5(P=0.78); I^2=0%							
Test for overall effect: Z=2.6(P=0.01)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.97), I^2=0%							



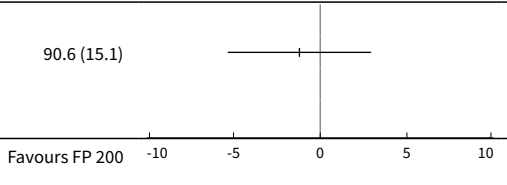
Analysis 3.17. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 17 HRQOL: Functional Status IIR questionaire (short version).

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.17.1 Children						
Allen 1998	104	95.7 (7.7)	101	95.3 (12)		0.4[-2.37,3.17]
3.17.2 Adults						



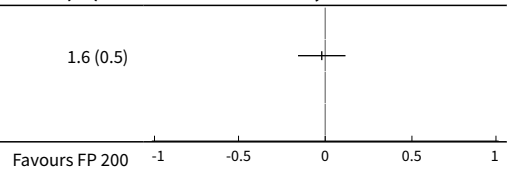
Analysis 3.18. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 18 HRQOL: Sleep Scale Children questionnaire.

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.18.1 Children						
Allen 1998	104	89.4 (15.1)	101	90.6 (15.1)		-1.2[-5.33,2.93]
3.18.2 Adults						



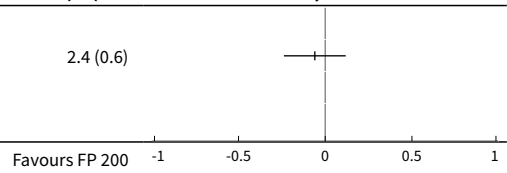
Analysis 3.19. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 19 HRQOL: Quality of Life of Parents of Asthmatic Children questionnaire, burden dimension.

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.19.1 Children						
Allen 1998	104	1.6 (0.5)	101	1.6 (0.5)		-0.02[-0.16,0.12]
3.19.2 Adults						



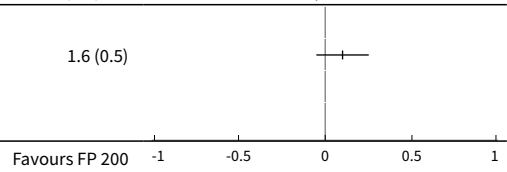
Analysis 3.20. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 20 HRQOL: Quality of Life of Parents of Asthmatic Children questionnaire, subjective norms dimension.

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.20.1 Children						
Allen 1998	104	2.3 (0.7)	101	2.4 (0.6)		-0.06[-0.24,0.12]
3.20.2 Adults						



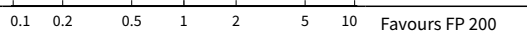
Analysis 3.21. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 21 HRQOL: Quality of Life of Parents of Asthmatic Children questionnaire, subjective norms dimension.

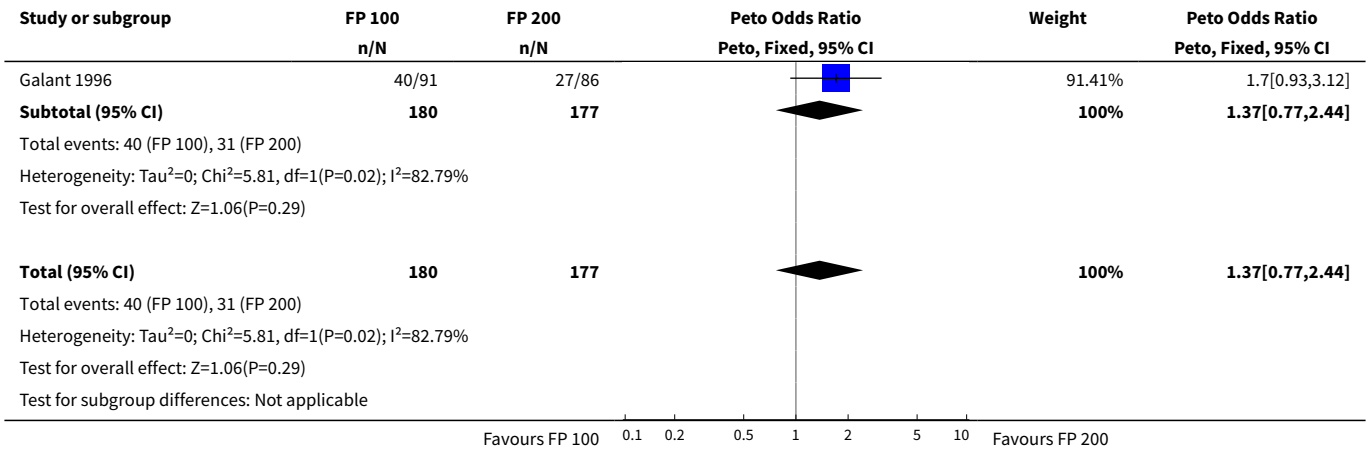
Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 200 N	FP 200 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
3.21.1 Children						
Allen 1998	104	1.7 (0.6)	101	1.6 (0.5)		0.1[-0.05,0.25]
3.21.2 Adults						



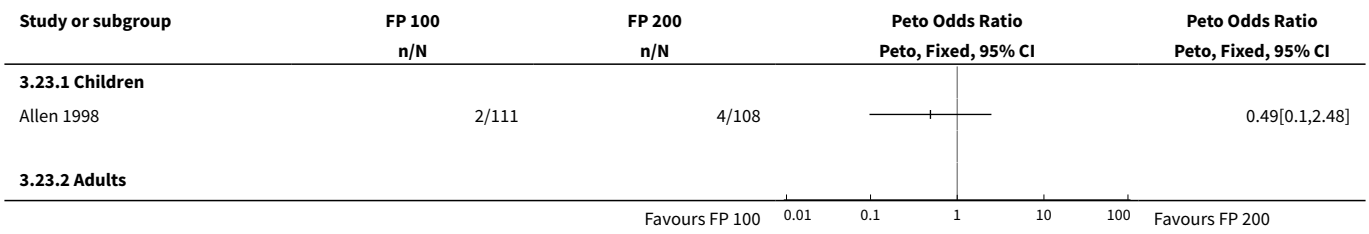
Analysis 3.22. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 22 Physician global rated efficacy: ineffective.

Study or subgroup	FP 100 n/N	FP 200 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.22.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 100), 0 (FP 200)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.22.2 Adults					
FLIP39	0/89	4/91		8.59%	0.13[0.02,0.97]

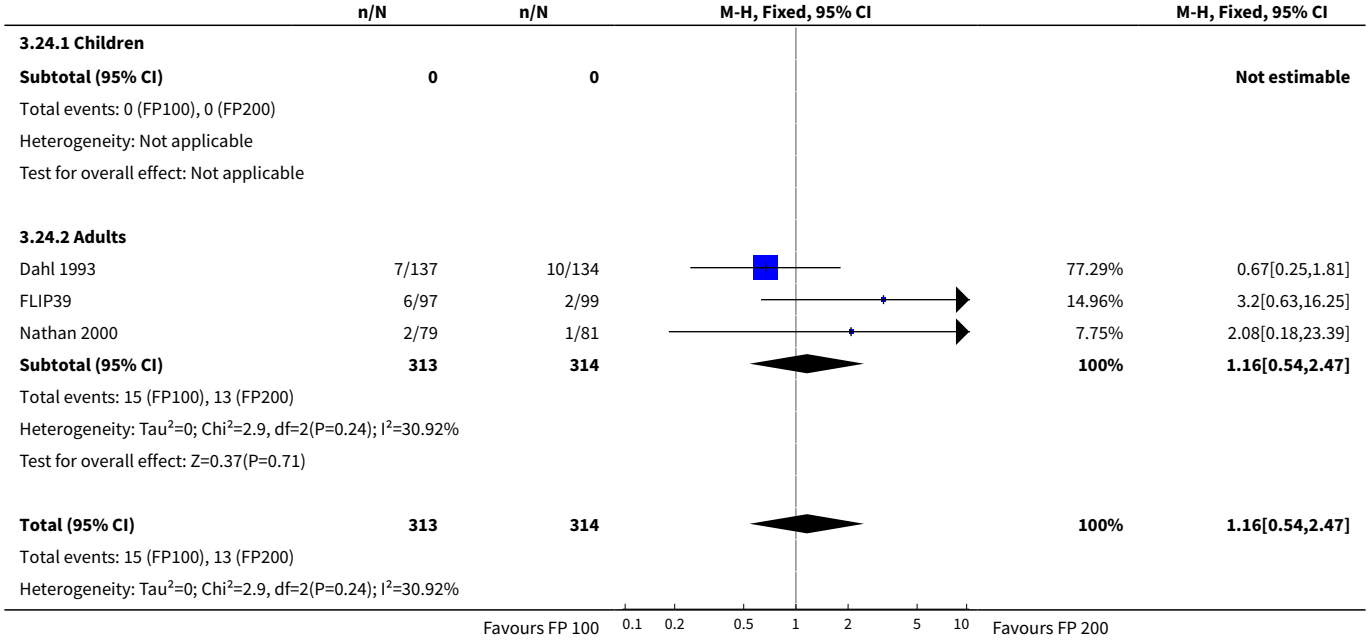


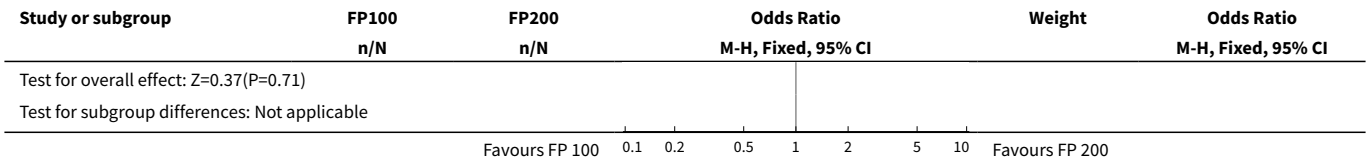


Analysis 3.23. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 23 Withdrawal due to asthma exacerbation (No. of patients).

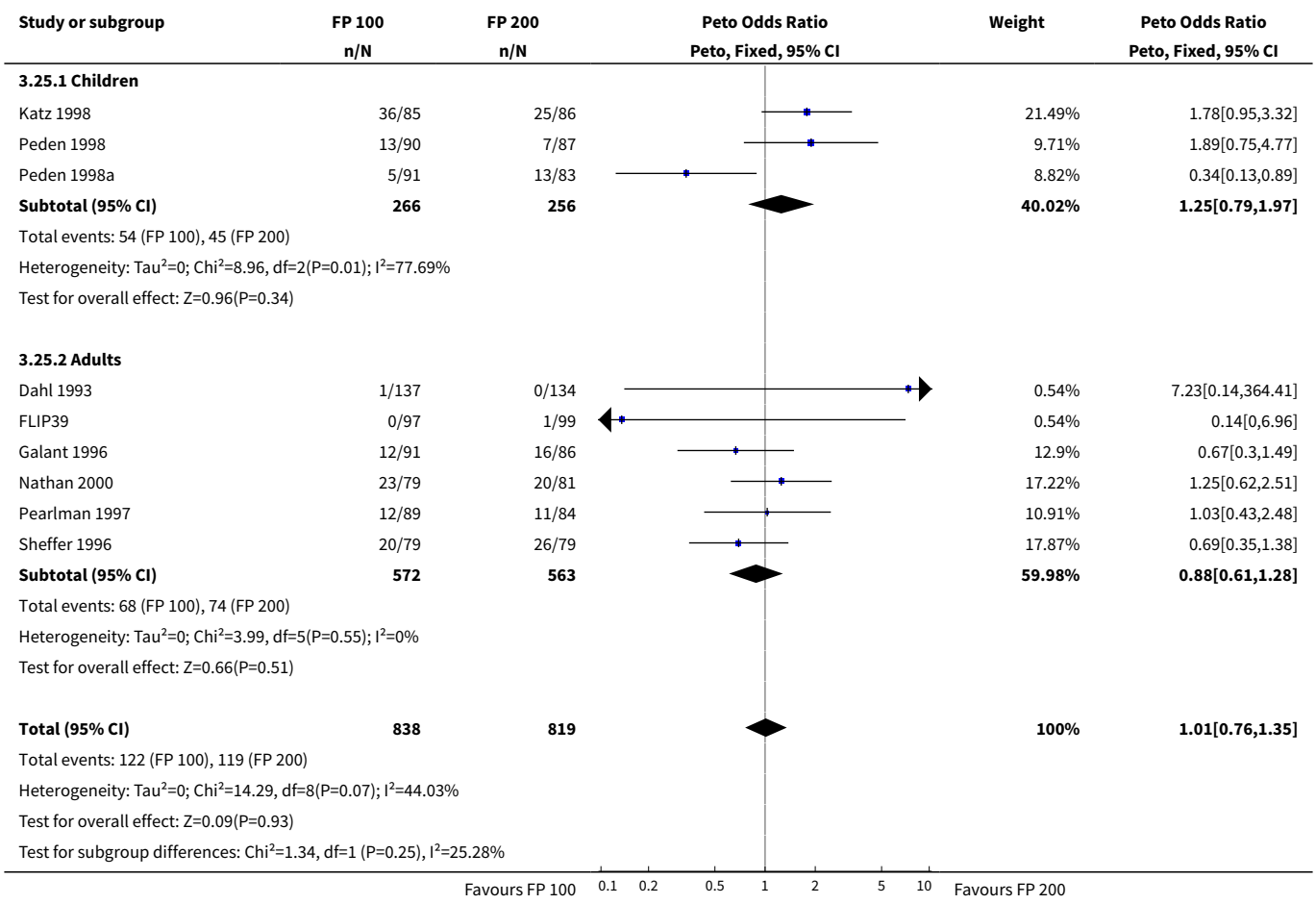


Analysis 3.24. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 24 Withdrawals due to adverse events.

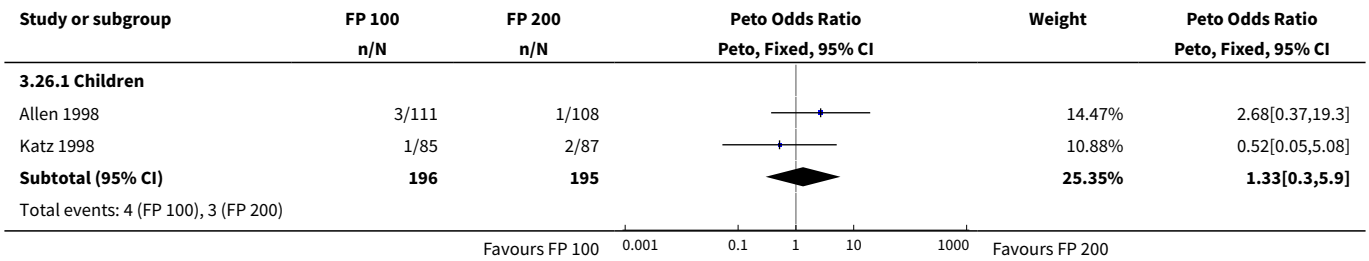


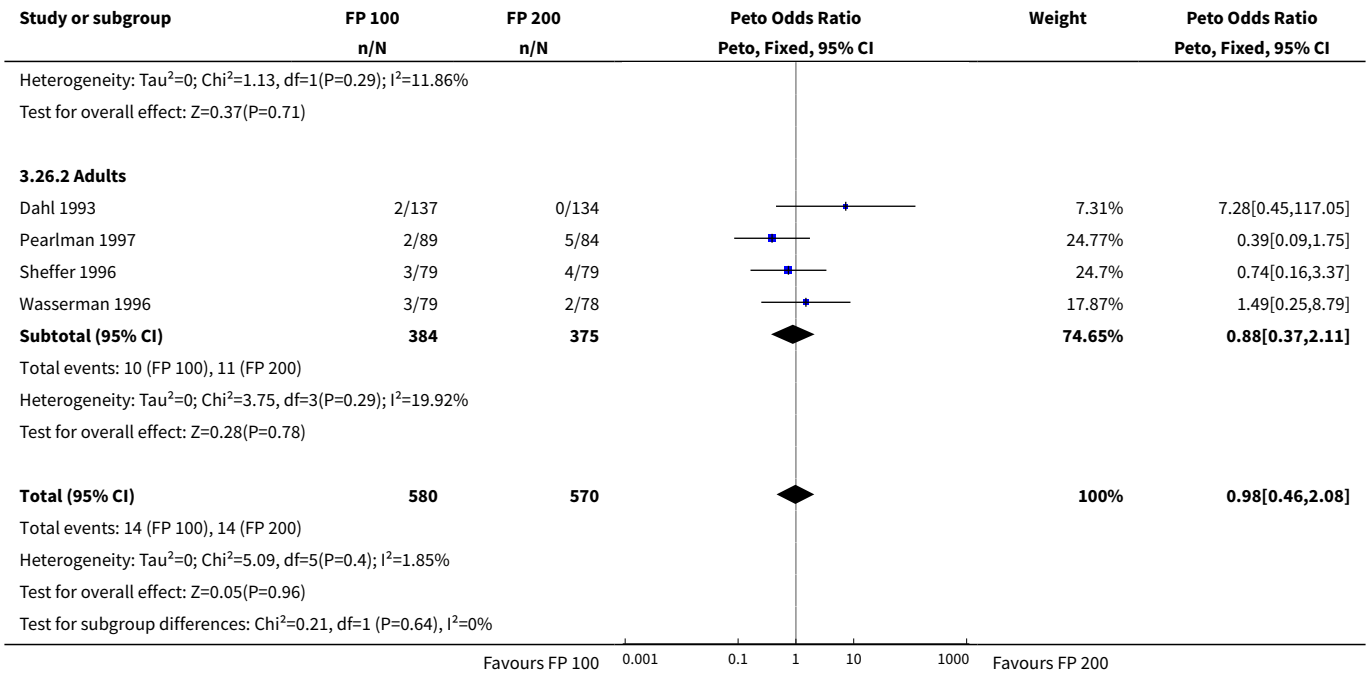


Analysis 3.25. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 25 Number of patients withdrawn due to lack of efficacy.

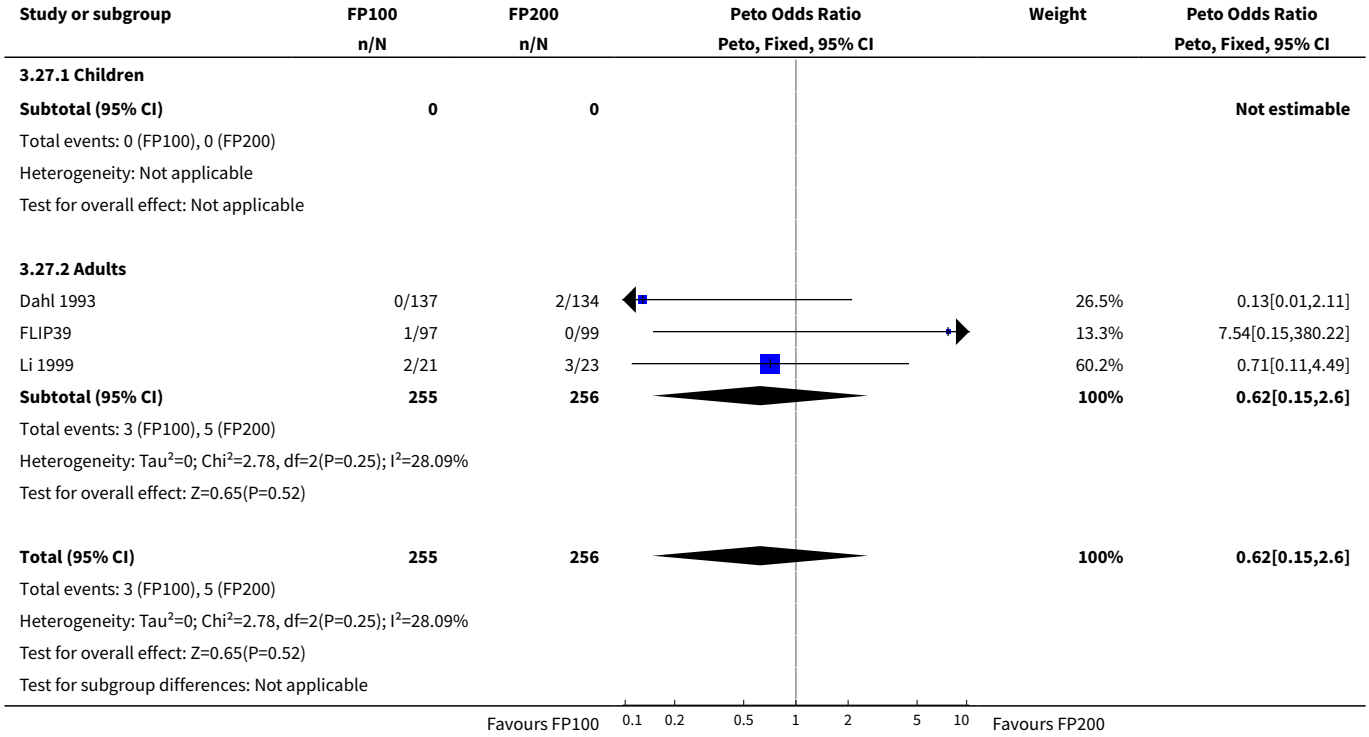


Analysis 3.26. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 26 Oral Candidiasis (No. of patients).



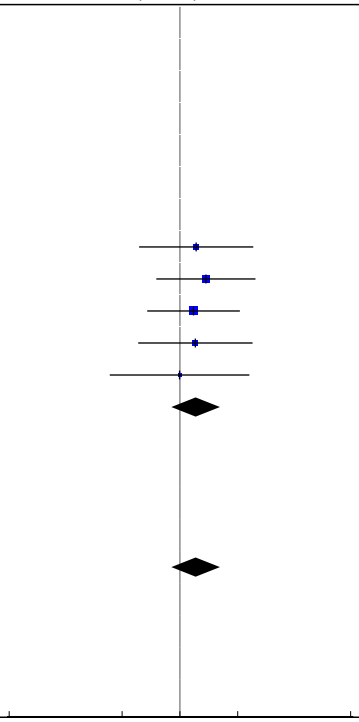


Analysis 3.27. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 27 Headaches.



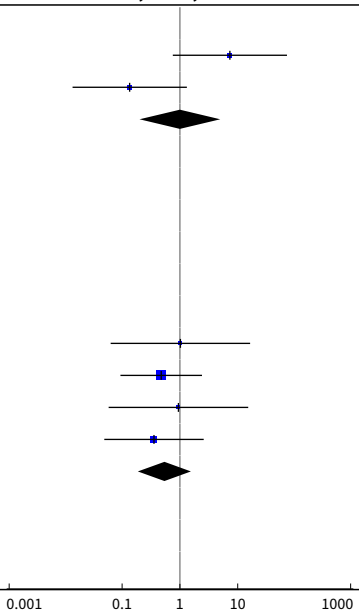
Analysis 3.28. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 28 Sore throat or pharyngitis (No. of patients).

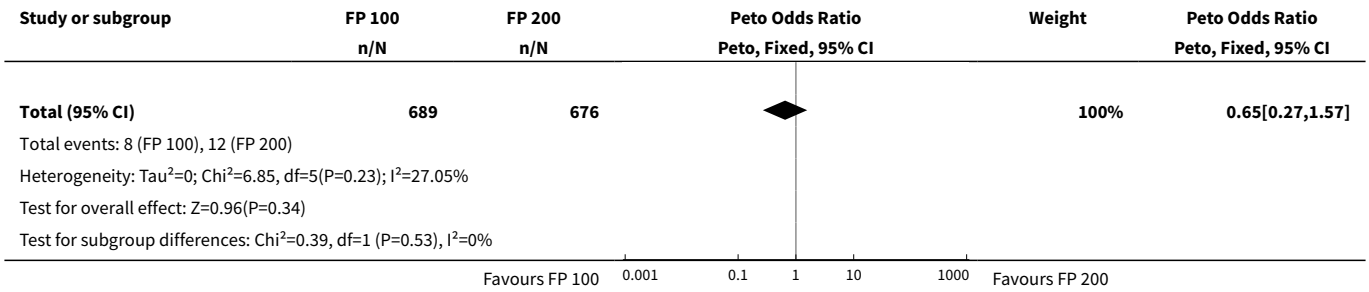
Study or subgroup	FP 100 n/N	FP 200 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.28.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 100), 0 (FP 200)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.28.2 Adults					
Dahl 1993	2/137	1/134		18.17%	1.91[0.2,18.56]
FLIP39	3/97	1/99		24.03%	2.82[0.39,20.32]
Li 1999	3/21	2/23		27.61%	1.72[0.27,10.86]
Pearlman 1997	2/89	1/84		18.08%	1.85[0.19,18.06]
Wasserman 1996	1/79	1/78		12.12%	0.99[0.06,15.93]
Subtotal (95% CI)	**423**	**418**		**100%**	**1.87[0.71,4.93]**
Total events: 11 (FP 100), 6 (FP 200)					
Heterogeneity: Tau^2=0; Chi^2=0.38, df=4(P=0.98); I^2=0%					
Test for overall effect: Z=1.27(P=0.2)					
Total (95% CI)	**423**	**418**		**100%**	**1.87[0.71,4.93]**
Total events: 11 (FP 100), 6 (FP 200)					
Heterogeneity: Tau^2=0; Chi^2=0.38, df=4(P=0.98); I^2=0%					
Test for overall effect: Z=1.27(P=0.2)					
Test for subgroup differences: Not applicable					



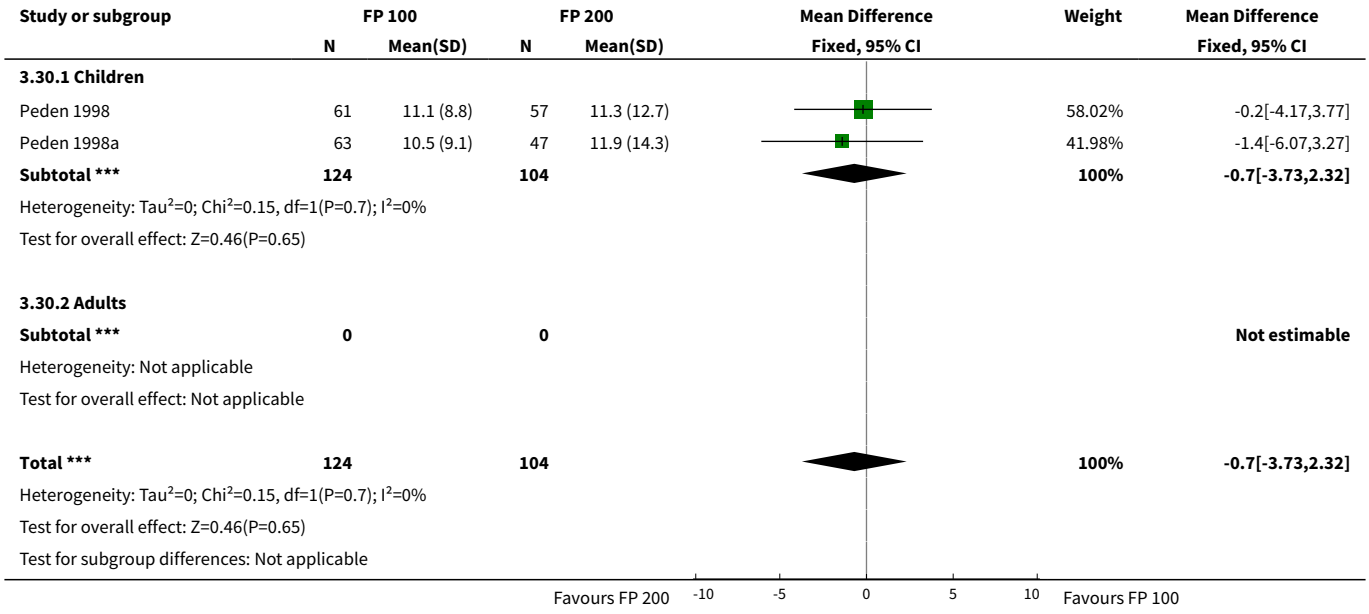
Analysis 3.29. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 29 Hoarseness or dysphonia (No. of patients).

Study or subgroup	FP 100 n/N	FP 200 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.29.1 Children					
Allen 1998	3/111	0/108		15.12%	7.32[0.75,71.17]
Katz 1998	0/85	3/87		15.08%	0.14[0.01,1.32]
Subtotal (95% CI)	**196**	**195**		**30.19%**	**1[0.2,4.99]**
Total events: 3 (FP 100), 3 (FP 200)					
Heterogeneity: Tau^2=0; Chi^2=5.91, df=1(P=0.02); I^2=83.08%					
Test for overall effect: Z=0(P=1)					
3.29.2 Adults					
Dahl 1993	0/137	0/134			Not estimable
FLIP39	1/97	1/99		10.12%	1.02[0.06,16.44]
Galant 1996	2/91	4/86		29.63%	0.47[0.09,2.41]
Pearlman 1997	1/89	1/84		10.11%	0.94[0.06,15.22]
Sheffer 1996	1/79	3/78		19.95%	0.36[0.05,2.58]
Subtotal (95% CI)	**493**	**481**		**69.81%**	**0.54[0.19,1.55]**
Total events: 5 (FP 100), 9 (FP 200)					
Heterogeneity: Tau^2=0; Chi^2=0.55, df=3(P=0.91); I^2=0%					
Test for overall effect: Z=1.14(P=0.25)					

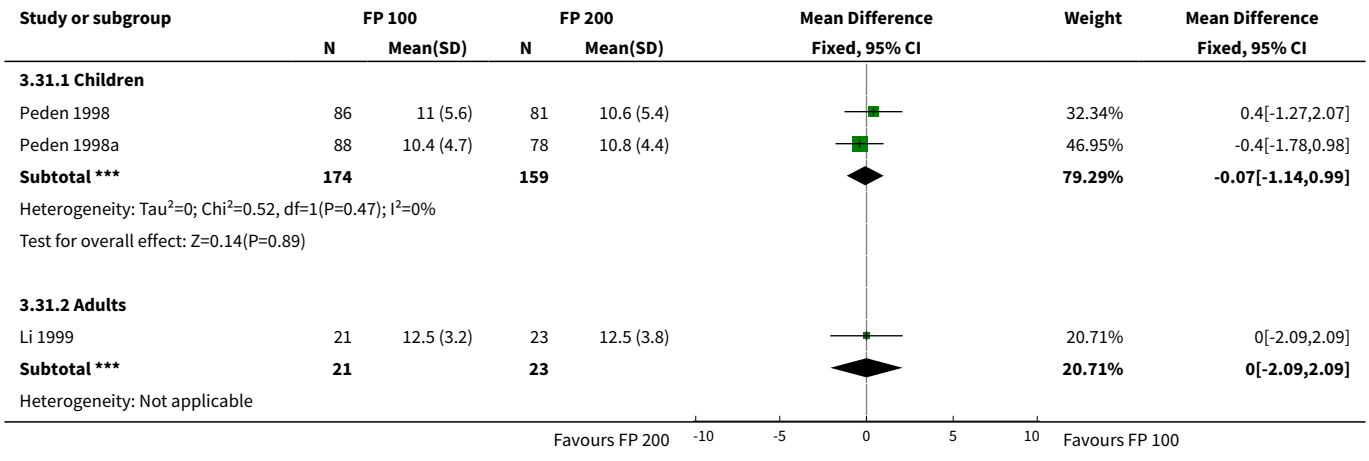


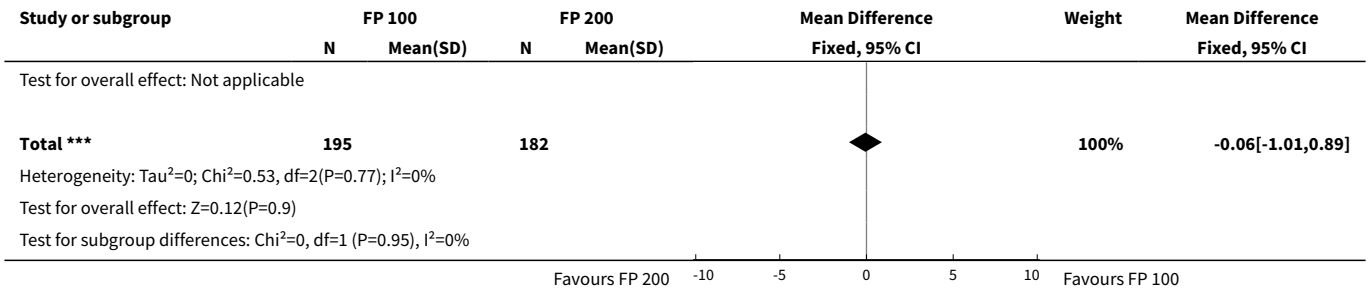


Analysis 3.30. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 30 Urinary free cortisol excretion (mcg/24 hours).



Analysis 3.31. Comparison 3 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (all ages), Outcome 31 Morning plasma cortisol (mcg/dL).





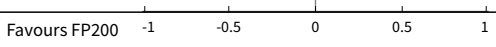
Comparison 4. Parallel group studies, no oral steroids: 100 versus 200 mcg/d (subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline based on study duration(litres) - children	3	490	Litres (Fixed, 95% CI)	-0.01 [-0.07, 0.05]
1.1 1-4 weeks	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 1-5 months	3	490	Litres (Fixed, 95% CI)	-0.01 [-0.07, 0.05]
1.3 6 months or more	0	0	Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in FEV1 compared to baseline based on study duration (litres) - adults	6		Litres (Fixed, 95% CI)	0.03 [-0.02, 0.07]
2.1 1-4 weeks	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 1-5 months	6		Litres (Fixed, 95% CI)	0.03 [-0.02, 0.07]
2.3 6 months or more	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in FEV1 compared to baseline (litres) based on delivery devices - children	3		Litres (Fixed, 95% CI)	-0.01 [-0.07, 0.05]
3.1 MDI	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 DPI	3		Litres (Fixed, 95% CI)	-0.01 [-0.07, 0.05]
4 Change in FEV1 compared to baseline based on delivery devices (litres) - adults	6		Litres (Fixed, 95% CI)	0.03 [-0.02, 0.07]
4.1 MDI	3		Litres (Fixed, 95% CI)	0.02 [-0.08, 0.12]
4.2 DPI	3		Litres (Fixed, 95% CI)	0.03 [-0.02, 0.08]
5 Change in FEV1 compared to baseline based on degrees of severity (litres) - children	3		Litres (Fixed, 95% CI)	-0.01 [-0.07, 0.05]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 Mild to moderate	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
5.2 Moderate	3		Litres (Fixed, 95% CI)	-0.01 [-0.07, 0.05]
6 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults	6		Litres (Fixed, 95% CI)	0.03 [-0.02, 0.07]
6.1 Mild to moderate	0		Litres (Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Moderate	6		Litres (Fixed, 95% CI)	0.03 [-0.02, 0.07]

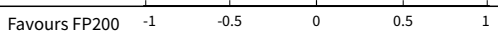
Analysis 4.1. Comparison 4 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (subgroups), Outcome 1 Change in FEV1 compared to baseline based on study duration(litres) - children.

Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
4.1.1 1-4 weeks						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.1.2 1-5 months						
Katz 1998	69	70	0 (0.066)		18.9%	0.01[-0.12,0.14]
Peden 1998	90	87	-0 (0.041)		49.45%	-0.02[-0.1,0.06]
Peden 1998a	91	83	-0 (0.051)		31.65%	-0.01[-0.11,0.09]
Subtotal (95% CI)					**100%**	**-0.01[-0.07,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=2(P=0.93); I^2=0%						
Test for overall effect: Z=0.39(P=0.7)						
4.1.3 6 months or more						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)					**100%**	**-0.01[-0.07,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=2(P=0.93); I^2=0%						
Test for overall effect: Z=0.39(P=0.7)						
Test for subgroup differences: Not applicable						



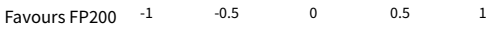
Analysis 4.2. Comparison 4 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (subgroups), Outcome 2 Change in FEV1 compared to baseline based on study duration (litres) - adults.

Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
4.2.1 1-4 weeks						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.2.2 1-5 months						
Galant 1996	91	86	0 (0.071)		11.53%	0.01[-0.13,0.15]
Nathan 2000	79	81	-0.1 (0.087)		7.82%	-0.07[-0.24,0.1]
Noonan 1998	35	34	-0.1 (0.122)		3.92%	-0.08[-0.32,0.16]
Pearlman 1997	85	81	-0 (0.092)		6.98%	-0.04[-0.22,0.14]
Sheffer 1996	79	79	0.1 (0.092)		6.98%	0.09[-0.09,0.27]
Wasserman 1996	79	78	0.1 (0.031)		62.78%	0.05[-0.01,0.11]
Subtotal (95% CI)					**100%**	**0.03[-0.02,0.07]**
Heterogeneity: Tau^2=0; Chi^2=3.64, df=5(P=0.6); I^2=0%						
Test for overall effect: Z=1.13(P=0.26)						
4.2.3 6 months or more						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)					**100%**	**0.03[-0.02,0.07]**
Heterogeneity: Tau^2=0; Chi^2=3.64, df=5(P=0.6); I^2=0%						
Test for overall effect: Z=1.13(P=0.26)						
Test for subgroup differences: Not applicable						



Analysis 4.3. Comparison 4 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (subgroups), Outcome 3 Change in FEV1 compared to baseline (litres) based on delivery devices - children.

Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
4.3.1 MDI						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.3.2 DPI						
Katz 1998	69	70	0 (0.066)		18.9%	0.01[-0.12,0.14]
Peden 1998	90	87	-0 (0.041)		49.45%	-0.02[-0.1,0.06]
Peden 1998a	91	83	-0 (0.051)		31.65%	-0.01[-0.11,0.09]
Subtotal (95% CI)					**100%**	**-0.01[-0.07,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=2(P=0.93); I^2=0%						
Test for overall effect: Z=0.39(P=0.7)						
Total (95% CI)					**100%**	**-0.01[-0.07,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=2(P=0.93); I^2=0%						



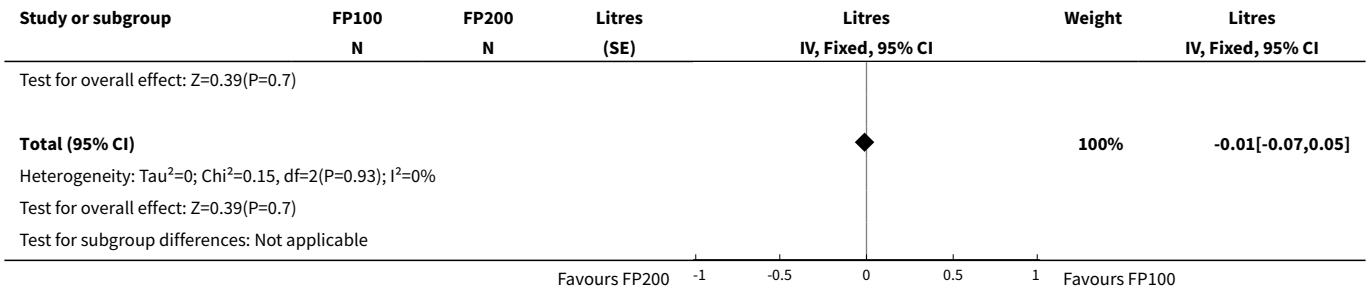
Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
Test for overall effect: Z=0.39(P=0.7)						
Test for subgroup differences: Not applicable						

Analysis 4.4. Comparison 4 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (subgroups), Outcome 4 Change in FEV1 compared to baseline based on delivery devices (litres) - adults.

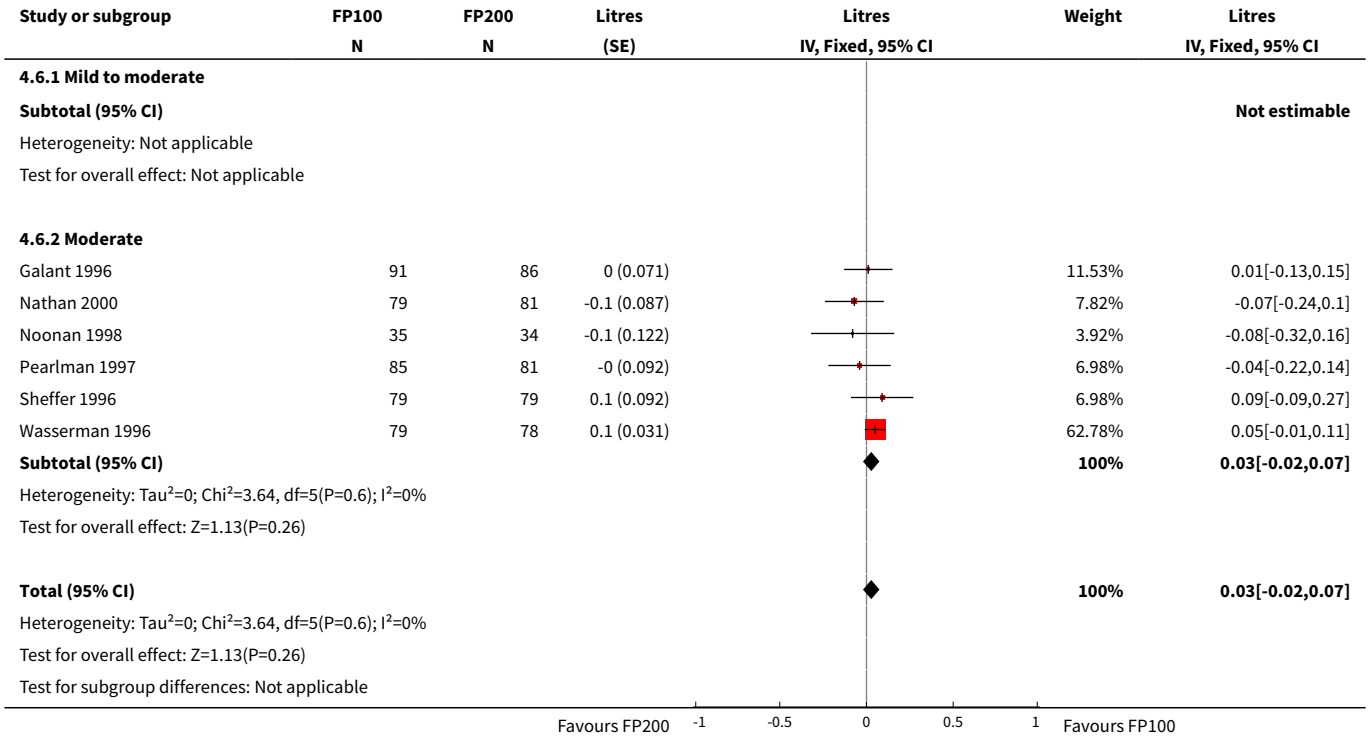
Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
4.4.1 MDI						
Galant 1996	91	86	0 (0.071)		11.53%	0.01[-0.13,0.15]
Noonan 1998	35	34	-0.1 (0.122)		3.92%	-0.08[-0.32,0.16]
Sheffer 1996	79	79	0.1 (0.092)		6.98%	0.09[-0.09,0.27]
Subtotal (95% CI)					**22.43%**	**0.02[-0.08,0.12]**
Heterogeneity: Tau^2=0; Chi^2=1.27, df=2(P=0.53); I^2=0%						
Test for overall effect: Z=0.37(P=0.71)						
4.4.2 DPI						
Nathan 2000	79	81	-0.1 (0.087)		7.82%	-0.07[-0.24,0.1]
Pearlman 1997	85	81	-0 (0.092)		6.98%	-0.04[-0.22,0.14]
Wasserman 1996	79	78	0.1 (0.031)		62.78%	0.05[-0.01,0.11]
Subtotal (95% CI)					**77.57%**	**0.03[-0.02,0.08]**
Heterogeneity: Tau^2=0; Chi^2=2.34, df=2(P=0.31); I^2=14.49%						
Test for overall effect: Z=1.08(P=0.28)						
Total (95% CI)					**100%**	**0.03[-0.02,0.07]**
Heterogeneity: Tau^2=0; Chi^2=3.64, df=5(P=0.6); I^2=0%						
Test for overall effect: Z=1.13(P=0.26)						
Test for subgroup differences: Chi^2=0.03, df=1 (P=0.85), I^2=0%						

Analysis 4.5. Comparison 4 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (subgroups), Outcome 5 Change in FEV1 compared to baseline based on degrees of severity (litres) - children.

Study or subgroup	FP100 N	FP200 N	Litres (SE)	Litres IV, Fixed, 95% CI	Weight	Litres IV, Fixed, 95% CI
4.5.1 Mild to moderate						
Subtotal (95% CI)						**Not estimable**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.2 Moderate						
Katz 1998	69	70	0 (0.066)		18.9%	0.01[-0.12,0.14]
Peden 1998	90	87	-0 (0.041)		49.45%	-0.02[-0.1,0.06]
Peden 1998a	91	83	-0 (0.051)		31.65%	-0.01[-0.11,0.09]
Subtotal (95% CI)					**100%**	**-0.01[-0.07,0.05]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=2(P=0.93); I^2=0%						



Analysis 4.6. Comparison 4 Parallel group studies, no oral steroids: 100 versus 200 mcg/d (subgroups), Outcome 6 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults.



Comparison 5. Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (% predicted)	4	551	Mean Difference (IV, Fixed, 95% CI)	-0.96 [-3.45, 1.53]
1.1 Children	2	114	Mean Difference (IV, Fixed, 95% CI)	-2.48 [-8.60, 3.64]
1.2 Adults	2	437	Mean Difference (IV, Fixed, 95% CI)	-0.66 [-3.39, 2.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Change in FEV1 compared to baseline (litres)	9	1283	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
2.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	9	1283	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
3 Change in FEV1 compared to baseline (litres - imputed estimates)	11	1720	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.04, 0.05]
3.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	11	1720	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.04, 0.05]
4 Change in FVC compared to baseline (litres)	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 FEF25-75 compared to baseline (L/second)	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 morning PEFR compared to baseline (L/min - imputed/estimated values)	13		Litres/min (Fixed, 95% CI)	Subtotals only
6.1 Children	2	876	Litres/min (Fixed, 95% CI)	-7.92 [-12.93, -2.91]
6.2 Adults	11	1713	Litres/min (Fixed, 95% CI)	-1.97 [-5.77, 1.82]
7 Change in morning PEFR compared to baseline (L/min)	13		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Children	2	876	Mean Difference (IV, Fixed, 95% CI)	-7.92 [-12.93, -2.91]
7.2 Adults	11	1703	Mean Difference (IV, Fixed, 95% CI)	-4.84 [-9.37, -0.31]
8 Change in evening PEFR compared to baseline (L/min)	7		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 Children	2	874	Mean Difference (IV, Fixed, 95% CI)	-9.36 [-14.37, -4.35]
8.2 Adults	5	776	Mean Difference (IV, Fixed, 95% CI)	-3.76 [-9.18, 1.66]
9 PC20	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]

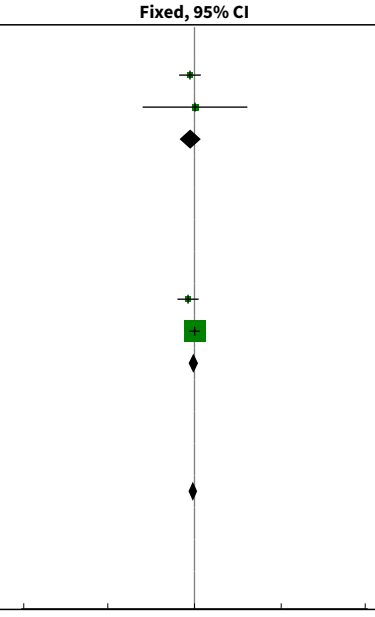
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 PD20	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10.1 Children	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Change in daily use of beta2 agonist compared to baseline (puffs/d)	7	931	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.08, 0.43]
11.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	7	931	Mean Difference (IV, Fixed, 95% CI)	0.18 [-0.08, 0.43]
12 Change in number of night-time awakenings/week compared to baseline	2	334	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.05, 0.04]
12.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	2	334	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.05, 0.04]
13 Change in % nights without waking	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 Change in daily asthma symptom score compared to baseline	7	930	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.02, 0.24]
14.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	7	930	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.02, 0.24]
15 Percentage of symptom-free days	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Health related quality of life - AQLQ (absolute scores)	0		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Adults	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Number of patients withdrawn due to lack of efficacy	7	1294	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [1.01, 1.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Adults	7	1294	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.41 [1.01, 1.98]
18 Exacerbations requiring oral steroids	2	883	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.72, 2.05]
18.1 Children	2	883	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.21 [0.72, 2.05]
18.2 Adults	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Exacerbations requiring hospitalisation	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
19.1 Children	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Adults	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Oral Candidiasis (No. of patients)	8	1752	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.87 [0.47, 1.61]
20.1 Children	1	528	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.65 [0.19, 2.27]
20.2 Adults	7	1224	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.47, 1.95]
21 Sore throat or pharyngitis (No. of patients)	8	1825	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.60, 1.63]
21.1 Children	2	883	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.58, 3.08]
21.2 Adults	6	942	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.44, 1.55]
22 Hoarseness or dysphonia (No. of patients)	7	1693	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.40, 1.46]
22.1 Children	1	528	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [0.29, 5.79]
22.2 Adults	6	1165	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.67 [0.32, 1.38]
23 Withdrawals due to adverse events	5	1161	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.22, 1.92]
23.1 Children	1	528	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.99]
23.2 Adults	4	633	Odds Ratio (M-H, Fixed, 95% CI)	0.55 [0.15, 2.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24 No. patients with </=18 mcg/dL poststimulation cortisol	2		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
24.1 Children	0		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.2 Adults	2		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 AUC serum cortisol	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
25.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Change in peak plasma cortisol expression	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
26.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
26.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

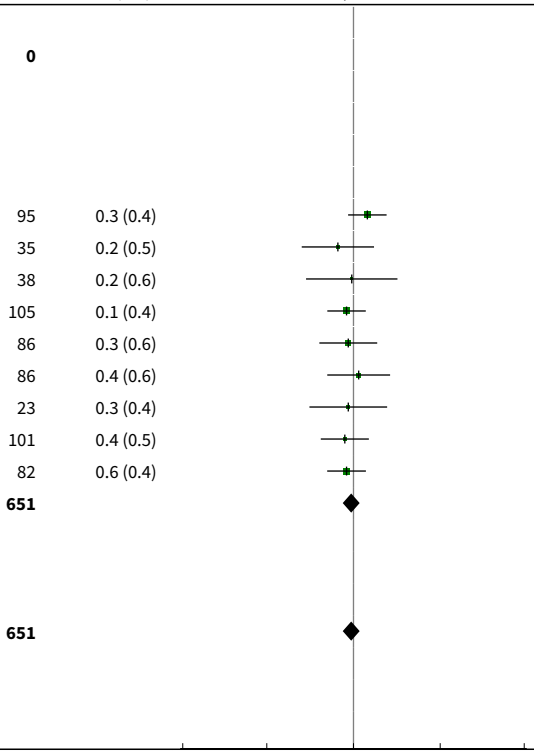
Analysis 5.1. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 1 FEV1 (% predicted).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.1.1 Children							
Boner 1999	44	90.1 (16)	45	92.7 (14)		15.87%	-2.6[-8.85,3.65]
Hofstra 2000	11	100 (29.9)	14	99.7 (46.8)		0.68%	0.3[-29.89,30.49]
Subtotal ***	**55**		**59**			**16.55%**	**-2.48[-8.6,3.64]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.85); I^2=0%							
Test for overall effect: Z=0.79(P=0.43)							
5.1.2 Adults							
Dahl 1993	124	73.5 (25.5)	123	77.2 (23.3)		16.72%	-3.7[-9.79,2.39]
Pinnas 2005	95	9.5 (10.7)	95	9.4 (10.7)		66.73%	0.1[-2.95,3.15]
Subtotal ***	**219**		**218**			**83.45%**	**-0.66[-3.39,2.06]**
Heterogeneity: Tau^2=0; Chi^2=1.2, df=1(P=0.27); I^2=16.36%							
Test for overall effect: Z=0.48(P=0.63)							
Total ***	**274**		**277**			**100%**	**-0.96[-3.45,1.53]**
Heterogeneity: Tau^2=0; Chi^2=1.51, df=3(P=0.68); I^2=0%							
Test for overall effect: Z=0.76(P=0.45)							
Test for subgroup differences: Chi^2=0.28, df=1 (P=0.59), I^2=0%							



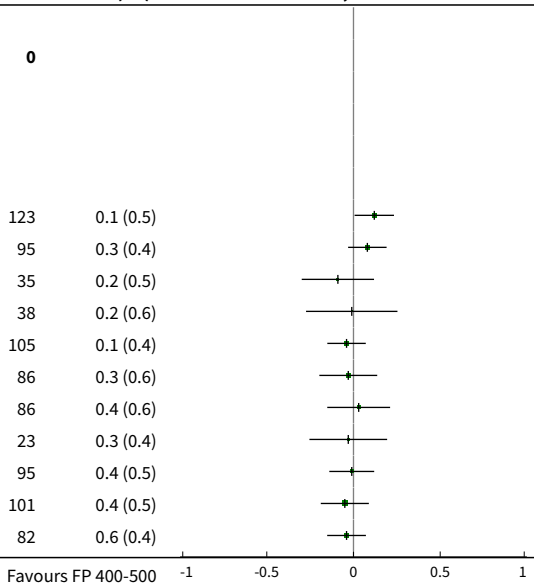
Analysis 5.2. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 2 Change in FEV1 compared to baseline (litres).

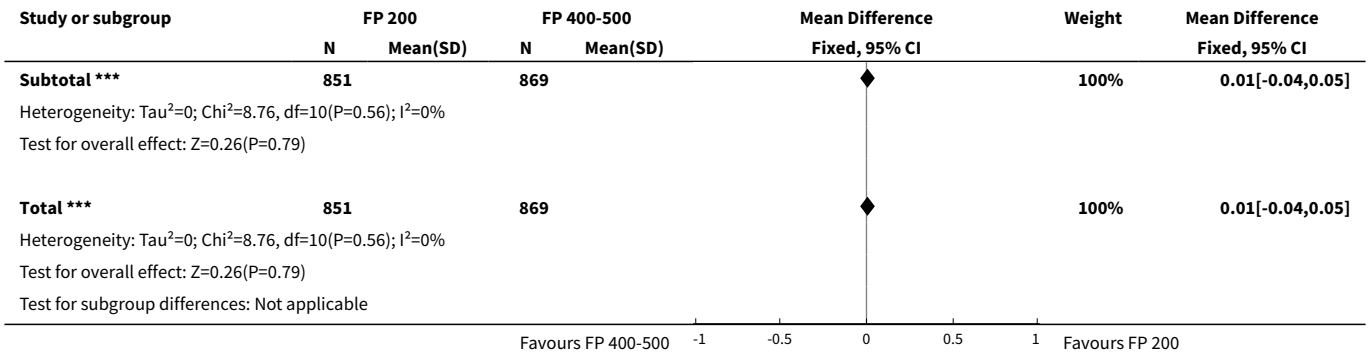
Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.2.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.2.2 Adults							
FLTA3014	95	0.4 (0.4)	95	0.3 (0.4)		19.42%	0.08[-0.03,0.19]
FLTA3020	37	0.1 (0.4)	35	0.2 (0.5)		5.5%	-0.09[-0.3,0.12]
FLTA3020a	38	0.2 (0.6)	38	0.2 (0.6)		3.44%	-0.01[-0.27,0.25]
Lumry 2006	100	0.1 (0.4)	105	0.1 (0.4)		19.42%	-0.04[-0.15,0.07]
Nathan 2000	81	0.3 (0.5)	86	0.3 (0.6)		8.58%	-0.03[-0.2,0.14]
Pearlman 1997	81	0.5 (0.6)	86	0.4 (0.6)		7.27%	0.03[-0.15,0.21]
Pearlman 1999	23	0.3 (0.3)	23	0.3 (0.4)		4.76%	-0.03[-0.25,0.19]
Raphael 1999	99	0.3 (0.5)	101	0.4 (0.5)		12.43%	-0.05[-0.19,0.09]
Wasserman 1996	78	0.5 (0.4)	82	0.6 (0.4)		19.18%	-0.04[-0.15,0.07]
Subtotal ***	**632**		**651**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Tau^2=0; Chi^2=4.23, df=8(P=0.84); I^2=0%							
Test for overall effect: Z=0.53(P=0.6)							
Total ***	**632**		**651**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Tau^2=0; Chi^2=4.23, df=8(P=0.84); I^2=0%							
Test for overall effect: Z=0.53(P=0.6)							
Test for subgroup differences: Not applicable							



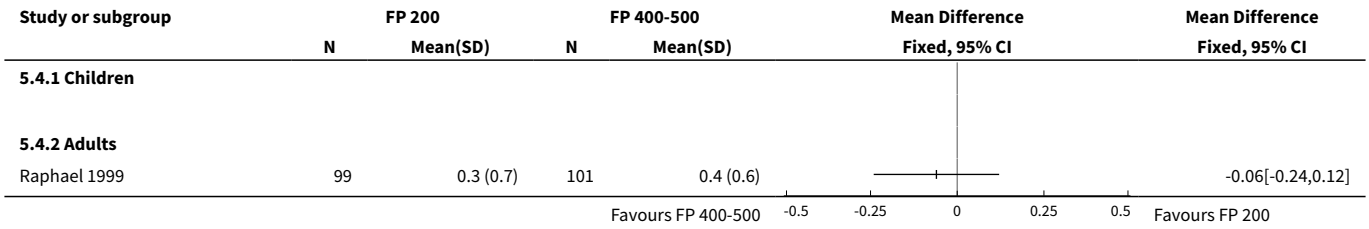
Analysis 5.3. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 3 Change in FEV1 compared to baseline (litres - imputed estimates).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.3.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.3.2 Adults							
Dahl 1993	124	0.2 (0.5)	123	0.1 (0.5)		13.96%	0.12[0.01,0.23]
FLTA3014	95	0.4 (0.4)	95	0.3 (0.4)		14.62%	0.08[-0.03,0.19]
FLTA3020	37	0.1 (0.4)	35	0.2 (0.5)		4.14%	-0.09[-0.3,0.12]
FLTA3020a	38	0.2 (0.6)	38	0.2 (0.6)		2.59%	-0.01[-0.27,0.25]
Lumry 2006	100	0.1 (0.4)	105	0.1 (0.4)		14.63%	-0.04[-0.15,0.07]
Nathan 2000	81	0.3 (0.5)	86	0.3 (0.6)		6.46%	-0.03[-0.2,0.14]
Pearlman 1997	81	0.5 (0.6)	86	0.4 (0.6)		5.48%	0.03[-0.15,0.21]
Pearlman 1999	23	0.3 (0.3)	23	0.3 (0.4)		3.58%	-0.03[-0.25,0.19]
Pinnas 2005	95	0.3 (0.5)	95	0.4 (0.5)		10.74%	-0.01[-0.14,0.12]
Raphael 1999	99	0.3 (0.5)	101	0.4 (0.5)		9.36%	-0.05[-0.19,0.09]
Wasserman 1996	78	0.5 (0.4)	82	0.6 (0.4)		14.44%	-0.04[-0.15,0.07]

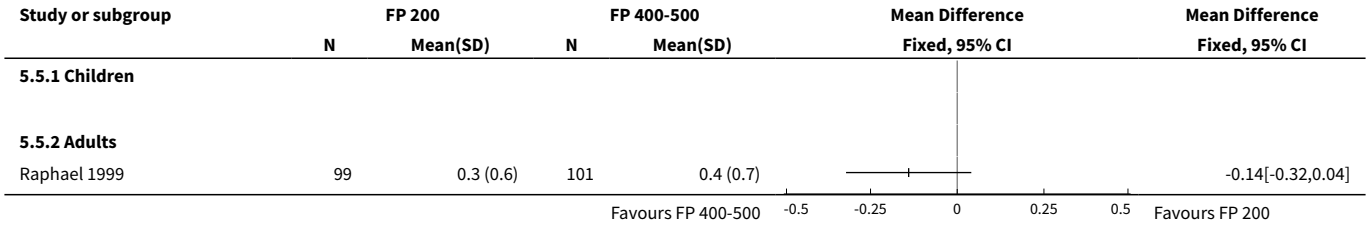




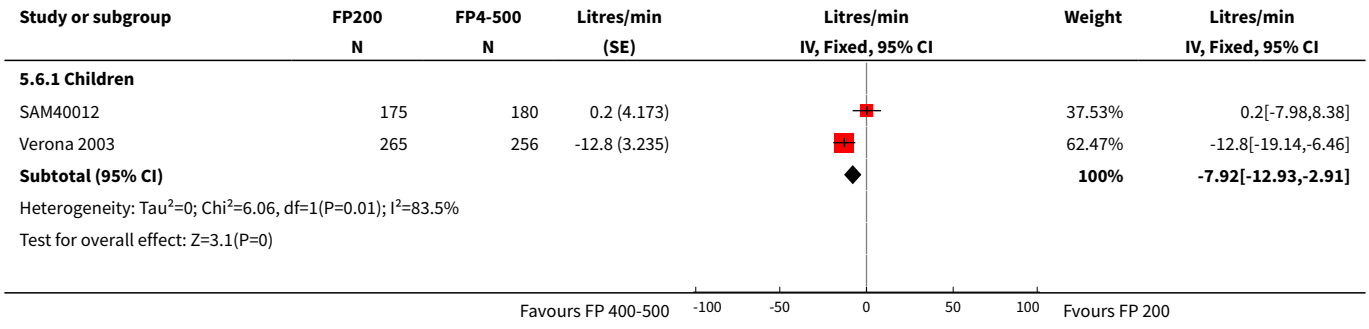
Analysis 5.4. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 4 Change in FVC compared to baseline (litres).



Analysis 5.5. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 5 Change in FEF25-75 compared to baseline (L/second).



Analysis 5.6. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 6 Change in morning PEFR compared to baseline (L/min - imputed/estimated values).



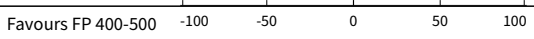
Study or subgroup	FP200 N	FP4-500 N	Litres/min (SE)	Litres/min IV, Fixed, 95% CI	Weight	Litres/min IV, Fixed, 95% CI
5.6.2 Adults						
Dahl 1993	132	133	-2 (4.122)		22.11%	-2[-10.08,6.08]
FLTA3020	37	34	-2.6 (11.03)		3.09%	-2.59[-24.21,19.03]
FLTA3020a	38	38	0.7 (12.28)		2.49%	0.66[-23.41,24.73]
Lumry 2006	100	105	1.5 (6.72)		8.32%	1.5[-11.67,14.67]
Nathan 2000	81	86	-17 (6.403)		9.16%	-17[-29.55,-4.45]
Pearlman 1997	81	86	-11 (7.786)		6.2%	-11[-26.26,4.26]
Pearlman 1999	23	23	-15 (12.041)		2.59%	-15[-38.6,8.6]
Pinnas 2005	97	97	-4 (6.24)		9.65%	-4[-16.23,8.23]
Raphael 1999	99	101	-7 (6.54)		8.78%	-7[-19.82,5.82]
Wasserman 1996	78	82	3 (7.077)		7.5%	3[-10.87,16.87]
Wolfe 1996	80	82	9 (4.322)		20.11%	9[0.53,17.47]
Subtotal (95% CI)					**100%**	**-1.97[-5.77,1.82]**
Heterogeneity: Tau²=0; Chi²=15.97, df=10(P=0.1); I²=37.4%						
Test for overall effect: Z=1.02(P=0.31)						
Test for subgroup differences: Chi²=3.43, df=1 (P=0.06), I²=70.88%						

Analysis 5.7. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 7 Change in morning PEFR compared to baseline (L/min).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.7.1 Children							
SAM40012	175	39.4 (39.7)	180	39.2 (38.9)		37.53%	0.2[-7.98,8.38]
Verona 2003	265	23 (31.6)	256	35.8 (41.4)		62.47%	-12.8[-19.14,-6.46]
Subtotal ***	**440**		**436**			**100%**	**-7.92[-12.93,-2.91]**
Heterogeneity: Tau²=0; Chi²=6.06, df=1(P=0.01); I²=83.51%							
Test for overall effect: Z=3.1(P=0)							
5.7.2 Adults							
Dahl 1993	132	13 (35)	133	15 (32)		31.49%	-2[-10.08,6.08]
FLTA3020	37	27.6 (50.3)	34	30.2 (42.6)		4.39%	-2.59[-24.21,19.03]
FLTA3020a	38	40.2 (56)	38	39.5 (51)		3.54%	0.66[-23.42,24.74]
Lumry 2006	100	20.4 (49)	105	18.9 (47.1)		11.84%	1.5[-11.67,14.67]
Nathan 2000	81	11 (36)	86	28 (46.4)		13.04%	-17[-29.55,-4.45]
Pearlman 1997	81	16 (54)	86	27 (46)		8.82%	-11[-26.26,4.26]
Pearlman 1999	23	10 (38.4)	23	25 (43.2)		3.69%	-15[-38.6,8.6]
Pinnas 2005	97	40 (0)	97	44 (0)			Not estimable
Raphael 1999	99	15.8 (50)	101	22.8 (42)		12.52%	-7[-19.81,5.81]
Wasserman 1996	78	42 (44.2)	82	39 (45.3)		10.68%	3[-10.87,16.87]
Wolfe 1996	80	25 (0)	72	16 (0)			Not estimable
Subtotal ***	**846**		**857**			**100%**	**-4.84[-9.37,-0.31]**
Heterogeneity: Tau²=0; Chi²=7.89, df=8(P=0.44); I²=0%							
Test for overall effect: Z=2.09(P=0.04)							
Test for subgroup differences: Chi²=0.8, df=1 (P=0.37), I²=0%							

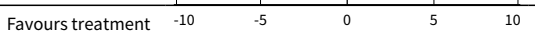
Analysis 5.8. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 8 Change in evening PEFR compared to baseline (L/min).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.8.1 Children							
SAM40012	175	38.2 (40.3)	180	38.8 (41)		35.14%	-0.6[-9.05,7.85]
Verona 2003	263	19.1 (30.1)	256	33.2 (41.2)		64.86%	-14.1[-20.32,-7.88]
Subtotal ***	**438**		**436**			**100%**	**-9.36[-14.37,-4.35]**
Heterogeneity: Tau^2=0; Chi^2=6.36, df=1(P=0.01); I^2=84.27%							
Test for overall effect: Z=3.66(P=0)							
5.8.2 Adults							
Dahl 1993	132	7 (35)	132	8 (31)		46.16%	-1[-8.98,6.98]
FLTA3020	37	23 (46.2)	35	24.3 (41)		7.24%	-1.34[-21.48,18.8]
FLTA3020a	37	36.9 (49.8)	36	34.8 (52.1)		5.37%	2.07[-21.31,25.45]
Nathan 2000	81	11 (36)	86	21 (46.4)		18.64%	-10[-22.55,2.55]
Raphael 1999	99	7.8 (44)	101	14.2 (38)		22.58%	-6.4[-17.8,5]
Subtotal ***	**386**		**390**			**100%**	**-3.76[-9.18,1.66]**
Heterogeneity: Tau^2=0; Chi^2=1.91, df=4(P=0.75); I^2=0%							
Test for overall effect: Z=1.36(P=0.17)							
Test for subgroup differences: Chi^2=2.21, df=1 (P=0.14), I^2=54.77%							



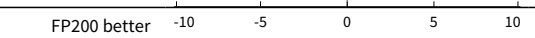
Analysis 5.9. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 9 PC20.

Study or subgroup	FP200 N	FP200 Mean(SD)	FP4-500 N	FP4-500 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.9.1 Children						
5.9.2 Adults						
Nieto 2001	9	0 (0)	9	2.2 (1.2)		Not estimable



Analysis 5.10. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 10 PD20.

Study or subgroup	FP200 N	FP200 Mean(SD)	FP4-500 N	FP4-500 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.10.1 Children						
Hofstra 2000	11	58.4 (0)	14	88.7 (0)		Not estimable
5.10.2 Adults						



Analysis 5.11. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 11 Change in daily use of beta2 agonist compared to baseline (puffs/d).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.11.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.11.2 Adults							
FLTA3020	37	-1 (1.6)	35	-1.1 (2)		9.7%	0.11[-0.71,0.93]
FLTA3020a	37	-1.2 (1.6)	37	-1.7 (2.1)		9.06%	0.49[-0.36,1.34]
Lumry 2006	105	-0.7 (2.2)	100	-0.7 (2)		20.33%	0.05[-0.52,0.62]
Nathan 2000	81	-0.2 (1.7)	86	-0.9 (1.8)		23.68%	0.71[0.18,1.24]
Pearlman 1997	81	-1.1 (2.8)	86	-1.2 (2.9)		9.06%	0.1[-0.75,0.95]
Pearlman 1999	23	-1.1 (1.4)	23	-1.4 (1.9)		6.82%	0.3[-0.68,1.28]
Raphael 1999	99	-0.9 (2)	101	-0.5 (2)		21.35%	-0.4[-0.95,0.15]
Subtotal ***	**463**		**468**			**100%**	**0.18[-0.08,0.43]**
Heterogeneity: Tau^2=0; Chi^2=8.93, df=6(P=0.18); I^2=32.81%							
Test for overall effect: Z=1.36(P=0.17)							
Total ***	**463**		**468**			**100%**	**0.18[-0.08,0.43]**
Heterogeneity: Tau^2=0; Chi^2=8.93, df=6(P=0.18); I^2=32.81%							
Test for overall effect: Z=1.36(P=0.17)							
Test for subgroup differences: Not applicable							

Analysis 5.12. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 12 Change in number of night-time awakenings/week compared to baseline.

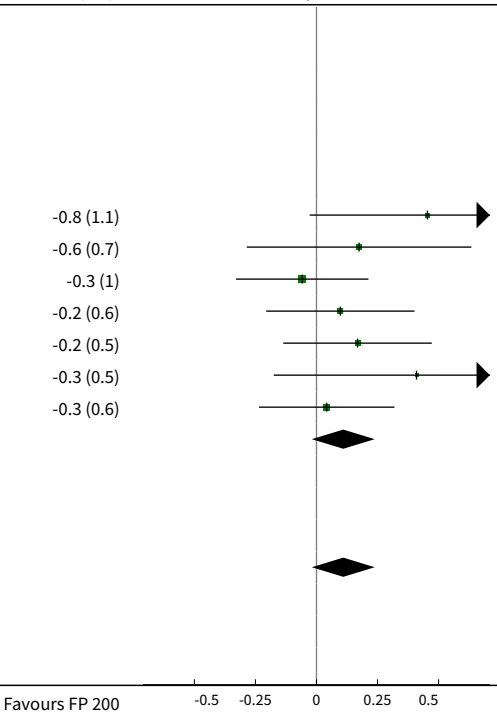
Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
5.12.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.12.2 Adults							
Nathan 2000	81	-0 (0.3)	86	-0 (0.3)		31.15%	-0.02[-0.1,0.06]
Pearlman 1997	81	-0 (0.2)	86	-0 (0.2)		68.85%	0[-0.06,0.06]
Subtotal ***	**162**		**172**			**100%**	**-0.01[-0.05,0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=0.26(P=0.79)							
Total ***	**162**		**172**			**100%**	**-0.01[-0.05,0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.15, df=1(P=0.7); I^2=0%							
Test for overall effect: Z=0.26(P=0.79)							
Test for subgroup differences: Not applicable							

Analysis 5.13. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 13 Change in % nights without waking.

Study or subgroup	FP200 N	FP200 Mean(SD)	FP4-500 N	FP4-500 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.13.1 Children						
5.13.2 Adults						
Pearlman 1999	23	4 (14.4)	23	12 (14.4)		-8[-16.32,0.32]

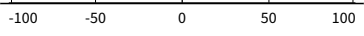
Analysis 5.14. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 14 Change in daily asthma symptom score compared to baseline.

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
5.14.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
5.14.2 Adults							
FLTA3020	35	-0.4 (0.7)	33	-0.8 (1.1)		7.15%	0.45[-0.03,0.94]
FLTA3020a	36	-0.4 (1)	37	-0.6 (0.7)		7.85%	0.17[-0.29,0.63]
Lumry 2006	103	-0.3 (1)	106	-0.3 (1)		22.57%	-0.06[-0.33,0.21]
Nathan 2000	81	-0.2 (0.5)	86	-0.2 (0.6)		18.01%	0.1[-0.21,0.4]
Pearlman 1997	81	-0.2 (0.4)	86	-0.2 (0.5)		17.96%	0.17[-0.14,0.47]
Pearlman 1999	23	-0.1 (0.5)	23	-0.3 (0.5)		4.86%	0.41[-0.18,0.99]
Raphael 1999	99	-0.2 (0.3)	101	-0.3 (0.6)		21.6%	0.04[-0.24,0.32]
Subtotal ***	**458**		**472**			**100%**	**0.11[-0.02,0.24]**
Heterogeneity: Tau^2=0; Chi^2=4.91, df=6(P=0.56); I^2=0%							
Test for overall effect: Z=1.67(P=0.1)							
Total ***	**458**		**472**			**100%**	**0.11[-0.02,0.24]**
Heterogeneity: Tau^2=0; Chi^2=4.91, df=6(P=0.56); I^2=0%							
Test for overall effect: Z=1.67(P=0.1)							
Test for subgroup differences: Not applicable							



Analysis 5.15. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 15 Percentage of symptom-free days.

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
5.15.1 Children						
5.15.2 Adults						
Dahl 1993	122	-33.9 (37.6)	119	-34.8 (41.3)		0.9[-9.08,10.88]

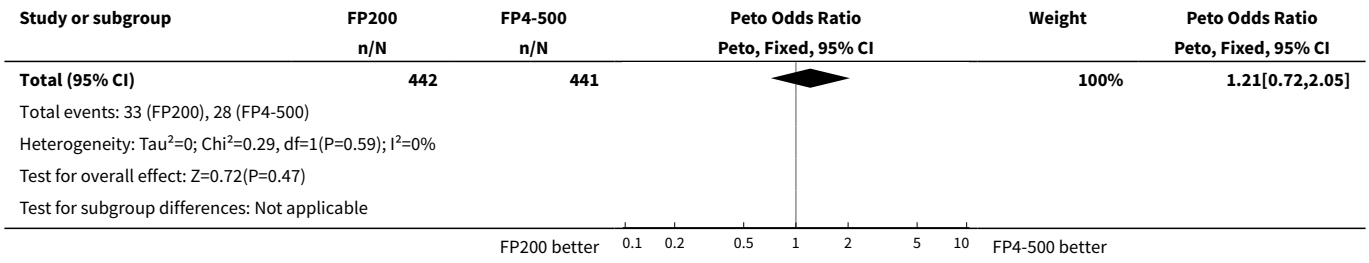


Analysis 5.17. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 17 Number of patients withdrawn due to lack of efficacy.

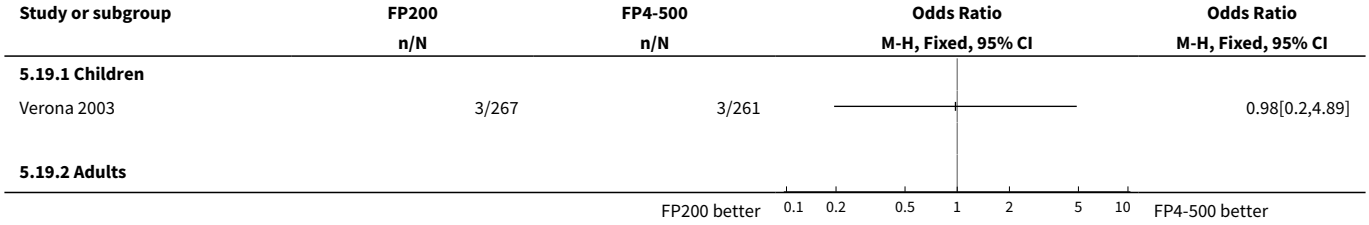
Study or subgroup	FP 200 n/N	FP 400-500 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
5.17.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 200), 0 (FP 400-500)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.17.2 Adults					
FLTA3014	9/95	4/95		9%	2.27[0.74,6.99]
Lumry 2006	11/103	11/106		14.61%	1.03[0.43,2.49]
Nathan 2000	20/81	12/86		19.21%	1.99[0.92,4.3]
Pearlman 1997	11/84	6/91		11.39%	2.09[0.77,5.67]
Pinnas 2005	9/100	6/98		10.29%	1.51[0.53,4.3]
Raphael 1999	17/99	16/104		20.51%	1.14[0.54,2.4]
Wolfe 1996	12/80	12/72		14.99%	0.88[0.37,2.11]
Subtotal (95% CI)	**642**	**652**		**100%**	**1.41[1.01,1.98]**
Total events: 89 (FP 200), 67 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=3.99, df=6(P=0.68); I^2=0%					
Test for overall effect: Z=2.01(P=0.04)					
Total (95% CI)	**642**	**652**		**100%**	**1.41[1.01,1.98]**
Total events: 89 (FP 200), 67 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=3.99, df=6(P=0.68); I^2=0%					
Test for overall effect: Z=2.01(P=0.04)					
Test for subgroup differences: Not applicable					

Analysis 5.18. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 18 Exacerbations requiring oral steroids.

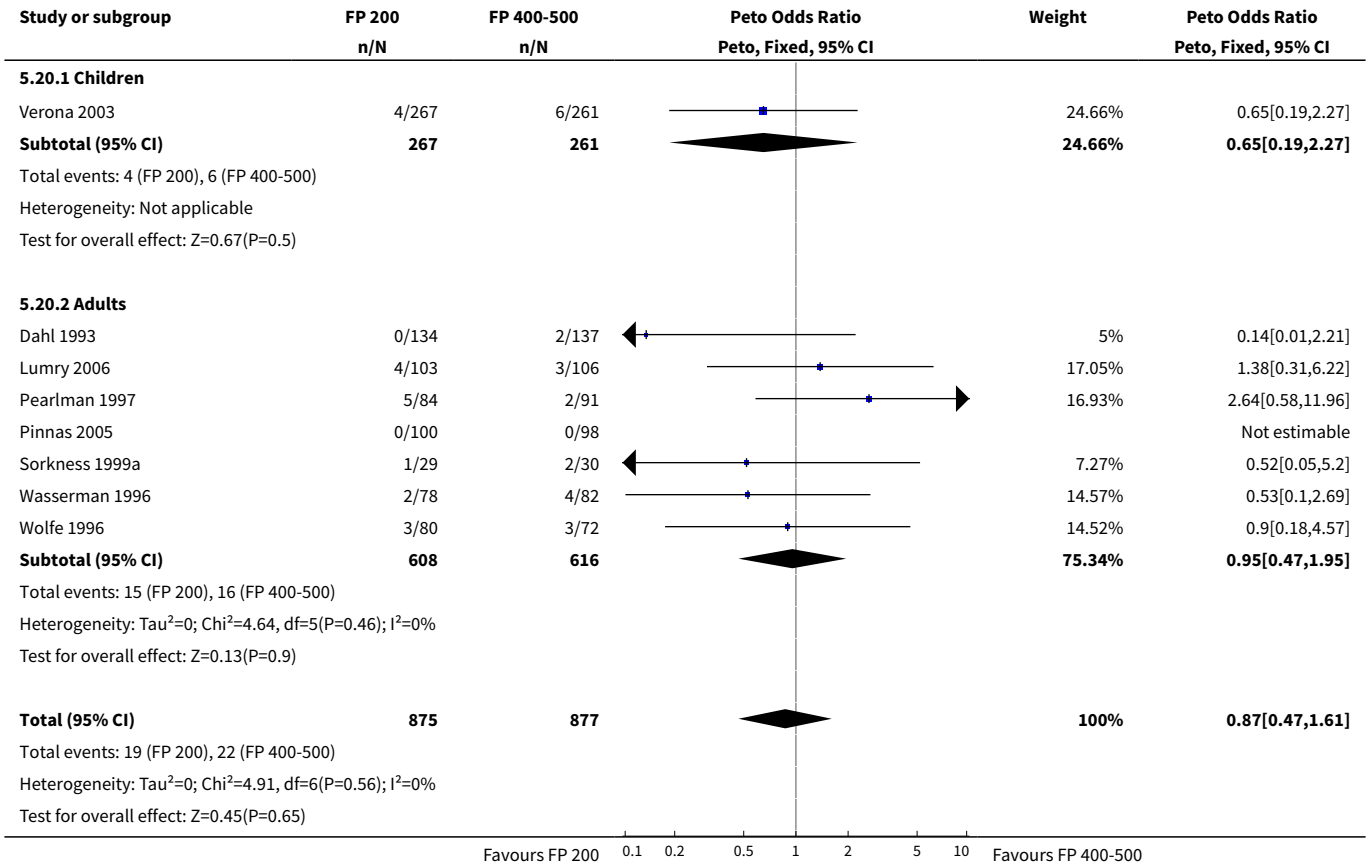
Study or subgroup	FP200 n/N	FP4-500 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
5.18.1 Children					
SAM40012	21/175	20/180		65.35%	1.09[0.57,2.09]
Verona 2003	12/267	8/261		34.65%	1.48[0.61,3.61]
Subtotal (95% CI)	**442**	**441**		**100%**	**1.21[0.72,2.05]**
Total events: 33 (FP200), 28 (FP4-500)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
5.18.2 Adults					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP200), 0 (FP4-500)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

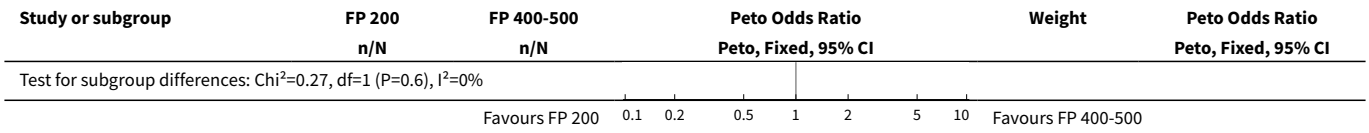


Analysis 5.19. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 19 Exacerbations requiring hospitalisation.

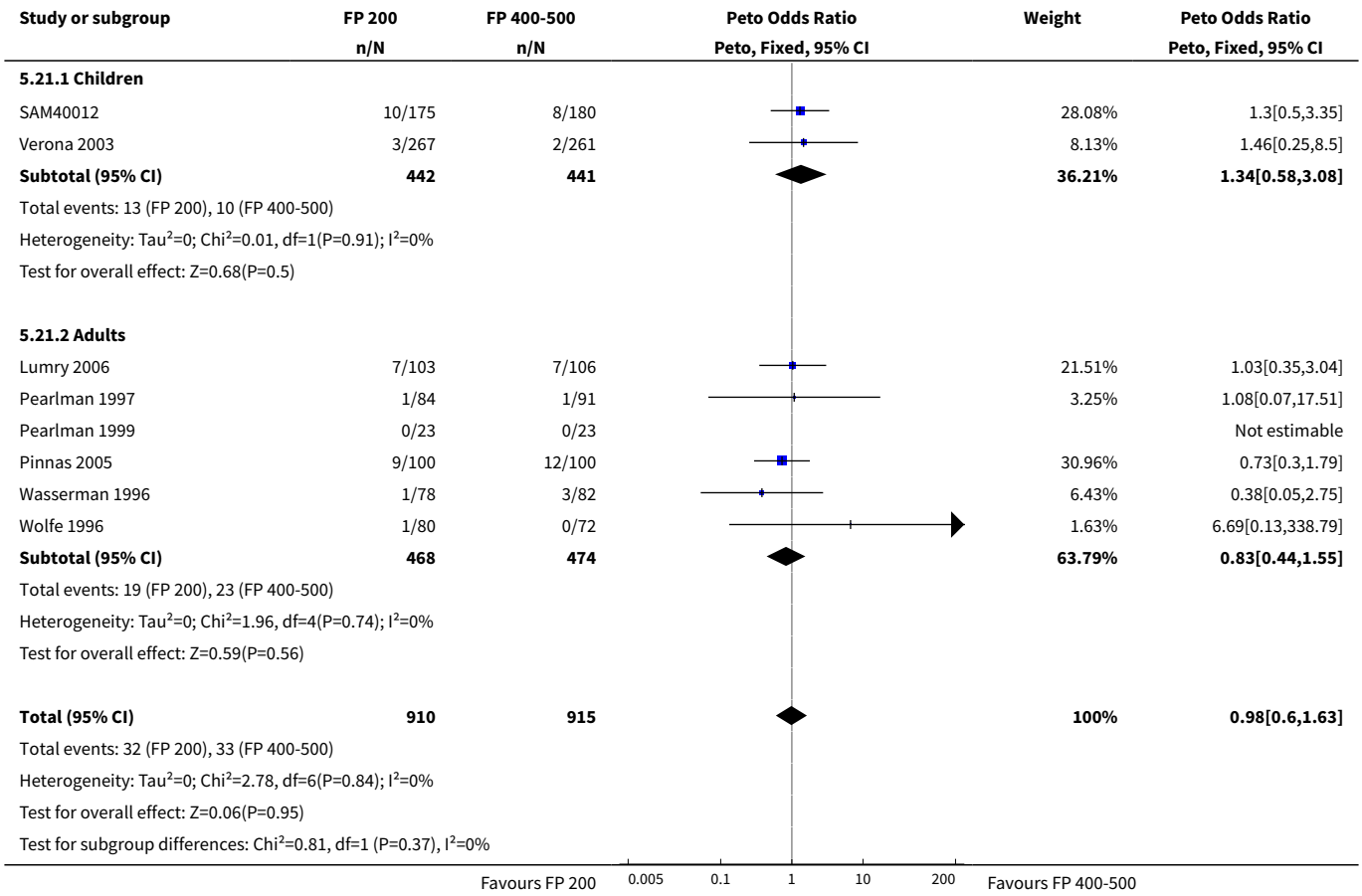


Analysis 5.20. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 20 Oral Candidiasis (No. of patients).

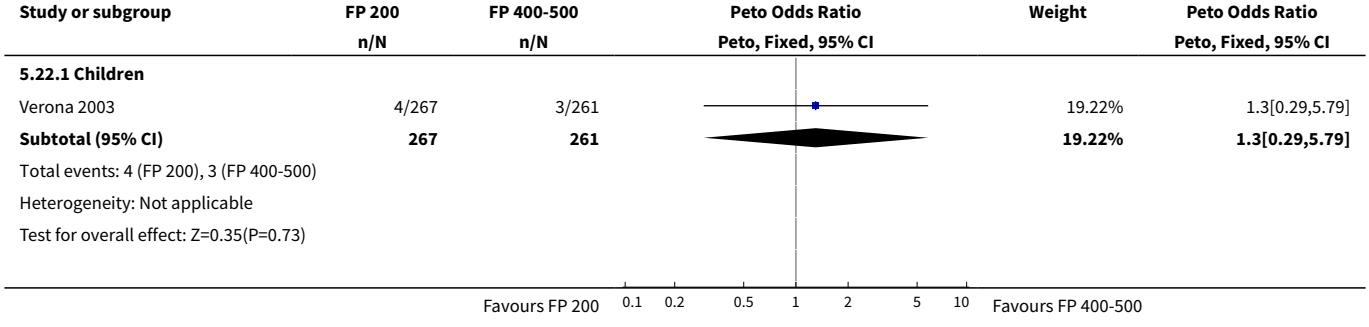


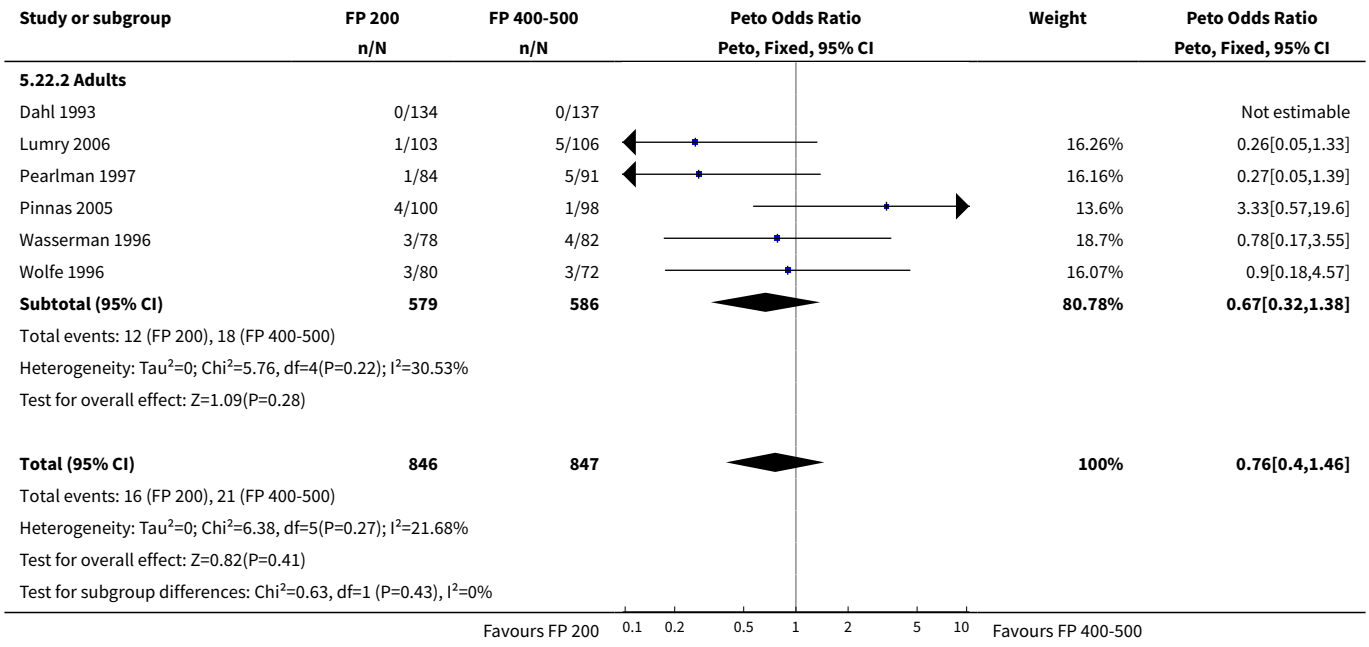


Analysis 5.21. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 21 Sore throat or pharyngitis (No. of patients).

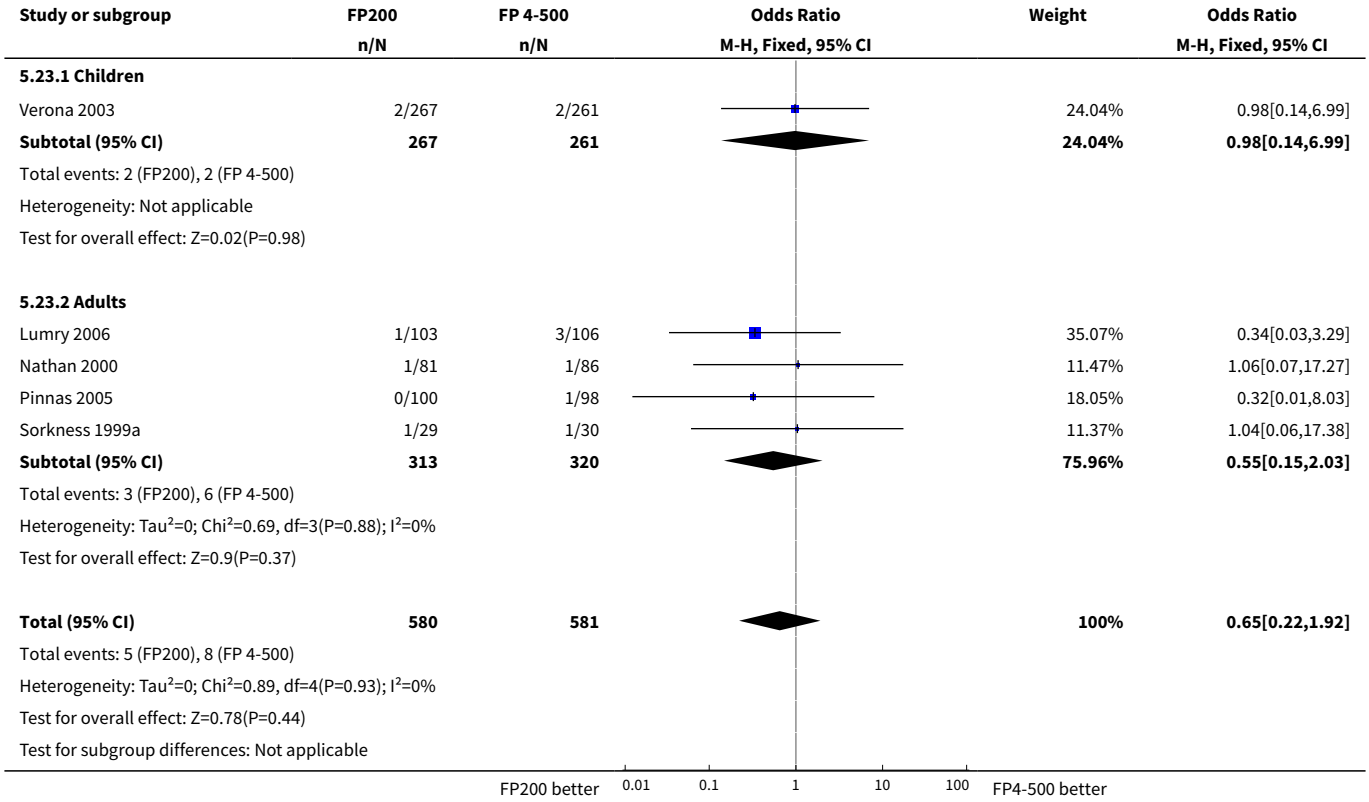


Analysis 5.22. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 22 Hoarseness or dysphonia (No. of patients).

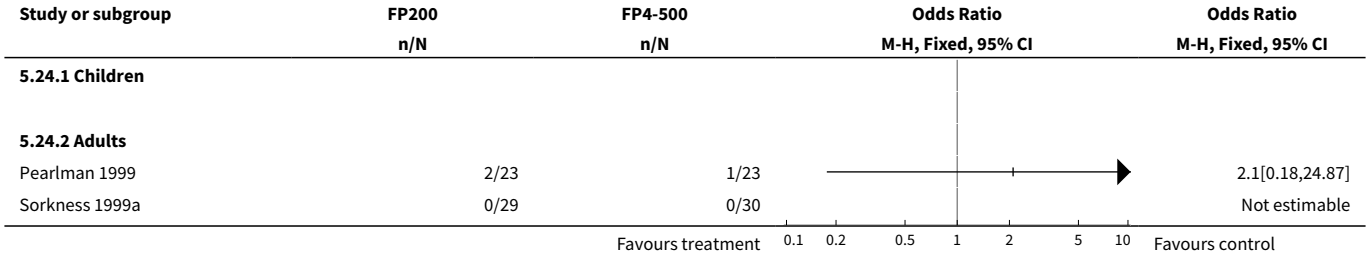




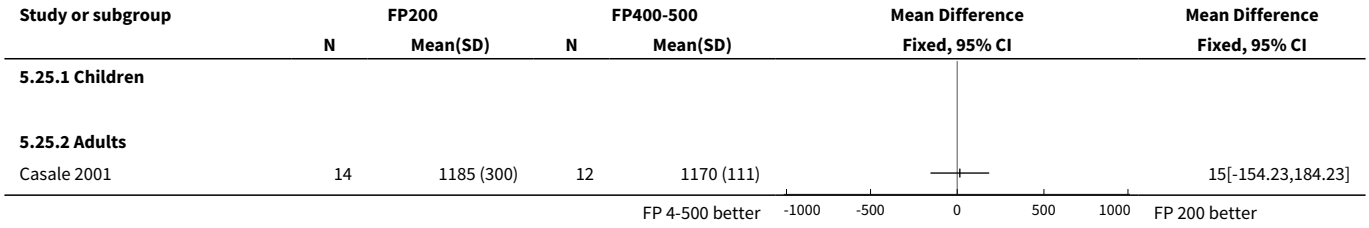
Analysis 5.23. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 23 Withdrawals due to adverse events.



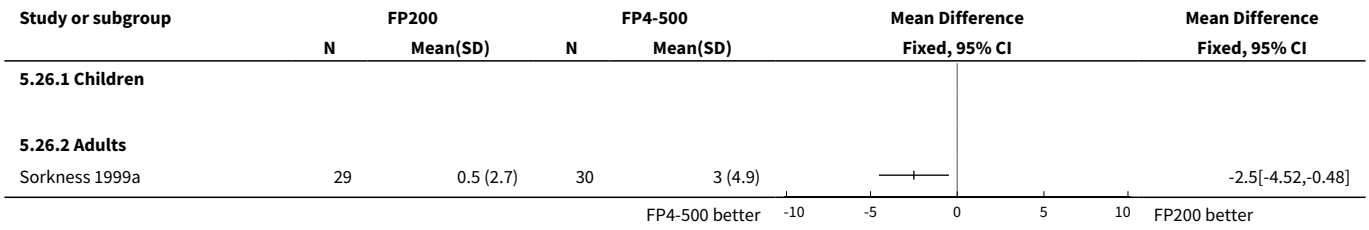
Analysis 5.24. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 24 No. patients with </=18 mcg/dL poststimulation cortisol.



Analysis 5.25. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 25 AUC serum cortisol.



Analysis 5.26. Comparison 5 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (all ages), Outcome 26 Change in peak plasma cortisol expression.



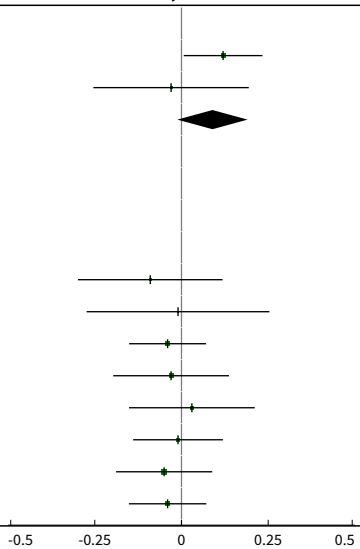
Comparison 6. Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (subgroups)

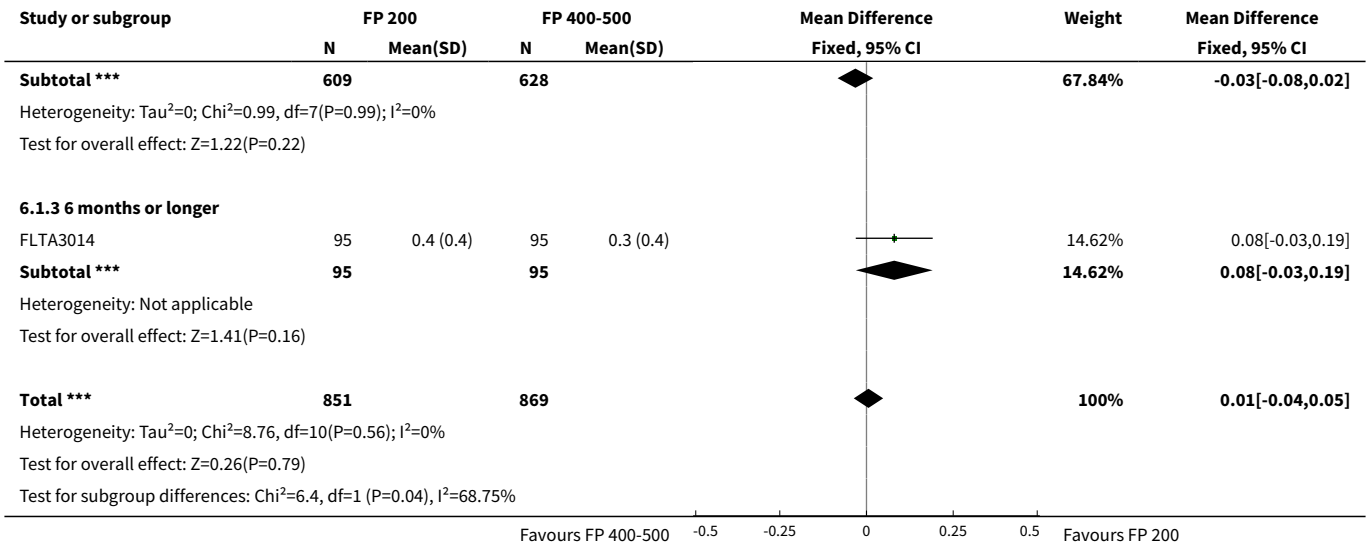
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change in FEV1 compared to baseline based on study duration (litres) - adults	11	1720	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.04, 0.05]
1.1 1-4 weeks	2	293	Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.01, 0.19]
1.2 1-5 months	8	1237	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.08, 0.02]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.3 6 months or longer	1	190	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.03, 0.19]
2 Change in FEV1 compared to baseline based on delivery devices (litres) - adults	11	1720	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.04, 0.05]
2.1 MDI	8	1226	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.03, 0.07]
2.2 DPI	3	494	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.11, 0.06]
3 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults	11	1720	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.04, 0.05]
3.1 Mild to moderate	3	194	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.18, 0.08]
3.2 Moderate	6	1136	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.05, 0.06]
3.3 Mixed	1	200	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.19, 0.09]
3.4 Unclear	1	190	Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.03, 0.19]

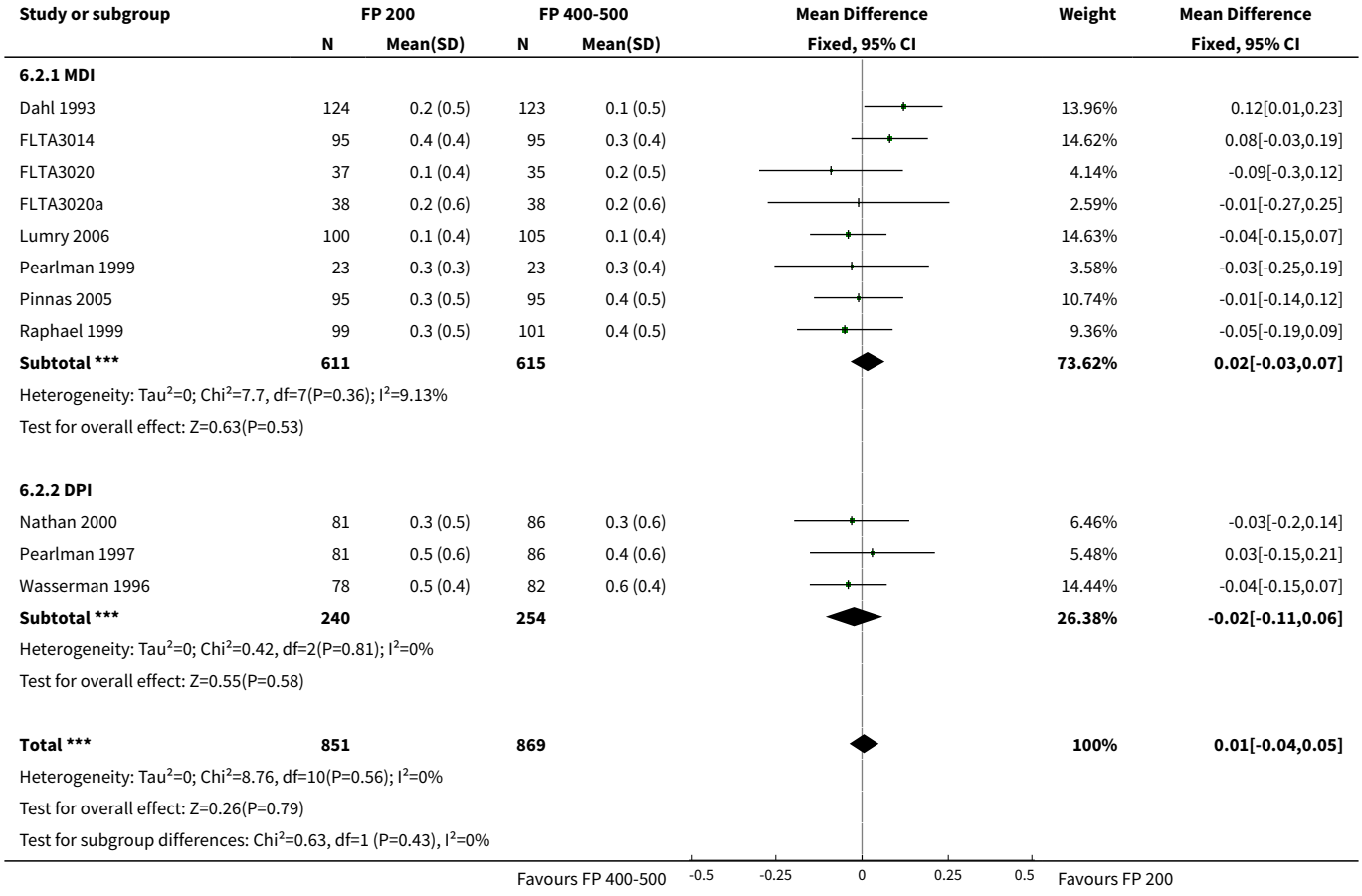
Analysis 6.1. Comparison 6 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (subgroups), Outcome 1 Change in FEV1 compared to baseline based on study duration (litres) - adults.

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
6.1.1 1-4 weeks							
Dahl 1993	124	0.2 (0.5)	123	0.1 (0.5)		13.96%	0.12[0.01,0.23]
Pearlman 1999	23	0.3 (0.3)	23	0.3 (0.4)		3.58%	-0.03[-0.25,0.19]
Subtotal ***	**147**		**146**			**17.54%**	**0.09[-0.01,0.19]**
Heterogeneity: Tau^2=0; Chi^2=1.37, df=1(P=0.24); I^2=27.03%							
Test for overall effect: Z=1.73(P=0.08)							
6.1.2 1-5 months							
FLTA3020	37	0.1 (0.4)	35	0.2 (0.5)		4.14%	-0.09[-0.3,0.12]
FLTA3020a	38	0.2 (0.6)	38	0.2 (0.6)		2.59%	-0.01[-0.27,0.25]
Lumry 2006	100	0.1 (0.4)	105	0.1 (0.4)		14.63%	-0.04[-0.15,0.07]
Nathan 2000	81	0.3 (0.5)	86	0.3 (0.6)		6.46%	-0.03[-0.2,0.14]
Pearlman 1997	81	0.5 (0.6)	86	0.4 (0.6)		5.48%	0.03[-0.15,0.21]
Pinnas 2005	95	0.3 (0.5)	95	0.4 (0.5)		10.74%	-0.01[-0.14,0.12]
Raphael 1999	99	0.3 (0.5)	101	0.4 (0.5)		9.36%	-0.05[-0.19,0.09]
Wasserman 1996	78	0.5 (0.4)	82	0.6 (0.4)		14.44%	-0.04[-0.15,0.07]

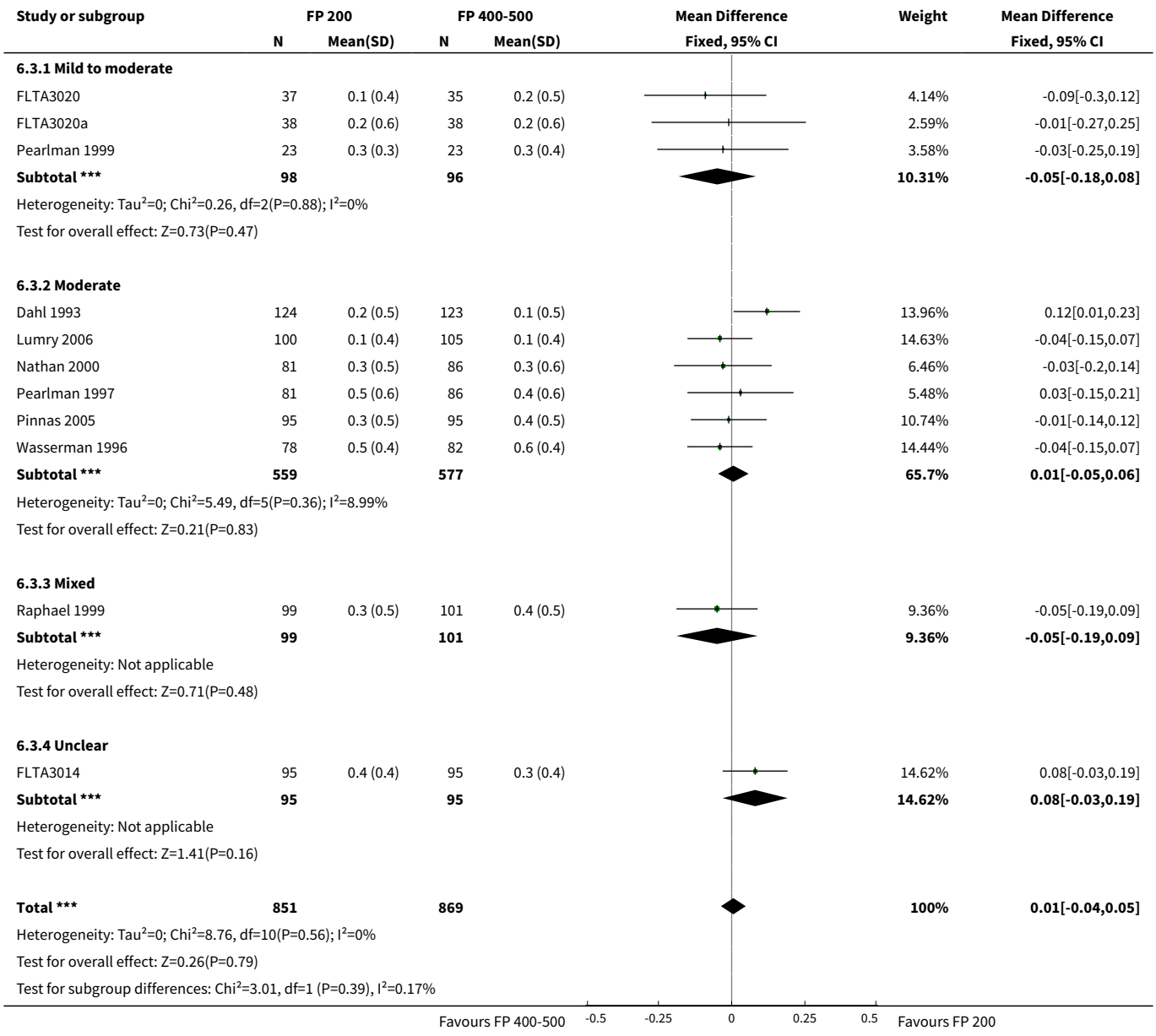




Analysis 6.2. Comparison 6 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (subgroups), Outcome 2 Change in FEV1 compared to baseline based on delivery devices (litres) - adults.



Analysis 6.3. Comparison 6 Parallel group studies, no oral steroids: 200 versus 400-500 mcg/d (subgroups), Outcome 3 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults.



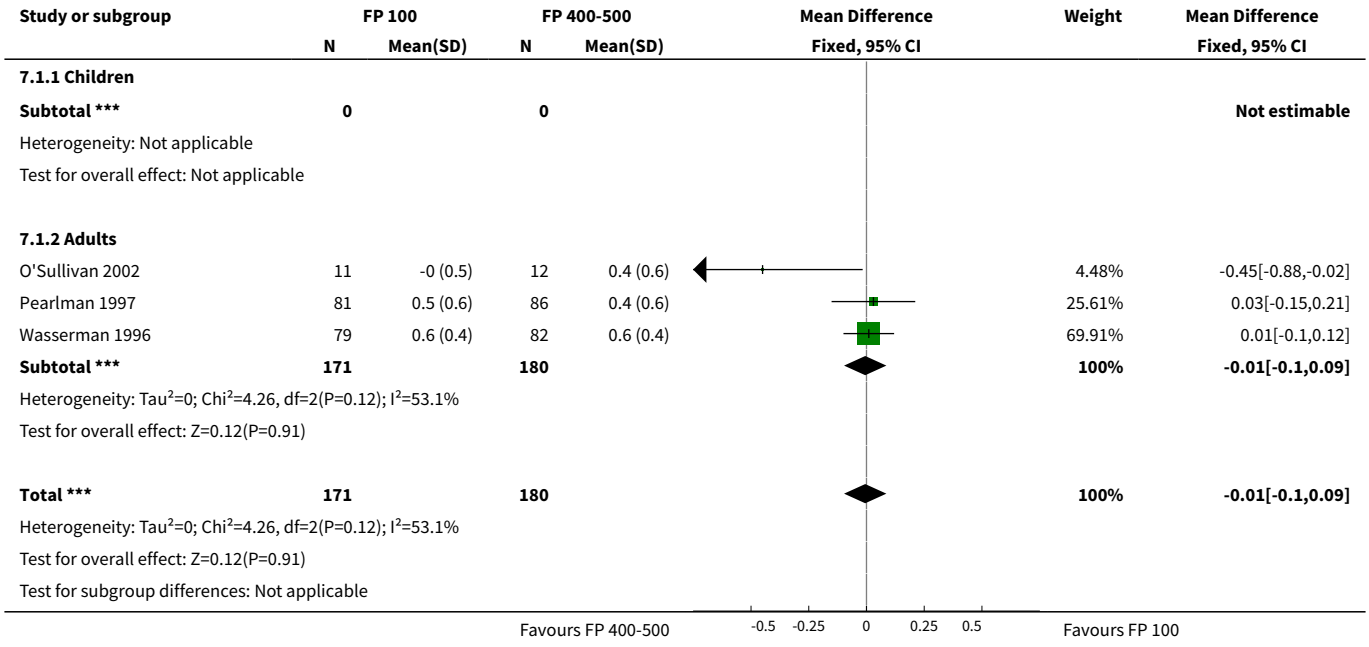
Comparison 7. Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline (litres)	3	351	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.10, 0.09]
1.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

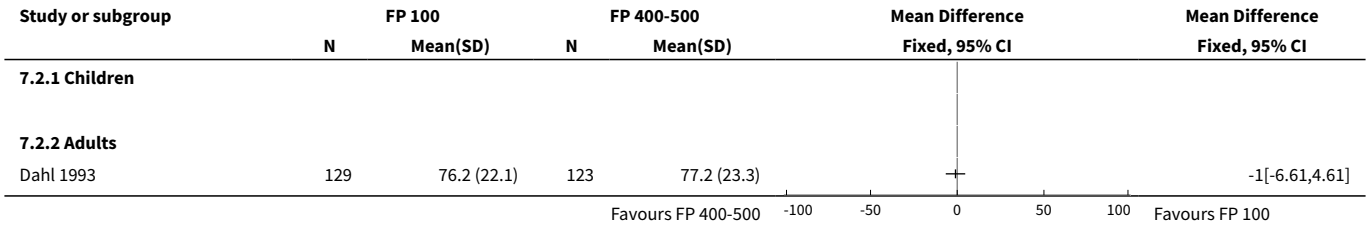
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Adults	3	351	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.10, 0.09]
2 FEV1 (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in morning PEFR compared to baseline (L/min)	3	593	Mean Difference (IV, Fixed, 95% CI)	-7.97 [-14.58, -1.35]
3.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	3	593	Mean Difference (IV, Fixed, 95% CI)	-7.97 [-14.58, -1.35]
4 Change in evening PEFR compared to baseline (L/min)	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 Percentage of symptom-free days	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 daily asthma symptom score compared to baseline	2	194	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [0.03, 0.60]
6.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	2	194	Std. Mean Difference (IV, Fixed, 95% CI)	0.31 [0.03, 0.60]
7 Change in number of night-time awakenings/week compared to baseline	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 Change in daily use of beta2 agonist compared to baseline (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Physician global rated efficacy: ineffective	2	400	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.81, 1.93]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
9.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	2	400	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.81, 1.93]
10 Number of patients withdrawn due to lack of efficacy	2	454	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.30 [0.90, 5.90]
10.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	2	454	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.30 [0.90, 5.90]
11 Sore throat or pharyngitis (No. of patients)	3	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.29, 3.56]
11.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	3	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.29, 3.56]
12 Hoarseness or dysphonia (No. of patients)	3	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.08, 0.92]
12.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	3	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.28 [0.08, 0.92]
13 Oral Candidiasis (No. of patients)	3	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.32, 2.49]
13.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	3	615	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.32, 2.49]
14 Plasma Cortisol (AUC)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Clinic PEF (L/min - change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

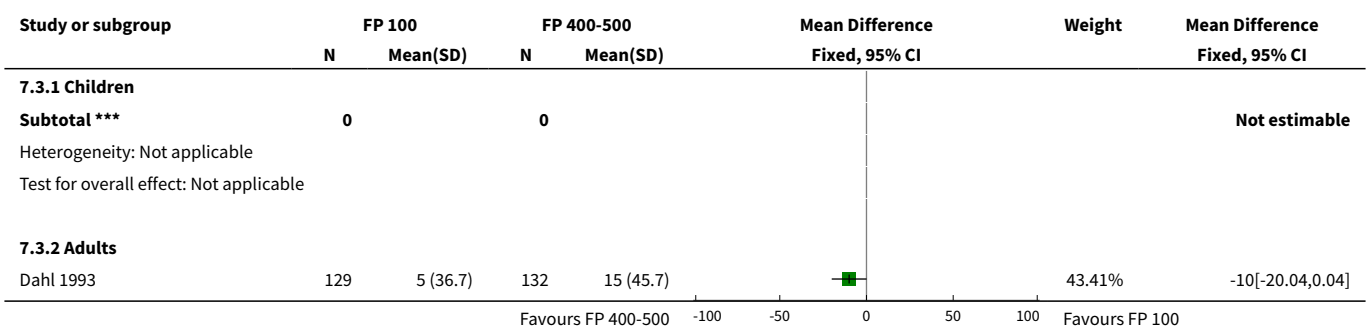
Analysis 7.1. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 1 Change in FEV1 compared to baseline (litres).

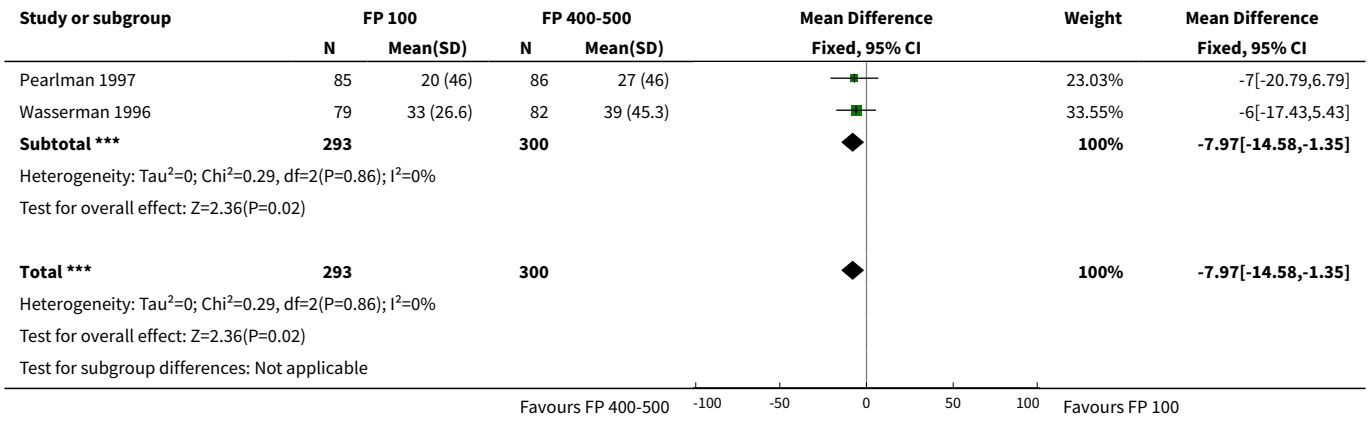


Analysis 7.2. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 2 FEV1 (% predicted).

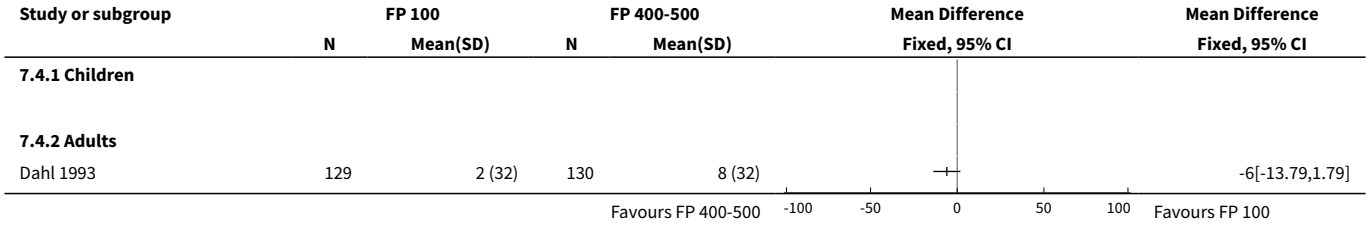


Analysis 7.3. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 3 Change in morning PEFR compared to baseline (L/min).

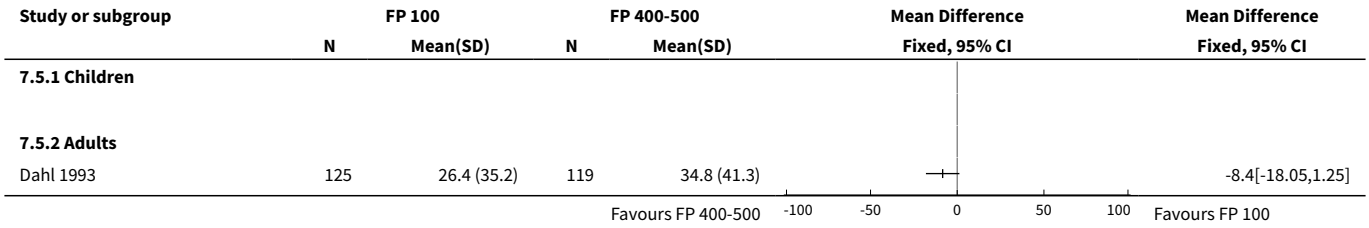




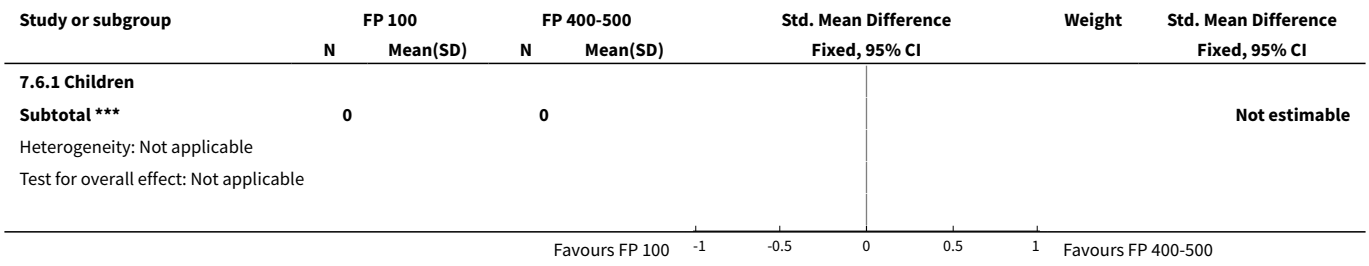
Analysis 7.4. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 4 Change in evening PEFR compared to baseline (L/min).

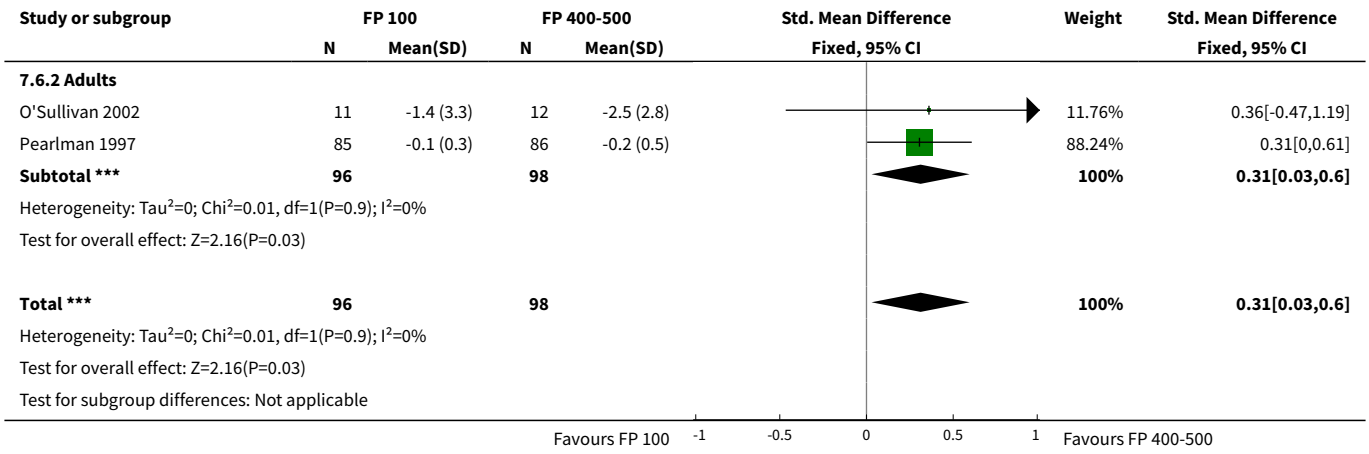


Analysis 7.5. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 5 Percentage of symptom-free days.

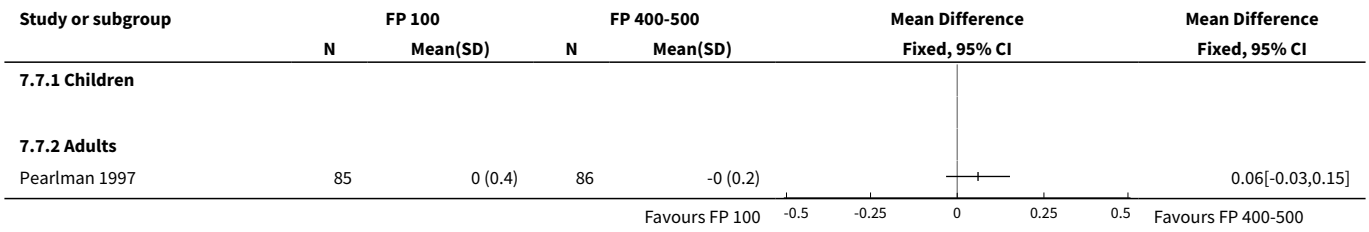


Analysis 7.6. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 6 Change in daily asthma symptom score compared to baseline.

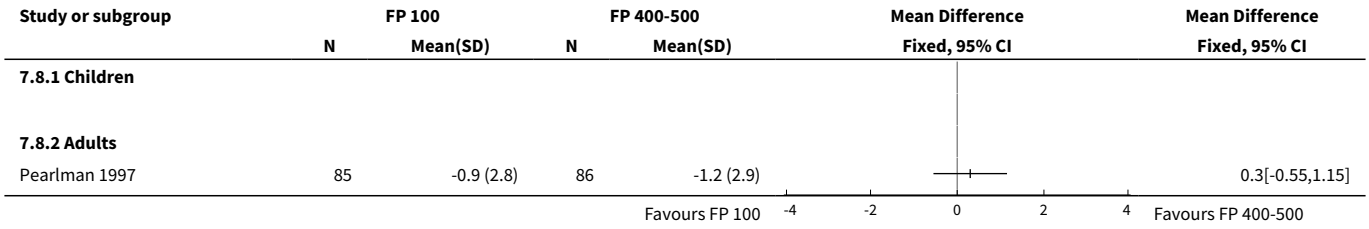




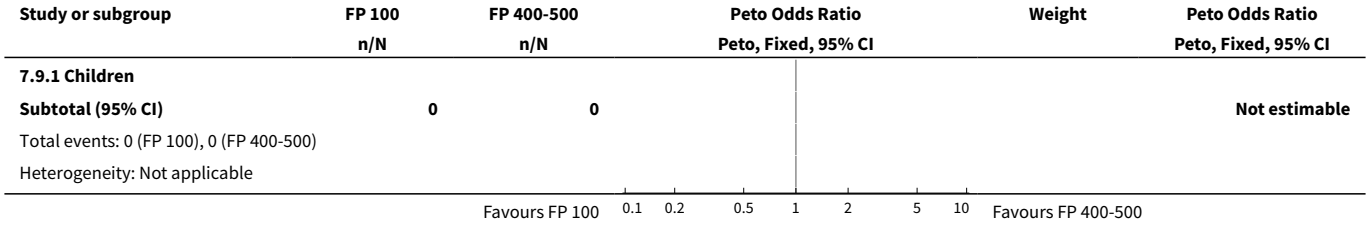
Analysis 7.7. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 7 Change in number of night-time awakenings/week compared to baseline.

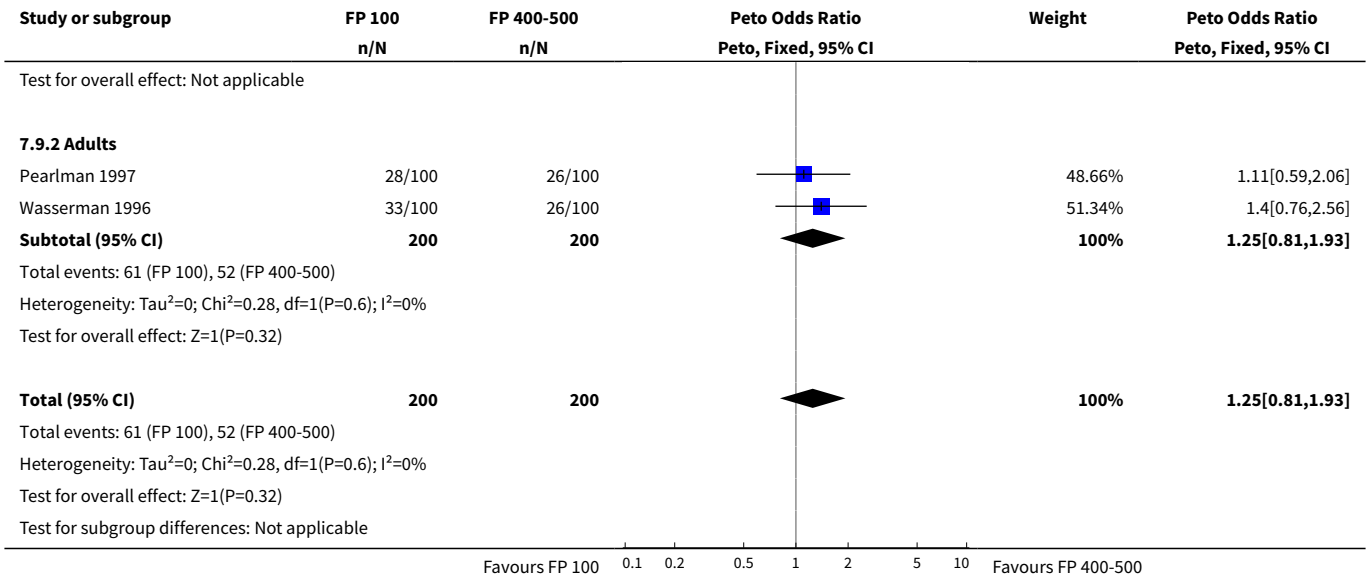


Analysis 7.8. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 8 Change in daily use of beta2 agonist compared to baseline (puffs/d).

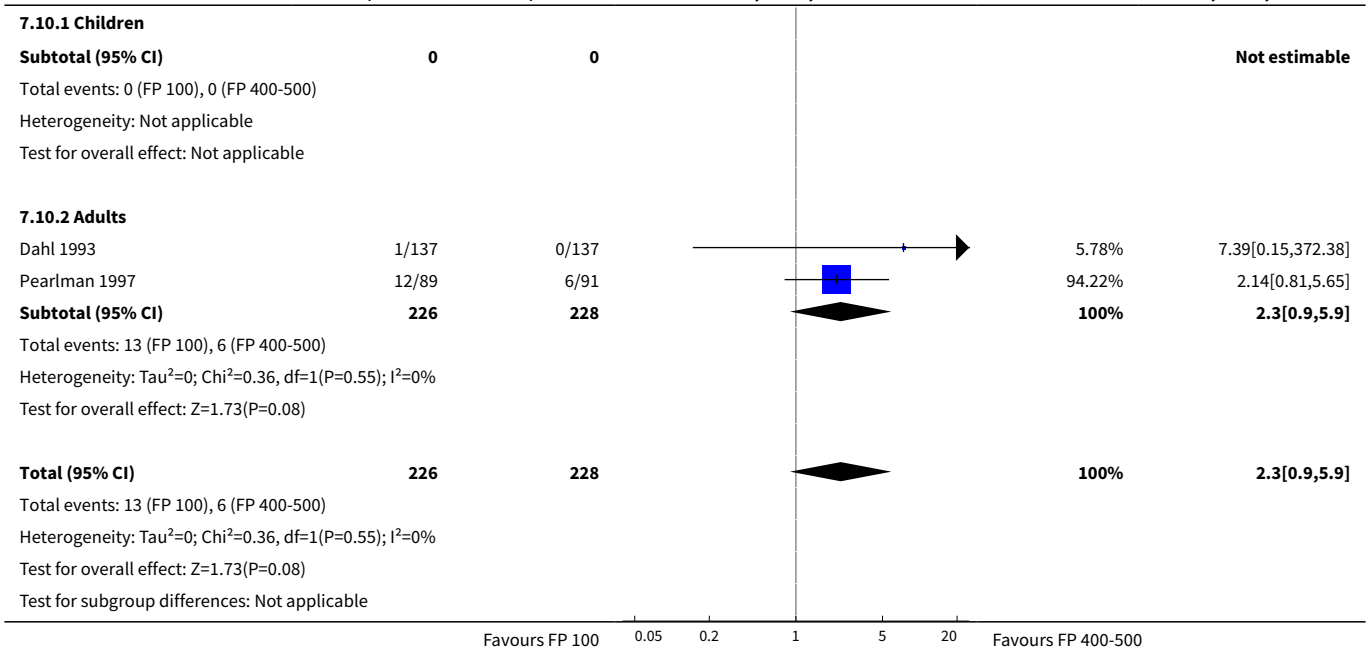


Analysis 7.9. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 9 Physician global rated efficacy: ineffective.



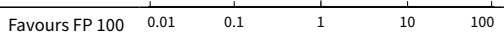


Analysis 7.10. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 10 Number of patients withdrawn due to lack of efficacy.



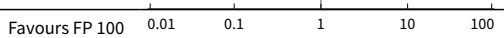
Analysis 7.11. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 11 Sore throat or pharyngitis (No. of patients).

Study or subgroup	FP 100 n/N	FP 400-500 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.11.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 100), 0 (FP 400-500)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
7.11.2 Adults					
Dahl 1993	2/137	1/137		30.18%	1.96[0.2,18.97]
Pearlman 1997	2/89	1/91		30.06%	2.01[0.21,19.55]
Wasserman 1996	1/79	3/82		39.76%	0.37[0.05,2.71]
Subtotal (95% CI)	**305**	**310**		**100%**	**1.02[0.29,3.56]**
Total events: 5 (FP 100), 5 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=1.64, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=0.03(P=0.97)					
Total (95% CI)	**305**	**310**		**100%**	**1.02[0.29,3.56]**
Total events: 5 (FP 100), 5 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=1.64, df=2(P=0.44); I^2=0%					
Test for overall effect: Z=0.03(P=0.97)					
Test for subgroup differences: Not applicable					



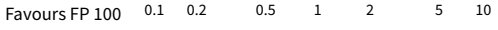
Analysis 7.12. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 12 Hoarseness or dysphonia (No. of patients).

Study or subgroup	FP 100 n/N	FP 400-500 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.12.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 100), 0 (FP 400-500)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
7.12.2 Adults					
Pearlman 1997	1/89	5/91		54.48%	0.26[0.05,1.32]
Wasserman 1996	1/79	4/82		45.52%	0.3[0.05,1.79]
Wolfe 1996	0/137	0/137			Not estimable
Subtotal (95% CI)	**305**	**310**		**100%**	**0.28[0.08,0.92]**
Total events: 2 (FP 100), 9 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=2.09(P=0.04)					
Total (95% CI)	**305**	**310**		**100%**	**0.28[0.08,0.92]**
Total events: 2 (FP 100), 9 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=2.09(P=0.04)					
Test for subgroup differences: Not applicable					



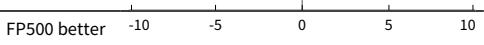
Analysis 7.13. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 13 Oral Candidiasis (No. of patients).

Study or subgroup	FP 100 n/N	FP 400-500 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
7.13.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 100), 0 (FP 400-500)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
7.13.2 Adults					
Dahl 1993	2/137	2/137		27.05%	1[0.14,7.18]
Pearlman 1997	2/89	2/91		26.89%	1.02[0.14,7.38]
Wasserman 1996	3/79	4/82		46.06%	0.77[0.17,3.5]
Subtotal (95% CI)	**305**	**310**		**100%**	**0.89[0.32,2.49]**
Total events: 7 (FP 100), 8 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=2(P=0.97); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
Total (95% CI)	**305**	**310**		**100%**	**0.89[0.32,2.49]**
Total events: 7 (FP 100), 8 (FP 400-500)					
Heterogeneity: Tau^2=0; Chi^2=0.07, df=2(P=0.97); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
Test for subgroup differences: Not applicable					



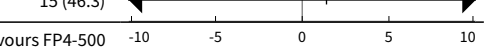
Analysis 7.14. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 14 Plasma Cortisol (AUC).

Study or subgroup	FP100 N	FP100 Mean(SD)	FP4-500 N	FP4-500 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
7.14.1 Children						
7.14.2 Adults						
Falcoz 2000	1	0 (0)	75	0.1 (0.3)		Not estimable



Analysis 7.15. Comparison 7 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (all ages), Outcome 15 Clinic PEF (L/min - change from baseline).

Study or subgroup	FP100 N	FP100 Mean(SD)	FP4-500 N	FP4-500 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
7.15.1 Children						
7.15.2 Adults						
O'Sullivan 2002	11	16.4 (39.5)	12	15 (46.3)		1.4[-33.68,36.48]

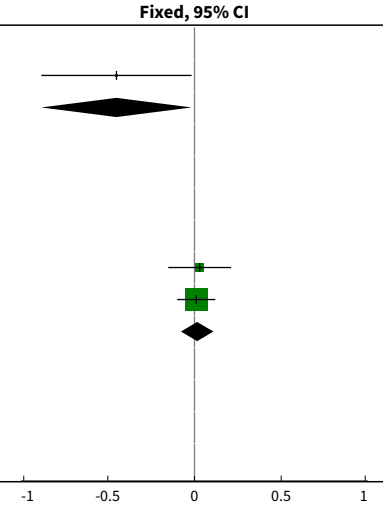


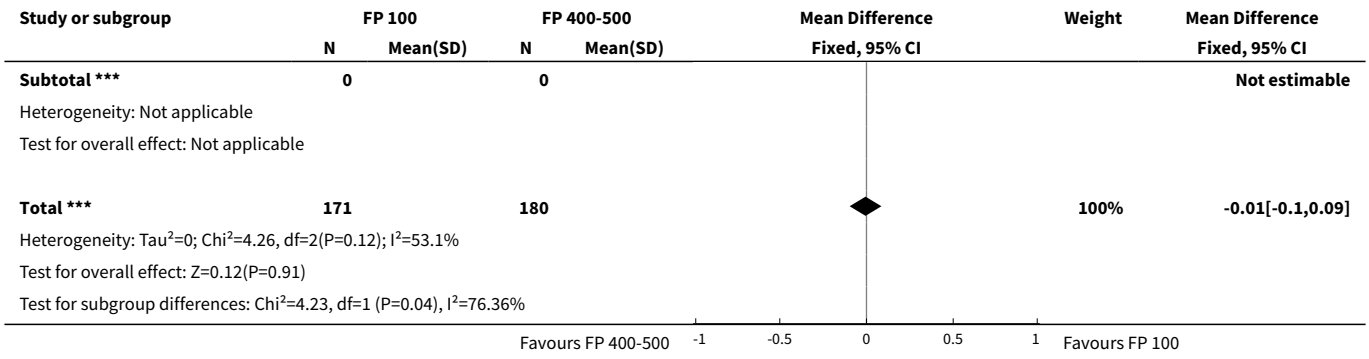
Comparison 8. Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline based on study duration (litres) - adults	3	351	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.10, 0.09]
1.1 1-4 weeks	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.88, -0.02]
1.2 1-5 months	2	328	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.08, 0.11]
1.3 6 months or longer	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in FEV1 compared to baseline based on delivery devices (litres) - adults	3	351	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.10, 0.09]
2.1 MDI	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.88, -0.02]
2.2 DPI	2	328	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.08, 0.11]
3 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults	3	351	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.10, 0.09]
3.1 Mild to moderate	1	23	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.88, -0.02]
3.2 Moderate	2	328	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.08, 0.11]

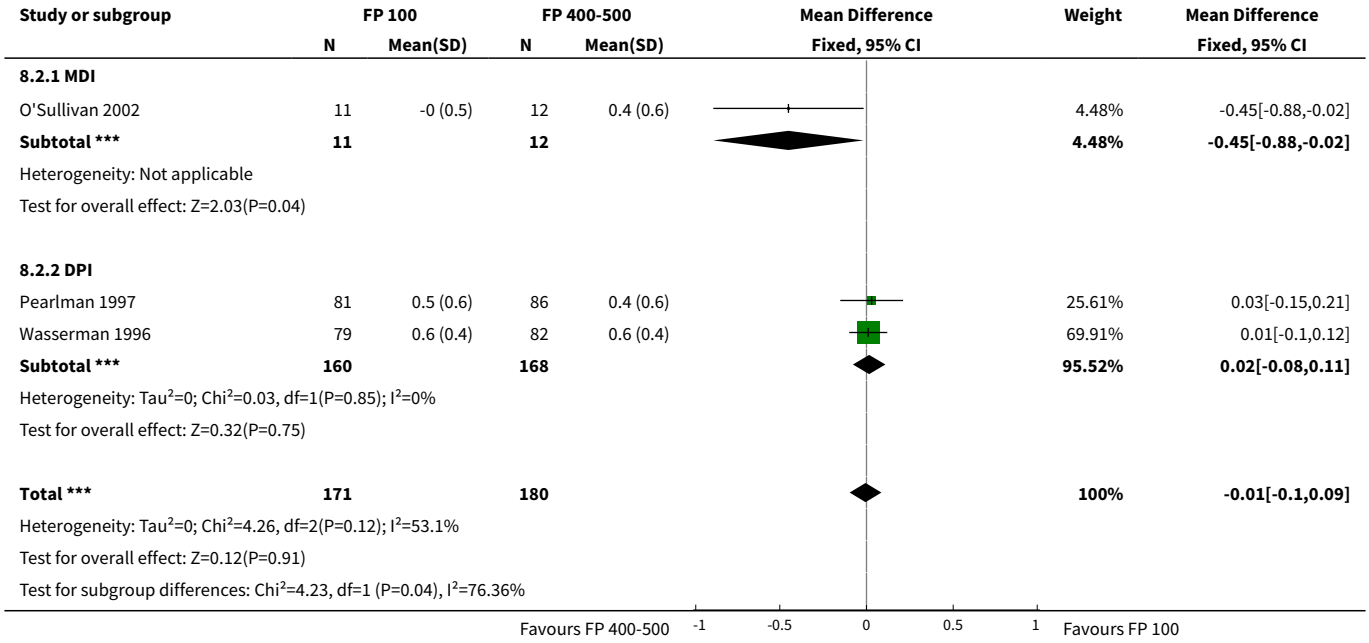
Analysis 8.1. Comparison 8 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (subgroups), Outcome 1 Change in FEV1 compared to baseline based on study duration (litres) - adults.

Study or subgroup	FP 100 N	FP 100 Mean(SD)	FP 400-500 N	FP 400-500 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
8.1.1 1-4 weeks							
O'Sullivan 2002	11	-0 (0.5)	12	0.4 (0.6)		4.48%	-0.45[-0.88,-0.02]
Subtotal ***	**11**		**12**			**4.48%**	**-0.45[-0.88,-0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.03(P=0.04)							
8.1.2 1-5 months							
Pearlman 1997	81	0.5 (0.6)	86	0.4 (0.6)		25.61%	0.03[-0.15,0.21]
Wasserman 1996	79	0.6 (0.4)	82	0.6 (0.4)		69.91%	0.01[-0.1,0.12]
Subtotal ***	**160**		**168**			**95.52%**	**0.02[-0.08,0.11]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.85); I²=0%							
Test for overall effect: Z=0.32(P=0.75)							
8.1.3 6 months or longer							

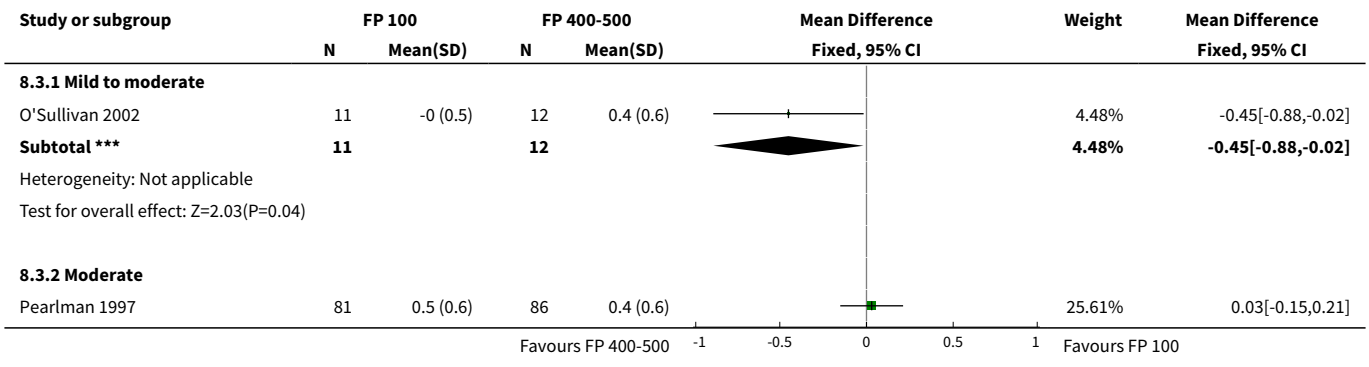


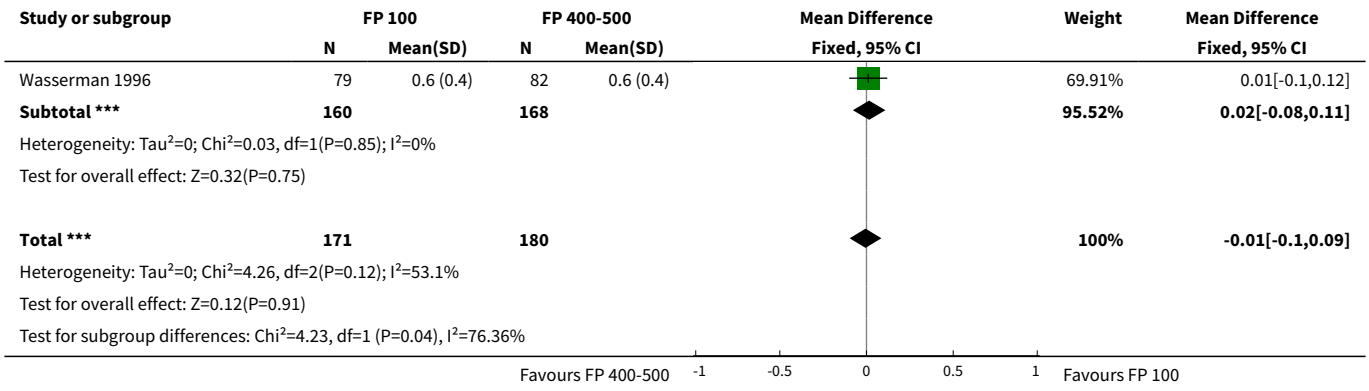


Analysis 8.2. Comparison 8 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (subgroups), Outcome 2 Change in FEV1 compared to baseline based on delivery devices (litres) - adults.



Analysis 8.3. Comparison 8 Parallel group studies, no oral steroids: 100 versus 400-500 mcg/d (subgroups), Outcome 3 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults.





Comparison 9. Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages)

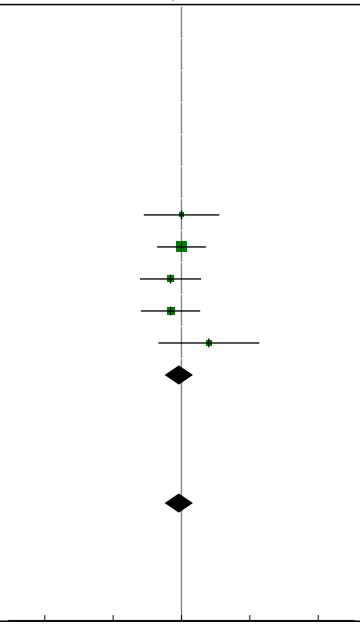
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (Change from baseline - litres)	5	900	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
1.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	5	900	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
2 Change in morning PEF (L/min)	4	905	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-7.94, 3.35]
2.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	4	905	Mean Difference (IV, Fixed, 95% CI)	-2.30 [-7.94, 3.35]
3 Change in evening PEF (L/min)	2	505	Mean Difference (IV, Fixed, 95% CI)	5.83 [-2.94, 14.60]
3.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	2	505	Mean Difference (IV, Fixed, 95% CI)	5.83 [-2.94, 14.60]
4 Change in rescue medication (puffs/d)	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 Health-related quality of life - AQLQ (absolute scores)	0		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	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Change in daily symptoms compared with baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Nocturnal awakenings (awakenings per night)	0		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	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Exacerbations requiring hospitalisation	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
8.1 Children	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Exacerbations requiring OCS treatment	2	363	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.77, 1.98]
9.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	2	363	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [0.77, 1.98]
10 Withdrawals (total)	5	1039	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.88, 1.83]
10.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	5	1039	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.88, 1.83]
11 Withdrawals (adverse events)	4	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.17, 1.25]
11.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.2 Adults	4	841	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.46 [0.17, 1.25]
12 Withdrawals (lack of efficacy)	2	537	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [0.73, 3.81]
12.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	2	537	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.67 [0.73, 3.81]
13 Drug-related adverse events	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
13.1 Children	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 HPA function data (am cortisol <5mcg/dL)	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
14.1 Children	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
14.2 Adults	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]

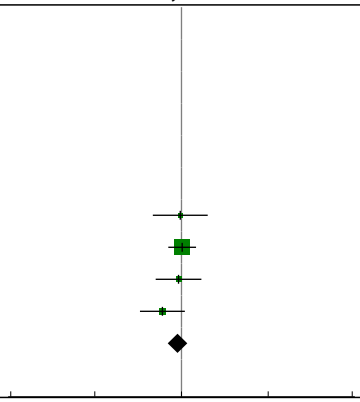
Analysis 9.1. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 1 FEV1 (Change from baseline - litres).

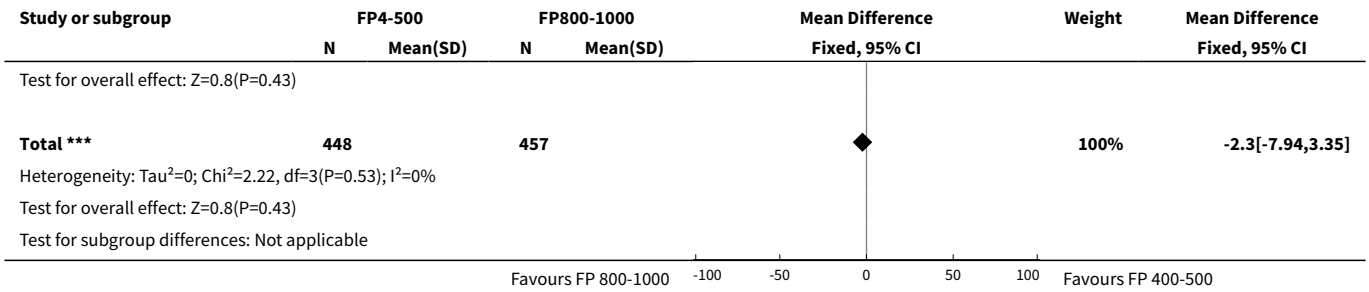
Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.1.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
9.1.2 Adults							
FAP30001	86	0.3 (0.5)	92	0.3 (0.5)		14.04%	0[-0.14,0.14]
Ind 2003	145	0.2 (0.4)	142	0.2 (0.4)		33.72%	0[-0.09,0.09]
Lumry 2006	105	0.1 (0.4)	98	0.2 (0.4)		21.56%	-0.04[-0.15,0.07]
Pinnas 2005	95	0.4 (0.4)	99	0.4 (0.4)		22.81%	-0.04[-0.15,0.07]
Wallin 2003	19	0.1 (0.3)	19	0 (0.3)		7.87%	0.1[-0.08,0.28]
Subtotal ***	**450**		**450**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Tau^2=0; Chi^2=2.01, df=4(P=0.73); I^2=0%							
Test for overall effect: Z=0.37(P=0.71)							
Total ***	**450**		**450**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Tau^2=0; Chi^2=2.01, df=4(P=0.73); I^2=0%							
Test for overall effect: Z=0.37(P=0.71)							
Test for subgroup differences: Not applicable							



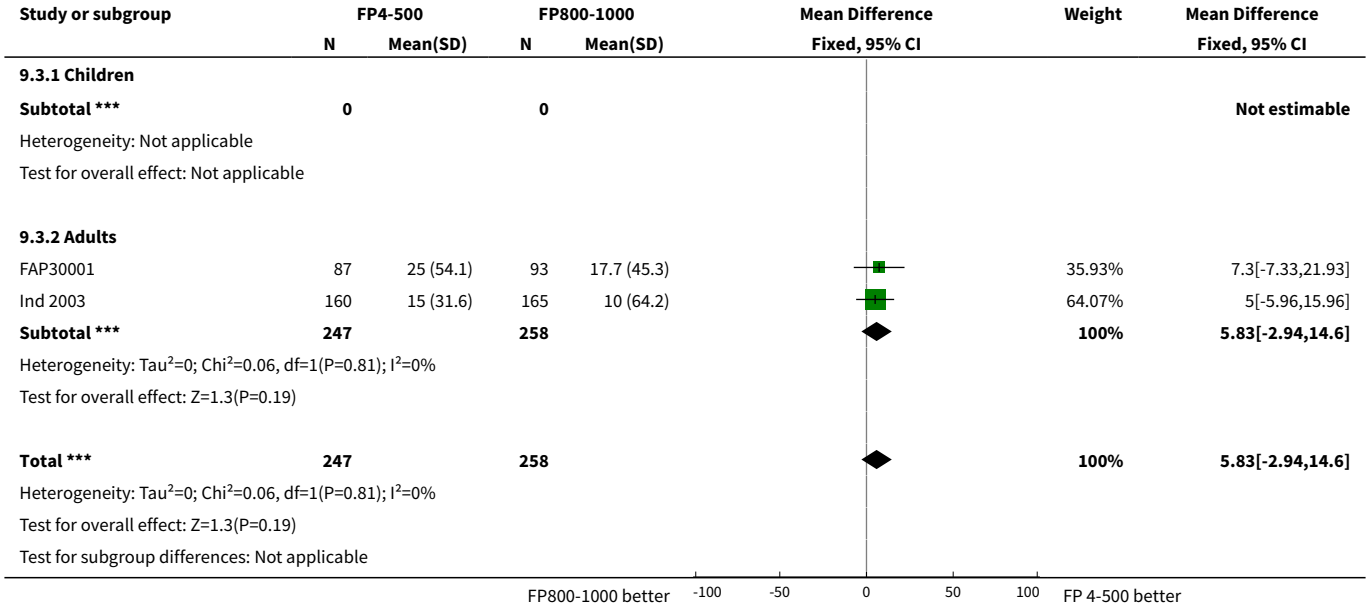
Analysis 9.2. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 2 Change in morning PEF (L/min).

Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
9.2.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
9.2.2 Adults							
FAP30001	86	26.3 (55.6)	93	27 (52.1)		12.74%	-0.7[-16.52,15.12]
Ind 2003	160	16.9 (34.7)	165	16.5 (38.8)		49.85%	0.4[-7.6,8.4]
Lumry 2006	105	18.9 (47.1)	100	20.6 (49)		18.37%	-1.7[-14.87,11.47]
Pinnas 2005	97	44 (45.8)	99	55 (46.6)		19.03%	-11[-23.94,1.94]
Subtotal ***	**448**		**457**			**100%**	**-2.3[-7.94,3.35]**
Heterogeneity: Tau^2=0; Chi^2=2.22, df=3(P=0.53); I^2=0%							

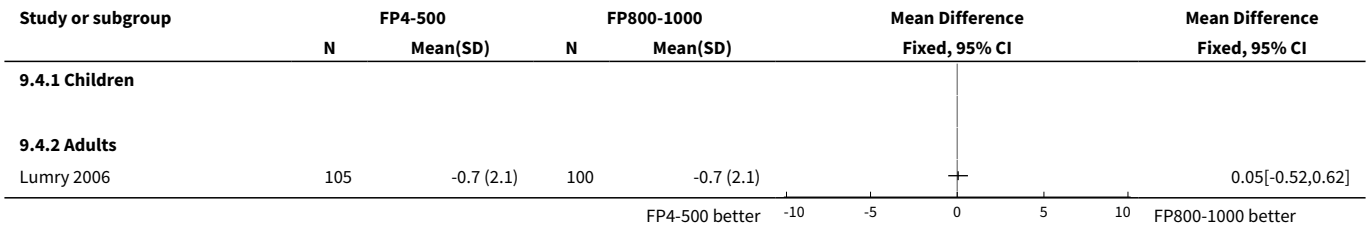




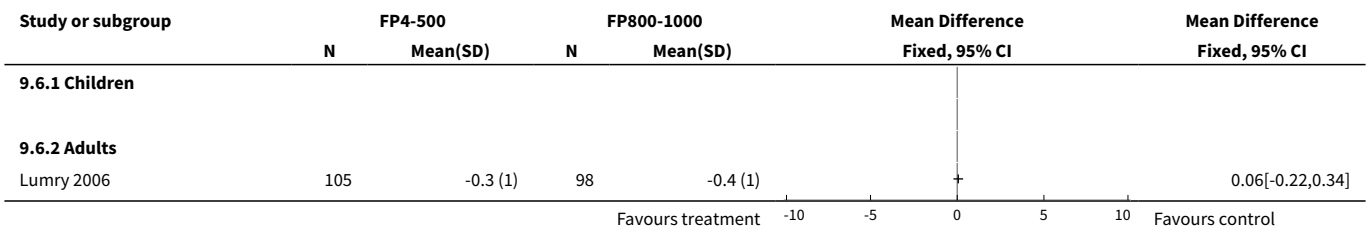
Analysis 9.3. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 3 Change in evening PEF (L/min).



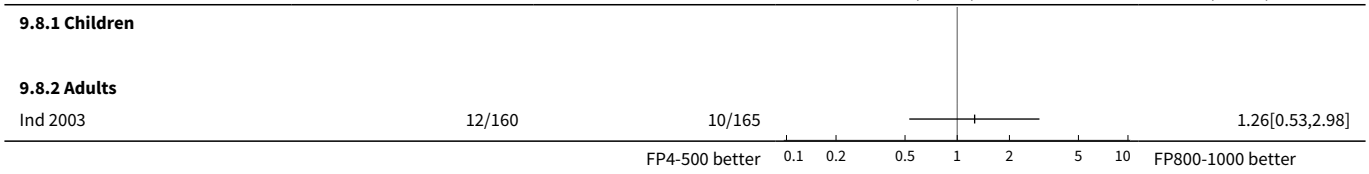
Analysis 9.4. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 4 Change in rescue medication (puffs/d).



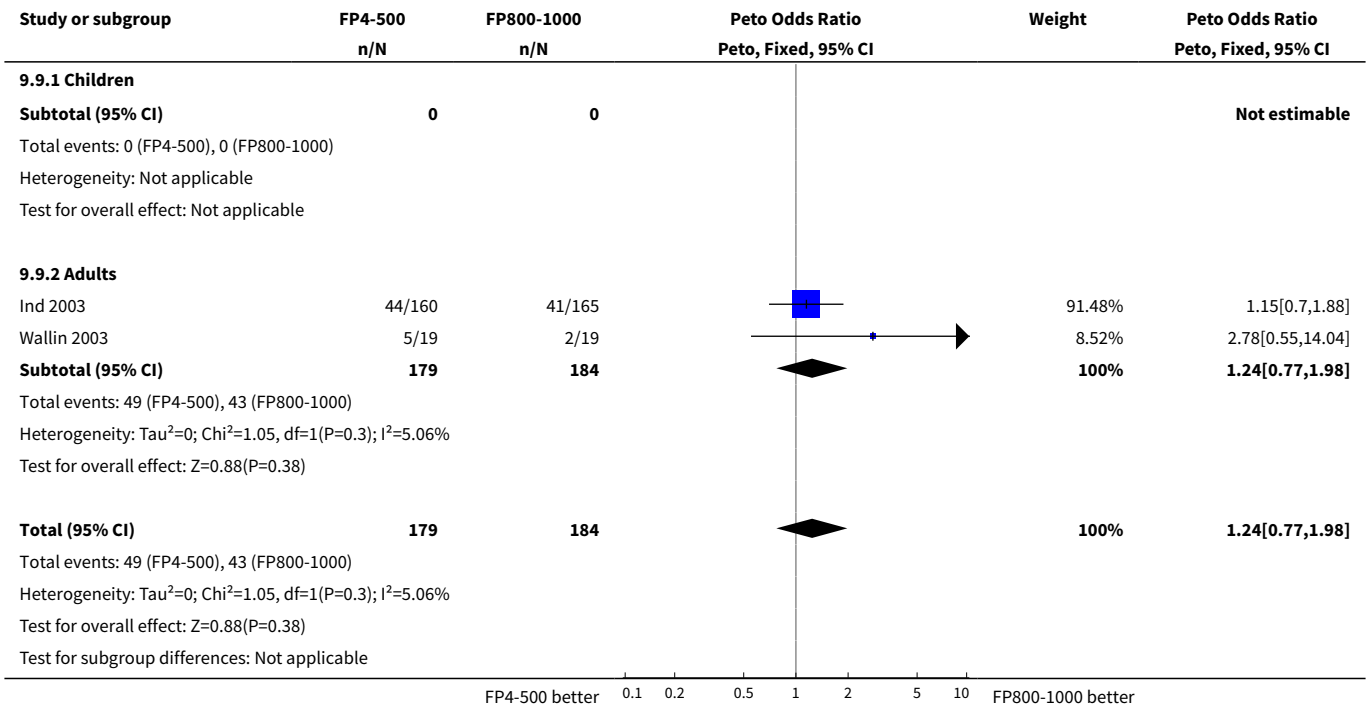
Analysis 9.6. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 6 Change in daily symptoms compared with baseline.



Analysis 9.8. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 8 Exacerbations requiring hospitalisation.

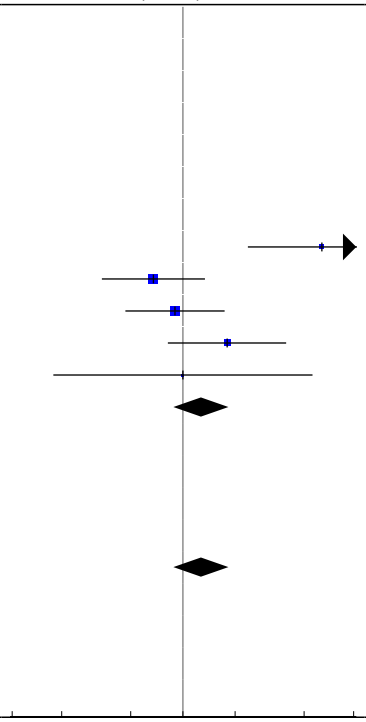


Analysis 9.9. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 9 Exacerbations requiring OCS treatment.



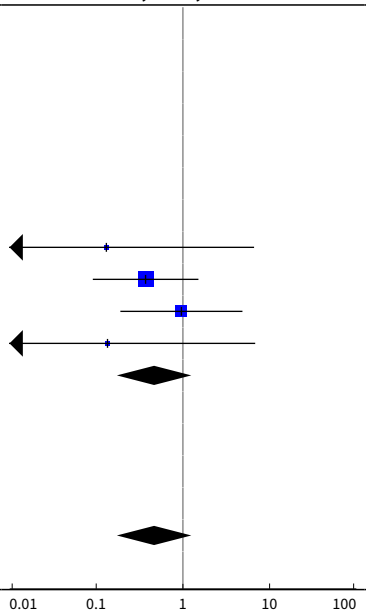
Analysis 9.10. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 10 Withdrawals (total).

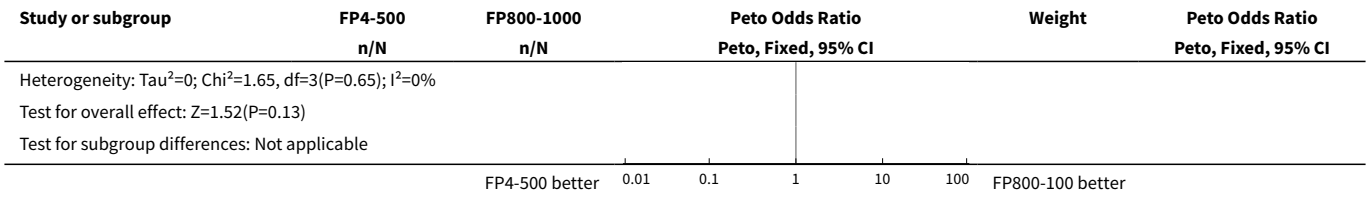
Study or subgroup	FP4-500 n/N	FP800-1000 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
9.10.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP4-500), 0 (FP800-1000)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.10.2 Adults					
Dahl 1993	16/137	1/133		13.98%	6.33[2.37,16.87]
Ind 2003	15/160	22/165		28.75%	0.68[0.34,1.34]
Lumry 2006	22/106	23/102		30.98%	0.9[0.47,1.74]
Pinnas 2005	18/98	11/100		21.75%	1.8[0.82,3.94]
Wallin 2003	3/19	3/19		4.54%	1[0.18,5.59]
Subtotal (95% CI)	**520**	**519**		**100%**	**1.27[0.88,1.83]**
Total events: 74 (FP4-500), 60 (FP800-1000)					
Heterogeneity: Tau^2=0; Chi^2=15.45, df=4(P=0); I^2=74.11%					
Test for overall effect: Z=1.29(P=0.2)					
Total (95% CI)	**520**	**519**		**100%**	**1.27[0.88,1.83]**
Total events: 74 (FP4-500), 60 (FP800-1000)					
Heterogeneity: Tau^2=0; Chi^2=15.45, df=4(P=0); I^2=74.11%					
Test for overall effect: Z=1.29(P=0.2)					
Test for subgroup differences: Not applicable					



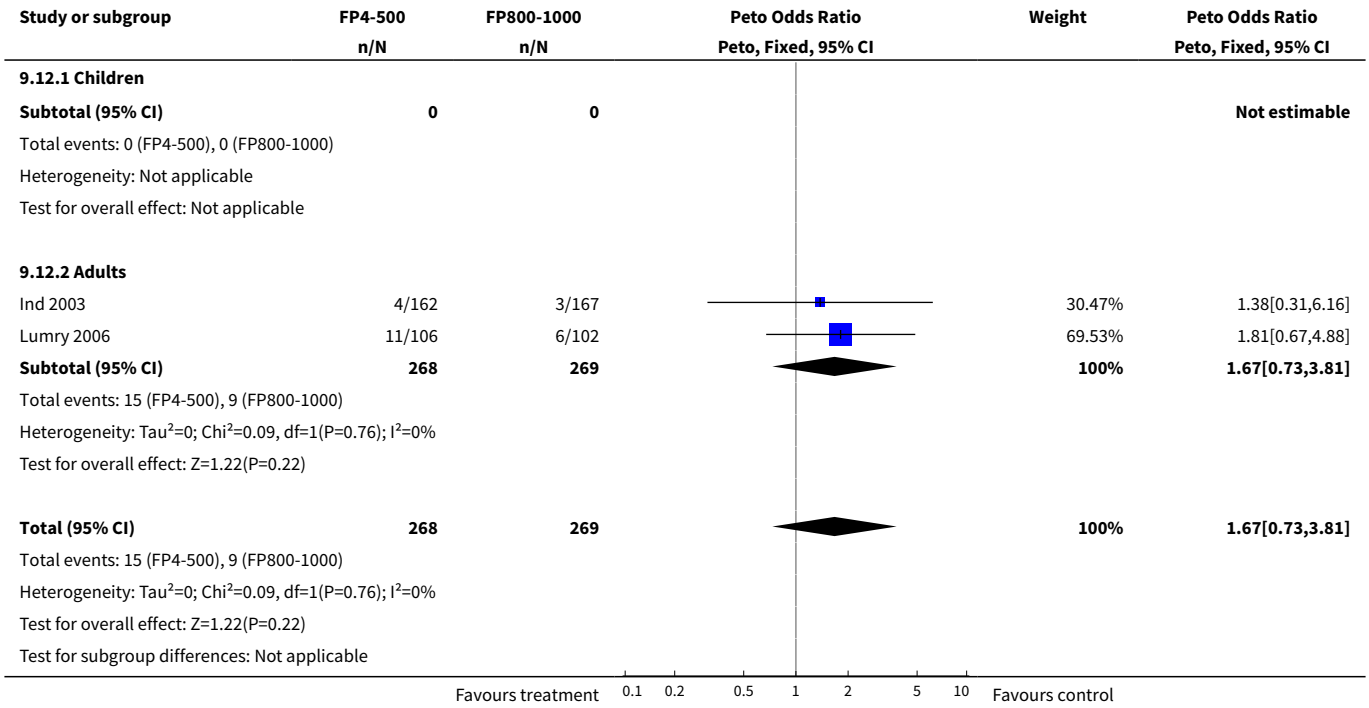
Analysis 9.11. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 11 Withdrawals (adverse events).

Study or subgroup	FP4-500 n/N	FP800-1000 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
9.11.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP4-500), 0 (FP800-1000)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
9.11.2 Adults					
Dahl 1993	0/137	1/133		6.38%	0.13[0,6.62]
Ind 2003	2/160	6/165		49.91%	0.37[0.09,1.51]
Lumry 2006	3/106	3/102		37.33%	0.96[0.19,4.86]
Wallin 2003	0/19	1/19		6.38%	0.14[0,6.82]
Subtotal (95% CI)	**422**	**419**		**100%**	**0.46[0.17,1.25]**
Total events: 5 (FP4-500), 11 (FP800-1000)					
Heterogeneity: Tau^2=0; Chi^2=1.65, df=3(P=0.65); I^2=0%					
Test for overall effect: Z=1.52(P=0.13)					
Total (95% CI)	**422**	**419**		**100%**	**0.46[0.17,1.25]**
Total events: 5 (FP4-500), 11 (FP800-1000)					





Analysis 9.12. Comparison 9 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (all ages), Outcome 12 Withdrawals (lack of efficacy).



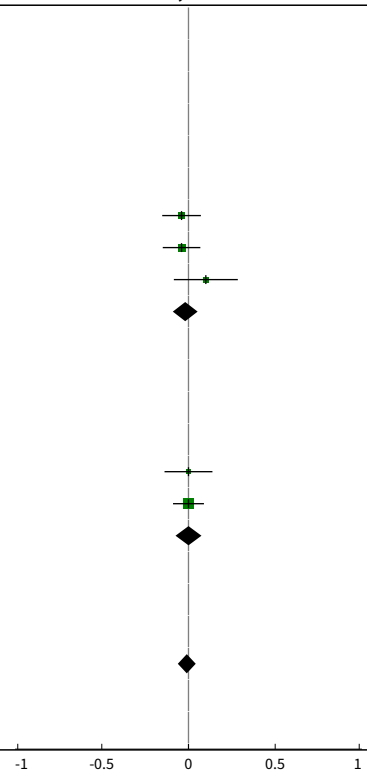
Comparison 10. Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (subgroups)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Change from baseline in FEV1 based on study duration (litres) - adults	5	900	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
1.1 1-4 weeks	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 1-5 months	3	435	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.09, 0.05]
1.3 6 months or longer	2	465	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.07, 0.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Change from baseline in FEV1 based on delivery devices (litres) - adults	5	900	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
2.1 MDI	3	435	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.09, 0.05]
2.2 DPI	2	465	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.07, 0.07]
3 Change from baseline in FEV1 based on degree of severity (litres) - adults	5	900	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.06, 0.04]
3.1 Mild to moderate	1	38	Mean Difference (IV, Fixed, 95% CI)	0.1 [-0.08, 0.28]
3.2 Moderate	3	575	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.10, 0.04]
3.3 Moderate to severe	1	287	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.09, 0.09]

Analysis 10.1. Comparison 10 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (subgroups), Outcome 1 Change from baseline in FEV1 based on study duration (litres) - adults.

Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
10.1.1 1-4 weeks							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
10.1.2 1-5 months							
Lumry 2006	105	0.1 (0.4)	98	0.2 (0.4)		21.56%	-0.04[-0.15,0.07]
Pinnas 2005	95	0.4 (0.4)	99	0.4 (0.4)		22.81%	-0.04[-0.15,0.07]
Wallin 2003	19	0.1 (0.3)	19	0 (0.3)		7.87%	0.1[-0.08,0.28]
Subtotal ***	**219**		**216**			**52.24%**	**-0.02[-0.09,0.05]**
Heterogeneity: Tau^2=0; Chi^2=1.88, df=2(P=0.39); I^2=0%							
Test for overall effect: Z=0.52(P=0.6)							
10.1.3 6 months or longer							
FAP30001	86	0.3 (0.5)	92	0.3 (0.5)		14.04%	0[-0.14,0.14]
Ind 2003	145	0.2 (0.4)	142	0.2 (0.4)		33.72%	0[-0.09,0.09]
Subtotal ***	**231**		**234**			**47.76%**	**0[-0.07,0.07]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%							
Test for overall effect: Not applicable							
Total ***	**450**		**450**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Tau^2=0; Chi^2=2.01, df=4(P=0.73); I^2=0%							
Test for overall effect: Z=0.37(P=0.71)							



Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Test for subgroup differences: Chi²=0.13, df=1 (P=0.72), I²=0%							

FP800-1000 better -1 -0.5 0 0.5 1 FP4-500 better

Analysis 10.2. Comparison 10 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (subgroups), Outcome 2 Change from baseline in FEV1 based on delivery devices (litres) - adults.

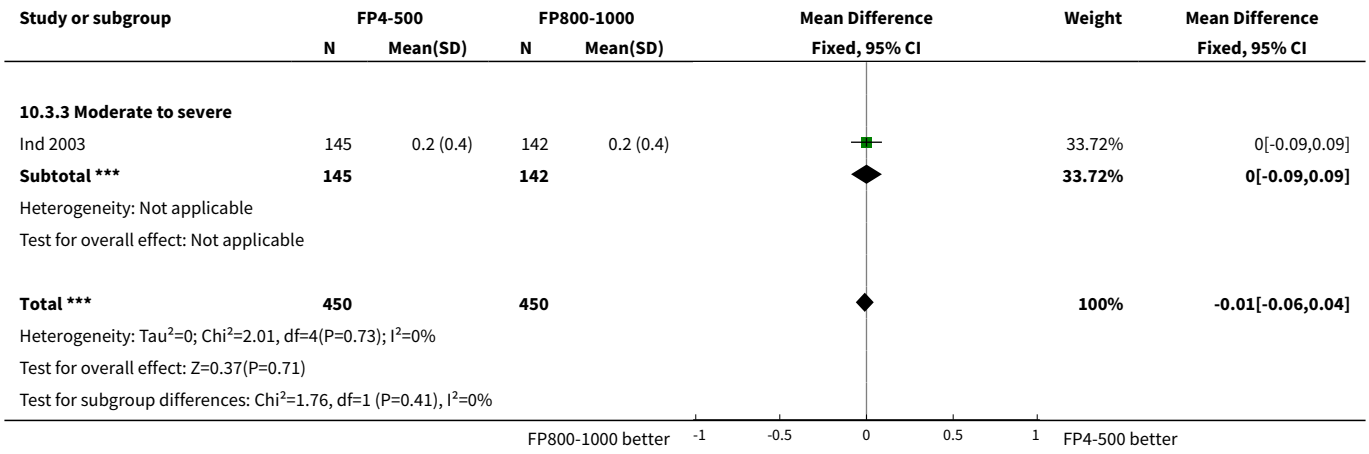
Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
10.2.1 MDI							
Lumry 2006	105	0.1 (0.4)	98	0.2 (0.4)		21.56%	-0.04[-0.15,0.07]
Pinnas 2005	95	0.4 (0.4)	99	0.4 (0.4)		22.81%	-0.04[-0.15,0.07]
Wallin 2003	19	0.1 (0.3)	19	0 (0.3)		7.87%	0.1[-0.08,0.28]
Subtotal ***	**219**		**216**			**52.24%**	**-0.02[-0.09,0.05]**
Heterogeneity: Tau²=0; Chi²=1.88, df=2(P=0.39); I²=0%							
Test for overall effect: Z=0.52(P=0.6)							
10.2.2 DPI							
FAP30001	86	0.3 (0.5)	92	0.3 (0.5)		14.04%	0[-0.14,0.14]
Ind 2003	145	0.2 (0.4)	142	0.2 (0.4)		33.72%	0[-0.09,0.09]
Subtotal ***	**231**		**234**			**47.76%**	**0[-0.07,0.07]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%							
Test for overall effect: Not applicable							
Total ***	**450**		**450**			**100%**	**-0.01[-0.06,0.04]**
Heterogeneity: Tau²=0; Chi²=2.01, df=4(P=0.73); I²=0%							
Test for overall effect: Z=0.37(P=0.71)							
Test for subgroup differences: Chi²=0.13, df=1 (P=0.72), I²=0%							

FP800-1000 better -1 -0.5 0 0.5 1 FP4-500 better

Analysis 10.3. Comparison 10 Parallel group studies, no oral steroids: 400-500 versus 800-1000 mcg/d (subgroups), Outcome 3 Change from baseline in FEV1 based on degree of severity (litres) - adults.

Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
10.3.1 Mild to moderate							
Wallin 2003	19	0.1 (0.3)	19	0 (0.3)		7.87%	0.1[-0.08,0.28]
Subtotal ***	**19**		**19**			**7.87%**	**0.1[-0.08,0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.06(P=0.29)							
10.3.2 Moderate							
FAP30001	86	0.3 (0.5)	92	0.3 (0.5)		14.04%	0[-0.14,0.14]
Lumry 2006	105	0.1 (0.4)	98	0.2 (0.4)		21.56%	-0.04[-0.15,0.07]
Pinnas 2005	95	0.4 (0.4)	99	0.4 (0.4)		22.81%	-0.04[-0.15,0.07]
Subtotal ***	**286**		**289**			**58.4%**	**-0.03[-0.1,0.04]**
Heterogeneity: Tau²=0; Chi²=0.24, df=2(P=0.88); I²=0%							
Test for overall effect: Z=0.88(P=0.38)							

FP800-1000 better -1 -0.5 0 0.5 1 FP4-500 better



Comparison 11. Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages)

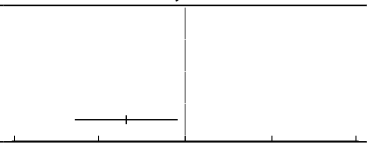
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline (litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 FEV1 (% predicted)	2	283	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-5.72, 4.87]
2.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	2	283	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-5.72, 4.87]
3 FEV1 (Litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Change in FVC compared to baseline (litres)	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 FEF25-75	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]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Change in FEF25-75 compared to baseline (L/second)	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]
6.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 am PEF (Litres/min)	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 Change in morning PEFR compared to baseline (L/min)	2	419	Mean Difference (IV, Fixed, 95% CI)	-21.86 [-29.19, -14.53]
8.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	2	419	Mean Difference (IV, Fixed, 95% CI)	-21.86 [-29.19, -14.53]
9 Change in evening PEFR compared to baseline (L/min)	2	419	Mean Difference (IV, Fixed, 95% CI)	-12.66 [-19.32, -5.99]
9.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.2 Adults	2	419	Mean Difference (IV, Fixed, 95% CI)	-12.66 [-19.32, -5.99]
10 Physician global rated efficacy: ineffective	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
10.1 Children	0		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Symptoms	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 Percentage of symptom-free days	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 Change in daily asthma symptom score compared to baseline	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13.1 Children	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
13.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Change in number of night-time awakenings/week compared to baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Rescue medication usage	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
15.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Change in daily use of beta2 agonist compared to baseline (puffs/d)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Oral Candidiasis (No. of patients)	2	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.32 [0.11, 0.97]
17.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Adults	2	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.32 [0.11, 0.97]
18 Hoarseness or dysphonia (No. of patients)	2	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.05, 0.59]
18.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
18.2 Adults	2	433	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.18 [0.05, 0.59]
19 Withdrawals (total)	2	294	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.29 [1.59, 17.60]
19.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
19.2 Adults	2	294	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.29 [1.59, 17.60]
20 Number of patients withdrawn due to lack of efficacy	2	427	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.31 [2.18, 12.96]
20.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
20.2 Adults	2	427	Peto Odds Ratio (Peto, Fixed, 95% CI)	5.31 [2.18, 12.96]

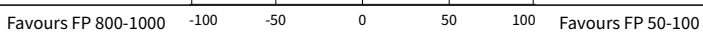
Analysis 11.1. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 1 Change in FEV1 compared to baseline (litres).

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.1.1 Children						
11.1.2 Adults						
Chervinsky 1994	78	0.1 (0.5)	79	0.3 (0.4)		-0.17[-0.32,-0.02]



Analysis 11.2. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 2 FEV1 (% predicted).

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.2.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
11.2.2 Adults							
Dahl 1993	129	76.2 (22.1)	130	76.7 (24.9)		85.36%	-0.5[-6.23,5.23]
Gershman 2000	12	77 (17.3)	12	77 (17.3)		14.64%	0[-13.84,13.84]
Subtotal ***	**141**		**142**			**100%**	**-0.43[-5.72,4.87]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%							
Test for overall effect: Z=0.16(P=0.87)							
Total ***	**141**		**142**			**100%**	**-0.43[-5.72,4.87]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%							
Test for overall effect: Z=0.16(P=0.87)							
Test for subgroup differences: Not applicable							

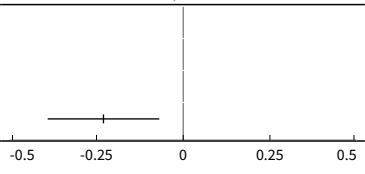


Analysis 11.3. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 3 FEV1 (Litres).

Study or subgroup	FP50-100 N	FP50-100 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.3.1 Children						
11.3.2 Adults						
Gershman 2000	12	3.1 (0.8)	12	2.8 (0.7)		0.34[-0.24,0.92]

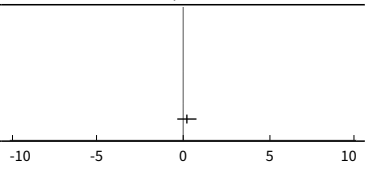
Analysis 11.4. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 4 Change in FVC compared to baseline (litres).

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.4.1 Children						
11.4.2 Adults						
Chervinsky 1994	78	-0 (0.6)	89	0.2 (0.5)		-0.23[-0.39,-0.07]



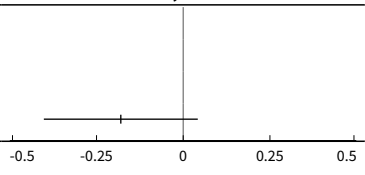
Analysis 11.5. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 5 FEF25-75.

Study or subgroup	FP50-100 N	FP50-100 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.5.1 Children						
11.5.2 Adults						
Gershman 2000	12	2.1 (0.8)	12	1.9 (0.5)		0.21[-0.34,0.76]



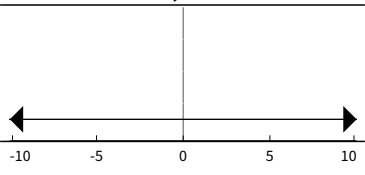
Analysis 11.6. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 6 Change in FEF25-75 compared to baseline (L/second).

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.6.1 Children						
11.6.2 Adults						
Chervinsky 1994	78	0.2 (0.7)	89	0.4 (0.7)		-0.18[-0.4,0.04]



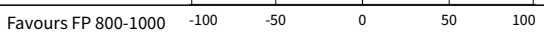
Analysis 11.7. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 7 am PEF (Litres/min).

Study or subgroup	FP50-100 N	FP50-100 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.7.1 Children						
11.7.2 Adults						
Gershman 2000	12	495 (75.2)	12	465 (113.8)		30[-47.15,107.15]



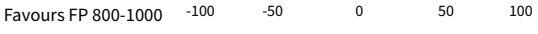
Analysis 11.8. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 8 Change in morning PEFR compared to baseline (L/min).

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.8.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
11.8.2 Adults							
Chervinsky 1994	78	11 (40)	79	39 (56)		23.24%	-28[-43.21,-12.79]
Dahl 1993	129	0 (32)	133	20 (37)		76.76%	-20[-28.37,-11.63]
Subtotal ***	**207**		**212**			**100%**	**-21.86[-29.19,-14.53]**
Heterogeneity: Tau^2=0; Chi^2=0.82, df=1(P=0.37); I^2=0%							
Test for overall effect: Z=5.84(P<0.0001)							
Total ***	**207**		**212**			**100%**	**-21.86[-29.19,-14.53]**
Heterogeneity: Tau^2=0; Chi^2=0.82, df=1(P=0.37); I^2=0%							
Test for overall effect: Z=5.84(P<0.0001)							
Test for subgroup differences: Not applicable							



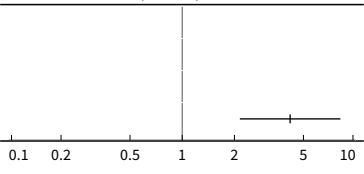
Analysis 11.9. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 9 Change in evening PEFR compared to baseline (L/min).

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
11.9.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
11.9.2 Adults							
Chervinsky 1994	78	7 (38)	79	25 (49)		23.67%	-18[-31.71,-4.29]
Dahl 1993	129	2 (32)	133	13 (31)		76.33%	-11[-18.63,-3.37]
Subtotal ***	**207**		**212**			**100%**	**-12.66[-19.32,-5.99]**
Heterogeneity: Tau^2=0; Chi^2=0.76, df=1(P=0.38); I^2=0%							
Test for overall effect: Z=3.72(P=0)							
Total ***	**207**		**212**			**100%**	**-12.66[-19.32,-5.99]**
Heterogeneity: Tau^2=0; Chi^2=0.76, df=1(P=0.38); I^2=0%							
Test for overall effect: Z=3.72(P=0)							
Test for subgroup differences: Not applicable							



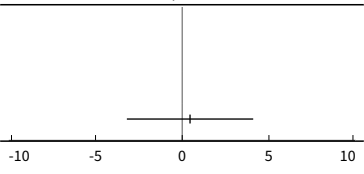
Analysis 11.10. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 10 Physician global rated efficacy: ineffective.

Study or subgroup	FP 50-100 n/N	FP 800-1000 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
11.10.1 Children				
11.10.2 Adults				
Chervinsky 1994	37/82	12/81		4.19[2.15,8.17]



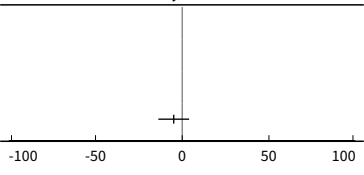
Analysis 11.11. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 11 Symptoms.

Study or subgroup	FP50-100 N	FP50-100 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.11.1 Children						
11.11.2 Adults						
Gershman 2000	12	4.1 (2.6)	12	3.6 (5.9)		0.45[-3.19,4.09]



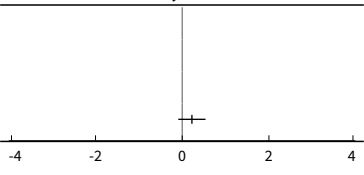
Analysis 11.12. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 12 Percentage of symptom-free days.

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.12.1 Children						
11.12.2 Adults						
Dahl 1993	125	26.4 (35.2)	132	31.3 (37.4)		-4.9[-13.78,3.98]



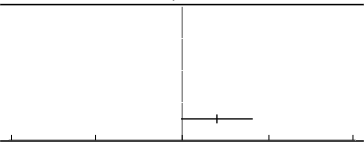
Analysis 11.13. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 13 Change in daily asthma symptom score compared to baseline.

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Std. Mean Difference Fixed, 95% CI	Std. Mean Difference Fixed, 95% CI
11.13.1 Children						
11.13.2 Adults						
Chervinsky 1994	78	-0.1 (0.4)	79	-0.2 (0.3)		0.22[-0.09,0.54]



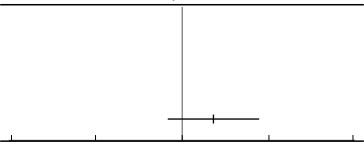
Analysis 11.14. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 14 Change in number of night-time awakenings/week compared to baseline.

Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.14.1 Children						
11.14.2 Adults						
Chervinsky 1994	78	0 (0.4)	79	-0.1 (0.2)		0.1[-0,0.2]



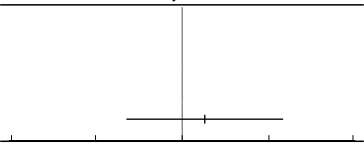
Analysis 11.15. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 15 Rescue medication usage.

Study or subgroup	FP50-100 N	FP50-100 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.15.1 Children						
11.15.2 Adults						
Gershman 2000	12	3.8 (4)	12	2 (2.4)		1.8[-0.84,4.44]



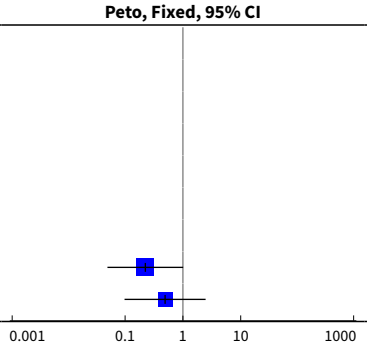
Analysis 11.16. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 16 Change in daily use of beta2 agonist compared to baseline (puffs/d).

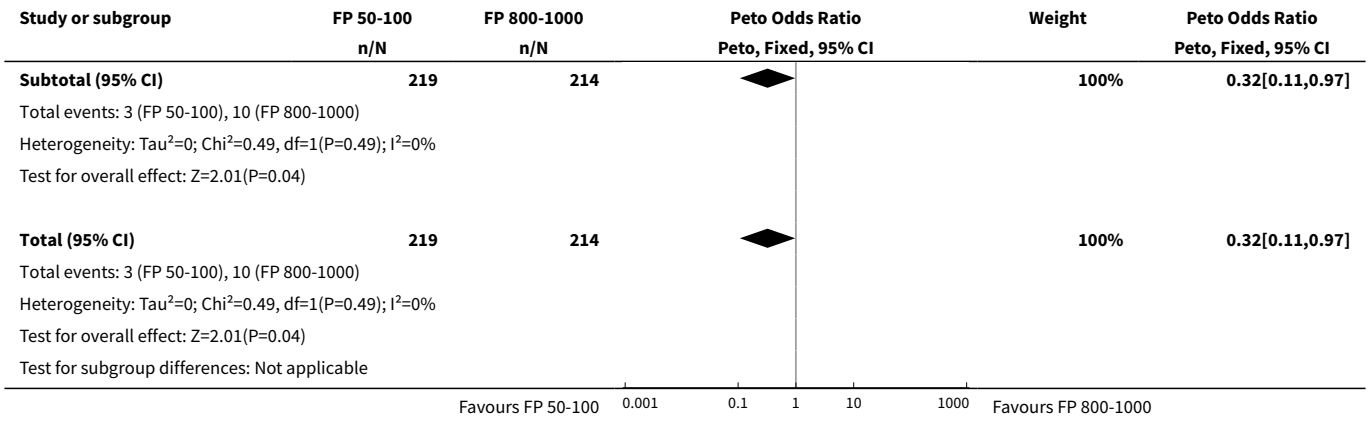
Study or subgroup	FP 50-100 N	FP 50-100 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
11.16.1 Children						
11.16.2 Adults						
Chervinsky 1994	78	-0.6 (1.6)	79	-0.8 (1.3)		0.13[-0.32,0.58]



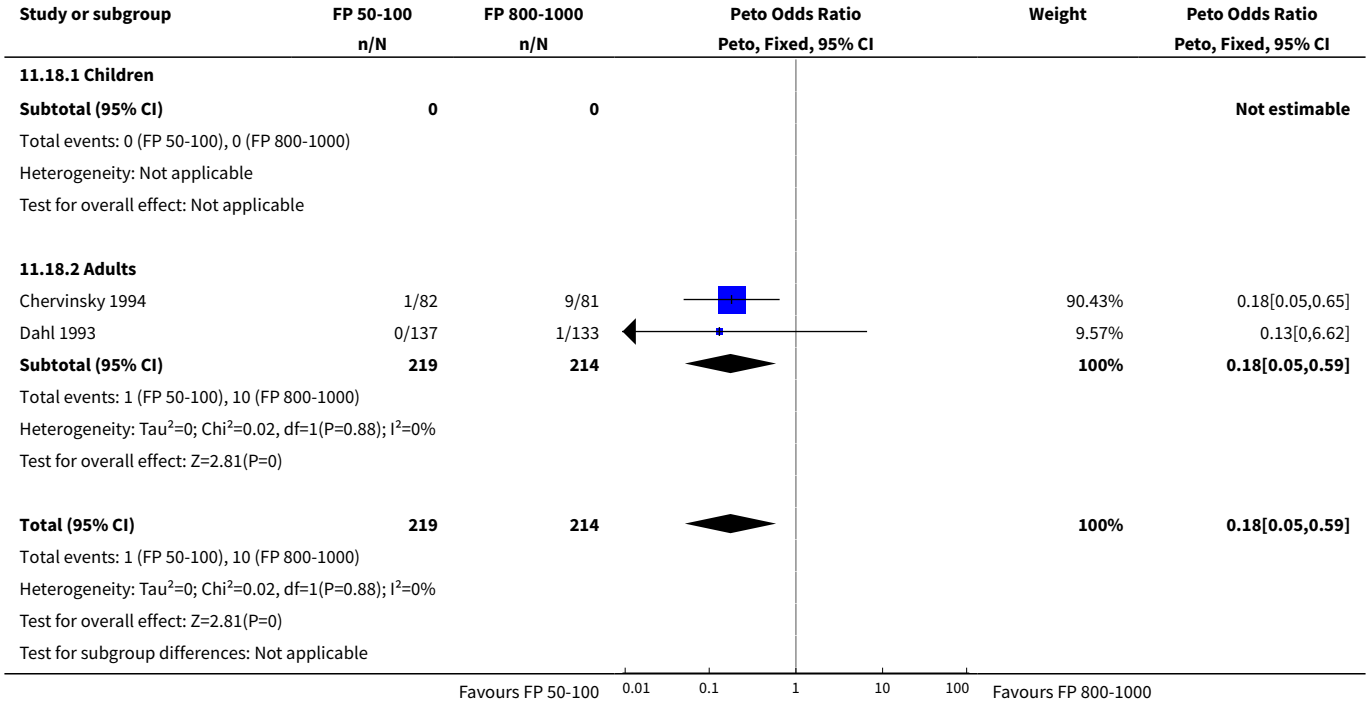
Analysis 11.17. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 17 Oral Candidiasis (No. of patients).

Study or subgroup	FP 50-100 n/N	FP 800-1000 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
11.17.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 50-100), 0 (FP 800-1000)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
11.17.2 Adults					
Chervinsky 1994	1/82	6/81		53.38%	0.22[0.05,1.01]
Dahl 1993	2/137	4/133		46.62%	0.49[0.1,2.47]

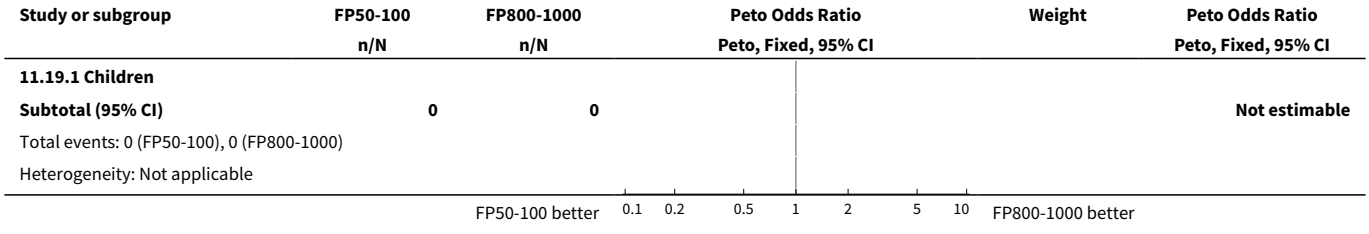


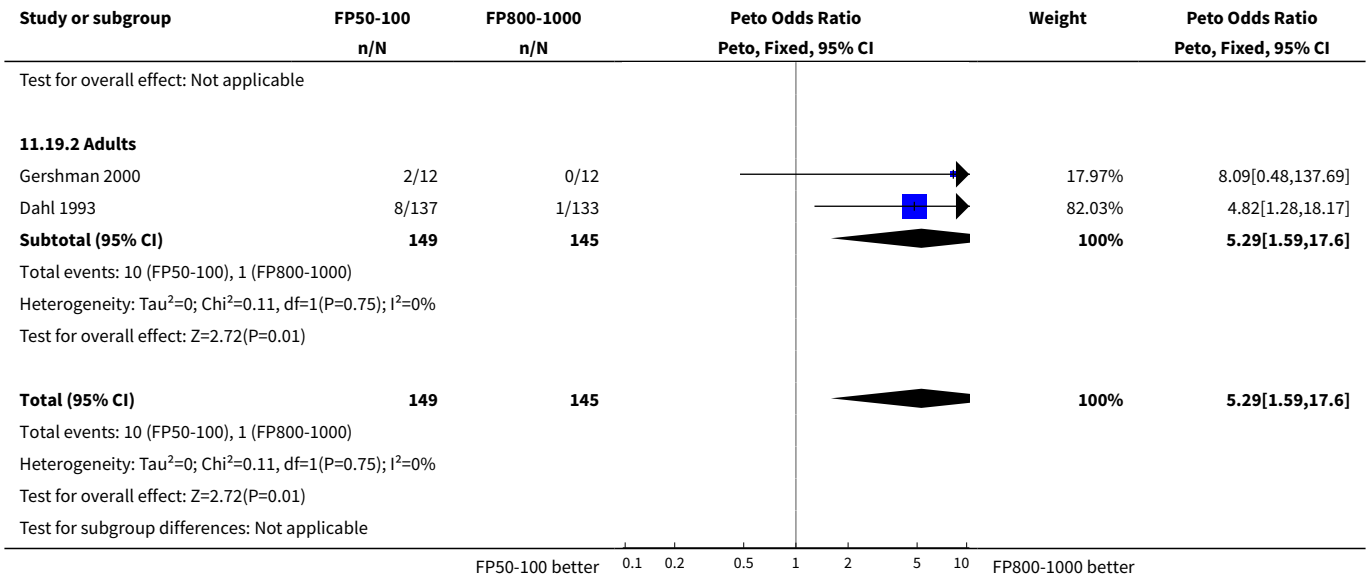


Analysis 11.18. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 18 Hoarseness or dysphonia (No. of patients).

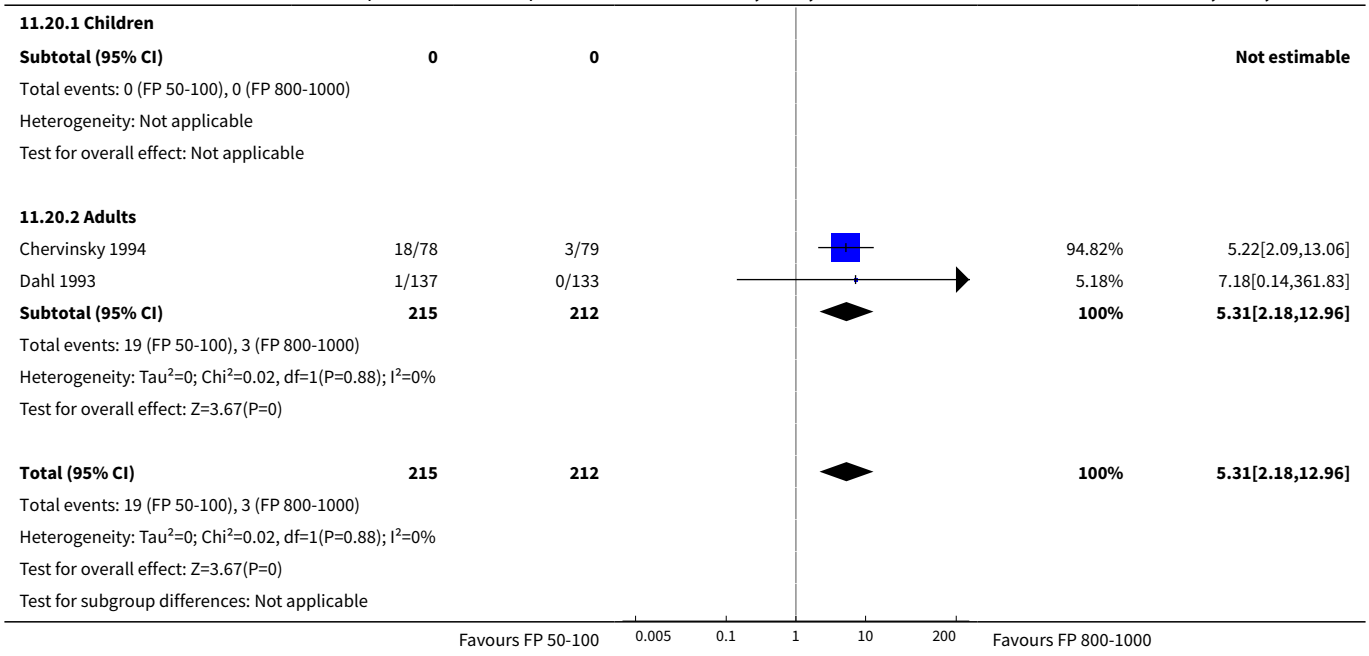


Analysis 11.19. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 19 Withdrawals (total).





Analysis 11.20. Comparison 11 Parallel group studies, no oral steroids: 50-100 versus 800-1000 mcg/d (all ages), Outcome 20 Number of patients withdrawn due to lack of efficacy.



Comparison 12. Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages)

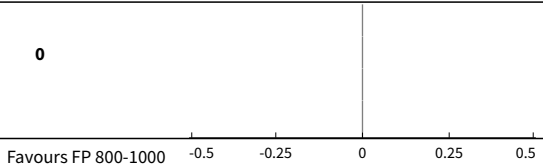
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline (litres)	3	489	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.04]
1.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	3	489	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.04]
2 Change in FEV1 compared to baseline (%)	1		Std. Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 Children	0		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 Adults	1		Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Change in FEV1 % predicted	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
3.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 FEV1 (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Change in morning PEFR compared to baseline (L/min)	4	763	Mean Difference (IV, Random, 95% CI)	-8.32 [-18.02, 1.37]
5.1 Children	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Adults	4	763	Mean Difference (IV, Random, 95% CI)	-8.32 [-18.02, 1.37]
6 Change in evening PEFR compared to baseline (L/min)	2	424	Mean Difference (IV, Fixed, 95% CI)	-7.81 [-14.66, -0.95]
6.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.2 Adults	2	424	Mean Difference (IV, Fixed, 95% CI)	-7.81 [-14.66, -0.95]
7 Change in FVC compared to baseline (litres)	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]

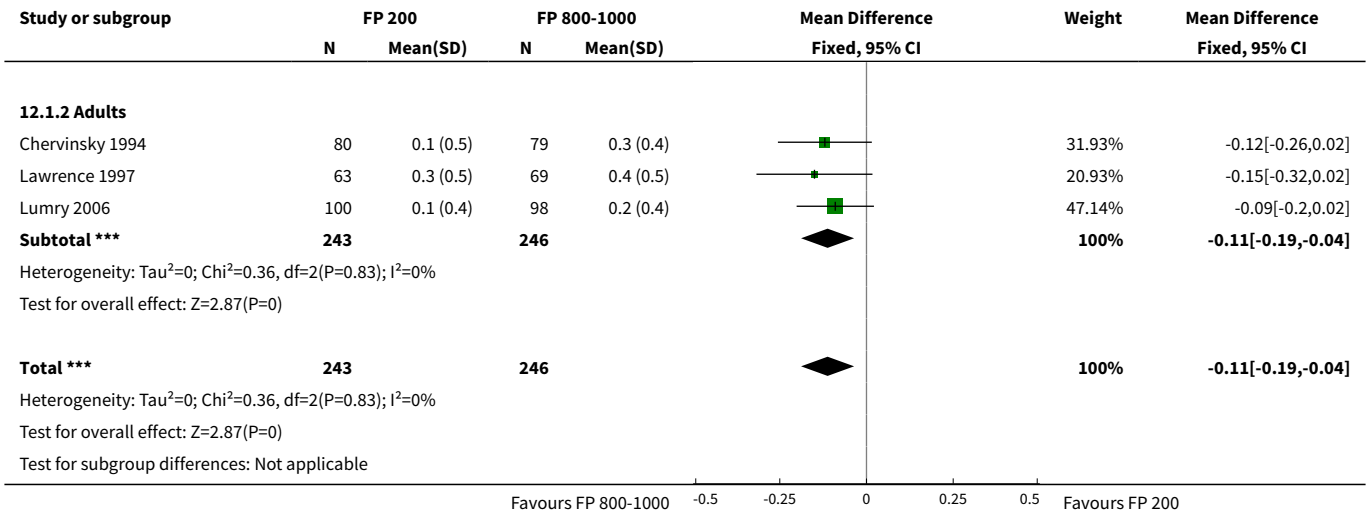
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Change in FEF25-75 compared to baseline (L/second)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 PD20	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 daily asthma symptom score compared to baseline	2	291	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.17, 0.29]
10.1 Children	0	0	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.2 Adults	2	291	Std. Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.17, 0.29]
11 Change in number of night-time awakenings/week compared to baseline	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 Physician global rated efficacy: ineffective	2	400	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.85, 2.12]
12.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.2 Adults	2	400	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.85, 2.12]
13 Change in daily use of beta2 agonist compared to baseline (puffs/d)	2	291	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.29, 0.50]
13.1 Children	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Adults	2	291	Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.29, 0.50]
14 Number of patients withdrawn due to lack of efficacy	4	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.73, 2.40]
14.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Adults	4	554	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.73, 2.40]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
15 Oral Candidiasis (No. of patients)	5	618	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.16, 0.70]
15.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.2 Adults	5	618	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.33 [0.16, 0.70]
16 Sore throat or pharyngitis (No. of patients)	4	452	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.18, 1.39]
16.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.2 Adults	4	452	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.49 [0.18, 1.39]
17 Hoarseness or dysphonia (No. of patients)	4	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.24, 1.08]
17.1 Children	0	0	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.2 Adults	4	561	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.51 [0.24, 1.08]
18 Change in peak plasma cortisol compared to baseline (mcg/dL)	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]
19 Change in morning plasma cortisol compared to baseline (mcg/dL)	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]

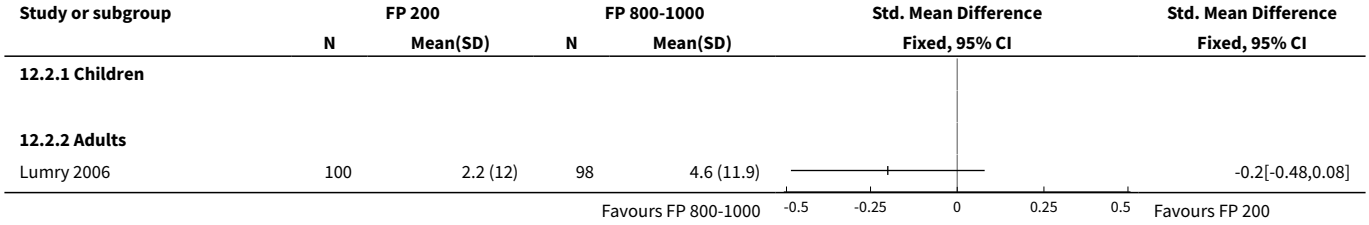
Analysis 12.1. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 1 Change in FEV1 compared to baseline (litres).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
12.1.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

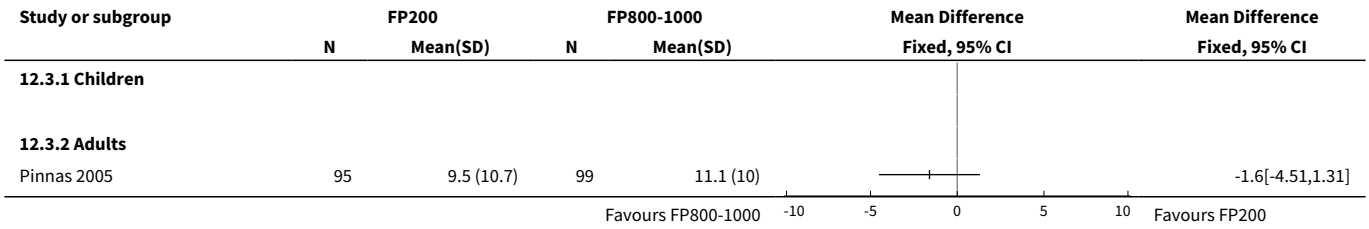




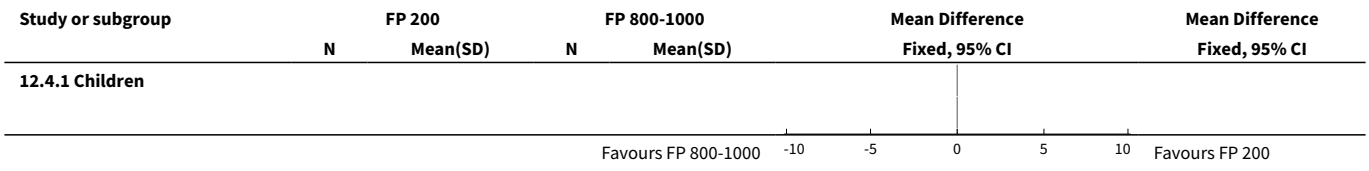
Analysis 12.2. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 2 Change in FEV1 compared to baseline (%).



Analysis 12.3. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 3 Change in FEV1 % predicted.



Analysis 12.4. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 4 FEV1 (% predicted).



Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
12.4.2 Adults						
Dahl 1993	132	77.2 (25.5)	130	76.7 (24.9)		0.5[-5.6,6.6]

Favours FP 800-1000 -10 -5 0 5 10 Favours FP 200

Analysis 12.5. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 5 Change in morning PEFR compared to baseline (L/min).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
12.5.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
12.5.2 Adults							
Chervinsky 1994	80	15 (38)	89	39 (56)		23%	-24[-38.31,-9.69]
Dahl 1993	129	13 (38.9)	133	20 (49.9)		29.28%	-7[-17.82,3.82]
Lawrence 1997	63	15 (40)	69	18 (42)		23.52%	-3[-16.99,10.99]
Lumry 2006	100	20.4 (49)	100	20.6 (49)		24.2%	-0.2[-13.78,13.38]
Subtotal ***	**372**		**391**			**100%**	**-8.32[-18.02,1.37]**
Heterogeneity: Tau^2=53.15; Chi^2=6.59, df=3(P=0.09); I^2=54.5%							
Test for overall effect: Z=1.68(P=0.09)							
Total ***	**372**		**391**			**100%**	**-8.32[-18.02,1.37]**
Heterogeneity: Tau^2=53.15; Chi^2=6.59, df=3(P=0.09); I^2=54.5%							
Test for overall effect: Z=1.68(P=0.09)							
Test for subgroup differences: Not applicable							

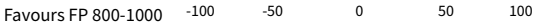
Favours FP 800-1000 -100 -50 0 50 100 Favours FP 200

Analysis 12.6. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 6 Change in evening PEFR compared to baseline (L/min).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
12.6.1 Children							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
12.6.2 Adults							
Chervinsky 1994	80	12 (37)	79	25 (49)		25.79%	-13[-26.51,0.51]
Dahl 1993	132	7 (35)	133	13 (31)		74.21%	-6[-13.96,1.96]
Subtotal ***	**212**		**212**			**100%**	**-7.81[-14.66,-0.95]**
Heterogeneity: Tau^2=0; Chi^2=0.77, df=1(P=0.38); I^2=0%							
Test for overall effect: Z=2.23(P=0.03)							
Total ***	**212**		**212**			**100%**	**-7.81[-14.66,-0.95]**

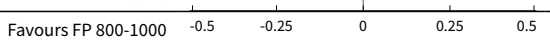
Favours FP 800-1000 -100 -50 0 50 100 Favours FP 200

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=0.77, df=1(P=0.38); I²=0%							
Test for overall effect: Z=2.23(P=0.03)							
Test for subgroup differences: Not applicable							



Analysis 12.7. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 7 Change in FVC compared to baseline (litres).

Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
12.7.1 Children						
12.7.2 Adults						
Chervinsky 1994	80	0.1 (0.6)	89	0.2 (0.5)		-0.13[-0.28,0.02]

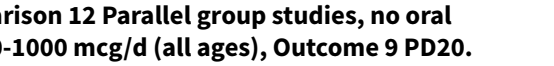


Analysis 12.8. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 8 Change in FEF25-75 compared to baseline (L/second).

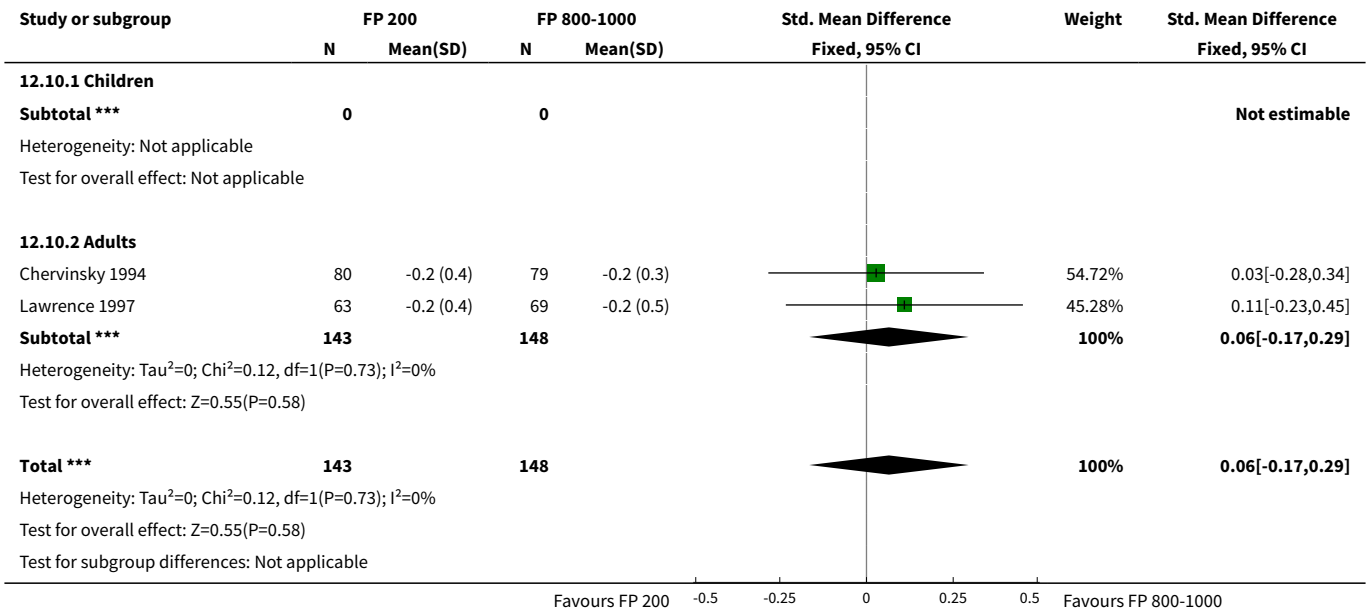
Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
12.8.1 Children						
12.8.2 Adults						
Chervinsky 1994	80	0.3 (0.8)	89	0.4 (0.7)		-0.1[-0.33,0.13]

Analysis 12.9. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 9 PD20.

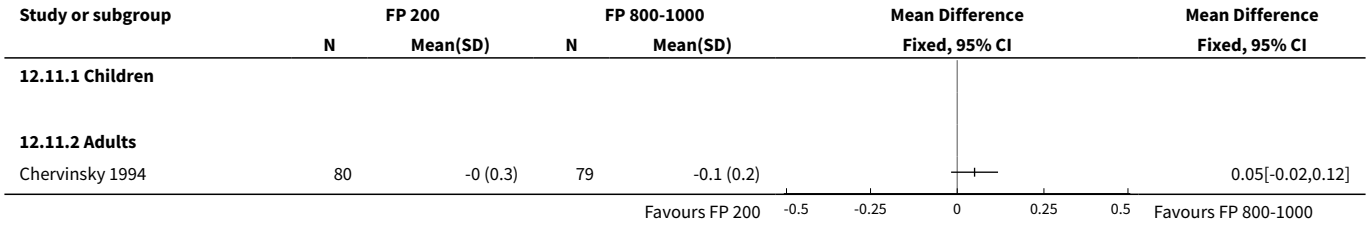
Study or subgroup	FP 200 N	FP 200 Mean(SD)	FP 800-1000 N	FP 800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
12.9.1 Children						
12.9.2 Adults						
Chetta 2003	8	3.8 (4.5)	8	3.4 (4.8)		0.42[-4.16,5]



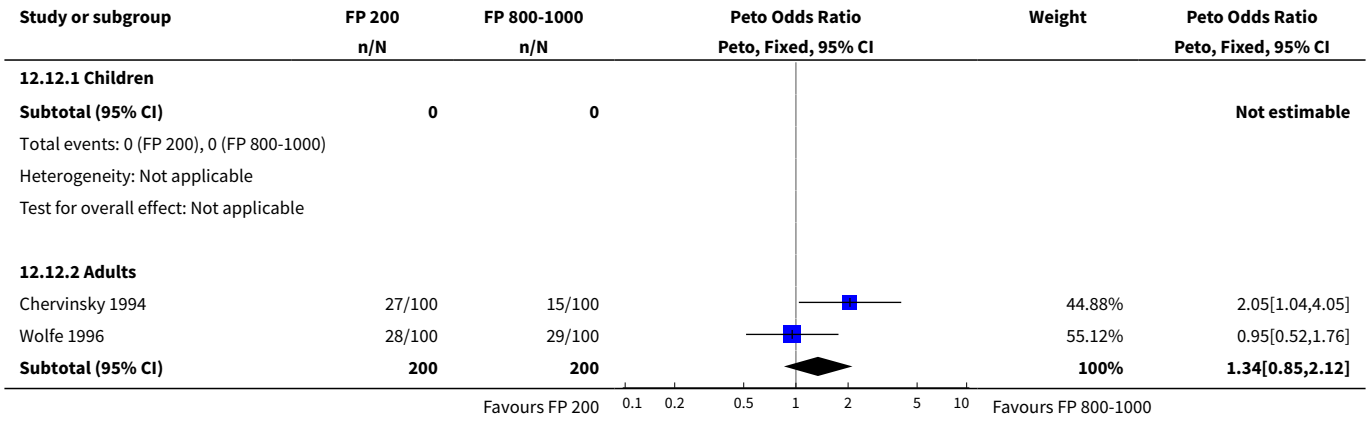
Analysis 12.10. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 10 Change in daily asthma symptom score compared to baseline.

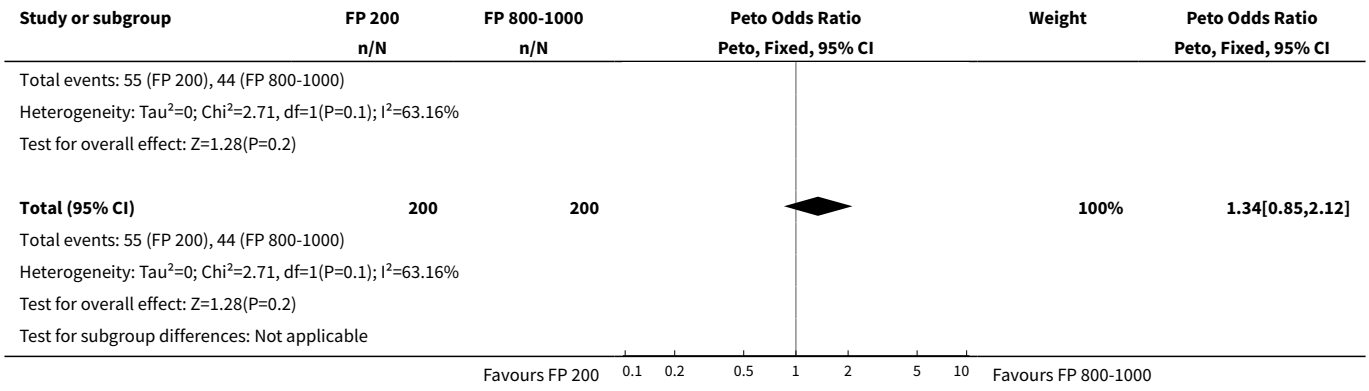


Analysis 12.11. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 11 Change in number of night-time awakenings/week compared to baseline.

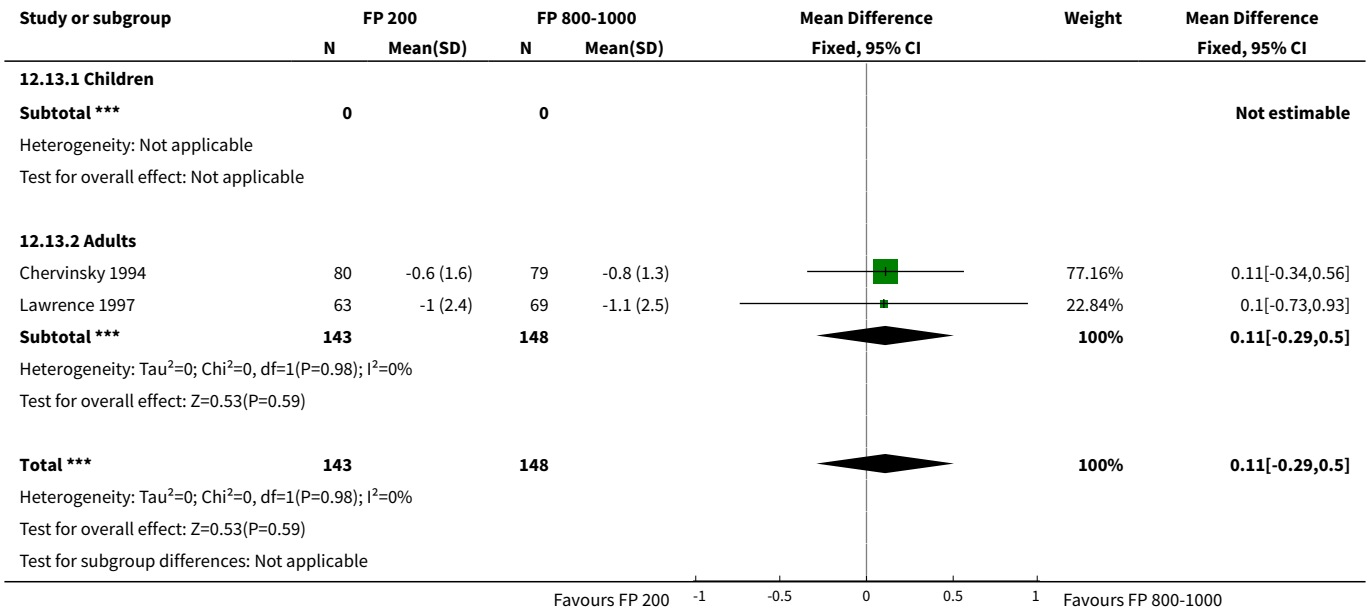


Analysis 12.12. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 12 Physician global rated efficacy: ineffective.

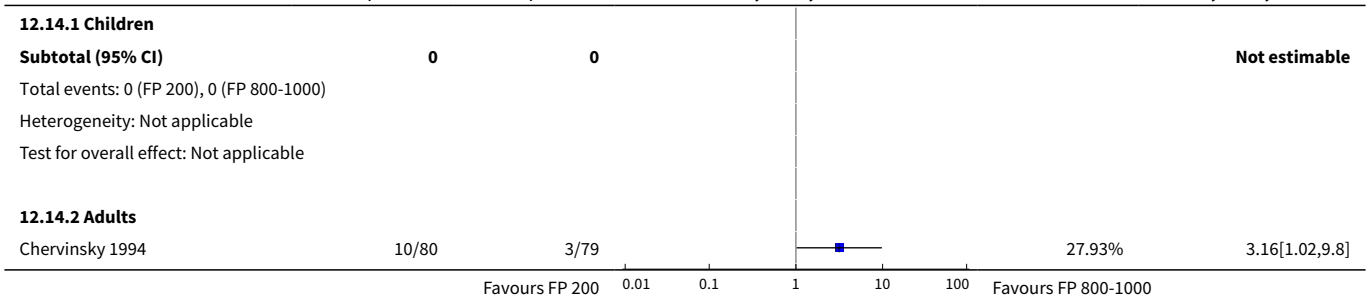


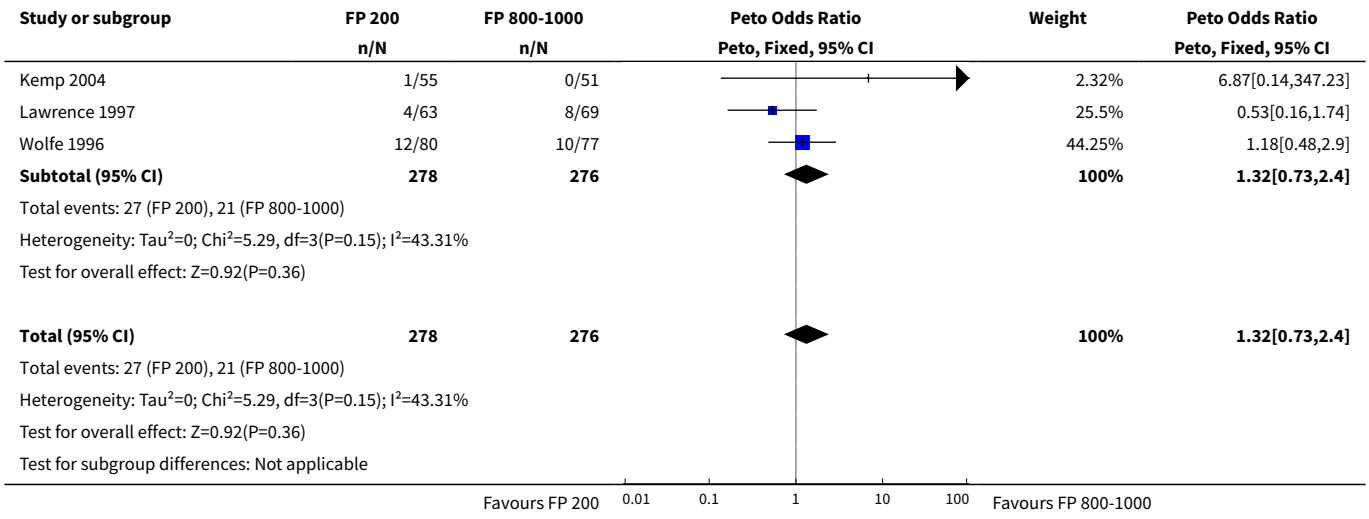


Analysis 12.13. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 13 Change in daily use of beta2 agonist compared to baseline (puffs/d).

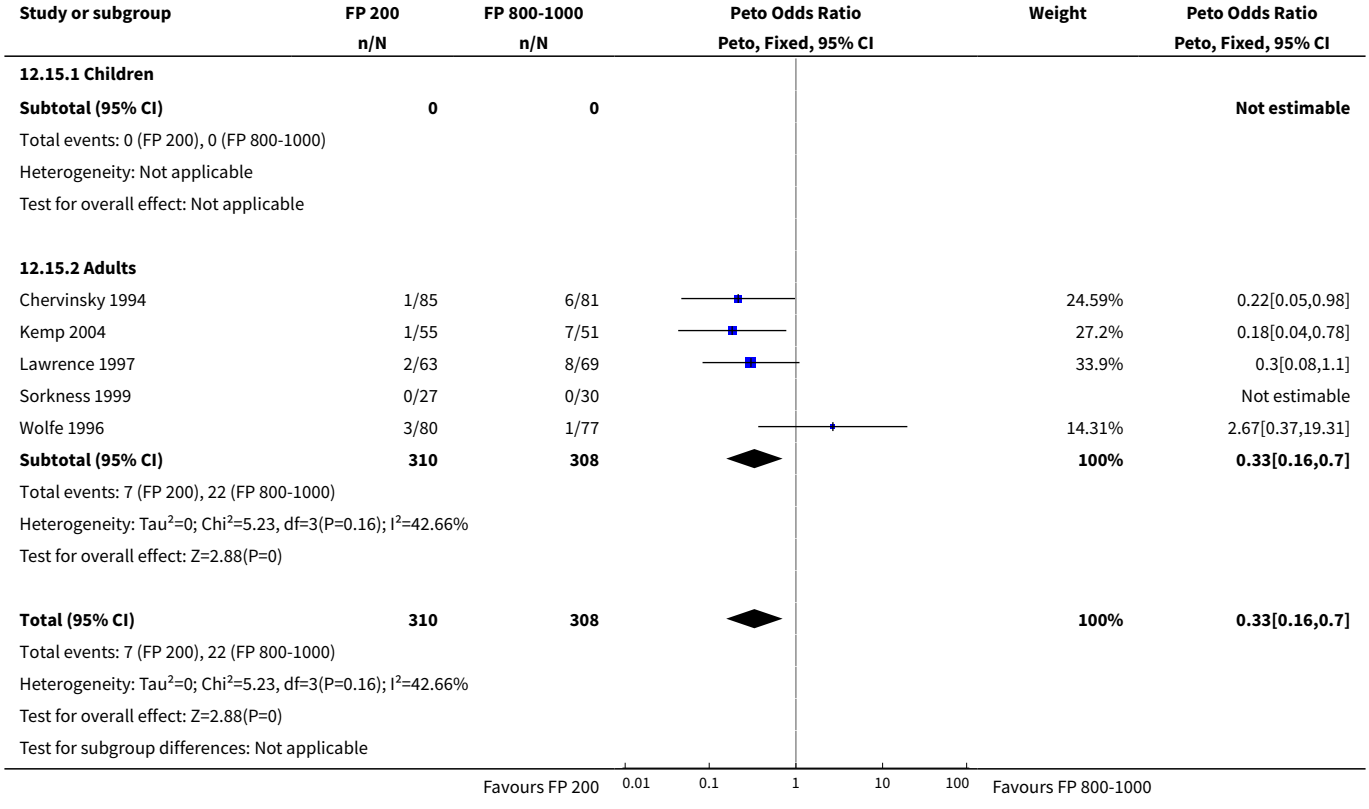


Analysis 12.14. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 14 Number of patients withdrawn due to lack of efficacy.



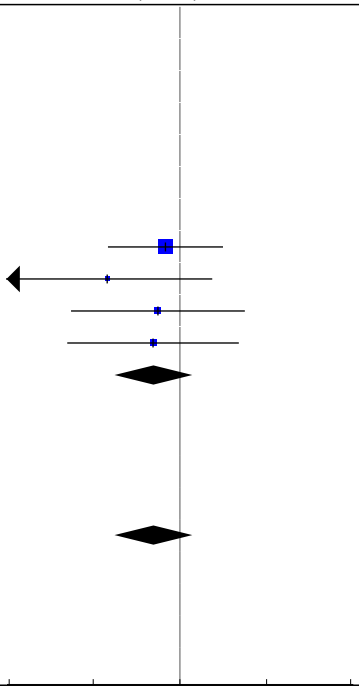


Analysis 12.15. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 15 Oral Candidiasis (No. of patients).



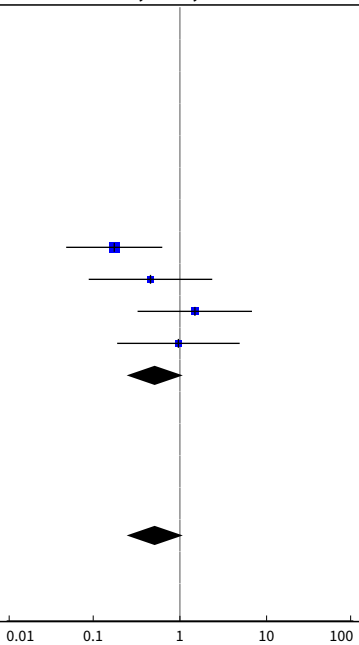
Analysis 12.16. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 16 Sore throat or pharyngitis (No. of patients).

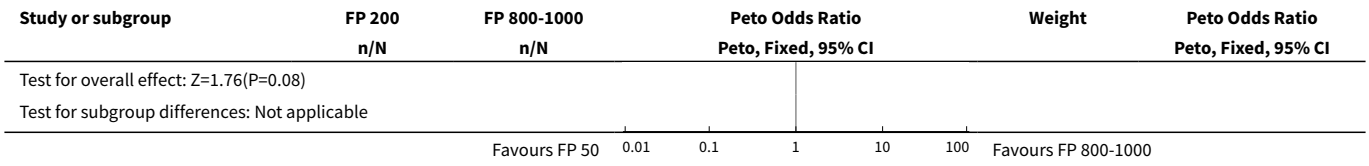
Study or subgroup	FP 200 n/N	FP 800-1000 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
12.16.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 200), 0 (FP 800-1000)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
12.16.2 Adults					
Kemp 2004	3/55	4/51		45.72%	0.68[0.15,3.14]
Lawrence 1997	0/63	2/69		13.74%	0.15[0.01,2.36]
Sorkness 1999	1/27	2/30		20.01%	0.56[0.06,5.61]
Wolfe 1996	1/80	2/77		20.54%	0.49[0.05,4.78]
Subtotal (95% CI)	**225**	**227**		**100%**	**0.49[0.18,1.39]**
Total events: 5 (FP 200), 10 (FP 800-1000)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=3(P=0.82); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					
Total (95% CI)	**225**	**227**		**100%**	**0.49[0.18,1.39]**
Total events: 5 (FP 200), 10 (FP 800-1000)					
Heterogeneity: Tau^2=0; Chi^2=0.92, df=3(P=0.82); I^2=0%					
Test for overall effect: Z=1.34(P=0.18)					
Test for subgroup differences: Not applicable					



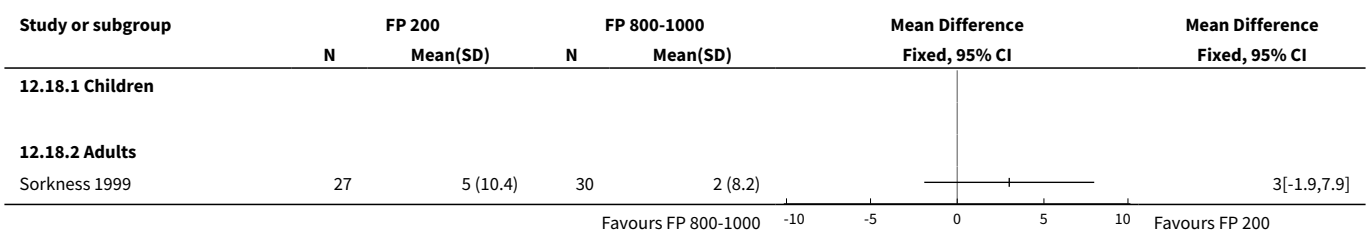
Analysis 12.17. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 17 Hoarseness or dysphonia (No. of patients).

Study or subgroup	FP 200 n/N	FP 800-1000 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
12.17.1 Children					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (FP 200), 0 (FP 800-1000)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
12.17.2 Adults					
Chervinsky 1994	1/85	9/81		34.2%	0.17[0.05,0.63]
Kemp 2004	2/55	4/51		20.65%	0.46[0.09,2.36]
Lawrence 1997	4/63	3/69		24.13%	1.49[0.33,6.78]
Wolfe 1996	3/80	3/77		21.01%	0.96[0.19,4.89]
Subtotal (95% CI)	**283**	**278**		**100%**	**0.51[0.24,1.08]**
Total events: 10 (FP 200), 19 (FP 800-1000)					
Heterogeneity: Tau^2=0; Chi^2=5.21, df=3(P=0.16); I^2=42.45%					
Test for overall effect: Z=1.76(P=0.08)					
Total (95% CI)	**283**	**278**		**100%**	**0.51[0.24,1.08]**
Total events: 10 (FP 200), 19 (FP 800-1000)					
Heterogeneity: Tau^2=0; Chi^2=5.21, df=3(P=0.16); I^2=42.45%					

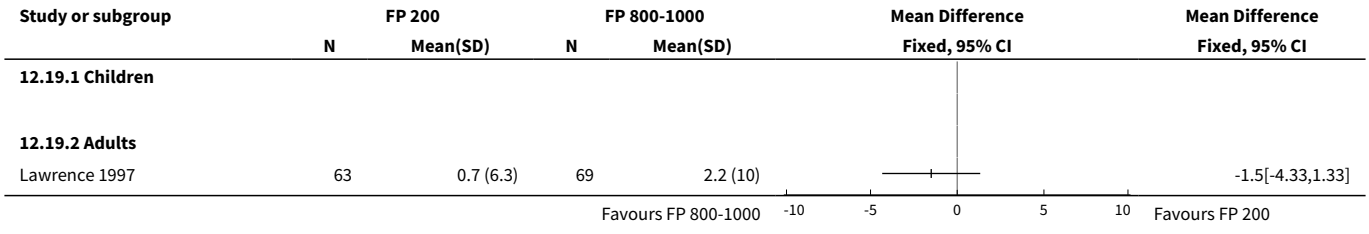




Analysis 12.18. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 18 Change in peak plasma cortisol compared to baseline (mcg/dL).



Analysis 12.19. Comparison 12 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (all ages), Outcome 19 Change in morning plasma cortisol compared to baseline (mcg/dL).



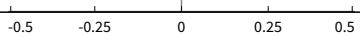
Comparison 13. Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (subgroups)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in FEV1 compared to baseline based on study duration (litres) - adults	3	489	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.04]
1.1 1-4 weeks	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 1-5 months	3	489	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.04]
1.3 6 months or longer	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Change in FEV1 compared to baseline based on delivery devices (litres) - adults	3	489	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 MDI	2	357	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.19, -0.02]
2.2 DPI	1	132	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.32, 0.02]
3 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults	3	489	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.04]
3.1 Mild to moderate	1	159	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.26, 0.02]
3.2 Moderate	2	330	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.20, -0.02]

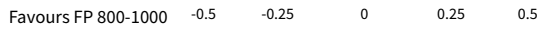
Analysis 13.1. Comparison 13 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (subgroups), Outcome 1 Change in FEV1 compared to baseline based on study duration (litres) - adults.

Study or subgroup	FP200 N	FP200 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
13.1.1 1-4 weeks							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
13.1.2 1-5 months							
Chervinsky 1994	80	0.1 (0.5)	79	0.3 (0.4)		31.93%	-0.12[-0.26,0.02]
Lawrence 1997	63	0.3 (0.5)	69	0.4 (0.5)		20.93%	-0.15[-0.32,0.02]
Lumry 2006	100	0.1 (0.4)	98	0.2 (0.4)		47.14%	-0.09[-0.2,0.02]
Subtotal ***	**243**		**246**			**100%**	**-0.11[-0.19,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.83); I^2=0%							
Test for overall effect: Z=2.87(P=0)							
13.1.3 6 months or longer							
Subtotal ***	**0**		**0**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total ***	**243**		**246**			**100%**	**-0.11[-0.19,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.83); I^2=0%							
Test for overall effect: Z=2.87(P=0)							
Test for subgroup differences: Not applicable							



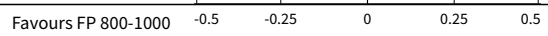
Analysis 13.2. Comparison 13 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (subgroups), Outcome 2 Change in FEV1 compared to baseline based on delivery devices (litres) - adults.

Study or subgroup	FP200 N	FP200 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
13.2.1 MDI							
Chervinsky 1994	80	0.1 (0.5)	79	0.3 (0.4)		31.93%	-0.12[-0.26,0.02]
Lumry 2006	100	0.1 (0.4)	98	0.2 (0.4)		47.14%	-0.09[-0.2,0.02]
Subtotal ***	**180**		**177**			**79.07%**	**-0.1[-0.19,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=0.11, df=1(P=0.74); I^2=0%							
Test for overall effect: Z=2.33(P=0.02)							
13.2.2 DPI							
Lawrence 1997	63	0.3 (0.5)	69	0.4 (0.5)		20.93%	-0.15[-0.32,0.02]
Subtotal ***	**63**		**69**			**20.93%**	**-0.15[-0.32,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.76(P=0.08)							
Total ***	**243**		**246**			**100%**	**-0.11[-0.19,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.83); I^2=0%							
Test for overall effect: Z=2.87(P=0)							
Test for subgroup differences: Chi^2=0.25, df=1 (P=0.62), I^2=0%							



Analysis 13.3. Comparison 13 Parallel group studies, no oral steroids: 200 versus 800-1000 mcg/d (subgroups), Outcome 3 Change in FEV1 compared to baseline based on degrees of severity (litres) - adults.

Study or subgroup	FP200 N	FP200 Mean(SD)	FP800-1000 N	FP800-1000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
13.3.1 Mild to moderate							
Chervinsky 1994	80	0.1 (0.5)	79	0.3 (0.4)		31.93%	-0.12[-0.26,0.02]
Subtotal ***	**80**		**79**			**31.93%**	**-0.12[-0.26,0.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.74(P=0.08)							
13.3.2 Moderate							
Lawrence 1997	63	0.3 (0.5)	69	0.4 (0.5)		20.93%	-0.15[-0.32,0.02]
Lumry 2006	100	0.1 (0.4)	98	0.2 (0.4)		47.14%	-0.09[-0.2,0.02]
Subtotal ***	**163**		**167**			**68.07%**	**-0.11[-0.2,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=0.34, df=1(P=0.56); I^2=0%							
Test for overall effect: Z=2.29(P=0.02)							
Total ***	**243**		**246**			**100%**	**-0.11[-0.19,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.36, df=2(P=0.83); I^2=0%							
Test for overall effect: Z=2.87(P=0)							
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.89), I^2=0%							

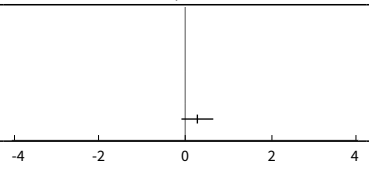


Comparison 14. Parallel group studies, no oral steroids: 4-500 versus 1500-2000mcg/d (all ages)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV1 (Change from baseline - litres)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Children	0		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Adults	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Clinic PEF (L/min - change from baseline)	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 PC20 (methacholine)	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 PC20 AMP	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 Symptoms (change from baseline)	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]

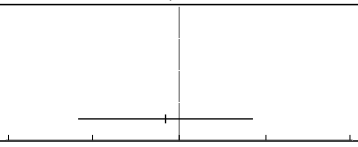
Analysis 14.1. Comparison 14 Parallel group studies, no oral steroids: 4-500 versus 1500-2000mcg/d (all ages), Outcome 1 FEV1 (Change from baseline - litres).

Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP1500-2000 N	FP1500-2000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.1.1 Children						
14.1.2 Adults						
O'Sullivan 2002	12	0.4 (0.6)	12	0.1 (0.3)		0.28[-0.09,0.65]



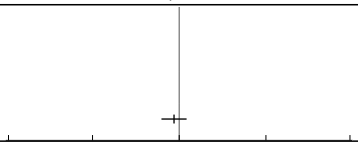
Analysis 14.2. Comparison 14 Parallel group studies, no oral steroids: 4-500 versus 1500-2000mcg/d (all ages), Outcome 2 Clinic PEF (L/min - change from baseline).

Study or subgroup	FP500 N	FP500 Mean(SD)	FP1500-2000 N	FP1500-2000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.2.1 Children						
14.2.2 Adults						
O'Sullivan 2002	12	15 (46.3)	12	22.9 (76.1)		-7.9[-58.31,42.51]



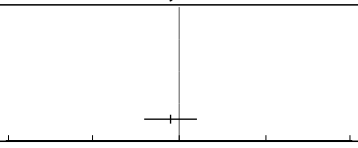
Analysis 14.3. Comparison 14 Parallel group studies, no oral steroids: 4-500 versus 1500-2000mcg/d (all ages), Outcome 3 PC20 (methacholine).

Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP1500-2000 N	FP1500-2000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.3.1 Children						
14.3.2 Adults						
Meijer 1999	40	1.7 (1.8)	40	2 (1.6)		-0.3[-1.02,0.42]



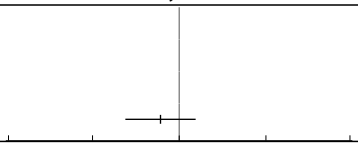
Analysis 14.4. Comparison 14 Parallel group studies, no oral steroids: 4-500 versus 1500-2000mcg/d (all ages), Outcome 4 PC20 AMP.

Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP1500-2000 N	FP1500-2000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.4.1 Children						
14.4.2 Adults						
Meijer 1999	40	3.5 (3.2)	40	4 (3.7)		-0.5[-2.02,1.02]



Analysis 14.5. Comparison 14 Parallel group studies, no oral steroids: 4-500 versus 1500-2000mcg/d (all ages), Outcome 5 Symptoms (change from baseline).

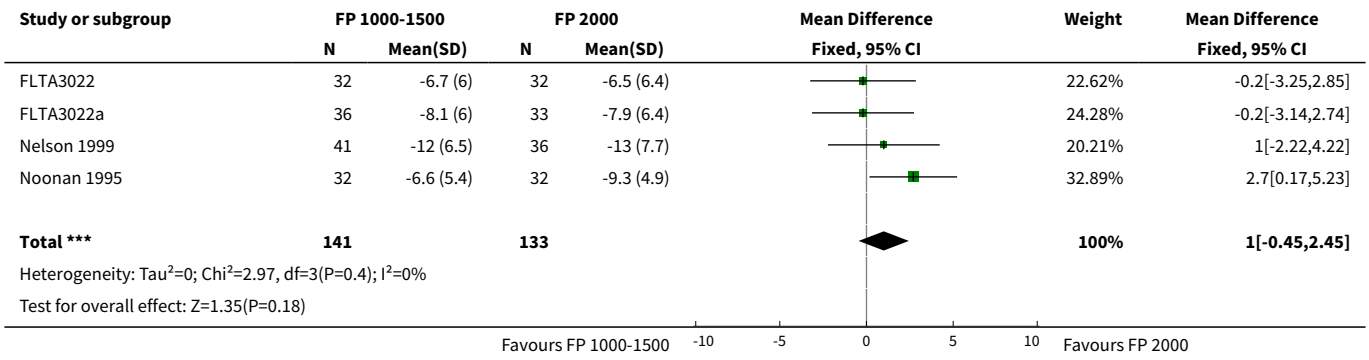
Study or subgroup	FP4-500 N	FP4-500 Mean(SD)	FP1500-2000 N	FP1500-2000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
14.5.1 Children						
14.5.2 Adults						
O'Sullivan 2002	12	-2.5 (2.8)	12	-1.4 (2.3)		-1.08[-3.11,0.95]



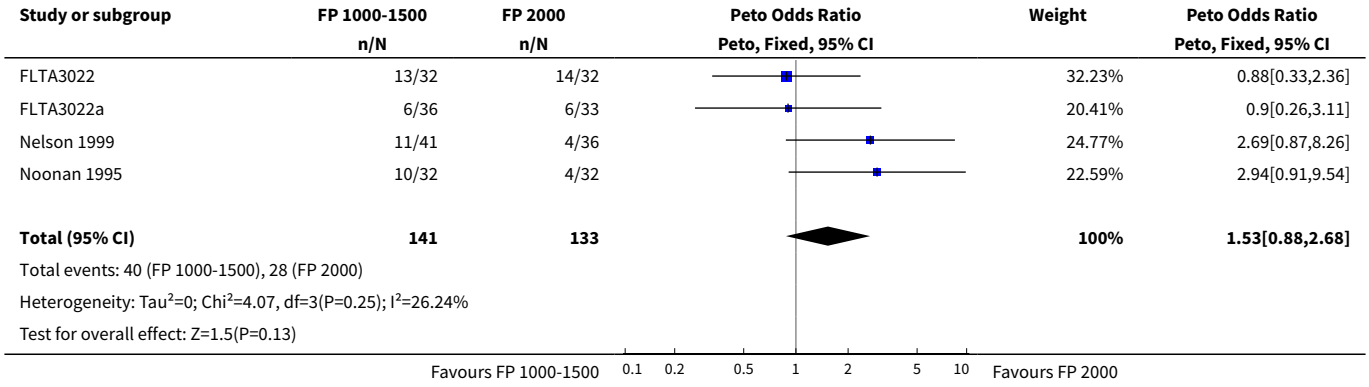
Comparison 15. Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in daily dose of oral prednisolone compared to baseline (mg)	4	274	Mean Difference (IV, Fixed, 95% CI)	1.00 [-0.45, 2.45]
2 Number of patients unable to discontinue OCS completely	4	274	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.53 [0.88, 2.68]
3 Change in FEV1 compared to baseline (litres)	4	274	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.24, -0.01]
4 Change in morning PEFR compared to baseline (L/min)	4	274	Mean Difference (IV, Fixed, 95% CI)	-19.63 [-34.98, -4.27]
5 Change in evening PEFR compared to baseline (L/min)	4	274	Mean Difference (IV, Fixed, 95% CI)	-21.58 [-35.20, -7.97]
6 Change in daily asthma symptom score compared to baseline	4	274	Std. Mean Difference (IV, Fixed, 95% CI)	0.15 [-0.09, 0.39]
7 Change in rescue beta2 agonist use compared to baseline (puffs/d)	4	274	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-1.05, 0.78]
8 Asthma Quality of Life Questionnaire: change in overall score compared to baseline	3	187	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.48, 0.23]
9 Asthma Quality of Life Questionnaire: change in activity limitation domain compared to baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
10 Asthma Quality of Life Questionnaire: change in symptom domain compared to baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
11 Asthma Quality of Life Questionnaire: change in emotional function domain compared to baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Asthma Quality of Life Questionnaire: change in environmental exposure domain compared to baseline	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
13 Sore throat (No. of patients)	2	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.70 [0.15, 3.18]
14 Hoarseness/dysphonia (No. of patients)	2	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.92 [0.28, 2.99]
15 Oral Candidiasis (No. of patients)	2	141	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.41, 2.24]

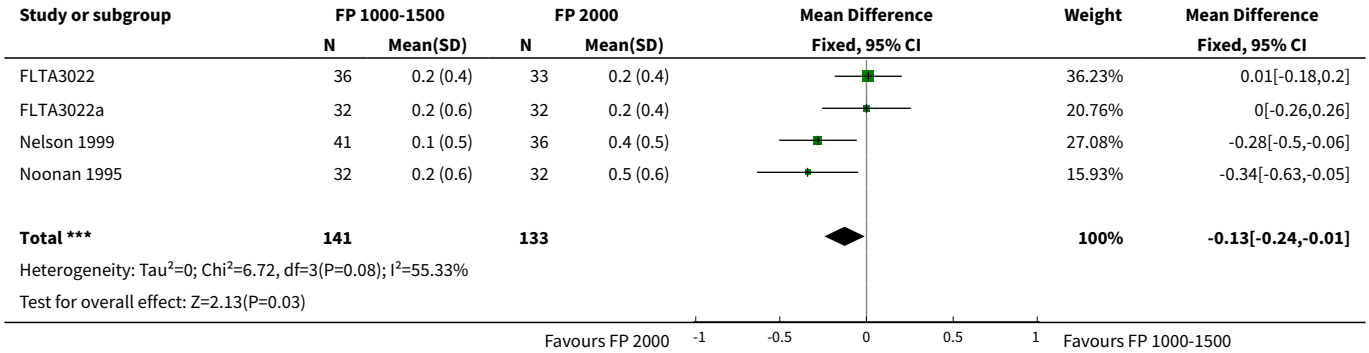
Analysis 15.1. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 1 Change in daily dose of oral prednisolone compared to baseline (mg).



Analysis 15.2. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 2 Number of patients unable to discontinue OCS completely.



Analysis 15.3. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 3 Change in FEV1 compared to baseline (litres).

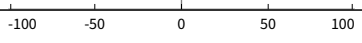


Analysis 15.4. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 4 Change in morning PEFR compared to baseline (L/min).

Study or subgroup	FP 1000-1500 N	FP 1000-1500 Mean(SD)	FP 2000 N	FP 2000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
FLTA3022	36	36.5 (64.2)	33	17.7 (56.8)		28.95%	18.83[-9.72,47.38]
FLTA3022a	32	18.1 (63.9)	32	36.5 (65.6)		23.41%	-18.44[-50.18,13.3]
Nelson 1999	41	23 (64)	36	67 (72)		25.18%	-44[-74.61,-13.39]
Noonan 1995	32	40.1 (61)	32	83.2 (70.9)		22.46%	-43.1[-75.51,-10.69]
Total ***	**141**		**133**			**100%**	**-19.63[-34.98,-4.27]**

Heterogeneity: Tau^2=0; Chi^2=11.43, df=3(P=0.01); I^2=73.75%

Test for overall effect: Z=2.5(P=0.01)



Analysis 15.5. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 5 Change in evening PEFR compared to baseline (L/min).

Study or subgroup	FP 1000-1500 N	FP 1000-1500 Mean(SD)	FP 2000 N	FP 2000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
FLTA3022	36	20.4 (55.6)	33	8.3 (53.7)		27.87%	12.09[-13.7,37.88]
FLTA3022a	32	2.3 (55.6)	32	23.3 (57.1)		24.32%	-20.95[-48.56,6.66]
Nelson 1999	41	3 (45)	36	48 (60)		32.31%	-45[-68.96,-21.04]
Noonan 1995	32	19.8 (59.4)	32	54.1 (80.2)		15.51%	-34.3[-68.88,0.28]
Total ***	**141**		**133**			**100%**	**-21.58[-35.2,-7.97]**

Heterogeneity: Tau^2=0; Chi^2=10.74, df=3(P=0.01); I^2=72.07%

Test for overall effect: Z=3.11(P=0)

Analysis 15.6. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 6 Change in daily asthma symptom score compared to baseline.

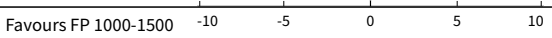
Study or subgroup	FP 1000-1500 N	FP 1000-1500 Mean(SD)	FP 2000 N	FP 2000 Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
FLTA3022	36	-0.1 (0.8)	33	-0.3 (0.7)		25.39%	0.15[-0.32,0.63]
FLTA3022a	32	-0.3 (0.9)	32	-0.1 (0.7)		23.4%	-0.3[-0.79,0.2]
Nelson 1999	41	-0.3 (0.5)	36	-0.5 (0.8)		27.99%	0.32[-0.13,0.77]
Noonan 1995	32	-0.4 (0.5)	32	-0.6 (0.5)		23.22%	0.38[-0.11,0.88]
Total ***	**141**		**133**			**100%**	**0.15[-0.09,0.39]**

Heterogeneity: Tau^2=0; Chi^2=4.53, df=3(P=0.21); I^2=33.82%

Test for overall effect: Z=1.22(P=0.22)

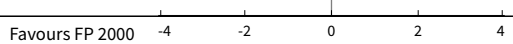
Analysis 15.7. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 7 Change in rescue beta2 agonist use compared to baseline (puffs/d).

Study or subgroup	FP 1000-1500 N	FP 1000-1500 Mean(SD)	FP 2000 N	FP 2000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
FLTA3022	36	-1.4 (4.1)	33	-0.8 (3.6)		25.56%	-0.67[-2.49,1.15]
FLTA3022a	32	-1.2 (3.1)	32	0.1 (3.5)		31.97%	-1.24[-2.86,0.38]
Nelson 1999	41	-2.1 (3.9)	36	-3.1 (4.1)		26.22%	1.07[-0.72,2.86]
Noonan 1995	32	-3 (4.7)	32	-4 (4.6)		16.25%	0.93[-1.35,3.21]
Total ***	**141**		**133**			**100%**	**-0.14[-1.05,0.78]**
Heterogeneity: Tau^2=0; Chi^2=4.68, df=3(P=0.2); I^2=35.92%							
Test for overall effect: Z=0.29(P=0.77)							



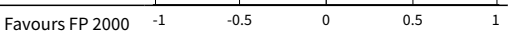
Analysis 15.8. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 8 Asthma Quality of Life Questionnaire: change in overall score compared to baseline.

Study or subgroup	FP 1000-1500 N	FP 1000-1500 Mean(SD)	FP 2000 N	FP 2000 Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
FLTA3022	34	1.2 (1.1)	29	1 (1.2)		38.21%	0.13[-0.44,0.7]
FLTA3022a	29	1 (1.5)	25	1 (1.2)		23.63%	-0.01[-0.73,0.71]
Nelson 1999	36	0.8 (1.3)	34	1.3 (1.2)		38.16%	-0.45[-1.02,0.12]
Total ***	**99**		**88**			**100%**	**-0.12[-0.48,0.23]**
Heterogeneity: Tau^2=0; Chi^2=2.12, df=2(P=0.35); I^2=5.7%							
Test for overall effect: Z=0.69(P=0.49)							



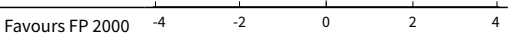
Analysis 15.9. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 9 Asthma Quality of Life Questionnaire: change in activity limitation domain compared to baseline.

Study or subgroup	FP 1000-1500 N	FP 1000-1500 Mean(SD)	FP 2000 N	FP 2000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Nelson 1999	31	0.9 (1.3)	30	1 (1.2)		-0.14[-0.78,0.5]



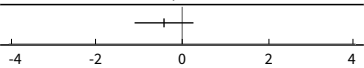
Analysis 15.10. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 10 Asthma Quality of Life Questionnaire: change in symptom domain compared to baseline.

Study or subgroup	FP 1000-1500 N	FP 1000-1500 Mean(SD)	FP 2000 N	FP 2000 Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Nelson 1999	37	0.8 (1.3)	35	1.5 (1.2)		-0.74[-1.33,-0.15]



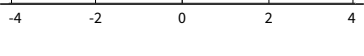
Analysis 15.11. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 11 Asthma Quality of Life Questionnaire: change in emotional function domain compared to baseline.

Study or subgroup	FP 1000-1500		FP 2000		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Nelson 1999	37	1.1 (1.5)	35	1.5 (1.4)		-0.42[-1.1,0.26]



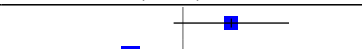
Analysis 15.12. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 12 Asthma Quality of Life Questionnaire: change in environmental exposure domain compared to baseline.

Study or subgroup	FP 1000-1500		FP 2000		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI	Fixed, 95% CI
Nelson 1999	37	0.8 (1.6)	34	1 (1.4)		-0.2[-0.89,0.49]



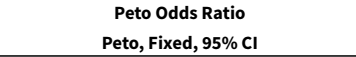
Analysis 15.13. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 13 Sore throat (No. of patients).

Study or subgroup	FP 1000-1500	FP 2000	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Nelson 1999	3/41	0/36		43.3%	6.88[0.69,68.53]
Noonan 1995	0/32	4/32		56.7%	0.12[0.02,0.91]
Total (95% CI)	**73**	**68**		**100%**	**0.7[0.15,3.18]**
Total events: 3 (FP 1000-1500), 4 (FP 2000)					
Heterogeneity: Tau^2=0; Chi^2=6.69, df=1(P=0.01); I^2=85.06%					
Test for overall effect: Z=0.46(P=0.64)					



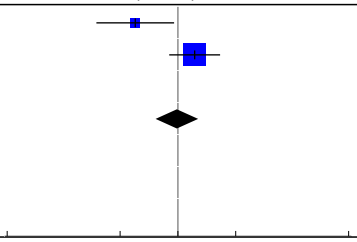
Analysis 15.14. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 14 Hoarseness/dysphonia (No. of patients).

Study or subgroup	FP 1000-1500	FP 2000	Peto Odds Ratio	Weight	Peto Odds Ratio
	n/N	n/N	Peto, Fixed, 95% CI		Peto, Fixed, 95% CI
Nelson 1999	3/41	4/36		57.83%	0.64[0.14,2.99]
Noonan 1995	3/32	2/32		42.17%	1.53[0.25,9.38]
Total (95% CI)	**73**	**68**		**100%**	**0.92[0.28,2.99]**
Total events: 6 (FP 1000-1500), 6 (FP 2000)					
Heterogeneity: Tau^2=0; Chi^2=0.52, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					



Analysis 15.15. Comparison 15 Parallel studies, oral steroid treated: 1000-1500 versus 2000 mcg/d, Outcome 15 Oral Candidiasis (No. of patients).

Study or subgroup	FP 1000-1500 n/N	FP 2000 n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Nelson 1999	1/41	6/36		30.02%	0.18[0.04,0.86]
Noonan 1995	14/32	9/32		69.98%	1.95[0.71,5.37]
Total (95% CI)	**73**	**68**		**100%**	**0.96[0.41,2.24]**
Total events: 15 (FP 1000-1500), 15 (FP 2000)					
Heterogeneity: Tau^2=0; Chi^2=6.29, df=1(P=0.01); I^2=84.11%					
Test for overall effect: Z=0.1(P=0.92)					



Comparison 16. Crossover studies, no oral steroids: 200 versus 1000 mcg (all ages)

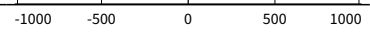
Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 FEV1	1		Litres (Fixed, 95% CI)	Totals not selected
2 PEF	1		Litres/min (Fixed, 95% CI)	Totals not selected

Analysis 16.1. Comparison 16 Crossover studies, no oral steroids: 200 versus 1000 mcg (all ages), Outcome 1 FEV1.

Study or subgroup	FP200 N	FP1000 N	Litres (SE)	Litres IV, Fixed, 95% CI	Litres IV, Fixed, 95% CI
Derom 1999	21	21	-0 (0)		Not estimable

Analysis 16.2. Comparison 16 Crossover studies, no oral steroids: 200 versus 1000 mcg (all ages), Outcome 2 PEF.

Study or subgroup	FP200 N	FP1000 N	Litres/min (SE)	Litres/min IV, Fixed, 95% CI	Litres/min IV, Fixed, 95% CI
Derom 1999	1	1	-0.7 (0)		Not estimable



ADDITIONAL TABLES

Table 2. Data not included in the meta-analysis

Study ID	Data
Allen 2000	Steroid consumption Side effects

Table 2. Data not included in the meta-analysis *(Continued)*

	Unclear reporting (no response from trialists)
Ayres 1995	Symptom free days and nights Rescue beta2 agonist free days and nights Daytime and night-time symptom scores Above outcomes analysed by investigators using non-parametric statistics Change in FEV1 compared to baseline Change in FVC compared to baseline Change in morning PEFR compared to baseline Change in evening PEFR compared to baseline Change in diurnal variability in PEFR compared to baseline Change in clinic PEFR compared to baseline No SD values available for above outcomes Morning plasma cortisol Data log transformed and reported using geometric means by investigators: log transformed values not available
Boner 1999	Methacholine BHR (PC20 FEV1) Log transformed data not available FEV1 No SD values available Overnight urinary cortisol No numerical data available
Bukovskis 2002	FEV1 change from baseline Unclear reporting (no response from trialists)
Chervinsky 1994	Change in urinary free cortisol compared to baseline Change in urinary 17-hydroxy steroids compared to baseline Change in morning plasma cortisol compared to baseline Change in plasma cortisol 60 min post co-syntropin No SD values available for above outcomes
Chetta 2002	FEV1 Unclear reporting (no response from trialists)
Dahl 1993	Morning plasma cortisol Plasma cortisol 30 min post 250 mcg ACTH Diurnal variation in PEFR FVC Daily beta2 agonist use (puffs/day) No SD values available for above outcomes
Derom 1999	Cortisol suppression Unclear reporting (no response from trialists)
Derom 2001	Cortisol suppression PC20 Unclear reporting (no response from trialists)

Table 2. Data not included in the meta-analysis *(Continued)*

Gershman 2000	PC20 ECP Data reported as medians
Hofstra 2000	PD20 No SDs presented.
Ind 2003	Medication usage Symptoms Data presented as medians
Katz 1998	Change in FEV1 compared to baseline Change in FVC compared to baseline Change in FEF25-75 compared to baseline Change in evening PEFR compared to baseline Change in night-time awakening score compared to baseline No SD values available for above outcomes
Meijer 1999	FEV1 PEF Symptoms Medication usage Cortisol Data presented as medians
Nieto 2001	PC20 Unclear reporting (no response from trialists)
Noonan 1998	Change in log e methacholine bronchial responsiveness PD20 FEV1 Error bars plotted on graphical display of results, but unclear whether these represent SD or SEM values
Pauwels 2002	Cortisol suppression PC20 Unclear reporting (no response from trialists)
Pearlman 1997	Change in evening PEFR compared to baseline Medical Outcomes Study Short Form (SF-36A) Living with asthma questionnaire No SD values available for above outcomes Morning serum cortisol No numerical data available for above outcome Physician rated global assessment of efficacy Data not presented in a form suitable for meta-analysis
SAM40012	% symptom free days rescue medication usage Data reported as medians.
Verona 2003	Medication usage Symptoms

Table 2. Data not included in the meta-analysis *(Continued)*

	Data reported as medians
Wallin 2003	am PEF/pm PEF Data reported as medians
Wasserman 1996	Physician-rated global assessment of effectiveness Data not presented in a form suitable for meta-analysis
Wolfe 1996	Change FEV1 compared to baseline No SD values available for above outcome Change in morning PEFR compared to baseline Change in evening PEFR compared to baseline Daily wheeze, cough, shortness of breath scores Daily beta2 agonist use Morning plasma cortisol No numerical data available for above outcomes

Table 3. Methods of imputations and estimates

Outcome	WMD/GIV	Study	Method
07:03	WMD	Pinnas 2005	Published means. SDs based on other studies.
07:07	GIV	Pinnas 2005	Published means. SDs based on other studies.
07:07	GIV	Wolfe 1996	Published P values (versus placebo), assumed same SEM between two FP groups.
20:01	WMD	Pinnas 2005	Published means. SDs based on other studies.
20:03	WMD	Ind 2003; Pinnas 2005	Published means. SDs based on other studies.

Table 4. Search History Detail

Date	N included/excluded
All Years searching to March 1999	Initial version of the review (All Years searching to March 1999): 6494 citations retrieved, 2162 unique citations imported to Inhaled Steroid Register. From this a fluticasone register was created consisting of 258 citations. 180 excluded on basis of abstract: 150 not RCT; 30 not chronic asthma in humans; 78 papers retrieved in full text form; 57 excluded on basis of full paper: 6 not RCT; 1 infants; 3 delivery device comparison; 1 treatment period < 1 week; 46 not a comparison of 2 or more doses of FP; 21 publications meeting inclusion criteria; 16 unique studies meeting inclusion criteria One study (Raphael 1999) was identified by Glaxo Wellcome. This study was published after the date of the final electronic search (March 1999). Three studies (Boner 1999, Hofstra 2000, Ind 2003) were identified as a result of searching respiratory society meeting abstracts.
Update (March 1999-January 2005)	From hand searching the updated inhaled steroids search results (additional 1301 references), a 'fluticasone' register was created consisting of 196 citations (121 references excluded from ab-

Table 4. Search History Detail *(Continued)*

	stracts as irrelevant comparisons). Forty-six references pertaining to 34 studies were retrieved in full for this review. One study reported findings from two data-sets and these studies have been given two identifiers (Sorkness 1999; Sorkness 1999a). We excluded 11 studies for the following reasons: Wrong comparator (9), outcomes not relevant (2) and varying dose of FP (1). 24 new studies met the inclusion criteria for the review (Allen 2000; Bukovskis 2002; Casale 2001; Chetta 2002; Derom 1999; Derom 2001; Falcoz 2000; Gershman 2000; Giannini 2003; Kemp 2004; Li 1999; Meijer 1999; Nathan 2000; Nielsen 2002; Nieto 2001; O'Sullivan 2002; Pauwels 2002; Pearlman 1999; Pearlman 2002; SAM40012; Sorkness 1999; Sorkness 1999a; Verona 2003; Wallin 2003). Data for two studies previously included as abstracts were published in full text form (Hofstra 2000; Ind 2003). One study was identified from an online repository of unpublished clinical trials (SAM40012).
January 2005-January 2006	References identified: 411 Number assessed for further scrutiny: 55

Table 5. Asthma severity: characteristics of included patients at baseline

Study ID	FEV1: incl. criteria	Basline FEV1	Symptom frequency	OCS treatment	ICS treatment	Author opinion	Overall estimation
Agertoft 1997	Not stated	Not stated	No	No	Not stated	Mild	Mild
Allen 1998	>60	88-89%	Not stated	No	Approx. 50% patients ICS naive at baseline, 50% previous regular ICS use	Mild to moderate	Mild to moderate
Allen 2000	Not stated	61%	Not stated	Yes (non-OCS dependents excluded)	Not stated	Severe	Severe
Ayres 1995	Not stated	Mean baseline morning PEFR 73-77 (% predicted)	Need for 2 or more doses beta2 agonist on 2 out of 7 days of run in period	Proportion of patients using OCS (<10 mg/d)	Yes: BDP 1-2 mg/d or BUD 0.8-1.6 mg/d	moderate to severe	Moderate to severe
Boner 1999	Not stated	Not stated	Not stated	No	Not stated	Not stated	Unclear
Bukovkis 2002	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Unclear
Casale 2001	>/=65%	3-3.2 L	Not stated	No	Not stated	Mild to moderate	Mild to moderate
Chervinsky 1994	60-90	71-73%	Not stated	No	Yes: at least 1 month regular treatment with BDP prior to study	Mild to moderate	Mild to moderate
Chetta 2002	>70%	100-110%	Well documented history of asthma	No	Not stated	Mild to moderate	Mild
Dahl 1993	Not stated	73-75%	daytime wheezing or night-time symptoms on at least 4 days of 7 day run-in period or PEFR variability 20% or greater	No	Yes: BDP 1000 mcg/d or less	Moderate	Moderate

Table 5. Asthma severity: characteristics of included patients at baseline *(Continued)*

Derom 1999	>/=40%	80%	Not stated	No	Not within 6 months	Not stated	Mild
Derom 2001	Not stated	Not stated	Not stated	Not stated	Not stated	Unclear	Unclear
Falcoz 2000	50-80%	Not stated	Not stated	Not stated	Not stated	Mild-to-moderate	Unclear
FAP30001	>/=45%	74-5%	Not stated	No	Yes	Not stated	Moderate
FLIC15	>/=60% predicted	Not stated	Not stated	No	No	Mild to moderate	Mild
FLIP01/a	Not reported	Not reported	Not reported	No	Yes	Not reported	Moderate
FLIP39	Not reported	Not reported	Perennial symptoms requiring ICS	No	Yes - up to 400mcg/d	Not stated	Moderate
FLTA3014	50-85%	Not reported	Not reported	No	Yes	Not stated	Unclear
FLTA3020/a	60-90%	Not reported	Not reported	No	No (low dose ceased 30 days prior to study entry)	Not stated	Mild to moderate
FLTA3022/a	40-85% predicted	Not reported	Not stated	Yes	Yes	Not stated	Severe
FLTA4030	50-80%	Not stated	Stable during 7 day run-in, controlled with SABA alone	No	No	Not stated	Mild to moderate
Galant 1996	45-75	60-62%	> 8 puffs/d beta2 agonist or 2-4 night-time awakenings in week run-in	No	No	Mild to moderate	Moderate
Gershman 2000	Not stated	66-69%	Not stated	Not stated	Not stated	Not stated	Unclear
Giannini 2003	Not stated	3.23 L	Requirement for beta-agonist treatment during run-in	Not stated	Not stated	Moderate	Mild to moderate
Hofstra 2000	Not stated	96.6-93.2%	Not stated	No	No	Not stated	Unclear

Table 5. Asthma severity: characteristics of included patients at baseline *(Continued)*

Ind 2003	FEV1 not stipulated at inclusion	No details	Symptomatic despite ICS treatment. History of exacerbations	No	Yes: 1000-1600 mcg/d of BDP or BUD	Moderate-severe	Moderate-severe
Katz 1998	Not stated	PEFR 75 (% predicted) or less	Asthma symptoms on at least 4 out of 10 days of run in period or at least one night-time awakening in 10 days or 4 or puffs beta2 agonist on at least 4 days	No	No	Not stated	Moderate
Kemp 2004	50-100% predicted	82-85% predicted	Mild stable asthma	No	No	Mild	Mild
Lawrence 1997	50-80	65-68%	"Mean beta2 agonist use 3.2 - 4.2 puffs/d "	No	Yes: 3 months treatment or longer prior to study	Not stated	Moderate
Li 1999	FEV1 </=50% predicted	82.5-88.2%	Not stated	No	No	Not stated	Mild
Lumry 2006	45-80%	65.3-65.5	Not stated	No	Yes	Not stated	Moderate
Meijer 1999	Not stipulated	79-81%	Participants who exacerbated needing OCS during run-in were excluded	No	Yes - treatment tapered prior to randomisation	Mild-moderate	Mild to moderate
Nathan 2000	45-75% predicted	63.3-64.3	Not stated	No	Yes	Moderate	Moderate
Nelson 1999	40-80	60-62%	Not stated	Yes	Almost 100% of patients receiving ICS	Severe	Severe
Nieto 2001	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Unclear
Noonan 1998	60-85	73-76%	"No more than 12 puffs/d beta2 agonist and no more than 3 nights with awakening due to asthma"	No	No	Mild to moderate	Moderate
Noonan 1995	40-80	56-57.4%	Requirement for rescue beta2 agonist for 2 weeks prior to study due to symptoms	Yes	87% of patients receiving ICS	Severe	Severe
O'Sullivan 2002	>/=60%	79-86%	Not stated	No	No	Mild-moderate	Mild to moderate

Table 5. Asthma severity: characteristics of included patients at baseline *(Continued)*

Pauwels 2002	Not stated	Not stated	Not stated	Not stated	Not stated	Not stated	Unclear
Pearlman 1997	50-80	66-67%	"Mean beta2 agonist use 3.4-4.1 puffs/dNo more than 12 puffs/d beta2 agonist and no more than 2 nights with awakening due to asthma symptoms in last 7 days"	No	Yes: at least 3 months	Moderate	Moderate
Pearlman 1999	50-80%	65-69%	Not stated	No	No	Mild-moderate	Mild to moderate
Peden 1998	50-85	72-73%	"No more than 12 puffs/d beta2 agonist and no more than 3 nights with awakening due to asthmaMean awakenings per night due to asthma 0.05 to 0.09Mean beta2 agonist use 1.4 to 2.0 puffs/d"	No	Some patients: amount and type of ICS not stated	Not stated	Moderate
Pinnas 2005	45-80	67%	'during the week before randomization, patients could not have had more than 3 days in which more than 12 inhalations of albuterol were used, more than 3 nights with awakenings due to asthma requiring albuterol, or asthma exacerbations requiring systemic corticosteroids and/or hospitalization.'	No	No	Moderate to severe	Moderate
Raphael 1999	45-65	64.7-65.7%	> 8 puffs/week beta 2 agonist or diurnal variability in PEFR > 20% during run-in if FEV > 65-80 (% predicted)	No	Yes: BDP or TA 8-12 puffs/d	mild/moderate and severe	mild/moderate and severe
SAM40012	Not stated	Not stated	Symptom score greater than 2 on at least 3 of previous 7 days	Not stated	Yes	Not stated	Moderate
Sheffer 1996	45-75	62-64%	"During 7 day run-in:> 2 night-time awakenings due to asthma in last 7 days20% or greater PEFR diurnal variability at least one day in which 8 puffs beta2 agonist used "	No	No	Mild to moderate	Moderate
Sorkness 1999a	>/=50%	86-88%	Not stated	No	No	Mild to moderate	Mild to moderate
Sorkness 1999	>/=50%	83-88%	Not stated	No	No	Mild to moderate	Mild to moderate

Table 5. Asthma severity: characteristics of included patients at baseline *(Continued)*

Verona 2003	Not stated	Not stated	Exacerbation in last year requiring hospitalisation	No	Yes	Moderate to severe	Moderate to severe
Wallin 2003	Not stated	91-2%	Symptomatoic during run-in period despite medication	Not stated	Yes	Mild to moderate	Mild to moderate
Wasserman 1996	50-80%	Not stated	"Mean beta2 agonist use 3.1 to 3.3 puffs/dDuring last 7 days run-in no more than 12 puffs/d beta2 agonist and no more than 2 nights with awakening due to asthma"	No	No	Not stated	Moderate
Wolfe 1996	50-80%	64-66%	During 2 week run-in period no more than 12 puffs/d beta2 agonist and no more than 2 nights with awakening due to asthma	No	Yes: dose not stated	Moderate	Moderate

Table 6. Criteria for withdrawal due to lack of efficacy

Study ID	FEV1	PEFR	Beta2 agonist use	Night-time awakening	Exacerbations
Chervinsky 1994	20% or greater decrease compared to baseline	20% decrease in morning or evening PEFR on 4 or more days out of 7 in week prior to clinic visit	12 or more puffs on 3 or more days out of 7 in week prior to clinic visit	2 or more nights with 2 awakening out of 7 in week prior to clinic visit	Any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist
Galant 1996	15% or greater decrease compared to baseline	20% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	12 or more puffs on 3 or more days out of 7 in week prior to clinic visit	3 or more awakening in week prior to clinic visit	
Katz 1997	15% or greater decrease compared to baseline	15% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	8 or more puffs on 2 or more days out of 7 in week prior to clinic visit	2 or more nights with awakening out of 7 in week prior to clinic visit	
Lawrence 1997	20% or greater decrease compared to baseline	20% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	12 or more puffs on 2 or more days out of 7 in week prior to clinic visit	2 or more nights with awakening out of 7 in week prior to clinic visit	any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist
Nathan 2000	20% or greater decrease compared to baseline	20% or greater decrease compared to baseline	12 or more puffs on 2 or more days out of 7 in week prior to clinic visit	2 or more awakening in week prior to clinic visit	Any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist
Pearlman 1997	20% or greater decrease compared to baseline	20% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	12 or more puffs on 2 or more days out of 7 in week prior to clinic visit	2 or more awakening in week prior to clinic visit	Any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist
Peden 1997	15% or greater decrease compared to baseline	20% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	12 or more puffs on 3 or more days out of 7 in week prior to clinic visit	3 or more awakening in week prior to clinic visit	Any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist
Raphael 1999	20% or greater decrease	20% or greater decrease in morning PEFR on 3 or more	12 or more puffs on 3 or more days out of 7	3 or more nights with awakening out	

Table 6. Criteria for withdrawal due to lack of efficacy *(Continued)*

	compared to baseline	days out of 7 in week prior to clinic visit	in week prior to clinic visit	of 7 in week prior to clinic visit	
Sheffer 1996	15% or greater decrease compared to baseline	20% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	12 or more puffs on 3 or more days out of 7 in week prior to clinic visit	3 or more nights with awakening out of 7 in week prior to clinic visit	Any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist
Wasserman 1996	20% or greater decrease compared to baseline	20% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	12 or more puffs on 3 or more days out of 7 in week prior to clinic visit	2 or more nights with awakening out of 7 in week prior to clinic visit	any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist
Wolfe 1996	20% or greater decrease compared to baseline	20% or greater decrease in morning PEFR on 3 or more days out of 7 in week prior to clinic visit	12 or more puffs on 3 or more days out of 7 in week prior to clinic visit	2 or more nights with awakening out of 7 in week prior to clinic visit	Any clinical exacerbation requiring emergency treatment, hospital admission or additional asthma medication other than rescue beta 2 agonist

Table 1. What's New

Issue	Detail
3, 2005	Impact of new evidence on findings of the review The addition of new data on the review has largely increased the precision of the effect estimates. The existence of a small dose response in the lower dose ranges of fluticasone (FP) has not been challenged by the new trials included in the review. The inclusion of data from three studies comparing FP at doses of 400 to 500 µg/day with 800 to 1000 µg/day raises the possibility that the upper limits of the dose response occur at medium doses for adults with moderate asthma. Evidence from one trial suggested that the response to higher doses of FP is greater in more severe asthma. Further work would help to confirm this. Detail of update - latest search date January 2005 A total of 23 new trials, contributing data for an additional 2370 participants met the inclusion criteria of the review (Allen 2000; Bukovskis 2002; Casale 2001; Chetta 2002; Derom 1999; Derom 2001; Falcoz 2000; Gershman 2000; Giannini 2003; Kemp 2004; Li 1999; Meijer 1999; Nathan 2000; Nielsen 2002; Nieto 2001; O'Sullivan 2002; Pauwels 2002; Pearlman 1999; Pearlman 2002; SAM40012; Sorkness 1999; Sorkness 1999a; Verona 2003; Wallin 2003). The latest search date was January 2004. Data from the full publications of studies previously available as abstracts were included (Ind 1998 (now Ind 2003); Hofstra 1998 (now Hofstra 2000)). Several trials contributed to more than one comparison as they were multi-arm studies. One unpublished trial was identified (SAM40012). Unless otherwise indicated, the addition of new data tightened confidence intervals around existing significant or non-significant pooled estimates. In the following summary of outcomes for different dose comparisons, outcomes marked * denote those that became significant with the addition of new data.

Table 1. What's New *(Continued)*

	Fluticasone 100 versus 200 µg/day (4 new studies) Change in forced expiratory volume in one minute (FEV1); change in morning peak expiratory flow (PEF); change in evening PEF; change in daily use of rescue medication; change in daily asthma symptoms; change in number of nocturnal awakenings*; withdrawal due to lack of efficacy; sore throat or pharyngitis Fluticasone 100 versus 400 to 500 µg/day (2 new studies) Change in FEV1; change in morning PEF; change in daily symptoms Fluticasone 200 versus 400 to 500 µg/day (9 new studies) Change in morning PEF; change in evening PEF; change in FEV1; change in daily symptoms; change in rescue medication usage; number of nocturnal awakenings; number of patients withdrawn due to lack of efficacy; sore throat or pharyngitis; hoarseness or dysphonia; oral candidiasis Fluticasone 400 to 500 versus 800 to 1000 µg/day (3 new studies, no studies previously included) Change in morning PEF; change in FEV1; exacerbations requiring oral corticosteroids (OCS); withdrawals Fluticasone 50 to 100 versus 800 to 1000 µg/day (2 new studies) FEV1 Fluticasone 200 versus 800 to 1000 µg/day (4 new studies) Change in FEV1; change in morning PEF; sore throat or pharyngitis; oral candidiasis* (fewer instances of candidiasis in lower dose group); withdrawals due to lack of efficacy, hoarseness or dysphonia

APPENDICES

Appendix 1. Previous assessment of study quality

Two authors (NPA and JB) were blinded to the authors' names, institutions and funding sources and independently assessed the methodological quality of included studies. Trials were scored using the following approach.

Grade A: adequate allocation concealment.
Grade B: unclear allocation concealment.
Grade C: clearly inadequate concealment.

Studies were also assessed using a five-point scoring instrument (Jadad 1996).
1. Was the study described as randomised? (yes = 1, no = 0).
2. Was the study described as double blind? (yes = 1, no = 0).
3. Was there a description of withdrawals and dropouts? (yes = 1, no = 0).
4. Was the method of randomisation well described and appropriate? (yes = 1, no = 0).
5. Was the method of double blinding well described and appropriate? (yes = 1, no = 0).
6. Deduct one point if method of randomisation or blinding inappropriate.
Inter-rater agreement was measured using the kappa statistic. Disagreement was resolved by consensus.

Appendix 2. GSK randomisation procedures

The procedures for randomising GSK sponsored studies has been detailed in correspondence between Richard Follows and TL, the details of which are given below:

The randomisation software is a computer-generated, centralised programme (RandAll). After verification that the randomisation sequence is suitable for the study design (crossover, block or stratification), Clinical Supplies then package the treatments according to the randomisation list generated. Concealment of allocation is maintained by a third party, since the sites phone in and are allocated treatments on that basis. Alternatively a third party may dispense the drug at the sites. Unblinding of data for interim analyses can only be done through RandAll, and are restricted so that only those reviewing the data are unblinded to treatment group allocation.

WHAT'S NEW

Date	Event	Description
27 April 2009	Amended	Software problem identified and bug fixed.

HISTORY

Protocol first published: Issue 1, 1999
Review first published: Issue 3, 2001

Date	Event	Description
24 July 2008	New citation required and conclusions have changed	Unpublished data: Agertoft 1997; Dahl 1993; Ind 2003; Kemp 2004; Katz 1998; Boner 1999; Allen 1998; Chervinsky 1994; Nathan 2000; Nelson 1999; Pearlman 1999; Peden 1998; Verona 2003 New trials: N = 10 (representing 11 randomised comparisons: FLIP39; Pinnas 2005; FAP30001; FLIP01; FLIP01a; FLTA3014; FLTA3020; FLTA3020a; FLTA3022; Lumry 2006; SLGF75) Previous descriptions of What's New are given in Table 1.
24 July 2008	Amended	Converted to new review format.
1 January 2008	New search has been performed	Literature search re-run
1 April 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Nick Adams retrieved papers identified by the electronic search, handsearched additional sources for relevant studies, assessed trials for methodological quality, contacted authors to clarify details of trial design and/or request missing data, extracted data from included trials and wrote the text of the review.

Janine Bestall retrieved papers identified by the search, assessed trials for methodological quality, contacted authors for clarification of trial details and/or to request missing data.

Paul Jones provided editorial support.

Toby Lasserson and Benedict Griffiths assisted with study selection, study assessment, data extraction, data entry and analysis, and interpretation and writing of the update of the review, in November 2004, and August 2008.

Chris Cates provided methodological support and guidance with the content for the November 2004 and August 2008 updates.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHS Research and Development, UK.
- Garfield Weston Foundation, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have opted against pooling data from studies in adults and children where outcomes are reported as litres (such as FEV1 and PEF). Heterogeneity in lung function outcomes such as FEV1 and PEF, are likely to be explained by differences in lung volume between these age groups since lower lung volumes in children may naturally yield results to those given by adults. However where metrics convert litres to percent predicted, and take into account age (as well as height and gender) we have retained combined estimates for adult and paediatric studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Inhalation; Androstadienes [*administration & dosage]; Anti-Inflammatory Agents [*administration & dosage]; Asthma [*drug therapy]; Chronic Disease; Fluticasone; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans