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# Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease (Review)

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[Intervention Review]

# Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease

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## ABSTRACT

### Background

Both long-acting beta$_2$-agonists (LABA) and inhaled corticosteroids (ICS) have been recommended in guidelines for the treatment of chronic obstructive pulmonary disease (COPD). Their coadministration in a combination inhaler may facilitate adherence to medication regimens and improve efficacy.

### Objectives

To determine the efficacy and safety of combined ICS and LABA for stable COPD in comparison with placebo.

### Search methods

We searched the Cochrane Airways Group Specialised Register of trials, reference lists of included studies and manufacturers' trial registries. The date of the most recent search was June 2013.

### Selection criteria

We included randomised and double-blind studies of at least four weeks' duration. Eligible studies compared combined ICS and LABA preparations with placebo.

### Data collection and analysis

Two review authors independently assessed study risk of bias and extracted data. Dichotomous data were analysed as fixed-effect odds ratios (OR) or rate ratios (RR) with 95% confidence intervals (95% CI), and continuous data as mean differences with 95% confidence intervals.

### Main results

Nineteen studies met the inclusion criteria (with 10,400 participants randomly assigned, lasting between 4 and 156 weeks, mean 42 weeks). Studies used three different combined preparations (fluticasone/salmeterol, budesonide/formoterol or mometasone/formoterol). The studies were generally at low risk of bias for blinding but at unclear or high risk for attrition bias because of participant dropouts. Compared with placebo, both fluticasone/salmeterol and budesonide/formoterol reduced the rate of exacerbations. Mometasone/formoterol reduced the number of participants experiencing one or more exacerbation. Pooled analysis of the combined therapies

indicated that exacerbations were less frequent when compared with placebo (Rate Ratio 0.73; 95% CI 0.69 to 0.78, 7 studies, 7495 participants); the quality of this evidence when GRADE criteria were applied was rated as moderate. Participants included in these trials had on average one or two exacerbations per year, which means that treatment with combined therapy would lead to a reduction of one exacerbation every two to four years in these individuals. An overall reduction in mortality was seen, but this outcome was dominated by the results of one study (TORCH) of fluticasone/salmeterol. Generally, deaths in the smaller, shorter studies were too few to contribute to the overall estimate. Further longer studies on budesonide/formoterol and mometasone/formoterol are required to clarify whether this is seen more widely. When a baseline risk of death of 15.2% from the placebo arm of TORCH was used, the three-year number needed to treat for an additional beneficial outcome (NNTB) with fluticasone/salmeterol to prevent one extra death was 42 (95% CI 24 to 775). All three combined treatments led to statistically significant improvement in health status measurements, although the mean differences observed are relatively small in relation to the minimum clinically important difference. Furthermore, symptoms and lung function assessments favoured combined treatments. An increase in the risk of pneumonia was noted with combined inhalers compared with placebo treatment (OR 1.62, 95% CI 1.36 to 1.94), and the quality of this evidence was rated as moderate, but no dose effect was seen. The three-year NNTH for one extra case of pneumonia was 17, based on a 12.3% risk of pneumonia in the placebo arm of TORCH. Fewer participants withdrew from the combined treatment arms for adverse events or lack of efficacy.

### Authors' conclusions

Combined inhaler therapy led to around a quarter fewer COPD exacerbations than were seen with placebo. A significant reduction in all-cause mortality was noted, but this outcome was dominated by one trial (TORCH), emphasising the need for further trials of longer duration. Furthermore, we note there has been some debate about the appropriateness of the analysis conducted in the TORCH trial (see Feeback). Increased risk of pneumonia is a concern; however, this did not translate into increased exacerbations, hospitalisations or deaths. Current evidence does not suggest any major differences between inhalers in terms of effects, but nor is the evidence strong enough to demonstrate that all are equivalent. Importantly, we cannot comment on the relative contribution of the individual components of combined therapy to the effects identified, as this review presents only the pair-wise comparison between combined therapy and placebo. To permit firmer conclusions about the effects of combined therapy, more data are needed, particularly in relation to the profile of adverse events and benefits in relation to different formulations and doses of inhaled ICS. Head-to-head comparisons are necessary to determine whether one combined inhaler is better than the others.

## PLAIN LANGUAGE SUMMARY

### Combined inhalers versus placebo for the treatment of chronic obstructive pulmonary disease (COPD)

### Review question

We reviewed the evidence on the effects of combined inhalers in people with COPD when compared with placebo. We particularly focused on whether combined inhalers are a good but safe treatment for adults with COPD.

### Background

COPD is a serious respiratory condition that affects millions of people worldwide. In most cases, it is caused by smoking. COPD is often treated by using inhalers. Currently, three types of inhalers combine a steroid and a 'long-acting beta$_2$-agonist' (LABA). Steroids work by reducing inflammation in the airways, and LABA work by relaxing the muscles in the airways and opening them up. Using combined inhalers is more convenient than taking the two drugs separately but is also more expensive. We looked for evidence on whether giving a combined inhaler is better or worse than giving placebo (dummy inhaler).

### Study characteristics

Nineteen studies involving 10,400 people were included in this review. The studies lasted between 4 and 156 weeks. All of the people included in the studies had COPD of different severity. Both men and women were included, and most of the studies included only adults aged 45 or older.

All studies compared a combined inhaler with a placebo that was identical in appearance to the combined inhaler, so the people in the trials did not know whether they were taking the drug or the dummy inhaler. Some of the studies included two groups treated with the combined inhaler; one group was getting a higher dose and one group was getting a lower dose.

The evidence presented here is current to June 2013.

Most of the studies were sponsored by the pharmaceutical industry.

### Key results

We found that people receiving a combined inhaler were less likely to have a flare-up (‘exacerbation’) of their COPD. The chance of having an exacerbation was reduced by about one quarter.

A small reduction in the risk of death was seen over three years, although most of the evidence about death comes from one large, long trial called TORCH. According to TORCH, approximately 42 people would need to be treated with a combined inhaler for three years to prevent one death.

We also found that people receiving combined inhalers had small improvements in quality of life, symptoms related to COPD and their breathing tests. However, these improvements may not have been very noticeable to them.

People treated with combined inhalers were more likely to have a lung infection called pneumonia. Again, most of the evidence about pneumonia comes from the TORCH trial. According to TORCH, when compared with placebo, for approximately every 17 people treated with combined inhaler, one extra person would get pneumonia.

People treated with combined inhalers were no more or less likely to experience serious unwanted events, including side effects, during treatment.

No consistent differences were found between the three different types of inhalers included in this review.

However, it is important to note that we cannot tell from this review whether it is the combination that is important or whether one of the two drugs in the combined inhaler may have had the real impact.

**Quality of the evidence**

The evidence presented in this review is generally considered to be of moderate quality. Most of the studies did not clearly explain how they decided which people would receive the combined inhaler and which would receive placebo, and this is an important part of a well-conducted study. Also, more people receiving placebo dropped out of the trials than those receiving a combined inhaler. This often happened because of exacerbations of COPD. This means that by the end of the trial, the groups might have been unbalanced, and this could affect the accuracy of the results.

## SUMMARY OF FINDINGS

**Summary of findings for the main comparison. Combined inhalers versus placebo (primary outcomes) for chronic obstructive pulmonary disease**

**Combined inhalers versus placebo (primary outcomes) for chronic obstructive pulmonary disease (COPD)**

**Patient or population:** patients with COPD
**Settings:** community
**Intervention:** combined inhalers

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Combined inhalers versus placebo (primary outcomes) | | | | |
| **Annual exacerbation rates** | **1.35** | **0.99** (0.93 to 1.05) | **Rate ratio 0.73** (0.69 to 0.78) | 7473 (seven studies) | ⊕⊕⊕⊖ **moderate**[1, 2] | |
| **Participants with at least one exacerbation**<br>**Duration of six months**[3] | **301 per 1000** | **251 per 1000** (221 to 286) | **OR 0.78** (0.66 to 0.93) | 3141 (eight studies) | ⊕⊕⊕⊖ **moderate**[1] | |
| **Mortality**<br>**Duration of 18 months**[3] | **60 per 1000** | **50 per 1000** (41 to 59) | **OR 0.82** (0.68 to 0.99) | 10129 (16 studies) | ⊕⊕⊕⊖ **moderate**[2, 4] | |
| **Pneumonia**<br>**Duration of 18 months**[3] | **55 per 1000** | **85 per 1000** (73 to 101) | **OR 1.62** (1.36 to 1.94) | 9620 (14 studies) | ⊕⊕⊕⊖ **moderate**[1, 2] | |
| **Hospitalisations due to COPD exacerbations** | **115 per 1000** | **108 per 1000** (95 to 121) | **OR 0.93** (0.81 to 1.06) | 9492 (12 studies) | ⊕⊕⊖⊖ **low** [3, 5] | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Duration of 18 months**[3] | | | | | | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Downgraded because of risk of attrition bias.
[2]Concerns have been raised about the analysis of the largest study, TORCH. We note that the protocol was published after the trial had recruited (See Feedback 1, Feedback 2). No downgrade.
[3]Weighted mean duration.
[4]Downgraded because of imprecision.
[5]Downgraded because of risk of attrition bias and imprecision.

## Summary of findings 2. Fluticasone/salmeterol (FPS) versus placebo for COPD

**Fluticasone/salmeterol (FPS) versus placebo for COPD**

**Patient or population:** patients with COPD
**Settings:** community
**Intervention:** fluticasone/salmeterol (FPS)

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Fluticasone/salmeterol (FPS) versus placebo (PLA) | | | | |
| **Adverse events—any**<br>**Duration of two years**[1] | **780 per 1000** | **794 per 1000**<br>(771 to 816) | **OR 1.09**<br>(0.95 to 1.25) | 5574<br>(nine studies) | ⊕⊕⊖⊖<br>**Low**[2, 3] | |
| **Adverse events—'serious'** | **271 per 1000** | **287 per 1000**<br>(261 to 314) | **OR 1.08**<br>(0.95 to 1.23) | 5531<br>(nine studies) | ⊕⊕⊖⊖<br>**Low**[2, 3] | |

| | |
|---|---|
| **Duration of two years**[1] | |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Weighted mean duration.
[2]Downgraded because of risk of attrition bias and imprecision.
[3]Concerns have been raised about the analysis of the largest study, TORCH. We note that the protocol was published after the trial had recruited (See Feedback 1, Feedback 2).

### Summary of findings 3. Budesonide/formoterol (BDF) versus placebo for COPD

**Budesonide/formoterol (BDF) versus placebo for COPD**

**Patient or population:** patients with COPD
**Settings:** community
**Intervention:** budesonide/formoterol (BDF)

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Budesonide/formoterol (BDF) versus placebo | | | | |
| **Adverse event—any—320/9**[4]<br><br>**Duration of nine months** [3] | **538 per 1000** | **623 per 1000**<br>(574 to 669) | **OR 1.42**<br>(1.16 to 1.74) | 1552<br>(two studies) | ⊕⊕⊝⊝<br>**low**[1] | |
| **Adverse event—any—160/9**[4]<br><br>**Duration of nine months** [3] | **538 per 1000** | **606 per 1000**<br>(557 to 652) | **OR 1.32**<br>(1.08 to 1.61) | 1556<br>(two studies) | ⊕⊕⊝⊝<br>**low**[1] | |

| | | | | | |
|---|---|---|---|---|---|
| **Adverse events—'serious'—320/9[4]**<br><br>**Duration of 10 months[3]** | **162 per 1000** | **184 per 1000** (155 to 219) | **OR 1.17** (0.95 to 1.45) | 2476 (four studies) | ⊕⊕⊖⊖ **low**[2] |
| **Adverse events—'serious'—160/9[4]**<br><br>**Duration of nine months [3]** | **113 per 1000** | **132 per 1000** (102 to 171) | **OR 1.2** (0.89 to 1.63) | 1556 (two studies) | ⊕⊕⊖⊖ **low**[2] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Downgraded because of risk of attrition bias and imprecision and heterogeneity.
[2]Downgraded because of risk of attrition bias and imprecision.
[3]Weighted mean duration.
[4]Delivered dose.

## Summary of findings 4. Mometasone/formoterol (MF/F) versus placebo for COPD

**Mometasone/formoterol (MF/F) versus placebo for COPD**

**Patient or population:** patients with chronic obstructive pulmonary disease
**Settings:** community
**Intervention:** mometasone/formoterol (MF/F)

**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Mometasone/formoterol (MF/F) versus placebo | | | | |

| | | | | | |
|---|---|---|---|---|---|
| **Adverse event—any—400/10[3]**<br>**Duration of six months** | **362 per 1000** | **357 per 1000**<br>(298 to 424) | **OR 0.98**<br>(0.75 to 1.3) | 890<br>(two studies) | ⊕⊕⊖⊖<br>**low**[1] |
| **Adverse event—any—200/10[3]**<br>**Duration of six months** | **362 per 1000** | **317 per 1000**<br>(260 to 382) | **OR 0.82**<br>(0.62 to 1.09) | 894<br>(two studies) | ⊕⊕⊖⊖<br>**low**[2] |
| **Adverse events—serious—400/10[3]**<br>**Duration of six months** | **74 per 1000** | **80 per 1000**<br>(50 to 125) | **OR 1.09**<br>(0.66 to 1.79) | 890<br>(two studies) | ⊕⊕⊖⊖<br>**low**[2] |
| **Adverse events—serious—200/10[3]**<br>**Duration of six months** | **74 per 1000** | **53 per 1000**<br>(32 to 89) | **OR 0.71**<br>(0.41 to 1.23) | 894<br>(two studies) | ⊕⊕⊖⊖<br>**low**[2] |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** Confidence interval; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Downgraded because of risk of attrition bias, imprecision and heterogeneity.
[2]Downgraded because of risk of attrition bias and imprecision.
[3]Delivered dose.

# BACKGROUND

## Description of the condition

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in most industrialised countries, and it is projected to be the third leading cause of death worldwide by 2020 (GOLD 2012). The disease is predominantly caused by smoking. An estimated three million people are affected by COPD in the UK (NCGC2010). COPD is a heterogeneous syndrome that is characterised by reduced post-bronchodilator lung function (forced expiratory volume in one second/forced vital capacity ($FEV_1$/FVC)) < 0.7 in all patients (GOLD 2012). Acute bronchodilator reversibility has traditionally been regarded as a characteristic of asthma, and only in the past few years has it been generally acknowledged that this clinical feature is also present in COPD (Hanania 2011), as it was found in the UPLIFT study (UPLIFT 2008), in which 53% of participants had an increase of at least 200 mL in $FEV_1$ post-salbutamol. In TORCH, an increase in predicted $FEV_1$ of 10% was an exclusion criterion (TORCH). Patients with COPD generally show progressive lung function loss, accompanied by worsening respiratory symptoms (e.g. dyspnoea, cough and sputum) and health status (GOLD 2012). These clinical features are a result of persisting and progressive airway inflammation (i.e. bronchial infiltration of neutrophils, macrophages, lymphocytes and mast cells) and increasing evidence of autoimmunity (Cosio 2009). Furthermore, it has been suggested that some phenotypes of COPD involve chronic systemic inflammation that has an impact on co-morbidities, such as cardiovascular disease (Garcia-Aymerich 2011).

## Description of the intervention

This review focusses on combined inhalers that contain both an inhaled corticosteroid (ICS) and a long-acting beta$_2$-agonist (LABA).

ICS, LABA and long-acting antimuscarinic agents (LAMA) have been shown to be effective in a range of outcomes in COPD. ICS have not been shown to reduce the rate of decline in $FEV_1$, although short-term increases in $FEV_1$ and significant reductions in exacerbations have been reported (Yang 2012). LABA and LAMA reduce exacerbation frequency and symptoms and improve quality of life. On the basis of the evidence, GOLD 2012 recommends that inhaled steroids should be used in patients with an $FEV_1$ < 50% predicted (GOLD stages 3 and 4 or quadrant C and D in the 2012 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria) and a history of exacerbations (GOLD 2012). National Institute for Health and Care Excellence (NICE) guidelines recommend either a LABA with an ICS in a combined inhaler, or with a LAMA, if $FEV_1$ is less than 50% predicted. Furthermore, the guidelines recommended combined ICS/LABA In people with stable COPD with an $FEV_1 \geq 50\%$ who remain breathless or have exacerbations despite maintenance therapy with a LABA (NCGC2010).

## How the intervention might work

The evidence base for the addition of long-acting beta$_2$-agonists to inhaled steroids in asthma is well established (Ducharme 2010; Ni Chroinin 2009). In asthma, the scientific rationale for combining LABA and ICS in a single inhaler relates to synergy of action. At a molecular level, ICS up-regulate the expression of beta$_2$-agonist receptors in bronchial smooth muscle. At the same time, LABA increase the genomic actions of ICS by promoting passage to the cellular nuclei. Thus, beta$_2$-agonists and ICS may interact in a beneficial way, with ICS preventing the loss of function of beta$_2$-agonists with long-term use, whereas beta$_2$-agonists may potentiate the local anti-inflammatory actions of ICS in people with asthma (Barnes 2002).

Some of these mechanisms may also be important in COPD. Several possible advantages associated with a combination of therapies have already been shown to improve outcomes. In particular, ICS in combination with LABA may have a greater effect than either treatment alone on the number of exacerbations, or on other outcomes such as quality of life (Nannini 2012; Nannini 2013). One clinical rationale is based on patient convenience, with the expectation that a simplified inhaler regimen may lead to greater treatment adherence (Barnes 2002).

## Why it is important to do this review

This is an update of a previous review, which considered the effect of combined therapy compared with placebo, as well as both monocomponents separately, in people with COPD (Nannini 2004). The availability of several new studies has prompted us to split the review between comparisons with placebo and those with monocomponents. This review summarises the evidence from clinical trials comparing combined ICS and LABA with placebo. Reviews of the comparison between combined therapy and ICS (Nannini 2013) or long-acting beta$_2$-agonists (Nannini 2012) are published separately.

Concerns have been raised recently regarding the safety of LABA in asthma (Walters 2007). Moreover, questions have surrounded the validity of summary estimates from clinical trials that assessed exacerbation rates without accounting for follow-up time or adjustment for between-participant variability (Suissa 2006). Two well-known COPD guidelines (GOLD 2012; NCGC2010) had issued a strong recommendation regarding ICS/LABA combined therapy. But others are more guarded: "Recommendation 5: ACP, ACCP, ATS, and ERS suggest that clinicians may administer combination inhaled therapies (long-acting inhaled anticholinergics, long-acting inhaled beta$_2$-agonists, or inhaled corticosteroids) for symptomatic patients with stable COPD and $FEV_1$ < 60% predicted (Grade: weak recommendation, moderate-quality evidence)" (ACP 2011). Finally, the largest randomised controlled trial (RCT) of combined therapy (TORCH) demonstrated a significant reduction in mortality versus placebo (P = 0.052). We wished to see whether other combined inhalers had a similar effect.

# OBJECTIVES

To determine the efficacy and safety of combined ICS and LABA for stable COPD in comparison with placebo.

# METHODS

## Criteria for considering studies for this review

### Types of studies

Randomised, double-blind, parallel-group clinical trials of at least four weeks' duration.

### Types of participants

Adult patients (age > 40 years) with known, stable COPD fulfilling American Thoracic Society (ATS), European Respiratory Society (ERS) or Global Initiative for Chronic Obstructive Lung Disease (GOLD) diagnostic criteria. Patients were to be clinically stable with no evidence of an exacerbation for one month before study entry. Patients with significant diseases other than COPD (e.g. with a diagnosis of asthma, cystic fibrosis, bronchiectasis or other lung diseases) were excluded. However, patients with partial reversibility on pulmonary function testing were included.

### Types of interventions

- Fluticasone propionate/salmeterol versus placebo (FPS).
- Budesonide/formoterol versus placebo (BDF).
- Mometasone furoate/formoterol versus placebo (MF/F).

Concomitant therapy was permitted, as long as no systematic difference was noted between treatment groups; however, trials in which participants were randomly assigned to tiotropium and combined ICS/LABA therapy versus tiotropium and placebo were excluded from the review, as this comparison is already considered in Karner 2011.

### Types of outcome measures

#### *Primary outcomes*

- Exacerbations, measured as rate or number of participants experiencing an exacerbation.
- All-cause mortality.
- Pneumonia.
- Hospitalisations due to COPD exacerbation (note that we accepted COPD reported as a serious adverse event as a surrogate marker for this outcome; the internationally recognised definition of a serious adverse event includes a life-threatening event or one that results in hospitalisation or prolonged hospitalisation).

#### *Secondary outcomes*

- Change in forced expiratory volume in 1 second ($FEV_1$) and change in forced vital capacity (FVC): trough, peak and average and other measures of pulmonary function.
- Exercise performance: six-minute walk and other measures.
- Quality of life scales: St George's Respiratory Questionnaire (SGRQ), Chronic Respiratory Disease Questionnaire (CRDQ).
- Symptoms.
- Inhaled rescue medication used during the treatment period and other concomitant medications used, including antibiotics and steroids.
- Adverse events: palpitations, tremor, hoarseness/dysphonia, oral candidiasis, cataracts, skin bruising, bone fracture, bone density, plasma cortisol level.
- Rate of withdrawal due to lack of efficacy or COPD deterioration.
- Withdrawal due to adverse events.

## Search methods for identification of studies

### Electronic searches

We identified trials 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; we also handsearched respiratory journals and meeting abstracts (see Appendix 1 for more details). All records in the Specialised Register coded as 'COPD' were searched using the following terms:

(((beta* and agonist*) and long*) or ((beta* and adrenergic*) and long*) and (*steroid or steroid* or corticosteroid*)) or (fluticasone and salmeterol) or Seretide or Advair or (formoterol and budesonide) or Symbicort.

The most recent search was done in June 2013. We applied no restrictions on language of publication or publication type.

### Searching other resources

We reviewed reference lists of all primary studies and review articles for additional references, and we contacted authors of identified randomised trials about other published and unpublished studies. In addition, we consulted the online trial registries of GlaxoSmithKline and AstraZeneca, manufacturers of FPS and BDF, respectively (www.ctr.gsk.co.uk; www.astrazenecaclinicaltrials.com).

## Data collection and analysis

### Selection of studies

Two review authors (LJN and PP) independently identified abstracts of trials that appeared potentially relevant. Using the full text of each study, these review authors independently selected trials for inclusion in the review. Consensus was by simple agreement, with third party adjudication used to resolve differences.

### Data extraction and management

Two review authors (RN and RH) independently extracted data from included trials. RN entered the data into Review Manager, and this work was checked by RH. In some cases, we estimated information regarding outcomes from graphs. This was performed independently. Data extraction included the following items.

- **Design:** method of randomisation, presence and type of run-in period, study design (parallel, cross-over).
- **Population:** age, gender, smoking status, study setting (country, practice setting), inclusion and exclusion criteria.
- **Intervention:** dose, delivery device, duration.
- **Control:** concurrent treatments (ipratropium, $beta_2$-agonist, inhaled and systemic corticosteroids).
- **Outcomes:** as above.

### Assessment of risk of bias in included studies

The risk of bias of included studies was assessed using The Cochrane Collaboration's risk of bias tool (Higgins 2011). Two review authors (RN and RH) assessed the risk of bias of all included studies with regard to random sequence generation, allocation concealment, blinding, incomplete outcome data and selective outcome reporting. Each item was assessed as having high, low or unclear risk of bias on the basis of relevant information reported in the randomised controlled trial.

### Measures of treatment effect

For dichotomous variables, data are expressed as odds ratios (OR) with 95% confidence intervals (CI). Data for continuous variables were reported as mean differences (MD) with 95% CI.

### Unit of analysis issues

The unit of analysis was the participant.

### Dealing with missing data

We contacted study sponsors and primary investigators to obtain information that we could not verify by reviewing the study reports.

We used reported confidence intervals or P values to calculate standard deviations, or standard errors, when necessary.

### Assessment of heterogeneity

For pooled effects, heterogeneity was assessed by using the $I^2$ measurement. This estimates the degree of variation between studies not attributable to the play of chance. $I^2$ was interpreted in relation to the following guidance (Higgins 2011).

- 0% to 40%: may not be important.
- 30% to 60%: may represent moderate heterogeneity.
- 50% to 90%: may represent substantial heterogeneity.
- 75% to 100%: may represent considerable heterogeneity (Higgins 2011).

We also considered the $Chi^2$ test (P value < 0.10). We regarded $I^2$ as our primary measure of heterogeneity.

### Assessment of reporting biases

We evaluated publication bias by using visual inspection of funnel plots when an adequate number of trials were aggregated in the analyses (more than ten). We recognised that an asymmetrical funnel plot can reflect heterogeneity, outcome reporting bias and small study effects and therefore is not necessarily a reflection of publication bias.

### Data synthesis

For continuous variables, we used a fixed-effect mean difference (MD) for outcomes measured on the same metric. A standardised mean difference (SMD) with 95% confidence interval (95% CI) was calculated for outcomes when data were combined from studies using different metrics. All similar studies were pooled using fixed-effect MD/SMD and 95% CI.

For dichotomous variables, we calculated a fixed-effect odds ratio (OR) with 95% CI. All similar studies were pooled using a fixed-effect OR and 95% CI.

When mean treatment differences were reported, data were entered as generic inverse variance (GIV), provided a standard error for the difference could be extracted or imputed. When this method was used, the effect size was reported from the original papers, for example, as a Rate Ratio (RR). This method (GIV) was not available when the protocol was written for the review, so it was not prespecified.

We used pooled OR with 95% CI to calculate numbers needed to treat for an additional beneficial outcome (NNTB) or harm (NNTH) using Visual Rx. Control event rates were taken from the event rates in the individual trials and are reported with the corresponding duration of the trial because NNTs are time dependent (Cates 2012).

### Subgroup analysis and investigation of heterogeneity

We separated the types of steroids and long-acting $beta_2$-agonists, and for the new studies included in this update, we also separated differing dosages of the same drug. We planned the following a priori subgroups.

- Disease severity (related to baseline $FEV_1$ and placebo group exacerbation rate) according to GOLD staging of IIA or IIB (moderate COPD, characterised by deteriorating lung function (IIA = $FEV_1$ ≤ 80% predicted; IIB = ≤ 50% predicted) with progression of symptoms) and III (severe COPD, characterised by severe airflow limitation ($FEV_1$ < 30% predicted) and the presence of respiratory failure or clinical signs of right heart failure (GOLD 2012).
- Prior inhaled corticosteroid plus long-acting $beta_2$-agonist use (dichotomised as yes/no).
- Concurrent therapy with routine $beta_2$-agonist (short- or long-acting), corticosteroid (systemic or inhaled) or theophylline (dichotomised as yes/no).
- Reversibility of airflow obstruction with $beta_2$-agonist therapy (dichotomised as partial/none). Definition: > 12% and > 200 mL from baseline $FEV_1$ or > 12% post-bronchodilator (metered-dose inhaler (MDI) salbutamol 200 to 400 mcg).
- Dose, duration and delivery method of therapy.

### Sensitivity analysis

For pooled effects, heterogeneity was to be tested by using the $I^2$ measurement of the degree of variation between studies, not attributable to the play of chance. If heterogeneity was found ($I^2$ statistic > 30%), a random-effects model was used to determine the impact of heterogeneity on the overall pooled effect. In addition, the robustness of the results was tested using a sensitivity analysis based on the quality of the trials when possible.

## RESULTS

## Description of studies

### Results of the search

For details of the search history, see Table 1.

### Included studies

Nineteen studies are included in this review. A previous ongoing study, Morgan 2004, has now been linked to the TRISTAN trial. For a full description of baseline characteristics, methods used and inclusion and exclusion entry criteria for the individual studies, see Characteristics of included studies.

#### *Design*

All trials had a randomised, double-blind, parallel-group design and were of at least four weeks' duration. Methods of randomisation were described in six studies (Bourbeau 2007; Lapperre 2009; Mahler 2002; Sin 2008; Tashkin 2008; Tashkin 2012). The method of blinding was not fully described in all studies. Through correspondence from GlaxoSmithKline, trial methodology

was confirmed for TRISTAN, and AstraZeneca confirmed the methodology for Szafranski 2003. Study characteristics were sufficiently described in two data sets without journal publication to justify their inclusion in the review (SFCT01 and SCO104925).

### *Participants*

A total of 10,400 participants were randomly assigned to interventions within studies included in this review. Participants suffered from COPD, with variable definitions of COPD and reversibility. COPD was defined by national or international criteria as follows: ATS (Hanania 2003; Mahler 2002); ERS (TORCH; TRISTAN); or GOLD (Barnes 2006; Bourbeau 2007; Calverley 2003; Dal Negro 2003; Lapperre 2009; Sin 2008; Szafranski 2003; Zheng 2006). In seven studies, definitions were not specified or were based on lung function tests and smoking history (Doherty 2012; O'Donnell 2006; Rennard 2009; SCO104925; SFCT01; Tashkin 2008; Tashkin 2012). Participant populations in the studies suffered from moderate to very severe COPD, with the exception of Bourbeau 2007, in which participants with mild COPD were also enrolled, and Sin 2008, in which enrolled participants had $FEV_1$ < 80% predicted. Two studies enrolled participants with reversible or non-reversible COPD (Hanania 2003; Mahler 2002). In TORCH, participants were not required to have had previous exacerbations requiring oral steroids or antibiotics to be included in the study. All participants were required to have a smoking history, with the exception of those enrolled in Zheng 2006, which included both smokers and never smokers.

### *Interventions*

All 19 studies compared combination therapy with placebo, but the therapies varied. Thirteen studies compared FPS with placebo, four compared BDF and two compared MF/F. In three of the FPS studies, the combination of ICS/LABA was 250 mcg/50 mcg twice daily (Dal Negro 2003; Hanania 2003; O'Donnell 2006). In the remainder of the FPS studies, the dose was 500 mcg/50 mcg twice daily. Previous versions of this review did not consider these dosage groups separately, and as the participant numbers are small, this has not been changed in the current update. In Calverley 2003 and Szafranski 2003, the combination ICS/LABA was BDF 320 mcg/9 mcg twice daily, whereas both Rennard 2009 and Tashkin 2008 included two combined inhaler active treatment arms: BDF 320 mcg/9 mcg twice daily and 160 mcg/9 mcg twice daily. The two studies of MF/F, Doherty 2012 and Tashkin 2012, also included two combined inhaler active treatment arms: 400/10 twice daily and 200/10 twice daily.

The nature of the run-in period varied between studies, but studies generally included a two- to four-week washout period from inhaled long-acting medication. In one study, all participants had a two-week run-in treatment with oral corticosteroids, inhaled formoterol and as required a short acting $beta_2$-agonist (SABA) (Calverley 2003). Full details are given in the tables of included studies.

Concomitant therapy was as-needed SABA, short-acting muscarinic antagonists (SAMA) and, in some studies, tiotropium. In five studies, theophylline was also used. Eleven per cent of participants in Hanania 2003 and all 18 participants in Dal Negro 2003 received theophylline, in addition to the study drugs. One participant in the FPS group in Bourbeau 2007 used theophylline. The exact proportion of participants in TRISTAN who were taking theophylline was not reported. In Zheng 2006, 2.7% of the active treatment group used theophylline compared with 7.4% of the placebo group. Oral steroids and/or antibiotics were used in all studies in the case of exacerbations.

### *Duration*

- 13 weeks or less: Barnes 2006; Bourbeau 2007; O'Donnell 2006; Sin 2008; SCO104925.
- 24 to 26 weeks: Doherty 2012; Hanania 2003; Mahler 2002; Tashkin 2008; Tashkin 2012; Zheng 2006.
- 52 weeks: Calverley 2003; Dal Negro 2003; SFCT01; Szafranski 2003; Rennard 2009; TRISTAN.
- 130 weeks: Lapperre 2009.
- 156 weeks: TORCH.

### *Outcomes*

The definition of an exacerbation varied between the included studies, and all definitions are summarised in Appendix 2. Hanania 2003 and Mahler 2002 withdrew participants whose condition was exacerbated. Lung function, if reported, was measured as $FEV_1$ or peak expiratory flow (PEF). Quality of life assessment by SGRQ or CRDQ was available for Calverley 2003; Doherty 2012; Hanania 2003; Mahler 2002; Rennard 2009; SFCT01; Szafranski 2003; Tashkin 2008; Tashkin 2012; TORCH; TRISTAN; and Zheng 2006. In addition, breathlessness, cough and sputum score (BCSS) was reported by Rennard 2009 and Tashkin 2008. All-cause mortality was reported by TORCH.

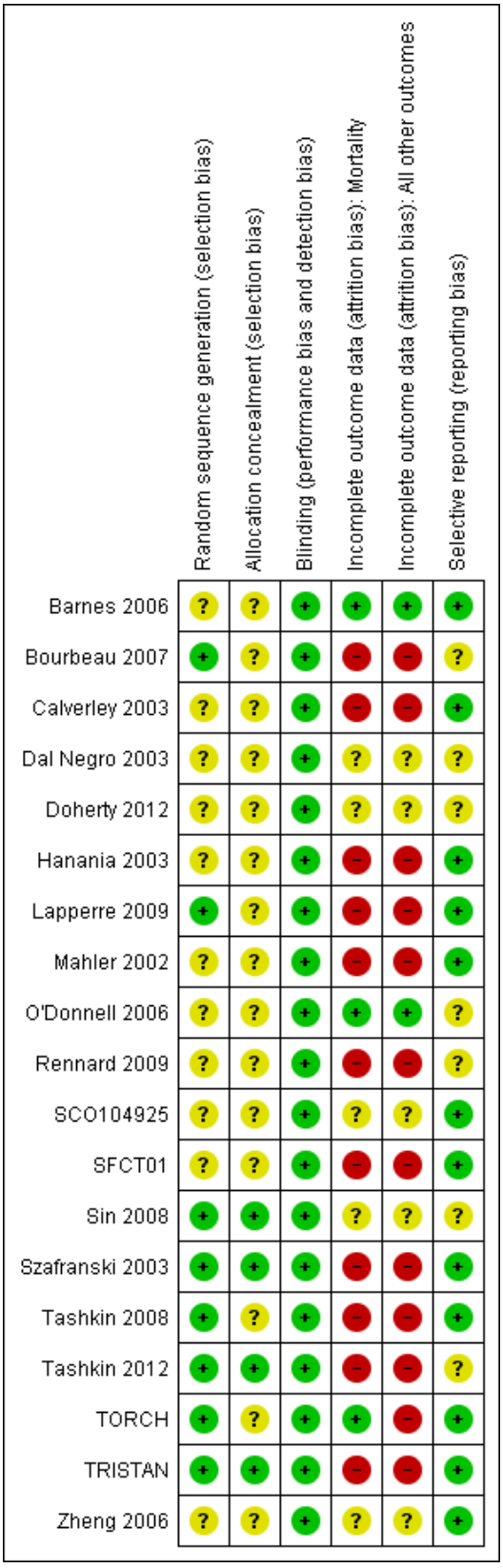
### Excluded studies

Studies that did not meet the entry criteria of this review are listed in Characteristics of excluded studies, together with a reason for exclusion.

## Risk of bias in included studies

A summary of the risk of bias assessment for each trial is provided in Figure 1.

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



### Allocation

Most of our judgements on allocation procedures were unclear because of the paucity of information provided in the trial reports. We were able to ascertain a low risk of bias in four large studies (Szafranski 2003; Tashkin 2012; TORCH; TRISTAN) and in one smaller study (Sin 2008). However, as most included studies are industry-sponsored, they are extremely likely to have followed gold standards for both random sequence generation and concealment of allocation and therefore to be at low risk of bias.

### Blinding

All studies were 'double-blinded', and the authors stated that identical inhaler devices were used to deliver active treatment and placebo; they therefore are likely to be at low risk of performance and detection bias. However, in all trials, further details of participant and assessor blinding were not given.

### Incomplete outcome data

Most studies had high attrition rates and therefore were deemed to be at unclear or high risk of bias for all outcomes, including mortality. The TORCH trial, however, attempted to follow up all participants for their vital status and therefore was deemed to be at low risk of bias for this outcome. It should be noted that attrition rates reported in the included studies are in keeping with, if not lower than, those expected in COPD trials; therefore these studies are at low risk of bias when compared with similar trials in this field.

### Selective reporting

Most included studies reported all prespecified outcomes and were deemed to be at low risk of reporting bias. However, as pointed out in feedback received, the trial protocol of the largest included study, TORCH, was submitted and published after recruitment of participants (Vestbo 2004).

### Other potential sources of bias

Both SCO104925 and SFCT01 are pharmaceutical company reports that have not been published in the peer-reviewed literature. However, the trials were sufficiently described to warrant their inclusion and are likely to be at low risk of bias.

## Effects of interventions

See: **Summary of findings for the main comparison** Combined inhalers versus placebo (primary outcomes) for chronic obstructive pulmonary disease; **Summary of findings 2** Fluticasone/salmeterol (FPS) versus placebo for COPD; **Summary of findings 3** Budesonide/formoterol (BDF) versus placebo for COPD; **Summary of findings 4** Mometasone/formoterol (MF/F) versus placebo for COPD

### Primary outcomes

#### *Rate of exacerbations*

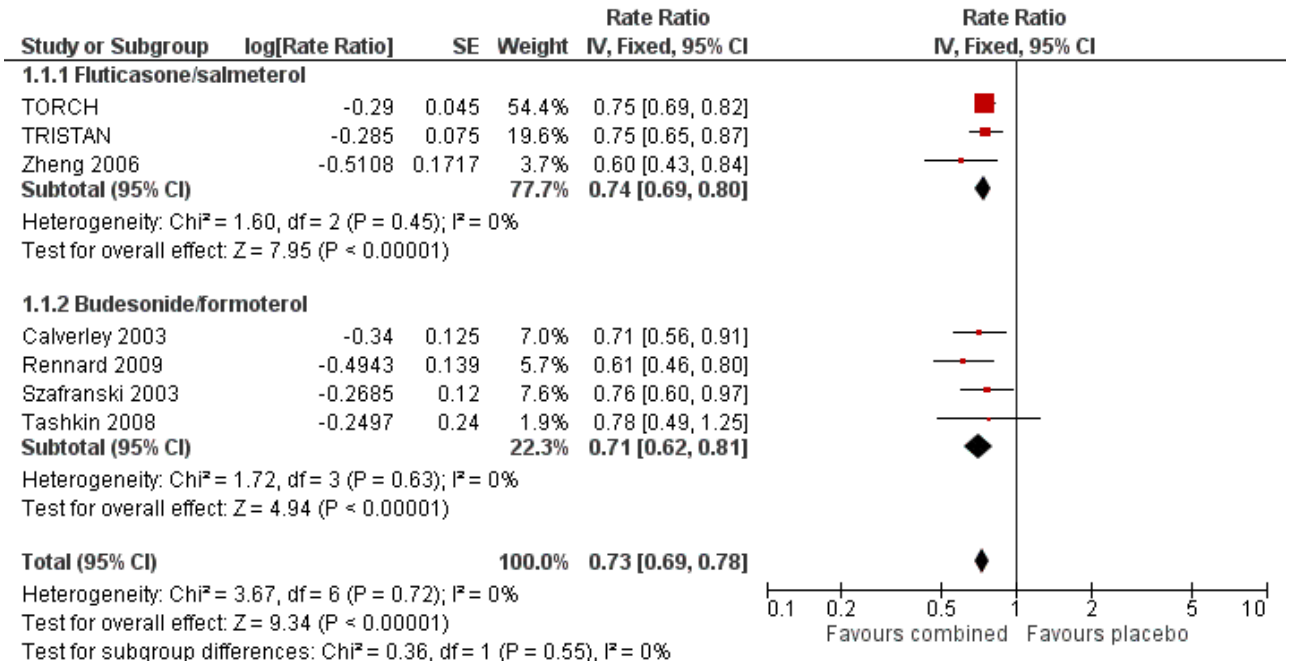
##### Pooled results of all combined inhalers versus placebo

When data from seven trials (N = 7495) were pooled, the overall reduction in the rate of exacerbations when FPS or BDF was used was 0.73 (95% CI 0.69 to 0.78; Analysis 1.1); the quality of this evidence when GRADE criteria were used was rated as moderate (Summary of findings for the main comparison).

##### FPS versus placebo

A significant reduction was noted in the rate of exacerbations with combination therapy when compared with placebo (RR 0.74, 95% CI 0.69 to 0.80, three studies, 4255 participants; Analysis 2.1). This result was not altered by removing TRISTAN, a study for which the summary estimate may have been biased by inadequate adjustment for between-participant variability (Suissa 2006); see Figure 2. Additional analyses were performed on exacerbations with specific definitions. Compared with placebo, FPS led to fewer exacerbations requiring oral steroids (RR 0.57, 95% CI 0.52 to 0.63, three studies), less requirement for antibiotics (RR 0.60, 95% CI 0.41 to 0.88) and fewer hospitalisations (RR 0.83, 95% CI 0.7 to 0.97, two studies).

**Figure 2. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.1 Exacerbation rates with combined inhalers versus placebo.**




#### BDF versus placebo

A significant effect on pooled exacerbation rates favoured BDF compared with placebo (RR 0.71, 95% CI 0.62 to 0.81); see Figure 2. These results are based on data on 3240 participants from four trials (Szafranski 2003; Calverley 2003; Rennard 2009 and Tashkin 2008).

### *Number of people experiencing at least one exacerbation*

#### FPS versus placebo

No significant difference was noted between FPS and placebo in terms of the number of participants experiencing at least one exacerbation (OR 0.83, 95% CI 0.64 to 1.07, seven studies, 1817 participants; Analysis 2.2)

#### MF/F versus placebo

The odds ratio for the numbers of participants experiencing at least one exacerbation for the 400/10 strength inhaler was 0.72 (95% CI 0.54 to 0.95, 882 participants; Doherty 2012; Tashkin 2012) and 0.76 (95% CI 0.58 to 1.01) for the 200/10 strength inhaler (886 participants; Doherty 2012; Tashkin 2012).

The point estimates are very similar, and the test for subgroup differences is negative. Thus it cannot be inferred from these results that one strength inhaler is significantly different from another ($Chi^2 = 0.10$, df = 1, P = 0.75, $I^2 = 0\%$).

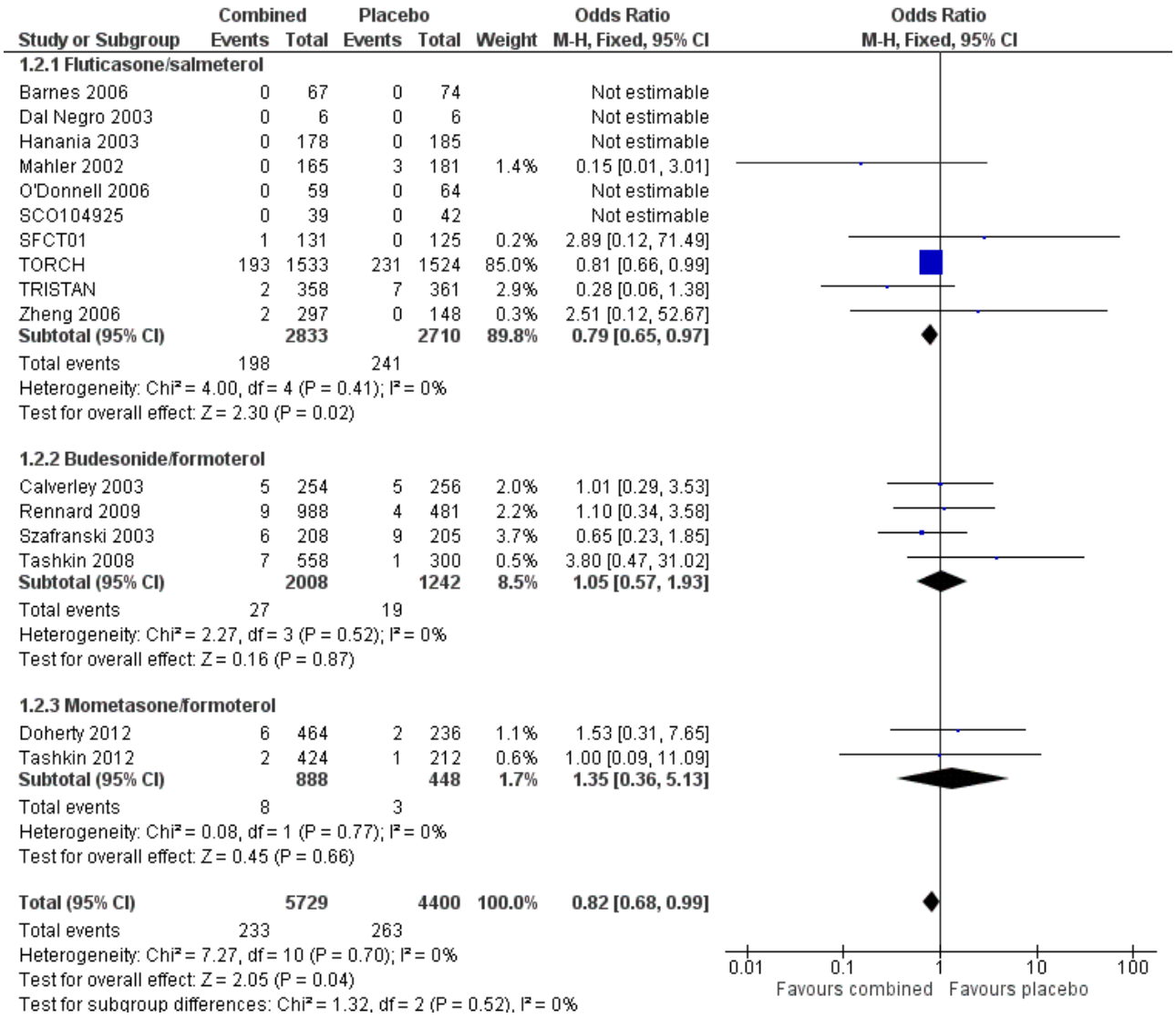
Of interest, a post hoc observation was made that the treatment effect is more pronounced when only participants with moderate or severe exacerbations are considered, that is, those requiring antibiotics and/or systemic steroids, emergency treatment or hospitalisation (OR 0.57, 95% CI 0.38 to 0.86 for 400/10; and OR 0.62, 95% CI 0.42 to 0.92 for 200/10; Analysis 4.2).

### *Mortality*

#### Pooled results of all combined inhalers versus placebo

When results were pooled, the overall reduction in mortality with FPS, BDF or MF/F compared with placebo was 0.82 (95% CI 0.68 to 0.99, 16 studies, N = 10,129); the quality of this evidence was rated as moderate (Summary of findings for the main comparison). Most of the weight for mortality comes from the TORCH trial, which is the only included trial that collected mortality as a primary outcome (Figure 3).

**Figure 3. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.2 Mortality.**




Because differing length of follow-up across studies hinders the calculation of a pooled NNTB, we have tabulated this for each study individually (see Table 2). The three-year NNTB (using the baseline risk of 15.2% in the placebo arm of TORCH) to prevent one extra death is 42 (95% CI 24 to 775).

#### FPS versus placebo

The adjusted hazard ratio (HR) from TORCH did not identify a significant effect of FPS over placebo (HR 0.825, 95% CI 0.681 to 1.002, P = 0.052; TORCH). When the number of deaths in each treatment group was analysed by odds ratio and was combined with data from four other studies, a significant reduction in the odds of death favoured FPS versus placebo (OR 0.79, 95% CI 0.65 to 0.97, N = 5543, 10 studies; Analysis 2.5). Data were separated according to the time point and were subgrouped for data reported at three years, data at one to three years, data at one year and data at six months.

#### BDF versus placebo

The four studies with duration of six months to one year involving 3250 participants did not detect a significant difference in mortality between BDF and placebo (OR 1.05, 95% CI 0.57 to 1.93; Analysis 3.3).

#### MF/F versus placebo

Neither of two very similar studies (Doherty 2012; Tashkin 2012) of 26 weeks' duration and including 1336 participants detected a significant difference between MF/F and placebo (OR 1.35, 95% CI 0.36 to 5.13; Analysis 4.3).

However, it should be noted that the confidence intervals for both MF/F and BDF are wide and overlap with those of FPS, so a decrease in mortality with MF/F or BDF cannot be excluded.

### *Pneumonia*

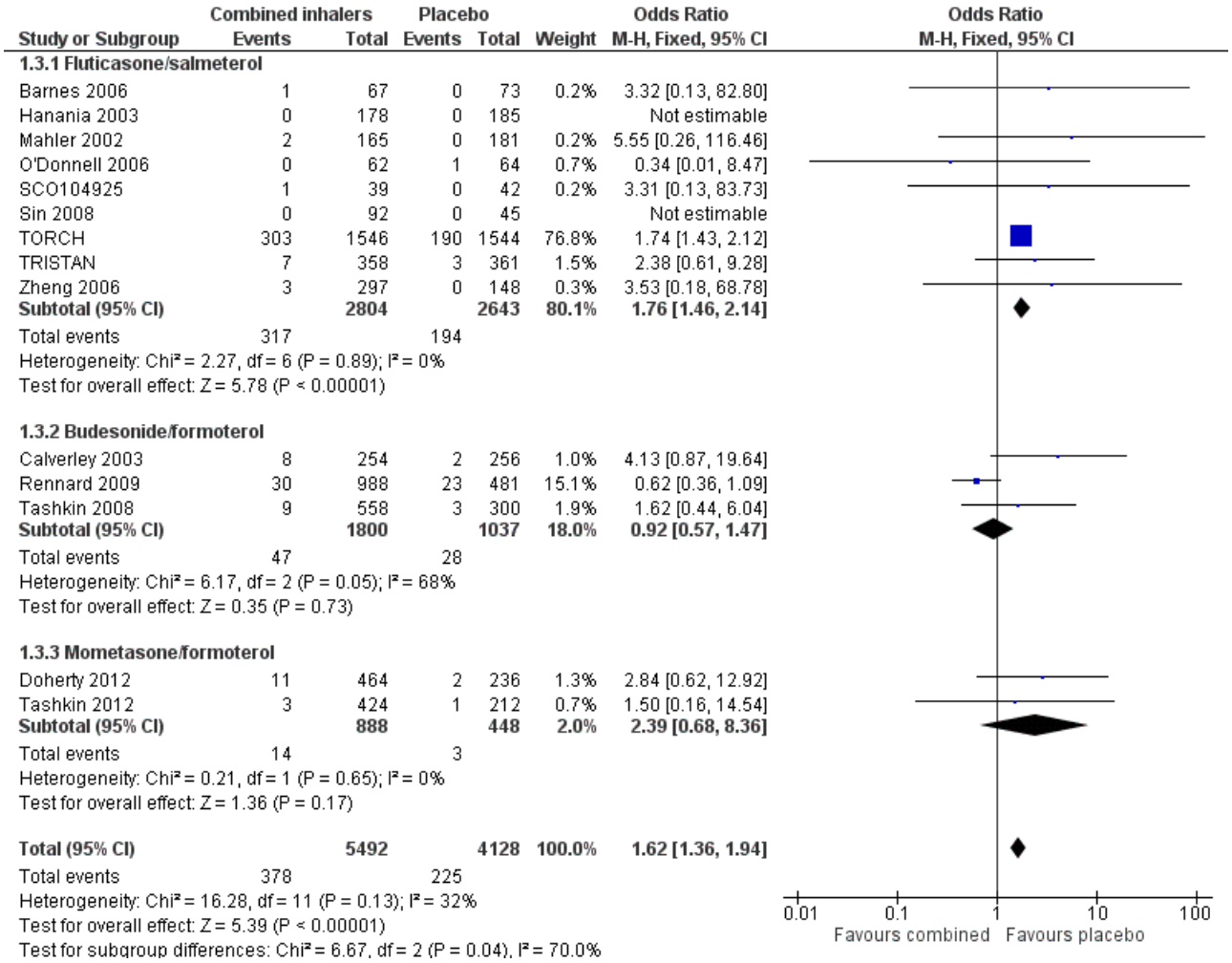
#### Pooled results of all combined inhalers versus placebo

For combined inhalers, the pooled OR for pneumonia is 1.62 (95% CI 1.36 to 1.94, N = 9620, fixed-effect model) with a moderate level of heterogeneity ($I^2$ = 32%); the quality of this evidence was rated as moderate (Summary of findings for the main comparison). When a random-effects model of analysis is used, the effect size is reduced but remains significant (OR 1.57, 95% CI 1.01 to 2.42). Most of the weight for this combined result again comes from the TORCH trial, which tested the FPS inhaler.

#### FPS versus placebo

Pooled data from nine FPS trials (N = 5447) show a significant increase in pneumonia among participants treated with FPS in comparison with placebo (OR 1.76, 95% CI 1.46 to 2.14; Figure 4).

**Figure 4. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.3 Pneumonia.**




#### BDF versus placebo

Calverley 2003, Rennard 2009 and Tashkin 2008 reported data on pneumonia; no significant difference was detected between BDF and placebo (OR 0.92, 95% CI 0.57 to 1.47). The test for subgroup differences between BDF and FPS was significant (P = 0.01) when a fixed-effect model was used. However, when a random-effects model was applied, no significant difference between subgroups was found (P = 0.65).

#### MF/F versus placebo

Data from Doherty 2012 and Tashkin 2012 suggest no significant difference between treatments in diagnoses of pneumonia (OR 2.39, 95% CI 0.68 to 8.36, N = 1336), but the test for a subgroup difference between MF/F and FPS was negative for both fixed-effect and random-effects models (P = 0.64 and 0.66, respectively).

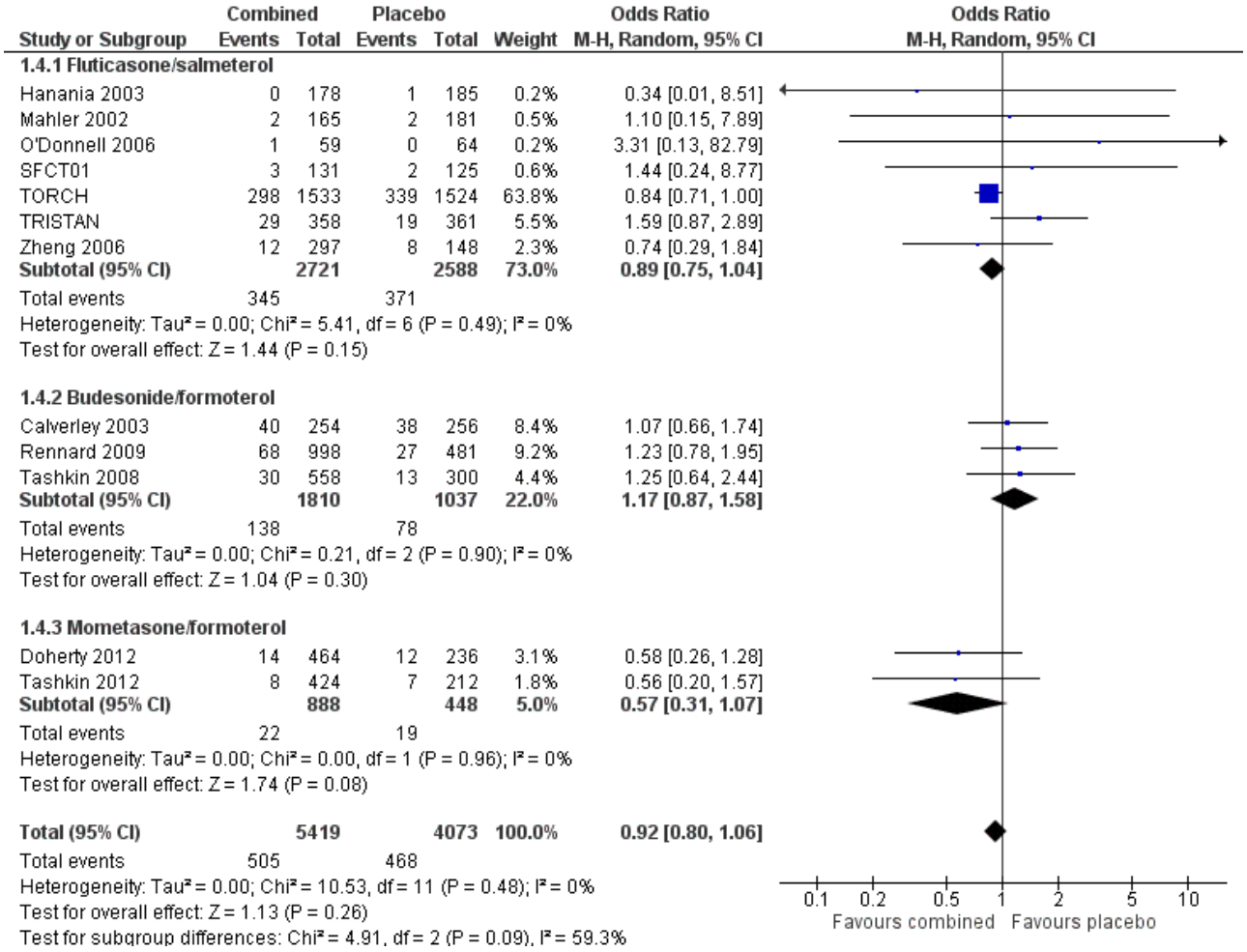
Table 2 gives the range of numbers needed to treat for an additional harmful outcome (NNTH) across the studies for pneumonia. A pooled NNTH was not calculated because of the wide differences in duration and the likely impact this would have on the calculation of a pooled event rate. The three-year NNTH (when the baseline risk of 12.3% was used in the combination therapy arm of TORCH) for one extra participant to suffer from pneumonia was 17 (95% CI 27 to 12).

### *Hospitalisations due to COPD*

#### Pooled results of combined inhalers versus placebo

No significant difference was observed between active treatment and placebo for hospitalisation (OR 0.93, 95% CI 0.81 to 1.06, N = 9492; Figure 5); the quality of this evidence was rated as low (Summary of findings for the main comparison).

**Figure 5. Forest plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.4 Hospitalisations due to COPD exacerbations.**




## Secondary outcomes

### *Quality of life*

#### FPS versus placebo

Treatment with FPS improved SGRQ scores by an average of -2.9 units versus placebo (95% CI -3.61 to -2.18, four studies, N = 3346). Pooled data from Mahler 2002 and Hanania 2003 indicated a statistically significant improvement in CRDQ for those treated with FPS compared with placebo (5 units, 95% CI 2.48 to 7.52).

#### BDF versus placebo

A significant effect favoured BDF compared with placebo: -3.29 units on the SGRQ (95% CI -4.45 to -2.13) for the 320/9 strength inhaler, and -3.39 units (95% CI -4.70 to -2.07) for the 160/9 strength inhaler. A high level of heterogeneity was noted when these data were pooled ($I^2$ = 70%). Random-effects modelling also generated a significant effect (MD -4.11, 95% CI -6.18 to -2.04 for 320/9; and MD -3.39, 95% CI -4.70 to -2.07 for 160/9). The magnitude of improvement in the Szafranski 2003 BDF group was 3.9 units from baseline and was not dissimilar from the change scores from post run-in treatment in Calverley 2003 (see graphical presentation of data in the published article, page 916). However, the placebo group deteriorated more in Calverley 2003, which possibly reflects the withdrawal of active treatment, with the subsequent loss of predosing effects achieved with high-dose oral corticosteroids and LABA. In comparison, BDF may have maintained the predosing treatment effects of quality of life more successfully.

#### MF/F versus placebo

Treatment with MF/F resulted in a significant improvement in SGRQ scores when compared with placebo. This was true for both 400/10 (MD -3.80, 95% CI -5.75 to -1.86) and 200/10 (MD -3.91, 95% CI -6.01 to -1.81) inhalers.

### *Symptom score*

#### FPS versus placebo

FPS led to improved symptom scores (transitional dyspnoea index) when compared with placebo (MD 1.04, 95% CI 0.56 to 1.53).

#### BDF versus placebo

Data were pooled for Calverley 2003 and Szafranski 2003. There was a significant effect in favour of BDF when compared with placebo (MD -0.63, 95% CI -0.90 to -0.37).

Rennard 2009 and Tashkin 2008 reported change from baseline in the breathlessness, cough and sputum score. Both trials described a significant improvement in average score over the treatment period for both strengths of combined inhalers (MD -0.43, 95% CI -0.59 to -0.26 for 320/9; and MD -0.44, 95% CI -0.60 to -0.28 for 160/9).

### *Lung function*

#### FPS versus placebo

Pooled analysis of data was conducted without findings from the Dal Negro 2003 study. Owing to the small size of this study, we were concerned that the standard deviation (SD) represented an inaccurate estimate for the SD of the population, and that the small variance increased the weight of the study out of all proportion to its size. Data pooled from seven studies revealed an MD in predose $FEV_1$ of 0.16 L (95% CI 0.14 to 0.19, N = 1408). Pooled data from Zheng 2006 and TORCH for postdose $FEV_1$ indicated a significant improvement in favour of FPS over placebo of 0.09 L (95% CI 0.07 to 0.11). Results from Rennard 2009 demonstrate a clear improvement in average 0- to 12-hour $FEV_1$ for inhalers of both strengths.

#### BDF versus placebo

$FEV_1$ data for mean percentage change from baseline were reported by two trials (Calverley 2003; Szafranski 2003). There was a significant increase in $FEV_1$ in favour of BDF versus placebo (MD 14.40% 95%CI 11.91 to 16.90).

Predose $FEV_1$ and one hour postdose $FEV_1$ data were reported by one study, which included 858 participants (Tashkin 2008). A significant improvement was noted for both outcomes for combined inhalers of both strengths compared with placebo. Rennard 2009 reported average 12-hour $FEV_1$ and $FEV_1$ at 12 hours compared with baseline. Again, a significant improvement was noted for both outcomes and for inhalers of both strengths when compared with placebo.

Both Rennard 2009 and Tashkin 2008 reported change from baseline morning and evening PEF, with significant benefit over placebo noted for inhalers of both strengths.

#### MF/F versus placebo

Both Doherty 2012 and Tashkin 2012 reported mean change from baseline in predose $FEV_1$ at 13 weeks and demonstrated a significant improvement for both 400/10 (MD 114.64, 95% CI 77.79 to 151.50) and 200/10 (MD 66.00, 95% CI 14.37 to 117.63) inhalers when compared with placebo. It should be noted that no significant difference was seen between the 400/10 and 200/10 groups (test for subgroup differences: $Chi_2 = 2.77$, df = 1, P = 0.10).

Mean change from baseline $FEV_1$ area under the curve (AUC) 0 to 12 hours is also reported by Doherty 2012 and Tashkin 2012 and shows significant improvement in favour of active treatment for inhalers of both strengths (MD 162.04, 95% CI 126.54 to 197.53 for 400/10; and MD 122.01, 95% CI 86.64 to 157.39 for 200/10).

### *Rescue medication*

#### FPS versus placebo

Pooled data from Mahler 2002 and Hanania 2003 indicated a significant reduction in mean puffs per day of short-acting $beta_2$-agonist usage for FPS versus placebo (MD -1.19 puffs/d, 95% CI -1.83 to -0.55).

Mahler 2002 reported significant increases in the percentage of nights with no awakenings requiring short-acting $beta_2$-agonist in favour of FPS versus placebo (5.7% vs -4.3%, respectively; P < 0.031).

TRISTAN reported a significant difference in median percentage of days without use of relief medication (FPS 14% vs placebo 0%, P < 0.001).

#### BDF versus placebo

BDF treatment reduced the requirement for reliever medication when compared with placebo. Combined results of Szafranski 2003; Calverley 2003; Rennard 2009 and Tashkin 2008 for the 320/9 strength inhaler show a reduction in use of rescue medication when compared with placebo (-0.98 puffs/d, 95% CI -1.18 to -0.79). Pooled results from Rennard 2009 and Tashkin 2008 compare the 160/9 strength inhaler with placebo and also reveal a reduction in the use of rescue medication (-1.28 puffs/d, 95% CI -1.55 to -1.00)

### *Safety and tolerability*

#### FPS versus placebo

No significant difference was noted between FPS and placebo in the occurrence of overall reported adverse events (OR 1.09, 95% CI 0.95 to 1.25) or serious adverse events (OR 1.08, 95% CI 0.95 to 1.23, N = 5574, nine studies). In both cases, the quality of evidence was rated as low (Summary of findings 2).

Pneumonia, candidiasis, nasopharyngitis, hoarseness and upper respiratory tract infection (URTI) occurred more frequently among FPS-treated participants.

- Pneumonia: OR 1.80, 95% CI 1.49 to 2.18, nine studies, N = 5447.
- Candidiasis: OR 5.73, 95% CI 3.07 to 10.67, seven studies, N = 2039.
- Hoarseness: OR 8.79, 95% CI 1.11 to 69.62, two studies, N = 585.
- Nasopharyngitis: OR 1.28, 95% CI 1.05 to 1.56, two studies, N = 3535.
- URTI: OR 1.23, 95% CI 1.04 to 1.47, five studies, N = 4963.

#### BDF

Rennard 2009 and Tashkin 2008 report overall adverse event data and demonstrate a significant difference favouring placebo for inhalers of both 320/9 and 160/9 strength (OR 1.42, 95% CI 1.16 to 1.74 for 320/9; and OR 1.32, 95% CI 1.08 to 1.61 for 160/9). In both cases, the quality of this evidence was rated as low (Summary of findings 3).

When only serious adverse events were considered, the odds ratios were 1.17 (95% CI 0.95 to 1.45) for the 320/9 strength inhaler and 1.20 (95% CI 0.89 to 1.63) for the 160/9 strength inhaler; again, the quality of this evidence was rated as low (Summary of findings 3).

No difference was noted between active treatment and placebo for specific adverse events associated with ICS use, with the exception of reported episodes of candidiasis, which were noted to be significantly higher among those receiving active treatment. In addition, more cases of dysphonia were reported in the active treatment group receiving the higher-dose inhaler, but not in the lower-dose group. However, the test for subgroup differences was negative, so we cannot be certain of a dose effect.

#### MF/F

No significant difference in the occurrence of overall reported adverse events was reported between either strength of MF/F inhaler and placebo (OR 0.98, 95% CI 0.75 to 1.30 for 400/10; and OR 0.82, 95% CI 0.62 to 1.09 for 200/10). This finding was consistent when only serious adverse events were considered. The quality of this evidence was rated as low in both cases (Summary of findings 4).

Also, no significant differences were noted between the groups when specific adverse events associated with ICS use were considered, although the overall numbers of events were small.

### *Withdrawals*

#### FPS versus placebo

Significantly fewer withdrawals from treatment were seen with FPS than with placebo (OR 0.69, 95% CI 0.62 to 0.78). Withdrawals due to adverse events and lack of efficacy also occurred less frequently on treatment with FPS than with placebo (withdrawal due to adverse event: OR 0.74, 95% CI 0.64 to 0.86, twelve studies, 5491 participants; withdrawal due to lack of efficacy: OR 0.30, 95% CI 0.22 to 0.41, eight studies, 5115 participants).

#### BDF versus placebo

Data were pooled from Calverley 2003; Rennard 2009; Szafranski 2003; and Tashkin 2008 for withdrawals due to adverse events, and from Calverley 2003; Rennard 2009 and Szafranski 2003 for withdrawals due to lack of efficacy or worsening COPD.

A significant difference favoured active treatment in withdrawals due to worsening of COPD symptoms when BDF was compared with placebo (OR 0.56, 95% CI 0.43 to 0.74, three studies, 2392 participants).

No significant difference was noted between BDF and placebo in the likelihood of withdrawal due to any adverse event (OR 0.85, 95% CI 0.70 to 1.03).

#### MF/F versus placebo

Significantly fewer withdrawals from treatment were seen with MF/F than with placebo for inhalers of both strengths (OR 0.56, 95% CI 0.40 to 0.77 for 400/10; and OR 0.55, 95% CI 0.40 to 0.76 for 200/10).

Of note, a significant difference favoured MF/F when withdrawals due to lack of efficacy of treatment or worsening of COPD symptoms were considered. This was true for inhalers of both strengths (OR 0.24, 95% CI 0.08 to 0.74 for 400/10; and OR 0.31, 95% CI 0.11 to 0.84 for 200/10).

## DISCUSSION

### Summary of main results

We reviewed data from 19 randomised controlled trials (10,400 participants) assessing the efficacy and safety of combined inhaled corticosteroids and long-acting beta$_2$-agonists versus placebo for the treatment of COPD. Thirteen studies involved a combined inhaler of fluticasone and salmeterol, four involved budesonide and formoterol and two involved mometasone and formoterol. The findings of this review complement those of two others assessing the effects of combination inhalers with their components, that is, LABA or ICS (Nannini 2012; Nannini 2013). Despite the addition of eight new studies for this update, most of the weight is still coming from the TORCH study, which is the largest trial of combined therapy (FPS) in COPD.

### Primary outcomes

The main findings related to the primary outcomes of exacerbations, mortality, pneumonia and hospitalisations appear in the Summary of findings for the main comparison. All eligible studies addressed at least one of the primary outcomes.

Combined therapy reduced the rate of moderate exacerbations compared with placebo by about a quarter (Analysis 1.1). But, as was found in the Cochrane reviews comparing combined inhalers with LABA alone or ICS alone (Nannini 2013), this did not translate to a statistically significant reduction in COPD hospitalisation rates. One explanation is that those receiving combined treatment who respond may have fewer and/or milder exacerbations, but equally the smaller number of hospitalisations means that less statistical power was present to show a significant difference. On the other hand, adverse effects were more common with combined treatment than with placebo, particularly the development of pneumonia. The NNTH for this outcome in studies of at least 52 weeks' duration varied from 17 to 197. Concern about pneumonia as an adverse event associated with ICS treatment has persisted ever since TORCH was published in 2006. Indeed our analysis shows that the excess of pneumonia is seen only with FPS, not with the other combined inhalers. If the TORCH study was not included, the significant OR disappeared, but heterogeneity among trials is still evident (Analysis 1.3), making it difficult to decide whether this effect is a true one. This may suggest ongoing difficulties with the accurate identification of pneumonia, or variations in participant populations, actions of medicines or the nature of lower respiratory tract infections and their treatment over the time course of a study. It is also possible that the heterogeneity in the pneumonia outcome is due to differential withdrawal rates. Withdrawal due to lack of efficacy in the FPS subgroup was greater in the placebo arm (Analysis 2.14), as was seen with BDF (Analysis 3.18) and MF/F studies (Analysis 4.8). It is interesting to note that withdrawals due to adverse events were not different between arms in BDF (Analysis 3.17), whereas for MF/F studies, withdrawals due to adverse events were greater in the placebo arm (Analysis 4.9). These findings suggest something different about the three-year TORCH study compared with the others. Whatever the case, it is reassuring that this apparent excess of pneumonia cases did not translate into greater numbers of hospitalisations or exacerbations, or greater

mortality rates. In fact, quite the opposite was noted—exacerbation rates and mortality were reduced with combined treatment.

We found that treatment with a combined inhaler led to a significant reduction in mortality compared with placebo when data from all studies were pooled. As with other outcomes, TORCH had a major influence on mortality; however, it should be noted that the TORCH investigators did not claim a significant reduction in mortality with FPS over placebo (P = 0.052). The difference between the study report and the OR reported in this Cochrane review may be due to variations in statistical methods. TORCH used a hazard ratio that was adjusted for repeated measurement. This analysis has been the subject of some debate as the study adopted a factorial design but did not report a factorial analysis (see Feedback 1, Feedback 2). Furthermore, although mortality was recorded in many of the studies, it was a primary outcome in TORCH. In that study, cause-specific mortality was also reported, but the definition of a primary cause of death continues to pose challenges in a population of patients who may suffer from co-morbidities such as lung cancer (McGarvey 2007).

### Secondary outcomes

We were unable to pool secondary outcomes and reported results for each type of combined inhaler separately. Although the only way to test whether one product is better than another is a head-to-head comparison, we found that the results for all secondary outcomes, except adverse events, were relatively similar, that is, each combined inhaler showed a small benefit over placebo in effects on health-related quality of life, symptoms, lung function, use of rescue medication and withdrawal rates. In some cases, the benefits reached accepted levels of clinical significance, but only just. Minimal clinical important differences (MCID) are sometimes used to help clinicians interpret trial findings in a meaningful way. The MCID for predose $FEV_1$ is thought to be approximately 100 mL (Donohue 2005). Leidy 2003 suggests that changes of 1.0 in the BCSS represent substantial symptomatic improvement, changes of approximately 0.6 can be interpreted as moderate and changes of 0.3 can be considered small. A four-unit difference is the generally accepted MCID for SGRQ score (Jones 2005). Mean differences reflect an unknown range of results from individual participants, and although an MCID may be achieved on average, this neither confirms nor rules out meaningful improvement over placebo for all. Furthermore, for some of these outcomes, a high degree of heterogeneity was noted, some of which may be due to differences in study protocols.

## Overall completeness and applicability of evidence

Participants and outcomes reported were typical of those described for COPD patients. The most abundant evidence comes from studies on the FPS combination, which was the only one to show a mortality benefit. Fewer data are available for the MF/F combination, but nothing has been discovered to suggest that it behaves differently from the other inhalers.

This review addresses the efficacy and safety of combined ICS and LABA in one inhaler versus placebo as a pair-wise comparison. We did not seek to address the efficacy of the individual components (LABA and ICS) versus combined treatment, although such comparisons were included in some of studies in this review, notably the TORCH trial. In this large trial, it appears that the mortality benefit, while not reaching statistical significance, is driven largely by the LABA component of combined therapy. The efficacy of the individual components versus combined therapy is addressed in two linked Cochrane reviews (Nannini 2012; Nannini 2013) and will be included in a forthcoming network meta-analysis (Oba 2017).

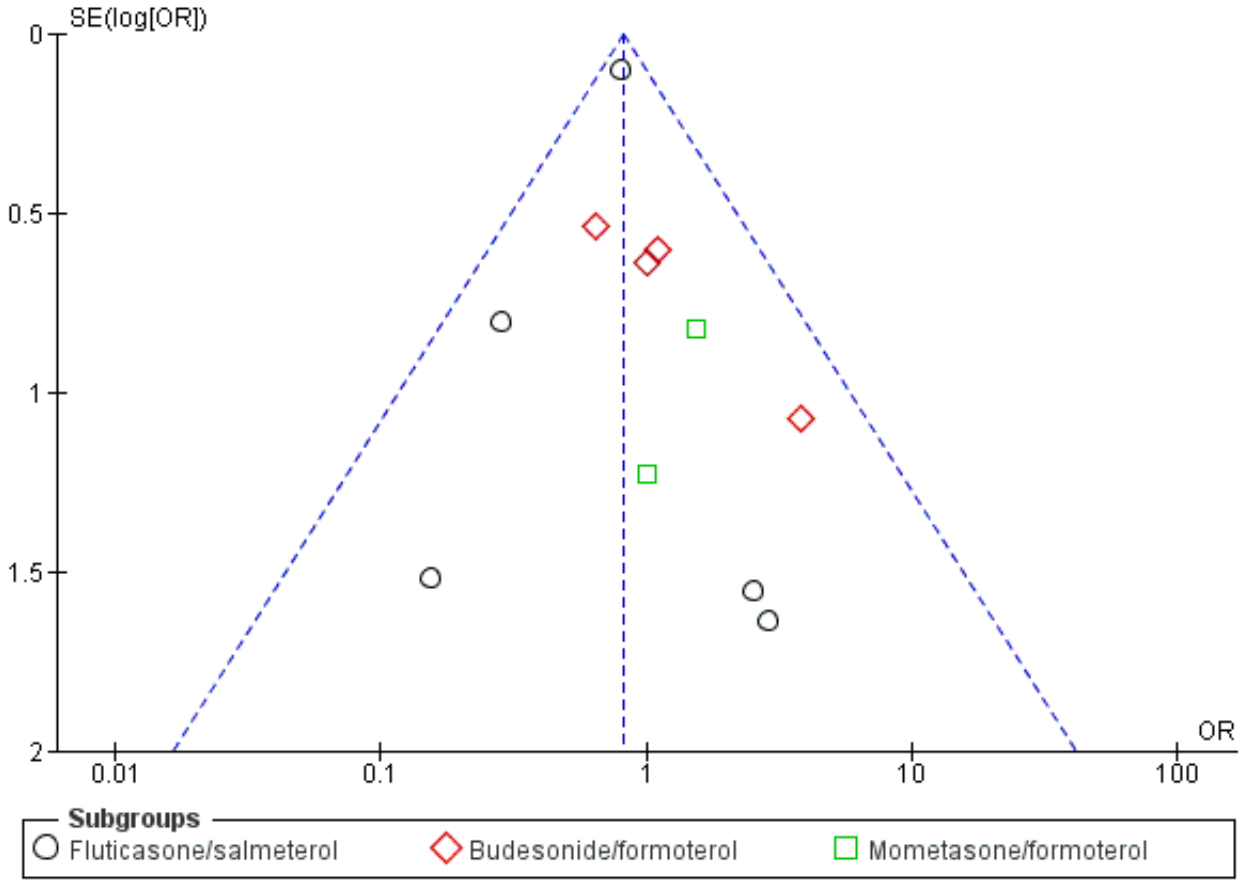
## Quality of the evidence

Most trials were industry-sponsored. The risk of bias in blinding was considered low for all trials. The risk of bias from attrition was considered higher because of the number of participants withdrawn (over 20% in most trials), especially as this group may represent a more severely involved subgroup (Kesten 2007). In addition, we found significantly greater participant withdrawal in the placebo arm across all three combined inhalers (Analysis 2.12, Analysis 3.16 and Analysis 4.7). However, the completion rate in the included trials was generally equal to, or better than, that of other trials involving participants with COPD. Selective reporting was generally considered to be of low risk.

Intention-to-treat analyses were conducted in all studies, but for outcomes such as mean exacerbation rates, withdrawal of severe frequent exacerbators from the studies may have distorted study findings because of the lower exacerbation rates seen with active treatment. Loss of participants with more frequent exacerbations from the studies may thus limit the accuracy of mean event rates. The question of exacerbations and the appropriate statistical analysis of rate ratios cast some doubt regarding the validity of some of the findings in this review. In particular, the large long-term studies (i.e. those in excess of six months), which are adequately powered to detect statistically significant findings, may overestimate the treatment effects of this therapy (Suissa 2006). The method of weighting counts of exacerbations as described by Suissa 2006 (using duration of person follow-up time as a denominator in calculating the mean group rate of exacerbations rather than an unweighted approach) was undertaken in Calverley 2003; Szafranski 2003;and TORCH. In these studies, the effects were consistent and significantly favoured combination therapy over placebo. However, the major primary outcome after mortality rate was hospitalisation due to COPD exacerbation, and this did not show any difference between treatments.

Visual inspection of a funnel plot for the mortality outcome does not suggest publication bias (Figure 6).

**Figure 6. Funnel plot of comparison: 1 Combined inhalers versus placebo (primary outcomes), outcome: 1.2 Mortality.**




### Potential biases in the review process

The Cochrane Airways Group provided an excellent level of support in the identification of potentially relevant trials. To minimise the risk of selection and publication bias, an exhaustive search of the published literature and the unpublished literature, with no language restrictions, for potentially relevant clinical trials was underpinned by a systematic search strategy. Trial selection and data extraction followed a prespecified protocol, and the process was independently conducted by two review authors. Nevertheless, we acknowledge that additional unidentified trials may exist.

### Agreements and disagreements with other studies or reviews

This Cochrane review confirms and builds upon an earlier one (Nannini 2004) and upon related reviews (Nannini 2012; Nannini 2013). For this update, we checked all previous data and added hospital admissions using COPD-related serious adverse events as a surrogate marker. To enhance clarity, several outcomes in the FPS subgroup with few contributing studies have been deleted from the current update. We have added data for MF/F versus placebo, as these studies took place after the previous review.

Our finding that combined inhaler therapy reduced death is concordant with that of another review of all inhaled medications in COPD, which concluded that ICS/LABA was associated with the lowest risk of death among all treatments (Dong 2013).

## AUTHORS' CONCLUSIONS

### Implications for practice

For people with moderate or severe COPD, clinical benefit is derived when a long-acting beta$_2$-agonist and an inhaled corticosteroid are co-administered, compared with treatment with placebo, in terms of fewer exacerbations and possibly reduced risk of death. Furthermore, small benefits for quality of life and symptoms are noted. However, the effect of combined treatment on all-cause mortality is heavily weighted by one trial, which in itself was not reported to show a significant reduction. (This point added value to this review because the TORCH study alone did not achieve significance in mortality.) Despite positive effects on exacerbations and mortality, no effect on hospitalisation was reported. Moreover, a paradoxical finding indicates that fluticasone/salmeterol led to an increased risk of pneumonia. The NNTH to cause one additional case of pneumonia may be as low as 17, whereas the NNTB to prevent one death during the study period is 42.

Importantly, we have not commented on the relative contribution of the individual components of combined therapy to the effects identified, as this review presents only pair-wise comparisons between combined therapy and placebo. However, several

included studies comprise intervention arms in which the individual components are compared to placebo and to combined therapy, providing information about the contributions of the individual components. We also note the debate about the appropriateness of analysis conducted in the TORCH trial (Feedback 1, Feedback 2). Furthermore, whether a combination is better than the two components taken separately was not addressed in this review.

Guidelines suggest that patients with symptomatic moderate to severe COPD should be given LABA or LAMA and possibly ICS; therefore it could be argued that this review is redundant. However, this review increased the level of evidence supporting the use of combined therapy (LABA/ICS) in COPD category "D" (GOLD 2012). On the other hand, this review shows that use of a combination inhaler is not associated with large benefit in terms of symptoms or quality of life over placebo. The high attrition rate presented in many studies (in TORCH, 56% completed in the placebo group) could have overshadowed the benefits of those outcomes. Our review therefore supports the current widely accepted guidance for a stepwise approach to treatment of patients with mild or moderate disease. Combined therapy seems best indicated for COPD patients with post-bronchodilator $FEV_1$ < 60% and frequent exacerbations and/or hospitalisations.

### Implications for research

Any study should carefully document trial participants using the new GOLD COPD grading criteria. A more standardised approach to recording of serious adverse events such as pneumonia, hospitalisation, intensive care support or death would provide a more accurate picture of the benefits and harms of the long-term effects of this form of therapy.

Pharmacoeconomic analyses would be helpful to assist purchasers of health care in making decisions about the cost-effectiveness of combined inhalers. Responder analyses should be reported; this might give an idea as to which COPD phenotypes may provide the greatest benefit.

Assessment of BDF and MF/F in larger and longer trials is required to reveal whether these preparations confer benefits for mortality similar to those provided by FPS. Head-to-head trials of combined inhalers are needed if benefits are to be compared in a robust fashion. Network meta-analysis may help further elucidate the relative contribution of the individual components of combined therapy to the effects identified, in addition to the information already provided by the multi-arm trials such as TORCH.

Combined therapy should be compared with separate administration of long-acting $beta_2$-agonist and inhaled corticosteroid at different doses in large-scale multi-centre studies using a double-dummy design, to assess whether combined therapy confers benefits over the simple addition of $beta_2$-agonist to different doses of inhaled steroid treatment in separate inhalers. A lower dose of ICS might still confer therapeutic benefit while reducing the incidence of pneumonia. The high attrition rate reported in many studies might be contemplated in future studies, to maintain the capacity of calculated sample size to show significant differences in outcomes such as quality of life, hospitalisation and death rates.

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# REFERENCES

## References to studies included in this review

**Barnes 2006** *{published and unpublished data}*

Barnes NC, Qiu Y, Pavord I, Parker D, Johnson M, Thompson M, et al. Salmeterol/fluticasone propionate (SFC) anti-inflammatory effects in COPD [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego. 2005:B93 [Poster 320].

* Barnes NC, Qiu Y-S, Pavord ID, Parker D, Davis PA, Zhu J, et al. Antiinflammatory effects of salmeterol/fluticasone propionate in chronic obstructive lung disease. *American Journal of Respiratory & Critical Care Medicine* 2006;**173**(7):736-43.

Qiu Y, Parker D, Barnes NC, Johnson M, Pavord L, et al. The effect of salmeterol/fluticasone propionate (SFC) on eosinophils and mast cells in COPD [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego. 2005:A43 [Poster F36].

Qiu YS, Davis P, Zhu J, Peachey L, Barnes NC, Pavord I, et al. Anti-inflammatory effects of salmeterol/fluticasone propionate (SFC) on airway T-lymphocyte populations in COPD. *European Respiratory Journal* 2005;**26 Suppl 49**:203s.

Qiu YS, Davis P, Zhu J, Peachey L, Barnes NC, Pavord I, et al. Effects of salmeterol/fluticasone propionate (SFC) on airway inflammation in COPD: a placebo-controlled study of endobronchial biopsies. *European Respiratory Journal* 2005;**26 Suppl 49**:203s.

SCO30005. A 13-week, double-blind, parallel-group, multicentre study to compare the bronchial anti-inflammatory activity of the combination of salmeterol/fluticasone propionate (SERETIDE™/ADVAIR™/VIANI™) 50/500 mcg twice daily compared with placebo twice daily in patients with chronic obstructive pulmonary disease. http://www.gsk-clinicalstudyregister.com/quick-search-list.jsp?tab=results&letterrange=All&type=GSK+Study+ID&item=SCO30005&studyType=All&phase=All&status=All&population=All&marketing=All&country=All&studyId=SCO30005 (accessed 10 June 2013).

Zhu J, Qiu Y, Barnes NC, Johnson M, Pavord I, Jeffery PK. The effect of salmeterol/fluticasone propionate (SFC) on pro-inflammatory gene expression in COPD [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego. 2005:A43 [Poster F6].

**Bourbeau 2007** *{published data only}*

* Bourbeau J, Christodoulopoulos P, Maltais F, Yamauchi Y, Olivenstein R, Hamid Q. Effect of salmeterol/fluticasone propionate on airway inflammation in COPD: a randomised controlled trial. Thorax 2007; Vol. 62, issue 11:938-43.

**Calverley 2003** *{published and unpublished data}*

AstraZeneca SD. A placebo-controlled 12-month efficacy study of the fixed combination budesonide/formoterol compared to budesonide and formoterol as monotherapies in patients with chronic obstructive pulmonary disease (COPD). http://www.astrazenecaclinicaltrials.com/drug-products/drugproducts/?itemId=8574657 (accessed 8 June 2013).

Borgstrom L, Asking L, Olsson H, Peterson S. Lack of interaction between disease severity and therapeutic response with budesonide/formoterol in a single inhaler [Abstract]. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:C22 [Poster 505].

* Calverley PM, Bonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. *European Respiratory Journal* 2003;**22**(6):912-9.

Calverley PM, Szafranski W, Andersson, Calverley PMA, Andersson A. Budesonide/formoterol is a well-tolerated long term maintenance therapy for COPD [Abstract]. European Respiratory Journal 2005; Vol. 26 Suppl 49:Abstract No. 1917.

Calverley PMA, Cseke Z, Peterson S. Budesonide/formoterol reduces the use of oral corticosteroids in the treatment of COPD [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P436.

Calverley PMA, Kuna P, Olsson H. COPD exacerbations are reduced by budesonide/formoterol in a single inhaler [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P1587.

Calverley PMA, Olsson H, Symbicort International COPD Study Group. Budesonide/formoterol ina single inhaler sustains improvements in lung function over 12 months compared with monocomponents and placebo in patients with COPD [abstract]. American Thoracic Society 99th International Conference; May 16-12; Seattle. 2003:B024 [Poster 418].

Calverley PMA, Peterson S. Combining budesonide/formoterol in a single inhale reduces exacerbation frequency in COPD [abstract]. American Thoracic Society 99th International Conference; May 16-21; Seattle. 2003:D092 [Poster 211].

Calverley PMA, Stahl E, Jones PW. Budesonide/formoterol improves the general health status of patients with COPD [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego. 2005:B93 [Poster 303].

Calverley PMA, Szafranski W, Andersson A. Budesonide/formoterol is a well-tolerated long term maintenance therapy for COPD. *European Respiratory Journal* 2005;**26 Suppl 49**:Poster 1917.

Calverley PMA, Thompson NC, Olsson H. Budesonide/formoterol in a single inhaler sustains lung function improvements in COPD [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P435.

Halpin D, Stahl E, Lundback B, Anderson F, Peterson S. Treatment costs and number needed to treat (NNT) with budesonide/formoterol to avoid one exacerbation of COPD [Abstract]. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:D22 [Poster 525].

Halpin DMG, Larsson T, Calverley PMA. How many patients with COPD must be treated with budesonide/formoterol compared with formoterol alone to avoid 1 day of oral steroid

use? [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego. 2005:B93 [Poster 314].

Jones PW, Stahl E. Budesonide/formoterol in a single inhaler improves health status in patients with COPD [abstract]. American Thoracic Society 99th International Conference; May 16-21; Seattle. 2003:B024 [Poster 419].

Jones PW, Ståhl E. Reducing exacerbations leads to a better health-related quality of life in patients with COPD. 13th ERS Annual Congress; 27 September; Vienna. 2003:P1586.

Jones PW, Ståhl E. Budesonide/formoterol sustains clinically relevant improvements in health status in COPD [Abstract]. *European Respiratory Journal* 2005;**26 Suppl 49**:Abstract 1352.

Lofdahl CG. Reducing the impact of COPD exacerbations: clinical efficacy of budesonide/formoterol. *European Respiratory Review* 2004;**13**(88):14-21.

Lofdahl CG, Andreasson E, Svensson K, Ericsson A. Budesonide/formoterol in a single inhaler improves health status in patients with COPD without increasing healthcare costs [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P433.

Lofdahl CG, Ericsson A, Svensson K, Andreasson E. Cost effectiveness of budesonide/formoterol in a single inhaler for COPD compared with each monocomponent used alone. *Pharmacoeconomics* 2005;**23**(4):365-75.

**Dal Negro 2003** *{published data only}*

Dal Negro R, Micheletto C, Trevsian F, Tognella S. [A98] Salmeterol and fluticasone 50ug/250ug BiD versus salmeterol 50ug bid and versus placebo in the long term treatment of COPD. Proceedings of the 98th International American Thoracic Society Conference; May 17-22; Atlanta. 2002.

* Dal Negro RW, Pomari C, Tognella S, Micheletto C. Salmeterol & fluticasone 50 microg/250 microg bid in combination provides a better long-term control than salmeterol 50 microg bid alone and placebo in COPD patients already treated with theophylline. *Pulmonary Pharmacology and Therapeutics* 2003;**16**(4):241-6.

**Doherty 2012** *{published data only}*

Doherty DE, Kerwin E, Tashkin DP, Matiz-Bueno CE, Shekar T, Banerjee S, et al. Combined mometasone furoate and formoterol in patients with moderate to very severe chronic obstructive pulmonary disease (COPD): phase 3 efficacy and safety study [Abstract]. Journal of Allergy and Clinical Immunology 2012; Vol. 129, issue 2 Suppl:AB75 [283].

Doherty DE, Tashkin DP, Kerwin E, Knorr BA, Shekar T, Banerjee S, et al. Effects of mometasone furoate/formoterol fumarate fixed-dose combination formulation on chronic obstructive pulmonary disease (COPD): results from a 52-week Phase III trial in subjects with moderate-to-very severe COPD. International Journal of Chronic Obstructive Pulmonary Disease 2012; Vol. 7:57-71.

NCT00383721. A randomized, 26-week, placebo-controlled efficacy and safety study with a 26-week long-term safety extension, of high- and medium-dose inhaled mometasone furoate/formoterol fixed-dose combination formulation compared with formoterol and high-dose inhaled mometasone furoate monotherapy in subjects with moderate to severe COPD. http://clinicaltrials.gov/show/NCT00383721 (accessed 10 June 2013). []

**Hanania 2003** *{published and unpublished data}*

* Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, et al. The efficacy and safety of fluticasone propionate (250 micro g)/salmeterol (50 micro g) combined in the diskus inhaler for the treatment of COPD. *Chest* 2003;**124**(3):834-43.

Hanania NA, Ramsdell J, Payne K, Davis S, Horstman D, Lee B, et al. Improvements in airflow and dyspnea in COPD patients following 24 weeks treatment with salmeterol 50mcg and fluticasone propionate 250mcg alone or in combination via the diskus. *American Journal of Respiratory & Critical Care Medicine* 2001;**163**(5 Suppl):A279.

Horstman D, Darken P, Davis S, Lee B. Improvements in FEV1 and symptoms in poorly reversible COPD patients following treatment with salmeterol 50mcg/fluticasone propionate 250mcg combination [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P434.

Mahler DA, Darken P, Brown CP, Knobil K. Predicting lung function responses to combination therapy in chronic obstructive pulmonary disease (COPD) [Abstract]. National COPD Conference November 14-15, Arlington, Virginia. 2003:Abstract 1081.

Mahler DA, Darken P, Brown CP, Knobil K. Predicting lung function responses to salmeterol/fluticasone propionate combination therapy in COPD [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P429.

SFCA3007. A randomized, double-blind, placebo-controlled, parallel-group trial evaluating the safety and efficacy of the DISKUS formulations of Salmeterol (SAL) 50mcg BID and Fluticasone Propionate (FP) 250mcg BID individually and in combination as Salmeterol 50mcg/Fluticasone Propionate 250mcg BID (SFC 50/250) compared to placebo in COPD subjects. . http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=SFCA3007&studyId=0A633AAD-F2BD-4DA0-B6A4-19A812646565&compound=SFCA3007&type=GSK+Study+ID&letterrange=All (accessed 10 June 2013).

Spencer M, Wire P, Lee B, Chang CN, Darken P, Horstman D. Patients with COPD using salmeterol/fluticasone propionate combination therapy experience improved quality of life. *European Respiratory Journal* 2003;**22 Suppl 45**:51s.

Spencer MD, Karia N, Anderson J. The clinical significance of treatment benefits with the salmeterol/fluticasone propionate 50/500mcg combination in COPD. *European Respiratory Journal* 2004;**24 Suppl 48**:290s.

**Lapperre 2009** *{published data only}*

Lapperre TS, Snoeck-Stroband JB, Gosman MM, Jansen DF, van Schadewijk A, Thiadens HA, et al. Effect of fluticasone with and without salmeterol on pulmonary outcomes in chronic

obstructive pulmonary disease: a randomized trial. Annals of Internal Medicine 2009; Vol. 151, issue 8:517-27.

**Mahler 2002** *{published and unpublished data}*

Mahler DA, Darken P, Brown CP, Knobil K. Predicting lung function responses to combination therapy in chronic obstructive pulmonary disease (COPD). http://www.abstracts2view.com (accessed 1 April 2004).

* Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T, et al. Effectiveness of fluticasone propionate and salmeterol combination delivered via the diskus device in the treatment of chronic obstructive pulmonary disease. *American Journal of Respiratory Critical Care Medicine* 2002;**166**(8):1084-91.

SFCA3006. A randomized, double-blind, placebo-controlled, parallel-group trial evaluating the safety and efficacy of the DISKUS formulations of Salmeterol (SAL) 50mcg BID and Fluticasone Propionate (FP) 500mcg BID individually and in combination as Salmeterol 50mcg/Fluticasone Propionate 500mcg BID (SFC 50/500) compared to placebo in COPD subjects. http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=SFCA3006&studyId=ECBB8395-5CCB-410C-91DA-1420726FB071&compound=fluticasone+propionate%2Fsalmeterol&type=Compound&letterrange=A-F (accessed 8 June 2013).

Spencer M, Wire P, Lee B, Chang CN, Darken P, Horstman D. Patients with COPD using salmeterol/fluticasone propionate combination therapy experience improved quality of life. *European Respiratory Journal* 2003;**22 Suppl 45**:51s.

Spencer MD, Anderson JA. Salmeterol/fluticasone combination produces clinically important benefits in dyspnea and fatigue [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego. 2005.

Spencer MD, Karia N, Anderson J. The clinical significance of treatment benefits with the salmeterol/fluticasone propionate 50/500mcg combination in COPD. *European Respiratory Journal* 2004;**24 Suppl 48**:290s.

**O'Donnell 2006** *{published and unpublished data}*

Celli B, Emmett A, Crater G, Kalberg C. Salmeterol/fluticasone propionate (SFC) improves the inspiratory to total lung capacity ratio (IC/TLC) and exercise endurance time in patients with COPD. *European Respiratory Journal* 2006;**28**(Suppl 50):764s.

Make B, Emmett A, Crater G, O'Dell D, Kalberg C. Improvement in exercise endurance time (EET) with fluticasone propionate/salmeterol correlations with spirometry and plethysmography. Proceedings of the American Thoracic Society; May 19-24; San Diego. 2006.

* O'Donnell DE, Sciurba F, Celli B, Mahler DA, Webb KA, Kalberg CJ, et al. Effect of fluticasone propionate/salmeterol on lung hyperinflation and exercise endurance in COPD. *Chest* 2006;**130**(3):647-56.

SCO40030. A randomized, double-blind, placebo-controlled, parallel group clinical trial evaluating the effect of the fluticasone propionate/salmeterol combination product 250/50mcg bid via DISKUS and salmeterol 50mcg bid via DISKUS on lung hyperinflation in subjects with chronic obstructive pulmonary disease (COPD). http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=SCO40030&studyId=8CE29C37-5F7D-4461-B1A6-1A1FDA5981A6&compound=SCO40030&type=GSK+Study+ID&letterrange=All (accessed 10 June 2013).

**Rennard 2009** *{published data only}*

A 12-month double-blind, double-dummy, randomized, parallel group, multicenter efficacy & safety study of SYMBICORT® pMDI 2 × 160/4.5 mcg bid and 2 × 80/4.5mcg bid compared to formoterol TBH 2 × 4.5 mcg bid and placebo in patients with COPD. http://www.astrazenecaclinicaltrials.com/therapy-areas/respiratory-inflammation/?itemId=8574296 (accessed 8 June 2013).

Laties A, Rennard SI, Tashkin DP, Suchower LJ, Martin UJ. Effect of budesonide/formoterol pressurized metered-dose inhaler (bud/fm pmdi) on ophthalmologic assessments in moderate to very severe chronic obstructive pulmonary disease (COPD) patients: results from a 1-year, randomized, controlled clinical trial [Abstract]. Chest 2010; Vol. 138, issue 4:468A.

NCT00206167. A 12-month double-blind, double-dummy, randomized, parallel group, multicenter efficacy and safety study of Symbicort® pMDI 2 × 160/4.5 Î¼g Bid and 2 × 80/4.5 Î¼g Bid compared to Formoterol Turbuhaler® 2 × 4.5 Î¼g Bid and placebo in patients with COPD. http://clinicaltrials.gov/show/NCT00206167 (accessed 8 June 2013). []

Rennard SI, Tashkin DP, McElhattan J, Goldman M, Ramachandran S, Martin UJ, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. Drugs. Adis Data Information BV., 2009; Vol. 69, issue 5:549-65.

Rennard SI, Tashkin DP, McElhattan J, Goldman M, Silkoff PE. Long-term tolerability of budesonide and formoterol administered in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease [Abstract]. Chest 2008; Vol. 134, issue 4_MeetingAbstracts:p103001.

Rennard SI, Tashkin DP, Suchower LJ, Martin UJ. Effect of budesonide/formoterol pressurized metered-dose inhaler (BUD/FM pMDI) on bone mineral density (BMD) in moderate to very severe chronic obstructive pulmonary disease (COPD) patients: results from a 1-year, randomized, controlled clinical trial [Abstract]. Chest 2010; Vol. 138, issue 4:863A.

**SCO104925** *{published data only}*

Evaluation of novel endpoints in subjects with chronic obstructive pulmonary disease (COPD) in a randomized, double-blind, placebo-controlled study of treatment with fluticasone propionate/salmeterol 500/50mcg combination and its individual components, fluticasone propionate 500mcg and salmeterol 50mcg. http://www.gsk-clinicalstudyregister.com/quick-search-list.jsp?item=SCO104925&type=GSK+Study+ID&studyId=SCO104925 (accessed 8 June 2013).

**SFCT01** *{unpublished data only}*

SCO30002. A multicentre, randomised, double-blind, parallel group, placebo-controlled study to compare the efficacy and safety of inhaled salmeterol/fluticasone propionate combination product 25/250 µg two puffs bd and fluticasone propionate 250µg two puffs bd alone, all administered via metered dose inhalers (MDI), in the treatment of subjects with chronic obstructive pulmonary disease (COPD) for 52 weeks. http://www.gsk-clinicalstudyregister.com/quick-search-list.jsp?item=SCO30002&type=GSK+Study+ID&studyId=SCO30002 (accessed 10 June 2013).

**Sin 2008** *{published data only}*

NCT00120978. Advair - CRP study. http://clinicaltrials.gov/show/NCT00120978 (accessed 10 June 2013). []

Sin DD, Man SF, Marciniuk DD, Ford G, FitzGerald M, Wong E, et al. ABC (Advair, Biomarkers in COPD) Investigators. Can inhaled fluticasone alone or in combination with salmeterol reduce systemic inflammation in chronic obstructive pulmonary disease? Study protocol for a randomized controlled trial [NCT00120978]. *BMC Pulmonary Medicine* 2006;**6**(3):3.

Sin DD, Man SF, Marciniuk DD, Ford G, FitzGerald M, Wong E, et al. The effects of fluticasone with or without salmeterol on systemic biomarkers of inflammation in chronic obstructive pulmonary disease [see comment]. American Journal of Respiratory and Critical Care Medicine 2008; Vol. 177, issue 11:1207-14.

**Szafranski 2003** *{published and unpublished data}*

Anderson P. Budesonide/formoterol in a single inhaler (Symbicort) provides early and sustained improvement in lung function in moderate to severe COPD [Abstract]. *Thorax* 2002;**57**(Suppl III):iii43.

AstraZeneca SD. A placebo-controlled 12 month efficacy study of the fixed combination budesonide/formoterol compared with budesonide and formoterol as monotherapies in patients with chronic obstructive pulmonary disease (COPD). http://www.astrazenecaclinicaltrials.com/diseases-and-conditions/diseaseandconditions/?itemId=8574657 (accessed 9 June 2013).

Borgstrom L, Asking L, Olsson H, Peterson S. Lack of interaction between disease severity and therapeutic response with budesonide/formoterol in a single inhaler [Abstract]. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:C22 [Poster 505].

Calverley P, Pauwels R, Lofdahl CG, Svensson K, Higenbottam T, et al. Relationship between respiratory symptoms and medical treatment in exacerbations of COPD. *European Respiratory Journal* 2005;**26**(3):406-13.

Calverley PMA. Effect of budesonide/formoterol on severe exacerbations and lung function in moderate to severe COPD. BTS Winter Meeting; London. December 2002:S145.

Calverley PMA, Szafranski W, Andersson A. Budesonide/formoterol is a well-tolerated long term maintenance therapy for COPD. *European Respiratory Journal* 2005;**26 Suppl 49**:Poster 1917.

Calverley PMA, Thompson NC, Olsson H. Budesonide/formoterol in a single inhaler sustains lung function improvements in COPD [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P435.

Campbell LM, Szafranski W. Budesonide/formoterol in a single inhaler (Symbicort) provides sustained relief from symptoms in moderate to severe COPD. BTS Winter Meeting. London. 2002:S143.

Campell LW, Szafranski W. Budesonide/Formoterol in a single inhaler (Symbicort) reduces severe exacerbations in patients with moderate-severe COPD. BTS Winter Meeting. London. 2002:S141.

Dahl R, Cukier A, Olsson H. Budesonide/formoterol in a single inhaler reduces severe and mild exacerbations in patients with moderate to severe COPD. *European Respiratory Journal* 2002;**20 Suppl 38**:242 [P1575].

Egede F, Menga G. Budesonide/formoterol in a single inhaler provides sustained relief from symptoms and night-time awakenings in moderate-severe COPD: results from symptoms and night-time awakenings in moderate to severe COPD: results from a 1-year study. *European Respiratory Journal* 2002;**20 Suppl 38**:242 [P1574].

Halpin D, Stahl E, Lundback B, Anderson F, Peterson S. Treatment costs and number needed to treat (NNT) with budesonide/formoterol to avoid one exacerbation of COPD [Abstract]. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:D22 [Poster 525].

Jones PW, Stahl E, Svensson K. Improvement in health status in patients with moderate to severe COPD after treatment with budesonide/formoterol in a single inhaler. *European Respiratory Journal* 2002;**20 Suppl 38**:250 [P1613].

Korsgaard J, Sansores R. Budesonide/formoterol (single inhaler) provides sustained relief from shortness of breath and chest tightness in a 1-year study of patients with moderate to severe COPD. *European Respiratory Journal* 2002;**20 Suppl 38**:242 [P1577].

Lange P, Saenz C. Budesonide/formoterol in a single inhaler is well tolerated in patients with moderate to severe COPD: results of a 1 year study. *European Respiratory Journal* 2002;**20 Suppl 38**:242 [P1573].

Lofdahl CG. Reducing the impact of COPD exacerbations: clinical efficacy of budesonide/formoterol. *European Respiratory Review* 2004;**13**(88):14-21.

Milanowski J, Nahabedian S. Budesonide/formoterol in a single inhaler acts rapidly to improve lung function and relieve symptoms in patients with moderate to severe COPD. *European Respiratory Journal* 2002;**20 Suppl 38**:242 [P1576].

* Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. *European Respiratory Journal* 2003;**21**(1):74-81.

**Tashkin 2008** *{published data only}*

Astrazeneca (D5899C00002). A 6-month double-blind, double-dummy, randomized, parallel group, multicenter efficacy & safety study of Symbicort® pMDI 2 × 160/4.5mg & 80/4.5mg bid compared to Formoterol TBH, Budesonide pMDI (& the combination) & placebo in COPD patients. www.astrazenecaclinicaltrials.com (accessed 8 April 2008).

Tashkin DP, Rennard SI, Martin P, Goldman M, Silkoff PE. Efficacy of budesonide/formoterol administered via one pressurized metered-dose inhaler over 6 months in patients with chronic obstructive pulmonary disease [Abstract]. Chest 2008; Vol. 134, issue 4:105001s.

Tashkin DP, Rennard SI, Martin P, Ramachandran S, Martin UJ, Silkoff PE, et al. Efficacy and safety of budesonide and formoterol in one pressurized metered-dose inhaler in patients with moderate to very severe chronic obstructive pulmonary disease : results of a 6-month randomized clinical trial. Drugs 2008; Vol. 68, issue 14:1975-2000.

**Tashkin 2012** *{published data only}*

Kerwin E, Tashkin DP, Matiz-Bueno CE, Doherty DE, Shekar T, Banerjee S, et al. Clinical efficacy and safety of combined mometasone furoate and formoterol in patients with moderate to very severe chronic obstructive pulmonary disease (COPD) [Abstract]. Journal of Allergy and Clinical Immunology 2012; Vol. 129, issue 2 Suppl:AB201 [759].

NCT00383435. A randomized, 26-week, placebo-controlled efficacy and safety study with a 26-week long-term safety extension, of high- and medium-dose inhaled mometasone furoate/formoterol fixed-dose combination formulation compared with formoterol and high-dose inhaled mometasone furoate monotherapy in subjects with moderate to severe COPD. http://clinicaltrials.gov/show/NCT00383435 (accessed 9 June 2013). []

Tashkin DP, Doherty DE, Kerwin E, Matiz-Bueno CE, Knorr B, Shekar T, et al. Efficacy and safety of a fixed-dose combination of mometasone furoate and formoterol fumarate in subjects with moderate to very severe COPD: results from a 52-week Phase III trial. *International Journal of Chronic Obstructive Pulmonary Disease* 2012;**7**:43-55.

**TORCH** *{published and unpublished data}*

Briggs AH, Glick HA, Lozano-Ortega G, Spencer M, Calverley PM, Jones PW, et al. Is treatment with ICS and LABA cost-effective for COPD? Multinational economic analysis of the TORCH study. *European Respiratory Journal* 2010;**35**(3):532-9.

Calverley P, Celli B, Anderson JA, Ferguson GT, Jenkins C, Jones PW, et al. The Towards a Revolution in COPD Health (TORCH) study: salmeterol/fluticasone propionate improves survival in COPD over three years. *Respirology* 2006;**11**(Suppl 5):A149.

Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease.[see comment]. New England Journal of Medicine 2007; Vol. 356, issue 8:775-89.

Calverley PM, Celli B, Anderson JA, Ferguson GT, Jenkins C, Jones PW, et al. The towards a revolution in COPD health (TORCH) study: fluticasone propionate /salmeterol improves survival in COPD over three years. *Chest* 2006;**130**(4):122s.

Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Cardiovascular events in patients with chronic obstructive pulmonary disease: TORCH study results. *Thorax* 2010;**65**:719-25.

* Calverley PMA, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. *New England Journal of Medicine* 2007;**356**(8):775-89.

Calverley PMA, Celli B, Andersen JA, Ferguson GT, Jenkins C, Jones PW, et al. The TORCH (towards a revolution in COPD health) study salmeterol/fluticasone propionate (SFC) improves survival in COPD over three years. *European Respiratory Journal* 2006;**28**(Suppl 50):34s.

Calverley PMA, Celli B, Ferguson G, Jenkins C, Jones PW, Pride NB, et al. Baseline characteristics of the first 5,000 COPD patients enrolled in the TORCH survival study. *European Respiratory Journal* 2003;**22 Suppl 45**:578s.

Celli B, Calverley PM, Anderson JA, Ferguson GT, Jenkins C, Jones P, et al. The TOwards a Revolution in COPD HEalth (TORCH) Study: salmeterol/fluticasone propionate reduces the rate of exacerbations over three years. *Respirology* 2006;**11**(Suppl 5):A140.

Celli B, Calverley PMA, Anderson JA, Ferguson GT, Jenkins C, Jones PW, et al. The TORCH (TOwards a Revolution in COPD Health) study: salmeterol/fluticasone propionate (SFC) improves health status, reduces exacerbations and improves lung function over three years. *European Respiratory Journal* 2006;**28 Suppl 50**:34s.

Celli B, Vestbo J, Jenkins CR, Jones PW, Ferguson GT, Calverley PM, et al. Sex differences in mortality and clinical expressions of patients with chronic obstructive pulmonary disease: the TORCH experience. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**(3):317-22.

Celli BR, Thomas NE, Anderson JA, Ferguson GT, Jenkins CR, Jones PW, et al. Effect of pharmacotherapy on rate of decline of lung function in chronic obstructive pulmonary disease: results from the TORCH study. *American Journal of Respiratory and Critical Care Medicine* 2008;**174**(4):332-8.

Corhay JL, Louis R. Clinical study of the month: the TORCH study (TOwards a Revolution in COPD Health) [L'étude clinique du mois. L'étude TORCH (TOwards a Revolution in COPD Health): vers une revolution de la santé des patients souffrant de BPCO]. *Revue Medicale de Liege* 2007;**62**(4):230-4.

Crim C, Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, et al. Pneumonia risk in COPD patients receiving inhaled corticosteroids alone or in combination: TORCH study results. *European Respiratory Journal* 2009;**34**(3):641-7.

Ferguson GT, Calverley PM, Anderson JA, Celli B, Jenkins C, Jones PW, et al. The towards a revolution in COPD health

(TORCH) study: fluticasone propionate/salmeterol is well tolerated in patients with COPD over 3 years. *Chest* 2006;**130**(4):178s.

Ferguson GT, Calverley PM, Anderson JA, Jenkins CR, Jones PW, Willits LR, et al. Prevalence and progression of osteoporosis in patients with COPD: results from the TOwards a Revolution in COPD Health study. Chest 2009; Vol. 136, issue 6:1456-65.

Ferguson GT, Calverley PMA, Anderson JA, et al. The TORCH (TOwards a Revolution in COPD Health) study: salmeterol/fluticasone propionate (SFC) improves survival in COPD over three years. *European Respiratory Journal* 2006;**28 Suppl 50**:34s.

Houghton CM, Lawson N, Borrill ZL, Wixon CL, Yoxall S, Langley SJ, et al. Comparison of the effects of salmeterol/fluticasone propionate with fluticasone propionate on airway physiology in adults with mild persistent asthma. *Respiratory Research* 2007;**8**:52.

Jenkins CR, Calverley PMA, Celli B, Ferguson G, Jones PW, Pride N, et al. Seasonal patterns of exacerbation rates in the TORCH survival study. http://www.abstracts2view.com (accessed 1 April 2007):A839.

Jenkins CR, Celli B, Anderson JA, Ferguson GT, Jones PW, Vestbo J, et al. Seasonality and determinants of moderate and severe COPD exacerbations in the TORCH study. *European Respiratory Journal* 2012;**39**(1):38-45.

Jenkins CR, Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, et al. Efficacy of salmeterol/fluticasone propionate by GOLD stage of chronic obstructive pulmonary disease: analysis from the randomised, placebo-controlled TORCH study. *Respiratory Research* 2009;**10**:59.

Johnson M, Agusti AG, Barnes NC. Reflections on TORCH: potential mechanisms for the survival benefit of salmeterol/fluticasone propionate in COPD patients. *COPD* 2008;**5**(6):369-75.

Jones PW, Anderson JA, Calverley PM, Celli BR, Ferguson GT, Jenkins C, et al. Health status in the TORCH study of COPD: treatment efficacy and other determinants of change. *Respiratory Research* 2011;**12**:71.

Jones PW, Calverley P, Celli B, Ferguson G, Jenkins C, Pride N. Trans-regional validity of the SGRQ in the TORCH survival study. http://www.abstracts2view.com (accessed 1 April 2004):A122.

Jones PW, Calverley PM, Celli B, Anderson JA, Ferguson GT, Jenkins C, et al. The towards study a revolution in COPD health (TORCH) study: fluticasone propionate/salmeterol improves and sustains health status in COPD over 3 years. *Chest* 2006;**130**(4):177s.

McGarvey LP, John M, Anderson JA, Zvarich MT, Wise RA. Ascertainment of cause-specific mortality in COPD: operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007;**62**:411-5.

NCT00268216. Survival of subjects with chronic obstructive pulmonary disease (COPD). http://clinicaltrials.gov/show/NCT00268216 (accessed 9 July 2013). []

SCO30003. A multicentre, randomised, double-blind, parallel group, placebo-controlled study to investigate the long-term effects of salmeterol/fluticasone propionate (SERETIDE®/VIANI®/ADVAIR®) 50/500mcg bd, salmeterol 50mcg bd and fluticasone propionate 500mcg bd, all delivered via the DISKUS®/ACCUHALER® inhaler, on the survival of subjects with chronic obstructive pulmonary disease (COPD) over 3 years of treatment, 2006. http://www.gsk-clinicalstudyregister.com/quick-search-list.jsp?tab=results&letterrange=All&type=GSK+Study+ID&item=SCO30003&studyType=All&phase=All&status=All&population=All (accessed 9 July 2013).

Vestbo J, Anderson JA, Calverley PM, Celli B, Ferguson GT, Jenkins C, et al. Adherence to inhaled therapy, mortality and hospital admission in COPD.. *Thorax* 2009;**64**(11):939-43.

Vestbo J, Calverley P, Celli B, Ferguson G, Jenkins C, Jones P, et al. The TORCH (TOwards a Revolution in COPD Health) survival study protocol. *European Respiratory Journal* 2004;**24**(2):206-10.

Vestbo J, The TORCH Study Group. The TORCH (TOwards a Revolution in COPD Health) survival study protocol. *European Respiratory Journal* 2004;**24**(2):206-10.

Wise RA, McGarvey LP, John M, Anderson JA, Zvarich MT. Reliability of cause-specific mortality adjudication in a COPD clinical trial. http://www.abstracts2view.com (accessed 1 April 2007):A120.

**TRISTAN** *{published and unpublished data}*

* Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2003;**361**(9356):449-56.

Calverley PMA, Pauwels RA, Vestbo J, Jones PW, Pride NB, Gulsvik A, et al. Salmeterol/Fluticasone propionate combination for one year provides greater clinical benefit than its individual components. Proceedings of the 98th International American Thoracic Society Conference; May 17-22; Atlanta. 2002:A98 [Poster 306].

Calverley PMA, Pauwels RA, Vestbo J, Jones PW, Pride NB, Gulsvik A, et al. Clinical improvements with salmeterol / fluticasone propionate combination in differing severities of COPD.. American Thoracic Society 99th International Conference; May 16-21; Seattle 2003:A035 [Poster D50].

Calverly PMA, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Safety of salmeterol/fluticasone propionate combination in the treatment of chronic obstructive pulmonary disease. *European Respiratory Journal* 2002;**20 Suppl 38**:242 [P1572].

Hunjan MK, Chandler F. Numbers needed to treat (NNT) to avoid an exacerbation in patients with chronic obstructive pulmonary disease (COPD) using salmeterol/fluticasone propionate combination (SFC) and associated costs [Abstract]. American

Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:D22 [Poster 503].

Hunjan MK, Williams DT. Costs of avoiding exacerbations in patients with chronic obstructive pulmonary disease (COPD) treated with salmeterol/ fluticasone propionate combination (seretide) and salmeterol. *European Respiratory Journal* 2004;**24 Suppl 48**:291s.

Hunjan MK, Williams DT. Salmeterol/ fluticasone propionate combination is clinically effective in avoiding exacerbations in patients with moderate/severe COPD. *European Respiratory Journal* 2004;**24 Suppl 48**:513s.

Jones PW, Edin HM, Anderson J. Salmeterol/fluticasone propionate combination improves health status in COPD patients. Proceedings of the 98th International American Thoracic Society Conference; May 17-22; Atlanta. 2002:A39 [Poster K39].

Jones PW, Ståhl E. Budesonide /formoterol sustains clinically relevant improvements in health status in COPD [Abstract]. *European Respiratory Journal* 2005;**26 Suppl 49**:Abstract 1352.

Jones PW, Vestbo J, Pauwels RA, Calverley PMA, Anderson JA, Spencer MD. Informative drop out in COPD studies. Investigation of health status of withdrawals in the TRISTAN study. 13th ERS Annual Congress, 27 Spetember, Vienna. 2003:P1593.

Morgan M. Salmetrol xinafoate/fluticasone propionate combination product in the treatment of chronic obstructive pulmonary disease. Publication ID: N0123137844 http://www.nihr.ac.uk/Profile/Pages/NRRResults.aspx?publication_id=N0123137844 (accessed 9 July 2013).

Nitschmann S. Inhalational combination therapy in chronic obstructive lung disease. Tristan study. *German Internist* 2004;**45**(6):727-8.

Pauwels R, Vestbo J, Calverley PMA, Jones PW, Pride NB, Gulsvik A. Characterization of exacerbations in the TRISTAN study of salmeterol/fluticasone propionate (SFC) combination in moderate to severe COPD. http://www.abstracts2view.com (accessed 2003).

Pauwels RA, Calverly PMA, Vestbo J, Jones PW, Pride N, Gulsvik A, et al. Reduction of exacerbations with salmeterol/fluticasone combination 50/500 mcg bd in the treatment of chronic obstructive pulmonary disease. *European Respiratory Journal* 2002;**20 Suppl 38**:240 [P1569].

SFCB3024. A multicentre, randomised, double-blind, parallel group, placebo-controlled study to compare the efficacy and safety of the salmeterol/FP combination product at a strength of 50/500mcg bd with salmeterol 50mcg bd alone and FP 500mcg bd alone, delivered via the DISKUS™/ACCUHALER™, in the treatment of subjects with chronic obstructive pulmonary disease (COPD) for 12 months. GlaxoSmithKline Clinical Trials Register http:ctr.gsk.co.uk (accessed 2005).

Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. *Pharmacoeconomics* 2005;**23**(6):619-37.

Spencer MD, Karia N, Anderson J. The clinical significance of treatment benefits with the salmeterol/fluticasone propionate 50/500mcg combination in COPD. *European Respiratory Journal* 2004;**24 Suppl 48**:290s.

Vestbo J, Calverley PMA, Pauwels R, Jones P, Pride N, Gulsvik A, et al. Absence of gender susceptibility to the combination of salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease. *European Respiratory Journal* 2002;**20 Suppl 38**:240 [P1570].

Vestbo J, Pauwels R, Anderson JA, Jones P, Calverley P. Early onset of effect of salmeterol and fluticasone propionate in chronic obstructive pulmonary disease. *Thorax* 2005;**60**(4):301-4.

Vestbo J, Pauwels RS, Calverley PMA, Jones PW, Pride NB, Gulsvik A. Salmeterol / fluticasone propionate combination produces improvement in lung function detectable within 24 Hours in moderate to severe COPD. American Thoracic Society 99th International Conference; May 16-21; Seattle. 2003.

Vestbo J, Soriano JB, Anderson JA, Calverley P, Pauwels R, Jones P. Gender does not influence the response to the combination of salmeterol and fluticasone propionate in COPD. *Respiratory Medicine* 2004;**98**(11):1045-50.

**Zheng 2006** *{published data only}*

SCO100540. A multi-centre, randomised, double-blind, parallel group study to investigate the efficacy and safety of the salmeterol/fluticasone propionate combination at a strength of 50/500µg BD, compared with placebo via Accuhaler™, added to usual chronic obstructive pulmonary disease (COPD) therapy, in subjects with COPD for 24 weeks. http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=100540&studyId=A8F0EC6F-5ECE-4FA6-9852-FBA8CC004B75&compound=100540&type=GSK+Study+ID&letterrange=All (accessed 9 July 2013).

* Zheng J, Zhong N, Yang L, Wu Y, Chen P, Wen Z, et al. The efficacy and safety of fluticasone propionate 500 mg/salmeterol 50 mg combined via diskus/accuhaler in Chinese patients with chronic obstructive pulmonary disease (COPD). *Chest* 2006;**130**(4):182s.

Zhong N, Zheng J, Yang L, Wu Y, Chen P, Wen Z, et al. The efficacy and safety of salmeterol 50µg/fluticasone propionate 500µg combined via accuhaler in Chinese patients with chronic obstructive pulmonary disease [Abstract]. *Respirology* 2006;**11**(Suppl 5):A150.

## References to studies excluded from this review

**Aaron 2004** *{published data only}*

Aaron SD, Vandemheen K, Ferguson D, FitzGerald M, Maltais F, Boureau J, et al. The Canadian optimal therapy of COPD trial: Design, organization and patient recruitment. *Canadian Respiratory Journal* 2004;**11**(8):581-5.

**Aaron 2007** *{published data only}*

Aaron SD, Vandemheen KL, Fergusson D, Maltais F, Bourbeau J, Goldstein R, et al. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial.[see comment][summary for patients in Ann Intern Med. 2007 Apr 17;146(8):I12; PMID: 17310044]. Annals of Internal Medicine 2007; Vol. 146, issue 8:545-55.

Kaplan A. Effects of tiotropium combined with either salmeterol or salmeterol/fluticasone in moderate to severe COPD. *Primary Care Respiratory Journal* 2007;**16**(4):258-60.

**Bathoorn 2008** *{published data only}*

Bathoorn E, Liesker JJ, Postma DS, Boorsma M, Bondesson E, Koëter GH, et al. Anti-inflammatory effects of combined budesonide/formoterol in COPD exacerbations. COPD 2008; Vol. 5, issue 5:282-90.

**Bleecker 2011** *{published data only}*

Bleecker ER, Meyers DA, Bailey WC, Sims AM, Bujac SR, Goldman M, et al. Effect of β2-adrenergic receptor gene polymorphism Gly16Arg on response to budesonide/formoterol pressurized metered-dose inhaler in chronic obstructive pulmonary disease [Abstract]. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**(Meeting Abstracts):A4086.

**Borgstrom 2003** *{published data only}*

* Borgstrom L, Lipniunas P. Budesonide/formoterol in Turbuhaler® is not affected by storage in hot and humid conditions. A clinical pharmacokinetic comparison with fluticasone in Diskus™ [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P1580.

**Cazzola 2000** *{published data only}*

Cazzola M, Di Lorenzo G, Di Perna F, Calderaro F, Testi R, Centanni S. Additive effects of salmeterol and fluticasone or theophylline in COPD. *Chest* 2000;**118**(6):1576-81.

**Cazzola 2002a** *{unpublished data only}*

Cazzola M, Santus P, Di Marco F, Boveri B, Castagna F, Carlucci P. Bronchodilator effect of an inhaled combination therapy with salmeterol + fluticasone and formoterol + budesonide in patients with COPD. *European Respiratory Journal* 2002;**20 Suppl 38**:386 [P2396].

**Cazzola 2003** *{published data only}*

Cazzola M, Salzillo A, De Giglio C, Noschee P, D'Amato G. Formoterol/budesonide (FBC) in the treatment of acute exacerbation of COPD [Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P1859.

**Cazzola 2004** *{published data only}*

* Cazzola M, Noschese P, Centanni S, Santus P, Di Marco F, Spicuzza L, et al. Salmeterol/fluticasone propionate in a single inhaler device versus theophylline + fluticasone propionate in patients with COPD. *Pulmonary Pharmacology and Therapeutics* 2004;**17**(3):141-5.

Cazzola M, Noschese P, D'Amato G, Santus P, Centanni S. Salmeterol/fluticasone propionate in a single inhaler device (SLM/FP) versus theophyline (THEO) + FP in patients with COPD. *European Respiratory Journal* 2002;**20 Suppl 38**:386 [P2393].

**Cazzola 2004b** *{published data only}*

Cazzola M, Santus P, Di Marco F, Carlucci P, Belloni E, Mondoni M, et al. Onset of action of budesonide/formoterol in single inhaler vs. formoterol in patients with COPD [abstract]. American Thoracic Society 99th International Conference; May 16-21; Seattle. 2003:B024 [Poster 410].

* Cazzola M, Santus P, Di Marco F, Carlucci P, Mondoni M, Matera MG, et al. Onset of action of formoterol/budesonide in single inhaler vs. formoterol in patients with COPD. *Pulmonary Pharmacology and Therapeutics* 2004;**17**(3):121-5.

**Chapman 2002** *{published data only}*

Chapman KR. Seretide for obstructive lung disease. *Expert Opinion on Pharmacotherapy* 2002;**3**(3):341-50.

**Cukier 2007** *{published data only}*

Cukier A, Ferreira CAS, Stelmach R, Ribeiro M, Cortopassi F, Calverley PMA. The effect of bronchodilators and oxygen alone and in combination on self-paced exercise performance in stable COPD. *Respiratory Medicine* 2007;**101**(4):743-53.

**De Backer 2011** *{published data only}*

De Backer L, De Backer J, Vos W, Van Holsbeke C, Vinchurkar S, De Backer W. Double blind, placebo controlled crossover study in COPD patients to assess the acute effect of budesonide/formoterol using HRCT and lung function tests [Abstract]. European Respiratory Society Annual Congress; September 24-28; Amsterdam. 2011; Vol. 38, issue 55:600s [P3362].

**Donohue 2004** *{published data only}*

* Donohue JF, Kalberg C, Emmett A, Merchant K, Knobil K. A short-term comparison of fluticasone propionate/salmeterol with ipratropium bromide/albuterol for the treatment of COPD. *Treatments in Respiratory Medicine* 2004;**3**(3):173-81.

Donohue JF, Kalberg C, Emmett A, Merchant K, Knobil K. Fluticasone/salmeterol combination (250/50) provides greater improvement in lung function and symptoms than the combination of ipratropium/albuterol in patients with COPD. *Chest* 2003;**124**(4):128S.

Kalberg C, Emmett A, Bourne E, Merchant K, Knobil K. Fluticasone propionate/salmeterol provides greater relief of dyspnea than ipratropium/albuterol in patients with COPD [Abstract]. American Thoracic Society 100th International Conference, May 21-26; Orlando. 2004:C22 [Poster 528].

Knobil K, Kalberg C, Merchant K, Emmett A, Cicale M. Maintenance of bronchodilator response for advair diskus 250/50 (fluticasone propionate/salmeterol) but not ipratropium/albuterol in patients with COPD [Abstract]. *Chest* 2004;**126**(4):807S.

Knobil K, Merchant K, Kalberg C, Emmett A, Cicale M. A comparison of patient perceived improvement in symptoms after initiating therapy with either advair diskus (fluticasone propionate/salmeterol) 250/50 or ipratropium/albuterol [Abstract]. *Chest* 2004;**126**(4 Suppl):806S-b - 807S-b.

Merchant K, Bourne E, Emmett A, Knobil K, Kalberg C. Greater improvement in dyspnea with fluticasone propionate/salmeterol 250/50 compared with salmeterol or ipratropium in patients with COPD [Abstract]. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:C22 [Poster 526].

Sciurba FC, Kalberg C, Emmett A, Merchant K, Brown C, Knobil K. Efficacy of advair diskus 250/50 (fluticasone propionate/salmeterol) or ipratropium/albuterol in patients with COPD associated with chronic bronchitis and/or emphysema [Abstract]. *Chest* 2004;**126**(4 Suppl):807S-a - 808S-a.

**Ferguson 2006** *{published data only}*

Ferguson GT. Cardiovascular safety of simultaneous therapy with advair and combivent in the treatment of COPD [Abstract]. Proceedings of the American Thoracic Society; May 19-24; San Diego. 2006:A109 [Poster J2].

**GlaxoSmithKline 2004** *{published data only}*

GlaxoSmithKline SAS. A Randomised, Double-Blind, Double-Dummy, Parallel-Group Comparison of SERETIDE DISKUS/ACCUHALER (50/100Âµg Strength) twice daily (bid) with Budesonide 400Âµg bid in Adolescents and Adults with Reversible Airways Obstruction. GlaxoSmithKline Clinical Trial Register 2004.

**GlaxoSmithKline 2004a** *{published data only}*

GlaxoSmithKline SAS. A Randomised, Double-Blind, Double-Dummy, Parallel-Group Comparison of Seretide DISKUS/ACCUHALER (50/250ìg Strength) b.i.d. with Budesonide 800ìg b.i.d. in Adolescents and Adults with Reversible Airways Obstruction. GlaxoSmithKline Clinical Trial Register 2004.

**Golabi 2006** *{published data only}*

Golabi P, Topaloglu N, Karakurt S, Celikel T. Effects of tiotropium and salmeterol/fluticasone combination on lung hyperinflation dyspnea and exercise tolerance in COPD [Abstract]. *European Respiratory Journal* 2006;**28**(Suppl 50):33s.

**Haque 2006** *{published data only}*

Haque RA, Torrego A, Essilfie-Quaye S, Kharitonov SA, Johnson M, Adcock IM, et al. Effect of salmeterol and fluticasone on glucocorticoid receptor translocation in sputum macrophages and peripheral blood mononuclear cells from patients with chronic obstructive pulmonary disease. Proceedings of the American Thoracic Society; May 19-24; San Diego. 2006:A848.

**INSPIRE** *{published data only}*

GlaxoSmithKline (SCO40036). Multicentre, randomised, double-blind, double-dummy, parallel group, 104-week study to compare the effect of the salmeterol/fluticasone propionate combination product (SERETIDE*) 50/500mcg delivered twice daily via the DISKUS*/ACCUHALER* inhaler with tiotropium bromide 18 mcg delivered once daily via the HandiHaler inhalation device on the rate of health care utilisation exacerbations in subjects with severe chronic obstructive pulmonary disease (COPD). http://ctr.gsk.co.uk (accessed 8 April 2008).

Seemungal T, Stockley R, Calverley P, Hagan G, Wedzicha JA. Investigating new standards for prophylaxis in reduction of exacerbations - The INSPIRE study methodology. *Journal of Chronic Obstructive Pulmonary Disease* 2007;**4**(3):177-83.

Wedzicha J, Stockley R, Seemungal T, Hagan G, Calverley P. The INSPIRE study: effect of salmeterol/fluticasone propionate versus tiotropium bromide on COPD exacerbations. *Respirology* 2007;**12**(Suppl 4):A112.

**Jiang 2011** *{published data only}*

Jiang YP, Zhao YF, Yang Y. Effect of seretide on quality of life in COPD: Measured with COPD assessment test [Abstract]. *Respirology (Carlton, Vic.)* 2011;**16**(Suppl 2):100 [344].

**Jung 2012** *{published data only}*

Jung KS, Park HY, Park SY, Kim SK, Kim YK, Shim JJ, et al. Comparison of tiotropium plus fluticasone propionate/salmeterol with tiotropium in COPD: a randomized controlled study. Respiratory Medicine 2012; Vol. 106, issue 3:382-9.

**Kardos 2007** *{published and unpublished data}*

Kardos P, Wencker M. Combination therapy with salmeterol and fluticasone propionate (SFC) is more effective than salmeterol (SAL) alone in reducing exacerbations of COPD [Abstract]. *European Respiratory Journal* 2005;**26 Suppl 49**:Abstract 1944.

* Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. *American Journal of Respiratory & Critical Care Medicine* 2007;**175**(2):144-9.

SCO30006. A randomised, double-blind, parallel-group study to investigate the protective effect of the combination of fluticasone and salmeterol (500/50µg bid via the DISKUS) compared with salmeterol (50µg bid via the DISKUS) on the incidence of moderate to severe exacerbations in patients with severe chronic obstructive pulmonary disease (COPD) (GOLD III/IV). http://www.gsk-clinicalstudyregister.com/result_detail.jsp?protocolId=SCO30006&studyId=AA5CBD03-AE61-4A49-B915-3A47C25E9C31&compound=SCO30006&type=GSK+Study+ID&letterrange=All (accessed 10 June 2013).

Vogelmeier C. Combination therapy with salmeterol and fluticasone propionate (SFC) improves quality of life (QoL) more than salmeterol (SAL) alone in COPD. *42nd Nordic Lung Conference Trondheim* 2005;**Suppl 22**:13.

**Lindberg 2007** *{published data only}*

Lindberg A, Szalai Z, Pullerits T, Radeczky E. Fast onset of effect of budesonide/formoterol versus salmeterol/fluticasone and salbutamol in patients with chronic obstructive pulmonary disease and reversible airway obstruction. *Respirology (Carlton, Vic.)* 2007;**12**(5):732-9.

**Lindenberg 2006** *{published data only}*

Lindenberg A, Szalai Z, Pullertis T, Radeczky E, Lindberg A. Budesonide/formoterol (B/F) has an onset of action that is similar to salbutamol and faster than salmeterol/fluticasone in patients with COPD [Abstract]. *European Respiratory Journal* 2006;**28**(Suppl 50):214s [P1273].

**Mittmann 2010** *{published data only}*

Mittmann N, Hernandez P, Mellstram C, Brannman L, Welte T, Mellström C, et al. Cost-effectiveness of budesonide/formoterol added to tiotropium in COPD patients in Canada, Australia and Sweden [Abstract].. European Respiratory Society Annual Congress; September 18-22; Barcelona. 2010:[5183].

**Mittmann 2011** *{published data only}*

Mittmann N, Hernandez P, Mellstrom C, Brannman L, Welte T. Cost effectiveness of budesonide/formoterol added to tiotropium bromide versus placebo added to tiotropium bromide in patients with chronic obstructive pulmonary disease: Australian, Canadian and Swedish healthcare perspectives. PharmacoEconomics 2011; Vol. 29, issue 5:403-14.

**NCT00144911** *{published data only}*

NCT00144911. See Detailed Description. http://clinicaltrials.gov/show/NCT00144911 (accessed 9 July 2013). []

**NCT00269126** *{published data only}*

NCT00269126. See Detailed Description. http://clinicaltrials.gov/show/NCT00269126 (accessed 9 July 2013). []

**NCT00476099** *{published data only}*

NCT00476099. A 48-Week, Double Blind, Double Dummy, Randomised, Multinational, Multicentre, 3-Arm Parallel Group Clinical Study of "Fixed Combination" Beclometasone Dipropionate Plus Formoterol Fumarate Administered Via pMDI With HFA-134a Propellant Versus "Fixed Combination" Budesonide Plus Formoterol DPI Versus Formoterol DPI in Patients With Stable Severe Chronic Obstructive Pulmonary Disease (COPD). Http://clinicaltrials.gov/show/NCT00476099 (accessed 9 July 2013). []

**Noschese 2003** *{published data only}*

Noschese P, De Michele F, D'Amato G, Cazzola M. Comparison of the acute effects of formoterol (F) and formoterol/budesonide combination (FBC) on blood gas tensions in patients with acute exacerbation of COPD (AECOPD)[Abstract]. *European Respiratory Journal* 2003;**22 Suppl 45**:P156.

**Sagcan 2007** *{published data only}*

Sagcan G, Memis U, Cuhadaroglu C, Sen C, Duygu E. The effects of formoterol/budesonide on sleep quality of COPD patients [Abstract]. *European Respiratory Journal* 2007;**30**(Suppl 51):507s [E3049].

**SAM40116** *{unpublished data only}*

* SAM40116. A 12-Week Multi-centre, Randomised, Double Blind, Parallel Group Study to Compare the Efficacy of Salmeterol/Fluticasone Propionate (Seretide TM) 50/100 mcg or 50/250 mcg Twice Daily and Fluticasone Propionate (Flixotide TM) 250 mcg or 500 mcg Twice Daily via the Diskus TM in Subjects With Asthma/COPD Symptoms. GlaxoSmithKline Clinical Trials Register http:ctr.gsk.co.uk (accessed 2005).

**Schermer 2007** *{published data only}*

Schermer TR, Albers JM, Verblackt HW, Costongs RJ, Westers P. Lower inhaled steroid requirement with a fluticasone/salmeterol combination in family practice patients with asthma or COPD. *Family Practice* 2007;**24**(2):181-8.

**SCO100250** *{unpublished data only}*

GlaxoSmithKline (SCO100250). A Randomized, Double-Blind, Parallel-Group, 52-Week Study to Compare the Effect of Fluticasone Propionate/Salmeterol DISKUS 250/50mcg bid With Salmeterol DISKUS 50mcg bid on the Annual Rate of Moderate/Severe Exacerbations in Subjects With Chronic Obstructive Pulmonary Disease (COPD). http://ctr.gsk.co.uk (accessed 8 April 2008).

**SCO100470** *{unpublished data only}*

SCO100470. A Multicentre, Randomised, Double-Blind, Parallel Group, 24-Week Study to Compare the Effect of the Salmeterol/Fluticasone Propionate Combination Product 50/250mcg, With Salmeterol 50mcg Both Delivered Twice Daily via the DISKUS/ACCUHALER Inhaler on Lung Function and Dyspnoea in Subjects With Chronic Obstructive Pulmonary Disease (COPD). GlaxoSmithKline Clinical Trials Register http:ctr.gsk.co.uk (accessed 2006).

**SCO40034** *{unpublished data only}*

A Multicentre, Randomised, Double-blind, Double Dummy, Parallel Group 12-Week Exploratory Study to Compare the Effect of the Salmeterol/Fluticasone Propionate Combination Product (SERETIDE) 50/500mcg bd via the DISKUS/ACCUHALER Inhaler With Tiotropium Bromide 18 mcg od via the Handihaler Inhalation Device on Efficacy and Safety in Patients With Chronic Obstructive Pulmonary Disease (COPD). GlaxoSmithKline Clinical Trials Register http:ctr.gsk.co.uk (accessed 2005).

**SCO40043** *{unpublished data only}*

SCO40043. A Randomized, Double-Blind, Parallel-Group, 52-Week Study to Compare the Effect of Fluticasone Propionate/Salmeterol DISKUS® 250/50mcg bid With Salmeterol DISKUS® 50mcg bid on the Annual Rate of Moderate/Severe Exacerbations in Subjects With Chronic Obstructive Pulmonary Disease (COPD). http://ctr.gsk.co.uk (accessed 8 April 2008).

**Sethi 2006** *{published data only}*

Sethi S, Grove L, Wrona C, Maloney J. Prevalence of bacterial colonization in COPD is not altered by fluticasone/salmeterol. Proceedings of the American Thoracic Society; May 19-22; San Diego. 2006:A115.

**Shaker 2009** *{published data only}*

Shaker SB, Dirksen A, Ulrik CS, Hestad M, Stavngaard T, Laursen LC, et al. The effect of inhaled corticosteroids on the development of emphysema in smokers assessed by annual computed tomography. *COPD* 2009;**6**(2):104-11.

**Sharafkhaneh 2011** *{published data only}*

Sharafkhaneh A, Southard J, Goldman M, Uryniak T, Martin UJ. Long-term effect of budesonide/formoterol pressurized metered-dose inhaler on exacerbations and pulmonary function in patients with chronic obstructive pulmonary disease [Abstract]. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**(Meeting Abstracts):A1599.

**Soriano 2002** *{published data only}*

* Soriano JB, Vestbo J, Pride NB, Kiri V, Maden C, Maier WC. Survival in COPD patients after regular use of fluticasone

propionate and salmeterol in general practice. *European Respiratory Journal* 2002;**20**(4):797-8.

**Southard 2011** *{published data only}*

Southard JG, Sharafkhaneh A, Goldman M, Uryniak T, Martin UJ. Long-term tolerability of budesonide/formoterol pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease and a history of exacerbations [Abstract]. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**(Meeting Abstracts):A1597.

**Stallberg 2008** *{published data only}*

Stallberg B, Andersson EBC, Ekstrom T, Selroos O, Vogelmeier C, Larsson K. Budesonide /formoterol for the treatment of COPD exacerbations in the primary healthcare setting [Abstract]. European Respiratory Society Annual Congress; October 4-8; Berlin. 2008:[P3610].

**Sun 2004** *{published data only}*

Sun D, Yang J, Xu X. Combined seretide and zafirlukast in the treatment of chronic obstructive pulmonary disease (COPD) [Abstract]. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:C22 [Poster 524].

**Sutherland 2006** *{published data only}*

Sutherland ER, Moss TA, Stevens AD, Pak J, Martin RJ. Modulation of sputum gene expression in COPD by fluticasone / salmeterol. *European Respiratory Journal* 2006;**28**(Suppl 50):662s.

**Trofimenko 2006** *{published data only}*

Trofimenko IN, Chernyak BA. The efficacy of salmeterol/ fluticasone (SF) for 6 month's therapy at severe COPD patients. *European Respiratory Journal* 2006;**28**(Suppl 50):30s.

**Vestbo 2004** *{published data only}*

Vestbo J. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease. *Dan. Ugeskrift for Laeger* 2004;**166**(4):271-4.

**Welte 2009** *{published data only}*

Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Efficacy and tolerability of budesonide/ formoterol added to tiotropium in patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2009;**180**(8):741-50.

**Welte 2009a** *{published data only}*

Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Addition of budesonide/formoterol to tiotropium reduces the number of exacerbation days compared with tiotropium alone [Abstract]. *Chest* 2009;**136**(4):26S-f.

**Welte 2009b** *{published data only}*

Welte T, Miravitlles M, Hernandez P, Eriksson G, Peterson S, Polanowski T, et al. Budesonide/formoterol added to tiotropium provides rapid improvements in lung function and ability to undertake morning activities [Abstract]. *Chest* 2009;**136**(4):24S-g.

**Welte 2009c** *{published data only}*

Welte T, Hartman L, Polanowski T, Hernandez P, Miravitlles M, Peterson S, et al. Budesonide/formoterol added to tiotropium is well tolerated and reduces risk of severe exacerbations in COPD patients [Abstract]. American Thoracic Society International Conference; May 15-20; San Diego. 2009:A6188 [Poster #215].

**Welte 2009d** *{published data only}*

Welte T, Miravitlles M, Hernandez P, Peterson S, Polanowski T, Kessler R, et al. Budesonide/formoterol added to tiotropium improves exacerbations and exacerbation-related antibiotic use in patients with COPD [Abstract]. European Respiratory Society Annual Congress; September 12-16; Vienna. 2009:[P2012].

**Wilson 2007** *{published data only}*

Wilson DS, Gillion MS, Rees PJ. Use of dry powder inhalers in COPD. *International Journal of Clinical Practice* 2007;**61**(12):2005-8.

**Worth 2009** *{published data only}*

Worth H, Foerster K, Peterson S, Nihlen U, Magnussen H, et al. Budesonide/formoterol improves exercise tolerance compared with placebo and formoterol in COPD patients [Abstract]. European Respiratory Society Annual Congress; September 12-16; Vienna. 2009:[201].

**Worth 2009a** *{published data only}*

Worth H, Peterson S, Nihlen U, Magnussen H. Improved exercise tolerance with budesonide/formoterol vs placebo and formoterol in COPD patients [Abstract]. American Thoracic Society International Conference, May 15-20, San Diego. 2009:A6193 [Poster #220].

**Worth 2010** *{published data only}*

Worth H, Förster K, Eriksson G, Nihlén U, Peterson S, Magnussen H. Budesonide added to formoterol contributes to improved exercise tolerance in patients with COPD. Respiratory Medicine 2010; Vol. 104, issue 10:1450-9.

**Wouters 2005** *{published data only}*

Creutzberg EC, Bookelmann YJH, Hop WCJ, Postma DS, Wouters EFM. Determinants of health status in patients with COPD. http://www.abstracts2view.com (accessed 1 April 2007):A107 [Poster C31].

Creutzberg EC, Bookelmann YJH, Hop WCJ, Postma DS, Wouters EFM. Predicting factors for an acute exacerbation of COPD in the COSMIC study. http://www.abstracts2view.com (accessed 1 April 2007).

Rizzato G. COPD: Immediate and sustained deterioration after withdrawal of fluticasone in patients under therapy with salmeterol + fluticasone. *Internista* 2005;**13**(4):225-30.

* Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, et al. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial. *Thorax* 2005;**60**(6):480-7.

Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF. The Cosmic COPD and Serentide: A Multi-Center Intervention

and Characterization Study Group. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes immediate and sustained disease deterioration: a randomised controlled trial [A remocao do propionato de fluticasona da terapeutica combinada com salmeterol/fluticasona em doentes com DPOC causa agravamento imediato e mantido; um estudo randomizado e controlado]. *Revista Portuguesa De Pneumologia* 2005;**11**(6):587-9.

Wouters EFM. COPD and seretide: a multi-center intervention and characterisation (COSMIC) study: a rationale and baseline characteristics. *European Respiratory Journal* 2002;**20**(38):P1571.

Wouters EFM, Postma DS, Fokkens B, Hop WCJ, Creutzberg EC. One year withdrawal of fluticasone after three month treatment with combined fluticasone/salmeterol in COPD [Abstract]. American Thoracic Society 100th International Conference; May 21-26; Orlando. 2004:C22 [Poster 516].

**Zhong 2011** *{published data only}*

Zhong N, Zheng J, Wen F, Yang L, Chen P, Xiu Q, et al. Efficacy and safety of inhalation of budesonide/formoterol via turbuhaler in Chinese patients with chronic obstructive pulmonary disease [Abstract]. *Chest* 2011;**140**(4):5225A.

**Zhong 2012** *{published data only}*

Zhong N, Zheng J, Wen F, Yang L, Chen P, Xiu Q, et al. Efficacy and safety of budesonide/formoterol via a dry powder inhaler in Chinese patients with chronic obstructive pulmonary disease. *Current Medical Research and Opinion* 2012;**28**(2):257-65.

## Additional references

**ACP 2011**

ACP, ACCP, ATS, ERS. Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. *Annals of Internal Medicine* 2011;**155**:179-91.

**Barnes 2002**

Barnes PJ. Scientific rationale for inhaled combination therapy with long-acting 2-agonists and corticosteroids. *European Respiratory Journal* 2002;**19**:182-91.

**Cates 2012**

Cates C J. Inhaled corticosteroids in COPD: quantifying risks and benefits. *Thorax* 2012;**68**(6):499-500. [DOI: 10.1136/thoraxjnl-2012-202959]

**Cosio 2009**

Cosio MG, Saetta, M, Agusti A. Immunologic aspects of chronic obstructive pulmonary disease. *New England Journal of Medicine* 2009;**360**:2445-54.

**Dong 2013**

Dong YH, Lin HH, Shau WY, Wu YC, Chang CH, Lai MS. Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials. *Thorax* Jan 2013;**68**(1):48-56.

**Donohue 2005**

Donohue JF. Minimally clinically important differences in COPD lung function. *COPD* 2005;**2**:111–24.

**Ducharme 2010**

Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled corticosteroids versus same dose inhaled corticosteroids for chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* 2010, Issue 5. [DOI: 10.1002/14651858.CD005535.pub2]

**Garcia-Aymerich 2011**

Garcia-Aymerich J, Serra Pons I, Mannino DM, Maas AK, Miller DP, Davis KJ. Lung function impairment, COPD hospitalisations and subsequent mortality. *Thorax* 2011;**66**(7):585-90.

**GOLD 2012**

GINA Science Committee. From the Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA) 2012. http://www.ginasthma.org (accessed 9 July 2013).

**Hanania 2011**

Hanania NA, Celli BR, Donohue JF, Martin UJ. Bronchodilator reversibility in COPD. *CHEST* Oct 2011;**140**(4):1055-63..

**Higgins 2011**

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. www.cochrane-handbook.org.

**Jones 2005**

Jones PW. St. George's Respiratory Questionnaire: MCID. *COPD* March 2005;**2**(1):75-9.

**Karner 2011**

Karner C, Cates CJ. Combination inhaled steroid and long-acting beta2-agonist in addition to tiotropium versus tiotropium or combination alone for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2011, Issue 3. [DOI: 10.1002/14651858.CD008532.pub2]

**Kesten 2007**

Kesten S, Plautz M, Piquette CA, Habib MP, Niewoehner DE. Premature discontinuation of patients: a potential bias in COPD clinical trials. *European Respiratory Journal* 2007;**30**:898-906.

**Leidy 2003**

Leidy NK, Rennard SI, Schmier J, Jones MKC, Goldman M. The Breathlessness, Cough, and Sputum Scale.* The Development of Empirically Based Guidelines for Interpretation. *Chest* 2003;**124**:2182-91.

**McGarvey 2007**

McGarvey LP, John M, Anderson JA, Zvarich MT, Wise RA. Ascertainment of cause-specific mortality in COPD - Operations of the TORCH Clinical Endpoint Committee. *Thorax* 2007;**62**:411-5.

**Nannini 2012**

Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 9. [DOI: 10.1002/14651858.CD006829.pub2]

**Nannini 2013**

Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta$_2$-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2013, Issue 8. [DOI: 10.1002/14651858.CD006826.pub2]

**NCGC2010**

National Clinical Guidelines Centre. Management of chronic obstructive pulmonary disease in adults in primary and secondary care. http://publications.nice.org.uk/chronic-obstructive-pulmonary-disease-cg101 (accessed 9 July 2013).

**Ni Chroinin 2009**

Ni Chroinin M, Greenstone I, Lasserson TJ, Ducharme FM. Addition of long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults and children. *Cochrane Database of Systematic Reviews* 2009, Issue 4. [DOI: 10.1002/14651858.CD005307.pub2]

**Oba 2017**

Oba Y, Fadila M, Keeney E, Dias S. Fixed-dose combination inhalers compared to long-acting bronchodilators for COPD: a network meta-analysis (Protocol). *Cochrane Database of Systematic Reviews* 2017, Issue 3. [DOI: 10.1002/14651858.CD012620]

**RevMan 2011 [Computer program]**

The Cochrane Collaboration. Copenhagen: The Nordic Cochrane Centre. Review Manager (RevMan). Version 5.1.. The Cochrane Collaboration. Copenhagen: The Nordic Cochrane Centre, 2011.

**Suissa 2006**

Suissa S. Statistical treatment of exacerbations in therapeutic trials of chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 2006;**173**(8):842-6.

**UPLIFT 2008**

Tashkin DP, Celli B, Senn S, Burkhart D, Kesten S, Menjoge S, et al. for the UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *New England Journal of Medicine* Oct 9 2008;**359**(15):1543-54.

**Vestbo 2004**

Vestbo J, The TORCH Study Group. The TORCH (TOwards a Revolution in COPD Health) survival study protocol. *European Respiratory Journal* 2004;**24**(2):206-10.

**Visual Rx**

Cates CJ. Visual Rx Version 3.0. www.nntonline.net (accessed 9 July 2013).

**Walters 2007**

Walters EH, Gibson PG, Lasserson TJ, Walters JAE. Long-acting beta2-agonists for chronic asthma in adults and children where background therapy contains varied or no inhaled corticosteroid. *Cochrane Database of Systematic Reviews* 2007, Issue 1. [DOI: 10.1002/14651858.CD001385.pub2]

**Yang 2012**

Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2012, Issue 7. [DOI: 10.1002/14651858.CD002991.pub3]

## References to other published versions of this review

**Nannini 2003**

Nannini L, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD003794.pub2]

**Nannini 2004**

Nannini L, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/14651858.CD003794.pub2]

**Nannini 2007**

Nannini L, Cates CJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta-agonist in one inhaler versus inhaled steroids for chronic obstructive pulmonary disease. *Cochrane Database of Systematic Reviews* 2007, Issue 4. [DOI: 10.1002/14651858.CD006826]

* Indicates the major publication for the study

# CHARACTERISTICS OF STUDIES

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

### Barnes 2006

| | |
|---|---|
| Methods | Parallel-group design |

**Barnes 2006** *(Continued)*

| | |
|---|---|
| | Randomisation: not clear<br>Blinding: double-blind, identical inhaler devices used<br>Allocation concealment: unclear<br>Excluded: not described<br>Withdrawals: described<br>Trial duration: 13 weeks<br>Baseline characteristics: comparable<br>Intention-to-treat analysis stated |
| Participants | • Setting: 18 centres in Western and Eastern Europe<br>• Participants randomly assigned: 141 (two groups: FP/SAL combination: 74; placebo: 67)<br>• Baseline characteristics: 64 years; mean $FEV_1$: 1.68 L; mean $FEV_1$: 59 %predicted; mean $FEV_1$ reversibility: 3.9 (of predicted)<br>• Inclusion criteria: M/F 40 to 80 years of age; diagnosis of COPD (according to GOLD criteria); ≥ 2 on Medical Research Council (MRC) dyspnoea scale; poor reversibility of < 10% predicted normal<br>• Exclusion criteria: current diagnosis of asthma; recent exacerbation (within four weeks); long-term oxygen therapy (LTOT); pulmonary rehabilitation; ICS, antileukotriene or tiotropium within 14 days of visit |
| Interventions | Run-in phase: four weeks. Treatment during this phase of the study not described<br>• FPS 500/50 mcg twice daily<br>• Placebo<br>Inhaler device: dry powder inhaler (DPI) |
| Outcomes | Exacerbations; withdrawals; adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised; no other information available |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | Low risk | All withdrawals clearly accounted for, although slightly higher completion rate in the placebo group (95% in the placebo group, 88% in the treatment group) |
| Incomplete outcome data (attrition bias): All other outcomes | Low risk | All withdrawals clearly accounted for, although slightly higher completion rate in the placebo group (95% in the placebo group, 88% in the treatment group) |
| Selective reporting (reporting bias) | Low risk | No evidence of reporting bias |

**Bourbeau 2007**

| | |
|---|---|
| Methods | Randomised, double-blind, parallel-group, placebo-controlled. Duration three months |
| Participants | • Setting: two respiratory centres: the Montreal Chest Institute and Hospital Laval, Canada<br>• Participants randomly assigned: 40 (FPS: 19, placebo: 21)<br>• Baseline characteristics: mean age: 64 years; mean $FEV_1$ % predicted: 59%; COPD severity (GOLD): mild to very severe; males: 90%<br>• Inclusion criteria: COPD (GOLD criteria), age ≥ 40 and ≤ 75 years; ≥ 10 pack-years smoking history; post-bronchodilator $FEV_1$ ≥ 25% of predicted; $FEV_1$/forced vital capacity (FVC) ≤ 0.70<br>• Exclusion criteria: asthma or atopy; any other active lung disease, requiring home oxygen or with raised carbon dioxide tension (> 44 mm Hg); α1-antitrypsin deficiency; recent exacerbation (in the past four weeks); controlled medical condition or hypersensitivity to inhaled corticosteroids and bronchodilators |
| Interventions | Four-week washout period from inhaled corticosteroids and long-acting $beta_2$-agonists<br>• FPS 500/50 mcg twice daily<br>• Placebo twice daily<br>Additonal treatment groups not covered in this review<br>• Fluticasone 500 mcg twice daily<br>Inhaler device: DPI (Diskus) |
| Outcomes | • Numbers of CD8+ T lymphocytes and CD68+ macrophages, neutrophils and eosinophils<br>• Spirometric measurements ($FEV_1$ and FVC)<br>• CRDQ (Chronic Respiratory Disease Questionnaire)<br>• Bronchoalveolar lavage (BAL) and sputum induction (baseline, week 4 and week 12)<br>• ATS-DLD 78 questionnaire<br>• Lung volumes and carbon monoxide transfer factor (TLCO)<br>• Adverse events |
| Notes | Powered to detect differences in cell numbers from bronchoscopy and BAL rather than clinical outcomes |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was performed using a central computer-generated list of random numbers, which was stratified by centre and used a block size of six set up by a data management/randomisation company |
| Allocation concealment (selection bias) | Unclear risk | Allocation procedure not described |
| Blinding (performance bias and detection bias) All outcomes | Low risk | A procedure was established by GEREQ, which was in possession of the treatment code, to ensure that the treatment code would be broken only in accordance with the protocol and the criteria set up for unbinding of the study<br>Observers were blinded not only to drug treatment but also to whether the biopsies were performed before or after treatment |
| Incomplete outcome data (attrition bias): Mortality | High risk | Higher attrition rates in placebo group (71% completed in placebo group vs 100% in treatment group) |

**Bourbeau 2007** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias): All other outcomes | High risk | Higher attrition rates in placebo group (71% completed in placebo group vs 100% in treatment group) |
| Selective reporting (reporting bias) | Unclear risk | "Analysis of bronchoalveolar lavage (BAL) and sputum induction results has not yet been completed and will be the subject of a future publication"<br><br>Spirometric data and CRQ data not presented numerically—"No evidence of improvement in clinical outcomes was observed as measured by lung function as well as health-related quality of life questionnaires" |

**Calverley 2003**

| | |
|---|---|
| Methods | Parallel-group study<br>Randomisation: unclear<br>Blinding: double-blind (identical inhaler devices)<br>Trial duration: 52 weeks with two-week run-in of treatment optimisation<br>Allocation concealment: unclear<br>Withdrawals: stated<br>Intention-to-treat analysis: stated |
| Participants | • Setting: 109 centres in 15 countries<br>• Participants randomly assigned: 510 (BDF: 254; placebo: 256). Additional treatment groups not covered in this review: budesonide: 257; formoterol: 255<br>• Baseline characteristics: mean age: 64; mean $FEV_1$ L: 1; mean $FEV_1$ % predicted: 36; mean SGRQ: 48<br>• Inclusion criteria: GOLD defined COPD (stages III and IV); ≥ 40 years; COPD symptoms > 2 years; smoking history ≥ 10 pack-years; $FEV_1/VC \leq 70\%$ pre-BD; $FEV_1 \leq 50\%$ predicted; use of SABAs as reliever medication; ≥ 1 COPD exacerbation requiring oral corticosteroids/antibiotics two to 12 months before first clinic visit<br>• Exclusion criteria: history of asthma/rhinitis before 40 years of age; any relevant cardiovascular disorders; exacerbation of COPD requiring medical intervention within four weeks of run-in/during run-in phase; non-allowed medications: oxygen therapy; ICS (aside from study medication), disodium cromoglycate, leukotriene-antagonists, 5-LO inhibitors, bronchodilators (other than study medication and prn terbutaline 0.5 mg), antihistamines, medication containing ephedrine, beta-blocking agents |
| Interventions | Run-in phase: All participants received 30 mg oral prednisolone twice daily and 2 × 4.5 mg formoterol twice daily (two weeks)<br><br>• BDF: 320/9 mcg twice daily<br>• Placebo (lactose monohydrate)<br><br>Additional treatment groups not covered in this review<br><br>• Budesonide: 400 mcg twice daily<br>• Formoterol: 9 mcg twice daily<br><br>Inhaler device: Turbuhaler |
| Outcomes | Time to first exacerbation; change in postmedication $FEV_1$; number of exacerbations; time to and number of oral corticosteroid–treated episodes; am and pm PEF, slow vital capacity, health-related quality of life (HRQL); symptoms; use of reliever medication; adverse events |
| Notes | Classified as 'poorly reversible population'<br><br>P values used to calculate pooled SEMs for the following outcomes: HRQL; $FEV_1$; rescue medication |

**Calverley 2003** *(Continued)*

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised; no other information available |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (71% completion in the BDF group and 59% in the placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (71% completion in the BDF group and 59% in the placebo group) |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

**Dal Negro 2003**

| | |
|---|---|
| Methods | Parallel-group study<br>Randomisation: unclear<br>Blinding: double-blind<br>Method of randomisation: not reported<br>Allocation concealment: unclear<br>Trial duration: 52 weeks<br>Withdrawals: stated<br>Baseline characteristics: comparable intention-to-treat analysis: yes |
| Participants | • Setting: single centre in Italy<br>• Participants randomly assigned: 12 (FPS: six; placebo: six). Additional treatment groups not covered in this review: salmeterol: six<br>• Baseline characteristics: age range: 53 to 78; moderate COPD; mean $FEV_1$ (L): 1.46; mean $FEV_1$ (% predicted): 48; mean PEF (L/min): 180; mean reversibility (% baseline): 3.2<br>• Inclusion criteria: baseline $FEV_1$ % predicted: ≤ 80%; $FEV_1$ > 800 mL; $FEV_1$/FVC ratio: ≤ 70% predicted; $FEV_1$ change ≤ 12% predicted post 400 mg salmeterol; regular treatment with oral theophylline 20 mg twice daily; SABA as required (for at least six months); current/ex-smokers with smoking history of at least 10 pack-years<br>• Exclusion criteria: current evidence of asthma or other pulmonary diseases; regular treatment with ICS; unstable respiratory disease requiring oral/parenteral corticosteroids within four weeks before the beginning of the study; changes in COPD medication in last four weeks before entering run-in; upper/lower respiratory tract infection within four weeks before last screening visit; unstable angina/unstable arrhythmias; recent myocardial infarction (MI)/heart failure; insulin-dependent diabetes mellitus; neuropsychiatric disorders; concurrent use of medications that affect COPD (e.g. beta-blockers) or interact with methylxanthine products (e.g. macrolides or fluoroquinolones); known/suspected hypersensitivity to ICS, $beta_2$-agonist or lactose; evidence of alcohol abuse. |
| Interventions | Run-in: two weeks' treatment with theophylline and as required SABA |

**Dal Negro 2003** *(Continued)*

| | |
|---|---|
| | • FPS 50/250 mcg twice daily<br>• Placebo<br><br>Additional treatment groups not covered in this review<br><br>• Salmeterol 50 mcg twice daily<br><br>Participants were receiving concomitant therapy: SABA as required and theophylline 400 µg/d for 12 months<br><br>Inhaler device: Diskus |
| Outcomes | $FEV_1$, Delta $FEV_1$, PEF am, symptom scores, rescue medication use, exacerbations (event rate and mean number per year) |
| Notes | Classified as 'poorly reversible population'<br><br>Mild exacerbation: requirement for increase in SABA as required by > 2 occasions/24 h on two or more consecutive days compared with baseline mean of last seven days of run-in<br><br>Moderate exacerbation: condition requiring treatment with antibiotics and/or oral corticosteroids<br><br>Severe exacerbation: condition requiring emergency hospital treatment and/or hospitalisation |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised; no other information available |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | Unclear risk | 100% completion in both groups but only 12 participants |
| Incomplete outcome data (attrition bias): All other outcomes | Unclear risk | 100% completion in both groups but only 12 participants |
| Selective reporting (reporting bias) | Unclear risk | All stated outcomes reported but choice of end points used for significance calculations not always clear |

**Doherty 2012**

| | |
|---|---|
| Methods | Randomized, placebo-controlled, double-blind, double-dummy, parallel groups. Duration 26 weeks with a 26-week safety extension |
| Participants | • Setting: 164 centres in North, Central and South America, Europe, Africa and Asia<br>• Participants randomly assigned: 700 (MF/F 400/10: 225, MF/F 200/10: 239, placebo: 236)<br>• Baseline characteristics: mean age 59.3; mean $FEV_1$ % predicted: 38.2%; COPD severity: moderate to very severe; males 74.3% |

**Doherty 2012** *(Continued)*

- Inclusion criteria: age ≥ 40 years; $FEV_1/FVC < 0.70$, postbronchodilator $FEV_1$ 25% to 60% predicted; symptoms of COPD (e.g. chronic cough and sputum production not attributable to another disease) for at least 24 months before enrolment; clinically acceptable laboratory tests at screening; adequate form of birth control if of child-bearing potential
- Exclusion criteria: asthma or significant reversibility; COPD exacerbation within four weeks; long-term oxygen; lung cancer; alpha-1-antitrypsin deficiency; lung surgery; cataract extractions in both eyes; glaucoma or intraocular pressure ≥ 22 mm Hg in either eye; clinically significant medical illness(es) that could interfere with the study

| | |
|---|---|
| Interventions | Two-week washout/run-in period, in which previous long-acting COPD treatments (LABA, ICS, LABA/ICS or long-acting anticholinergic (e.g. tiotropium)) were discontinued and substituted<br><br>with a short-acting beta$_2$-agonist (SABA)/short-acting anticholinergic combination<br><br>• MF/F 400/10 mcg twice daily (26 weeks + 26-week safety extension)<br>• MF/F 200/10 mcg twice daily (26 weeks + 26-week safety extension)<br>• Placebo (26 weeks)<br><br>Additional treatment groups not covered in this review<br><br>• MF 400 mcg twice daily (26 weeks + 26-week safety extension)<br>• F 10 µg twice daily (26 weeks + 26-week safety extension)<br>• Inhaler device: MDI |
| Outcomes | • MF/F 400/10 µg compared with MF 400 µg for $FEV_1$ area under the curve from 0 to 12 hours postdose at 13-week end point<br>• MF/F 400/10 µg and MF/F 200/10 µg compared with F 10 µg for AM predose (trough) FEV1<br>• Changes from baseline in $FEV_1$ area under the curve from 0 to 12 hours postdose day 1; weeks 1, 13, 26; and the 26-week end point<br>• Changes from baseline in trough $FEV_1$ each visit and at the 26-week end point<br>• Serial spirometry tests<br>• Respiratory health status (SGRQ)<br>• COPD symptom-free nights<br>• Partly stable COPD<br>• Time to first COPD exacerbation<br>• Adverse events |
| Notes | Post hoc in a subgroup of participants with baseline $FEV_1$ < 50% predicted (severe or very severe COPD) for coprimary end points<br><br>COPD exacerbations were categorised as mild, moderate or severe<br><br>A mild exacerbation was defined as a clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of<br><br>SABA/short-acting anticholinergic, or ≥ two nebulized treatments/d of 2.5 mg SABA/short-acting anti-cholinergic) on any two consecutive days<br><br>A moderate exacerbation was defined as a clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease<br><br>A severe exacerbation was defined as a deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**Doherty 2012** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "At baseline, subjects were randomised in a 1:1:1:1:1 ratio"—no further details, but likely to be low risk |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Placebo-controlled, double-blind, double-dummy |
| Incomplete outcome data (attrition bias): Mortality | Unclear risk | Moderate attrition rate across all treatment groups (84% completion in higher-dose treatment group, 85% in the lower-dose treatment group, 80% in the placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | Unclear risk | Moderate attrition rate across all treatment groups (84% completion in higher-dose treatment group, 85% in the lower-dose treatment group, 80% in the placebo group) |
| Selective reporting (reporting bias) | Unclear risk | Not all outcomes are supported with data |

**Hanania 2003**

| | |
|---|---|
| Methods | Parallel-group study<br>Randomisation: method unclear<br>Blinding: double-blind<br>Allocation concealment: unclear<br>Excluded: described<br>Withdrawals: described<br>Trial duration: 24 weeks with 2-week run-in period<br>Baseline characteristics: comparable<br>Intention-to-treat analysis: not stated |
| Participants | • Setting: USA, multi-centre (76 hospitals)<br>• Participants randomly assigned: 368 (FPS: 183; placebo: 185). Additional treatment groups not covered in this review: salmeterol: 177; fluticasone: 183<br>• Baseline characteristics: mean age: 64; mean $FEV_1$: 1.27 L (42% predicted)<br>• Inclusion criteria: stable COPD; $FEV_1$ 40% to 65% predicted; $FEV_1$/FVC < 70% predicted; symptoms of chronic bronchitis and moderate dyspnoea<br>• Exclusion criteria: current diagnosis of asthma, use of oral steroids in past six weeks, abnormal electrocardiogram (ECG), LTOT, moderate to severe exacerbation in run-in. Other significant medical disorder |
| Interventions | Run-in: two weeks' treatment with placebo inhaler and as required SABA<br>• FPS 50/250 mcg twice daily<br>• Placebo<br>Additional treatment groups not covered in this review<br>• Salmeterol 50 mcg twice daily<br>• Fluticasone 250 mcg twice daily<br>Inhaler device: Diskus |

**Hanania 2003** *(Continued)*

| | |
|---|---|
| Outcomes | Lung function: change in $FEV_1$ from baseline to end of study (M); PEF data not stratified by reversibility; quality of life: CRDQ, chronic bronchitis symptoms questionnaire (CBSQ) not stratified by reversibility; Dyspnoea and symptoms: transitional dyspnoea index (TDI); baseline dyspnoea index not stratified by reversibility; exacerbations; rescue salbutamol use |
| Notes | $FEV_1$ reversibility < 12% or 200 mL (of baseline $FEV_1$). Reversibility stratified data. Mean percentage increase in non-reversible participants = 8.8 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised; no other information available |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (70% completion in treatment group, 68% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (70% completion in treatment group, 68% in placebo group) |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

**Lapperre 2009**

| | |
|---|---|
| Methods | Ramdomised, placebo-controlled, parallel-group study. Duration 30 months |
| Participants | • Setting: two university medical centres in The Netherlands<br>• Participants randomly assigned: 57 (FPS: 28, placebo: 29)<br>• Baseline characteristics: mean age: 60.5; mean percentage predicted $FEV_1$: 61%; COPD severity: moderate to severe (GOLD); males: 85.5%<br>• Inclusion criteria: age: 45 to 75 years; ≥ 10 pack-years smoking history; lung function GOLD stages II and III<br>• Exclusion criteria: asthma, ICS within six months |
| Interventions | No run-in<br>• FPS 500/50 mcg twice daily for 30 months<br>• Placebo twice daily for 30 months<br>Additonal treatment groups not covered in this review<br>• Fluticasone 500 mcg twice daily for the first six months, followed by placebo, twice daily, for 24 months<br>• Fluticasone 500 mcg twice daily for 30 months<br>Inhaler device: DPI (Diskus) |

**Lapperre 2009** *(Continued)*

| | |
|---|---|
| Outcomes | • Inflammatory cell counts in bronchial biopsies and induced sputum<br>• Postbronchodilator spirometry rate of $FEV_1$ decline<br>• Hyperresponsiveness to methacholine PC20 assessed by standardised procedures<br>• Dyspnoea score by modified Medical Research Council (MRC) dyspnoea scale<br>• Health status by St George's Respiratory Questionnaire (SGRQ)<br>• Clinical COPD Questionnaire (CCQ) |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | At entry, an independent randomisation centre provided participant and medication numbers by using a minimisation procedure that balanced treatment groups |
| Allocation concealment (selection bias) | Unclear risk | No details given of allocation procedure |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Study medications were individually numbered, with 60 doses per inhaler; all active treatment medications and placebo were identical in appearance |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (75% completion in treatment group, 69% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (75% completion in treatment group, 69% in placebo group) |
| Selective reporting (reporting bias) | Low risk | All outcome measures described are reported |

**Mahler 2002**

| | |
|---|---|
| Methods | Parallel-group study<br>Randomisation: stratified by reversibility and investigative site<br>Blinding: double-blind<br>Allocation concealment: unclear<br>Excluded: described.<br>Withdrawals: described.<br>Trial duration: 24 weeks<br>Baseline characteristics: comparable<br>Intention-to-treat analysis: stated |
| Participants | • Setting: multi-centre study (65 centres)<br>• Participants randomly assigned: 346 (FPS: 165; placebo: 181); additional treatment groups not covered in this review: salmeterol: 160; fluticasone: 168<br>• Baseline characteristics: mean age: 63; $FEV_1$: 1.2 to 3 L<br>• Inclusion criteria: participants with COPD according to ATS guidelines; baseline prebronchodilation $FEV_1$ < 65% predicted and > 0.70 L; baseline prebronchodilation $FEV_1$/FVC < 70% predicted; age > 40 years; 20 pack-years history smoking; day or night symptoms present on four of last seven days during run-in period |

**Mahler 2002** *(Continued)*

| | |
|---|---|
| | • Exclusion criteria: history of asthma; corticosteroid use in last six weeks; abnormal ECG; oxygen therapy; moderate or severe exacerbation during run-in; significant concurrent disease |
| Interventions | Run-in: two weeks' treatment with placebo inhaler and as required SABA<br>• FPS 500/50 mcg twice daily<br>• Placebo<br>Additional treatment groups not covered in this review<br>• Salmeterol 50 mcg twice daily<br>• Fluticasone 500 mcg twice daily<br>Inhaler device: Diskus |
| Outcomes | Lung function: change in $FEV_1$ from baseline to end of study (M); quality of life: CRDQ, CBSQ not stratified by reversibility; dyspnoea and symptoms: end of study dyspnoea (TDI) Exacerbations. Rescue salbutamol use |
| Notes | COPD participants reversible and non-reversible; < 15% (baseline) improvement in $FEV_1$ to salbutamol; reversibility stratified data; mean $FEV_1$ reversibility 11.0% |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised; stratified by reversibility and investigative site |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (68% completion in treatment group, 62% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (68% completion in treatment group, 62% in placebo group) |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

**O'Donnell 2006**

| | |
|---|---|
| Methods | Parallel-group design<br>Randomisation: not clear<br>Blinding: double-blind<br>Allocation concealment: unclear<br>Excluded: not described<br>Withdrawals: described<br>Trial duration: 8 weeks<br>Baseline characteristics: comparable |

**O'Donnell 2006** *(Continued)*

| | |
|---|---|
| | Intention-to-treat analysis stated |
| Participants | • Setting: 22 centres in North America<br>• Participants randomly assigned: 126 (FPS: 62; placebo: 64)<br><br>Additional treatment groups not covered in this review<br><br>• Salmeterol: 59<br><br>Baseline characteristics: 65 years; $FEV_1$: 1.12 L<br>Inclusion criteria: M/F ≥ 40 years of age; diagnosis of COPD; ≥ 10 pack-years; baseline Borg dyspnoea index < 7; $FEV_1$ < 70% predicted; functional residual capacity (FRC) ≥ 120% predicted<br>Exclusion criteria: current diagnosis of asthma; use of xanthines/LABA/oral corticosteroids/ICS |
| Interventions | Run-in: two weeks; single-blind placebo<br><br>• FPS 500/50 mcg twice daily<br>• Placebo<br><br>Additional treatment groups not covered in this review<br><br>• Salmeterol 50 mcg twice daily<br><br>Inhaler device: DPI |
| Outcomes | Withdrawals; exercise time; $FEV_1$; adverse events |
| Notes | Study downloaded from ctr.gsk.co.uk |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised; no other information available |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | Low risk | Low attrition rates in both groups (95% completion in treatment group, 92% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | Low risk | Low attrition rates in both groups (95% completion in treatment group, 92% in placebo group) |
| Selective reporting (reporting bias) | Unclear risk | Does not contribute data to the analysis of exacerbations as rate ratios, mortality or hospitalisations |

**Rennard 2009**

| | |
|---|---|
| Methods | Randomized, double-blind, double-dummy, parallel-group, active- and placebo-controlled. Duration 12 months |

**Rennard 2009** *(Continued)*

| | |
|---|---|
| Participants | • Setting: 237 centres in US, Europe and Mexico<br>• Participants randomly assigned: 1469 (BDF 320/9: 494, BDF 160/9: 494, placebo 481)<br>• Baseline characteristics: mean age: 62.3; mean % predicted $FEV_1$: 39.7%; COPD severity: moderate to very severe; males: 63.5%<br>• Inclusion criteria: age ≥ 40 years; COPD for > 2 years; ≥ 10 pack-years smoking history; pre-bronchodilator ($FEV_1$) ≤ 50% predicted; pre-bronchodilator $FEV_1$/forced vital capacity (FVC) < 70%; modified Medical Research Council dyspnoea scale score ≥ 2; COPD exacerbation within one to 12 months (see Tashkin 2008)<br>• Exclusion criteria: asthma or allergic rhinitis before 40 years of age; oral steroid use; any significant disease or disorder that may jeopardise the safety of the participant (see Tashkin 2008) |
| Interventions | Two-week run-in period, during which participants received ICS monotherapy if previously stable on ICS (alone or in combination) and ipratropium bromide at a fixed dose if previously receiving anticholinergics. Albuterol (salbutamol) was permitted for rescue use throughout the study<br>• BDF 320/9 mcg twice daily<br>• BDF 160/9 mg twice daily<br>• Placebo twice daily<br>Additional treatment groups not covered in this review<br>• Formoterol 9 mg twice daily<br>Inhaler device: pMDI/DPI |
| Outcomes | • Predose and one hour postdose $FEV_1$ over the 12-month treatment period<br>• Participant-reported outcome variables regarding disease status (including PEF), collected via questionnaires and diaries<br>• Health care utilisation<br>• Safety variables, including adverse events, vital signs, ECG, physical examination, haematology and clinical chemistry |
| Notes | Subgroup performed serial spirometry assessment<br>COPD exacerbation was defined as worsening of COPD requiring an oral corticosteroid<br>or hospitalisation |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised, but no details given of sequence generation |
| Allocation concealment (selection bias) | Unclear risk | No details of allocation procedure given |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Double-blind, double-dummy; blinding maintained until end of 12-month study period |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rate across all treatment groups (73% completion in higher-dose treatment group, 71% in lower-dose treatment group, 64% in placebo group) |

**Rennard 2009** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rate across all treatment groups (73% completion in higher-dose treatment group, 71% in lower-dose treatment group, 64% in placebo group) |
| Selective reporting (reporting bias) | Unclear risk | All primary and secondary outcomes reported, although numerical data not available for all outcomes<br><br>Average $FEV_1$ was listed as a coprimary outcome in the methods section but as a secondary outcome in the results section |

**SCO104925**

| | |
|---|---|
| Methods | Randomized, double-blind, placebo-controlled, parallel-group. Duration 12 weeks |
| Participants | • Setting: 11 centres: four centres in the Russian Federation, four centres in the United States, two centres in Chile and one centre in Estonia<br>• Participants randomly assigned: 81 (FPS: 39, placebo: 42)<br>• Baseline characteristics: mean age: 64.4; mean $FEV_1$ 5 predicted: not given; COPD severity: moderate to severe; males: 79%<br>• Inclusion criteria: ≥ 40 years of age; clinical history of COPD with evidence of bronchitis; ≥ 10 pack-years smoking history; $FEV_1$/FVC ≤ 70% and measured postalbuterol $FEV_1$ ≥ 30% and ≤ 70% of predicted normal<br>• Exclusion criteria: child-bearing potential |
| Interventions | No run-in described<br><br>• FPS 500/50 mcg<br>• Placebo<br><br>Additional treatment groups not covered in this review<br><br>• Fluticasone 500 mcg<br>• Salmeterol 50 mcg |
| Outcomes | • Predose resistance difference between 5 Hz and 15 Hz (R5 to R15) as measured by IOS<br>• Predose and two hours postdose low-frequency reactance area (AX); two hours postdose R5 to R15; postalbuterol computed tomography (CT) parameters of area of airway wall (Aaw) and area of airway lumen (Ai)<br>• Adverse events |
| Notes | Trial designed to assess novel outcome measures, clinical efficacy. No relevant outcomes for meta-analysis apart from adverse events |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised but no details of sequence generation |
| Allocation concealment (selection bias) | Unclear risk | No details of allocation procedure |
| Blinding (performance bias and detection bias) | Low risk | "Double-blind, placebo-controlled" |

**SCO104925** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias): Mortality | Unclear risk | Moderate attrition rates in both groups (90% completion in treatment group, 90% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | Unclear risk | Moderate attrition rates in both groups (90% completion in treatment group, 90% in placebo group) |
| Selective reporting (reporting bias) | Low risk | All outcome measures reported |

**SFCT01**

| | |
|---|---|
| Methods | Parallel-group design<br>Randomisation: not clear<br>Blinding: double-blind<br>Allocation concealment: unclear<br>Excluded: not described<br>Withdrawals: described<br>Trial duration: 52 weeks<br>Baseline characteristics: comparable<br><br>Intention-to-treat analysis stated |
| Participants | • Setting: 49 centres in Italy, 7 in Poland<br>• Participants randomly assigned: 256 (FPS: 131; placebo: 125)<br><br>Additional treatment groups not covered in this review<br><br>• Fluticasone: 131<br><br>Baseline characteristics: 65 years; $FEV_1$: not reported<br>Inclusion criteria: M/F ≥ 40 years of age; diagnosis of COPD; ≥ 10 pack-years; $FEV_1$ < 70% predicted and > 800 mL; reversibility < 10% predicted normal (and < 200 mL)<br>Exclusion criteria: not described |
| Interventions | Run-in: two weeks. All maintenance LABA and ICS treatment ceased<br><br>• FPS 500/50 mcg twice daily<br>• Placebo<br><br>Additional treatment groups not covered in this review<br><br>• Fluticasone 500 mcg twice daily<br><br>Inhaler device: MDI |
| Outcomes | Withdrawals; exacerbations; $FEV_1$; adverse events |
| Notes | Unpublished study downloaded from ctr.gsk.co.uk |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|

**SFCT01** *(Continued)*

| | | |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Described as randomised; no other information available |
| Allocation concealment (selection bias) | Unclear risk | Information not available |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (66% completion in treatment group, 68% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (66% completion in treatment group, 68% in placebo group) |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

**Sin 2008**

| | |
|---|---|
| Methods | Double-blind, randomised, placebo-controlled, parallel-group. Duration four weeks |
| Participants | • Setting: 11 centres, Western Canada<br>• Participants randomly assigned: 137 (FPS: 92, placebo: 45)<br>• Baseline characteristics: mean age: 68.4; mean $FEV_1$ % predicted: 46.4%; COPD severity: moderate to very severe; males: 62.7%<br>• Inclusion criteria: age ≥ 40 years; clinical diagnosis of COPD (GOLD); $FEV_1$ < 80% predicted; $FEV_1$/FVC < 0.70; ≥ 10 pack-years smoking history<br>• Exclusion criteria: exacerbations in last four weeks: known chronic systemic infections or inflammatory conditions; solid organ transplantation; myocardial infarction or cerebrovascular accident within the past three months; child-bearing potential; participation in a drug trial within the past four weeks; unlikely to survive longer than six months; URTI in last four weeks; unable to follow instructions; long-term oral theophylline use and unable or unwilling to stop<br>• Use of oral corticosteroids or long-term immunosuppressive agents |
| Interventions | Run-in phase during which participants received fluticasone (500 mcg twice daily) for four weeks (short-acting $beta_2$-agonists (e.g. salbutamol) and/or anticholinergic (ipratropium) were allowed as rescue medication) followed by a medication withdrawal phase, wherein inhaled corticosteroids, LABA and theophylline products were withdrawn for four weeks (SABA (e.g. salbutamol) and/or anticholinergic (ipratropium) inhalers allowed as rescue medications)<br>• FPS 500/50 mcg twice daily<br>• Placebo twice daily<br>Additonal treatment groups not covered in this review<br>• Fluticasone 500 mcg twice daily<br>Inhaler device: DPI (Diskus) |
| Outcomes | • Serum C-reactive protein (CRP), interleukin-6 (IL-6) and surfactant protein D (SPD)<br>• Health status (SGRQ)<br>• $FEV_1$ and FVC |

**Sin 2008** *(Continued)*

Notes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomisation was carried out centrally according to a computer-generated sequence stratified according to current smoking status with allocation concealment in a 1 (placebo arm) to 2 (fluticasone four arms) to 2 (fluticasone/salmeterol) distribution ratio |
| Allocation concealment (selection bias) | Low risk | “With allocation concealment”; however, further details not given |
| Blinding (performance bias and detection bias) All outcomes | Low risk | During this phase (RCT), all participants and study personnel will be blinded to the treatment assignment. (For safety reasons, during severe exacerbations (i.e. those requiring hospitalisation or emergency visit for COPD), the treating physician can break the "code" and place study participants on medications needed to treat the exacerbation) |
| Incomplete outcome data (attrition bias): Mortality | Unclear risk | Higher attrition in placebo group (96% completion in treatment group, 87% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | Unclear risk | Higher attrition in placebo group (96% completion in treatment group, 87% in placebo group) |
| Selective reporting (reporting bias) | Unclear risk | All outcome measures stated in protocol have been reported, with exception of “Other secondary molecules such as IL-8, tumour necrosis factor-alpha, monocyte chemoattractant protein and other molecules will be measured at a later date as part of a post hoc exploratory work”. Also SPD levels reported extensively but did not feature in the protocol |

**Szafranski 2003**

| | |
|---|---|
| Methods | Parallel-group study<br>Randomisation: randomised, double-blind, placebo-controlled parallel-group trial<br>Duration: 52 weeks<br>Methods of randomisation: computer-generated scheme at AstraZeneca, Lund, Sweden. At each centre, eligible participants received an enrolment code, and then after run-in, participants were allocated the next consecutive participant number.<br>Allocation concealment: adequate<br>Blinding: All Turbuhaler inhalers were identical to ensure that the participant, the pharmacist and the investigator were blinded to the allocated treatment<br>Excluded: not stated<br>Withdrawals: stated<br>Intention-to treat-analysis: stated |
| Participants | • Setting: 89 centres in Central and South America, Europe and South Africa<br>• Participants: 413 (BDF: 208; placebo: 205)<br><br>Additional treatment groups not covered in this review<br><br>• Formoterol: 201; budesonide: 198<br><br>Baseline characteristics: mean age: 64 years; mean $FEV_1$ % predicted: 36%; mean reversibility: 6% predicted normal |

**Szafranski 2003** *(Continued)*

| | |
|---|---|
| | Inclusion criteria: age ≥ 40 years; COPD for ≥ 2 years; smoking history ≥ 10 pack-years; $FEV_1$ ≤ 50% predicted; $FEV_1$/FVC ≤ 70%; symptom score ≥ 2 during at least seven days of run-in; use of bronchodilators for reliever medication; ≥ 1 severe COPD exacerbation within two to 12 months before study entry<br>Exclusion criteria: history of asthma/rhinitis before age 40; using beta-blockers; current respiratory tract disease other than COPD |
| Interventions | Run-in: two weeks. Treatment with prn SABA only<br>• BDF 320/9 mcg twice daily<br>• Placebo<br>Additional treatment groups not covered in this review<br>• Budesonide 400 µg twice daily<br>• Formoterol 9 µg twice daily<br>Inhaler device: Turbuhaler |
| Outcomes | Symptoms, adverse events, exacerbations, lung function |
| Notes | Classified as 'poorly reversible' subgroup; exacerbation defined as requirement of oral steroids and/or antibiotics and/or hospitalisation for respiratory symptoms; mild exacerbation defined as requirement of ≥ 4 inhalations per day<br>P values used to calculate pooled standard errors of the mean (SEMs) for following outcomes: symptoms; rescue medication usage |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated scheme |
| Allocation concealment (selection bias) | Low risk | At each centre, eligible participants received an enrolment code, and then after run-in, participants were allocated to the next consecutive participant number |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (72% completion in treatment group, 56% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (72% completion in treatment group, 56% in placebo group) |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

**Tashkin 2008**

| | |
|---|---|
| Methods | Randomised, double-blind, double-dummy, placebo-controlled, parallel-group. Duration six months |
| Participants | • Setting: 194 centres in the US, Czech Republic, the Netherlands, Poland and South Africa |

**Tashkin 2008** *(Continued)*

- Participants randomly assigned: 858 (BDF 320/9: 277, BDF 160/9: 281, placebo 300)
- Baseline characteristics: mean age: 63.3; mean $FEV_1$ % predicted: 40.1%; COPD severity: moderate to very severe; males: 67.1%
- Inclusion criteria: ≥ 40 years, pre-bronchodilator $FEV_1$ ≤ 50% predicted, pre-bronchodilator $FEV_1$/forced vital capacity < 70%; symptoms for ≥ two years; ≥ 10 pack-years smoking history; ≥ one COPD exacerbation within one to 12 months; ≥ 2 Modified Medical Research Council dyspnoea scale score; ≥ 2 BCSS score for at least half of the two-week run-in period
- Exclusion criteria: asthma or allergic rhinitis before 40 years of age; significant/unstable cardiovascular disorder; clinically significant respiratory tract disorder other than COPD; alpha-1 antitrypsin deficiency; oral steroid use; any other significant disease or disorder that may jeopardise the safety of the participant; oral or ophthalmic non-cardioselective beta-adrenoceptor antagonist use; pregnancy and breast-feeding

| | |
|---|---|
| Interventions | Two-week run-in period; participants continued ICS monotherapy if they had previously been receiving ICS alone or in combination with LABA, and participants who had previously been receiving anticholinergic therapies were placed on stable doses of ipratropium bromide. A short-acting $beta_2$-agonist was allowed for rescue use<br>• BDF 320/9 twice daily<br>• BDF 160/9 twice daily<br>• Placebo twice daily<br>Additional treatment groups not covered in this review<br>• Budesonide 320 mcg twice daily + formoterol 9 mcg twice daily<br>• Budesonide 320 mcg twice daily<br>• Formoterol 9 mcg twice daily<br>Inhaler device: MDI and Turbohaler (double-dummy) |
| Outcomes | • Predose and one hour postdose $FEV_1$ over the six-month treatment period<br>• Participant-reported outcome variables regarding disease status (including PEF), collected via questionnaires and diaries<br>• Health care utilisation<br>• Safety variables, including adverse events, vital signs, ECG, physical examination, hematology and clinical chemistry<br>• Serial spirometry<br>• Pharmacokinetics |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Randomly assigned in balanced blocks according to computer-generated randomisation to one of the treatments administered twice daily |
| Allocation concealment (selection bias) | Unclear risk | No details of allocation procedure |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Randomised, double-blind, double-dummy |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (86% completion in both treatment groups, 74% completion in placebo group) |

**Tashkin 2008** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (86% completion in both treatment groups, 74% completion in placebo group) |
| Selective reporting (reporting bias) | Low risk | All outcomes reported, no evidence of reporting bias |

**Tashkin 2012**

| | |
|---|---|
| Methods | Randomized, placebo-controlled, double-blind, double-dummy, parallel groups. Duration 26 weeks with 26-week safety extension |
| Participants | • Setting: 131 centres located in South America, Asia, Africa, Europe and North America<br>• Participants randomly assigned: 636 (MF/F 400/10: 217, MF/F 200/10: 207, placebo 212)<br>• Baseline characteristics: mean age: 59.8; mean $FEV_1$ % predicted: not stated; COPD severity: moderate to very severe; males: 79%<br>• Inclusion criteria: ≥ 40 years; current or ex-smokers with ≥ 10 pack-years history; moderate to very severe COPD (pre-bronchodilator $FEV_1$/forced vital capacity (FVC) ratio ≤ 0.70), symptoms of COPD (chronic cough and sputum production not attributable to another disease process) for at least 24 months; postbronchodilator $FEV_1$ ≤ 60% predicted normal and ≥ 25% predicted normal at screening; medically acceptable form of birth control<br>• Exclusion criteria: significant reversibility (> 400 mL postalbuterol/salbutamol); long-term oxygen; exacerbation of COPD requiring medical intervention within four weeks before randomisation; beta-blocking agents; or treatment with additional excluded medication (other than SABA short-acting anticholinergic to be used as rescue medication); history of significant medical illness or a disorder that might interfere with the study; pregnancy or breast-feeding; asthma; lung cancer; alpha-1-antitrypsin deficiency; lobectomy; pneumonectomy; lung volume reduction surgery; cataract extractions in both eyes; or other significant ocular problems (glaucoma, trauma, opacification) |
| Interventions | Two-week open-label wash out/run-in period in which long-acting bronchodilators and corticosteroids were discontinued and substituted with a short-acting $beta_2$-agonist-anticholinergic fixed-dose combination<br>• MF/F 400/10 mcg twice daily<br>• MF/F 200/10 mcg twice daily<br>• Placebo<br>Additonal treatment groups not covered in this review<br>• MF 400 mcg twice daily<br>• Formoterol 10 mcg twice daily<br>Inhaler device: MDI |
| Outcomes | • Mean change from baseline in $FEV_1$ area under the curve (AUC) from 0 to 12 hours postdose (AUC 0 to 12 hours) at the week 13 end point<br>• Mean change from baseline in morning predose $FEV_1$ at the week 13 end point<br>• Change in health status as assessed according to total scores on St George's Respiratory Questionnaire (SGRQ)<br>• Change in symptom-free nights<br>• Time to first mild, moderate or severe COPD exacerbation<br>• Proportion of participants with partly stable COPD<br>• Adverse events |

**Tashkin 2012** *(Continued)*

Notes

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | The sponsor's statistician produced a computer-generated randomisation schedule with treatment codes in blocks using SAS. Randomization was stratified according to the participant's smoking status at the time of randomisation |
| Allocation concealment (selection bias) | Low risk | Randomised treatment assignment was provided to the investigative site by means of an interactive voice response system at the time participants were randomly assigned |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Placebo-controlled, double-blind, double-dummy study<br><br>NB: Sponsor's statistician was used |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in all groups (81% completion in higher-dose treatment group and 82% in lower-dose treatment group, 75% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in all groups (81% completion in higher-dose treatment group and 82% in lower-dose treatment group, 75% in placebo group) |
| Selective reporting (reporting bias) | Unclear risk | Numerical data for multiple outcomes not presented, as failed to reach significance |

**TORCH**

| | |
|---|---|
| Methods | Parallel-group design<br>Randomisation: permuted block randomisation with stratification for smoking status and country<br>Blinding: double-blind (identical inhaler devices)<br>Allocation concealment: adequate<br>Excluded: described<br>Withdrawals: described<br>Trial duration: 156 weeks<br>Baseline characteristics: comparable<br>Intention-to-treat analysis: stated |
| Participants | • Setting: 444 centres in North America, Central America and Asia Pacific<br>• Participants randomly assigned: 3091 (FPS: 1546; placebo: 1545)<br><br>Additional treatment groups not covered in this review<br><br>• Salmeterol: 1542; fluticasone: 1551<br><br>Baseline characteristics: 65 years; male: 76%<br>Inclusion criteria: M/F 40 to 80 years of age; diagnosis of COPD (ERS); < 10% reversibility of predicted $FEV_1$; $FEV_1/FVC$ ratio < 70%; $FEV_1$ < 60% predicted; ≥ 10 pack-year smoking history<br>Exclusion criteria: asthma or respiratory diseases other than COPD; lung volume reduction surgery (LVRS)/lung transplant; requirement for > 12 hours/d LTOT; long-term oral corticosteroid therapy; serious uncontrolled disease likely to interfere with medication/cause death in next three years |
| Interventions | Run-in: two weeks. All maintenance treatment with ICS and LABA ceased |

**TORCH** *(Continued)*

| | |
|---|---|
| | • FPS combination 500/50 mcg twice daily<br>• Placebo<br><br>Additional treatment groups not covered in this review<br><br>• Fluticasone 500 mcg twice daily<br>• Salmeterol 50 mcg twice daily<br><br>Inhaler device: DPI |
| Outcomes | All-cause mortality; change in SGRQ; exacerbations (requiring antibiotics, steroids, hospitalisation or combination of these); lung function; withdrawals; adverse events |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated scheme. Permuted block randomisation with stratification for smoking status and country |
| Allocation concealment (selection bias) | Unclear risk | Centralised randomisation schedule but no details of allocation procedures |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler devices |
| Incomplete outcome data (attrition bias): Mortality | Low risk | Mortality was the primary outcome, and vital status was checked in those who withdrew |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates for other outcomes in both groups (66% completion in treatment group, 56% completion in placebo group) |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias, but as highlighted in feedback received, the trial protocol was submitted for publication in October 2003 after recruitment of participants (2000 to 2002) (Feedback 1; Feedback 2) |

**TRISTAN**

| | |
|---|---|
| Methods | Parallel-group design<br>Randomisation: computer-generated; numbers were generated off-site; once a treatment number had been assigned to a participant, it could not be assigned to any other participant<br>Blinding: double-blind; participants received identically packaged and presented placebos<br>Excluded: described<br>Withdrawals: described<br>Trial duration: two-week run-in period; 52 weeks treatment; 2-week follow-up<br>Baseline characteristics: comparable intention-to-treat analysis: stated |
| Participants | • Setting: 196 centres in Europe, South Africa and Australia<br>• Participants randomly assigned: 719 (FPS: 358; placebo: 361)<br><br>Additional treatment groups not covered in this review<br><br>• Salmeterol: 372; fluticasone: 375 |

**TRISTAN** *(Continued)*

| | |
|---|---|
| | Baseline characteristics: mean age 63 years; mean $FEV_1$ 1.26 L (44% predicted)<br>Inclusion criteria: baseline $FEV_1$ 25% to 75% predicted; $FEV_1$/ FVC ratio ≤ 70%; poor reversibility: < 10% increase in predicted $FEV_1$ 30 minutes after inhalation of 400 mcg salbutamol; at least 10 pack-years smoking history; history of exacerbations (at least one in the last year) requiring OCS and/or antibiotics; at least one episode of acute COPD per year in the previous three years<br>Exclusion criteria: respiratory disorders other than COPD; oxygen treatment; systemic corticosteroids, high doses of inhaled corticosteroids (> 1000 mcg daily beclomethasone dipropionate, budesonide or flunisolide or > 500 mcg daily fluticasone) or antibiotics in the four weeks before the two-week run-in period |
| Interventions | Run-in: two weeks. All maintenance treatment with ICS and LABA ceased<br>• FPS 50 mcg/500 mcg twice daily<br>• Placebo<br>Additional treatment groups not covered in this review<br>• Salmeterol 50 mcg twice daily<br>• Fluticasone 500 mcg twice daily<br>Inhaler device: DPI |
| Outcomes | $FEV_1$; PEF; exercise tolerance; quality of life: SGRQ; dyspnoea and symptoms (symptom score for shortness of breath, cough and sputum production); exacerbations (defined as requirement for antibiotics, oral steroids or both); rescue salbutamol use |
| Notes | $FEV_1$ reversibility (% predicted normal); mean reversibility (% predicted) 3.8 |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated randomisation schedule |
| Allocation concealment (selection bias) | Low risk | Numbers were generated off-site. Once a treatment number had been assigned to a participant, it could not be assigned to any other participant. Participants who satisfied the eligibility criteria were assigned the next sequential treatment number from the list |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Identical inhaler device |
| Incomplete outcome data (attrition bias): Mortality | High risk | High attrition rates in both groups (75% completion in treatment group and 61% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | High risk | High attrition rates in both groups (75% completion in treatment group and 61% in placebo group) |
| Selective reporting (reporting bias) | Low risk | No apparent indication of reporting bias |

**Zheng 2006**

| | |
|---|---|
| Methods | Randomised, double-blind, placebo-controlled, parallel-group. Duration 24 weeks |
| Participants | • Setting: 12 hospitals in China<br>• Participants randomly assigned: 445 (FPS: 297, placebo: 148)<br>• Baseline characteristics: mean age: 66.32; mean $FEV_1$ % predicted: 47%; COPD severity: moderate to very severe; males: 88.5%<br>• Inclusion criteria: 40 to 79 years; COPD as per GOLD criteria; poor reversibility of airflow obstruction (increase of < 10%); $FEV_1$/FVC ratio (postbronchodilator) < 70%<br>• Exclusion criteria: asthma, lung cancer, sarcoidosis, active tuberculosis, lung fibrosis, bronchiectasis, serious uncontrolled other system disorders; long-term oxygen therapy (LTOT); had received inhaled corticosteroids at a dose of > 1000 µg/d (beclomethasone or budesonide) or > 500 µg/d (fluticasone) or had received systemic corticosteroids in the last four weeks before entry to the run-in period |
| Interventions | Two-week run-in period during which participants stopped taking ICSs and LABAs<br>• FPS 500/50 twice daily<br>• Placebo<br>Inhaler device: DPI (Diskus) |
| Outcomes | • Prebronchodilator $FEV_1$<br>• St George's Respiratory Questionnaire (SGRQ)<br>• Use of relief bronchodilator and nighttime awakenings from Daily Record Cards<br>• Postbronchodilator $FEV_1$<br>• COPD exacerbations<br>• Adverse events |
| Notes | Trial included non-smokers (11% from FPS arm and 14% from placebo arm) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | "Randomization was stratified at week 0 by smoking status"—sequence generation not described but likely to be low risk |
| Allocation concealment (selection bias) | Unclear risk | Allocation procedure not described |
| Blinding (performance bias and detection bias) All outcomes | Low risk | Double-blind. FPS combination product 50/500 µg twice daily or matched placebo twice daily for 24 weeks of treatment |
| Incomplete outcome data (attrition bias): Mortality | Unclear risk | Moderate attrition rates in both groups (88% completion in treatment group and 89% in placebo group) |
| Incomplete outcome data (attrition bias): All other outcomes | Unclear risk | Moderate attrition rates in both groups (88% completion in treatment group and 89% in placebo group) |
| Selective reporting (reporting bias) | Low risk | All stated outcomes reported |

AUC: Area under the curve; BCSS: Breathless, Cough and Sputum Score; BDF: Budesonide/formoterol combination; CBSQ: Chronic Bronchitis Symptom Questionnaire; COPD: chronic obstructive pulmonary disease; CRDQ: Chronic Respiratory Disease Questionnaire;

DPI: Dry powder inhaler; ERS: European Respiratory Society; $FEV_1$: Forced expiratory volume in one second; FPS: Fluticasone/salmeterol combination; FVC: Forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICS: inhaled corticosteroid; LABA: long-acting $beta_2$-agonists; LAMA: long-acting muscarinic antagonist; LTOT: Long-term oxygen therapy; MDI: Metered-dose inhaler; MMRC: Modified Medical Research Council; PEF: Peak expiratory flow; SABA: short-acting beta-agonist; SAMA: Short-acting muscarinic antagonist; SD: Standard deviation; SGRQ: St George's Respiratory Questionnaire.

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

| Study | Reason for exclusion |
|---|---|
| Aaron 2004 | Irrelevant comparison |
| Aaron 2007 | Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo |
| Bathoorn 2008 | Trial focuses on treatment of COPD exacerbations |
| Bleecker 2011 | Assessment of effects of Gly16Arg genotype in response to budesonide/ formoterol in two clinical trials |
| Borgstrom 2003 | Healthy volunteers |
| Cazzola 2000 | Single-blind assessment of additive benefit of inhaled fluticasone to salmeterol. Although dosage was identical to Seretide/Advair (i.e. FP 500ug: SAL 50mcg), treatment was administered through separate inhalers |
| Cazzola 2002a | Single-blind randomised crossover study comparing combination salmeterol and fluticasone with formoterol and budesonide - excluded as duration of study was too short (12 hours) |
| Cazzola 2003 | Acute phase COPD |
| Cazzola 2004 | Randomised trial comparing combination salmeterol/fluticasone with separately administered fluticasone and theophylline for 4 months. Excluded as the comparison was not within the scope of the review |
| Cazzola 2004b | The duration of this study was too short (<1 week) |
| Chapman 2002 | Review article |
| Cukier 2007 | Crosssover trial investigating use of nebulised saline versus nebulised salbutamol |
| De Backer 2011 | Assessment of the acute effect of budesonide/formoterol |
| Donohue 2004 | Irrelevant comparison |
| Ferguson 2006 | Trial did not compare combined ICS/LABA therapy versus placebo |
| GlaxoSmithKline 2004 | Trial includes patients with asthma |
| GlaxoSmithKline 2004a | Trial includes patients with asthma |
| Golabi 2006 | Crossover trial comparing tiotropium versus salmeterol/fluticasone |
| Haque 2006 | Focus on macrophages and glucoreceptor proteins |
| INSPIRE | Trial compared tiotropium versus seretide |
| Jiang 2011 | Study not blinded |

| Study | Reason for exclusion |
|---|---|
| Jung 2012 | Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo |
| Kardos 2007 | Comparison of combination therapy long-acting beta-agonist |
| Lindberg 2007 | Crossover study examining effect of only a single dose (two inhalations) of budesonide/formoterol , salmeterol/fluticasone, salbutamol or placebo |
| Lindenberg 2006 | Crossover study examining effect of only a single dose (two inhalations) of budesonide/formoterol, salmeterol/fluticasone, salbutamol or placebo |
| Mittmann 2010 | Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo |
| Mittmann 2011 | Patients were randomised to tiotropium+combined ICS/LABA therapy versus tiotropium+placebo |
| NCT00144911 | Combined ICS/LABA not compared to placebo |
| NCT00269126 | Crossover study examining effect of adding fluticasone to salmeterol |
| NCT00476099 | Combined ICS/LABA not compared to placebo |
| Noschese 2003 | Non-randomised study. |
| Sagcan 2007 | Focus of study is on sleep quality of COPD patients |
| SAM40116 | Within study treatment group imbalances in dosage of steroids/combination therapy based upon historical steroid dose |
| Schermer 2007 | Combined ICS/LABA not compared to placebo |
| SCO100250 | Trial compared fluticasone/salmeterol versus salmeterol |
| SCO100470 | Comparison of combination therapy long-acting beta-agonist |
| SCO40034 | Comparison of tiotropium and combination therapy |
| SCO40043 | Trial compared fluticasone/salmeterol versus salmeterol |
| Sethi 2006 | Trial focuses on bacterial colonisation of sputum |
| Shaker 2009 | Trial compared budesonide versus placebo |
| Sharafkhaneh 2011 | Combined ICS/LABA not compared to placebo |
| Soriano 2002 | Non-randomised retrospective survival analysis |
| Southard 2011 | Combined ICS/LABA not compared to placebo |
| Stallberg 2008 | Trial focuses on treatment of COPD exacerbations |
| Sun 2004 | Irrelevant comparison |
| Sutherland 2006 | Trial focuses on Seretide compared to salmeterol |
| Trofimenko 2006 | Study not blinded and no placebo arm |

| Study | Reason for exclusion |
|---|---|
| Vestbo 2004 | Review article. |
| Welte 2009 | Trial focuses on budesonide/formoterol added to tiotropium |
| Welte 2009a | Trial focuses on budesonide/formoterol added to tiotropium |
| Welte 2009b | Trial focuses on budesonide/formoterol added to tiotropium |
| Welte 2009c | Trial focuses on budesonide/formoterol added to tiotropium |
| Welte 2009d | Trial focuses on budesonide/formoterol added to tiotropium |
| Wilson 2007 | Study compares patients' preferences of 4 dry powder inhalers |
| Worth 2009 | Study duration less than minimum of four weeks |
| Worth 2009a | Study duration less than minimum of four weeks |
| Worth 2010 | Study duration less than minimum of four weeks |
| Wouters 2005 | Study excluded as it assessed the withdrawal of FP from combination therapy |
| Zhong 2011 | Combined ICS/LABA not compared to placebo |
| Zhong 2012 | Combined ICS/LABA not compared to placebo |

## DATA AND ANALYSES

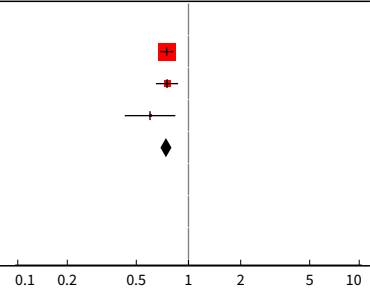
### Comparison 1. Combined inhalers versus placebo (primary outcomes)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbation rates with combined inhalers versus placebo | 7 | | Rate Ratio (Fixed, 95% CI) | 0.73 [0.69, 0.78] |
| 1.1 Fluticasone/salmeterol | 3 | | Rate Ratio (Fixed, 95% CI) | 0.74 [0.69, 0.80] |
| 1.2 Budesonide/formoterol | 4 | | Rate Ratio (Fixed, 95% CI) | 0.71 [0.62, 0.81] |
| 2 Mortality | 16 | 10129 | Odds Ratio (M-H, Fixed, 95% CI) | 0.82 [0.68, 0.99] |
| 2.1 Fluticasone/salmeterol | 10 | 5543 | Odds Ratio (M-H, Fixed, 95% CI) | 0.79 [0.65, 0.97] |
| 2.2 Budesonide/formoterol | 4 | 3250 | Odds Ratio (M-H, Fixed, 95% CI) | 1.05 [0.57, 1.93] |

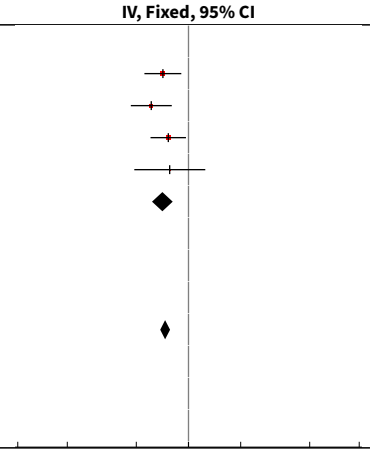
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.3 Mometasone/formoterol | 2 | 1336 | Odds Ratio (M-H, Fixed, 95% CI) | 1.35 [0.36, 5.13] |
| 3 Pneumonia | 14 | 9620 | Odds Ratio (M-H, Fixed, 95% CI) | 1.62 [1.36, 1.94] |
| 3.1 Fluticasone/salmeterol | 9 | 5447 | Odds Ratio (M-H, Fixed, 95% CI) | 1.76 [1.46, 2.14] |
| 3.2 Budesonide/formoterol | 3 | 2837 | Odds Ratio (M-H, Fixed, 95% CI) | 0.92 [0.57, 1.47] |
| 3.3 Mometasone/formoterol | 2 | 1336 | Odds Ratio (M-H, Fixed, 95% CI) | 2.39 [0.68, 8.36] |
| 4 Hospitalisations due to COPD exacerbations | 12 | 9492 | Odds Ratio (M-H, Random, 95% CI) | 0.92 [0.80, 1.06] |
| 4.1 Fluticasone/salmeterol | 7 | 5309 | Odds Ratio (M-H, Random, 95% CI) | 0.89 [0.75, 1.04] |
| 4.2 Budesonide/formoterol | 3 | 2847 | Odds Ratio (M-H, Random, 95% CI) | 1.17 [0.87, 1.58] |
| 4.3 Mometasone/formoterol | 2 | 1336 | Odds Ratio (M-H, Random, 95% CI) | 0.57 [0.31, 1.07] |
| 5 Number of participants with at least one exacerbation | 9 | 3141 | Odds Ratio (M-H, Fixed, 95% CI) | 0.78 [0.66, 0.93] |
| 5.1 Fluticasone/salmeterol | 7 | 1817 | Odds Ratio (M-H, Fixed, 95% CI) | 0.83 [0.64, 1.07] |
| 5.2 Mometasone/formoterol | 2 | 1324 | Odds Ratio (M-H, Fixed, 95% CI) | 0.74 [0.58, 0.94] |

**Analysis 1.1. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 1 Exacerbation rates with combined inhalers versus placebo.**

| Study or subgroup | Combined inhalers N | Placebo N | log[Rate Ratio] (SE) | Rate Ratio IV, Fixed, 95% CI | Weight | Rate Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.1 Fluticasone/salmeterol** | | | | | | |
| TORCH | 1534 | 1524 | -0.3 (0.045) | | 54.38% | 0.75[0.69,0.82] |
| TRISTAN | 358 | 361 | -0.3 (0.075) | | 19.58% | 0.75[0.65,0.87] |
| Zheng 2006 | 0 | 0 | -0.5 (0.172) | | 3.74% | 0.6[0.43,0.84] |
| **Subtotal (95% CI)** | | | | | **77.69%** | **0.74[0.69,0.8]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.6, df=2(P=0.45); $I^2$=0% | | | | | | |
| Test for overall effect: Z=7.95(P<0.0001) | | | | | | |

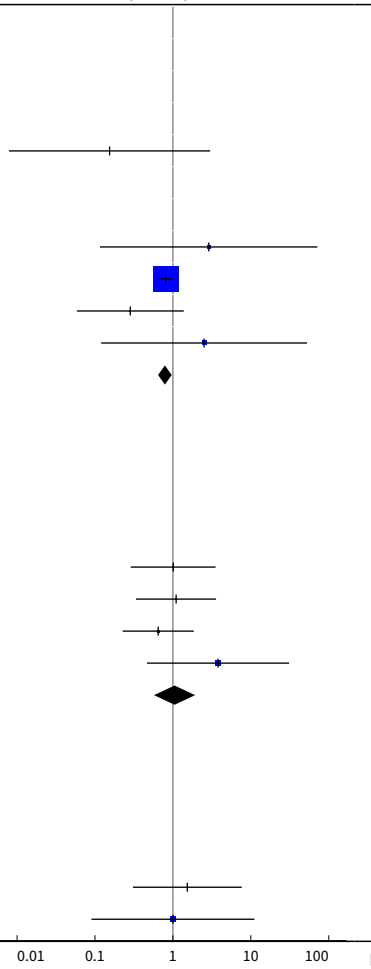


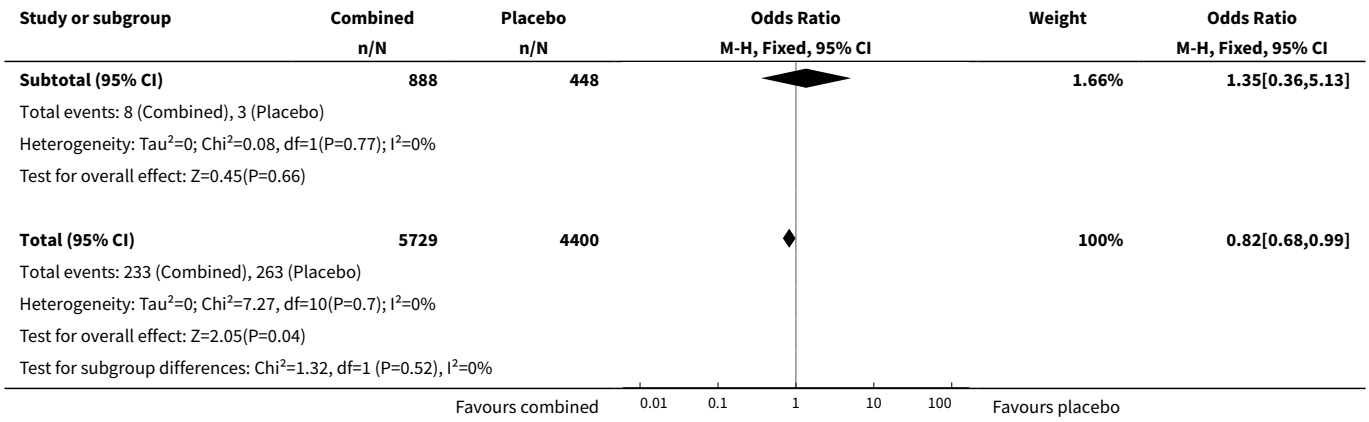
| Study or subgroup | Combined inhalers N | Placebo N | log[Rate Ratio] (SE) | Rate Ratio IV, Fixed, 95% CI | Weight | Rate Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **1.1.2 Budesonide/formoterol** | | | | | | |
| Calverley 2003 | 1 | 1 | -0.3 (0.125) | | 7.05% | 0.71[0.56,0.91] |
| Rennard 2009 | 0 | 0 | -0.5 (0.139) | | 5.7% | 0.61[0.46,0.8] |
| Szafranski 2003 | 1 | 1 | -0.3 (0.12) | | 7.65% | 0.76[0.6,0.97] |
| Tashkin 2008 | 0 | 0 | -0.2 (0.24) | | 1.91% | 0.78[0.49,1.25] |
| **Subtotal (95% CI)** | | | | | **22.31%** | **0.71[0.62,0.81]** |
| Heterogeneity: Tau²=0; Chi²=1.72, df=3(P=0.63); I²=0% | | | | | | |
| Test for overall effect: Z=4.94(P<0.0001) | | | | | | |
| **Total (95% CI)** | | | | | **100%** | **0.73[0.69,0.78]** |
| Heterogeneity: Tau²=0; Chi²=3.67, df=6(P=0.72); I²=0% | | | | | | |
| Test for overall effect: Z=9.34(P<0.0001) | | | | | | |
| Test for subgroup differences: Chi²=0.36, df=1 (P=0.55), I²=0% | | | | | | |



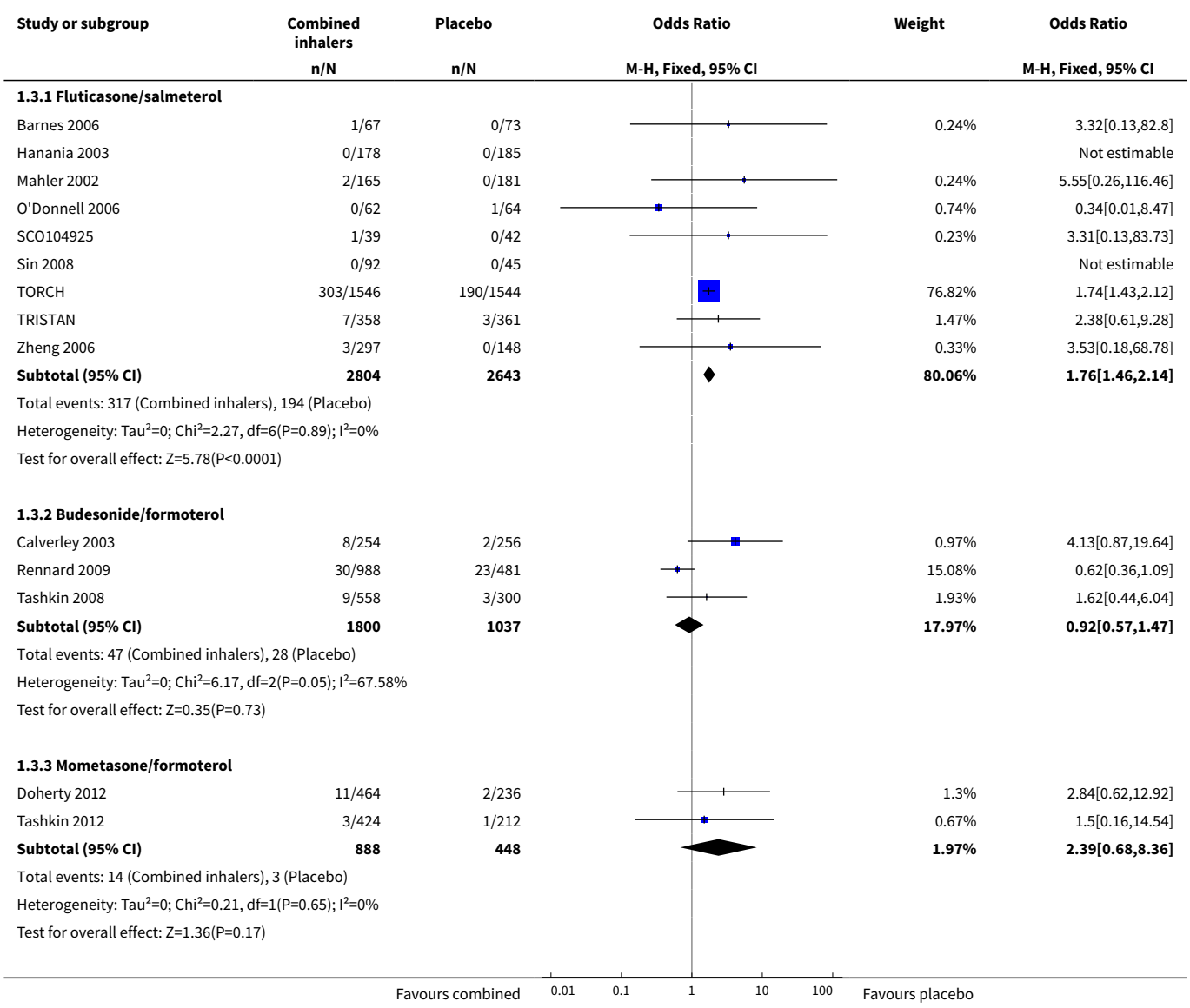

## Analysis 1.2. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 2 Mortality.

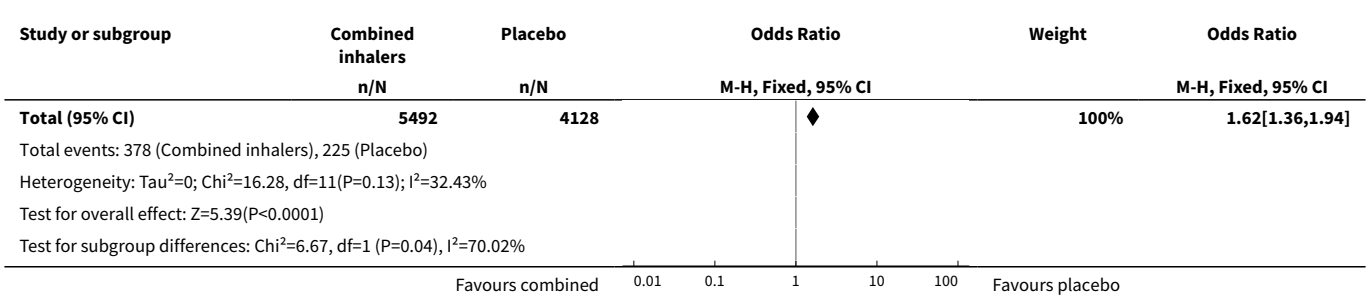
| Study or subgroup | Combined n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **1.2.1 Fluticasone/salmeterol** | | | | | |
| Barnes 2006 | 0/67 | 0/74 | | | Not estimable |
| Dal Negro 2003 | 0/6 | 0/6 | | | Not estimable |
| Hanania 2003 | 0/178 | 0/185 | | | Not estimable |
| Mahler 2002 | 0/165 | 3/181 | | 1.4% | 0.15[0.01,3.01] |
| O'Donnell 2006 | 0/59 | 0/64 | | | Not estimable |
| SCO104925 | 0/39 | 0/42 | | | Not estimable |
| SFCT01 | 1/131 | 0/125 | | 0.21% | 2.89[0.12,71.49] |
| TORCH | 193/1533 | 231/1524 | | 85.02% | 0.81[0.66,0.99] |
| TRISTAN | 2/358 | 7/361 | | 2.91% | 0.28[0.06,1.38] |
| Zheng 2006 | 2/297 | 0/148 | | 0.28% | 2.51[0.12,52.67] |
| **Subtotal (95% CI)** | **2833** | **2710** | | **89.82%** | **0.79[0.65,0.97]** |
| Total events: 198 (Combined), 241 (Placebo) | | | | | |
| Heterogeneity: Tau²=0; Chi²=4, df=4(P=0.41); I²=0% | | | | | |
| Test for overall effect: Z=2.3(P=0.02) | | | | | |
| **1.2.2 Budesonide/formoterol** | | | | | |
| Calverley 2003 | 5/254 | 5/256 | | 2.05% | 1.01[0.29,3.53] |
| Rennard 2009 | 9/988 | 4/481 | | 2.24% | 1.1[0.34,3.58] |
| Szafranski 2003 | 6/208 | 9/205 | | 3.7% | 0.65[0.23,1.85] |
| Tashkin 2008 | 7/558 | 1/300 | | 0.54% | 3.8[0.47,31.02] |
| **Subtotal (95% CI)** | **2008** | **1242** | | **8.52%** | **1.05[0.57,1.93]** |
| Total events: 27 (Combined), 19 (Placebo) | | | | | |
| Heterogeneity: Tau²=0; Chi²=2.27, df=3(P=0.52); I²=0% | | | | | |
| Test for overall effect: Z=0.16(P=0.87) | | | | | |
| **1.2.3 Mometasone/formoterol** | | | | | |
| Doherty 2012 | 6/464 | 2/236 | | 1.1% | 1.53[0.31,7.65] |
| Tashkin 2012 | 2/424 | 1/212 | | 0.56% | 1[0.09,11.09] |



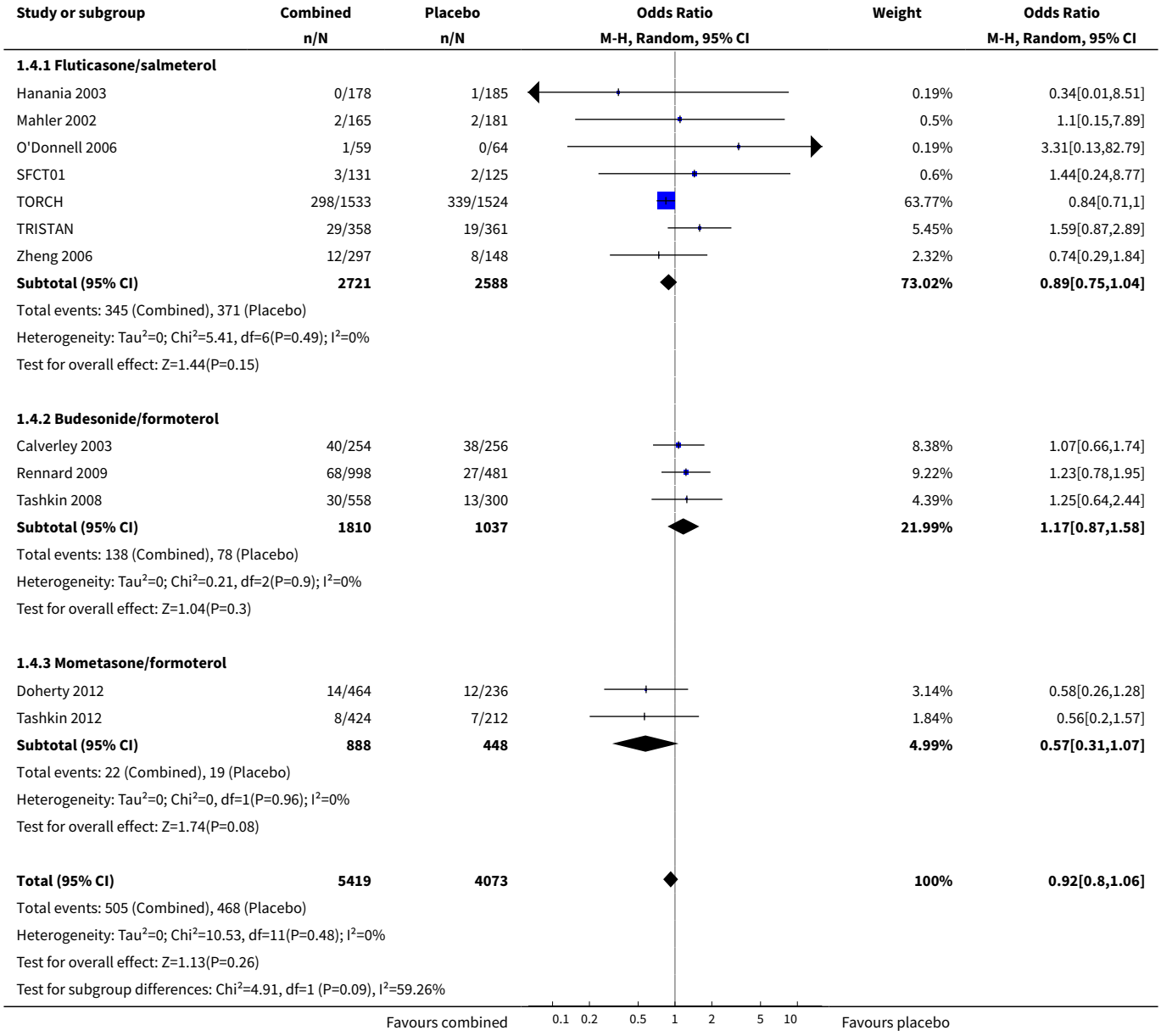



## Analysis 1.3. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 3 Pneumonia.

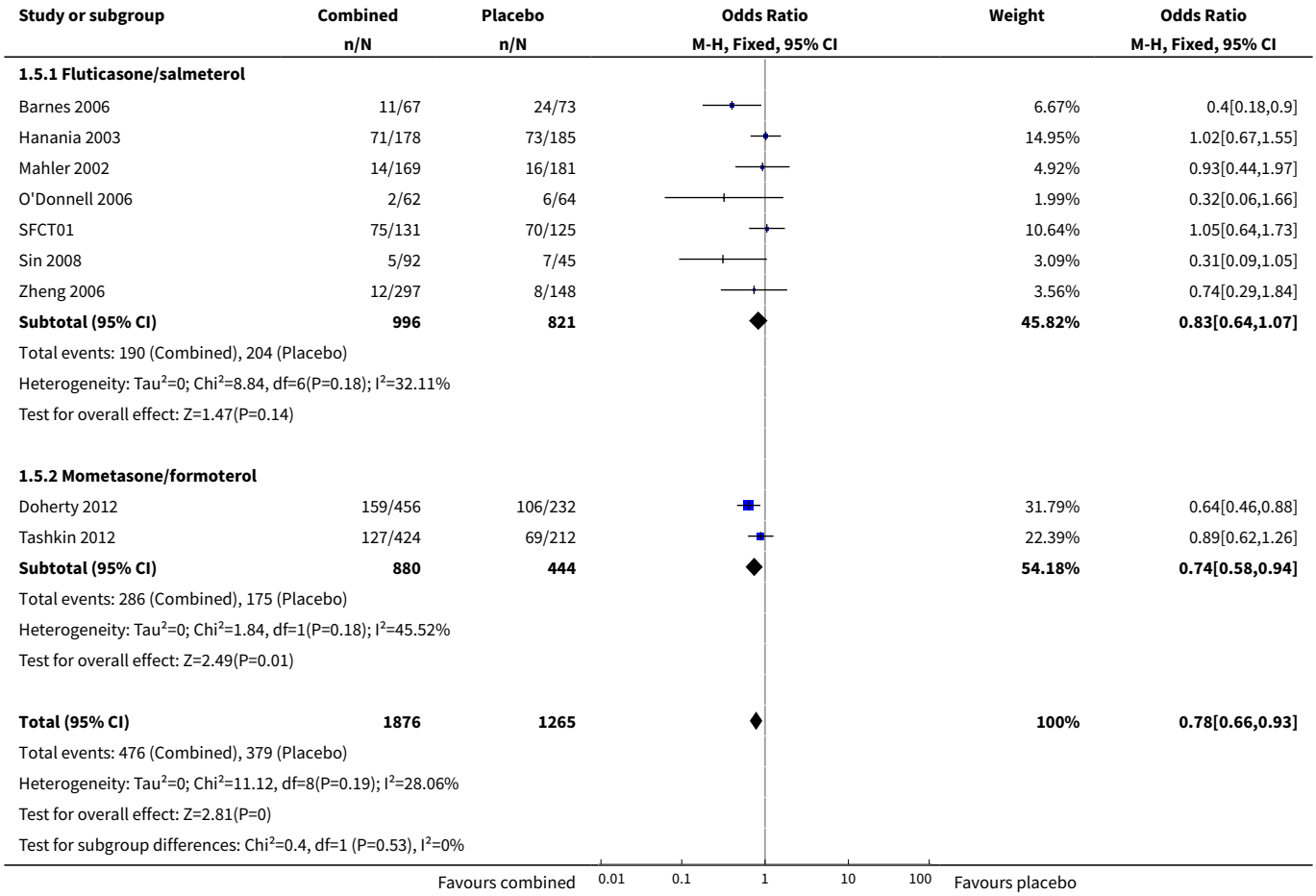





## Analysis 1.4. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 4 Hospitalisations due to COPD exacerbations.



**Analysis 1.5. Comparison 1 Combined inhalers versus placebo (primary outcomes), Outcome 5 Number of participants with at least one exacerbation.**




## Comparison 2. Fluticasone/salmeterol (FPS) versus placebo (PLA)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations | 3 | 3777 | Rate ratio (Fixed, 95% CI) | 0.74 [0.69, 0.80] |
| 1.1 Poorly reversible population | 3 | 3777 | Rate ratio (Fixed, 95% CI) | 0.74 [0.69, 0.80] |
| 2 Number of participants with at least one exacerbation | 7 | 1817 | Odds Ratio (M-H, Fixed, 95% CI) | 0.83 [0.64, 1.07] |
| 2.1 Reversible population | 1 | 126 | Odds Ratio (M-H, Fixed, 95% CI) | 0.32 [0.06, 1.66] |
| 2.2 Partially reversible population (mixed population) | 2 | 713 | Odds Ratio (M-H, Fixed, 95% CI) | 1.00 [0.69, 1.44] |
| 2.3 Poorly reversible population | 3 | 841 | Odds Ratio (M-H, Fixed, 95% CI) | 0.79 [0.54, 1.15] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 2.4 Unclear reversibility | 1 | 137 | Odds Ratio (M-H, Fixed, 95% CI) | 0.31 [0.09, 1.05] |
| 3 Participants with at least one exacerbation by type | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 Requirement for oral steroids | 2 | 417 | Odds Ratio (M-H, Fixed, 95% CI) | 1.01 [0.61, 1.68] |
| 3.2 Requirement for antibiotic treatment | 1 | 140 | Odds Ratio (M-H, Fixed, 95% CI) | 0.80 [0.26, 2.44] |
| 3.3 Requirement for oral steroid or antibiotic treatment | 1 | 140 | Odds Ratio (M-H, Fixed, 95% CI) | 3.32 [0.13, 82.80] |
| 3.4 Hospitalisation | 1 | 140 | Odds Ratio (M-H, Fixed, 95% CI) | 3.32 [0.13, 82.80] |
| 4 Exacerbations by type | 3 | | Rate ratio (Fixed, 95% CI) | Subtotals only |
| 4.1 Requirement for oral steroids | 3 | | Rate ratio (Fixed, 95% CI) | 0.57 [0.52, 0.63] |
| 4.2 Requirement for antibiotic treatment | 1 | | Rate ratio (Fixed, 95% CI) | 0.60 [0.41, 0.88] |
| 4.3 Hospitalisation | 2 | | Rate ratio (Fixed, 95% CI) | 0.83 [0.70, 0.97] |
| 5 Mortality | 10 | 5543 | Odds Ratio (M-H, Fixed, 95% CI) | 0.79 [0.65, 0.97] |
| 5.1 Mortality: three-year data | 1 | 3057 | Odds Ratio (M-H, Fixed, 95% CI) | 0.81 [0.66, 0.99] |
| 5.2 Mortality: one-year data | 3 | 987 | Odds Ratio (M-H, Fixed, 95% CI) | 0.46 [0.13, 1.65] |
| 5.3 Mortality: six-month data | 3 | 1154 | Odds Ratio (M-H, Fixed, 95% CI) | 0.54 [0.11, 2.75] |
| 5.4 Mortality: three-month data | 3 | 345 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 6 Change from baseline in St George's Respiratory Questionnaire (total score) | 4 | | Mean Difference (Fixed, 95% CI) | -2.90 [-3.61, -2.18] |
| 6.1 Poorly reversible population | 4 | | Mean Difference (Fixed, 95% CI) | -2.90 [-3.61, -2.18] |
| 7 Change from baseline in Chronic Respiratory Disease Questionnaire scores | 2 | 712 | Mean Difference (IV, Fixed, 95% CI) | 5.0 [2.48, 7.52] |
| 7.1 Partially reversible population (mixed population) | 2 | 712 | Mean Difference (IV, Fixed, 95% CI) | 5.0 [2.48, 7.52] |
| 8 Change from baseline in Transitional Dyspnoea Index (TDI) scores | 2 | 707 | Mean Difference (IV, Fixed, 95% CI) | 1.04 [0.56, 1.53] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8.1 Partially reversible population (mixed population) | 2 | 707 | Mean Difference (IV, Fixed, 95% CI) | 1.04 [0.56, 1.53] |
| 9 Change from baseline in predose $FEV_1$ | 5 | | Mean Difference (Fixed, 95% CI) | 0.16 [0.14, 0.19] |
| 9.1 Reversible population | 3 | | Mean Difference (Fixed, 95% CI) | 0.19 [0.15, 0.24] |
| 9.2 Poorly reversible population | 4 | | Mean Difference (Fixed, 95% CI) | 0.15 [0.11, 0.18] |
| 10 Change from baseline in postdose $FEV_1$ | 2 | | Mean Difference (Fixed, 95% CI) | 0.09 [0.07, 0.11] |
| 10.1 Poorly reversible population | 2 | | Mean Difference (Fixed, 95% CI) | 0.09 [0.07, 0.11] |
| 11 Change from baseline in rescue medication usage (puffs/d) | 2 | 703 | Mean Difference (IV, Fixed, 95% CI) | -1.19 [-1.83, -0.55] |
| 11.1 Partially reversible population (mixed population) | 2 | 703 | Mean Difference (IV, Fixed, 95% CI) | -1.19 [-1.83, -0.55] |
| 12 Withdrawals—total | 13 | 5769 | Odds Ratio (M-H, Fixed, 95% CI) | 0.69 [0.62, 0.78] |
| 12.1 Reversible population | 1 | 121 | Odds Ratio (M-H, Fixed, 95% CI) | 2.95 [0.30, 29.18] |
| 12.2 Partially reversible population (mixed population) | 2 | 709 | Odds Ratio (M-H, Fixed, 95% CI) | 0.82 [0.60, 1.13] |
| 12.3 Poorly reversible population | 6 | 4632 | Odds Ratio (M-H, Fixed, 95% CI) | 0.68 [0.60, 0.76] |
| 12.4 Unclear reversibility | 4 | 307 | Odds Ratio (M-H, Fixed, 95% CI) | 0.55 [0.25, 1.17] |
| 13 Withdrawals due to adverse events | 11 | 5491 | Odds Ratio (M-H, Fixed, 95% CI) | 0.74 [0.64, 0.86] |
| 13.1 Reversible population | 1 | 123 | Odds Ratio (M-H, Fixed, 95% CI) | 0.36 [0.01, 8.90] |
| 13.2 Partially reversible population (mixed population) | 1 | 354 | Odds Ratio (M-H, Fixed, 95% CI) | 0.69 [0.31, 1.51] |
| 13.3 Poorly reversible population | 6 | 4630 | Odds Ratio (M-H, Fixed, 95% CI) | 0.76 [0.65, 0.89] |
| 13.4 Unclear reversibility | 4 | 384 | Odds Ratio (M-H, Fixed, 95% CI) | 0.31 [0.11, 0.93] |
| 14 Withdrawals due to lack of efficacy | 8 | 5115 | Odds Ratio (M-H, Fixed, 95% CI) | 0.30 [0.22, 0.41] |
| 14.1 Partially reversible population (mixed population) | 1 | 346 | Odds Ratio (M-H, Fixed, 95% CI) | 0.29 [0.08, 1.04] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 14.2 Poorly reversible population | 6 | 4632 | Odds Ratio (M-H, Fixed, 95% CI) | 0.30 [0.21, 0.42] |
| 14.3 Unclear reversibility | 1 | 137 | Odds Ratio (M-H, Fixed, 95% CI) | 0.30 [0.08, 1.11] |
| 15 Adverse events—any | 9 | 5574 | Odds Ratio (M-H, Fixed, 95% CI) | 1.09 [0.95, 1.25] |
| 15.1 Reversible population | 1 | 126 | Odds Ratio (M-H, Fixed, 95% CI) | 1.20 [0.59, 2.46] |
| 15.2 Partially reversible population (mixed population) | 2 | 717 | Odds Ratio (M-H, Fixed, 95% CI) | 1.42 [1.03, 1.96] |
| 15.3 Poorly reversible population | 5 | 4650 | Odds Ratio (M-H, Fixed, 95% CI) | 1.03 [0.88, 1.21] |
| 15.4 Unclear reversibility | 1 | 81 | Odds Ratio (M-H, Fixed, 95% CI) | 0.58 [0.19, 1.79] |
| 16 Adverse events—'serious' | 9 | 5531 | Odds Ratio (M-H, Fixed, 95% CI) | 1.08 [0.95, 1.23] |
| 16.1 Reversible population | 1 | 123 | Odds Ratio (M-H, Fixed, 95% CI) | 0.53 [0.05, 6.05] |
| 16.2 Partially reversible population | 2 | 709 | Odds Ratio (M-H, Fixed, 95% CI) | 0.71 [0.38, 1.35] |
| 16.3 Poorly reversible population | 6 | 4699 | Odds Ratio (M-H, Fixed, 95% CI) | 1.10 [0.97, 1.26] |
| 17 Adverse events—pneumonia | 9 | 5447 | Odds Ratio (M-H, Fixed, 95% CI) | 1.80 [1.49, 2.18] |
| 17.1 Reversible population | 1 | 126 | Odds Ratio (M-H, Fixed, 95% CI) | 0.34 [0.01, 8.47] |
| 17.2 Partially reversible population (mixed population) | 2 | 709 | Odds Ratio (M-H, Fixed, 95% CI) | 5.55 [0.26, 116.46] |
| 17.3 Poorly reversible population | 4 | 4394 | Odds Ratio (M-H, Fixed, 95% CI) | 1.80 [1.48, 2.18] |
| 17.4 Unclear reversibility | 2 | 218 | Odds Ratio (M-H, Fixed, 95% CI) | 3.31 [0.13, 83.73] |
| 18 Adverse events—candidiasis | 7 | 2039 | Odds Ratio (M-H, Fixed, 95% CI) | 5.73 [3.07, 10.67] |
| 18.1 Reversible population | 1 | 126 | Odds Ratio (M-H, Fixed, 95% CI) | 1.03 [0.06, 16.88] |
| 18.2 Partially reversible population (mixed population) | 2 | 717 | Odds Ratio (M-H, Fixed, 95% CI) | 11.13 [3.36, 36.90] |
| 18.3 Poorly reversible population | 3 | 1115 | Odds Ratio (M-H, Fixed, 95% CI) | 4.40 [2.01, 9.62] |
| 18.4 Unclear reversibility | 1 | 81 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 19 Adverse events—hoarseness | 2 | 585 | Odds Ratio (M-H, Fixed, 95% CI) | 1.61 [0.61, 4.26] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 19.1 Poorly reversible population | 2 | 585 | Odds Ratio (M-H, Fixed, 95% CI) | 1.61 [0.61, 4.26] |
| 20 Adverse events—palpitations | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 20.1 Poorly reversible population | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 21 Adverse events—blood glucose increased | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 21.1 Poorly reversible population | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 22 Adverse event—skin bruising | 1 | 445 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 22.1 Poorly reversible population | 1 | 445 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 23 Adverse events—bronchitis | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Totals not selected |
| 23.1 Poorly reversible population | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 24 Adverse events—upper respiratory tract infection | 5 | 4963 | Odds Ratio (M-H, Fixed, 95% CI) | 1.23 [1.04, 1.47] |
| 24.1 Partially reversible population (mixed population) | 2 | 709 | Odds Ratio (M-H, Fixed, 95% CI) | 1.25 [0.81, 1.92] |
| 24.2 Poorly reversible population | 3 | 4254 | Odds Ratio (M-H, Fixed, 95% CI) | 1.23 [1.02, 1.48] |
| 25 Adverse events—nasopharyngitis | 2 | 3535 | Odds Ratio (M-H, Fixed, 95% CI) | 1.28 [1.05, 1.56] |
| 25.1 Poorly reversible population | 2 | 3535 | Odds Ratio (M-H, Fixed, 95% CI) | 1.28 [1.05, 1.56] |
| 26 Adverse events—cough | 3 | 612 | Odds Ratio (M-H, Fixed, 95% CI) | 0.55 [0.23, 1.27] |
| 26.1 Reversible population | 1 | 126 | Odds Ratio (M-H, Fixed, 95% CI) | 3.15 [0.13, 78.72] |
| 26.2 Partially reversible population (mixed population) | 1 | 346 | Odds Ratio (M-H, Fixed, 95% CI) | 0.49 [0.18, 1.31] |
| 26.3 Poorly reversible population | 1 | 140 | Odds Ratio (M-H, Fixed, 95% CI) | 0.35 [0.04, 3.48] |
| 27 Adverse events—headache | 4 | 3922 | Odds Ratio (M-H, Fixed, 95% CI) | 1.05 [0.84, 1.31] |
| 27.1 Reversible population | 1 | 123 | Odds Ratio (M-H, Fixed, 95% CI) | 0.22 [0.02, 2.01] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 27.2 Partially reversible population (mixed population) | 2 | 709 | Odds Ratio (M-H, Fixed, 95% CI) | 1.38 [0.91, 2.10] |
| 27.3 Poorly reversible population | 1 | 3090 | Odds Ratio (M-H, Fixed, 95% CI) | 0.96 [0.73, 1.26] |

**Analysis 2.1. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 1 Exacerbations.**

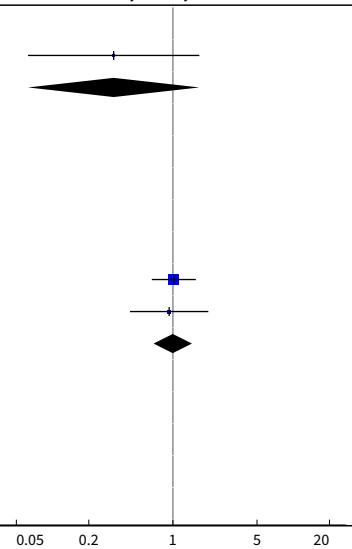
| Study or subgroup | FPS N | Placebo N | log[Rate ratio] (SE) | Rate ratio IV, Fixed, 95% CI | Weight | Rate ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.1.1 Poorly reversible population** | | | | | | |
| TORCH | 1534 | 1524 | -0.3 (0.045) | | 69.99% | 0.75[0.69,0.82] |
| TRISTAN | 358 | 361 | -0.3 (0.075) | | 25.2% | 0.75[0.65,0.87] |
| Zheng 2006 | 0 | 0 | -0.5 (0.172) | | 4.81% | 0.6[0.43,0.84] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.74[0.69,0.8]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.6, df=2(P=0.45); $I^2$=0% | | | | | | |
| Test for overall effect: Z=7.95(P<0.0001) | | | | | | |
| **Total (95% CI)** | | | | | **100%** | **0.74[0.69,0.8]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.6, df=2(P=0.45); $I^2$=0% | | | | | | |
| Test for overall effect: Z=7.95(P<0.0001) | | | | | | |



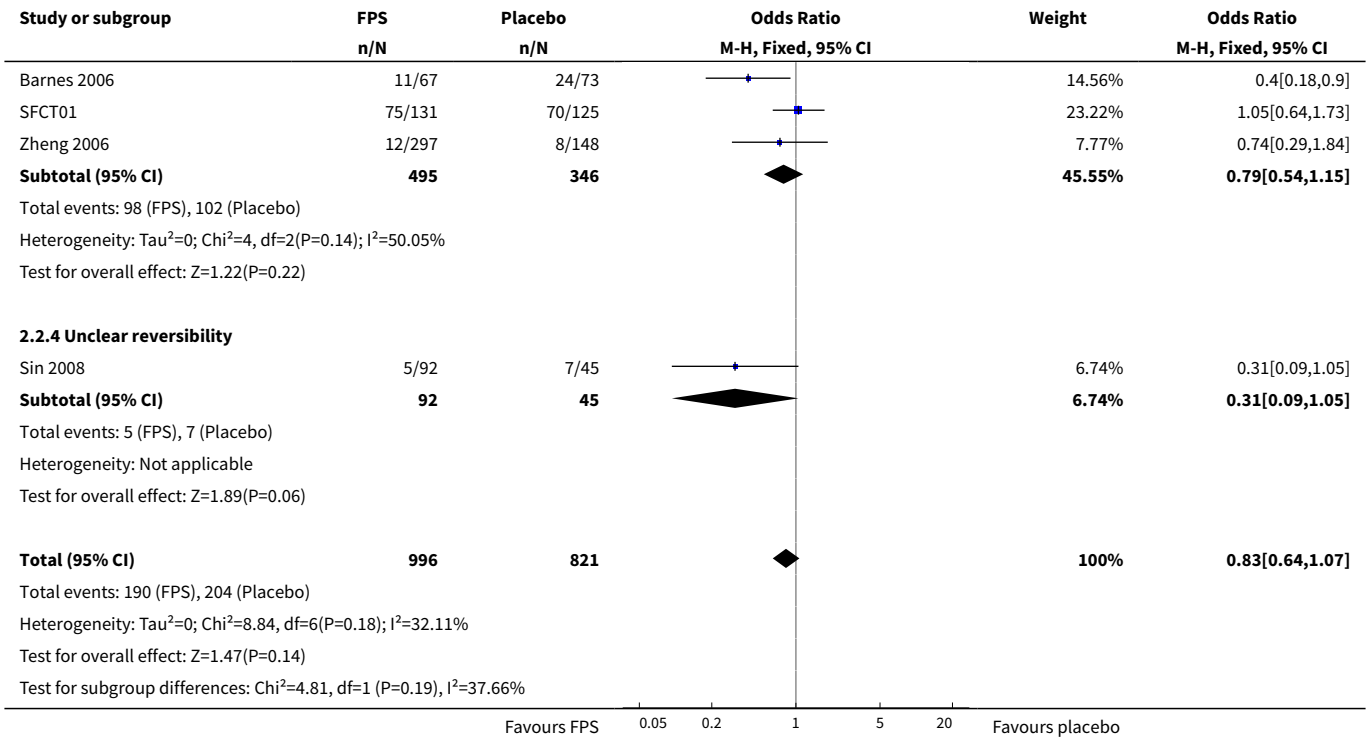

Favours FPS — Favours placebo

**Analysis 2.2. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 2 Number of participants with at least one exacerbation.**

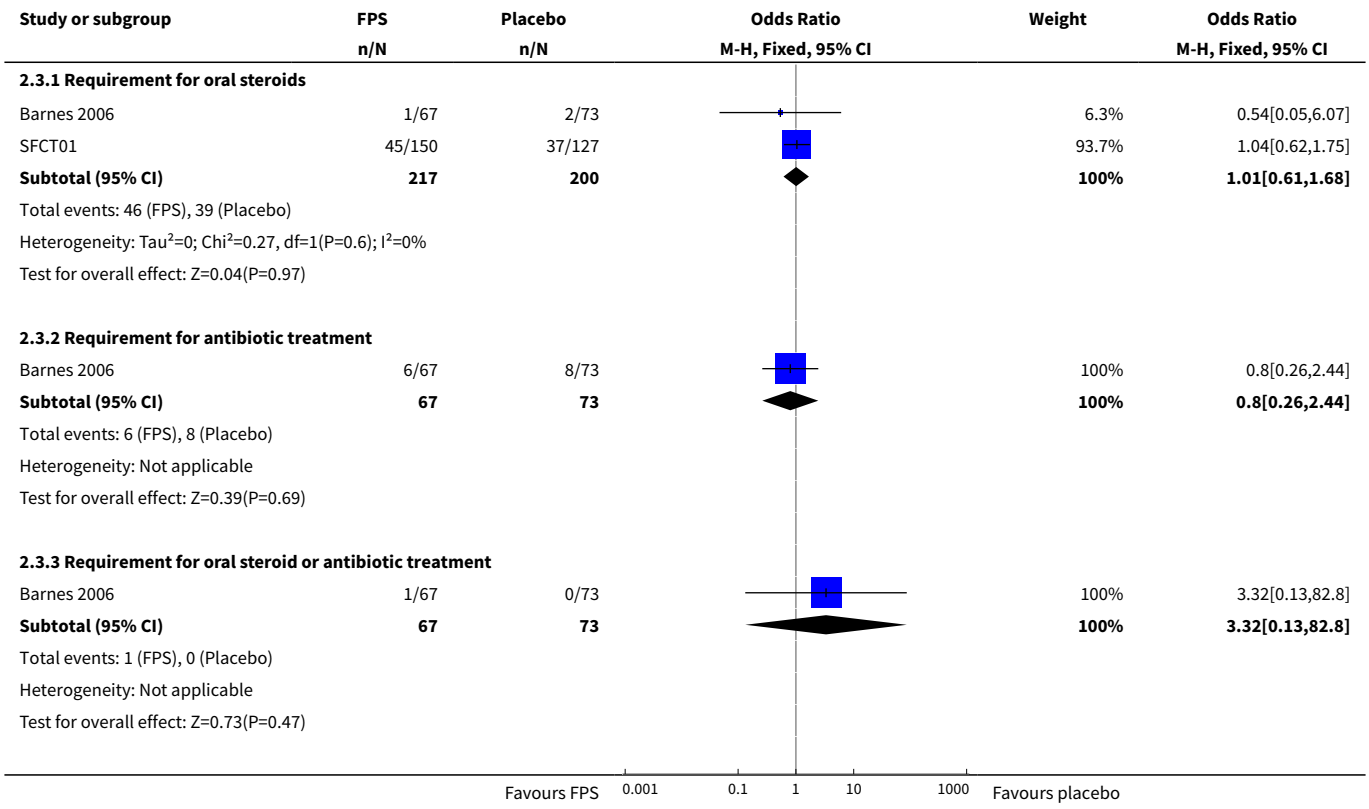
| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.2.1 Reversible population** | | | | | |
| O'Donnell 2006 | 2/62 | 6/64 | | 4.33% | 0.32[0.06,1.66] |
| **Subtotal (95% CI)** | **62** | **64** | | **4.33%** | **0.32[0.06,1.66]** |
| Total events: 2 (FPS), 6 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.35(P=0.18) | | | | | |
| **2.2.2 Partially reversible population (mixed population)** | | | | | |
| Hanania 2003 | 71/178 | 73/185 | | 32.63% | 1.02[0.67,1.55] |
| Mahler 2002 | 14/169 | 16/181 | | 10.75% | 0.93[0.44,1.97] |
| **Subtotal (95% CI)** | **347** | **366** | | **43.38%** | **1[0.69,1.44]** |
| Total events: 85 (FPS), 89 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.04, df=1(P=0.84); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.02(P=0.99) | | | | | |
| **2.2.3 Poorly reversible population** | | | | | |

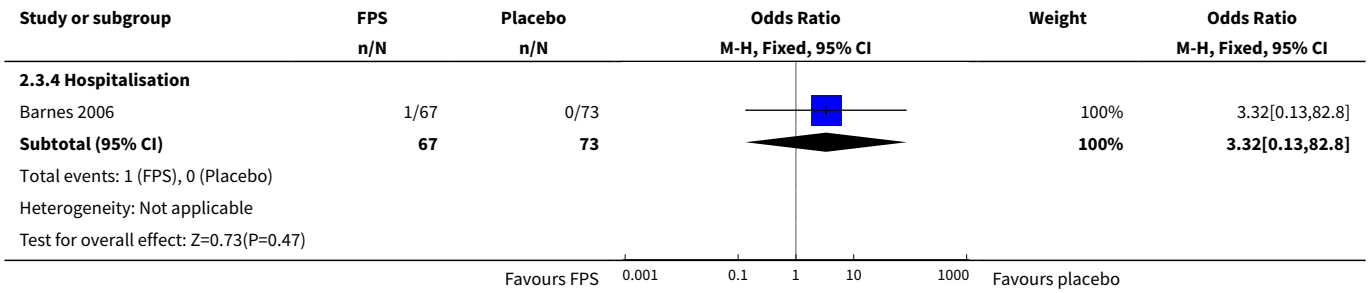



Favours FPS — Favours placebo

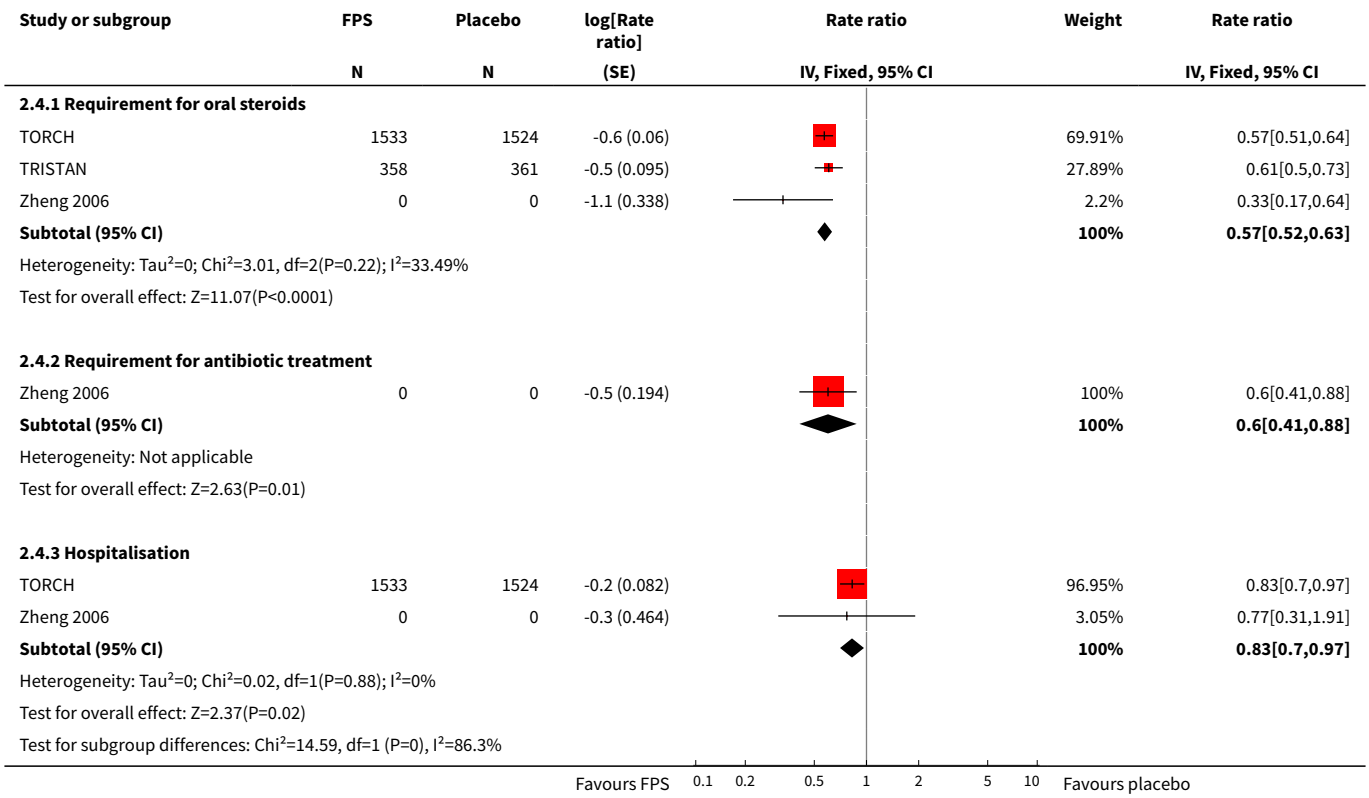



## Analysis 2.3. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 3 Participants with at least one exacerbation by type.

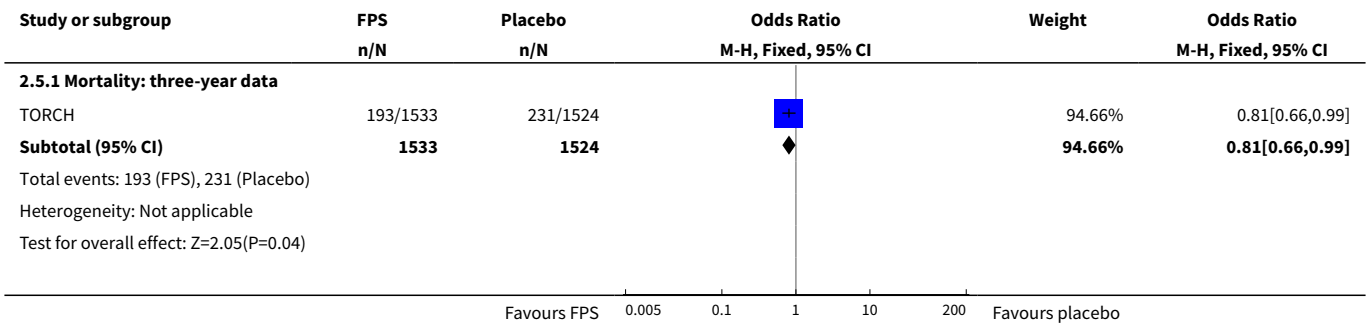


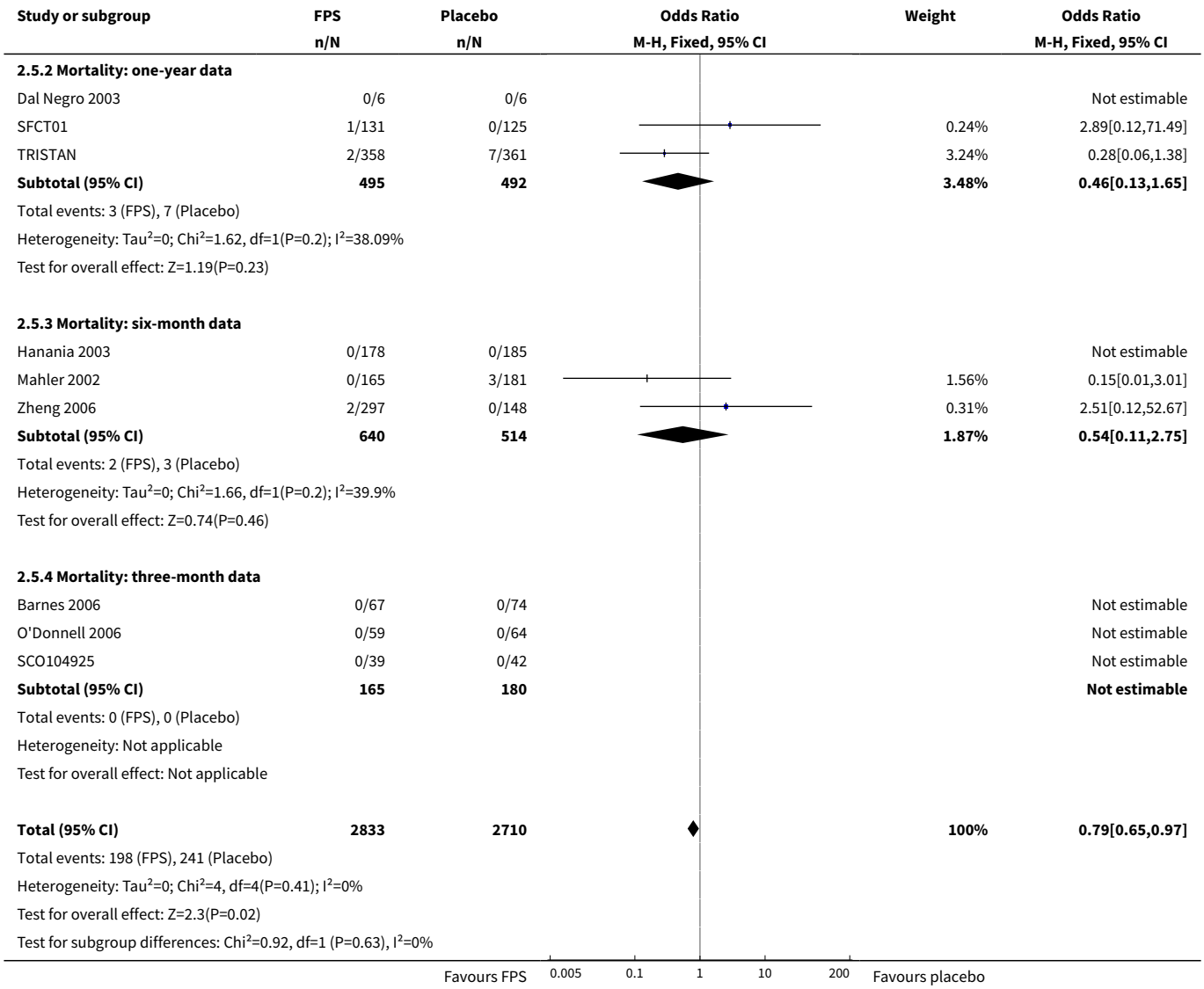



## Analysis 2.4. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 4 Exacerbations by type.

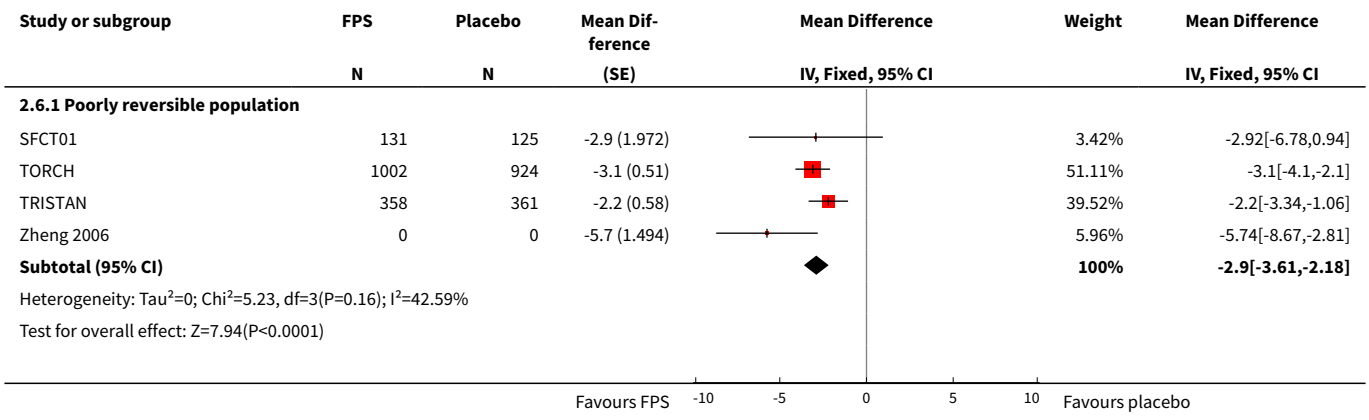


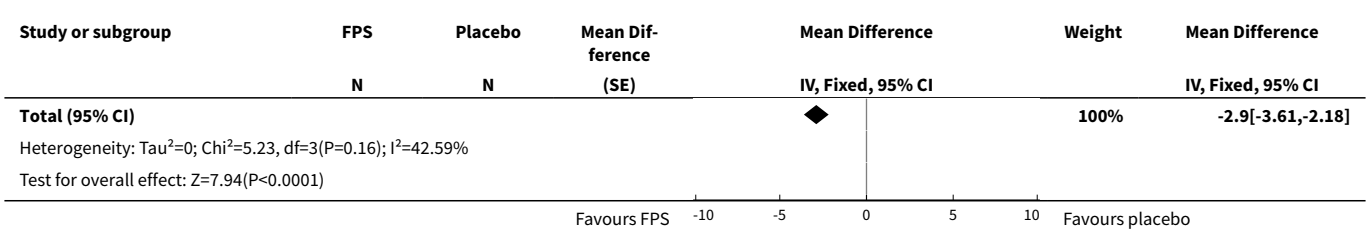

## Analysis 2.5. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 5 Mortality.



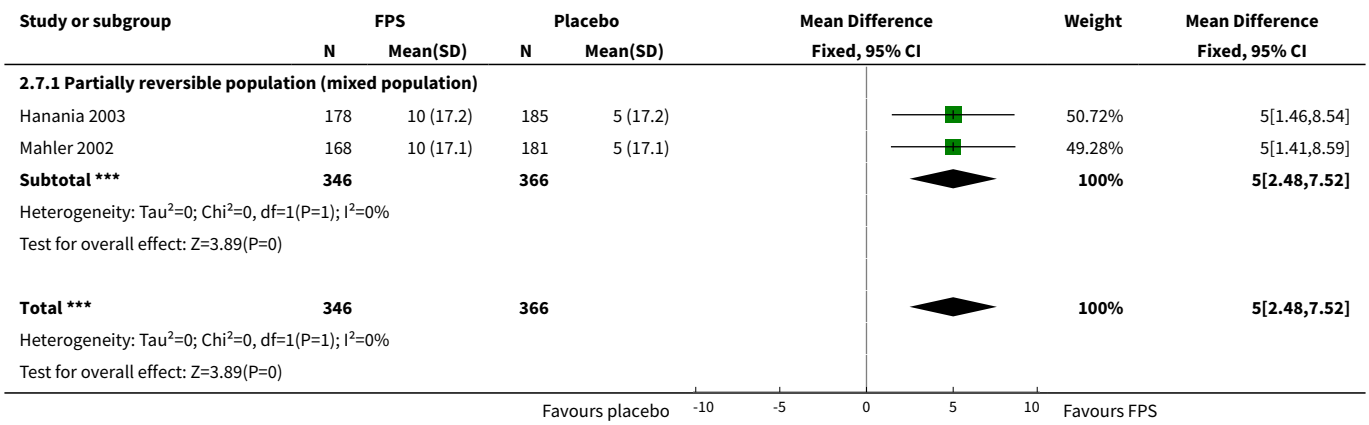



## Analysis 2.6. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 6 Change from baseline in St George's Respiratory Questionnaire (total score).

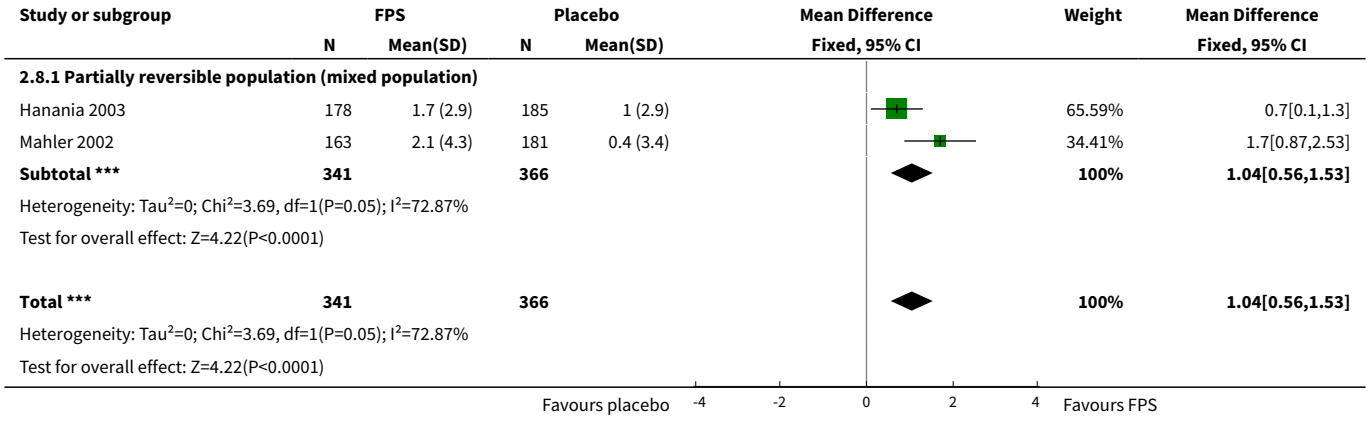





## Analysis 2.7. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 7 Change from baseline in Chronic Respiratory Disease Questionnaire scores.

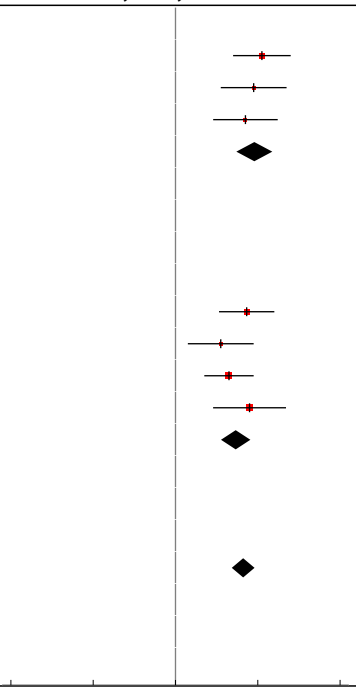



## Analysis 2.8. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 8 Change from baseline in Transitional Dyspnoea Index (TDI) scores.



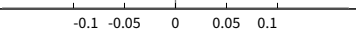
## Analysis 2.9. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 9 Change from baseline in predose $FEV_1$.

| Study or subgroup | FPS N | Placebo N | Mean Difference (SE) | Mean Difference IV, Fixed, 95% CI | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.9.1 Reversible population** | | | | | | |
| Hanania 2003 | 100 | 102 | 0.2 (0.036) | | 15.63% | 0.21[0.14,0.28] |
| Mahler 2002 | 91 | 92 | 0.2 (0.041) | | 11.97% | 0.19[0.11,0.27] |
| O'Donnell 2006 | 62 | 64 | 0.2 (0.04) | | 12.45% | 0.17[0.09,0.25] |
| **Subtotal (95% CI)** | | | | | **40.06%** | **0.19[0.15,0.24]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.56, df=2(P=0.76); $I^2$=0% | | | | | | |
| Test for overall effect: Z=8.59(P<0.0001) | | | | | | |
| **2.9.2 Poorly reversible population** | | | | | | |
| Barnes 2006 | 67 | 73 | 0.2 (0.034) | | 16.94% | 0.17[0.11,0.24] |
| Hanania 2003 | 78 | 83 | 0.1 (0.041) | | 11.97% | 0.11[0.03,0.19] |
| Mahler 2002 | 72 | 79 | 0.1 (0.031) | | 21.28% | 0.13[0.07,0.19] |
| Zheng 2006 | 0 | 0 | 0.2 (0.045) | | 9.75% | 0.18[0.09,0.27] |
| **Subtotal (95% CI)** | | | | | **59.94%** | **0.15[0.11,0.18]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=2.24, df=3(P=0.52); $I^2$=0% | | | | | | |
| Test for overall effect: Z=8.02(P<0.0001) | | | | | | |
| **Total (95% CI)** | | | | | **100%** | **0.16[0.14,0.19]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=5.27, df=6(P=0.51); $I^2$=0% | | | | | | |
| Test for overall effect: Z=11.65(P<0.0001) | | | | | | |
| Test for subgroup differences: $Chi^2$=2.47, df=1 (P=0.12), $I^2$=59.55% | | | | | | |



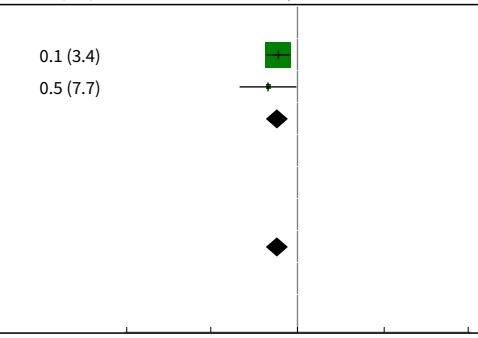

## Analysis 2.10. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 10 Change from baseline in postdose $FEV_1$.

| Study or subgroup | FPS N | Placebo N | Mean Difference (SE) | Mean Difference IV, Fixed, 95% CI | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **2.10.1 Poorly reversible population** | | | | | | |
| TORCH | 1392 | 1261 | 0.1 (0.008) | | 90.42% | 0.09[0.08,0.11] |
| Zheng 2006 | 0 | 0 | 0.1 (0.026) | | 9.58% | 0.07[0.01,0.12] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.09[0.07,0.11]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.99, df=1(P=0.32); $I^2$=0% | | | | | | |
| Test for overall effect: Z=11.19(P<0.0001) | | | | | | |
| **Total (95% CI)** | | | | | **100%** | **0.09[0.07,0.11]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.99, df=1(P=0.32); $I^2$=0% | | | | | | |
| Test for overall effect: Z=11.19(P<0.0001) | | | | | | |



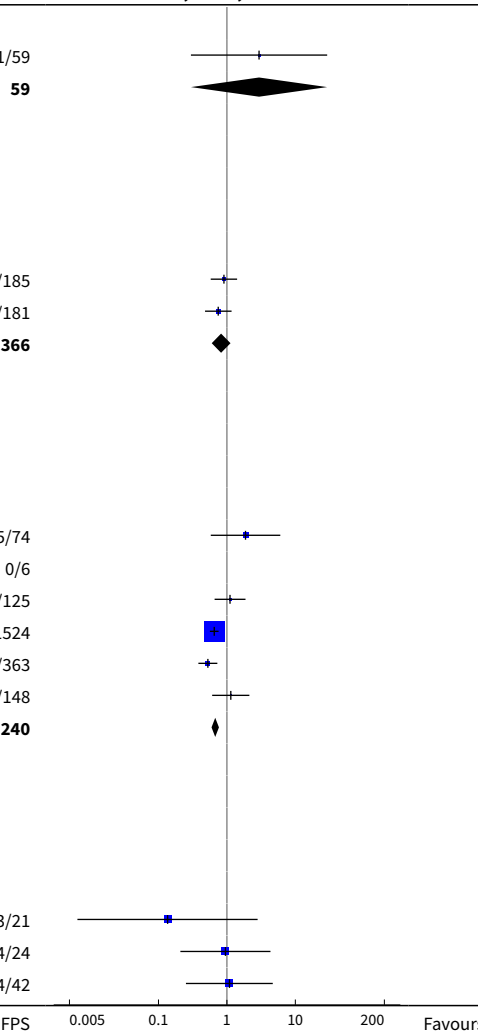
## Analysis 2.11. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 11 Change from baseline in rescue medication usage (puffs/d).

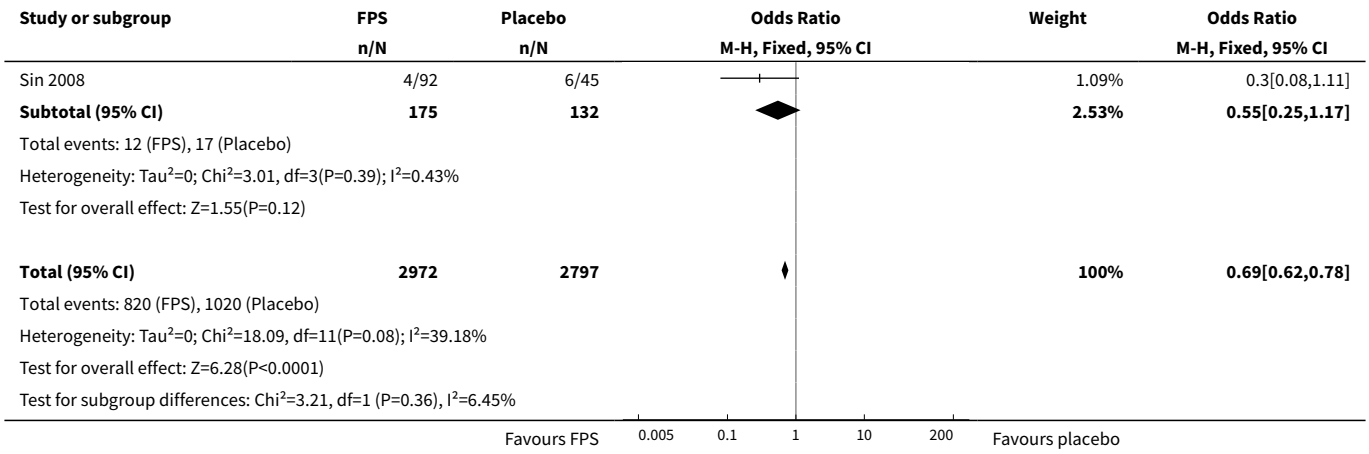
| Study or subgroup | FPS N | FPS Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.11.1 Partially reversible population (mixed population)** | | | | | | | |
| Hanania 2003 | 178 | -1 (3.4) | 185 | 0.1 (3.4) | | 84.97% | -1.1[-1.79,-0.41] |
| Mahler 2002 | 161 | -1.2 (7.7) | 179 | 0.5 (7.7) | | 15.03% | -1.7[-3.34,-0.06] |
| **Subtotal ***** | **339** | | **364** | | | **100%** | **-1.19[-1.83,-0.55]** |
| Heterogeneity: Tau²=0; Chi²=0.44, df=1(P=0.51); I²=0% | | | | | | | |
| Test for overall effect: Z=3.67(P=0) | | | | | | | |
| **Total ***** | **339** | | **364** | | | **100%** | **-1.19[-1.83,-0.55]** |
| Heterogeneity: Tau²=0; Chi²=0.44, df=1(P=0.51); I²=0% | | | | | | | |
| Test for overall effect: Z=3.67(P=0) | | | | | | | |



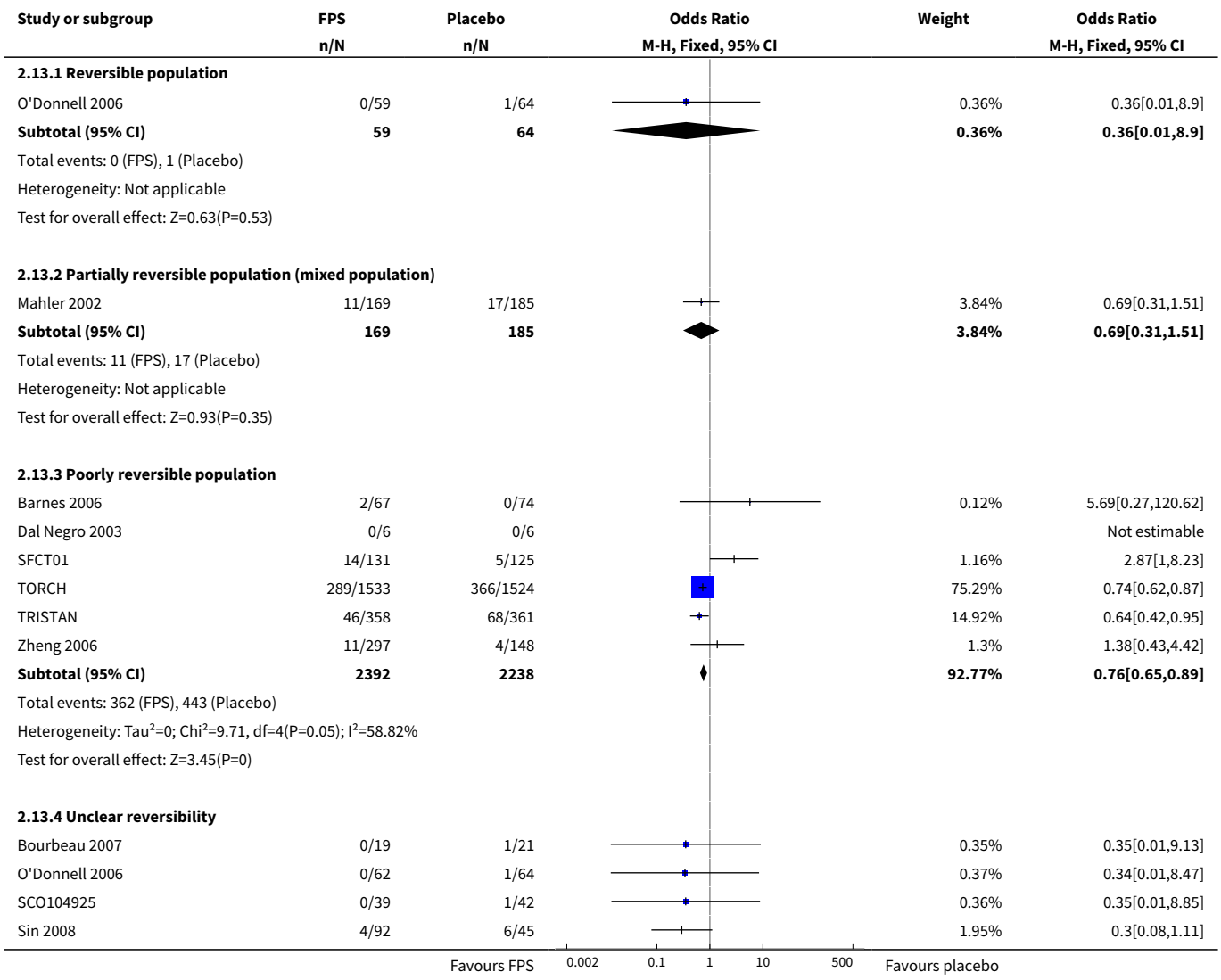

## Analysis 2.12. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 12 Withdrawals—total.

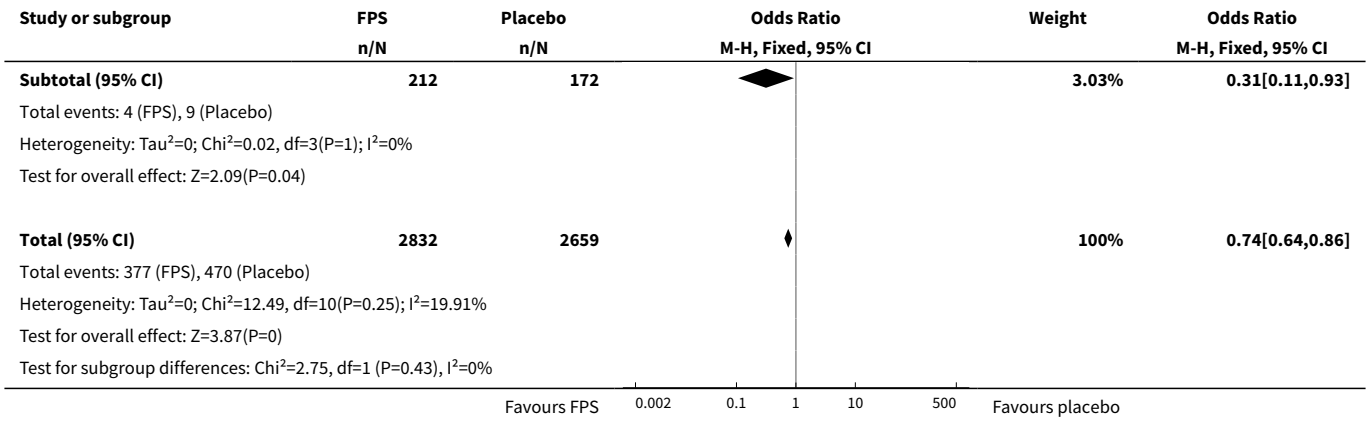
| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.12.1 Reversible population** | | | | | |
| O'Donnell 2006 | 3/62 | 1/59 | | 0.14% | 2.95[0.3,29.18] |
| **Subtotal (95% CI)** | **62** | **59** | | **0.14%** | **2.95[0.3,29.18]** |
| Total events: 3 (FPS), 1 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.92(P=0.36) | | | | | |
| **2.12.2 Partially reversible population (mixed population)** | | | | | |
| Hanania 2003 | 53/178 | 59/185 | | 5.77% | 0.91[0.58,1.41] |
| Mahler 2002 | 52/165 | 69/181 | | 6.4% | 0.75[0.48,1.17] |
| **Subtotal (95% CI)** | **343** | **366** | | **12.17%** | **0.82[0.6,1.13]** |
| Total events: 105 (FPS), 128 (Placebo) | | | | | |
| Heterogeneity: Tau²=0; Chi²=0.36, df=1(P=0.55); I²=0% | | | | | |
| Test for overall effect: Z=1.22(P=0.22) | | | | | |
| **2.12.3 Poorly reversible population** | | | | | |
| Barnes 2006 | 8/67 | 5/74 | | 0.59% | 1.87[0.58,6.03] |
| Dal Negro 2003 | 0/6 | 0/6 | | | Not estimable |
| SFCT01 | 45/131 | 40/125 | | 3.82% | 1.11[0.66,1.87] |
| TORCH | 522/1533 | 673/1524 | | 63.23% | 0.65[0.56,0.76] |
| TRISTAN | 89/358 | 140/363 | | 14.84% | 0.53[0.38,0.73] |
| Zheng 2006 | 36/297 | 16/148 | | 2.67% | 1.14[0.61,2.13] |
| **Subtotal (95% CI)** | **2392** | **2240** | | **85.15%** | **0.68[0.6,0.76]** |
| Total events: 700 (FPS), 874 (Placebo) | | | | | |
| Heterogeneity: Tau²=0; Chi²=11.63, df=4(P=0.02); I²=65.61% | | | | | |
| Test for overall effect: Z=6.17(P<0.0001) | | | | | |
| **2.12.4 Unclear reversibility** | | | | | |
| Bourbeau 2007 | 0/19 | 3/21 | | 0.46% | 0.14[0.01,2.81] |
| Lapperre 2009 | 4/25 | 4/24 | | 0.49% | 0.95[0.21,4.33] |
| SCO104925 | 4/39 | 4/42 | | 0.49% | 1.09[0.25,4.68] |



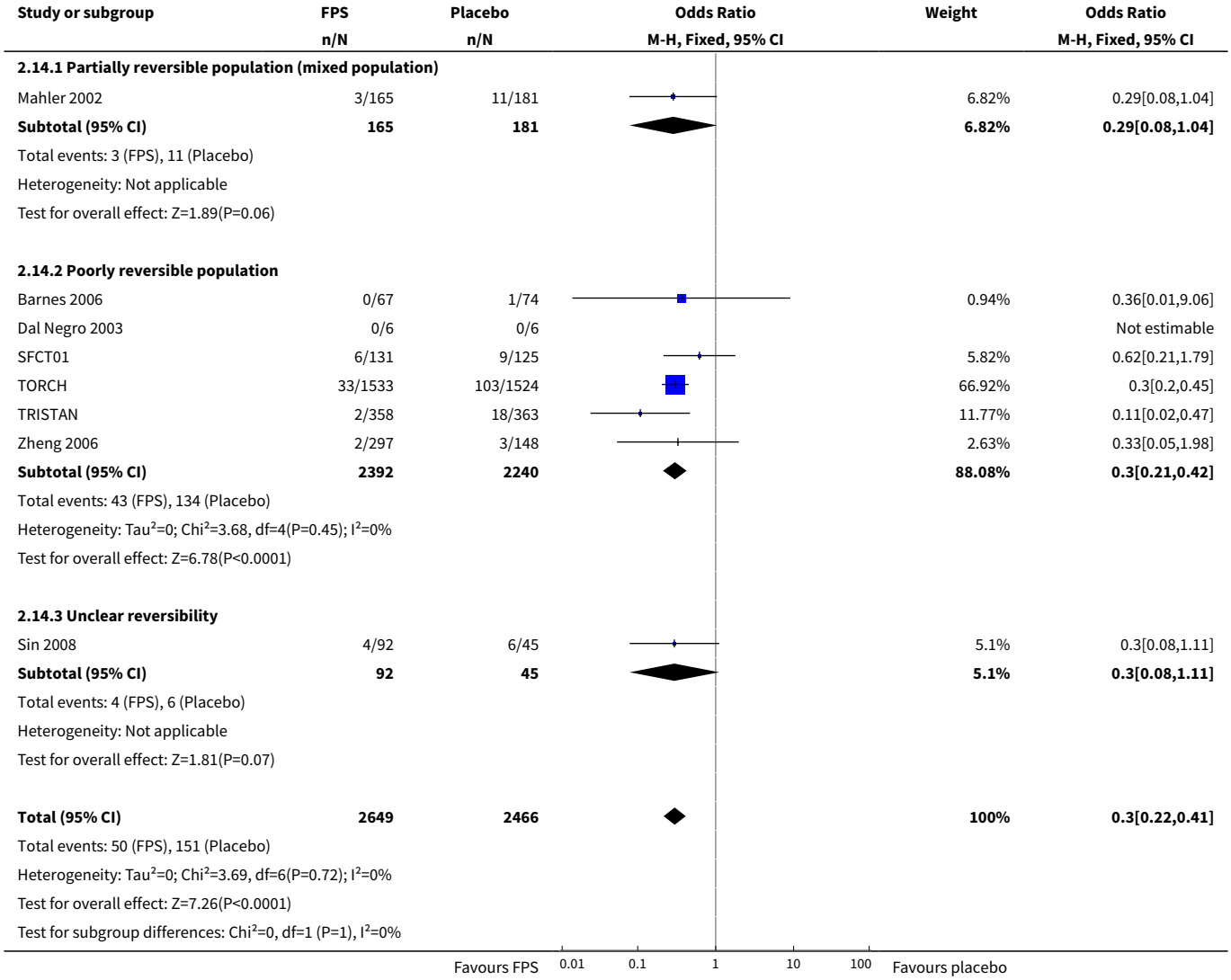



## Analysis 2.13. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 13 Withdrawals due to adverse events.



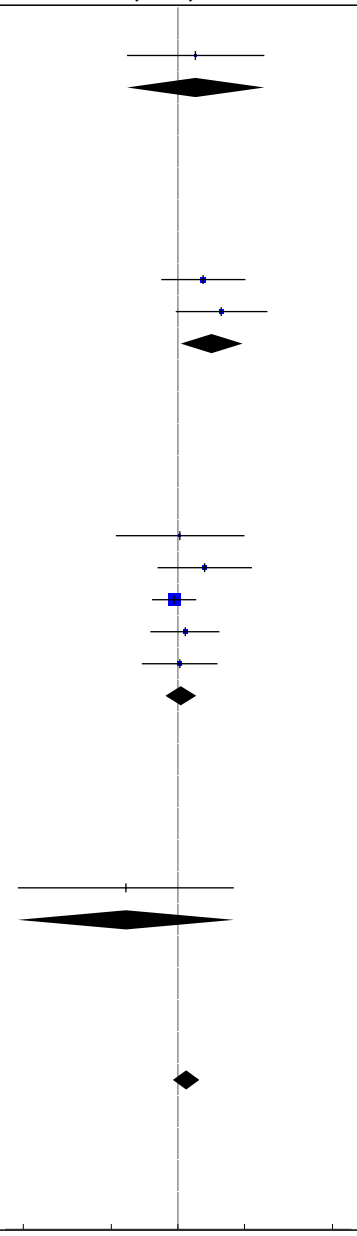



## Analysis 2.14. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 14 Withdrawals due to lack of efficacy.



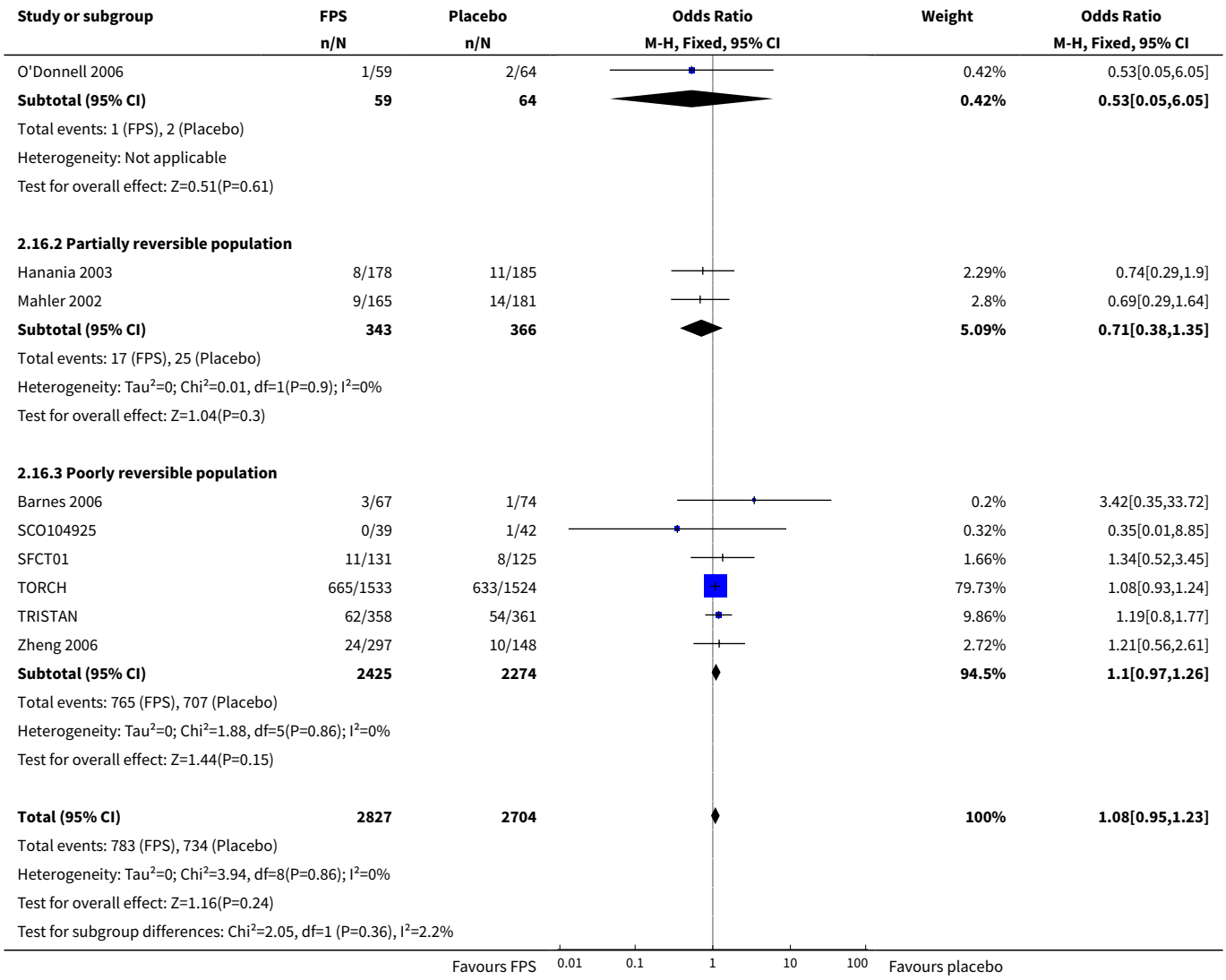
## Analysis 2.15. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 15 Adverse events—any.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.15.1 Reversible population** | | | | | |
| O'Donnell 2006 | 26/62 | 24/64 | | 3.58% | 1.2[0.59,2.46] |
| **Subtotal (95% CI)** | **62** | **64** | | **3.58%** | **1.2[0.59,2.46]** |
| Total events: 26 (FPS), 24 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.51(P=0.61) | | | | | |
| **2.15.2 Partially reversible population (mixed population)** | | | | | |
| Hanania 2003 | 124/178 | 118/185 | | 9.17% | 1.3[0.84,2.02] |
| Mahler 2002 | 131/169 | 127/185 | | 7.12% | 1.57[0.98,2.54] |
| **Subtotal (95% CI)** | **347** | **370** | | **16.29%** | **1.42[1.03,1.96]** |
| Total events: 255 (FPS), 245 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.33, df=1(P=0.57); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.14(P=0.03) | | | | | |
| **2.15.3 Poorly reversible population** | | | | | |
| Barnes 2006 | 38/67 | 41/73 | | 4.44% | 1.02[0.52,2] |
| SFCT01 | 72/131 | 60/125 | | 7.22% | 1.32[0.81,2.16] |
| TORCH | 1381/1546 | 1385/1544 | | 38.62% | 0.96[0.76,1.21] |
| TRISTAN | 285/358 | 283/361 | | 15% | 1.08[0.75,1.54] |
| Zheng 2006 | 158/297 | 78/148 | | 12.72% | 1.02[0.69,1.51] |
| **Subtotal (95% CI)** | **2399** | **2251** | | **78.01%** | **1.03[0.88,1.21]** |
| Total events: 1934 (FPS), 1847 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.4, df=4(P=0.84); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.36(P=0.72) | | | | | |
| **2.15.4 Unclear reversibility** | | | | | |
| SCO104925 | 6/39 | 10/42 | | 2.13% | 0.58[0.19,1.79] |
| **Subtotal (95% CI)** | **39** | **42** | | **2.13%** | **0.58[0.19,1.79]** |
| Total events: 6 (FPS), 10 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.95(P=0.34) | | | | | |
| **Total (95% CI)** | **2847** | **2727** | | **100%** | **1.09[0.95,1.25]** |
| Total events: 2221 (FPS), 2126 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=6.1, df=8(P=0.64); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.22(P=0.22) | | | | | |
| Test for subgroup differences: $Chi^2$=4.38, df=1 (P=0.22), $I^2$=31.58% | | | | | |

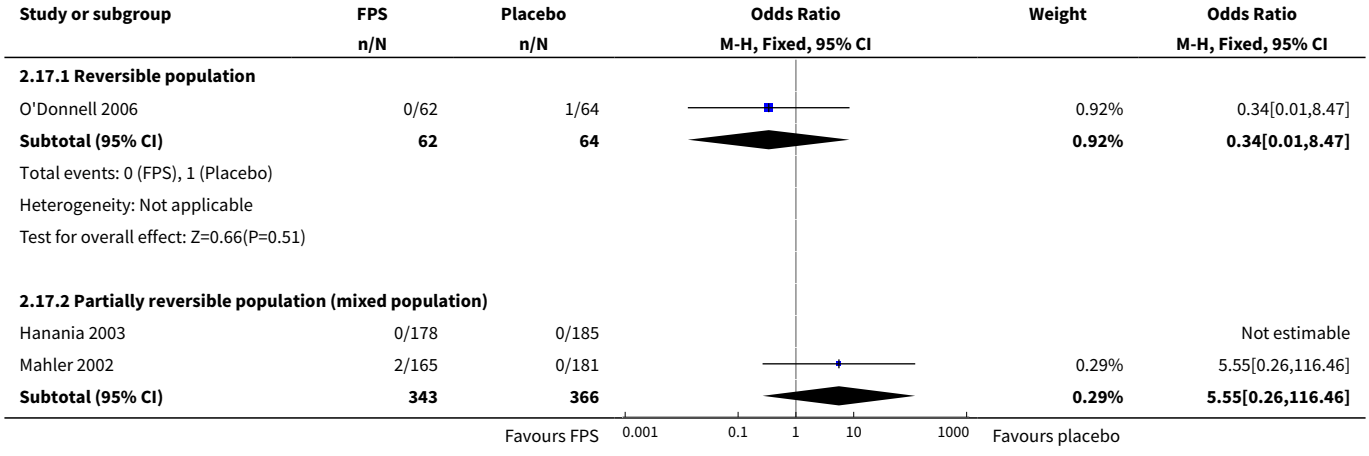


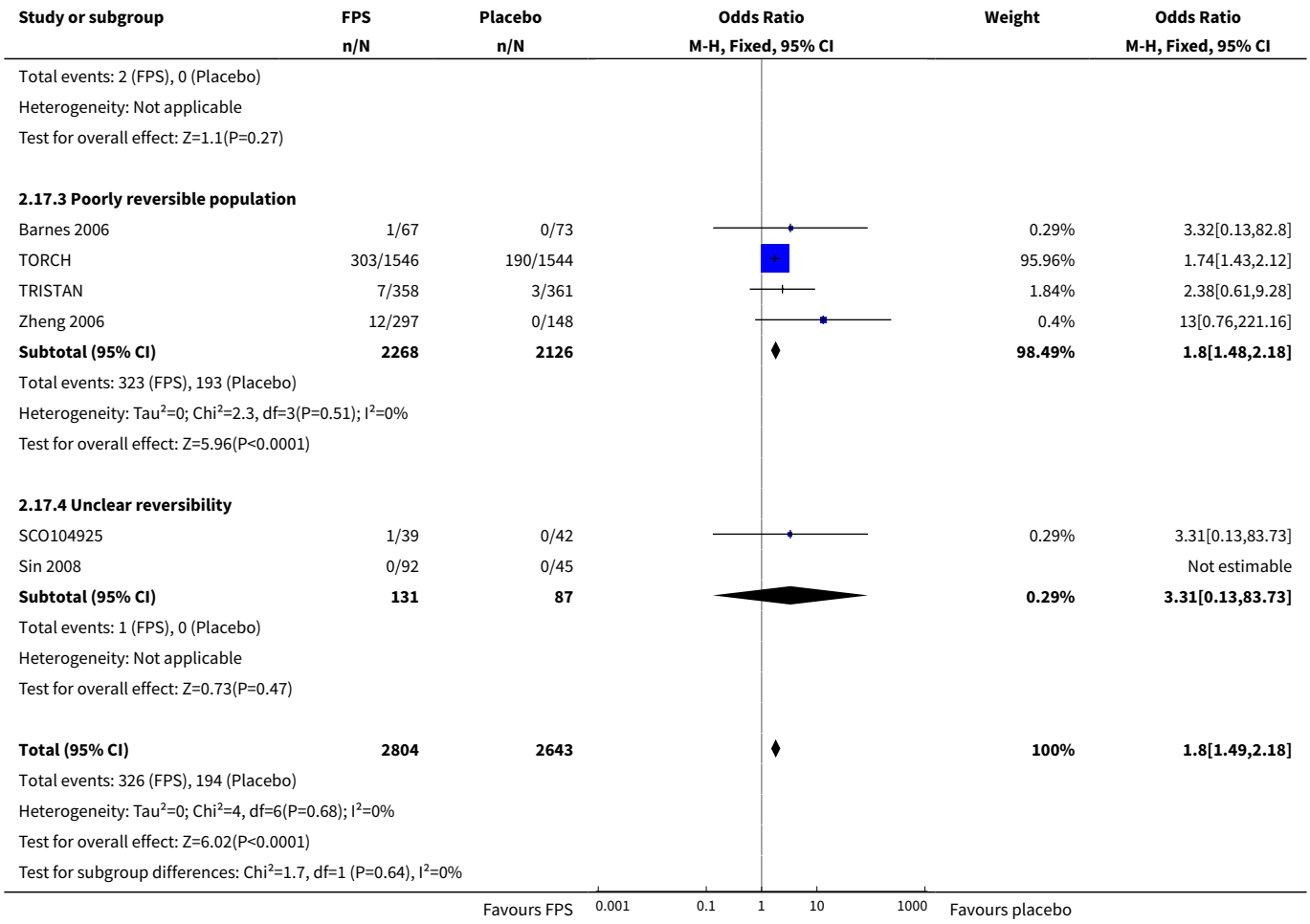

## Analysis 2.16. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 16 Adverse events—'serious'.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.16.1 Reversible population** | | | | | |

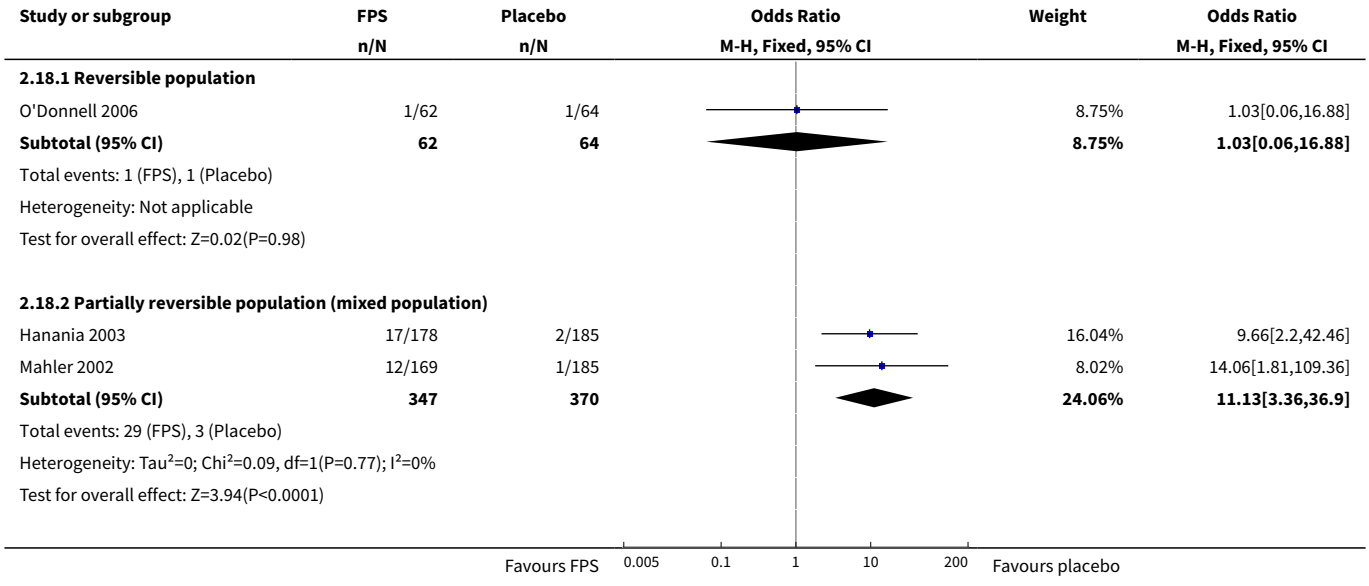


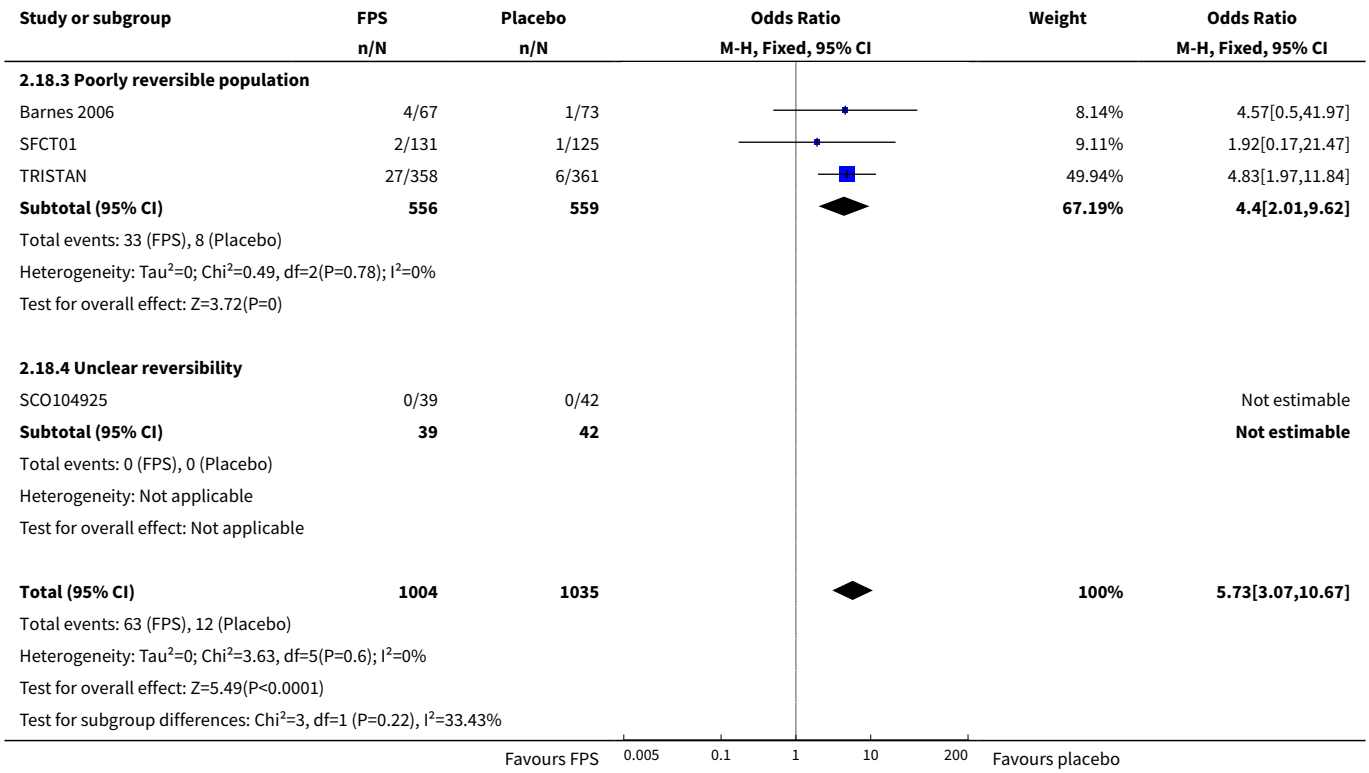

## Analysis 2.17. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 17 Adverse events—pneumonia.



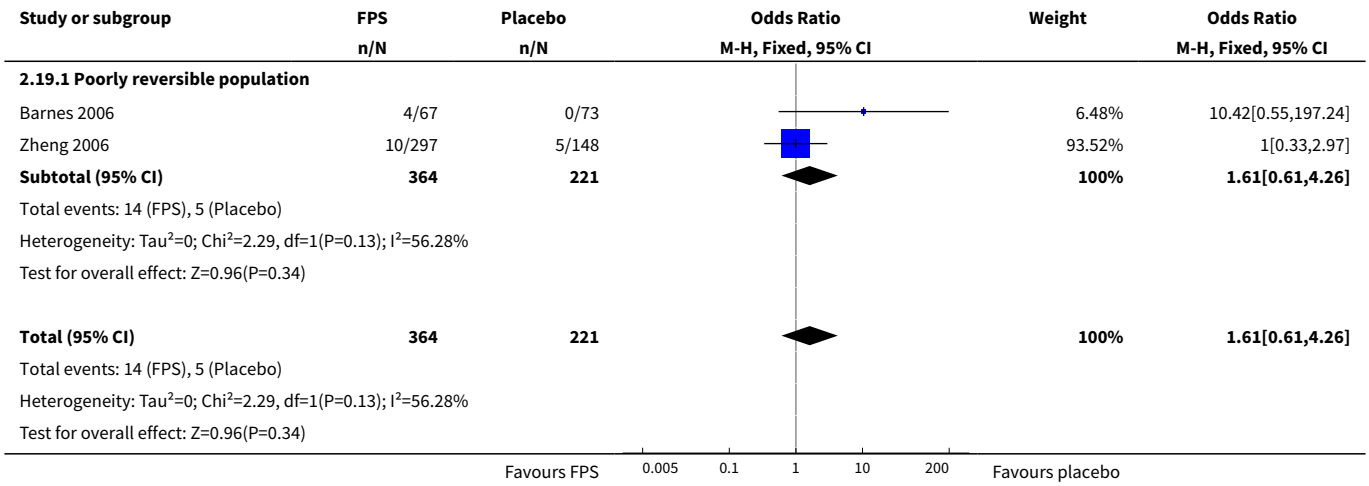



## Analysis 2.18. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 18 Adverse events—candidiasis.



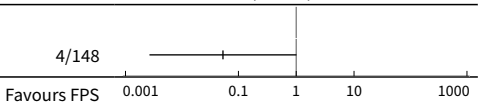



## Analysis 2.19. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 19 Adverse events—hoarseness.



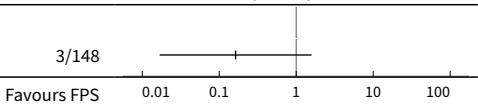
## Analysis 2.20. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 20 Adverse events—palpitations.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **2.20.1 Poorly reversible population** | | | | |
| Zheng 2006 | 0/297 | 4/148 | | 0.05[0,1.01] |



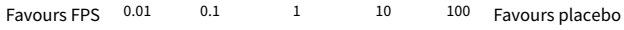

## Analysis 2.21. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 21 Adverse events—blood glucose increased.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **2.21.1 Poorly reversible population** | | | | |
| Zheng 2006 | 1/297 | 3/148 | | 0.16[0.02,1.58] |



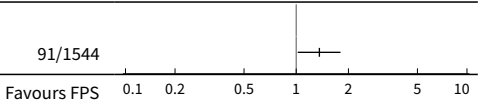

## Analysis 2.22. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 22 Adverse event—skin bruising.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.22.1 Poorly reversible population** | | | | | |
| Zheng 2006 | 0/297 | 0/148 | | | Not estimable |
| **Subtotal (95% CI)** | **297** | **148** | | | **Not estimable** |
| Total events: 0 (FPS), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |
| **Total (95% CI)** | **297** | **148** | | | **Not estimable** |
| Total events: 0 (FPS), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Not applicable | | | | | |



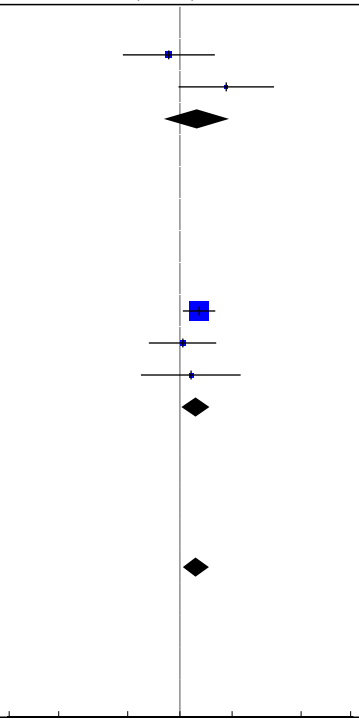

## Analysis 2.23. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 23 Adverse events—bronchitis.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|
| **2.23.1 Poorly reversible population** | | | | |
| TORCH | 121/1546 | 91/1544 | | 1.36[1.02,1.8] |



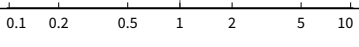
## Analysis 2.24. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 24 Adverse events—upper respiratory tract infection.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.24.1 Partially reversible population (mixed population)** | | | | | |
| Hanania 2003 | 22/178 | 26/185 | | 9.41% | 0.86[0.47,1.59] |
| Mahler 2002 | 28/165 | 18/181 | | 6% | 1.85[0.98,3.49] |
| **Subtotal (95% CI)** | **343** | **366** | | **15.41%** | **1.25[0.81,1.92]** |
| Total events: 50 (FPS), 44 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=2.9, df=1(P=0.09); $I^2$=65.48% | | | | | |
| Test for overall effect: Z=1(P=0.32) | | | | | |
| **2.24.2 Poorly reversible population** | | | | | |
| TORCH | 213/1546 | 170/1544 | | 61.76% | 1.29[1.04,1.6] |
| TRISTAN | 44/358 | 43/361 | | 15.81% | 1.04[0.66,1.62] |
| Zheng 2006 | 32/297 | 14/148 | | 7.02% | 1.16[0.6,2.24] |
| **Subtotal (95% CI)** | **2201** | **2053** | | **84.59%** | **1.23[1.02,1.48]** |
| Total events: 289 (FPS), 227 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.79, df=2(P=0.67); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.2(P=0.03) | | | | | |
| **Total (95% CI)** | **2544** | **2419** | | **100%** | **1.23[1.04,1.47]** |
| Total events: 339 (FPS), 271 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=3.69, df=4(P=0.45); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.42(P=0.02) | | | | | |
| Test for subgroup differences: $Chi^2$=0, df=1 (P=0.96), $I^2$=0% | | | | | |



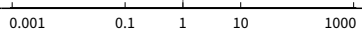

## Analysis 2.25. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 25 Adverse events—nasopharyngitis.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.25.1 Poorly reversible population** | | | | | |
| TORCH | 215/1546 | 165/1544 | | 82.24% | 1.35[1.09,1.68] |
| Zheng 2006 | 53/297 | 28/148 | | 17.76% | 0.93[0.56,1.55] |
| **Subtotal (95% CI)** | **1843** | **1692** | | **100%** | **1.28[1.05,1.56]** |
| Total events: 268 (FPS), 193 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.74, df=1(P=0.19); $I^2$=42.68% | | | | | |
| Test for overall effect: Z=2.39(P=0.02) | | | | | |
| **Total (95% CI)** | **1843** | **1692** | | **100%** | **1.28[1.05,1.56]** |
| Total events: 268 (FPS), 193 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.74, df=1(P=0.19); $I^2$=42.68% | | | | | |
| Test for overall effect: Z=2.39(P=0.02) | | | | | |



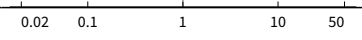
## Analysis 2.26. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 26 Adverse events—cough.

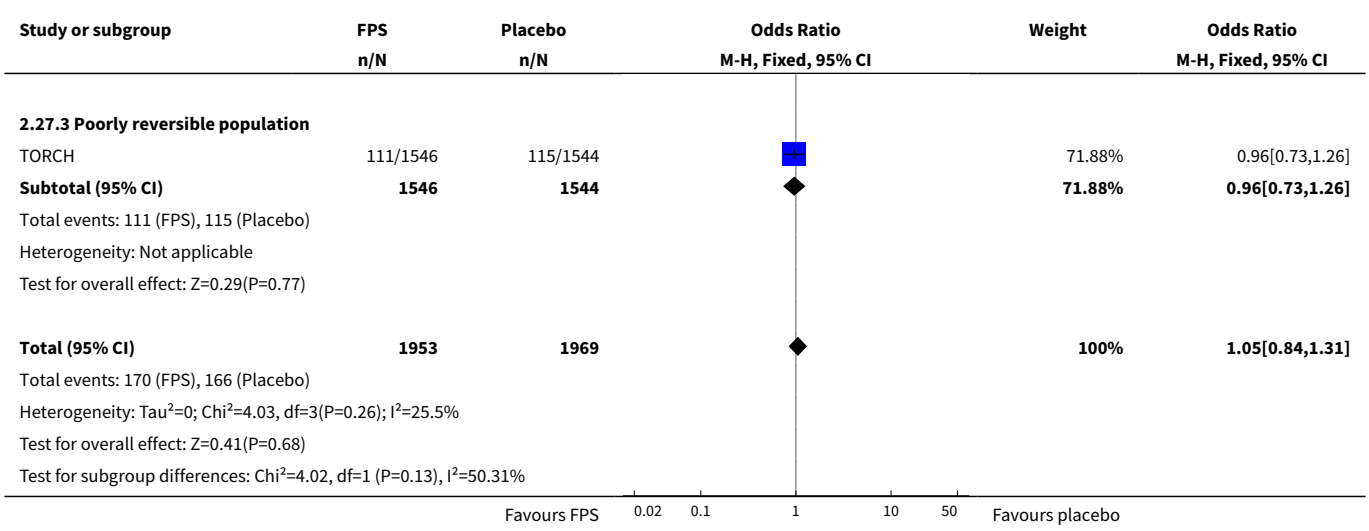
| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.26.1 Reversible population** | | | | | |
| O'Donnell 2006 | 1/62 | 0/64 | | 3.15% | 3.15[0.13,78.72] |
| **Subtotal (95% CI)** | **62** | **64** | | **3.15%** | **3.15[0.13,78.72]** |
| Total events: 1 (FPS), 0 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.7(P=0.49) | | | | | |
| **2.26.2 Partially reversible population (mixed population)** | | | | | |
| Mahler 2002 | 6/165 | 13/181 | | 78.31% | 0.49[0.18,1.31] |
| **Subtotal (95% CI)** | **165** | **181** | | **78.31%** | **0.49[0.18,1.31]** |
| Total events: 6 (FPS), 13 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.42(P=0.16) | | | | | |
| **2.26.3 Poorly reversible population** | | | | | |
| Barnes 2006 | 1/67 | 3/73 | | 18.54% | 0.35[0.04,3.48] |
| **Subtotal (95% CI)** | **67** | **73** | | **18.54%** | **0.35[0.04,3.48]** |
| Total events: 1 (FPS), 3 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=0.89(P=0.37) | | | | | |
| **Total (95% CI)** | **294** | **318** | | **100%** | **0.55[0.23,1.27]** |
| Total events: 8 (FPS), 16 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.33, df=2(P=0.52); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.4(P=0.16) | | | | | |
| Test for subgroup differences: $Chi^2$=1.32, df=1 (P=0.52), $I^2$=0% | | | | | |




## Analysis 2.27. Comparison 2 Fluticasone/salmeterol (FPS) versus placebo (PLA), Outcome 27 Adverse events—headache.

| Study or subgroup | FPS n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **2.27.1 Reversible population** | | | | | |
| O'Donnell 2006 | 1/64 | 4/59 | | 2.76% | 0.22[0.02,2.01] |
| **Subtotal (95% CI)** | **64** | **59** | | **2.76%** | **0.22[0.02,2.01]** |
| Total events: 1 (FPS), 4 (Placebo) | | | | | |
| Heterogeneity: Not applicable | | | | | |
| Test for overall effect: Z=1.34(P=0.18) | | | | | |
| **2.27.2 Partially reversible population (mixed population)** | | | | | |
| Hanania 2003 | 28/178 | 22/185 | | 12.24% | 1.38[0.76,2.52] |
| Mahler 2002 | 30/165 | 25/181 | | 13.13% | 1.39[0.78,2.47] |
| **Subtotal (95% CI)** | **343** | **366** | | **25.36%** | **1.38[0.91,2.1]** |
| Total events: 58 (FPS), 47 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=1(P=1); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.53(P=0.13) | | | | | |






## Comparison 3. Budesonide/formoterol (BDF) versus placebo (PLA)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Severe exacerbations | 2 | | Rate ratio (Fixed, 95% CI) | 0.74 [0.62, 0.88] |
| 1.1 Poorly reversible | 2 | | Rate ratio (Fixed, 95% CI) | 0.74 [0.62, 0.88] |
| 2 Mean severe exacerbation rates per participant per year | 2 | | Mean Difference (IV, Fixed, 95% CI) | Totals not selected |
| 2.1 Poorly reversible population | 2 | | Mean Difference (IV, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 3 Mortality | 4 | 3250 | Odds Ratio (M-H, Fixed, 95% CI) | 1.05 [0.57, 1.93] |
| 4 Change from baseline in St George's Respiratory Questionnaire (total score) | 4 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 4.1 320/9 mcg | 4 | 2350 | Mean Difference (IV, Fixed, 95% CI) | -3.73 [-4.83, -2.63] |
| 4.2 160/9 mcg | 2 | 1442 | Mean Difference (IV, Fixed, 95% CI) | -3.39 [-4.70, -2.07] |
| 5 Quality of life—change scores | 2 | | SGRQ (Fixed, 95% CI) | -6.06 [-7.90, -4.22] |
| 5.1 Poorly reversible | 2 | | SGRQ (Fixed, 95% CI) | -6.06 [-7.90, -4.22] |
| 6 Symptoms (change scores) | 2 | | Symptom scale (Fixed, 95% CI) | -0.63 [-0.90, -0.37] |
| 6.1 Poorly reversible | 2 | | Symptom scale (Fixed, 95% CI) | -0.63 [-0.90, -0.37] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7 Breathlessness, cough and sputum score (BCSS) change from baseline—average over treatment period | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 7.1 320/9 mcg | 2 | 1533 | Mean Difference (IV, Fixed, 95% CI) | -0.43 [-0.59, -0.26] |
| 7.2 160/9 mcg | 2 | 1536 | Mean Difference (IV, Fixed, 95% CI) | -0.44 [-0.60, -0.28] |
| 8 Rescue medication usage | 4 | | Mean Difference (Fixed, 95% CI) | Subtotals only |
| 8.1 320/9 mcg | 4 | | Mean Difference (Fixed, 95% CI) | -0.98 [-1.18, -0.79] |
| 8.2 160/9 mcg | 2 | | Mean Difference (Fixed, 95% CI) | -1.28 [-1.55, -1.00] |
| 9 Mean $FEV_1$ (% change from baseline) | 2 | | Mean Difference (Fixed, 95% CI) | 14.40 [11.91, 16.90] |
| 9.1 Poorly reversible | 2 | | Mean Difference (Fixed, 95% CI) | 14.40 [11.91, 16.90] |
| 10 Average 12-hour $FEV_1$ change from baseline—end of treatment (L) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 10.1 320/9 mcg | 1 | 246 | Mean Difference (IV, Fixed, 95% CI) | 0.19 [0.12, 0.26] |
| 10.2 160/9 mcg | 1 | 245 | Mean Difference (IV, Fixed, 95% CI) | 0.16 [0.10, 0.22] |
| 11 Predose $FEV_1$ [L] change from baseline to the average over the randomised treatment period | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 11.1 320/9 mcg | 1 | 577 | Mean Difference (IV, Fixed, 95% CI) | 0.08 [0.04, 0.12] |
| 11.2 160/9 mcg | 1 | 581 | Mean Difference (IV, Fixed, 95% CI) | 0.06 [0.03, 0.09] |
| 12 1 Hour postdose $FEV_1$ [L] change from baseline to the average over the randomised treatment period | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 12.1 320/9 mcg | 1 | 577 | Mean Difference (IV, Fixed, 95% CI) | 0.17 [0.14, 0.20] |
| 12.2 160/9 mcg | 1 | 581 | Mean Difference (IV, Fixed, 95% CI) | 0.16 [0.13, 0.19] |
| 13 $FEV_1$ at 12-hour change from baseline—end of treatment (L) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |

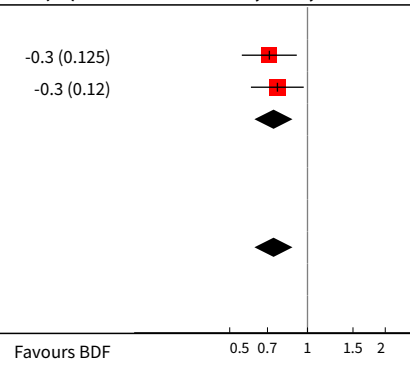
| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 13.1 320/9 mcg | 1 | 246 | Mean Difference (IV, Fixed, 95% CI) | 0.1 [0.03, 0.17] |
| 13.2 160/9 mcg | 1 | 245 | Mean Difference (IV, Fixed, 95% CI) | 0.07 [0.00, 0.14] |
| 14 Morning PEFR change from baseline, average over treatment period (L/min) | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 14.1 320/9 mcg | 2 | 1530 | Mean Difference (IV, Fixed, 95% CI) | 19.12 [15.69, 22.55] |
| 14.2 160/9 mcg | 2 | 1535 | Mean Difference (IV, Fixed, 95% CI) | 14.63 [11.47, 17.80] |
| 15 Evening PEFR mean change from base-line, average over treatment period (L/min) | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 15.1 320/9 mcg | 2 | 1529 | Mean Difference (IV, Fixed, 95% CI) | 16.09 [12.61, 19.57] |
| 15.2 160/9 mcg | 2 | 1531 | Mean Difference (IV, Fixed, 95% CI) | 12.74 [9.56, 15.91] |
| 16 Withdrawals—total | 4 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 16.1 320/9 mcg | 4 | 2475 | Odds Ratio (M-H, Fixed, 95% CI) | 0.57 [0.48, 0.68] |
| 16.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 0.62 [0.50, 0.78] |
| 17 Withdrawals due to adverse events | 4 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 17.1 320/9 mcg | 4 | 2475 | Odds Ratio (M-H, Fixed, 95% CI) | 0.79 [0.61, 1.01] |
| 17.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 0.95 [0.70, 1.30] |
| 18 Withdrawals due to lack of efficacy | 3 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 18.1 320/9 mcg | 3 | 1898 | Odds Ratio (M-H, Fixed, 95% CI) | 0.46 [0.34, 0.63] |
| 18.2 160/9 mcg | 1 | 975 | Odds Ratio (M-H, Fixed, 95% CI) | 1.01 [0.60, 1.71] |
| 19 Adverse event—any | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 19.1 320/9 mcg | 2 | 1552 | Odds Ratio (M-H, Fixed, 95% CI) | 1.42 [1.16, 1.74] |
| 19.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 1.32 [1.08, 1.61] |
| 20 Adverse events—'serious' | 4 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 20.1 320/9 mcg | 4 | 2476 | Odds Ratio (M-H, Fixed, 95% CI) | 1.17 [0.95, 1.45] |
| 20.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 1.20 [0.89, 1.63] |

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 21 Adverse events—pneumonia | 3 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 21.1 320/9 mcg | 3 | 2062 | Odds Ratio (M-H, Fixed, 95% CI) | 0.89 [0.52, 1.52] |
| 21.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 0.80 [0.45, 1.42] |
| 22 Adverse events—candidiasis | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 22.1 320/9 mcg | 2 | 1552 | Odds Ratio (M-H, Fixed, 95% CI) | 3.45 [1.88, 6.34] |
| 22.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 2.05 [1.07, 3.92] |
| 23 Adverse events—dysphonia | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 23.1 320/9 mcg | 2 | 1552 | Odds Ratio (M-H, Fixed, 95% CI) | 4.07 [1.52, 10.90] |
| 23.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 1.17 [0.37, 3.67] |
| 24 Adverse events—cataracts | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 24.1 320/9 mcg | 1 | 975 | Odds Ratio (M-H, Fixed, 95% CI) | 0.32 [0.01, 7.97] |
| 24.2 160/9 mcg | 1 | 975 | Odds Ratio (M-H, Fixed, 95% CI) | 1.95 [0.18, 21.59] |
| 25 Adverse events—COPD | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 25.1 320/9 mcg | 2 | 1552 | Odds Ratio (M-H, Fixed, 95% CI) | 0.92 [0.69, 1.22] |
| 25.2 160/9 mcg | 2 | 1556 | Odds Ratio (M-H, Fixed, 95% CI) | 1.16 [0.88, 1.53] |
| 26 Adverse events—tremor | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 26.1 320/9 mcg | 1 | 577 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 26.2 160/9 mcg | 1 | 581 | Odds Ratio (M-H, Fixed, 95% CI) | 7.55 [0.39, 146.88] |
| 27 Adverse events—palpitations | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 27.1 320/9 mcg | 1 | 577 | Odds Ratio (M-H, Fixed, 95% CI) | 3.26 [0.13, 80.37] |
| 27.2 160/9 mcg | 1 | 581 | Odds Ratio (M-H, Fixed, 95% CI) | 0.0 [0.0, 0.0] |
| 28 Adverse events—lumbar spine bone density change from baseline ($g/cm^2$) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 28.1 320/9 mcg | 1 | 149 | Mean Difference (IV, Fixed, 95% CI) | -0.02 [-0.03, -0.01] |
| 28.2 160/9 mcg | 1 | 149 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [-0.01, 0.01] |
| 29 Adverse events—hip bone density change from baseline ($g/cm^2$) | 1 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |

| Outcome or subgroup title | No. of studies | No. of partici-pants | Statistical method | Effect size |
|---|---|---|---|---|
| 29.1 320/9 mcg | 1 | 149 | Mean Difference (IV, Fixed, 95% CI) | 0.0 [-0.01, 0.01] |
| 29.2 160/9 mcg | 1 | 147 | Mean Difference (IV, Fixed, 95% CI) | 0.01 [0.00, 0.02] |

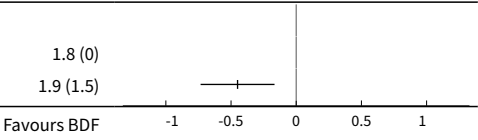
**Analysis 3.1. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 1 Severe exacerbations.**

| Study or subgroup | BDF N | Placebo N | log[Rate ratio] (SE) | Rate ratio IV, Fixed, 95% CI | Weight | Rate ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.1.1 Poorly reversible** | | | | | | |
| Calverley 2003 | 1 | 1 | -0.3 (0.125) | | 47.96% | 0.71[0.56,0.91] |
| Szafranski 2003 | 1 | 1 | -0.3 (0.12) | | 52.04% | 0.76[0.6,0.97] |
| **Subtotal (95% CI)** | | | | | **100%** | **0.74[0.62,0.88]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.17, df=1(P=0.68); $I^2$=0% | | | | | | |
| Test for overall effect: Z=3.5(P=0) | | | | | | |
| **Total (95% CI)** | | | | | **100%** | **0.74[0.62,0.88]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.17, df=1(P=0.68); $I^2$=0% | | | | | | |
| Test for overall effect: Z=3.5(P=0) | | | | | | |



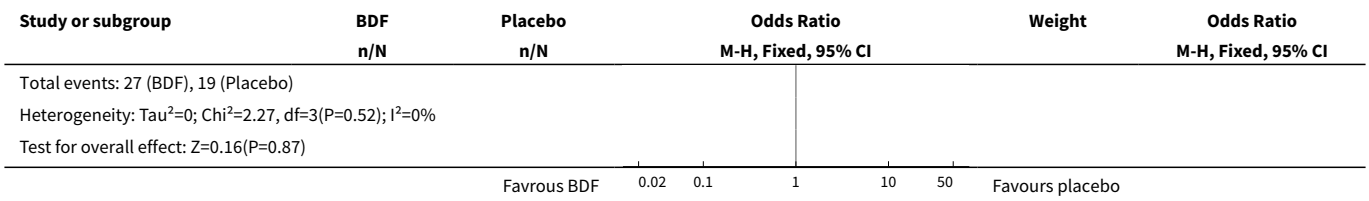

**Analysis 3.2. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 2 Mean severe exacerbation rates per participant per year.**

| Study or subgroup | BDF N | BDF Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.2.1 Poorly reversible population** | | | | | | |
| Calverley 2003 | 254 | 1.4 (0) | 256 | 1.8 (0) | | Not estimable |
| Szafranski 2003 | 208 | 1.4 (1.5) | 205 | 1.9 (1.5) | | -0.45[-0.73,-0.17] |

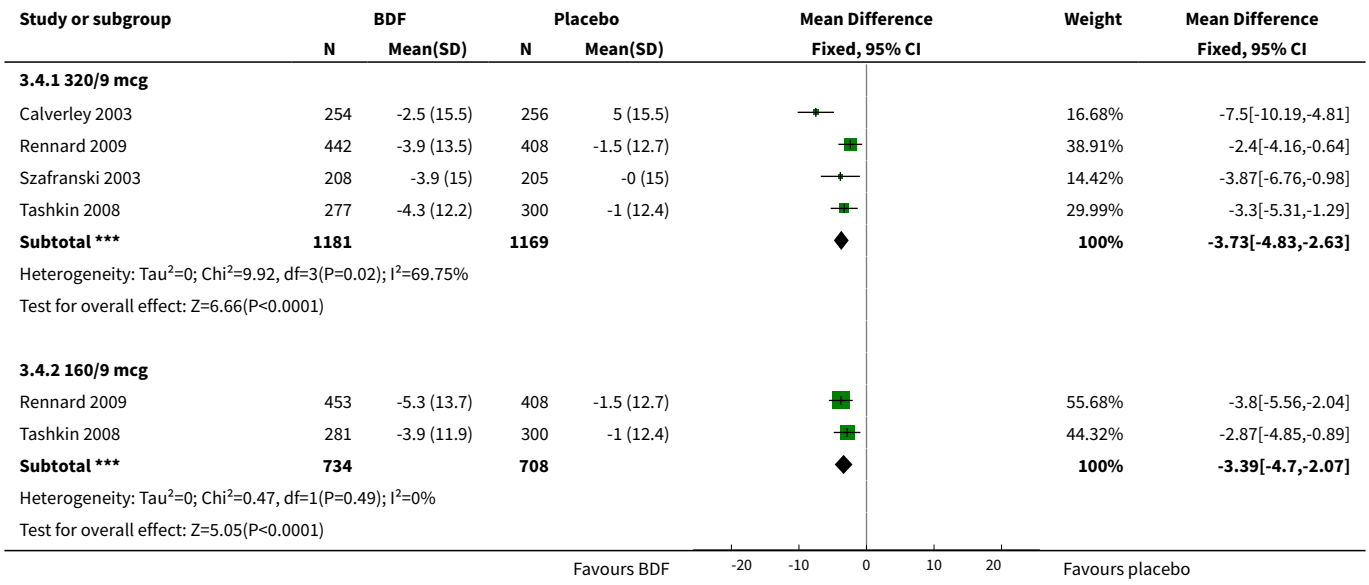



**Analysis 3.3. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 3 Mortality.**

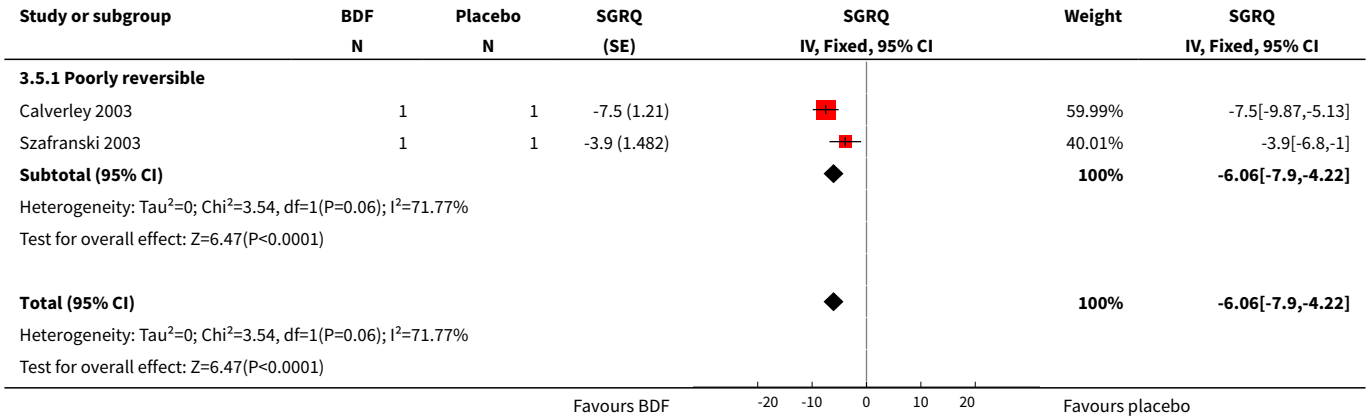
| Study or subgroup | BDF n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Calverley 2003 | 5/254 | 5/256 | | 24.05% | 1.01[0.29,3.53] |
| Rennard 2009 | 9/988 | 4/481 | | 26.26% | 1.1[0.34,3.58] |
| Szafranski 2003 | 6/208 | 9/205 | | 43.36% | 0.65[0.23,1.85] |
| Tashkin 2008 | 7/558 | 1/300 | | 6.33% | 3.8[0.47,31.02] |
| **Total (95% CI)** | **2008** | **1242** | | **100%** | **1.05[0.57,1.93]** |




## Analysis 3.4. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 4 Change from baseline in St George's Respiratory Questionnaire (total score).




## Analysis 3.5. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 5 Quality of life—change scores.



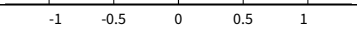
## Analysis 3.6. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 6 Symptoms (change scores).

| Study or subgroup | BDF N | Pacebo N | Symptom scale (SE) | Symptom scale IV, Fixed, 95% CI | Weight | Symptom scale IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.6.1 Poorly reversible** | | | | | | |
| Calverley 2003 | 1 | 1 | -0.6 (0.166) | | 66.12% | -0.56[-0.88,-0.24] |
| Szafranski 2003 | 1 | 1 | -0.8 (0.232) | | 33.88% | -0.77[-1.22,-0.32] |
| **Subtotal (95% CI)** | | | | | **100%** | **-0.63[-0.9,-0.37]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.54, df=1(P=0.46); $I^2$=0% | | | | | | |
| Test for overall effect: Z=4.68(P<0.0001) | | | | | | |
| **Total (95% CI)** | | | | | **100%** | **-0.63[-0.9,-0.37]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.54, df=1(P=0.46); $I^2$=0% | | | | | | |
| Test for overall effect: Z=4.68(P<0.0001) | | | | | | |



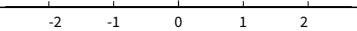

## Analysis 3.7. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 7 Breathlessness, cough and sputum score (BCSS) change from baseline—average over treatment period.

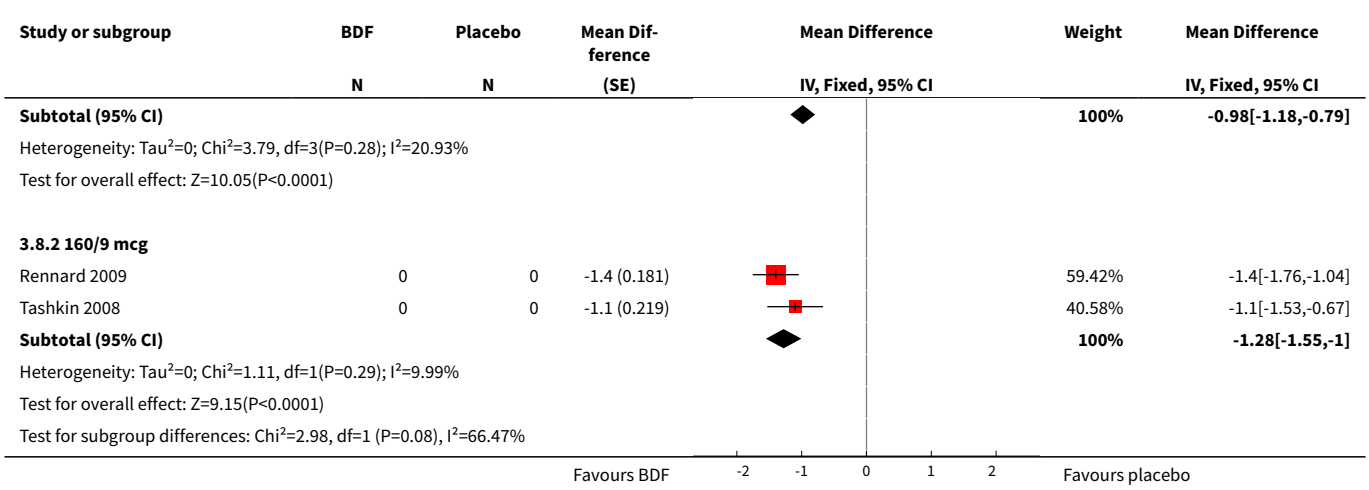
| Study or subgroup | BDF N | BDF Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.7.1 320/9 mcg** | | | | | | | |
| Rennard 2009 | 489 | -0.8 (1.8) | 467 | -0.3 (1.7) | | 57.08% | -0.5[-0.72,-0.28] |
| Tashkin 2008 | 277 | -0.6 (1.6) | 300 | -0.3 (1.5) | | 42.92% | -0.33[-0.59,-0.07] |
| **Subtotal ***** | **766** | | **767** | | | **100%** | **-0.43[-0.59,-0.26]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.97, df=1(P=0.33); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=4.99(P<0.0001) | | | | | | | |
| **3.7.2 160/9 mcg** | | | | | | | |
| Rennard 2009 | 488 | -0.8 (1.7) | 467 | -0.3 (1.7) | | 57.12% | -0.5[-0.72,-0.28] |
| Tashkin 2008 | 281 | -0.6 (1.5) | 300 | -0.3 (1.5) | | 42.88% | -0.36[-0.61,-0.11] |
| **Subtotal ***** | **769** | | **767** | | | **100%** | **-0.44[-0.6,-0.28]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.69, df=1(P=0.4); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=5.29(P<0.0001) | | | | | | | |
| Test for subgroup differences: $Chi^2$=0.01, df=1 (P=0.91), $I^2$=0% | | | | | | | |



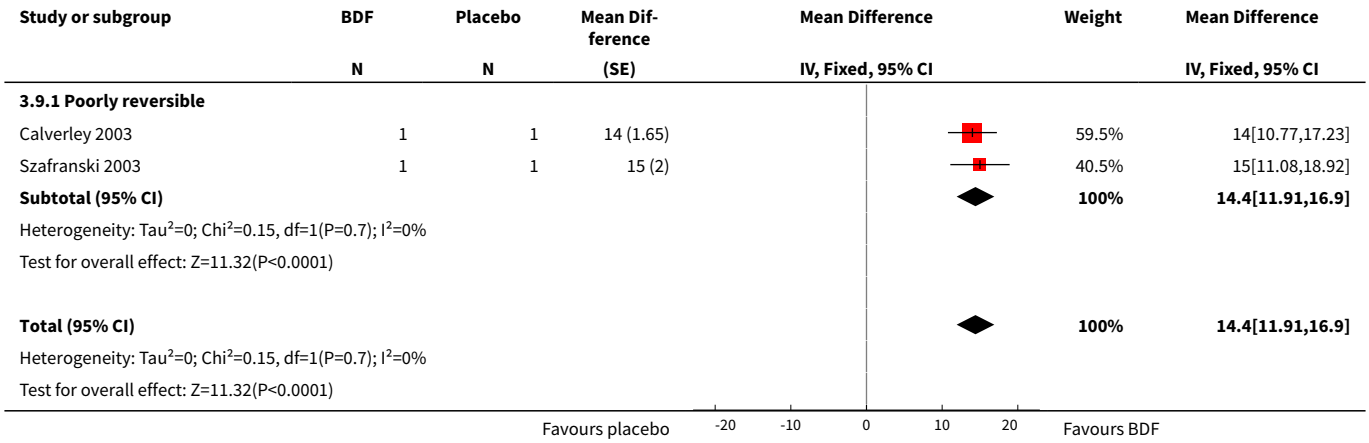

## Analysis 3.8. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 8 Rescue medication usage.

| Study or subgroup | BDF N | Placebo N | Mean Difference (SE) | Mean Difference IV, Fixed, 95% CI | Weight | Mean Difference IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| **3.8.1 320/9 mcg** | | | | | | |
| Calverley 2003 | 1 | 1 | -0.8 (0.156) | | 39.36% | -0.8[-1.11,-0.49] |
| Rennard 2009 | 0 | 0 | -1.2 (0.171) | | 32.64% | -1.2[-1.54,-0.86] |
| Szafranski 2003 | 1 | 1 | -1.3 (0.391) | | 6.26% | -1.3[-2.07,-0.53] |
| Tashkin 2008 | 0 | 0 | -0.9 (0.21) | | 21.74% | -0.9[-1.31,-0.49] |

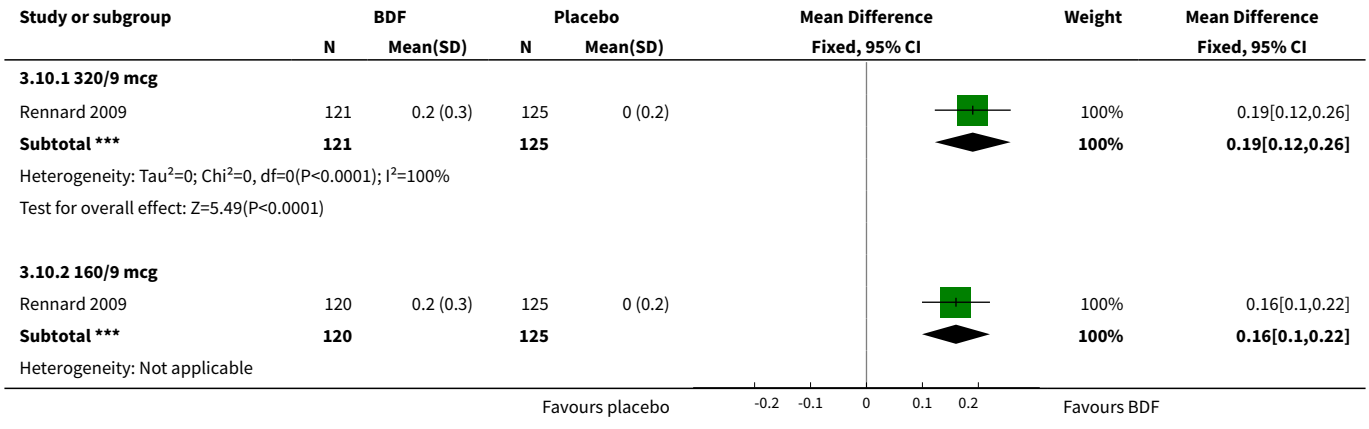


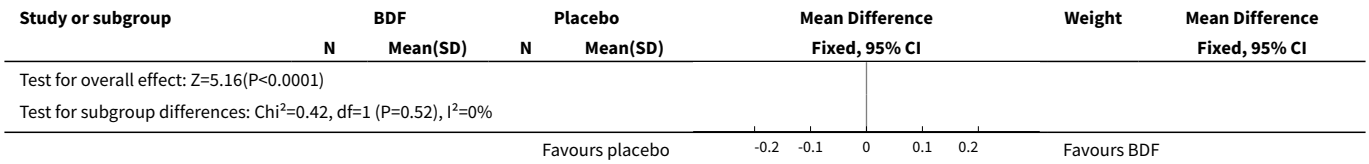



## Analysis 3.9. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 9 Mean $FEV_1$ (% change from baseline).

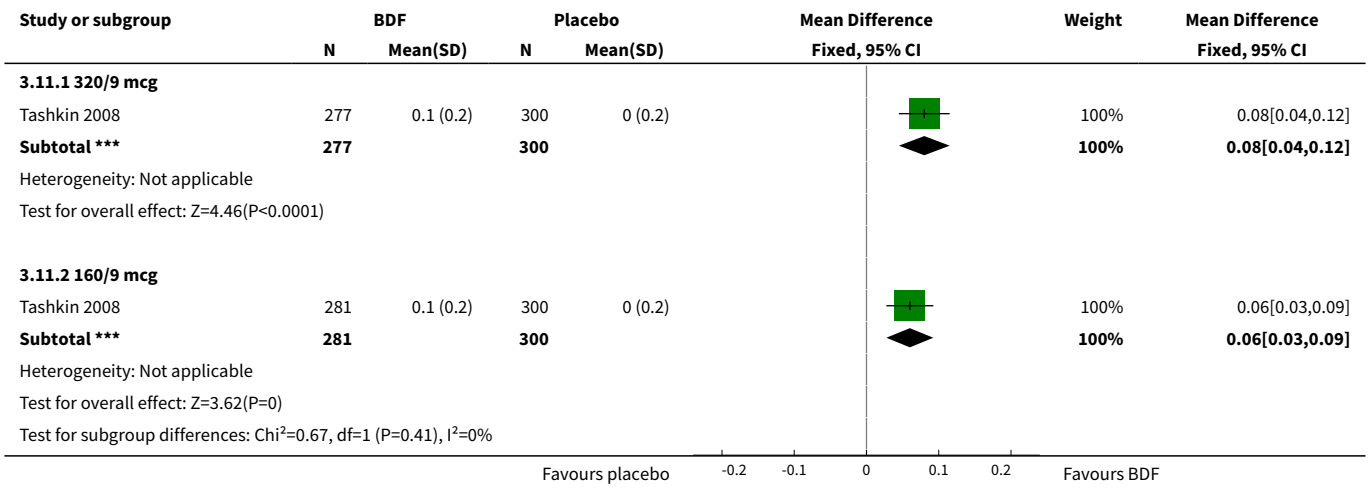



## Analysis 3.10. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 10 Average 12-hour $FEV_1$ change from baseline—end of treatment (L).

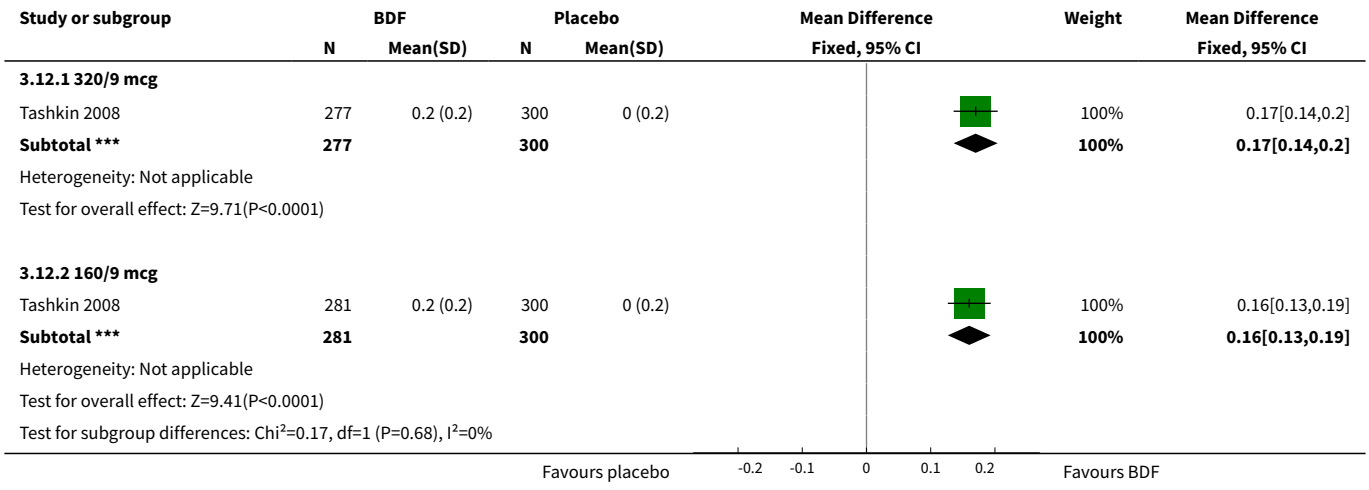





**Analysis 3.11. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 11 Predose $FEV_1$ [L] change from baseline to the average over the randomised treatment period.**

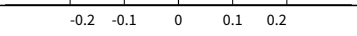



**Analysis 3.12. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 12 1 Hour postdose $FEV_1$ [L] change from baseline to the average over the randomised treatment period.**



## Analysis 3.13. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 13 $FEV_1$ at 12-hour change from baseline—end of treatment (L).

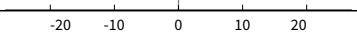
| Study or subgroup | BDF N | BDF Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.13.1 320/9 mcg** | | | | | | | |
| Rennard 2009 | 121 | 0.1 (0.3) | 125 | 0 (0.3) | | 100% | 0.1[0.03,0.17] |
| **Subtotal ***** | **121** | | **125** | | | **100%** | **0.1[0.03,0.17]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=0(P<0.0001); $I^2$=100% | | | | | | | |
| Test for overall effect: Z=2.74(P=0.01) | | | | | | | |
| **3.13.2 160/9 mcg** | | | | | | | |
| Rennard 2009 | 120 | 0.1 (0.3) | 125 | 0 (0.3) | | 100% | 0.07[0,0.14] |
| **Subtotal ***** | **120** | | **125** | | | **100%** | **0.07[0,0.14]** |
| Heterogeneity: Not applicable | | | | | | | |
| Test for overall effect: Z=2.03(P=0.04) | | | | | | | |
| Test for subgroup differences: $Chi^2$=0.36, df=1 (P=0.55), $I^2$=0% | | | | | | | |




Favours placebo — Favours BDF

## Analysis 3.14. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 14 Morning PEFR change from baseline, average over treatment period (L/min).

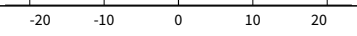
| Study or subgroup | Experimental N | Experimental Mean(SD) | Control N | Control Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.14.1 320/9 mcg** | | | | | | | |
| Rennard 2009 | 487 | 20.7 (39.5) | 466 | 1.9 (33.5) | | 54.5% | 18.8[14.16,23.44] |
| Tashkin 2008 | 277 | 19.5 (34) | 300 | -0 (27.7) | | 45.5% | 19.5[14.42,24.58] |
| **Subtotal ***** | **764** | | **766** | | | **100%** | **19.12[15.69,22.55]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.04, df=1(P=0.84); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=10.93(P<0.0001) | | | | | | | |
| **3.14.2 160/9 mcg** | | | | | | | |
| Rennard 2009 | 488 | 15.2 (33.4) | 466 | 1.9 (33.5) | | 55.57% | 13.3[9.05,17.55] |
| Tashkin 2008 | 281 | 16.3 (30.6) | 300 | -0 (27.7) | | 44.43% | 16.3[11.55,21.05] |
| **Subtotal ***** | **769** | | **766** | | | **100%** | **14.63[11.47,17.8]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.85, df=1(P=0.36); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=9.06(P<0.0001) | | | | | | | |
| Test for subgroup differences: $Chi^2$=3.55, df=1 (P=0.06), $I^2$=71.84% | | | | | | | |



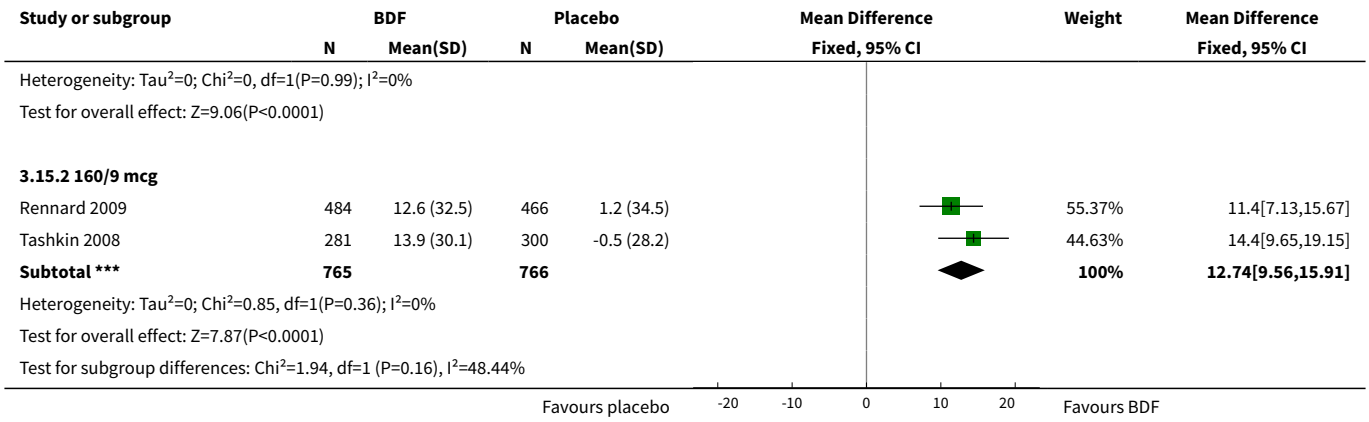

Favours placebo — Favours BDF

## Analysis 3.15. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 15 Evening PEFR mean change from baseline, average over treatment period (L/min).

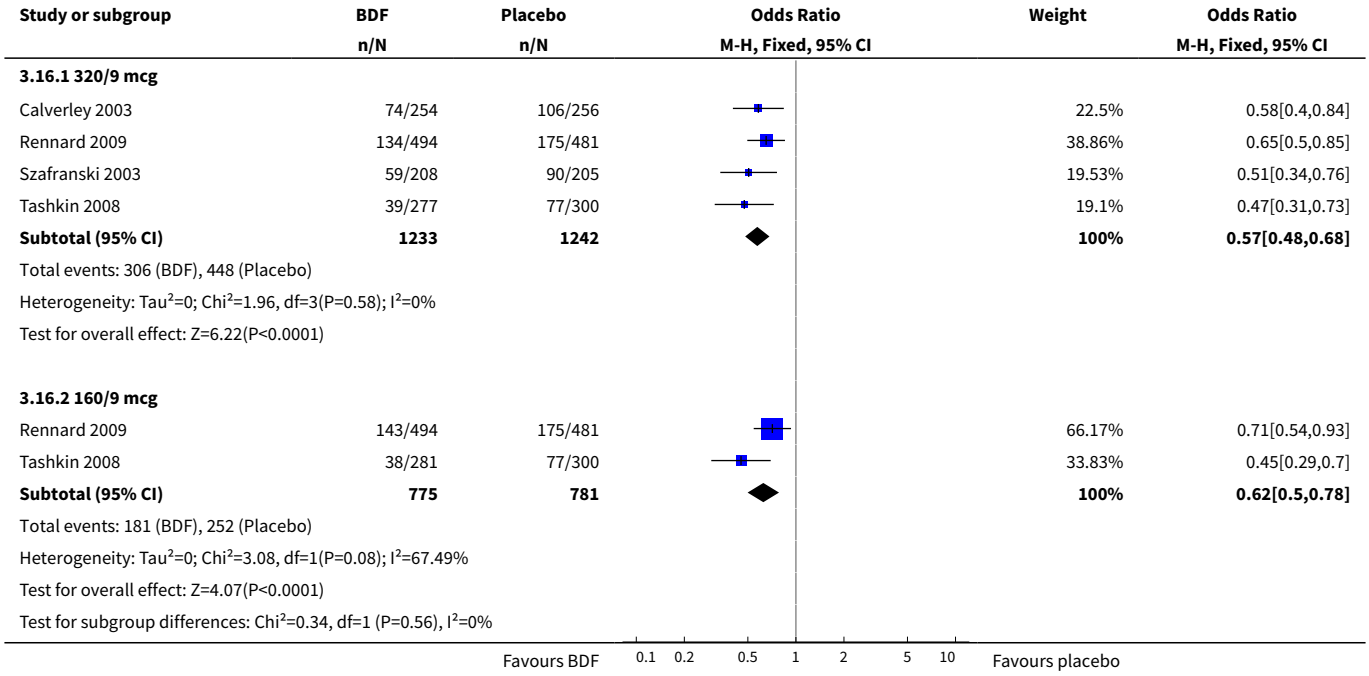
| Study or subgroup | BDF N | BDF Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **3.15.1 320/9 mcg** | | | | | | | |
| Rennard 2009 | 486 | 17.3 (39.7) | 466 | 1.2 (34.5) | | 54.41% | 16.1[11.38,20.82] |
| Tashkin 2008 | 277 | 15.5 (34.4) | 300 | -0.5 (28.2) | | 45.59% | 16.07[10.91,21.23] |
| **Subtotal ***** | **763** | | **766** | | | **100%** | **16.09[12.61,19.57]** |



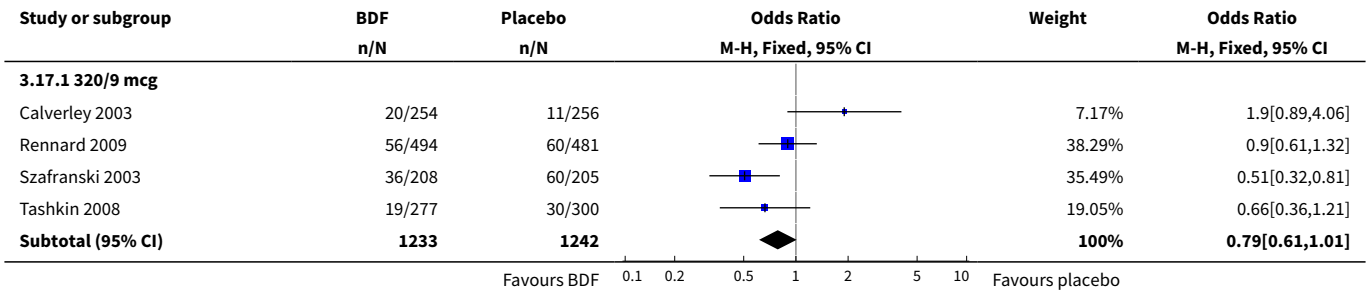

Favours placebo — Favours BDF

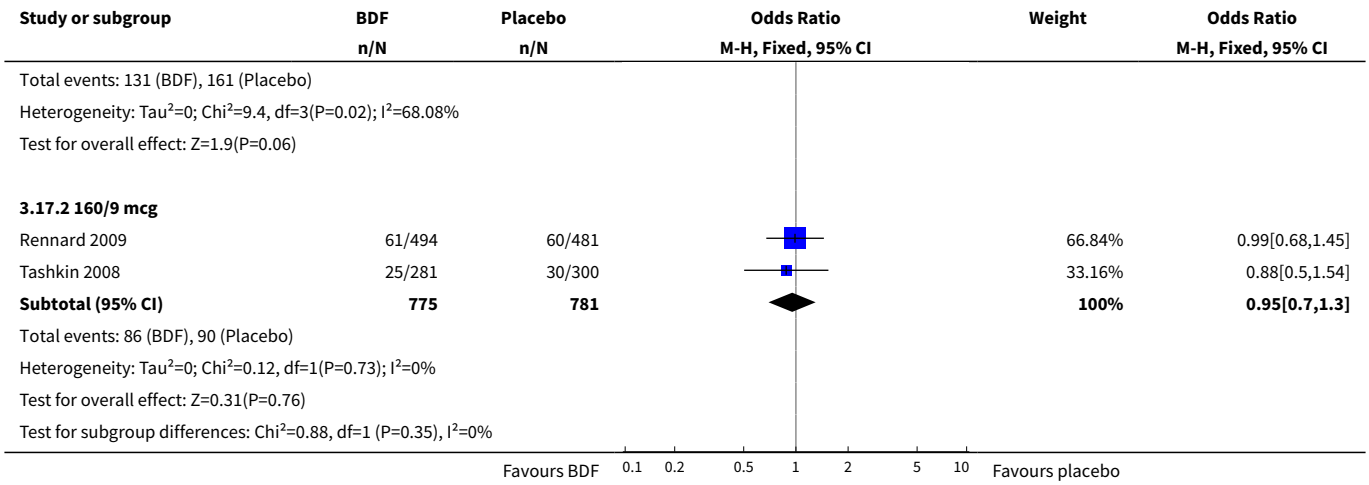



## Analysis 3.16. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 16 Withdrawals—total.

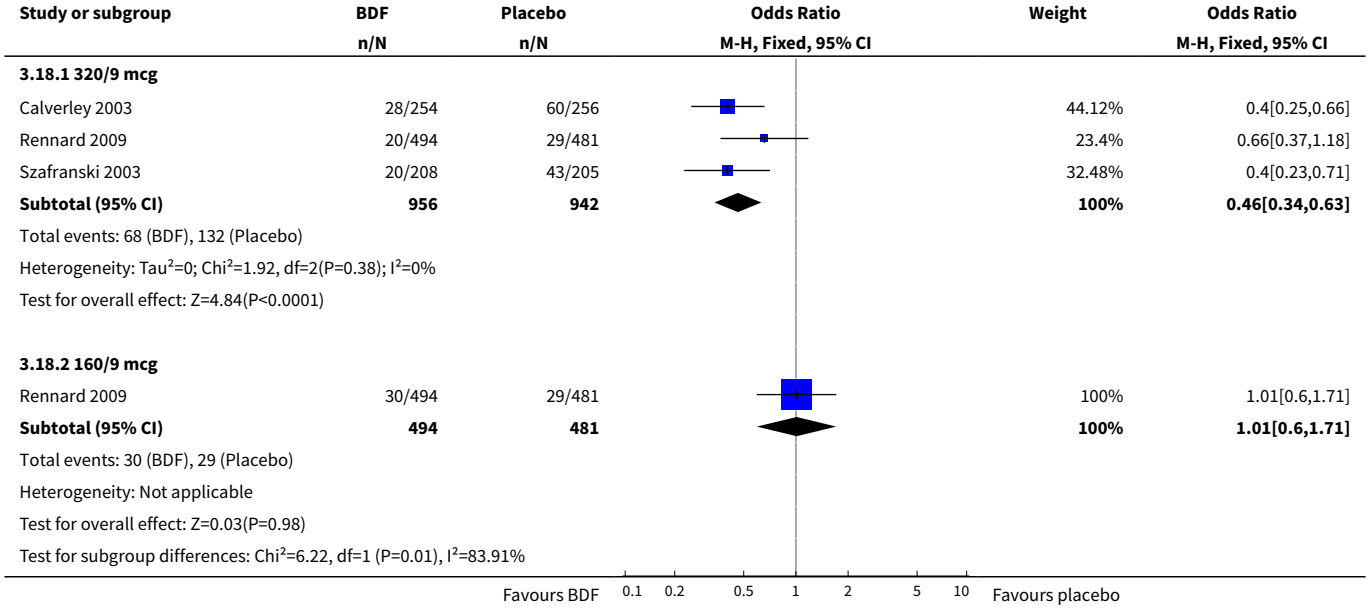



## Analysis 3.17. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 17 Withdrawals due to adverse events.

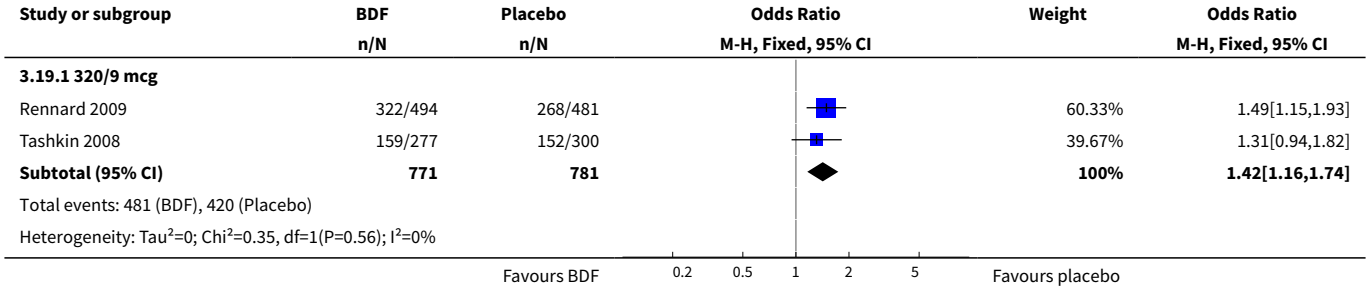


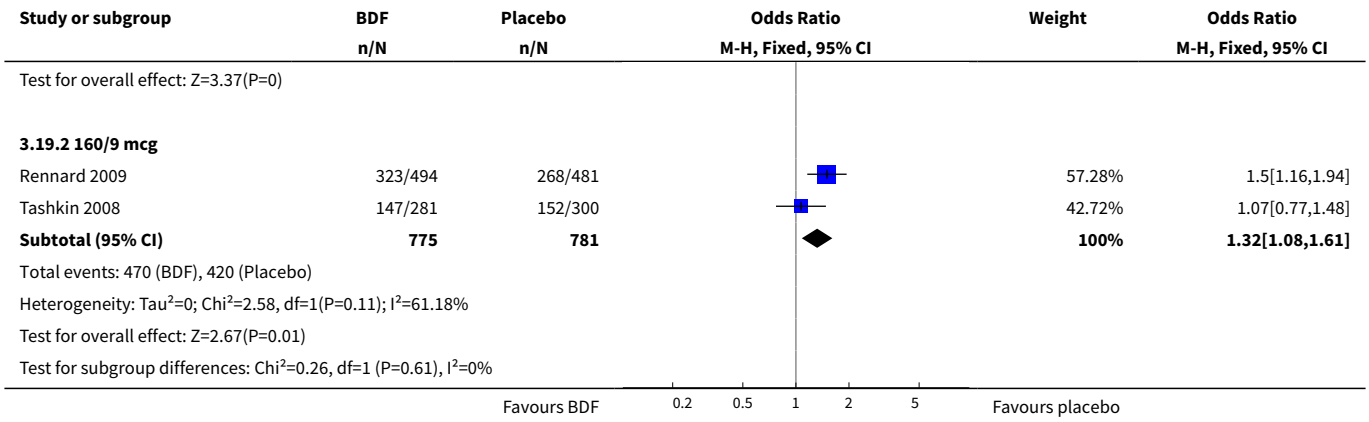



## Analysis 3.18. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 18 Withdrawals due to lack of efficacy.

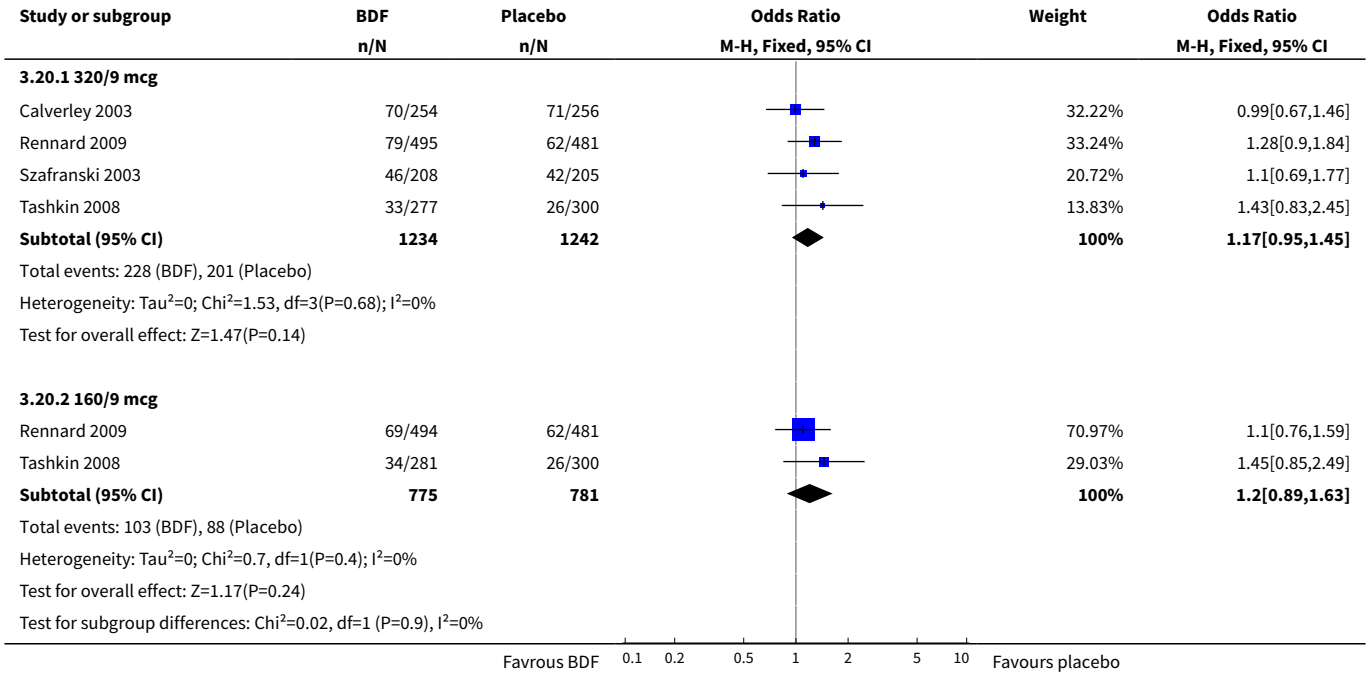



## Analysis 3.19. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 19 Adverse event—any.

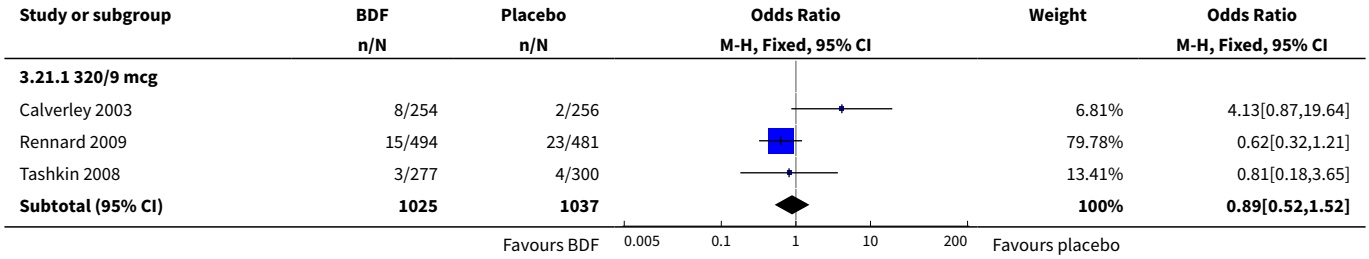


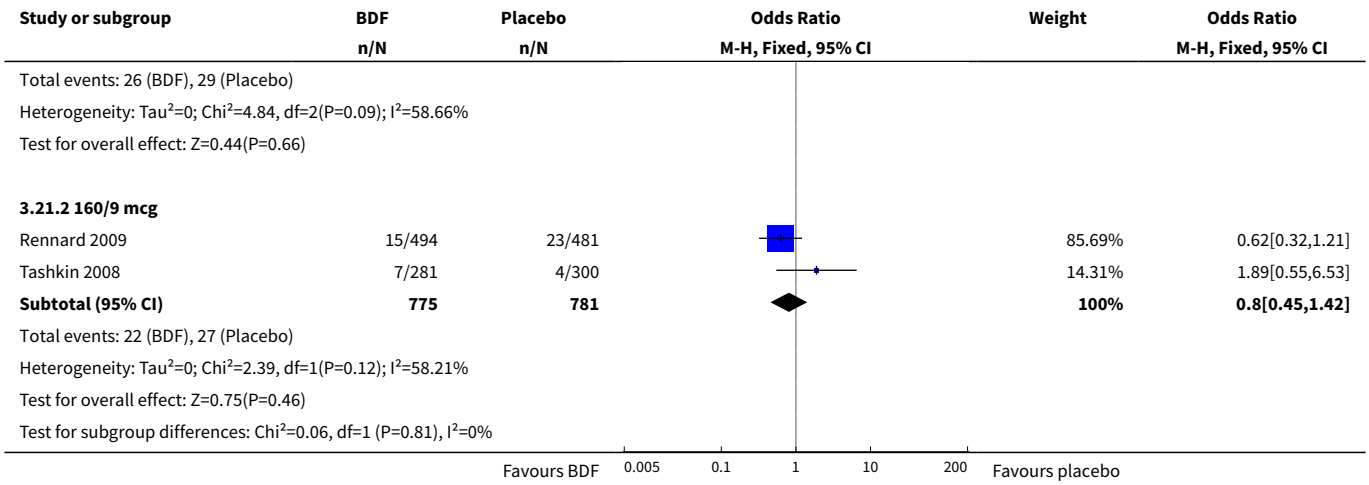



## Analysis 3.20. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 20 Adverse events—'serious'.

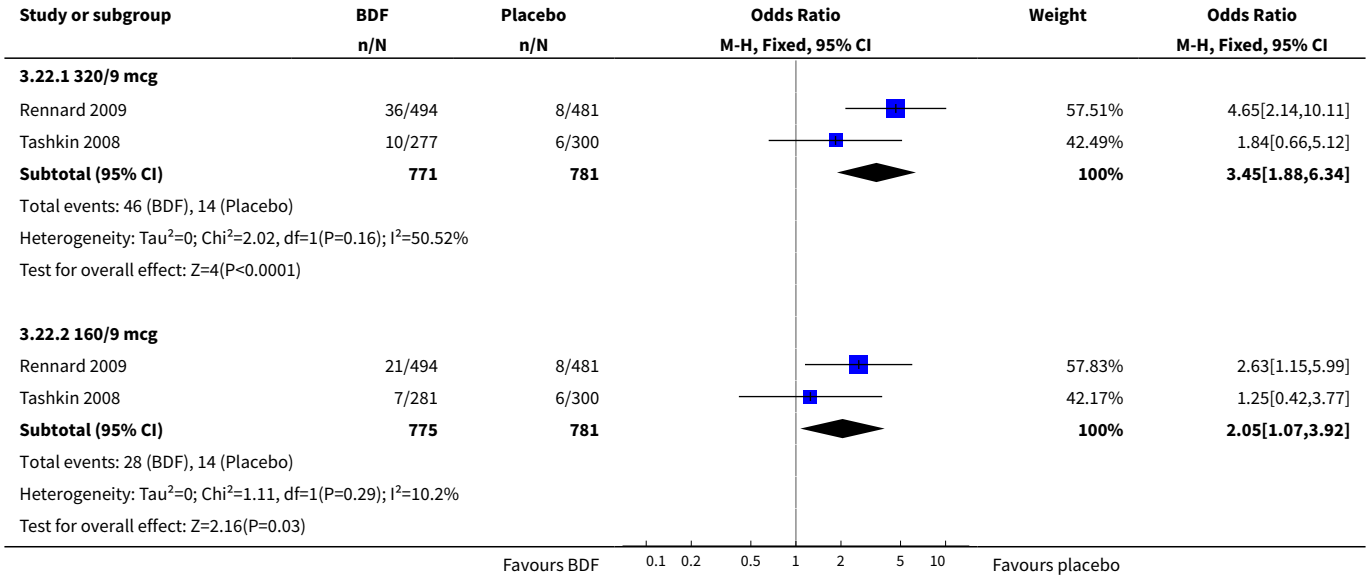



## Analysis 3.21. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 21 Adverse events—pneumonia.

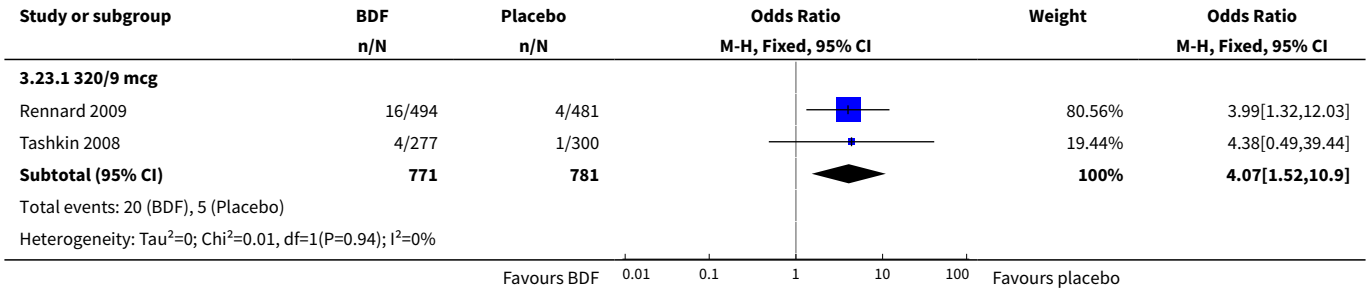


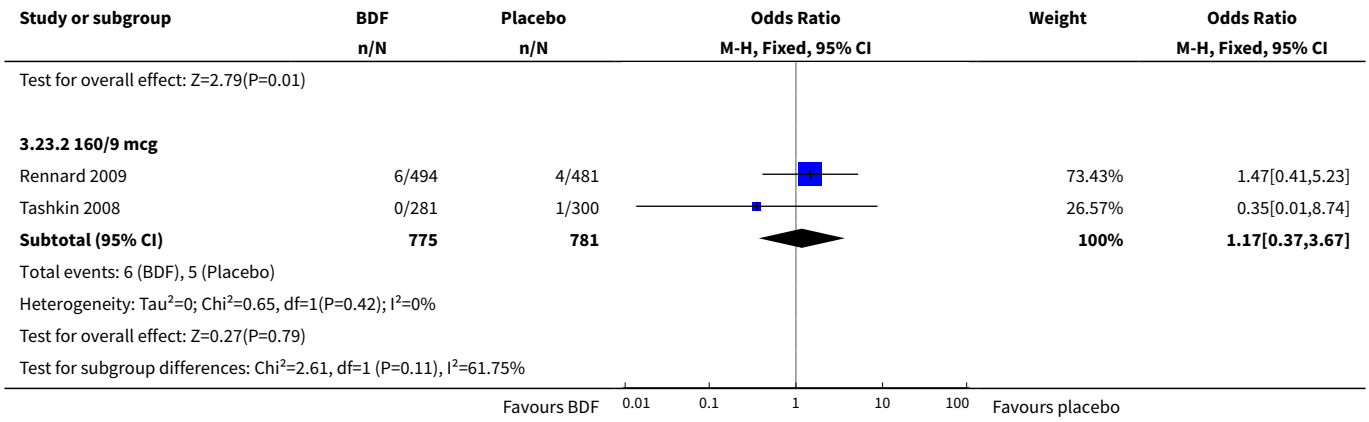



## Analysis 3.22. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 22 Adverse events—candidiasis.

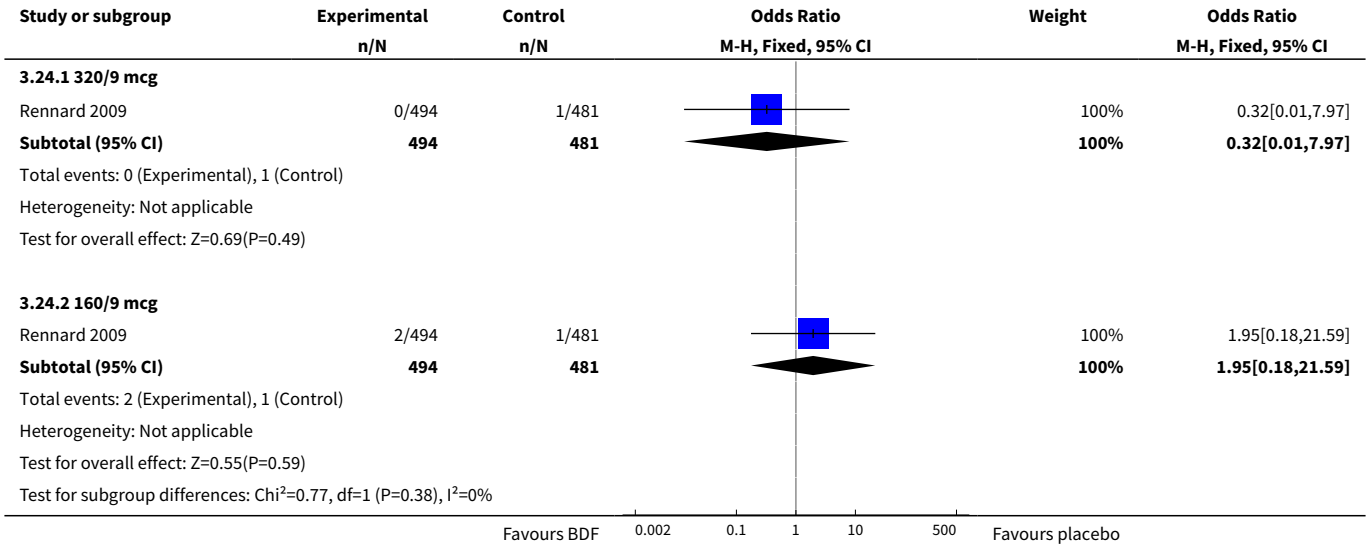



## Analysis 3.23. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 23 Adverse events—dysphonia.

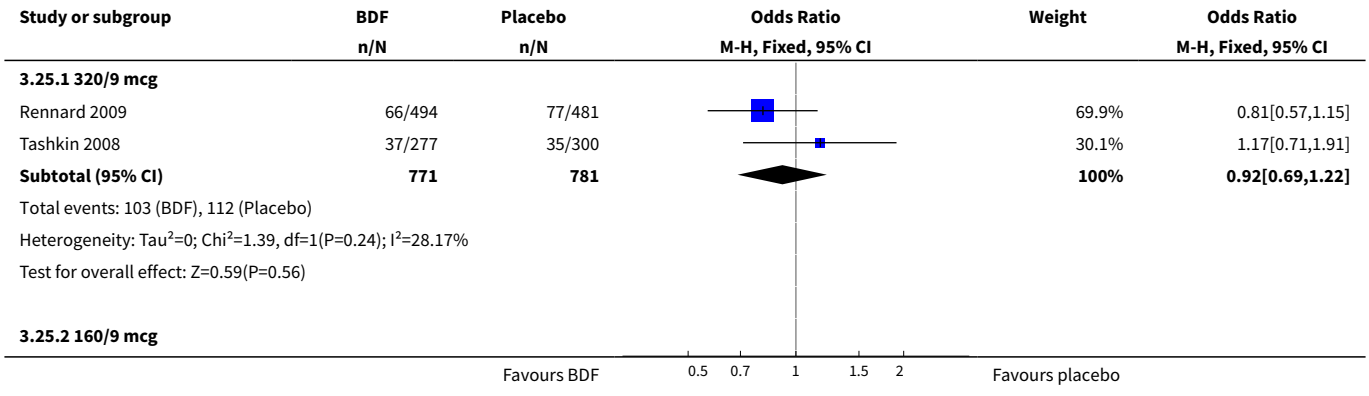


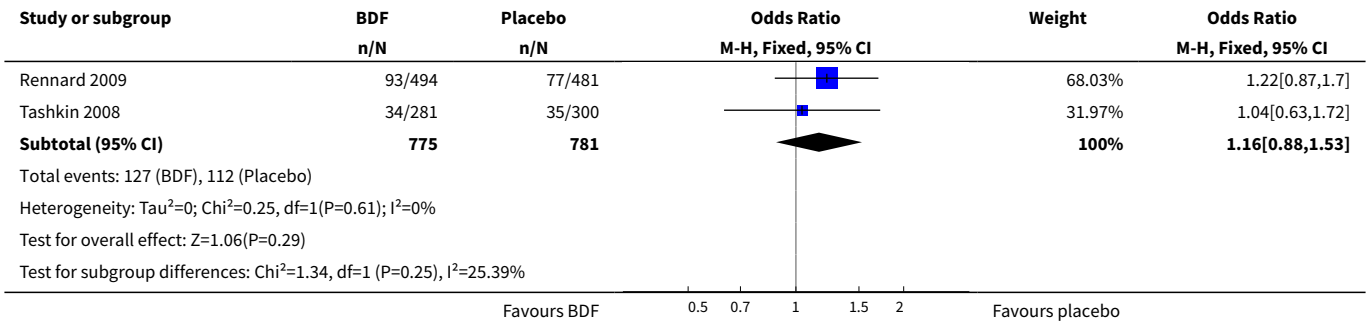



## Analysis 3.24. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 24 Adverse events—cataracts.

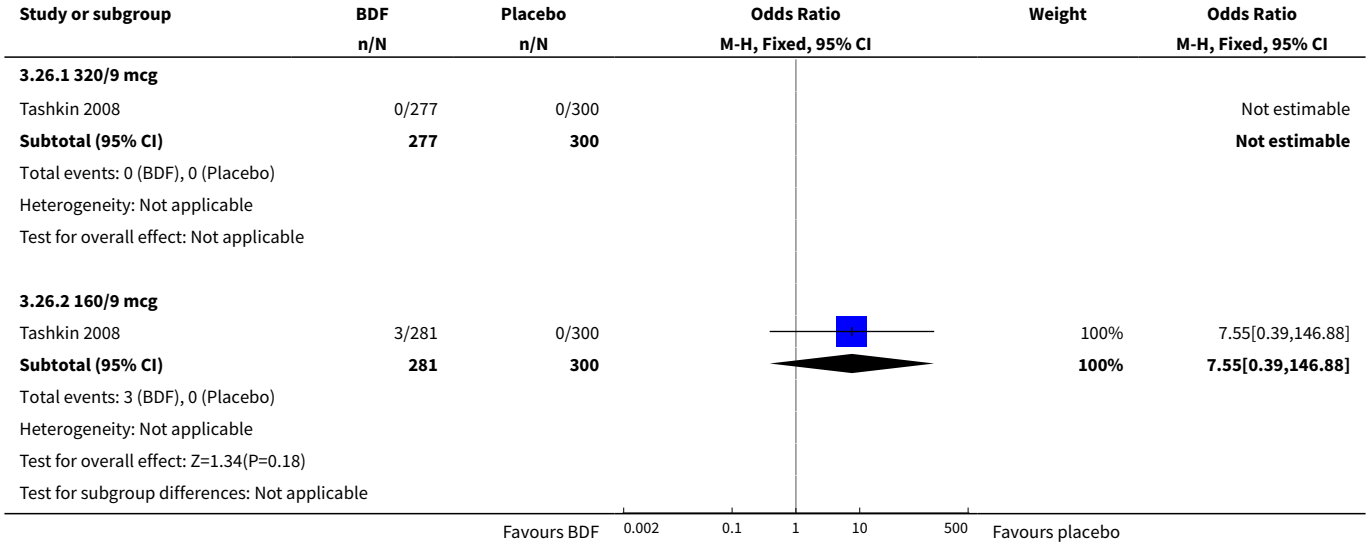



## Analysis 3.25. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 25 Adverse events—COPD.

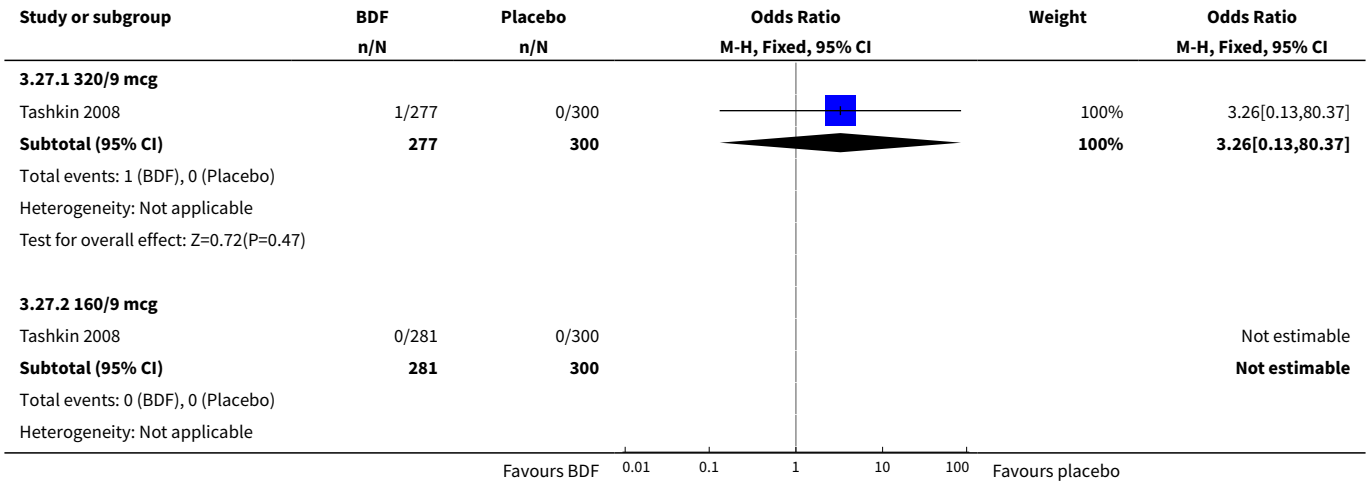


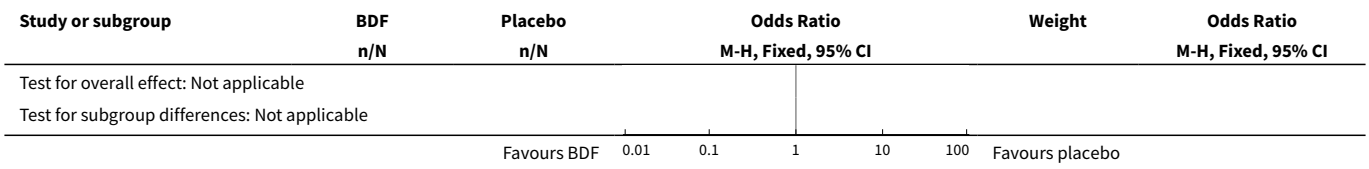



## Analysis 3.26. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 26 Adverse events—tremor.

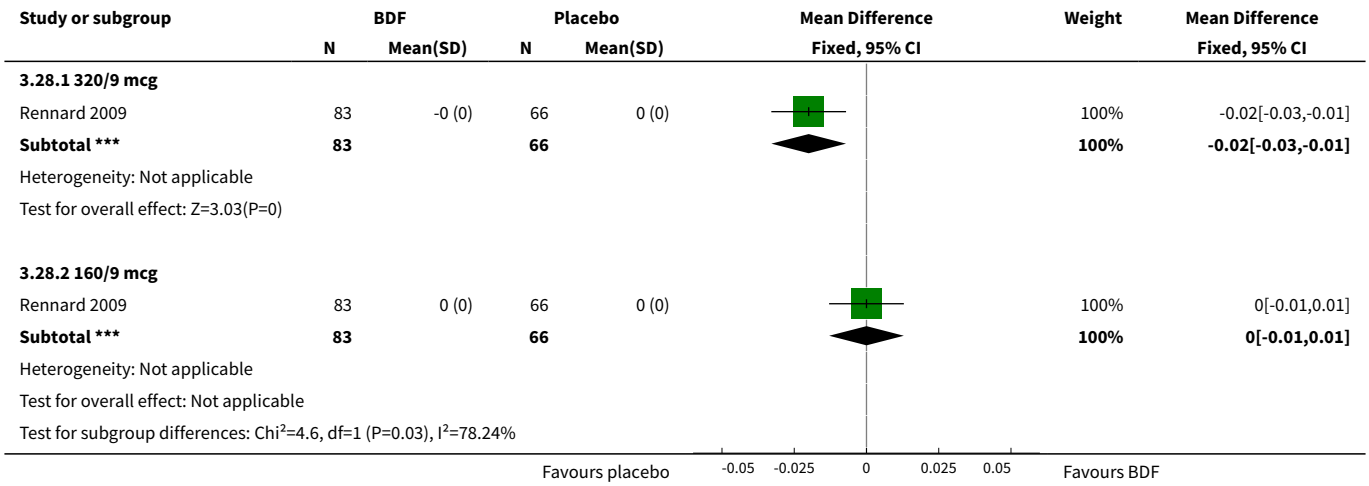



## Analysis 3.27. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 27 Adverse events—palpitations.

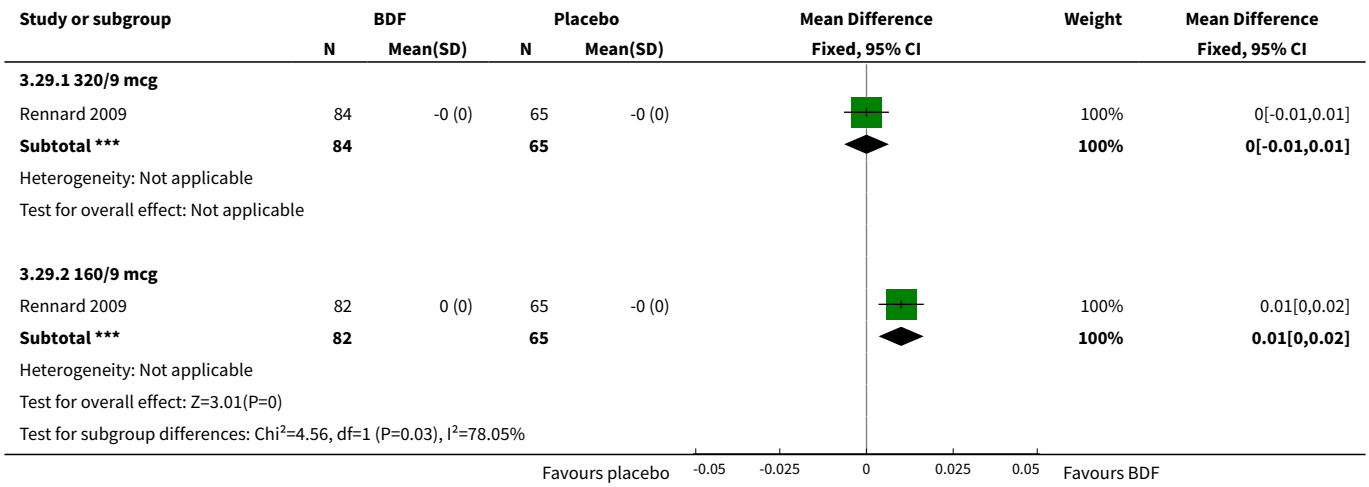





## Analysis 3.28. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 28 Adverse events—lumbar spine bone density change from baseline (g/cm²).




## Analysis 3.29. Comparison 3 Budesonide/formoterol (BDF) versus placebo (PLA), Outcome 29 Adverse events—hip bone density change from baseline (g/cm²).



**Comparison 4. Mometasone/formoterol (MF/F) versus placebo**

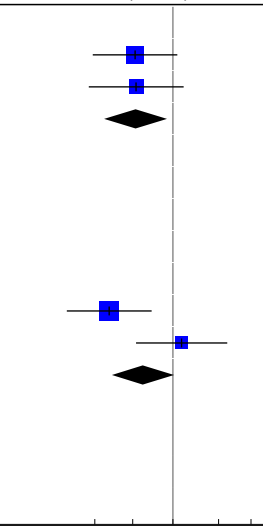
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Number of participants with at least one exacerbation | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 1.1 400/10 mcg | 2 | 882 | Odds Ratio (M-H, Fixed, 95% CI) | 0.72 [0.54, 0.95] |
| 1.2 200/10 mcg | 2 | 886 | Odds Ratio (M-H, Fixed, 95% CI) | 0.76 [0.58, 1.01] |
| 2 Number of participants having at least one moderate or severe exacerbation | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 2.1 400/10 mcg | 2 | 882 | Odds Ratio (M-H, Fixed, 95% CI) | 0.57 [0.38, 0.86] |
| 2.2 200/10 mcg | 2 | 886 | Odds Ratio (M-H, Fixed, 95% CI) | 0.62 [0.42, 0.92] |
| 3 Mortality | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 3.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 1.72 [0.41, 7.25] |
| 3.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 1.00 [0.20, 4.98] |
| 4 Change from baseline in St George's Respiratory Questionnaire (total score) | 2 | | Mean Difference (Fixed, 95% CI) | Subtotals only |
| 4.1 400/10 mcg | 2 | 866 | Mean Difference (Fixed, 95% CI) | -3.80 [-5.75, -1.86] |
| 4.2 200/10 mcg | 2 | 869 | Mean Difference (Fixed, 95% CI) | -3.91 [-6.01, -1.81] |
| 5 Change from baseline in $FEV_1$ AUC0–12 hours (mL)—week 13 | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 5.1 400/10 mcg | 2 | 862 | Mean Difference (IV, Fixed, 95% CI) | 162.04 [126.54, 197.53] |
| 5.2 200/10 mcg | 2 | 869 | Mean Difference (IV, Fixed, 95% CI) | 122.01 [86.64, 157.39] |
| 6 Mean change from baseline AM predose $FEV_1$ at 13 weeks (mL) | 2 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 6.1 400/10 mcg | 2 | 856 | Mean Difference (IV, Fixed, 95% CI) | 114.64 [77.79, 151.50] |
| 6.2 200/10 mcg | 2 | 859 | Mean Difference (IV, Fixed, 95% CI) | 70.43 [33.63, 107.23] |
| 7 Withdrawals—total | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 7.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 0.56 [0.40, 0.77] |
| 7.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 0.55 [0.40, 0.76] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 8 Withdrawals due to lack of efficacy | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 8.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 0.24 [0.08, 0.74] |
| 8.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 0.31 [0.11, 0.84] |
| 9 Withdrawals due to adverse events | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 9.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 1.07 [0.58, 1.98] |
| 9.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 0.37 [0.16, 0.84] |
| 10 Adverse events—any | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 10.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 0.98 [0.75, 1.30] |
| 10.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 0.82 [0.62, 1.09] |
| 11 Adverse events—serious | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 11.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 1.09 [0.66, 1.79] |
| 11.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 0.71 [0.41, 1.23] |
| 12 Adverse events—pneumonia | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 12.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 3.14 [0.84, 11.65] |
| 12.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 1.67 [0.40, 7.04] |
| 13 Adverse events—candidiasis | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 13.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 2.22 [0.50, 9.91] |
| 13.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 1.01 [0.17, 5.87] |
| 14 Adverse events—dysphonia | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 14.1 400/10 mcg | 1 | 461 | Odds Ratio (M-H, Fixed, 95% CI) | 2.11 [0.19, 23.41] |
| 14.2 200/10 mcg | 1 | 475 | Odds Ratio (M-H, Fixed, 95% CI) | 1.98 [0.18, 22.02] |
| 15 Adverse events—cataract | 1 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 15.1 400/10 mcg | 1 | 429 | Odds Ratio (M-H, Fixed, 95% CI) | 0.98 [0.06, 15.72] |
| 15.2 200/10 mcg | 1 | 419 | Odds Ratio (M-H, Fixed, 95% CI) | 1.02 [0.06, 16.48] |
| 16 Adverse events—COPD requiring hospitalisation | 2 | | Odds Ratio (M-H, Fixed, 95% CI) | Subtotals only |
| 16.1 400/10 mcg | 2 | 890 | Odds Ratio (M-H, Fixed, 95% CI) | 0.80 [0.40, 1.60] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 16.2 200/10 mcg | 2 | 894 | Odds Ratio (M-H, Fixed, 95% CI) | 0.36 [0.15, 0.86] |

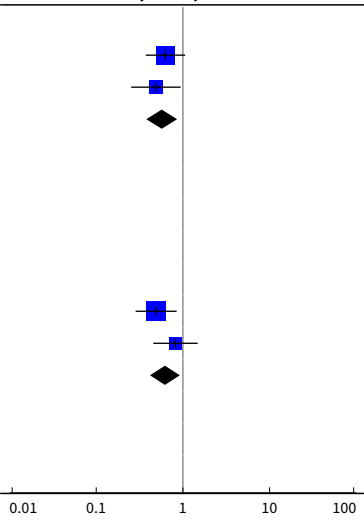
### Analysis 4.1. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 1 Number of participants with at least one exacerbation.

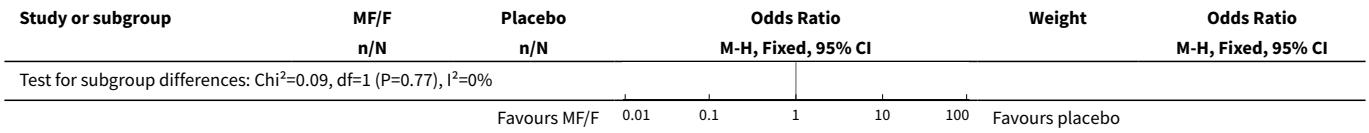
| Study or subgroup | MF/F n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **4.1.1 400/10 mcg** | | | | | |
| Doherty 2012 | 83/221 | 106/232 | | 55.5% | 0.71[0.49,1.04] |
| Tashkin 2012 | 56/217 | 69/212 | | 44.5% | 0.72[0.47,1.1] |
| **Subtotal (95% CI)** | **438** | **444** | | **100%** | **0.72[0.54,0.95]** |
| Total events: 139 (MF/F), 175 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=1(P=0.98); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.33(P=0.02) | | | | | |
| **4.1.2 200/10 mcg** | | | | | |
| Doherty 2012 | 76/235 | 106/232 | | 61.71% | 0.57[0.39,0.83] |
| Tashkin 2012 | 71/207 | 69/212 | | 38.29% | 1.08[0.72,1.62] |
| **Subtotal (95% CI)** | **442** | **444** | | **100%** | **0.76[0.58,1.01]** |
| Total events: 147 (MF/F), 175 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=5.2, df=1(P=0.02); $I^2$=80.78% | | | | | |
| Test for overall effect: Z=1.92(P=0.06) | | | | | |
| Test for subgroup differences: $Chi^2$=0.1, df=1 (P=0.75), $I^2$=0% | | | | | |



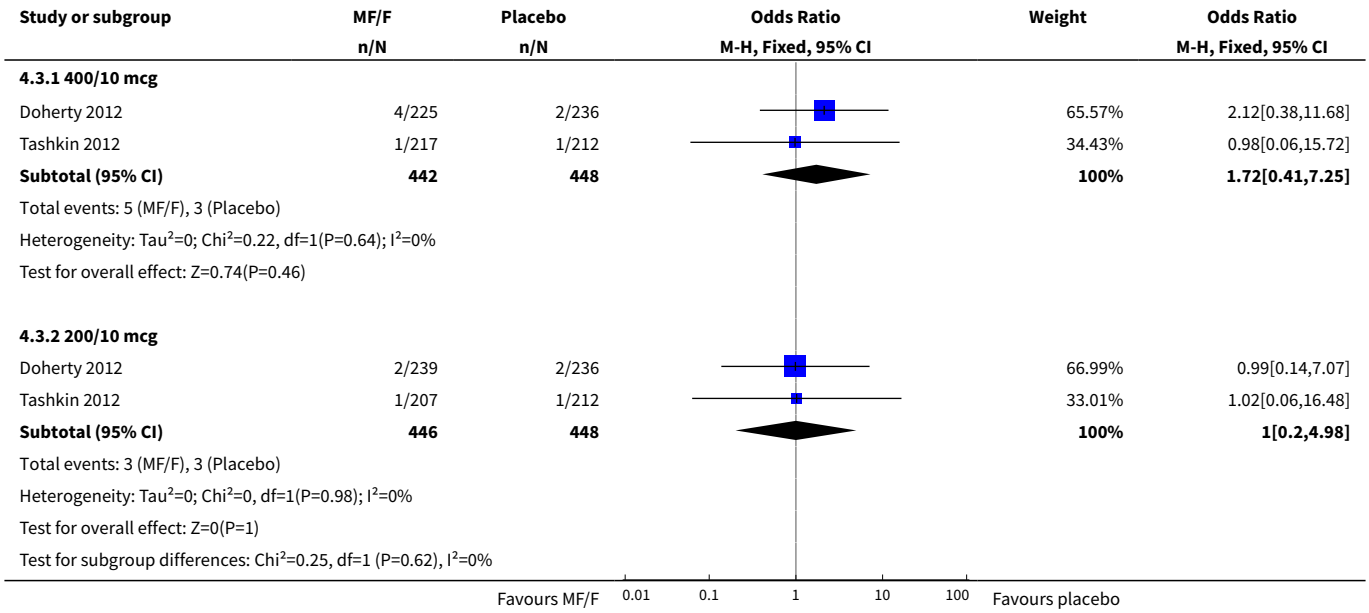

### Analysis 4.2. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 2 Number of participants having at least one moderate or severe exacerbation.

| Study or subgroup | MF/F n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **4.2.1 400/10 mcg** | | | | | |
| Doherty 2012 | 27/221 | 42/232 | | 57.7% | 0.63[0.37,1.06] |
| Tashkin 2012 | 15/217 | 28/212 | | 42.3% | 0.49[0.25,0.94] |
| **Subtotal (95% CI)** | **438** | **444** | | **100%** | **0.57[0.38,0.86]** |
| Total events: 42 (MF/F), 70 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.35, df=1(P=0.55); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.7(P=0.01) | | | | | |
| **4.2.2 200/10 mcg** | | | | | |
| Doherty 2012 | 23/235 | 42/232 | | 60.79% | 0.49[0.28,0.85] |
| Tashkin 2012 | 23/207 | 28/212 | | 39.21% | 0.82[0.46,1.48] |
| **Subtotal (95% CI)** | **442** | **444** | | **100%** | **0.62[0.42,0.92]** |
| Total events: 46 (MF/F), 70 (Placebo) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.59, df=1(P=0.21); $I^2$=36.93% | | | | | |
| Test for overall effect: Z=2.35(P=0.02) | | | | | |

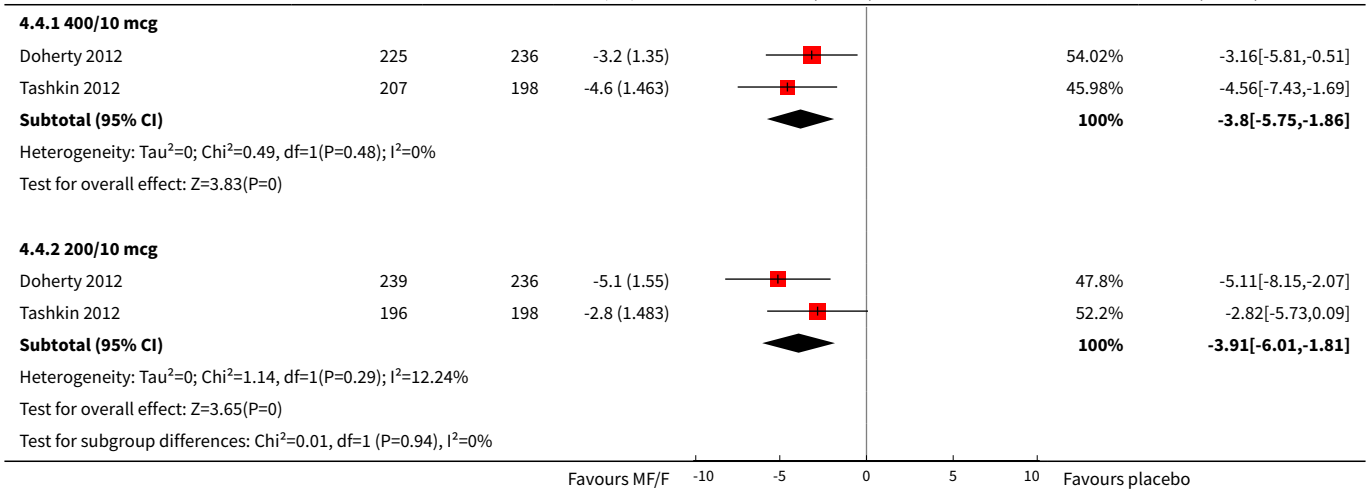





## Analysis 4.3. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 3 Mortality.

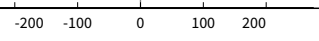



## Analysis 4.4. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 4 Change from baseline in St George's Respiratory Questionnaire (total score).



## Analysis 4.5. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 5 Change from baseline in $FEV_1$ AUC0–12 hours (mL)—week 13.

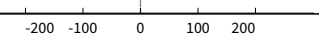
| Study or subgroup | MF/F N | MF/F Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **4.5.1 400/10 mcg** | | | | | | | |
| Doherty 2012 | 216 | 179 (274) | 225 | 18 (274) | | 48.15% | 161[109.84,212.16] |
| Tashkin 2012 | 214 | 166 (258) | 207 | 3 (258) | | 51.85% | 163[113.7,212.3] |
| **Subtotal ***** | **430** | | **432** | | | **100%** | **162.04[126.54,197.53]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=1(P=0.96); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=8.95(P<0.0001) | | | | | | | |
| **4.5.2 200/10 mcg** | | | | | | | |
| Doherty 2012 | 230 | 139 (274) | 225 | 18 (274) | | 49.35% | 121[70.64,171.36] |
| Tashkin 2012 | 207 | 126 (258) | 207 | 3 (258) | | 50.65% | 123[73.3,172.7] |
| **Subtotal ***** | **437** | | **432** | | | **100%** | **122.01[86.64,157.39]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0, df=1(P=0.96); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=6.76(P<0.0001) | | | | | | | |
| Test for subgroup differences: $Chi^2$=2.45, df=1 (P=0.12), $I^2$=59.19% | | | | | | | |




Favours placebo — Favours MF/F

## Analysis 4.6. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 6 Mean change from baseline AM predose $FEV_1$ at 13 weeks (mL).

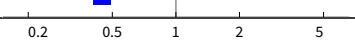
| Study or subgroup | MF/F N | MF/F Mean(SD) | Placebo N | Placebo Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **4.6.1 400/10 mcg** | | | | | | | |
| Doherty 2012 | 215 | 98 (280) | 224 | -3 (280) | | 49.47% | 101[48.6,153.4] |
| Tashkin 2012 | 213 | 111 (270) | 204 | -17 (270) | | 50.53% | 128[76.16,179.84] |
| **Subtotal ***** | **428** | | **428** | | | **100%** | **114.64[77.79,151.5]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.52, df=1(P=0.47); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=6.1(P<0.0001) | | | | | | | |
| **4.6.2 200/10 mcg** | | | | | | | |
| Doherty 2012 | 228 | 63 (280) | 224 | -3 (280) | | 50.8% | 66[14.37,117.63] |
| Tashkin 2012 | 203 | 58 (270) | 204 | -17 (270) | | 49.2% | 75[22.54,127.46] |
| **Subtotal ***** | **431** | | **428** | | | **100%** | **70.43[33.63,107.23]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.06, df=1(P=0.81); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=3.75(P=0) | | | | | | | |
| Test for subgroup differences: $Chi^2$=2.77, df=1 (P=0.1), $I^2$=63.89% | | | | | | | |



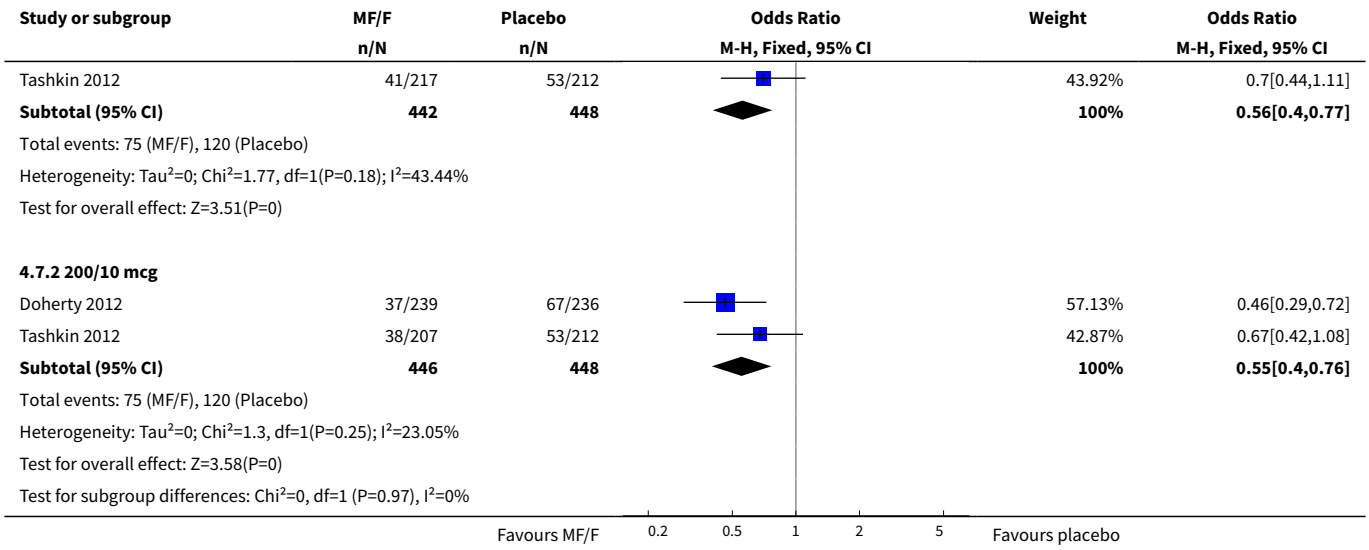

Favours placebo — Favours MF/F

## Analysis 4.7. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 7 Withdrawals—total.

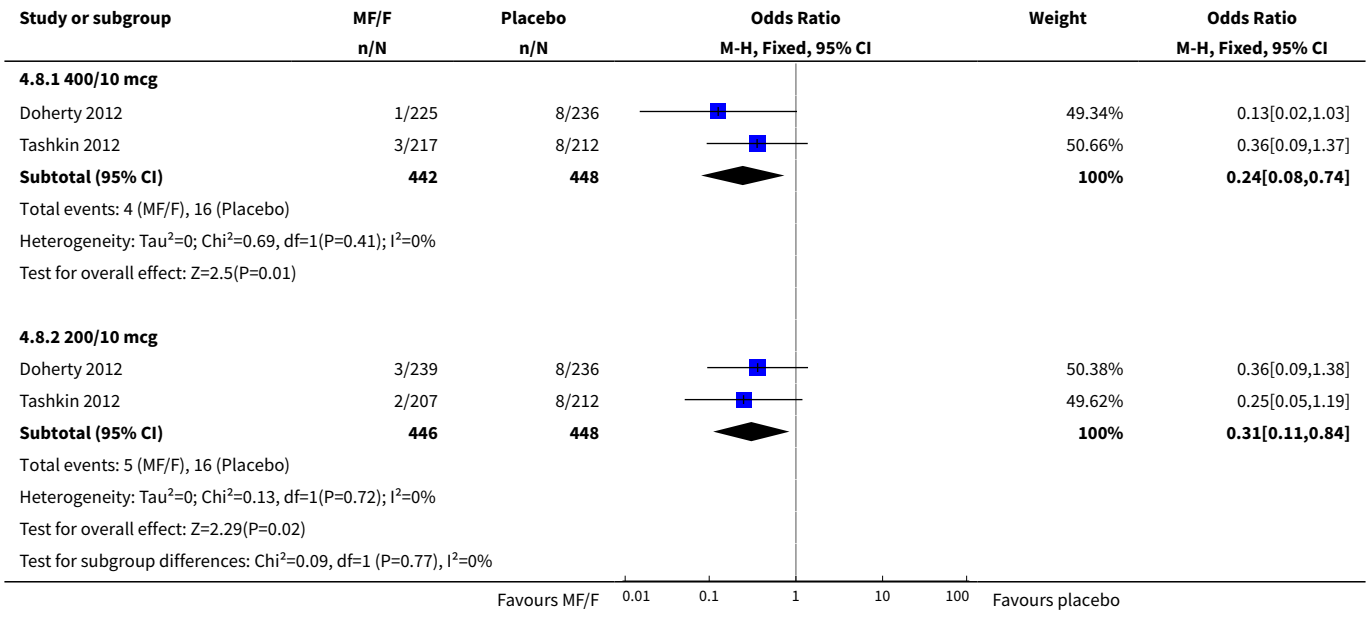
| Study or subgroup | MF/F n/N | Placebo n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| **4.7.1 400/10 mcg** | | | | | |
| Doherty 2012 | 34/225 | 67/236 | | 56.08% | 0.45[0.28,0.71] |



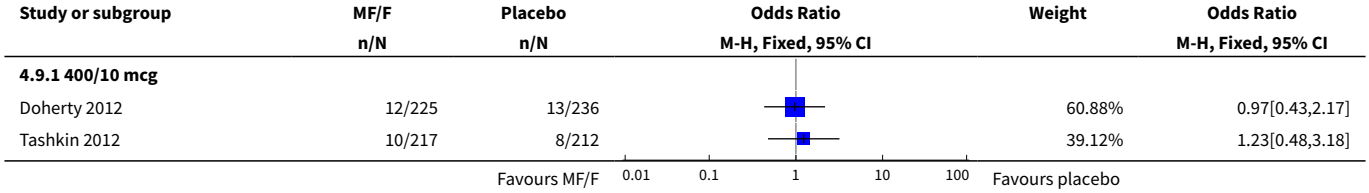

Favours MF/F — Favours placebo

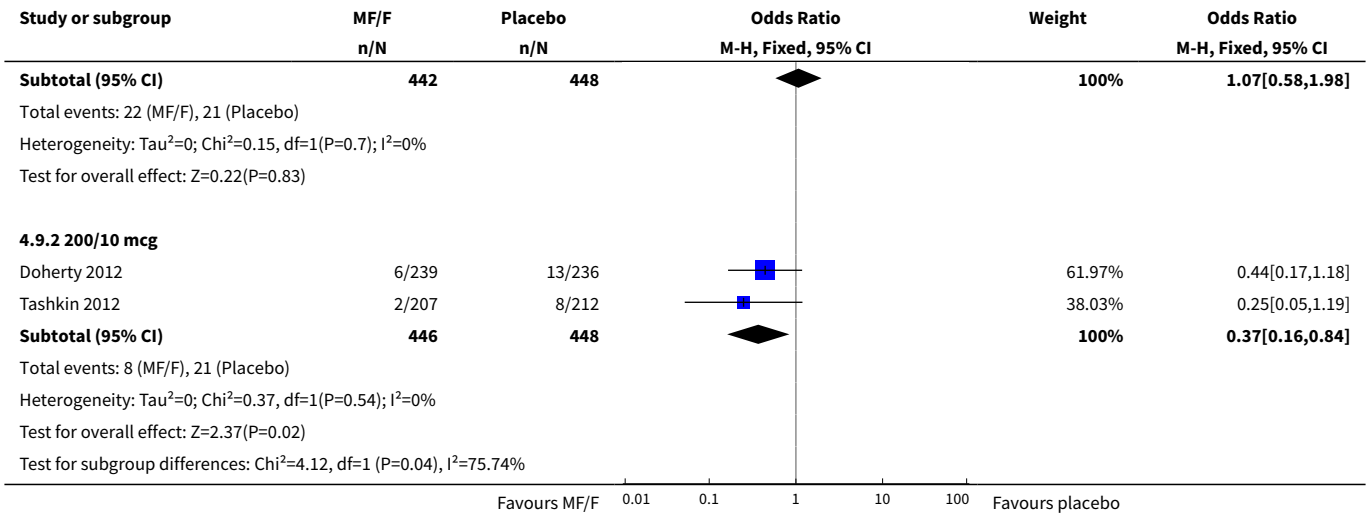



## Analysis 4.8. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 8 Withdrawals due to lack of efficacy.

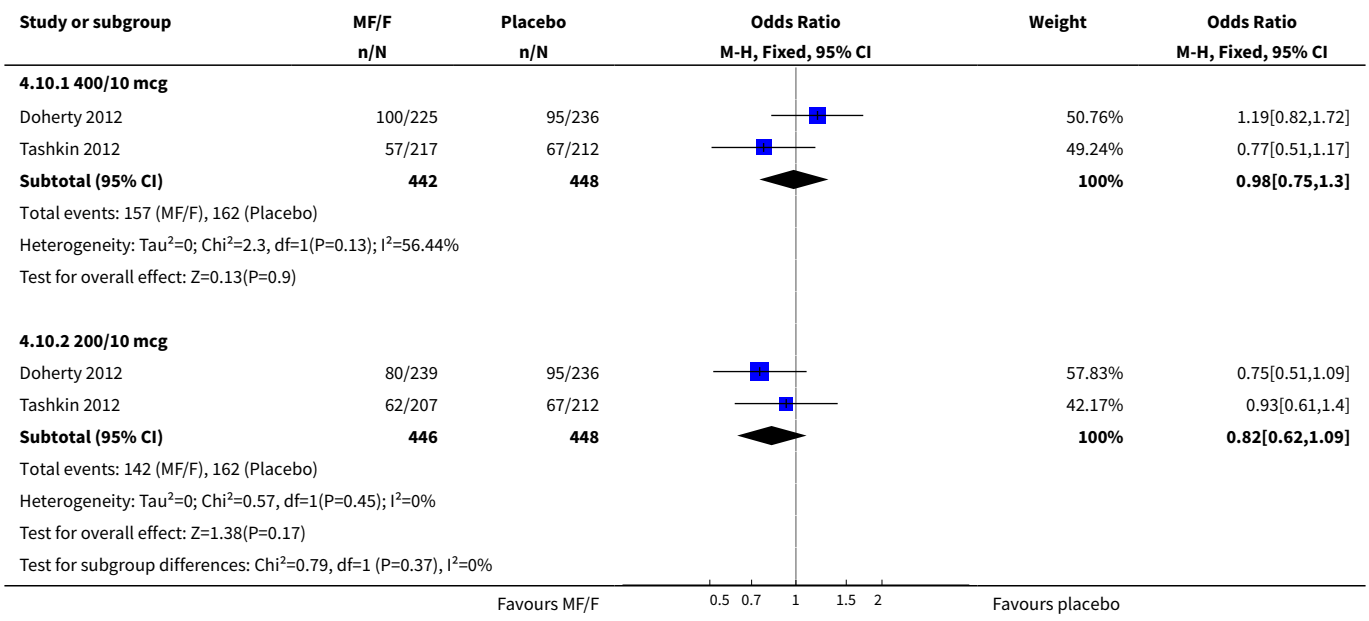



## Analysis 4.9. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 9 Withdrawals due to adverse events.

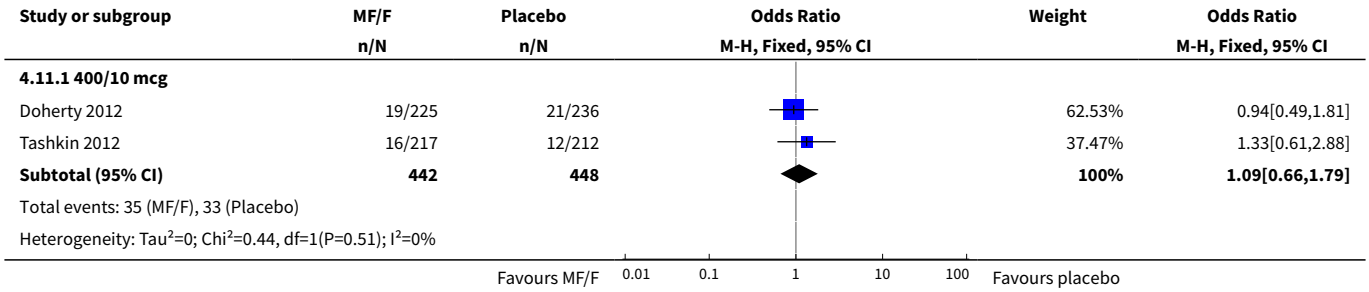


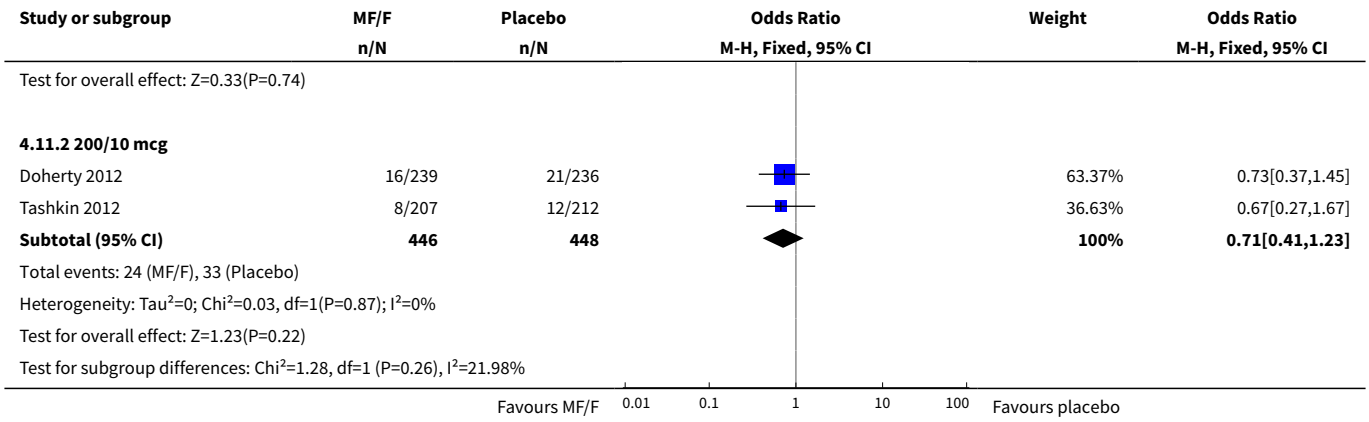



## Analysis 4.10. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 10 Adverse events—any.

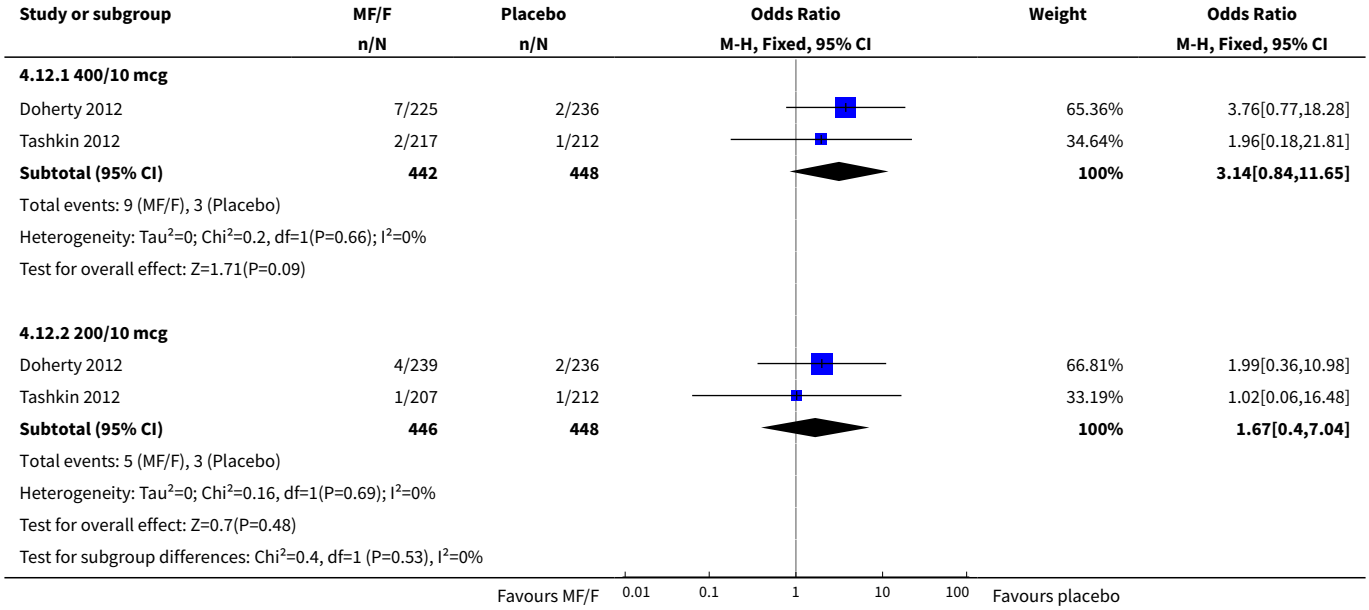



## Analysis 4.11. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 11 Adverse events—serious.

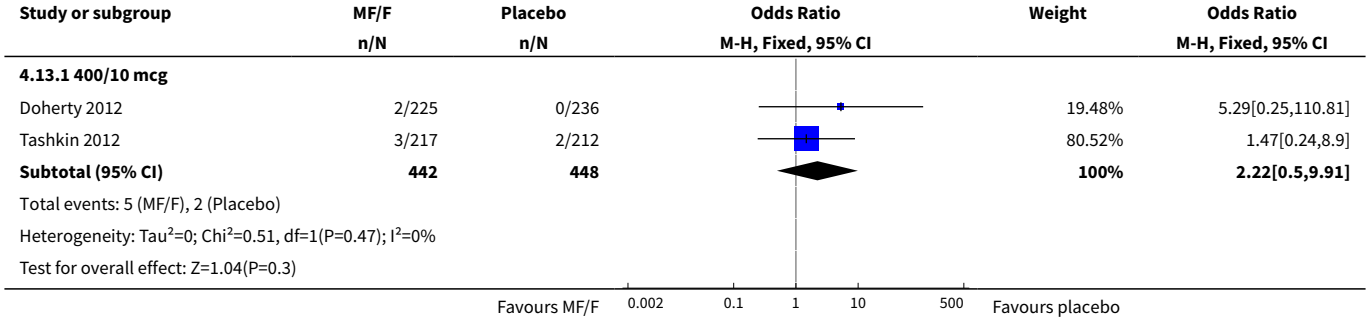


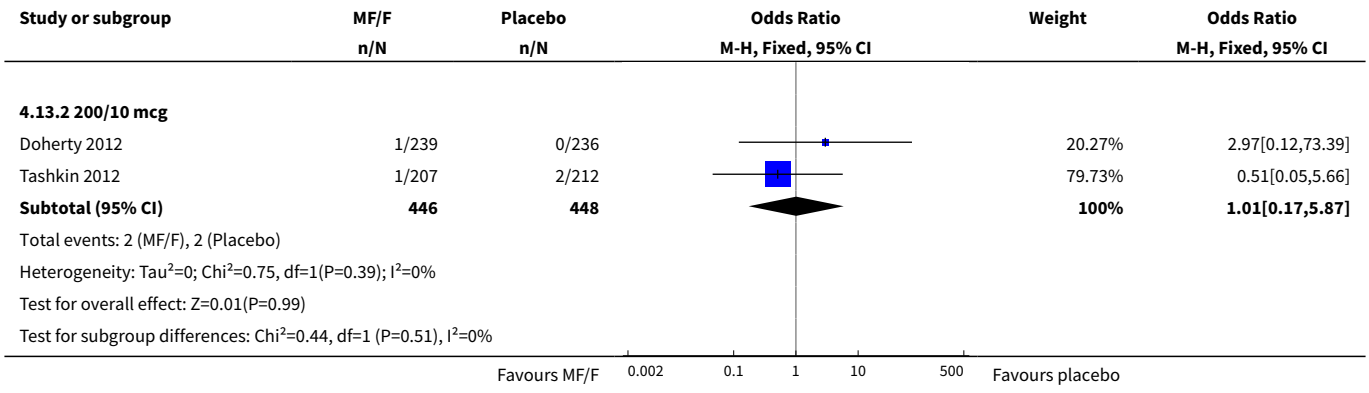



## Analysis 4.12. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 12 Adverse events—pneumonia.

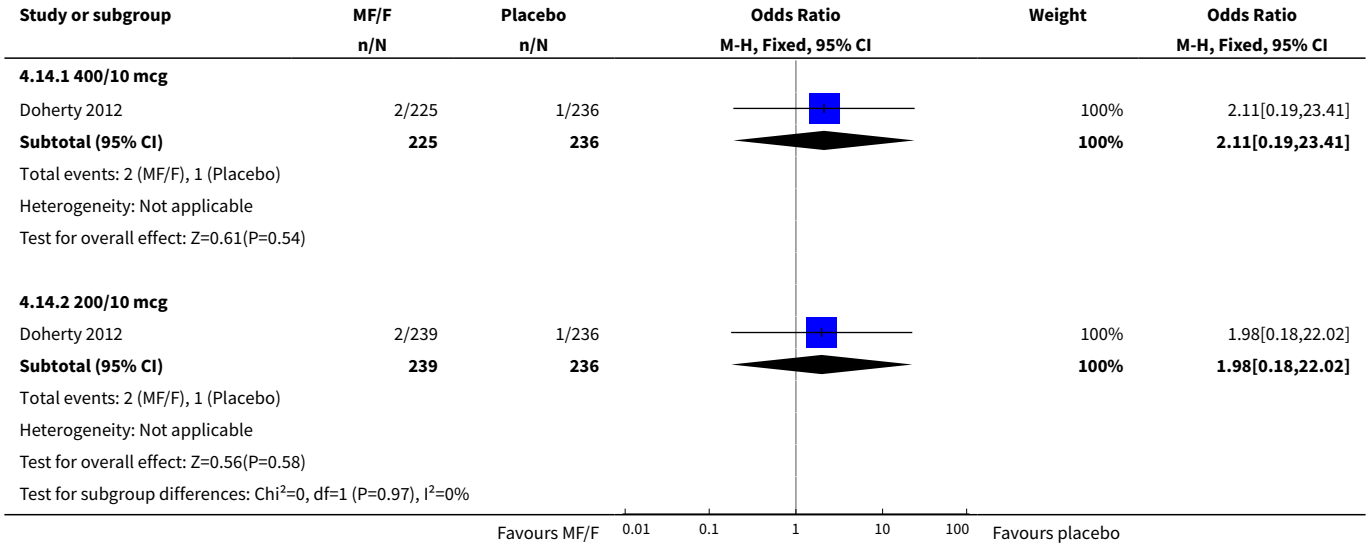



## Analysis 4.13. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 13 Adverse events—candidiasis.

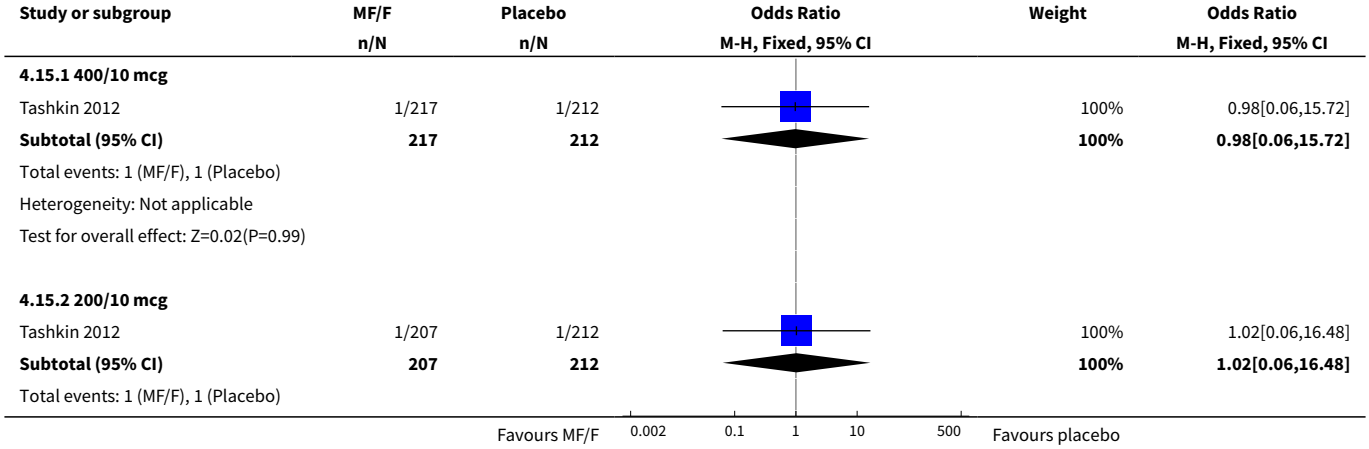


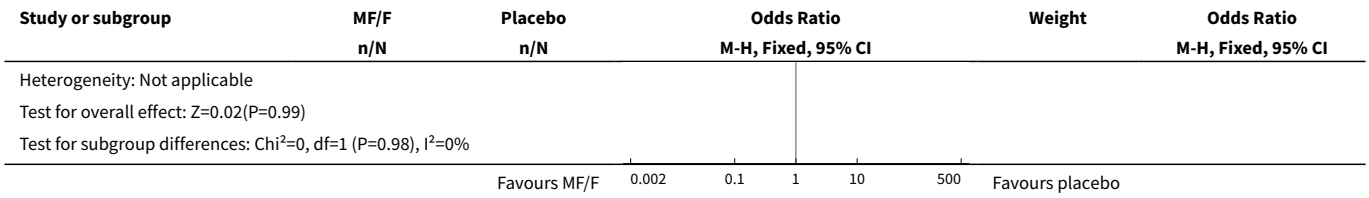



## Analysis 4.14. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 14 Adverse events—dysphonia.

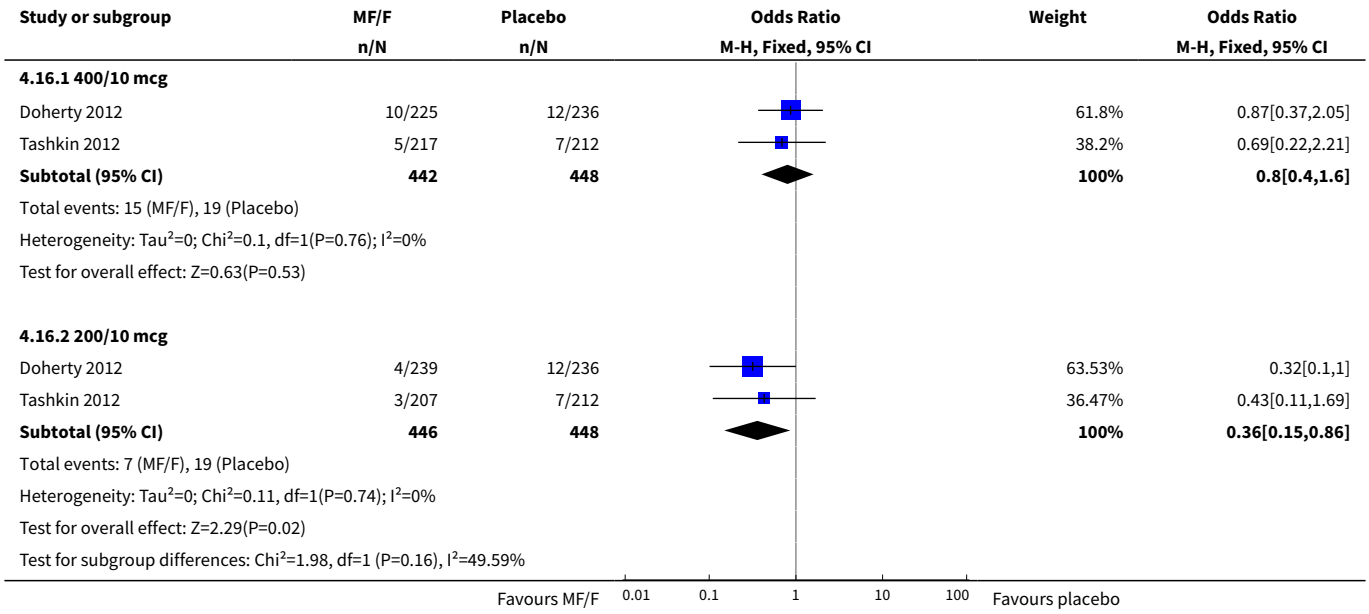



## Analysis 4.15. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 15 Adverse events—cataract.






**Analysis 4.16. Comparison 4 Mometasone/formoterol (MF/F) versus placebo, Outcome 16 Adverse events—COPD requiring hospitalisation.**




## ADDITIONAL TABLES

### Table 1. Search history

| Version | Detail |
|---|---|
| First published version—Issue 4, 2003 (all years to April 2002) | References identified: 34<br>References retrieved: seven<br>Studies excluded: three (Cazzola 2000; Chapman 2002; Soriano 2002)<br>Studies identified from supplementary searching: four (Dal Negro 2003; Hanania 2003—both included; Cazzola 2002a; Cazzola 2004—both excluded).<br>Studies included: four |
| Second published version—Issue 3, 2004 (April 2003 to April 2004) | References identified: 12<br>References retrieved: three (two papers full publications of previously included or cited studies (Dal Negro 2003; Hanania 2003). Handsearching identified two further references to the COSMIC 2003 study<br>Studies identified from supplementary searching: one (TRISTAN 2003)<br>New studies included: two<br>Total studies included: six |

**Table 1. Search history** *(Continued)*

| | |
|---|---|
| Third published version—Issue 3, 2005 (April 2004 to April 2005) | References identified: 52<br>References retrieved: 46 (references to studies already included/excluded/ongoing: 24)<br>New unique studies identified: 10 (ongoing studies: two)<br>New studies included: zero<br>Total studies included: six |
| Fourth published version (April 2005 to April 2007) | References identified: 66<br>References retrieved: 27 (references to studies already included/excluded/ongoing)<br>New unique studies identified: five (ongoing studies: zero)<br>New studies included: five<br>Total studies included: 11 |
| Fifth published version (April 2007 to June 2013) | References identified: 129<br>New unique studies identified: eight (ongoing studies: zero)<br>New studies included: eight<br>Total studies included: 19 |

**Table 2. Rates and NNTB of mortality and NNTH of pneumonia**

| Study ID | Study duration | Placebo rate (%) mortality | NNTB for mortality | Placebo rate (%) pneumonia | NNTH for pneumonia |
|---|---|---|---|---|---|
| TORCH | 156 weeks | 15.2 | 42 (24 to 775) | 12.3 | 17 (27 to 12) |
| TRISTAN | 52 weeks | 1.94 | 292 (164 to 5256) | 0.83 | 197 (339 to 131) |
| Calverley 2003 | 52 weeks | 1.95 | 249 (149 to 1307) | 3.6 | 48 (82 to 32) |
| Szafranski 2003 | 52 weeks | 4.5 | 110 (66 to 581) | 0 | N/A |
| Rennard 2009 | 52 weeks | 0.83 | 674 (379 to 12,149) | 4.78 | 37 (63 to 25) |
| Tashkin 2008 | 26 weeks | 0.33 | 1689 (950 to 30,403) | 1 | 164 (282 to 109) |
| Doherty 2012 | 26 weeks | 0.85 | 659 (370 to 11,865) | 0.85 | 193 (331 to 128) |
| Tashkin 2012 | 26 weeks | 0.47 | 1187 (668 to 21,377) | 0.47 | 346 (595 to 229) |
| Mahler 2002 | 24 weeks | 1.66 | 340 (191 to 6125) | 0 | N/A |
| O'Donnell 2006 | 8 weeks | 0 | N/A | 1.56 | 107 (182 to 71) |

# APPENDICES

## Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

**Electronic searches: core databases**

| Database | Frequency of search |
|---|---|
| CENTRAL (*The Cochrane Library*) | Monthly |
| MEDLINE (Ovid) | Weekly |
| EMBASE (Ovid) | Weekly |
| PsycINFO (Ovid) | Monthly |
| CINAHL (EBSCO) | Monthly |
| AMED (EBSCO) | Monthly |

**Handsearches: core respiratory conference abstracts**

| Conference | Years searched |
|---|---|
| American Academy of Allergy, Asthma and Immunology (AAAAI) | 2001 onwards |
| American Thoracic Society (ATS) | 2001 onwards |
| Asia Pacific Society of Respirology (APSR) | 2004 onwards |
| British Thoracic Society Winter Meeting (BTS) | 2000 onwards |
| Chest Meeting | 2003 onwards |
| European Respiratory Society (ERS) | 1992, 1994, 2000 onwards |
| International Primary Care Respiratory Group Congress (IPCRG) | 2002 onwards |
| Thoracic Society of Australia and New Zealand (TSANZ) | 1999 onwards |

**MEDLINE search strategy used to identify trials for the CAGR**

**COPD search**

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

**Filter to identify RCTs**

1. exp "clinical trial (publication type)"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and the RCT filter are adapted to identify trials in other electronic databases.

## Appendix 2. Definitions of exacerbations

| Study ID | Definition of exacerbation |
|---|---|
| Barnes 2006 | No definition found |
| Bourbeau 2007 | No definition found |
| Calverley 2003 | **Mild exacerbations** = number of days with intake of four or more puffs of rescue medication<br><br>**Severe exacerbation** = intake of a course of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms |
| Dal Negro 2003 | **Mild exacerbation** = requiring increased use of salbutamol prn by > 2 occasions/24 hour period on two or more consecutive days compared with the baseline mean of last seven days of run-in period<br><br>**Moderate exacerbation** = requiring treatment with antibiotics and/or oral corticosteroids<br><br>**Severe exacerbation** = requiring emergency hospital treatment and/or hospitalisation |

(Continued)

| | |
|---|---|
| Doherty 2012 | **Mild exacerbation** = clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of SABA/short-acting anticholinergic, or ≥ 2 nebulized treatments/d of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days<br><br>**Moderate exacerbation** = clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease<br><br>**Severe exacerbation** = deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD |
| Hanania 2003 | **Moderate exacerbation** = requiring treatment with antibiotics and/or corticosteroids<br><br>**Severe exacerbation** = requiring hospitalisation |
| Lapperre 2009 | No definition found |
| Mahler 2002 | "exacerbations defined by treatment"—no further details |
| O'Donnell 2006 | No definition found |
| Rennard 2009 | "a course of oral steroids and/or hospitalisation due to a worsening of COPD" |
| SCO104925 | No definition found |
| SFCT01 | No definition found |
| Sin 2008 | "Exacerbations were defined as worsening of COPD symptoms leading to hospitalisation, a visit to the emergency room, or use of an antimicrobial agent and/or systemic corticosteroids as an outpatient" |
| Szafranski 2003 | **Mild exacerbations** = a day with ≥ 4 inhalations of reliever medication above the mean run-in use<br><br>**Severe exacerbation** = use of oral steroids and/or antibiotics and/or hospitalisation due to respiratory symptoms |
| Tashkin 2008 | "Worsening of COPD symptoms that required treatment with oral corticosteroids and/or hospitalisation" |
| Tashkin 2012 | **Mild exacerbation** = clinically judged deterioration of COPD symptoms (managed with increased short-acting bronchodilator use: ≥ 12 inhalations/d of SABA/short-acting anticholinergic, or ≥ 2 nebulized treatments/d of 2.5 mg SABA/short-acting anticholinergic) on any two consecutive days<br><br>**Moderate exacerbation** = clinically judged deterioration of COPD with an acute change in symptoms that required antibiotic and/or oral steroid treatment for lower airway disease<br><br>**Severe exacerbation** = deterioration of COPD that resulted in emergency treatment or hospitalisation due to COPD |
| TORCH | "A symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalisation, or a combination of these" |
| TRISTAN | "Exacerbations were defined a priori as a worsening of COPD symptoms that required treatment with antibiotics, oral corticosteroids, or both. Episodes that required corticosteroid treatment or hospital admission were noted separately" |
| Zheng 2006 | "A worsening of symptoms that required treatment with antibiotics or oral corticosteroids and/or hospitalisation" (analysed separately as those requiring antibiotics, those requiring corticosteroids, those requiring hospitalisation) |

## Appendix 3. Definitions of pneumonia

| Study ID | Definition of pneumonia |
|---|---|
| Barnes 2006 | No definition found |
| Bourbeau 2007 | No definition found |
| Calverley 2003 | No definition found |
| Dal Negro 2003 | No definition found |
| Doherty 2012 | "Including the AE terms of pneumonia, pneumonia viral, pneumonia aspiration, and lobar pneumonia" |
| Hanania 2003 | No definition found |
| Lapperre 2009 | No definition found |
| Mahler 2002 | No definition found |
| O'Donnell 2006 | No definition found |
| Rennard 2009 | "Pneumonia events were reported by physicians based on the Medical Dictionary for Regulatory Activities (version 10.0) pneumonia-related preferred terms (pneumonia, bronchopneumonia, lobar pneumonia or pneumonia staphylococcal)" |
| SCO104925 | No definition found |
| SFCT01 | No definition found |
| Sin 2008 | No definition found |
| Szafranski 2003 | No definition found |
| Tashkin 2008 | "Diagnosis of pneumonia was generally based on clinical judgment, without radiological confirmation in all cases" |
| Tashkin 2012 | "Including the AE terms of pneumonia, pneumonia viral, pneumonia aspiration, and lobar pneumonia" |
| TORCH | "Since the finding was unexpected, there was no prospective definition of pneumonia in the study protocol (e.g. confirmation on chest radiography)" |
| TRISTAN | No definition found |
| Zheng 2006 | No definition found |

## FEEDBACK

### Comment on analysis choice in TORCH trial and presentation in Cochrane review, 24 August 2017

#### Summary

The authors compared inhalers with combination drugs (a steroid plus a long-acting beta-2 agonist), with placebo and write in their abstract that the number needed to treat to prevent one death with fluticasone/salmeterol was 42 (1). They explain, just before Objectives, that the largest randomised trial of combination therapy (TORCH) demonstrated a significant reduction in mortality versus placebo (P = 0.052) and that they wished to see whether other combined inhalers had a similar effect. Just above "Implications for research," we are told that "whether a combination is better than the two components taken separately was not addressed in this review," and under "Authors' Conclusions" the authors advocate that the combination should be compared with its two components.

I find this information misleading. Firstly, the review authors overlook that the TORCH trial (and several other trials) was designed to answer what they call for in future research, namely whether the combination was better than any of its components.

Secondly, the authors give readers the impression that the combination reduces mortality. However, the fact is that the steroid contributes absolutely nothing to the mortality benefit. The primary outcome in the TORCH trial was total mortality (2). GlaxoSmithKline randomised 6184 patients to four groups: placebo; salmeterol; fluticasone; and both drugs together. By definition, this design is factorial. It is powerful, as it allows the investigators to study three research questions with a sample size that would usually only allow one question to be answered. Such a trial can tell us whether the two drugs are effective, and whether the combination is better than any of its components. However, the analysis in the TORCH trial included only half of the patients, thereby spoiling the advantage of the factorial design, although the published trial protocol stated that a factorial analysis was to be performed (3).

Nowhere in the 15-page trial report is the factorial analysis to be found, and the abstract of the TORCH trial gives readers the impression that the combination was better than any of its components, which is the result the authors of the Cochrane review quote.

The authors of a letter to the editor used a factorial analysis and showed that the effect of the combination was entirely due to salmeterol (4); the hazard ratio for fluticasone was 1.00 (0.87 to 1.15), p = 0.99. In other similar trials, both GlaxoSmithKline and AstraZeneca did not perform a factorial analysis (5).

Peter C Gøtzsche, pcg@cochrane.dk, Director of the Nordic Cochrane Centre

#### References

1. Nannini LJ, Poole P, Milan SJ, et al. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2013;11:CD003794.

2. Calverley PM, Anderson JA, Celli B, et al. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775–89.

3. Gøtzsche PC. Questionable research and marketing of a combination drug for smoker's lungs. J R Soc Med 2014;107:256-7.

4. La Vecchia C and Fabbri LM. Prevention of death in COPD. N Engl J Med 2007;356:2211–2.

5. Suissa S, Ernst P, Vandemheen KL, et al. Methodological issues in therapeutic trials of COPD. Eur Respir J 2008;31:927–33.

#### Reply

We thank Professor Gøtzsche for his interest in our Cochrane Review and thought-provoking feedback.

This review addressed the efficacy and safety of combined inhaled corticosteroid (ICS) and long acting beta-agonist (LABA) in one inhaler versus placebo as a pair-wise comparison. We did not seek to address the efficacy of the individual components (LABA and ICS) versus combined treatment; this was addressed in other Cochrane reviews (1, 2) and will be included in a forthcoming network meta-analysis (3).

We note from the correspondence cited that the appropriateness of factorial analysis of the TORCH trial is the subject of debate (4). We have now highlighted this debate in the discussion and referenced this feedback in the review.

Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. RN prepared the response and all authors agreed to its publication.

1. Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD006826. DOI: 10.1002/14651858.CD006826.pub2.

2. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD006829. DOI: 10.1002/14651858.CD006829.pub2.

3. Oba Y, Fadila M, Keeney E, Dias S. Fixed-dose combination inhalers compared to long-acting bronchodilators for COPD: a network meta-analysis (Protocol). Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD012620. DOI: 10.1002/14651858.CD012620.

4. Calverley PM, Anderson JA and Celli B. Prevention of Death in COPD. N Engl J Med 2007; 356:2213-2214. DOI: 10.1056/NEJMc070783

**Contributors**

Peter C Gøtzsche, pcg@cochrane.dk, Director of the Nordic Cochrane Centre

## My concerns about the analysis of TORCH remain, 27 October 2017

**Summary**

The authors of the Cochrane review have changed their review because of my comment. However, the only thing they changed was that they added this sentence about the TORCH trial in the discussion section: "This analysis has been the subject of some debate as the study adopted a factorial design but reported [sic] did not use factorial analysis (see Feedback 1)."

It is misleading to say that the analysis of the TORCH trial "has been the subject of some debate." As I explained in my comment, the analysis of the TORCH trial is wrong and in violation of the published trial protocol, which stated that a factorial analysis was to be performed. The correct factorial analysis showed that the effect of the combination on mortality was entirely due to salmeterol; the hazard ratio for fluticasone was 1.00 (0.87 to 1.15), p = 0.99.

Since the steroid contributed absolutely nothing to the mortality reduction, the Cochrane review is misleading because it gives readers the impression that the reduction in mortality was due to the combination. Nowhere in the Cochrane review is it mentioned that the analysis of the TORCH trial was seriously misleading; in fact, its reported result is believed.

In the abstract and in the plain language summary, the Cochrane authors still mention that a reduction in mortality was seen without explaining that the steroid did not contribute to this. In their background section, they mention that combined therapy in the TORCH trial reduced mortality versus placebo, and under results (FPS versus placebo) they mention again this mortality benefit without any reservations that it was only one of the drugs in the combination that caused this.

The Cochrane review needs to be amended to reflect the above.

Peter C Gøtzsche, pcg@cochrane.dk, Director of the Nordic Cochrane Centre

**Reply**

***Reply from the authors 22 November 2017***

We thank Professor Gøtzsche for his continued interest in our review. We would like to re-emphasise this review did not set out to elucidate the relative contribution of long-acting beta –agonist (LABA) and inhaled corticosteroids (ICS) to the benefits or harms associated with combination therapy. A separate Cochrane Review, comparing combined therapy with LABA alone, goes some way to addressing this issue; it shows no significant difference between treatments for mortality, but the confidence interval is too wide to support an assertion of no difference. ("There was no significant difference in mortality between people on combined inhalers and those on LABA, from 10 studies on 10,680 participants (OR 0.92; 95% CI 0.76 to 1.11, downgraded to moderate quality evidence due to statistical imprecision"[1])

Furthermore, we disagree that the post-hoc factorial analysis of TORCH proves that fluticasone contributes "absolutely nothing" to the mortality benefit as the confidence interval (0.87 to 1.15) is again not sufficiently narrow to rule out possible benefit or harm.

Indeed, the authors of the article cited by Professor Gøtzsche acknowledge there is uncertainty about the impact of ICS, rather than completely ruling out a benefit: "in conclusion, after proper consideration of the various methodological shortcomings in the design and analysis of randomised trials, the effectiveness of inhaled corticosteroids in treating chronic obstructive pulmonary disease remains doubtful, while the benefit observed with combination therapy may be due exclusively to the beneficial effects of the long-acting bronchodilator alone."[2]

We note from previous correspondence published in the New England Journal Medicine that there is some uncertainty about whether ICS and LABA may have some synergistic effect, and therefore factorial analysis would be less appropriate. In a response in 2007 the authors of the TORCH trial state: "factorial analysis assumes that each treatment has the same additive effect in the absence and presence of the other treatment. This was not the case for the TORCH trial. Our data show the clear clinical superiority of combination treatment with salmeterol and fluticasone, including fewer exacerbations and better health status."[3]

It is a Cochrane standard that conclusions are based solely on the evidence presented in the review. However, we have made some minor adjustments to the abstract, plain language summary and conclusions to highlight that we cannot comment on the relative contribution of the different components of combined therapy and it may not be the combination, per se, which is beneficial.

Nannini LJ, Poole P, Milan SJ, Holmes R, Normansell R. RN prepared the response and all authors agreed to its publication.

1. Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta2-agonist in one inhaler versus long-acting beta2-agonists for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD006829. DOI: 10.1002/14651858.CD006829.pub2.

2. Suissa S, Ernst P, Vandemheen KL, et al. Methodological issues in therapeutic trials of COPD. Eur Respir J 2008;31:927–33

3. Calverley PM, Anderson JA and Celli B. Prevention of Death in COPD. N Engl J Med 2007; 356:2213-2214. DOI: 10.1056/NEJMc070783

***Indepent methodological assessment, 27/02/2018***

Following a further comment from Professor Gøtzsche over the authors response to his concerns, the Cochrane Editorial Unit arranged for an independent review of the Cochrane review and the evidence about the TORCH trial. Here is the review by Professor Julian Higgins:

The review addresses combination therapy versus placebo. The TORCH trial has a primary analysis that addresses this comparison, and all indications from the protocol documents are that this was planned as the primary analysis ("The primary objective of this study is to determine whether there is a significant reduction in all-cause mortality in COPD patients treated with SFC compared with placebo", from Vestbo et al, Eur Respir J 2004). Representation of the trial in the body of the review therefore looks entirely appropriate to me.

The question of whether the finding for combined therapy vs placebo is driven by one or other of the components does not seem relevant to the selection of the result or its inclusion in the Cochrane review, or indeed in conclusions drawn about the effect of combined therapy. I assume here that the objectives of the Cochrane review were not driven by observed findings of the TORCH trial, and in any case, I welcome the plans to perform a network meta-analysis to cover single and combined therapies.

I do not find any evidence in the 2004 protocol or the supplement to the 2007 paper (a more detailed protocol) that a factorial-style analysis was planned. I therefore do not concur with Peter Gøtzsche's apparent belief that the following text implies a factorial approach: "The other objectives of the study include comparisons of mortality in the SFC group with that seen in the salmeterol and FP groups, and in the salmeterol and FP groups compared with the placebo group." To me, these imply pair-wise comparisons of specific treatment groups, and not a plan to compare salmeterol vs no salmeterol and FP vs no FP, and similarly do not indicate a plan to investigate interaction between the two components (furthermore, the results of these particular analyses are clearly to be seen in Table 2 of the NEJM paper). Although I would consider the approach to analysing the trial to be surprising (NB not 'wrong'), given its factorial design, the analyses performed do seem to concur with the documents described as protocols. It is a concern, however, that the initial published protocol was submitted in October 2003, while within it, the protocol clearly indicates that it is retrospectively written: "The first patient was recruited in September 2000 and the last in November 2002."

I believe that remarks in the Authors' Conclusions sections of the Cochrane review would benefit from some clarifications. There is a claim that "Network meta-analysis may help elucidate the relative contribution of the individual components of combined therapy to the effects identified". Quite a lot of information about this is provided by the results of the TORCH trial for the particular components it evaluated, and it seems a little remiss to fail to comment on this. For issues around single vs combined therapy, the indication from the TORCH trial that salmeterol was driving the main result appears very relevant, and might be commented upon before calling for network meta-analyses to address the same question.

A subsequent comment is as follows: "Combined therapy should be compared with separate administration of long-acting $beta_2$-agonist and inhaled corticosteroid at different doses in large-scale multi-centre studies using a double dummy design". Again, it looks as if the TORCH trial does this to some extent, so the call for new trials without recognizing this might be misplaced.

**Contributors**

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## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 14 March 2018 | Amended | The Cochrane Editorial Unit (CEU) conducted an independent review following on from two pieces of feedback received about the analysis of the TORCH trial. The results of the independent review have been added to Feedback 2 and some changes have been made within the review to note to the possible issues in the TORCH trial. |

## HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 4, 2003

| Date | Event | Description |
|---|---|---|
| 20 November 2017 | Feedback has been incorporated | Feedback incorporated to review - see Feedback. |
| 23 October 2017 | Amended | Feedback and author response to feedback attributed to the respective author(s). |
| 9 October 2017 | Feedback has been incorporated | Feedback added to the review together with a response from the author team and an additional sentence to highlight this debate in the discussion section. |
| 26 June 2013 | New citation required and conclusions have changed | Inclusion of a new combination inhaler (Mometasone furoate/formoterol (MF/F)). Eight new studies included (Bourbeau 2007; Doherty 2012; Lapperre 2009; Rennard 2009; SCO104925; Sin 2008; Tashkin 2008; Tashkin 2012). Background was rewritten, outcomes were redefined, withdrawals were included as an outcome, and methods now reflect the latest version of the *Cochrane Handbook for Systematic Reviews of Interventions*. We presented data in subgroups according to different doses of the same drug for this update. Conclusions are strengthened by the addition of eight new studies. |
| 26 June 2013 | New search has been performed | New literature search run. |
| 11 November 2009 | Amended | Spelling corrections and minor reformatting |
| 8 April 2008 | Amended | Converted to new review format. |
| 26 February 2008 | Amended | Summary of findings table now added to review prepared centrally in GRADEpro by the Summary of Findings table working party (Nancy Santesso) |
| 2 August 2007 | New citation required and conclusions have changed | Seven new studies met the entry criteria of the review (Barnes 2006; Kardos 2007; TORCH; SCO100470; SCO40030; SFCT01; SCO10054). New unpublished data have been incorporated for three studies previously included (Hanania 2003; Mahler 2002; TRISTAN).<br><br>What was known before:<br>Statistically significant findings in favour of combination treatment over placebo. Conflicting findings when combination treatment compared with monocomponent therapies.<br><br>What new data contribute to the review:<br>Data on all primary and secondary endpoints. Combined estimates now indicate that combination fluticasone and salmeterol is significantly more effective than fluticasone alone in reducing the rate of exacerbations. |
| 30 April 2004 | New citation required and conclusions have changed | Two new studies are included in this update (Calverly 2003; Hanania 2003). One study previously reported in abstract form has now been published and baseline and outcome data incorporated in this version of the review (Dal Negro 2003). |

| Date | Event | Description |
|---|---|---|
| | | Data on lung function have been pooled on a WMD rather than a SMD. Pooled SEMs have been calculated from the published p values, and have been used to calculate some exacerbation outcomes, as well as symptoms, quality of life and lung function for some of the comparators.<br><br>The Discussion and Conclusion reflect the incorporation of the new data, and the data calculated from previously published and included studies. |

## CONTRIBUTIONS OF AUTHORS

In the 2013 update, LJN and PP updated the background section with input from SJM; SJM and RN updated the methods section. Studies were selected and appraised by LJN and PP, and data were extracted by RN and RH and then were entered by RN and checked by RH. RN and RH conducted the analysis with input from RH, LJN and PP. The results section was written by RN with input from RH, LJN and PP. The discussion, conclusion and abstract were written by LJN and PP with input from RN and RH.

LJN and PP developed the protocol. In previous versions of the review, studies were assessed by LJN and Toby Lasserson (TJL). TJL and LJN checked data and entered them into RevMan 2011. TJL and LJN conducted the analysis. TJL and LJN developed the discussion with input from PP. Chris Cates (CJC) participated in the 2004 and 2007 updates of the review and offered statistical advice and input in calculating SEM and SD for the included studies when appropriate.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Hamamelis Trust, UK.
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- NIHR, UK.

  Progam grant

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have provided estimates of mortality from all included studies.

Since the protocol of this Cochrane review was published, several different aspects of review methodology have changed in light of more recent recommendations regarding the methodology of Cochrane reviews.

- Risk of bias assessment (*Cochrane Handbook for Systematic Reviews of Interventions*, Chapter 8): This has now displaced the Jadad scores used to determine study quality in previous versions of the review.
- Generic inverse variance (*Cochrane Handbook for Systematic Reviews of Interventions*, Chapters 7 and 9): This method of meta-analysing adjusted effect estimates from clinical trials has enabled us to measure exacerbation outcomes as rate ratios.
- Summary of findings tables: We have adopted the GRADE methodology for assessing the strength of evidence and determining effect size in absolute terms for key outcomes in this review (GRADE working group).
- In 2012, the inclusion criteria were clarified as *randomised, double-blind, parallel-group clinical trials of at least 4 weeks' duration.* This was done to bring consistency to the inclusion criteria of the three Cochrane reviews considering combined corticosteroid and long-acting beta$_2$-agonist in a single inhaler for chronic obstructive pulmonary disease.
- In 2012, we added the comparison of mometasone furoate/formoterol versus placebo.
- In 2012 we presented data subgrouped according to dose.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Adrenergic beta-2 Receptor Agonists [*therapeutic use]; Bronchodilator Agents [*therapeutic use]; Drug Combinations; Nebulizers and Vaporizers; Pulmonary Disease, Chronic Obstructive [*drug therapy]; Randomized Controlled Trials as Topic

### MeSH check words

Humans