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Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis (Review)

Skilton M, Krishan A, Patel S, Sinha IP, Southern KW

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[Intervention Review]

Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis (CF) is the commonest inherited life-shortening illness in white populations, caused by a mutation in the gene that codes for the cystic fibrosis transmembrane regulator protein (CFTR), which functions as a salt transporter. This mutation mainly affects the airways where excess salt absorption dehydrates the airway lining leading to impaired mucociliary clearance. Consequently, thick, sticky mucus accumulates making the airway prone to chronic infection and progressive inflammation; respiratory failure often ensues. Other complications include malnutrition, diabetes and subfertility.

Increased understanding of the condition has allowed pharmaceutical companies to design mutation-specific therapies targeting the underlying molecular defect. CFTR potentiators target mutation classes III and IV and aim to normalise airway surface liquid and mucociliary clearance, which in turn impacts on the chronic infection and inflammation. This is an update of a previously published review.

Objectives

To evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with CF.

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles, reviews and online clinical trial registries. Last search: 21 November 2018.

Selection criteria

Randomised controlled trials (RCTs) of parallel design comparing CFTR potentiators to placebo in people with CF. A separate review examines trials combining CFTR potentiators with other mutation-specific therapies.

Data collection and analysis

The authors independently extracted data, assessed the risk of bias in included trials and used GRADE to assess evidence quality. Trial authors were contacted for additional data.

Main results

We included five RCTs (447 participants with different mutations) lasting from 28 days to 48 weeks, all assessing the CFTR potentiator ivacaftor. The quality of the evidence was moderate to low, mainly due to risk of bias (incomplete outcome data and selective reporting) and imprecision of results, particularly where few individuals experienced adverse events. Trial design was generally well-documented. All trials were industry-sponsored and supported by other non-pharmaceutical funding bodies.

F508del (class II) (140 participants)

One 16-week trial reported no deaths, or changes in quality of life (QoL) or lung function (either relative or absolute change in forced expiratory volume in one second (FEV1) (moderate-quality evidence). Pulmonary exacerbations and cough were the most reported adverse events in ivacaftor and placebo groups, but there was no difference between groups (low-quality evidence); there was also no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Number of days until the first exacerbation was not reported, but there was no difference between groups in how many participants developed pulmonary exacerbations. There was also no difference in weight. Sweat chloride concentration decreased, mean difference (MD) -2.90 mmol/L (95% confidence interval (CI) -5.60 to -0.20).

G551D (class III) (238 participants)

The 28-day phase 2 trial (19 participants) and two 48-week phase 3 trials (adult trial (167 adults), paediatric trial (52 children)) reported no deaths. QoL scores (respiratory domain) were higher with ivacaftor in the adult trial at 24 weeks, MD 8.10 (95% CI 4.77 to 11.43) and 48 weeks, MD 8.60 (95% CI 5.27 to 11.93 (moderate-quality evidence). The adult trial reported a higher relative change in FEV1 with ivacaftor at 24 weeks, MD 16.90% (95% CI 13.60 to 20.20) and 48 weeks, MD 16.80% (95% CI 13.50 to 20.10); the paediatric trial reported this at 24 weeks, MD 17.4% ($P < 0.0001$) (moderate-quality evidence). These trials demonstrated absolute improvements in FEV1 (% predicted) at 24 weeks, MD 10.80% (95% CI 8.91 to 12.69) and 48 weeks, MD 10.44% (95% CI 8.56 to 12.32). The phase 3 trials reported increased cough, odds ratio (OR) 0.57 (95% CI 0.33 to 1.00) and episodes of decreased pulmonary function, OR 0.29 (95% CI 0.10 to 0.82) in the placebo group; ivacaftor led to increased dizziness in adults, OR 10.55 (95% CI 1.32 to 84.47). There was no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Fewer participants taking ivacaftor developed serious pulmonary exacerbations; adults taking ivacaftor developed fewer exacerbations (serious or not), OR 0.54 (95% CI 0.29 to 1.01). A higher proportion of participants were exacerbation-free at 24 weeks with ivacaftor (moderate-quality evidence). Ivacaftor led to a greater absolute change from baseline in FEV1 (% predicted) at 24 weeks, MD 10.80% (95% CI 8.91 to 12.69) and 48 weeks, MD 10.44% (95% CI 8.56 to 12.32); weight also increased at 24 weeks, MD 2.37 kg (95% CI 1.68 to 3.06) and 48 weeks, MD 2.75 kg (95% CI 1.74 to 3.75). Sweat chloride concentration decreased at 24 weeks, MD -48.98 mmol/L (95% CI -52.07 to -45.89) and 48 weeks, MD -49.03 mmol/L (95% CI -52.11 to -45.94).

R117H (class IV) (69 participants)

One 24-week trial reported no deaths. QoL scores (respiratory domain) were higher with ivacaftor at 24 weeks, MD 8.40 (95% CI 2.17 to 14.63), but no relative changes in lung function were reported (moderate-quality evidence). Pulmonary exacerbations and cough were the most reported adverse events in both groups, but there was no difference between groups; there was no difference between groups in participants interrupting or discontinuing treatment (low-quality evidence). Number of days until the first exacerbation was not reported, but there was no difference between groups in how many participants developed pulmonary exacerbations. No changes in absolute change in FEV1 or weight were reported. Sweat chloride concentration decreased, MD -24.00 mmol/L (CI 95% -24.69 to -23.31).

Authors' conclusions

There is no evidence supporting the use of ivacaftor in people with the F508del mutation. Both G551D phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes at 24 and 48 weeks in adults and children (over six years of age) with CF. The R117H trial demonstrated an improvement in the respiratory QoL score, but no improvement in respiratory function.

As new mutation-specific therapies emerge, it is important that trials examine outcomes relevant to people with CF and their families and that adverse events are reported robustly and consistently. Post-market surveillance is essential and ongoing health economic evaluations are required.

PLAIN LANGUAGE SUMMARY

Ivacaftor (marketed as Kalydeco®), a new specific therapy for cystic fibrosis

Review question

How does ivacaftor affect clinical outcomes (survival, quality of life and lung function) in people with cystic fibrosis (CF)?

Background

In people with CF, airway surfaces do not have enough water because of an abnormal protein; this makes it difficult to clear thick and sticky mucus, which leads to lung infections. Ivacaftor works on the abnormal protein in people with some mutations to allow the airways retain more water and better clear mucus, so fewer lung infections develop.

Ivacaftor was aimed at people with class III and IV mutations, and has been studied in people with G551D (class III), R117H (class IV) and F508del (class II) mutations.

Trial characteristics

We included five trials (447 participants) comparing ivacaftor to placebo (dummy treatment with no active medication) lasting between four and 48 weeks. Three trials enrolled a total of 238 people with at least one copy of the G551D mutation, one trial enrolled 140 people with two copies of the F508del mutation and one enrolled 69 people with at least one copy of the R117H mutation. The evidence is up to date as of 21 November 2018.

Key results

F508del mutation

The trial did not report any deaths or show improvements in lung function, quality of life scores or weight. Cough and pulmonary exacerbations (flare ups of lung disease) were the most reported adverse events when taking both ivacaftor and placebo; there were a similar number of flare ups for both groups. Sweat chloride concentrations were reduced with ivacaftor.

G551D mutation

No deaths were reported. Both children and adults taking ivacaftor showed improvements in lung function, but only adults reported higher quality of life scores. People given placebo reported more coughing and experienced more episodes of decreased lung function; more adults taking ivacaftor reported episodes of dizziness. Similar numbers of people taking ivacaftor and placebo delayed the course of medication, or withdrew from the trial altogether, due to side effects (e.g. psychological issues, liver disease, severe breathing problems). There were more serious pulmonary exacerbations whilst taking placebo compared to ivacaftor. Adults taking ivacaftor were admitted to hospital less often and had fewer courses of intravenous antibiotics for exacerbations. Both children and adults and children increased their weight with ivacaftor. There was a drop in sweat chloride concentrations with ivacaftor.

R117H mutation

No deaths occurred in this trial. While quality of life scores improved with ivacaftor, lung function did not. Cough and pulmonary exacerbations (flare ups of lung disease) were the most reported adverse events when taking both ivacaftor and placebo; there were a similar number of flare ups for both groups. There was no difference in weight; but as for other mutations there was a reduction in sweat chloride concentration with ivacaftor.

Evidence suggests that ivacaftor is an effective treatment for people (over six years of age) with cystic fibrosis and the G551D mutation, but not for those with the F508del or R117H mutations.

Quality of the evidence

In most trials, individuals were put into different treatment groups at random with equal chances of being given either placebo or ivacaftor; no one could work out which treatment the next person would receive, so that healthier people did not receive ivacaftor and make the results seem better. We were not sure whether anyone involved in the trial knew who was receiving which treatment and how this might affect results. No trials reported all results clearly; sometimes they did not report them in a way that we could use in the review and sometimes they did not report the data at all. This affected our certainty regarding the overall results. Information about some side effects was limited as not many people experienced them, therefore, it is difficult to judge whether there was a difference between treatment groups

We judged the evidence in this review to be moderate to low quality.

Trial funding sources

All trials were sponsored by Vertex Pharmaceuticals Incorporated. The National Institute of Health (NIH), the Cystic Fibrosis Foundation (CFF) and other non-pharmaceutical funding bodies also supported the trials.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings - ivacaftor compared with placebo for cystic fibrosis with the F508del CFTR mutation

Ivacaftor compared with placebo for cystic fibrosis with the F508del CFTR mutation

Patient or population: adults and children with cystic fibrosis and with the F508del CFTR mutation

Settings: outpatients

Intervention: ivacaftor

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				
	Placebo	Ivacaftor				
Survival Follow-up: 16 weeks	No deaths reported.	No deaths reported.	NA	140 (1 study)	NA	
QoL Total score Follow-up: NA	Not reported.		NA	NA	NA	
QoL (CFQ-R) Respiratory domain Follow-up: 16 weeks	See comment. ¹	See comment. ¹	NA	140 (1 study)	⊕⊕⊕⊕ moderate ³	There was no significant difference between groups at 16 weeks.
FEV₁ % predicted Relative change from baseline Follow-up: 16 weeks	Not reported. ²	The mean FEV ₁ (% predicted) was 2.4% higher (0.95% lower to 5.75% higher) in the ivacaftor group.	NA	140 (1 study)	⊕⊕⊕⊕ moderate ³	There was no significant difference between groups at 16 weeks.
FEV₁ % predicted Absolute change from baseline Follow-up: 16 weeks	Not reported. ²	The mean FEV ₁ (% predicted) was 1.7% higher (0.65% lower to 4.05% higher) in the ivacaftor group.	NA	140 (1 study)	⊕⊕⊕⊕ moderate ³	There was no significant difference between groups at 16 weeks.

Adverse events Follow-up:16 weeks	The most commonly reported adverse events in the placebo group were: pulmonary exacerbation, cough, oropharyngeal pain and fatigue.	The most commonly reported adverse events in the ivacaftor group were: cough, pulmonary exacerbation, upper respiratory tract infection and nasal congestion.	NA	140 (1 study)	⊕⊕⊕⊕ low ^{3,4}	There was no significant difference between groups in terms of any other adverse events.
Time to first pulmonary exacerbation Follow-up: 16 weeks	Not reported.		NA	NA	NA	

*The basis for the **assumed risk** is the mean placebo group risk across studies, unless otherwise stated. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CFTR:** cystic fibrosis transmembrane regulator; **CI:** confidence interval; **FEV₁:** forced expiratory volume at 1 second; **HR:** hazard ratio; **MD:** mean difference; **QoL:** quality of life.

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. Presentation of the data prevented including data in analysis therefore results are presented narratively.
2. Only differences between placebo and ivacaftor groups were presented, results within the placebo group were not presented therefore an assumed risk cannot be calculated.
3. Downgraded once due to risk of bias from incomplete outcome data and/or selective reporting in all of the included studies.
4. Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide (also see [Analysis 1.2](#))

Summary of findings 2. Summary of findings - ivacaftor compared with placebo for cystic fibrosis with at least one G551D CFTR mutation

Ivacaftor compared with placebo for cystic fibrosis with at least one G551D CFTR mutation

Patient or population: adults and children with cystic fibrosis and with at least one G551D CFTR mutation

Settings: outpatients

Intervention: ivacaftor

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
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	Assumed risk	Corresponding risk				
	Placebo	Ivacaftor				
Survival Follow-up: 2 - 48 weeks	No deaths reported.	No deaths reported.	NA	238 (3 studies)	NA	
QoL Total score Follow-up: NA	Not reported.		NA	NA	NA	
QoL (CFQ-R) Respiratory domain Follow-up: 2 - 48 weeks	See comment. ¹	See comment. ¹	NA	222 (3 studies)	⊕⊕⊕⊖ moderate ²	A small phase 2 trial (n = 19) showed no significant difference at 2 or 4 weeks. A phase 3 trial (n = 151) in adults showed significantly higher quality of life in the ivacaftor group compared to placebo at 48 weeks A phase 3 trial (n = 52) showed no significant difference at 24 or 48 weeks in the child version of the CFQ-R. The same trial showed a significantly higher quality of life in the ivacaftor group compared to placebo at 48 weeks in the parent / caregiver version at 24 weeks but not at 48 weeks. ⁵
FEV₁ % predicted Relative change from baseline Follow-up: 2 - 48 weeks	See comment. ¹	See comment. ¹	NA	232 (3 studies)	⊕⊕⊕⊖ moderate ²	A small phase 2 trial (n = 19) showed no significant difference at 2 or 4 weeks. Two phase 3 trials (n = 213) showed a significant improvement in FEV ₁ at 24 weeks (MD ranged between 16.9% to 17.4%) One phase 3 trial (n = 161) showed a significant improvement in FEV ₁ at 48 weeks (MD 16.8%). ⁶
FEV₁ L and % predicted Absolute change from baseline	See comment. ¹	See comment. ¹	NA	232 (3 studies)	⊕⊕⊕⊖ low ^{2,3}	A small phase 2 trial (n = 19) showed no significant difference at 2 or 4 weeks. Two phase 3 trials (n = 213) showed a significant improvement in FEV ₁ (L and % predicted) at 24 weeks and 48 weeks. ⁷

Follow-up: 2 to 48 weeks						
Adverse events Follow-up: 2 - 48 weeks	The most commonly reported adverse events in the placebo group were: pulmonary exacerbation, cough, oropharyngeal pain and headache.	The most commonly reported adverse events in the ivacaftor group were: cough, pulmonary exacerbation, upper respiratory tract infection and headache.	NA	232 (3 studies)	⊕⊕⊕⊕ low^{2,4}	Pulmonary exacerbations were significantly more common in the placebo group. There was no significant difference between groups in terms of any other adverse events. ⁸
Time to first pulmonary exacerbation Follow-up: 48 weeks	41% of the placebo group were exacerbation free at 48 weeks.	67% of the ivacaftor group were exacerbation free at 48 weeks.	HR 0.46 (95% CI 0.29 to 0.73)	161 (1 study)	⊕⊕⊕⊕ moderate²	There was also a statistically significant difference between groups at 24 weeks; 78% and 51% of the ivacaftor and placebo groups were exacerbation free respectively; HR 0.46 (95% CI 0.28 to 0.76).

*The basis for the **assumed risk** is the mean placebo group risk across studies, unless otherwise stated. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CFTR:** cystic fibrosis transmembrane regulator; **CI:** confidence interval; **FEV₁:** forced expiratory volume at 1 second; **HR:** hazard ratio; **MD:** mean difference; **QoL:** quality of life.

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. Presentation of the data prevented pooling the data from all three studies therefore results are summarised narratively.
2. Downgraded once due to risk of bias from incomplete outcome data and/or selective reporting in all of the included studies.
3. Downgraded once due to unexplained heterogeneity.
4. Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide (also see [Analysis 2.5](#), [Analysis 2.6](#) and [Analysis 2.8](#)).
5. See analyses for numerical results ([Analysis 2.1](#); [Analysis 2.2](#); [Analysis 2.3](#)).
6. See analysis for numerical results ([Analysis 2.4](#)).
7. See analyses for numerical results ([Analysis 2.14](#); [Analysis 2.15](#)).
8. See analyses for numerical results ([Analysis 2.5](#); [Analysis 2.6](#); [Analysis 2.8](#)).

Summary of findings 3. Summary of findings - ivacaftor compared with placebo for cystic fibrosis with at least one R117H CFTR mutation

Ivacaftor compared with placebo for cystic fibrosis with at least one R117H CFTR mutation

Patient or population: adults and children with cystic fibrosis and with at least one R117H CFTR mutation

Settings: outpatients

Intervention: ivacaftor

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				
	Placebo	Ivacaftor				
Survival Follow-up: 2 - 24 weeks	No deaths reported.	No deaths reported.	NA	69 (1 study)	NA	
QoL Total score Follow-up: NA	Not reported.		NA	NA	NA	
QoL (CFQ-R) Respiratory domain Follow-up: 2 - 24 weeks	Not reported.	The mean adjusted CFQ-R respiratory domain score was 8.40% higher (2.17% higher to 14.63% higher) in the ivacaftor group.	NA	69 (1 study)	⊕⊕⊕⊕ moderate ²	There was a significant improvement in CFQ-R respiratory domain scores at 24 weeks. ³
FEV₁ % predicted Relative change from baseline Follow-up: 2 - 24 weeks	See comment. ¹	The mean adjusted FEV ₁ (% predicted) was 5.00% higher (0.24% lower to 10.24% higher) in the ivacaftor group.	NA	69 (1 study)	⊕⊕⊕⊕ moderate ²	There was no significant difference between groups at 24 weeks. ³
FEV₁ L and % predicted	See comment. ¹	The mean adjusted FEV ₁ (% predicted) was 2.10% higher (1.13% lower to 5.33% higher) in the ivacaftor group.	NA	69 (1 study)	⊕⊕⊕⊕ moderate ²	There was no significant difference between groups at 24 weeks. ³

Absolute change from baseline						
Follow-up: 2 - 24 weeks						
Adverse events	The most commonly reported adverse events in the placebo group were: pulmonary exacerbation and cough.	The most commonly reported adverse events in the ivacaftor group were: pulmonary exacerbation, cough, headache, nasal congestion, oropharyngeal pain, diarrhoea and increased sputum.	NA	69 (1 study)	⊕⊕⊕⊕ low^{2,4}	There was no significant difference between groups in terms of any other adverse events.
Follow-up: 2 - 24 weeks						
Time to first pulmonary exacerbation	63% of the placebo group were exacerbation free at 24 weeks.	68% of the ivacaftor group were exacerbation free at 24 weeks.	HR 0.93 (95% CI 0.42 to 2.08)	69 (1 study)	⊕⊕⊕⊕ moderate²	There was no significant difference between groups at 24 weeks.
Follow-up: 24 weeks						

*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% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CFTR:** cystic fibrosis transmembrane regulator; **CI:** confidence interval; **FEV₁:** forced expiratory volume at 1 second; **HR:** hazard ratio; **MD:** mean difference; **QoL:** quality of life.

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. Presentation of the data prevented including data in analysis therefore results are presented narratively.
2. Downgraded once due to risk of bias from selective reporting.
3. Treatment effect was adjusted for baseline values of age and % predicted FEV₁.
4. Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide (also see [Analysis 3.4](#))

BACKGROUND

A glossary of terms specific to this review can be found in the appendices ([Appendix 1](#)); a more general glossary of terms used in Cochrane Reviews can be accessed at [Cochrane Glossary](#).

Description of the condition

Cystic fibrosis (CF) is the most common inherited life-shortening illness in white populations, with a prevalence of 1 in 2000 at birth in Europeans ([Bobadilla 2002](#)) and varying prevalence in North American populations depending on ethnic composition ([Hamosh 1998](#)). According to the data report from the UK CF Registry which was published in July 2014, there were 10,338 people with a confirmed diagnosis of CF in the UK ([UK CF Registry Report 2013](#)). The clinical features of CF arise from abnormalities in a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) ([Riordan 1989](#); [Southern 1997](#)). Normally, CFTR protein is transported to the outer cell membrane, where it has a role in co-ordinating the transport of the salt ions, sodium (Na⁺) and chloride (Cl⁻), in and out of the cell. This salt transport role is particularly important in the airways, pancreas, sweat gland, and vas deferens.

In the lungs of people with CF, defective salt transport leads to a reduction in airway surface liquid volume. This, in turn, leads to compromised mucociliary clearance, which initiates a cycle of infection, inflammation and progressive lung damage, eventually causing respiratory failure and premature death. Other consequences of CFTR dysfunction, including those related to abnormalities in the inflammatory response, are probably important but not as well characterized. In addition, CFTR-related ion transport abnormalities can lead to other systemic complications. These include malnutrition and diabetes (through pancreatic damage, salt depletion through excess loss in sweat) and subfertility (in men and women) caused by various factors.

Over 1900 mutations have been identified in the CFTR gene, which can be categorised according to the impact they have on CFTR synthesis, processing, or function ([CFMD 2012](#)). These categories have been described ([Rowntree 2003](#); [Southern 2007](#)); and a summary is presented in the additional tables ([Table 1](#)). The most common mutation is the delta F508 (F508del) mutation (class II mutation) and is present on at least one allele in 7990 (90.8%) people with CF in the UK. The second most common mutation in the UK is the G551D mutation (class III mutation). This mutation exists in 514 (5.84%) people with CF in the UK. The R117H mutation (class IV mutation) is the third most common mutation, present in 398 (4.52%) people with CF in the UK ([UK CF Registry Report 2013](#)).

Description of the intervention

Understanding how the mutations, which are described in the additional tables ([Table 1](#)), affect the production, structure, and function of CFTR has led to the concept of mutation-specific therapies. One strategy, relating mainly to mutations classes III to V but also to class II, is to improve the function of CFTR that has reached the cell membrane, but whose function is compromised ([McKone 2004](#)). Drugs that improve CFTR function in the cell membrane are called potentiators and have the potential to correct the abnormal salt transport that characterises CF. Potentiators can be administered orally, or as an inhaled preparation.

Two distinct approaches have resulted in the recognition of candidate drugs with this mode of action ([Amaral 2007](#)):

1. testing of compounds known to affect CFTR or other ion-channels (either pharmaceutical drugs or chemicals which occur naturally in plants, herbs, fruits or food components);
2. high throughput screening, which involves testing large numbers of diverse chemicals, on laboratory cell lines, to identify which of these may stimulate CFTR.

In addition to potentiators, other drugs which aim to correct defects of the CFTR are also under investigation in clinical trials. These include correctors (which increase the amount of CFTR in the cell membrane by preventing early degradation - class II mutations) and 'stop-codon therapies' which act to prevent structural abnormalities of CFTR that occur when premature stop codons terminate protein synthesis too early - class I mutations). Cochrane Reviews of trials assessing correctors and one assessing stop codon therapies have been published ([Aslam 2017](#); [Southern 2018](#)).

How the intervention might work

The CFTR potentiator ivacaftor was identified through high-throughput screening by Vertex Pharmaceuticals Incorporated. In cell and animal models, it was able to restore CFTR function for class III mutations and correct the abnormal transmembrane salt transport ([Van Goor 2009](#)). However, the precise mechanism of action of ivacaftor is unclear, owing to the limited amount of data.

The correction of the basic defect in CF in the airways of the lung could lead to the normalization of airway surface liquid; the resulting re-establishment of mucociliary clearance, would then have a beneficial impact on the chronic infection and inflammation that characterizes CF lung disease.

Why it is important to do this review

Since CFTR potentiators are novel therapies, it is important that randomised controlled trials (RCTs) testing these agents are critically appraised. This will enable examination of the evidence relating to the benefits and harms of CFTR potentiators. It is important that funding bodies have a clear evidence base on which to assess new therapies for CF that aim to correct the basic defect, particularly given the large prevalence of people with mutations that might be impacted by CFTR potentiators. It is likely that these therapies will represent a significant healthcare resource. In addition, critical appraisal of included trials will help inform future trial design.

This review aims to collate evidence from RCTs that have evaluated the benefits and harms of CFTR potentiators in people with CF. This is an update of a previously published version ([Patel 2012](#); [Patel 2015](#)).

OBJECTIVES

To evaluate the effects of CFTR potentiators on clinically important outcomes in children and adults with CF.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs of parallel design (published or unpublished). Cross-over trials were considered inappropriate given the potential longer-term impact of this therapy on outcomes.

Types of participants

We have included trials involving children or adults with CF, as confirmed either by the presence of two disease-causing mutations, or by a combination of a positive sweat test and recognised clinical features of CF. We included trials involving people with any level of disease severity and any relevant mutation class, where CFTR has been demonstrated to successfully embed within the cell membrane and display defective function.

Types of interventions

In a post hoc change we have only included trials comparing CFTR potentiators to placebo or another intervention. Trials where CFTR potentiators are used in combination with other CFTR function modulators were excluded. There are many ongoing trials that use a CFTR potentiator alongside a CFTR corrector and we believe it would be more appropriate to conduct a separate systematic review for these trials ([Southern 2018](#)).

Types of outcome measures

Primary outcomes

1. Survival (in a post hoc change mortality data were also considered)
2. Quality of life (QoL) (measured using validated quantitative scales or scores (e.g. Cystic Fibrosis Questionnaire-Revised (CFQ-R) ([Quittner 2009](#)))
 - a. total QoL score
 - b. different sub-domains which may be reported
3. Forced expiratory flow rate at one second (FEV₁) (relative change from baseline)

Secondary outcomes

1. Adverse effects
 - a. graded by review authors as mild (therapy does not need to be discontinued)
 - b. graded by review authors as moderate (therapy is discontinued, and the adverse effect ceases)
 - c. graded by review authors as severe (life-threatening or debilitating, or which persists even after treatment is discontinued)
 - d. other adverse effects of therapy (of any severity) that are not classifiable according to these categories, including pulmonary exacerbation (protocol defined or physician defined) and time-to-exacerbation data
2. Hospitalisation
 - a. number of days
 - b. number of episodes
3. School or work attendance (i.e. number of days missed)
4. Other physiological measures of lung function (litres or per cent (%) predicted for age, sex and height)

- a. FEV₁ absolute values (rather than "relative change from baseline", which is specified as primary outcome)
 - b. forced vital capacity (FVC) (absolute values and change from baseline)
5. Extra courses of antibiotics (measured as time-to the next course of antibiotics and the total number of courses of antibiotics)
 - a. oral
 - b. intravenous
 - c. inhaled
 6. Radiological measures of lung disease (assessed using any scoring system)
 - a. chest radiograph scores
 - b. computerised tomogram (CT) score
 7. Acquisition of respiratory pathogens
 - a. *Pseudomonas aeruginosa*
 - b. *Staphylococcus aureus*
 - c. *Haemophilus influenzae*
 - d. other significant pathogen
 8. Eradication of respiratory pathogens (as defined by trial authors)
 - a. *P aeruginosa*
 - b. *S aureus*
 - c. *H influenzae*
 - d. other significant pathogen
 9. Nutrition and growth (measured as relative change from baseline) (including z scores or centiles)
 - a. weight
 - b. body mass index (BMI)
 - c. height
 10. Sweat chloride (change from baseline) as a measure of CFTR function
 11. Cost of treatment

Search methods for identification of studies

There are no restrictions regarding language or publication status.

Electronic searches

We identified relevant trials from the Group's Cystic Fibrosis Trials Register using the term: 'drugs that augment function of abnormal CFTR protein in the cell membrane'. Relevant trials have been tagged with this term for indexing purposes in the Group's Cystic Fibrosis Trials Register.

This is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of the Cochrane Library), weekly searches of MEDLINE, a search of Embase to 1995 and the handsearching of two journals – *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work was identified by searching through the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Group's [website](#).

Date of latest search of the Group's Cystic Fibrosis Trials Register: 21 November 2018.

We also searched online clinical trial registries ([Appendix 1](#)). Date of last search of clinical trial registries: 21 November 2018.

Searching other resources

We screened references of included trials to identify other potentially relevant trials. We also contacted authors of included trials, leaders in the field, and companies known to be developing and investigating CFTR potentiators, to identify any trials that may have been missed by these searches.

Data collection and analysis

Selection of studies

For the original review, two authors (SP and IS) independently assessed the suitability of each trial identified by the search. From the 2018 update onwards MS and IS independently assessed the suitability of each trial and if disagreement arose regarding suitability for inclusion, we attempted to reach a consensus by discussion, failing which a third author (KWS) arbitrated.

Data extraction and management

For the updated review, two authors (MS and IS) independently extracted relevant data from each included trial using a standardised data extraction form. If disagreement arose on data extraction, we attempted to reach a consensus by discussion, failing which a fourth author (KWS) arbitrated.

We intended to report on our primary outcome 'survival' as survival to time X (time-to-event data). However, these data were not available, so we considered mortality data (number of deaths) as an alternative outcome (post hoc change). For lung function, where possible we reported the relative change from baseline in FEV₁, since this way of presenting FEV₁ is very important in clinical practice. If this was not possible, we reported absolute change from baseline in FEV₁ as a secondary outcome. We extracted QoL as the absolute change from baseline.

With regards to the secondary outcome 'Adverse effects', we extracted the total number of participants who experienced adverse effects or required trial drug interruption or termination. When extracting data on pulmonary exacerbations, we noted whether they were protocol-defined or physician-defined. We reported the number of participants who experienced episodes of pulmonary exacerbation or reported time-to-exacerbation data. We extracted the number of participants who required hospitalisations. With regards to 'Extra courses of antibiotics', we reported on the total number of courses of antibiotics.

For the secondary outcomes 'Change from baseline in weight' and 'Change from baseline in sweat chloride concentration', we extracted the absolute change from baseline results.

For continuous outcomes, where standard deviations (SDs) were not provided, we calculated the standard error of the mean (SEM) from the 95% confidence intervals (CIs) and inserted the results into a generic inverse variance (GIV) analysis.

If the trial author presented non-parametric data, we reported results in the written text and not in the analysis.

We have reported data at 4 weeks, 16 weeks, 24 weeks and 48 weeks.

Assessment of risk of bias in included studies

Two authors (MS and IS) assessed the risk of bias for each trial using the Cochrane risk of bias tool ([Higgins 2011a](#)). This includes assessment of the following methodological aspects of the included trials:

1. procedure for randomisation (selection bias);
2. allocation concealment (selection bias);
3. masking (blinding) of the intervention from participants, clinicians, and trial personnel evaluating outcomes (performance bias);
4. missing outcome data (attrition bias);
5. selective outcome reporting (reporting bias);
6. other sources of bias.

We also assessed whether all participants were included in an intention-to-treat analysis, regardless of whether they completed the treatment schedule or not. If disagreement arose on the assessment of risk of bias of a trial, we attempted to reach a consensus by discussion, failing which a third author (KWS) arbitrated.

Measures of treatment effect

For binary outcomes, we calculated a pooled estimate of the treatment effect for each outcome using the pooled odds ratio (OR) and 95% CIs or 99% confidence intervals for analysis of separate adverse events. If calculating a pooled OR was not appropriate, we calculated an estimate of the treatment effect for each outcome using the OR and 95% CIs.

For continuous outcomes, we calculated the mean change from baseline for each group or the mean post-intervention values and 95% CIs for each group. We produced a pooled estimate of treatment effect by calculating the mean difference (MD) and 95% CIs. For QoL, CFQ-R was the most frequently used questionnaire and so we calculated the MD and 95% CIs. No other questionnaire was used.

For time-to-event outcomes, such as 'Time to first pulmonary exacerbation', we used measures of survival analysis, and calculated hazard ratios (HR) and 95% CIs between different arms of the trial.

In future updates of this review, if different trials present data for the same outcomes in different forms (e.g. absolute values of lung function measures, or change in these measures from a baseline), we will combine these in a meta-analysis where appropriate.

Where the trials did not report change data, but instead presented absolute post-treatment data without baseline data (so it was not possible to calculate change data), we planned to use absolute post-treatment data instead of change from baseline. However, if the report presented baseline and post-treatment data for any outcome, we calculated SDs for the change from baseline, for example if the CI was available. If there was not enough information available to calculate the SDs for the changes, we planned to impute them from other trials in the review, where data were available and trials were similar (i.e. when they used the same measurement scale, had the same degree of measurement error, had the same time periods between baseline and final value measurement and had conducted the randomisation process

appropriately). If neither of these methods were possible, we planned to calculate a change-from-baseline SD, making use of an imputed correlation coefficient (methods described in chapter 16 in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011b)).

Unit of analysis issues

Within this review, we have only included results from RCTs of parallel design in which individual trial participants were randomised. We excluded cross-over trials, because they are not appropriate for evaluating therapies that potentially correct the underlying defect (Higgins 2011b). We did not identify any cluster RCTs. Further updates of this review will include any eligible cluster RCTs identified and these will be included and analysed as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Where trials with multiple intervention groups reported dichotomous data i.e. adverse effects, we pooled the data to form one intervention group and compared data to the placebo group as recommended in chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

Dealing with missing data

In order to allow an intention-to-treat analysis, we extracted data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up. We calculated the number of participants with outcome data and checked if this was consistent with the number of originally randomised participants. We checked that this finding was consistent with findings on the online ongoing trials database (clinicaltrials.gov). If there were any discrepancies or any uncertainty, we contacted the primary investigators for clarification. For more detail about what we requested and what information we were provided with, see the risk of bias section below (*Incomplete outcome data (attrition bias)*).

Assessment of heterogeneity

We assessed heterogeneity through a visual examination of the forest plots, and by considering the I^2 statistic (Higgins 2003) together with the χ^2 test ($P < 0.1$) (Deeks 2011). The I^2 statistic reflects the likelihood that the variation of results across trials is due to heterogeneity rather than chance, and we interpreted this statistic using the following classification:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

If we had identified heterogeneity between trials, we would have conducted a sensitivity analysis including only homogenous trials to determine the effect of heterogeneity on the overall treatment effect of the intervention.

Assessment of reporting biases

In order to identify selective outcome reporting, where possible we compared outcomes described in the trial protocol with those reported in the publication(s). We requested protocols for specific trials from the primary investigators, corresponding author, or

relevant pharmaceutical company when they were not available. We have recorded the proportion of protocols that were available to us. If the protocol was not available, we checked published information on the trial registry databases. We also compared outcomes listed in the 'Methods' section of the final paper with those presented in the 'Results' section. If the published papers partially reported negative findings (i.e. $P > 0.05$), we contacted the primary investigators for these data.

We planned to assess publication bias by constructing and assessing the symmetry of a funnel plot. This would have been possible if we had included more than 10 trials in the review.

Data synthesis

We used a fixed-effect model to analyse data from trials which we did not consider to be heterogeneous (see classifications above). If substantial or considerable heterogeneity had been present (I^2 greater than 50%), we used a random-effects model to analyse data.

Subgroup analysis and investigation of heterogeneity

We planned to investigate any heterogeneity that we identified using subgroup analyses of potential confounding factors. For this review, we planned that these confounding factors would be:

- age (children (defined as younger than 18 years of age) versus adults);
- gender;
- different mutation classes (Table 1).

As we did not seek individual patient data from trial investigators, we did not undertake a subgroup analysis on the basis of disease severity. Such an analysis may be incorporated in future updates of this review.

Sensitivity analysis

If we had been able to combine a sufficient number of trials (at least 10), we planned to examine the impact of risk of bias on the results examined by comparing meta-analyses including and excluding trials with concerns of high risk of selection or reporting bias due to issues relating to randomisation, allocation concealment, or masking of interventions from participants or trial personnel.

Summary of findings and quality of the evidence (GRADE)

In a post hoc change from protocol, we have presented three summary of findings tables (*Summary of findings for the main comparison*; *Summary of findings 2*; *Summary of findings 3*) under the comparison of 'Ivacaftor compared to placebo' according to mutation class (see Table 1).

The following outcomes were reported in all tables (chosen based on relevance to clinicians and consumers):

- survival;
- QoL (total score);
- QoL (respiratory domain);
- FEV₁ (relative and absolute change);
- adverse events; and
- time to first pulmonary exacerbation.

For clarity in the tables, adverse events are not presented according to the subdomains in [Effects of interventions](#); instead the authors have inserted a general statement about the summary of findings for these outcomes and the evidence is graded based on all of the subdomains combined.

We determined the quality of the evidence using the GRADE approach; and downgraded evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results, high probability of publication bias. We evidence by one level if they considered the limitation to be serious and by two levels if very serious.

RESULTS

Description of studies

Results of the search

The search of the Group's Cystic Fibrosis Trials Register identified a total of 201 publications (abstracts and full papers) representing 67 trials. A further 91 trials were identified from ongoing trials databases. Five trials (67 references) were included and 62 trials (115 references) were excluded. The two trials (two references) awaiting classification have both been published as conference abstracts; further details below ([Kazani 2016](#); [Uttamsingh 2016](#)). In a post hoc change (2018), references to corrector and potentiator combination therapy trials have not been listed in the review, meaning 79 trials (110 references) identified have not been listed in the reference section of this review. The results of the search are displayed in the PRISMA diagram below ([Figure 1](#)).

Figure 1. Study flow diagram.

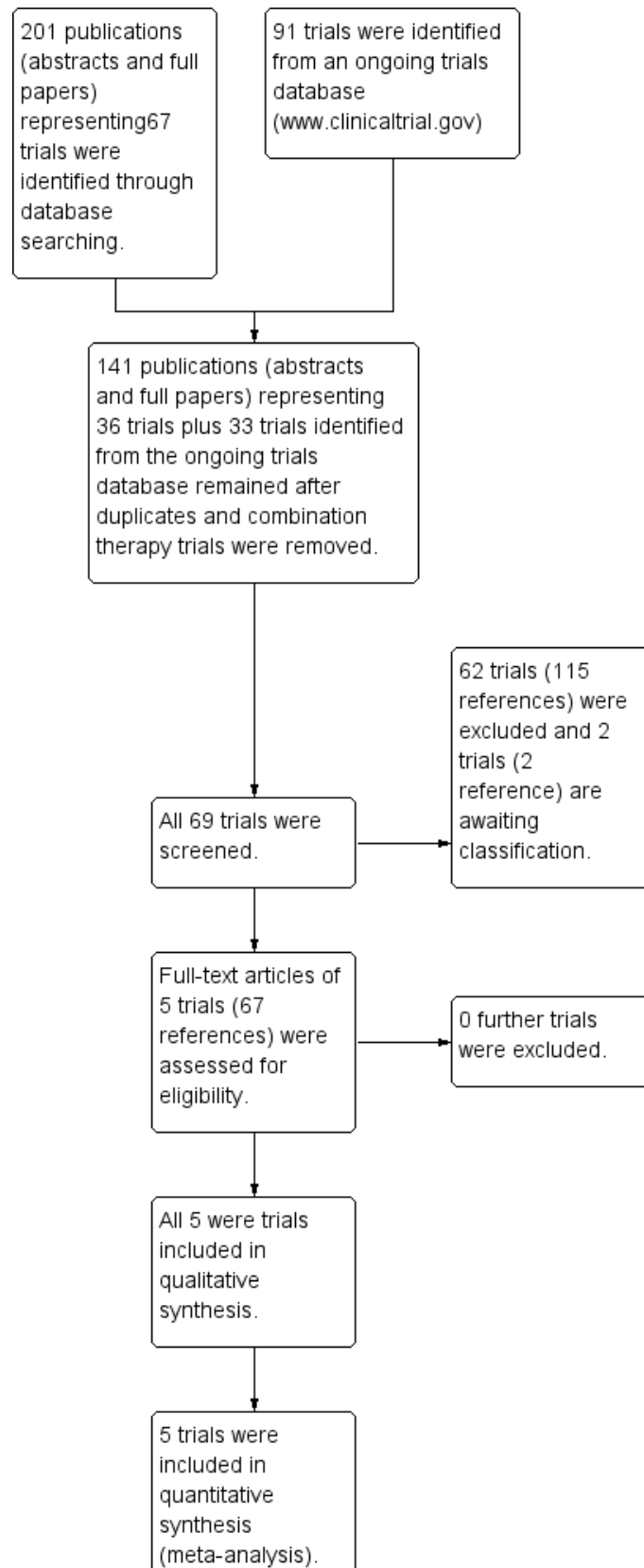


Figure 1. (Continued)

synthesis
 (meta-analysis).

No additional trials were identified by screening references of included trials or by contacting authors of included trials, leaders in the field, and companies known to be developing and investigating CFTR potentiators.

Included studies

We included five trials (67 references) with 447 participants in this review (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). All trials were available as full texts.

Trial design

All five included trials were RCTs of parallel design. The responsible funding body in all included trials was Vertex Pharmaceuticals Incorporated. The National Institute of Health (NIH), the Cystic Fibrosis Foundation (CFF) and other non-pharmaceutical funding bodies were also involved in supporting the trials (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011).

The F508del trial (n = 140) was a phase 2 trial that lasted 16 weeks (DISCOVER 2011). Participants who met pre-defined eligibility criteria and completed Part A of the trial were continued onto an open-label extension phase (Part B) lasting 96 weeks (n = 48); data from this extension were not eligible for inclusion in this review (DISCOVER 2011). There were three trials of people with the G551D mutation; the phase 2 trial had three arms and lasted 28 days (Accurso 2010); the two phase 3 trials lasted 48 weeks (ENVISION 2013; STRIVE 2011). Participants in these trials who completed 48 weeks of treatment (n = 194) were entered into an open-label extension phase, which lasted up to 96 weeks; participants from this trial were not eligible for inclusion in this review because they were not re-randomised to treatment or control (PERSIST 2014). The phase 3 R117H trial (n = 69) lasted for 24 weeks (KONDUCT 2015). Participants that completed 24 weeks of treatment were eligible to enrol into an open-label extension phase which lasted up to 104 weeks with an interim analysis at 12 weeks (KONTINUE 2017). Data from KONTINUE were not eligible for inclusion as participants were not re-randomised (KONTINUE 2017).

All trials were conducted at multiple centres (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). The F508del trial was run across 34 sites in North America (DISCOVER 2011). Although this trial recruited participants with a class II mutation, we included it in the initial version of the review on the basis that the trial evaluated ivacaftor and its effect of the minimal amount of CFTR reaching the cell surface in this mutation. The phase 2 G551D trial recruited participants from 13 sites in North America and Europe (Accurso 2010). The paediatric G551D trial (65 sites) and the adult G551D trial (29 sites) were conducted in North America, Europe and Australia (ENVISION 2013; STRIVE 2011). The phase 3 R117H trial was conducted at 31 sites across Europe and North America (KONDUCT 2015).

Outcome data were reported at time frames ranging from 2 to 48 weeks (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011).

Participants

All 447 participants in the included trials had a confirmed diagnosis of CF. The F508del trial examined the effect of ivacaftor on people homozygous for the F508del mutation (class II mutation) (DISCOVER 2011). In the three G551D trials (class III mutation), participants were required to possess at least one G551D-CFTR allele (Accurso 2010; ENVISION 2013; STRIVE 2011). The R117H trial required participants to have at least one R117H-CFTR allele (KONDUCT 2015).

Two trials recruited participants aged 12 years and older (DISCOVER 2011; STRIVE 2011); participants in the F508del trial had a mean age of 25.5 years (DISCOVER 2011) and participants in the adult G551D trial had a mean age of 23.2 years (STRIVE 2011). The phase 2 G551D trial recruited participants aged 18 years and over and participants had a median 21 age of years (Accurso 2010). The paediatric phase 3 G551D trial enrolled participants aged 6 to 11 years of age and participants had a mean age of 8.9 years (ENVISION 2013). The R117H trial recruited those over 6 years of age and participants had a mean age of 31 years (KONDUCT 2015).

In the F508del trial 140 participants were allocated in a 4:1 ratio to either intervention or placebo (DISCOVER 2011). Sample sizes in the G551D trials ranged between 19 participants (Accurso 2010) and 167 participants (STRIVE 2011). The phase 2 G551D trial allocated 19 participants in a 2:2:1 ratio to either one of two intervention groups or a placebo group respectively (Accurso 2010). In the phase 3 G551D trials, 52 children and 167 adults were allocated in a 1:1 ratio to either intervention or placebo (ENVISION 2013; STRIVE 2011). During randomisation, the adults were stratified according to age (less than 18 years versus 18 years and over) and pulmonary function (less than 70% versus 70% and over of the predicted FEV₁) (STRIVE 2011). Similarly, a 1:1 ratio was used to allocate participants to intervention or placebo groups in the R117H trial; participants were stratified by age (6 to 11 years, 12 to 17 years, and 18 years and over) and % predicted FEV₁ (< 70%, ≥ 70% to ≤ 90% and > 90%) during randomisation (KONDUCT 2015).

All participants had a baseline FEV₁ reading of 40% or over for age, sex and height and where baseline information was available, similar characteristics were seen (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011).

Interventions

Ivacaftor was the intervention drug in all included trials (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). Four trials compared 150 mg of ivacaftor every 12 hours to placebo (ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). The phase 2 G551D trial compared 150 mg and 250 mg of ivacaftor every 12 hours to placebo (Accurso 2010).

To determine the doses to be used, two G551D trials (the phase 2 trial and the paediatric phase 3 trial) conducted earlier investigations (Accurso 2010; ENVISION 2013). Ivacaftor dose levels used in the phase 2 G551D trial were determined based on pharmacokinetic modelling of data from a previous cross-over trial

(Accurso 2010). Pre-trial single-dose pharmacokinetic analysis and phase 2a data were used to determine doses in the paediatric phase 3 G551D trial (ENVISION 2013).

Participants in four of the five included trials continued on prescribed medications, that were approved for CF, during the trial period (Accurso 2010; ENVISION 2013; DISCOVER 2011; STRIVE 2011). No information was provided for the R117H trial regarding how drug dosage was determined or whether participants continued taking prescribed medications (KONDUCT 2015).

Outcomes

The primary end points in the trials were safety (Accurso 2010) or absolute change in FEV₁ (ENVISION 2013; KONDUCT 2015; STRIVE 2011) or both (DISCOVER 2011).

All trials employed the CFQ-R respiratory domain to measure QoL (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). One trial reported data for all domains (Accurso 2010). In the adult phase 3 G551D trial, data for other CFQ-R domains were reported where improvements were seen in the ivacaftor group (STRIVE 2011). Relative change from baseline in FEV₁ was reported in the full text by four trials (Accurso 2010; DISCOVER 2011; KONDUCT 2015; STRIVE 2011) and in a conference abstract by the fifth trial (24-week interim data only) (ENVISION 2013).

All trials reported on the safety profile of ivacaftor and the total number of participants who developed pulmonary exacerbations (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). The adult G551D trial and R117H trial also reported data for hospitalisation and number of days of hospitalisation (KONDUCT 2015; STRIVE 2011). Three trials reported on the number of participants who required extra courses of antibiotics (DISCOVER 2011; KONDUCT 2015; STRIVE 2011).

All trials examined the effect of ivacaftor on absolute change in FEV₁ (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). Two trials reported on absolute change from baseline in FEV₁ for subgroups, according to pulmonary function, geographic region and gender (ENVISION 2013; STRIVE 2011).

Three trials reported on weight (change from baseline), BMI and BMI as z score for age (ENVISION 2013; DISCOVER 2011; STRIVE 2011) and one trial reported change in BMI from baseline (KONDUCT 2015). Two trials reported on height z scores (ENVISION 2013; STRIVE 2011).

All included trials reported on change from baseline in sweat chloride concentration (Accurso 2010; ENVISION 2013; DISCOVER 2011; KONDUCT 2015; STRIVE 2011).

Nasal potential difference, a primary outcome in the Accurso trial, was not included in this review, as it is not yet a validated outcome measure (Accurso 2010).

Excluded studies

A total of 62 trials (115 references) were listed as excluded. We excluded 12 trials which were of cross-over design (Altes 2011; Berkers 2017; Edgeworth 2017; Davies 2012; KONNECTION 2013; EudraCT Number: 2016-001619-19; McGarry 2015; NCT01685801;

NCT01784419; NCT02709109; NCT02742519; NCT03068312) and one trial which carried out secondary analysis on trials of cross-over design (Accurso 2013). Eleven trials were excluded as they used treatments to correct the molecular defect and were not potentiators (ALBATROSS 2017; Chadwick 1998; Clancy 2012; FLAMINGO 2017; Horsley 2018; McCarty 2002; NCT03474042; NCT02323100; Rubenstein 1998; Rubenstein 2006; Zeitlin 2002). Six trials were excluded as they examined stop codon therapies for class I mutations (Kerem 2014; Pradal 2002; Romano 2000; Sermet-Gaudelus 2010; Wilschanski 2003; Wilschanski 2008). We excluded 12 trials due to an observational study design (EudraCT Number: 2016-001440-18; Hubert 2018; NCT01549314; NCT01863238; NCT02039986; NCT02141464; NCT02311140; NCT02445053; NCT02722057; NCT03390985; NCT03652090; Seliger 2015) and a further 12 trials were excluded as they had a single interventional arm with no comparator (ARRIVAL 2018; Davies 2016; EudraCT Number: 2014-000817-30; NCT01946412; NCT02310789; NCT02690519; NCT02707562; NCT02934698; NCT03256799; NCT03256968; NCT03277196; PERSIST 2014). Three trials used treatments to amplify or modify the molecular defect rather than potentiate it (NCT02718495; NCT02724527; NCT03258424). Four trials did not use mutation-specific treatments e.g. antibiotic therapy (EUudraCT Number: 2016-001785-29; NCT02443688; NCT02759562; RIO-CF 2017). One trial excluded people with CF (TOPIC 2018).

We excluded 79 trials (110 references) comparing potentiator and corrector combination therapy to placebo, but these have not been referenced within the list of excluded studies as a separate systematic review has been conducted which focuses on combination therapy (Southern 2018).

Studies awaiting classification

Two trials are listed as awaiting classification (Kazani 2016; Uttamsingh 2016), one of which has been terminated according to the record on clinicaltrials.gov (Kazani 2016).

Trial design

Both trials are double-blind RCTs of parallel design, but one is a phase 1 trial (Uttamsingh 2016) and the second is a phase 2 trial (Kazani 2016). The phase 1 trial lasted for seven days with no additional follow-up (Uttamsingh 2016). The phase 2 trial had a duration of 14 days with a follow-up to 42 days (Kazani 2016).

Participants

In the phase 1 trial, investigators enrolled 40 participants with a confirmed diagnosis of CF, but no details of participants' baseline characteristics are available (Uttamsingh 2016).

In the three-arm phase 2 trial, only the third phase of the trial was eligible which randomised 49 adults with CF heterozygous with one allele represented as any CFTR mutation and the other allele must represent a class III, IV, V, VI CFTR mutation (Kazani 2016). In the phase 2 trial the mean age of participants was 31.7 years. With regards to gender split the trial randomised more males (n = 30) than females (n = 19).

Intervention

Investigators enrolled 40 participants and allocated them in a 4:1 ratio to either intervention or placebo (Uttamsingh 2016). CTP-656 (a deuterated analogue of ivacaftor) was used as the

intervention drug. Participants received either 75mg, 150mg, or 225mg of CTP-656. Dose escalation was initiated only after safety and tolerability were found to support proceeding to the higher dose. All participants were dosed under fed conditions; a high-fat breakfast was provided on Day 1 through Day 7 approximately 30 minutes prior to dosing (Uttamsingh 2016). (Since this trial was undertaken CTP-656 has been sold by its developers (Concert Pharmaceuticals Inc.) to Vertex and has been renamed VX-561.)

The phase 2 trial compared QBW251 (a membrane-associated wild-type CFTR potentiator) at two doses - 150 mg twice daily and 450 mg twice daily - to placebo. The 450 mg daily dose group was split into participants with a number of different mutations (n = 12) and a second group who were homozygous for F508del (n = 19) (Kazani 2016).

Outcomes

The phase 1 trial's main outcome was the pharmacokinetic (PK) profile and PK blood samples were collected at several time points

post-dose on Day 1 and Day 7, and at 12 and 24 hours post-dose on Day 2 through Day 6. The plasma concentrations of CTP-656 and its metabolites, (D-M1 and D-M6) were analysed by a combination of liquid chromatography with mass spectrometry for all three dose cohorts (Uttamsingh 2016).

In the phase 2 trial, the primary outcomes were the change in LCI and adverse events; secondary outcomes included the change in FEV₁, the change in CFQR reported outcomes and the change in sweat chloride. Some limited results have been published on clinicaltrials.gov (Kazani 2016).

Risk of bias in included studies

A summary of the risk of bias judgements can be found in the figures (Figure 2; Figure 3).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. This Figure demonstrates the high proportion of trials that were judged to have a high risk of attrition bias (incomplete outcome data addressed) and selective reporting bias.

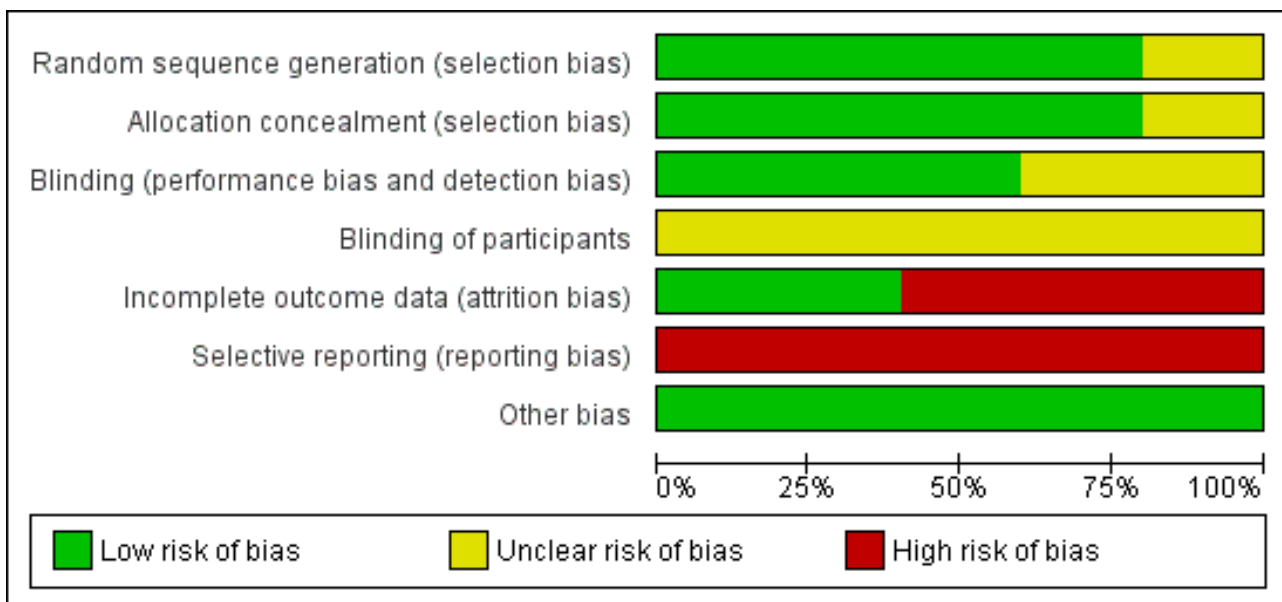


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding (performance bias and detection bias)	Blinding of participants	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Accurso 2010	+	+	+	?	+	-	+
DISCOVER 2011	+	+	+	?	-	-	+
ENVISION 2013	?	?	?	?	-	-	+
KONDUCT 2015	+	+	?	?	+	-	+
STRIVE 2011	+	+	+	?	-	-	+

Allocation

Sequence generation

Four trials reported on random sequence generation; all four employed an unblinded statistician (not otherwise associated with the trial) to produce the final randomisation list using a code produced by the trial sponsor and we judged these to have a low risk of bias for sequence generation (Accurso 2010; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). One phase 3 G551D trial did not report on how the children were randomised and we judged this to have an unclear risk of bias (ENVISION 2013).

Allocation concealment

Four trials reported on allocation concealment (Accurso 2010; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). Participants were allocated to groups using an interactive voice response system (IVRS) according to the concealed randomisation list and we judged these to have a low risk of bias with regards to allocation

concealment (Accurso 2010; DISCOVER 2011; KONDUCT 2015; STRIVE 2011). The paediatric phase 3 G551D trial did not report on allocation concealment and we judged this to have an unclear risk of bias (ENVISION 2013).

Blinding

Three trials reported on the blinding of trial personnel (Accurso 2010; DISCOVER 2011; STRIVE 2011). All trial personnel were blinded to participant treatment assignments. Tasks requiring unblinded personnel were conducted by people not otherwise involved in the trials; hence we judged these three trials to have a low risk of bias for blinding of personnel (Accurso 2010; DISCOVER 2011; STRIVE 2011). Two trials stated that they were 'double-blinded' but did not provide sufficient information to allow a clear judgement giving an unclear risk of bias (ENVISION 2013; KONDUCT 2015).

With regards to the blinding of participants, none of the included trials reported details of the oral tablets such as colour, size, consistency or taste; therefore we judge them all to have an unclear

risk of bias with regards to the blinding of participants ([Accurso 2010](#); [DISCOVER 2011](#); [ENVISION 2013](#); [KONDUCT 2015](#); [STRIVE 2011](#)).

Incomplete outcome data

There was low attrition (less than 15%) in all included trials ([Accurso 2010](#); [DISCOVER 2011](#); [ENVISION 2013](#); [KONDUCT 2015](#); [STRIVE 2011](#)).

In the phase 2 G551D trial, one participant withdrew consent prior to dosing, but all 19 remaining participants completed the trial and were included in the analysis of reported outcomes; therefore, we judged this trial to have a low risk of attrition bias ([Accurso 2010](#)). In the R117H trial, two participants from the ivacaftor group withdrew after dosing due to one participant becoming pregnant and one for non-compliance. All 69 participants who received at least one dose of the trial drug were included in the analysis. We judged this trial to also have a low risk of attrition bias ([KONDUCT 2015](#)).

In the remaining three trials, some participant data were excluded from the analysis and these trials were judged to have a high risk of attrition bias ([DISCOVER 2011](#); [ENVISION 2013](#); [STRIVE 2011](#)).

A total of 10 participants (7.1%) withdrew from the F508del trial ([DISCOVER 2011](#)); eight out of 112 (7.1%) participants withdrew from the ivacaftor group (three due to adverse events, two for non-compliance, one refused medication, one was lost to follow up; and one due to "early termination per sponsor decision") and two participants out of 28 (7.1%) withdrew from the placebo group due to adverse events ([DISCOVER 2011](#)). Participant data were excluded from the analysis of the change from baseline in sweat chloride concentration (one participant excluded from the ivacaftor group) and the absolute change from baseline in FEV₁ (one participant excluded from the ivacaftor group). The author was approached for information on these missing data ([DISCOVER 2011](#)).

In the paediatric phase 3 G551D trial, 4 out of 52 children (7.7%) withdrew from the placebo group, one for each of the following reasons: adverse events; refusal of medication; withdrawal of consent; and wrong genotype. Participant data were excluded from the analysis for absolute change from baseline in % predicted FEV₁ (one child excluded from placebo group), change from baseline in sweat chloride concentration (three children excluded from ivacaftor group and three children excluded from the placebo group) and CFQ-R respiratory domain paediatric version (one child excluded from placebo group). The author was approached for information on these missing data and revealed that a modified intention-to-treat analysis (not per protocol) was employed, where data were excluded from the analysis ([ENVISION 2013](#)).

In the adult phase 3 G551D trial, 10 out of 167 participants (6.0%) withdrew from the placebo group; four due to adverse events, one on the physician's decision, two required prohibited medication; one withdrew consent; one was the wrong genotype; and one had "Increased Lab Draws/Difficult Lab Stick". Six out of 167 participants (3.6%) withdrew from the ivacaftor group; one due to adverse events; two for non-compliance; one became pregnant; one refused medication; and one withdrew consent. After these 16 randomised participants (9.6%) withdrew, a total of 161 participants (78 in the placebo group and 83 in the ivacaftor group) were included in the analysis. However, in the analysis of change from baseline in CFQ-R respiratory domain scores, data

from 10 participants (seven participants from the placebo group and three participants from the ivacaftor group) were excluded; and data from nine participants (four participants from the placebo group and five participants from the ivacaftor group) were excluded from the analysis of the change from baseline in sweat chloride concentration. The author was approached for information on these missing data ([STRIVE 2011](#)).

Selective reporting

Trial protocols were available for the phase 2 G551D and the adult phase 3 G551D trials ([Accurso 2010](#); [STRIVE 2011](#)). In the phase 2 trial, weight was measured at days 1, 3, 14, 21 and 28, but not reported. In such a trial, the change in weight of participants from baseline is a key outcome and by not reporting this outcome, the trial is at high risk of selective reporting bias ([Accurso 2010](#)). In the adult trial, the following tertiary outcomes were not reported in the full text: change from baseline in oxygen saturation; change from baseline in EuroQol Questionnaire (EQ-5D); and outpatient sick visits to the clinic or hospital for CF-related complications. Also CFQ-R domain scores were reported for domains where improvements were seen in the ivacaftor group only. Hence, this trial was also judged to have a high risk of selective reporting bias ([STRIVE 2011](#)).

Full protocols were not available, either online or upon request, for the remaining three trials ([DISCOVER 2011](#); [ENVISION 2013](#); [KONDUCT 2015](#)). In the paediatric phase 3 G551D trial, FVC was measured at days 1 and 15, then at weeks 8, 16, 24, 32, 40 and 48; but results were not reported in the full text; also, relative change in FEV₁ from baseline was reported at 24 weeks, but not at any other time point ([ENVISION 2013](#)). In such trials, the change from baseline in FVC and relative change from baseline in FEV₁ are key outcomes and by not reporting these outcomes, the trial is at high risk of selective reporting ([ENVISION 2013](#)). In the F508del trial, there were missing data for change from baseline in FEV₁ score (at day 15 and week 8) and in change from baseline in FVC or mid-forced expiratory flow (FEF_{25-75%}) measured throughout the trial. Also, one withdrawal from the ivacaftor group was due to "early termination per sponsor decision" and attempts to illicit further information about this were unsuccessful; we therefore found the risk of selective reporting in this trial to be high ([DISCOVER 2011](#)). In the R117H trial, a protocol synopsis was made available by the trial sponsor which reported a number of tertiary outcomes; however, no results were made available for these outcomes. We therefore judged the trial to be at high risk of selective reporting bias ([KONDUCT 2015](#)).

Other potential sources of bias

The baseline characteristics of participants were similar in all included trials ([Accurso 2010](#); [ENVISION 2013](#); [DISCOVER 2011](#); [KONDUCT 2015](#); [STRIVE 2011](#)).

In the phase 2 G551D trial, drug dosing was monitored by clinical staff via returned dosage units and dosing diaries; an adherence rate of 100% (range 92.6 to 100) was achieved ([Accurso 2010](#)). In the paediatric phase 3 G551D trial, reviewing dosing with participants and caregivers ensured correct doses were taken; mean rates of compliance of 94.4% in the ivacaftor group and of 95.7% in the placebo group were reported ([ENVISION 2013](#)). Two trials ensured adherence by drug accountability ([DISCOVER 2011](#); [STRIVE 2011](#)).

No information was provided regarding drug adherence for the R117H trial (KONDUCT 2015).

In the R117H trial additional age subgroup analyses were performed for participants aged 6 to 11 years and ≥ 18 years, however, there were only two participants between 12 to 17 years of age so no statistical analysis was performed for this group (KONDUCT 2015). No reason was provided for the low numbers in 12 to 17 age group (KONDUCT 2015).

All trials were funded by a single company, Vertex Pharmaceuticals Incorporated (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings - ivacaftor compared with placebo for cystic fibrosis with the F508del CFTR mutation; **Summary of findings 2** Summary of findings - ivacaftor compared with placebo for cystic fibrosis with at least one G551D CFTR mutation; **Summary of findings 3** Summary of findings - ivacaftor compared with placebo for cystic fibrosis with at least one R117H CFTR mutation

In the summary of findings tables, the quality of the evidence has been graded for pre-defined outcomes (see above) and definitions of these gradings provided.

Ivacaftor versus placebo

Primary outcomes

1. Survival

No survival data or deaths were reported by any of the included trials ($n = 447$) (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

2. QoL

a. total QoL score

None of the trials reported on total QoL scores ($n = 447$) (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

b. different sub-domains

All five trials reported the CFQ-R respiratory domain scores ($n = 447$) (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011). The phase 2 G551D trial also reported scores for all other CFQ-R domains (Accurso 2010) and the adult phase 3 G551D trial reported scores for CFQ-R domains where improvements were reported in the ivacaftor group (STRIVE 2011).

In the F508del trial, investigators reported lower scores on the CFQ-R respiratory domain score in the ivacaftor group (MD -1.3) at 16 weeks, but this difference was not significant (DISCOVER 2011) (moderate-quality evidence). Insufficient data for this outcome were reported for inclusion in the analysis.

Data from both phase 3 G551D trials have not been combined as the paediatric trial reported individual change from baseline respiratory domain scores, for both children and parents or caregivers (ENVISION 2013), but the adult trial pooled the CFQ-R respiratory domain scores from adult and child questionnaires (STRIVE 2011). In the paediatric trial, at 24 weeks children in the

ivacaftor group reported higher CFQ-R respiratory domain scores, MD 6.10 (95% CI -1.35 to 13.55), but the difference between groups was not significant (ENVISION 2013) (Analysis 2.1) (moderate-quality evidence). In the same trial at 24 weeks, the parents or caregivers of children in the ivacaftor group reported significantly higher CFQ-R respiratory domain scores, MD 5.90 (95% CI 0.41 to 11.39) (Analysis 2.2) (moderate-quality evidence). In the adult trial, at 24 weeks participants reported significantly higher CFQ-R respiratory domain scores in the ivacaftor group, MD 8.10 (95% CI 4.77 to 11.43) (STRIVE 2011) (Analysis 2.3) (moderate-quality evidence).

At 48 weeks, both children and parents or caregivers reported higher CFQ-R respiratory domain scores in the ivacaftor group, MD 5.10 (95% CI -1.56 to 11.76) and MD 4.90 (95% CI -0.39 to 10.19) respectively (Analysis 2.1; Analysis 2.2) (moderate-quality evidence); in neither case were treatment differences significant (ENVISION 2013). In the adult trial at 48 weeks, investigators reported significantly higher CFQ-R respiratory domain scores in the ivacaftor group, MD 8.60 (95% CI 5.27 to 11.93) (STRIVE 2011) (Analysis 2.3) (moderate-quality evidence). At the same time-point, significantly higher CRQ-R scores in the physical functioning scale ($P < 0.001$), social functioning scale ($P = 0.0026$), eating disturbances scale ($P = 0.0021$) and treatment burden scale ($P = 0.0419$) were observed (STRIVE 2011). Higher scores for the body, emotion and digestive scales were also seen but the treatment differences between groups for these domains were not significant (STRIVE 2011).

Accurso reported on improvement in the respiratory domain score at two weeks and four weeks using medians and ranges, precluding the analysis of these data in RevMan (Accurso 2010). At two weeks, a median (range) increase of 5.6 (0.0 to 16.7) points was achieved in the 150 mg ivacaftor group and 5.6 (-11.1 to 11.1) in the 250 mg ivacaftor group. The median (range) change of 2.8 (-5.6 to 11.1) in the placebo group meant the difference between the two treatment and the placebo groups was not significant. At four weeks, there were no significant differences between treatment groups and the placebo group; the 150 mg group reported a median (range) improvement of 8.3 (0.0 to 16.7) points, the 250 mg group reported a median (range) improvement of 11.1 (-5.6 to 33.3) points and the placebo group reported a median (range) improvement of 2.8 (-5.6 to 11.1) points (Accurso 2010). Accurso also presented median (range) scores for all other CFQ-R domains which are shown in the additional tables (Table 2). None of the improvements were significant (Accurso 2010) (moderate-quality evidence).

In the R117H trial, investigators reported a significant improvement in the CFQ-R respiratory domain scores in the ivacaftor group, MD 8.40 (95% CI 2.17 to 14.63) (KONDUCT 2015) (Analysis 3.1) (moderate-quality evidence). The treatment effect was adjusted for continuous baseline values of age and % predicted FEV₁ (KONDUCT 2015). The R117H trial conducted a further subgroup analysis by age, which only showed a significant improvement in the respiratory domain score for adults in the ivacaftor group and not children (Table 3).

3. FEV₁ (relative change from baseline)

All included trials reported this outcome ($n = 447$) (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

At 16 weeks investigators reported no significant difference in the relative change from baseline in FEV₁ between groups in the F508del trial, MD 2.40% (95% CI -0.95 to 5.75) (DISCOVER 2011) (Analysis 1.1) (moderate-quality evidence).

At 24 weeks in the phase 3 G551D trials, both children and adults in the ivacaftor group reported significant improvements in the relative change from baseline in FEV₁ (ENVISION 2013; STRIVE 2011). For the paediatric trial, only interim data were reported in a conference abstract which were insufficient for inclusion into the meta-analysis, MD 17.4% (P < 0.0001) (ENVISION 2013); but for the adult trial investigators reported MD 16.90% (95% CI 13.60 to 20.20) (Analysis 2.4). Data at 48 weeks were not reported in the paediatric trial (ENVISION 2013); however, the adult trial reported a significant improvement in the relative change from baseline in FEV₁ in the ivacaftor group at 48 weeks, MD 16.80% (95% CI 13.50 to 20.10) (STRIVE 2011) (Analysis 2.4) (moderate-quality evidence).

Again Accurso reported medians (range) from the phase 2 G551D trial; at four weeks there was a relative improvement from baseline in % predicted FEV₁ of 8.7% (2.3 to 31.3) in the 150 mg group, 4.4% (0.0 to 18.3) in the 250 mg group and 7.3% (5.2 to 8.2) in the placebo group (Accurso 2010). Treatment differences between ivacaftor arms and the placebo group were not significant (Accurso 2010) (moderate-quality evidence).

In the R117H trial, investigators included the relative change from baseline in FEV₁ data in a results table; however, the absolute change in FEV₁ was a primary outcome and this was the focus of the text (KONDUCT 2015). At 24 weeks investigators reported no significant difference in the relative change from baseline in FEV₁ between treatment groups MD 5.00% (95% CI -0.24 to 10.24) (Analysis 3.2) (moderate-quality evidence). Treatment effect was adjusted for continuous baseline values of age and % predicted FEV₁ (KONDUCT 2015).

Secondary outcomes

1. Adverse effects

All included trials reported the number of participants who experienced adverse effects (n = 447) (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

The F508del trial reported the number of participants who experienced adverse effects that occurred in at least 5% of participants taking ivacaftor (DISCOVER 2011) (Analysis 1.2). Accurso reported the number of participants who experienced any adverse effect in the phase 2 G551D trial (Accurso 2010); we have pooled data for the 150 mg group and 250 mg group and compared these to the placebo group (Analysis 2.6). Both phase 3 G551D trials reported the number of participants who experienced any serious adverse effect and the number of participants who experienced all adverse effects that occurred in more than 5% of participants in either treatment arm (ENVISION 2013; STRIVE 2011). We have combined the data from both trials (Analysis 2.5). Serious adverse effects were defined as life-threatening or debilitating, which is consistent with our definition of severe. The R117H trial reported the number of participants with any adverse event, serious adverse events (the authors' definition of a serious adverse event was not present in the text), adverse events leading to discontinuation and

adverse events occurring in 15% of participants in any ivacaftor treatment group (KONDUCT 2015) (Analysis 3.3; Analysis 3.4).

For the F508del trial, phase 3 G551D trials and the R117H trial, we have reported on adverse effects that occurred more frequently in either the ivacaftor or placebo groups where there was greater or equal to 5% incidental difference between groups in the number of participants affected (DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011). Given the small sample size in the phase 2 G551D trial by Accurso (n = 19), we have not reported on the most common adverse effects from this trial (Accurso 2010). For all trials we have present below the results that were statistically significant in trial reports. Where numerical data were not provided, we have discussed the results narratively.

a. mild (therapy does not need to be discontinued)

In the F508del trial, episodes of cough, nausea, rash and contact dermatitis were experienced by more participants assigned to ivacaftor compared to those assigned to placebo. Pulmonary exacerbations were more common in participants in the placebo group (DISCOVER 2011) (Analysis 1.2) (low-quality evidence). In the adult phase 3 G551D trial, more adults in the placebo group experienced episodes of pulmonary exacerbation, cough, haemoptysis, and decreased pulmonary function in comparison to participants in the ivacaftor group. Adverse effects that occurred in more adults in the ivacaftor group were headache, upper respiratory tract infection, nasal congestion, rash, and dizziness (STRIVE 2011) (Analysis 2.5) (low-quality evidence). In the paediatric phase 3 G551D trial, episodes of cough, productive cough, vomiting, rales, and decreased pulmonary function were experienced by more children in the placebo group in comparison to children in the ivacaftor group. Episodes of oropharyngeal pain, headache, nasopharyngitis, upper respiratory tract infection, otitis media, diarrhoea, and an increased blood eosinophil count were reported in more children in the ivacaftor group (ENVISION 2013) (Analysis 2.5) (low-quality evidence). In the R117H trial more episodes of nasal congestion, oropharyngeal pain, abdominal pain, wheeze and CF lung pathogen colonisation were experienced in the ivacaftor group compared to the placebo group (KONDUCT 2015) (Analysis 3.4) (low-quality evidence).

There were no statistically significant differences at the 1% significance level to allow for multiple analyses related to adverse events in any of the included trials (Analysis 2.5; Analysis 2.6, Analysis 1.2; Analysis 3.4).

b. moderate (therapy is discontinued and the adverse effect ceases)

The F508del trial and both phase 3 G551D trials reported the number of participants who experienced adverse effects that required interruption of the intervention (DISCOVER 2011; ENVISION 2013; STRIVE 2011). The R117H trial did not report any participants requiring interruption of the intervention (KONDUCT 2015).

In the F508del trial, two participants in the ivacaftor group (1.8%) stopped receiving the intervention due to elevated liver enzyme values; but the intervention was subsequently restarted as both cases were found to be caused by concurrent pathology (DISCOVER 2011). No trial drug interruption occurred in the placebo group. The difference between groups in number of participants who required trial interruption was not significant, OR 1.29 (95% CI 0.06 to 27.62) (Analysis 1.3) (low-quality evidence). In the paediatric phase 3

G551D trial, three participants from the placebo group experienced adverse effects requiring interruption of the intervention compared to one participant in the ivacaftor group; but the details of these adverse events were not reported (ENVISION 2013) (low-quality evidence). In the adult trial, 11 adverse events in the ivacaftor group (13.3%) compared to four in the placebo group (5.1%) required trial drug interruption. Adverse events in the ivacaftor group were: haemoptysis (n = 1); migraine (n = 1); upper respiratory tract infection (n = 1); pulmonary exacerbation (n = 1); increased hepatic enzyme (n = 2); pulmonary exacerbation and anaphylactic shock (n = 1); lymph node pain and gynaecomastia (n = 1); myalgia and diarrhoea (n = 1); decreased weight and pulmonary exacerbation (n = 1); and vulvovaginal mycotic infection, oral candidiasis and two episodes of pulmonary exacerbation (n = 1). Adverse events in the placebo group were: migraine (n = 1); pulmonary exacerbation (n = 1); increased blood lactate dehydrogenase and increased hepatic enzymes (n = 1); and rash, nephrolithiasis and renal colic (n = 1). Investigators reported that five participants in the placebo group required drug interruption; however, one of these participants subsequently withdrew from the trial and will be discussed under 'severe' adverse events (STRIVE 2011) (low-quality evidence). Combined data for both phase 3 G551D trials showed no significant difference between treatment arms, OR 1.18 (95% CI 0.14 to 9.92) (Analysis 2.7) (low-quality evidence). Heterogeneity was substantial ($I^2 = 64%$) which is possibly due to the difference in ages between the adult and paediatric trials.

c. severe (life-threatening or debilitating, or which persists even after treatment is discontinued)

All included trials reported the number of participants who developed adverse effects that required discontinuation of the intervention (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

In the F508del trial, three participants in the ivacaftor group (2.7%) discontinued due to asthenia, fatigue and headache (n = 1), arthritis (n = 1) and myopathy (n = 1); a further participant in this group developed fatigue, depression and suicidal ideation that was considered to be life-threatening (DISCOVER 2011). In comparison, two participants in the placebo group (7.1%) discontinued medication because of abnormal feelings of cognitive disorder (n = 1) and elevated liver enzymes and increased lactate dehydrogenase levels (n = 1). The abnormal liver enzyme profile was considered to be caused by concomitant use of an anabolic steroid like a nutritional supplement (DISCOVER 2011). The number of participants requiring trial drug discontinuation between treatment arms was not significant, OR 0.36 (95% CI 0.06 to 2.25) (Analysis 1.3) (low-quality evidence).

In the paediatric phase 3 G551D trial, one participant from the placebo group withdrew due to anxiety and psychological issues (ENVISION 2013). In the adult trial, four participants from the placebo group withdrew from the trial; one each due to increased hepatic enzyme levels, atrioventricular block, panic attack and respiratory failure. There was one dropout from the ivacaftor group due to increased hepatic enzymes (STRIVE 2011). Combined data for the phase 3 G551D trials showed no significant difference between treatment arms in the number of participants discontinuing the trial drug, OR 0.25 (95% CI 0.04 to 1.57) (Analysis 2.7) (low-quality evidence). Likewise, combined data from the two trials for serious adverse effects, did not show an increase with ivacaftor compared with placebo (Analysis 2.8), with the exception

of pulmonary exacerbation which will be discussed under other adverse effects of therapy (below).

No severe adverse effects were reported in any of the participants in the phase 2 G551D trial and all adverse events resolved without discontinuation of the intervention (Accurso 2010) (low-quality evidence).

The R117H trial reported six (17%) severe adverse events in the placebo group and four (12%) in the ivacaftor group with no participants discontinuing the intervention due to adverse events (KONDUCT 2015). There was no significant difference in the number of serious adverse events between treatment arms, OR 0.64 (95% CI 0.16 to 2.52) (Analysis 3.3) (low-quality evidence).

d. other adverse effects of therapy (of any severity) that are not classifiable according to these categories

The number of participants who experienced episodes of pulmonary exacerbation was reported by all trials (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011) (low-quality evidence). In all cases pulmonary exacerbations were protocol-defined; both phase 3 G551D trials and also the F508del trial employed the same definition (DISCOVER 2011; ENVISION 2013; STRIVE 2011), but this was different to the definition employed by the phase 2 G551D trial (Accurso 2010). The R117H trial reported protocol-defined pulmonary exacerbations, but the full protocol was not available to determine this definition (KONDUCT 2015). Data for all G551D participants in this review are shown separately (Analysis 2.9). In the adult phase 3 G551D trial, there were minor differences in the number of participants experiencing episodes of pulmonary exacerbations between the full text, supplementary appendix and an online trials database (clinicaltrials.gov). Data were extracted from the online trials database where data for serious and other cases of pulmonary events were reported.

In the phase 2 G551D trial, one participant from each of the treatment arms experienced an exacerbation compared to none in the placebo group (Accurso 2010); when analysed, there was no significant difference in the number of participants who experienced pulmonary exacerbations between the ivacaftor group (combined data from 150 mg and 250 mg groups) and the placebo group at one month, OR 1.67 (95% CI 0.07 to 41.64) (Analysis 2.9). In the phase 3 G551D trials, at 48 weeks significantly fewer participants in the ivacaftor group experienced serious episodes of pulmonary exacerbations compared to participants in the placebo group, OR 0.34 (99% CI 0.13 to 0.88) (Analysis 2.8). Combined data for all exacerbations in these trials was not significant between groups at this time-point, OR 0.64; 95% CI 0.36 to 1.12) (Analysis 2.9). In the adult trial, the meta-analysis of all exacerbations shows significantly fewer participants in the ivacaftor group experienced exacerbations than in the placebo group, OR 0.54 (95% CI 0.29 to 1.01) (STRIVE 2011) (Analysis 2.9). In the F508del trial, investigators reported a non-significant lower frequency of pulmonary exacerbations in the ivacaftor group, OR 0.44 (99% CI 0.14 to 1.41) (Analysis 1.2).

The adult phase 3 G551D trial reported data for the time-to-first pulmonary exacerbation (STRIVE 2011). At 24 weeks, a significantly greater proportion of participants in the ivacaftor group (78%) were exacerbation-free in comparison to participants in the placebo group (51%). This corresponds to a hazard ratio (HR) of 0.46 (95% CI

0.28 to 0.76) ($P = 0.002$) so within the first 24 weeks, adults receiving ivacaftor were 54% less likely to experience an exacerbation than those assigned to placebo ([Analysis 2.10](#)). At 48 weeks, 67% of participants in the ivacaftor group and 41% of participants in the placebo group were exacerbation-free, HR 0.46 (95% CI 0.29 to 0.73), and the difference between groups remained significant ($P < 0.001$) ([Analysis 2.10](#)) (moderate-quality evidence). Therefore during the 48-week trial period, participants receiving ivacaftor were 54% less likely to experience an exacerbation than those assigned to placebo ([STRIVE 2011](#)).

The R117H trial reported that at 24 weeks there was no significant difference between treatment groups for the time-to-first pulmonary exacerbation, HR 0.93 (95% CI 0.42 to 2.08) ([KONDUCT 2015](#)) ([Analysis 3.6](#)) (moderate-quality evidence). Additionally, there was no significant difference between the ivacaftor and placebo groups in the number of participants experiencing a pulmonary exacerbation, OR 0.81 (95% CI 0.30 to 2.19) ([Analysis 3.5](#)).

There was no significant difference in the hepatic enzyme profile between groups in either phase 3 G551D trial ([Analysis 2.5](#); [Analysis 2.11](#)). The majority of participants in the F508del trial had aspartate aminotransferase (AST), alanine aminotransferase (ALT) and bilirubin values less than or equal to two times ULN ([DISCOVER 2011](#)).

2. Hospitalisation

The adult phase 3 G551D trial ($n = 167$) reported on the number of hospitalisations for episodes of pulmonary exacerbation and also on the number of days admitted ([STRIVE 2011](#)). The R117H trial reported the number of hospital admissions for episodes of pulmonary exacerbation ([KONDUCT 2015](#)).

a. number of days

In the G551D trial, of the episodes of pulmonary exacerbation that required hospitalisations, those occurring in participants in the ivacaftor group required less time in hospital, MD -0.23 days (95% CI -3.74 to 3.28) ([Analysis 2.12](#)). We note this non-significant summary statistic conflicts with the trial report. The Supplementary table 2B of the supplementary appendix reports a P value of 0.0275 for this difference; however, this has been calculated from a Wilcoxon rank-sum test, stratified by baseline % predicted FEV₁ severity and age group ([STRIVE 2011](#)). This is a non-parametric test used when data are skewed and where values are usually given as medians and ranges. In this trial, however, mean and SDs have been reported. As stated above, after entering these data into Review Manager, we have calculated a different P value of 0.90 which was not significant ([Analysis 2.12](#)).

b. number of episodes

Similarly, in the G551D trial significantly fewer episodes of pulmonary exacerbation required hospitalisation in participants in the ivacaftor group, OR 0.37 (95% CI 0.16 to 0.81) ([Analysis 2.13](#)) ([STRIVE 2011](#)). The R117H trial did not show a significant difference between treatment groups in the number of participants requiring hospital admission for pulmonary exacerbations ([Analysis 3.5](#)) ([KONDUCT 2015](#)).

3. School or work attendance

No individual data for school or work attendance was reported by any trial ($n = 447$) ([Accurso 2010](#); [DISCOVER 2011](#); [ENVISION 2013](#); [KONDUCT 2015](#); [STRIVE 2011](#)).

4. Other physiological measures of lung function

a. FEV₁ (absolute values)

All included trials reported on the absolute change from baseline in FEV₁ ($n = 447$) ([Accurso 2010](#); [DISCOVER 2011](#); [ENVISION 2013](#); [KONDUCT 2015](#); [STRIVE 2011](#)). For the four phase three trials, this outcome was a primary endpoint ([DISCOVER 2011](#); [ENVISION 2013](#); [KONDUCT 2015](#); [STRIVE 2011](#)). The data in the paediatric phase 3 G551D trial were adjusted based on the continuous baseline value of % of predicted FEV₁ ([ENVISION 2013](#)). Data in the R117H trial were adjusted for continuous baseline values of age and % predicted FEV₁ ([KONDUCT 2015](#)).

Investigators reported no significant differences between groups in the F508del trial for change from baseline of % predicted FEV₁ at 16 weeks, MD 1.70% (95% CI -0.65 to 4.05) ([DISCOVER 2011](#)) ([Analysis 1.4](#)) (moderate-quality evidence).

Both phase 3 G551D trials reported results early (day 15), but we are unable to include these results in our analysis ([ENVISION 2013](#); [STRIVE 2011](#)). At this time point, an estimated MD of 13.0% points can be deduced from the graph (Figure 2 in the full paper) for the paediatric trial ([ENVISION 2013](#)) and the adult trial reported a significant MD of 9.2% points ($P < 0.001$) ([STRIVE 2011](#)). At 24 weeks combined data from both of these trials show a significant increase in FEV₁ (% predicted) from baseline in the ivacaftor group, MD 10.80% (95% CI 8.91 to 12.69) ($P < 0.00001$) with no heterogeneity ($I^2 = 0\%$) ([Analysis 2.14](#)) (low-quality evidence). Combined data at 48 weeks still demonstrate a significant change from baseline in FEV₁ (% predicted), MD 10.44% (95% CI 8.56 to 12.32), again with no heterogeneity ($I^2 = 0\%$) ([Analysis 2.14](#)) (low-quality evidence). For the change from baseline in FEV₁ (L), combined data at 24 weeks show a significant increase in the ivacaftor group, MD 0.33 L (95% CI 0.17 to 0.49), but with considerable heterogeneity ($I^2 = 85\%$) ([Analysis 2.15](#)) (low-quality evidence). At 48 weeks the combined data still demonstrate a significant improvement, MD 0.31 L (95% CI 0.11 to 0.50), but again with considerable heterogeneity ($I^2 = 90\%$) ([Analysis 2.15](#)) (low-quality evidence). We do not know why the I^2 values are different between the meta-analyses of % predicted FEV₁ and FEV₁ (L); we are not able to infer anything from it as there are only two trials in the analysis ([ENVISION 2013](#); [STRIVE 2011](#)).

At four weeks, in the phase 2 G551D trial, investigators reported a median (range) change from baseline in FEV₁ of 0.25 L (0.05 to 0.75) in the 150 mg group, 0.17 L (0 to 0.37) in the 250 mg group and 0.20 L (0.12 to 0.33) in the placebo group (low-quality evidence). Treatment differences between the ivacaftor arms and the placebo arm were not significant ([Accurso 2010](#)).

Subgroup analysis of the G551D trials

Improvements in the absolute change from baseline in FEV₁ amongst pre-defined subgroups were reported at 48 weeks by the phase 3 G551D trials ([ENVISION 2013](#); [STRIVE 2011](#)).

In the paediatric trial at 48 weeks, children in three subgroups demonstrated significant improvements in the change from baseline in % predicted FEV₁ in the ivacaftor group compared to the placebo group:

- a baseline % predicted FEV₁ below 90%, MD 14.90 (95% CI 7.30 to 22.50);
- were from Europe, MD 24.60 (95% CI 6.40 to 42.80); and
- were female, MD 13.80 (95% CI 4.20 to 23.40) (ENVISION 2013).

However, there was no significant difference in the change from baseline in % predicted FEV₁ between treatment and placebo in the following subgroups:

- baseline % predicted FEV₁ over 90%, MD 6.90% (95% CI -3.80 to 17.60);
- from North America, MD 5.80% (95% CI -2.60 to 14.20);
- from Australia, MD 4.20% (95% CI -3.70 to 12.10); and
- male, MD 5.20% (95% CI -2.20 to 12.60) (ENVISION 2013) (Analysis 2.16).

The adult phase 3 G551D trial reported significant improvements in FEV₁ % predicted favouring ivacaftor over placebo in all subgroups (Table 4); insufficient data precludes inclusion of these results in a meta-analysis (STRIVE 2011).

The R117H trial reported that at 24 weeks there was no significant treatment differences in absolute % predicted FEV₁ between the ivacaftor and placebo groups, MD 2.10% (95% CI -1.13 to 5.33) (Analysis 3.7) (KONDUCT 2015) (low-quality evidence).

b. FVC (absolute values and change from baseline)

Three trials reported on the change from baseline in FVC (Accurso 2010; DISCOVER 2011; STRIVE 2011). None of the data were included in a meta-analysis as they were either non-parametric data (reported as median and ranges) (Accurso 2010) or insufficient data were provided (DISCOVER 2011; STRIVE 2011).

The F508del trial reported no significant differences between groups in FVC, but no numerical data were provided (DISCOVER 2011).

The phase 2 G551D trial reported a relative improvement from baseline FVC at two weeks in all three groups; there was a 9.0% improvement in the 150 mg ivacaftor group, a 7.4% improvement in the 250 mg ivacaftor group and a 1.0% improvement in the placebo group (Accurso 2010). Treatment differences between the ivacaftor groups and the placebo group were not significant. At four weeks a median (range) change from baseline of 0.18 L (-0.29 to 0.48) in the 150 mg group, 0.09 L (-0.09 to 0.43) in the 250 mg group and 0.10 L in the placebo group were reported. These values corresponded to relative changes from baseline of 4.6% in the 150 mg group, 2.6% in the 250 mg group and 2.3% in the placebo group. Treatment differences between the ivacaftor groups and the placebo group were not significant (Accurso 2010).

The adult phase 3 G551D trial reported on the absolute change from baseline in FVC in the form of a graph (supplemental figure 4B of the supplementary appendix) (STRIVE 2011). From the graph, an estimated MD between intervention and placebo arms of 11.5% at 24 weeks and 7.0% at 48 weeks can be deduced. These results

should be interpreted with caution, as they are not accurate (STRIVE 2011).

5. Extra courses of antibiotics

Three trials reported on extra courses of antibiotics required by participants (n = 376) (DISCOVER 2011; KONDUCT 2015; STRIVE 2011).

The F508del trial reported on the number of new sinopulmonary signs or symptom events that required new or changed antibiotic therapy; however, the route of administration was not stated (DISCOVER 2011). Investigators reported proportionately fewer episodes of new sinopulmonary signs or symptom events requiring antibiotic treatment in the ivacaftor group, OR 0.56 (95% CI 0.24 to 1.30); however, the difference was not significant (Analysis 1.5).

The adult phase 3 G551D trial reported firstly the number of episodes of pulmonary exacerbation that required intravenous antibiotics and secondly the number of days on intravenous antibiotics to treat pulmonary exacerbations (see below) (STRIVE 2011). The R117H trial reported the number of episodes of pulmonary exacerbation requiring intravenous antibiotics (KONDUCT 2015).

a. oral

This outcome was not reported in any trial.

b. intravenous

In the adult phase 3 G551D trial, Ramsey reported significantly fewer episodes of pulmonary exacerbations requiring intravenous antibiotics occurred in participants in the ivacaftor group, OR 0.34 (95% CI 0.18 to 0.64) (P = 0.0009) (Analysis 2.17). In addition, more days of intravenous antibiotic administration were required for exacerbations occurring in participants in the placebo group, MD -4.35 (95% CI -10.51 to 1.81) (Analysis 2.18). Supplementary table 2B of the supplementary appendix reports a P value of 0.0183 for this difference; however, this has been calculated from a Wilcoxon rank-sum test, stratified by baseline % predicted FEV₁ severity and age group (STRIVE 2011). This is a non-parametric test used when data are skewed and where values are usually given as medians and ranges. In this trial however, mean and SDs have been reported. After entering these data into Review Manager, we have calculated a different P value of 0.17 which was not significant (Analysis 2.18).

In the R117H trial, investigators reported fewer episodes of pulmonary exacerbation requiring intravenous antibiotics in the ivacaftor group, OR 0.30 (95% CI 0.06 to 1.62), however, this result was not significant (P = 0.16) (Analysis 3.5) (KONDUCT 2015).

c. inhaled

This outcome was not reported in either trial.

6. Radiological measures of lung disease

No trials reported chest radiograph scores or CT scores.

7. Acquisition of respiratory pathogen

No trial reported on the acquisition of any respiratory pathogens (e.g. *P aeruginosa*, *S aureus*, *H influenzae*).

8. Eradication of respiratory pathogens

No trial reported on the eradication of any respiratory pathogens (e.g. *P. aeruginosa*, *S. aureus*, *H. influenzae*).

9. Nutrition and growth

a. weight

Three trials (n = 359) reported the absolute change from baseline in weight (kg) (DISCOVER 2011; ENVISION 2013; STRIVE 2011); one of these additionally reported on weight-for-age z score (DISCOVER 2011).

The F508del trial, reported no significant difference in weight gain between the ivacaftor group and the placebo group at 16 weeks, MD -0.20 kg (95% CI -1.18 to 0.78) (Analysis 1.6). There was also no significance difference between groups in weight-for-age z scores (MD 0.43), but insufficient data prevented inclusion of this outcome in the analysis (DISCOVER 2011).

Combined data from the phase 3 G551D trials at 24 weeks demonstrated significant weight gain in the ivacaftor group, MD 2.37 kg (95% CI 1.68 to 3.06) with moderate heterogeneity ($I^2 = 38%$) (ENVISION 2013; STRIVE 2011) (Analysis 2.19). Combined data from the same trials at 48 weeks also demonstrated significant weight gain in the ivacaftor group compared to placebo, MD 2.75 kg (95% CI 1.74 to 3.75), but with no heterogeneity ($I^2 = 0%$) (ENVISION 2013; STRIVE 2011) (Analysis 2.19).

b. BMI

Four trials reported on the change from baseline in BMI (DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011) and three additionally reported BMI for age z score (DISCOVER 2011; ENVISION 2013; STRIVE 2011), but none of them provided sufficient information for inclusion into a meta-analysis (DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

In the F508del trial, a lower BMI score was reported in the ivacaftor group in comparison to the placebo group at 16 weeks, MD -0.04 mg/m², but the difference between groups was not significant (DISCOVER 2011). In the phase 3 G551D trials, both children and adults in the ivacaftor group scored significantly higher BMI values at 48 weeks, MD 1.09 kg/m² (P = 0.0003) and MD 0.93 kg/m² (P < 0.0001) respectively (ENVISION 2013; STRIVE 2011).

In the F508del trial, at 16 weeks there was no significant difference between the ivacaftor group and the placebo group in BMI-for-age z score amongst a subgroup of participants aged 20 years or below, MD 0.75 (DISCOVER 2011). The paediatric phase 3 G551D trial reported significantly higher BMI-for-age-z scores in the ivacaftor group compared to placebo at 24 weeks, MD 0.34 (P ≤ 0.001), and 48 weeks, MD 0.45 (P < 0.001) (ENVISION 2013). At 48 weeks, the adult phase 3 G551D trial reported significantly higher BMI-for-age-z scores in the ivacaftor group amongst a subgroup of 47 participants aged 12 to 20 years, MD 0.33 (P = 0.0490) (STRIVE 2011).

The R117H trial reported a higher BMI score in the ivacaftor group compared to placebo at 24 weeks, MD 0.26 kg/m² (95% CI -1.57 to 2.09), but this was not significant (P = 0.1) (KONDUCT 2015) (Analysis 3.8). Treatment effect was adjusted for age and categorical % predicted FEV₁ at baseline (KONDUCT 2015).

c. height

Two trials reported on height z scores (ENVISION 2013; STRIVE 2011). The paediatric phase 3 G551D trial reported improvements in the ivacaftor group at both 24 weeks (MD 0.06) and 48 weeks (MD 0.12) (ENVISION 2013). In the adult phase 3 G551D trial reported improvements in the ivacaftor group at 24 weeks (MD 0.05) and 48 weeks (MD 0.06) amongst a subset of 47 participants aged 12 to 20 years (STRIVE 2011).

10. Sweat chloride (change from baseline)

The change from baseline in sweat chloride concentration was reported by all trials (n = 447) (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

In the F508del trial, investigators reported significant reductions in sweat chloride concentration at 16 weeks in the ivacaftor group compared to the placebo group, MD -2.90 mmol/L (95% CI -5.60 to -0.20) (DISCOVER 2011) (Analysis 1.7).

In the phase 2 G551D trial, at four weeks there was a significant difference in the median (range) change from baseline in sweat chloride concentration between the 150 mg group (within group change -59.5 mmol/L (-66.0 to -19.0) and the placebo group (within group change 5.0 mmol/L (-2.0 to 11.0) (P = 0.02); a similar significant difference was seen between the 250 mg group (within group change -38.0 mmol/L (-47.0 to -10.5) and placebo group (within group change 5.0 mmol/L (-2.0 to 11.0) (P = 0.03) (Accurso 2010).

In the phase 3 G551D trials, reduced sweat chloride concentrations were reported early (day 15) in children, MD -50 mmol/L (estimated from a graph) (ENVISION 2013) and in adults, MD -47.1 mmol/L (P < 0.001) (STRIVE 2011). Combined data from these trials demonstrated significant reductions in sweat chloride concentration at 24 weeks, MD -50.19 mmol/L (95% CI -56.20 to -44.18) with a moderate level of heterogeneity ($I^2 = 57%$) (Analysis 2.20), and at 48 weeks, MD -49.74 mmol/L (95% CI -54.61 to -44.87) with a moderate level of heterogeneity ($I^2 = 40%$) (Analysis 2.20). Secondary analysis of combined data from these trials reported that the number needed to treat (NNT) for a reduction of 20 mmol/L in sweat chloride concentration was 1.03. Data from each phase 3 G551D trial demonstrated that significant changes in sweat chloride were reported regardless of whether participants were FEV₁ responders (5% point improvement) or minimal responders (less than 5% point improvement) (ENVISION 2013; STRIVE 2011) (Table 5).

In the R117H trial, at 24 weeks a significant reduction in sweat chloride concentrations was reported in the ivacaftor group compared to placebo group, MD -24.00 mmol/L (95% CI -28.01 to -19.99) (P = <0.0001) (KONDUCT 2015) (Analysis 3.9). Treatment effect was adjusted for continuous baseline values of age and % predicted FEV₁ (KONDUCT 2015). In addition, age subgroup analysis showed significant reductions in sweat chloride concentrations for both participants aged 6 to 11 years and 18 years and over (Table 3).

11. Cost of treatment

No trials reported on the cost of ivacaftor treatment.

DISCUSSION

Summary of main results

The CFTR protein product of a class III mutation is transported to the cell membrane, but displays defective chloride ion gating and dysregulation of sodium channels resulting in a severe CF phenotype; characterised by chronic airway infection and inflammation and pancreatic insufficiency. Agents that repair the underlying gating defects (CFTR potentiators) restore CFTR function for class III mutations and correct the abnormal transmembrane salt transport in cell and animal models (Van Goor 2009). These CFTR potentiators may also have a role in repairing the underlying gating defect in the minimal amounts of class II CFTR that are transported to the cell membrane and for the restrictive movement of chloride ions in class IV CFTR.

This review examines whether CFTR potentiators improve clinically relevant endpoints in CF. Five trials with 447 participants met the inclusion criteria for this review; one compared 150 mg and 250 mg doses of ivacaftor (a potentiator) to placebo (Accurso 2010) and four compared 150 mg of ivacaftor to placebo (DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011). Three trials examined the impact of ivacaftor on people with a class III mutation (G551D) (Accurso 2010; ENVISION 2013; STRIVE 2011). One trial enrolled participants with a class II mutation (F508del) (DISCOVER 2011) and one enrolled participants with a class IV mutation (R117H) (KONDUCT 2015).

The trial that evaluated ivacaftor for people with F508del enrolled participants aged 12 years or over ($n = 140$) for a duration of 16 weeks (DISCOVER 2011). The first G551D trial was a phase 2 trial enrolling participants 18 years and over and measuring a number of outcomes at 14 and 28 days (Accurso 2010). This was followed by two phase 3 trials, the first enrolling participants aged 12 years and older ($n = 167$) (STRIVE 2011) and the second enrolled participants aged 6 to 11 years ($n = 52$) (ENVISION 2013). These trials reported outcomes at 24 and 48 weeks. The R117H trial enrolled participants over six years of age ($n = 69$) and measured outcomes at 24 weeks (KONDUCT 2015).

The primary end points for these trials were safety (Accurso 2010) or change in FEV₁ (ENVISION 2013; KONDUCT 2015; STRIVE 2011) or both (DISCOVER 2011). With respect to this review's primary outcomes, there were no deaths reported in any of the trials and the length and size of the trials precluded valid assessment of the impact of ivacaftor on survival. For CFQ-R scores, no significant difference was reported in the F508del trial (DISCOVER 2011). The adults randomised to ivacaftor in the phase 2 G551D trial did not report significantly higher CFQ-R respiratory domain scores 28 days (Accurso 2010). However, adults in the phase 3 G551D trial reported significantly higher CFQ-R respiratory scores at 24 weeks, MD 8.10 (95% CI 4.63 to 11.57) and at 48 weeks, MD 8.70 (95% CI 5.51 to 11.89) (Analysis 2.3). This finding was not reproduced in the paediatric participants (ENVISION 2013). The R117H trial reported significantly higher CFQ-R scores at 24 weeks in participants randomised to ivacaftor, MD 8.40 (95% CI 2.17 to 14.63) (Analysis 3.1) (KONDUCT 2015). Again, for relative change in FEV₁, no significant improvement was reported in the F508del trial (DISCOVER 2011). The phase 2 G551D trial did not report treatment with ivacaftor resulted in a significant improvement in relative change in FEV₁ (Accurso 2010). However, in the adult G551D

phase 3 trial, significant improvements in relative change in FEV₁ were seen early (after 15 days) and maintained through to 48 weeks, MD 16.80% (95% CI 13.50 to 20.10) (STRIVE 2011). Significant improvements in this outcome were also seen at 24 weeks in the paediatric trial, MD 17.4% ($P < 0.0001$), but results at 48 weeks were not published (ENVISION 2013). The R117H did not report any significant improvement in relative change in FEV₁ (KONDUCT 2015).

We compared the number of participants experiencing adverse effects between the ivacaftor group and the placebo group. Combined data from both G551D phase 3 trials demonstrated a reduced reporting of cough, OR 0.57 (95% CI 0.33 to 1.00) and reduced episodes of decreased pulmonary function, OR 0.29 (95% CI 0.10 to 0.82) in the ivacaftor group (Analysis 2.5). Increased reports of dizziness were recorded in participants receiving ivacaftor in the adult G551D trial (STRIVE 2011), but this adverse effect was not reported by any other trial (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015). Data from the R117H trial showed increased reporting of adverse effects in the ivacaftor group except for pulmonary exacerbation, OR 0.93 (95% CI 0.35 to 2.44), however, these results were not significant (KONDUCT 2015) (Analysis 3.4). No trial reported a significant increase in adverse effects leading to interruption or termination of the trial drug (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

Combined data from the phase 3 G551D trials demonstrated significantly fewer participants experienced 'serious' cases of pulmonary exacerbation in the ivacaftor group, OR 0.34 (95% CI 0.17 to 0.70) (Analysis 2.13). When considering all data for exacerbations, fewer adults in the ivacaftor group reported exacerbations in the adult phase 3 G551D trial, OR 0.54 (95% CI 0.29 to 1.01) (Analysis 2.9); also, more participants in the placebo group required hospitalisation and IV antibiotics for pulmonary exacerbations and a greater proportion of participants in the ivacaftor group were exacerbation-free at the 24 and 48 week time points (Analysis 2.10) (STRIVE 2011). In the R117H trial fewer participants in the ivacaftor group experienced pulmonary exacerbations, hospitalisation and IV antibiotics for the exacerbation, but results were not significant (Analysis 3.5) (KONDUCT 2015). This effect was not reported by the remaining three trials (Accurso 2010; DISCOVER 2011; ENVISION 2013).

The adverse effects profile of ivacaftor should be interpreted with caution as it was based on small numbers of participants. Furthermore, none of the included trials were powered to assess this outcome (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011).

No significant weight gain or change in BMI scores were reported in the F508del or R117H trials (DISCOVER 2011; KONDUCT 2015). Participants in both phase 3 G551D trials demonstrated significant weight gain on ivacaftor at 24 weeks, MD 2.37 kg (95% CI 1.68 to 3.06) and 48 weeks, MD 2.75 kg (95% CI 1.74 to 3.75) (Analysis 2.19). These two trials also reported that significantly higher BMI scores were achieved in the ivacaftor group; for children, MD 1.09 kg/m² ($P = 0.0003$) and for adults, MD 0.93 kg/m² ($P < 0.0001$). Significantly higher BMI for age z scores were reported for children in the ivacaftor group at 24 weeks, MD 0.34 ($P \leq 0.001$) and at 48 weeks, MD 0.45 ($P < 0.001$) (ENVISION 2013). In a subset of participants aged 12 to 20 years old from the adult trial, a higher

BMI for age Z score was reported at 48 weeks, MD 0.33 (P = 0.0490) (STRIVE 2011).

All trials reported significant reductions in sweat chloride concentrations (Accurso 2010; DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011). The F508del trial reported a MD of -2.90 mmol/L (95% CI -5.60 to -0.20) (DISCOVER 2011). The phase 2 G551D trial reported median values at 28 days; in the 150 mg ivacaftor group, median -64.5 mmol/L (P = 0.02) and in the 250 mg ivacaftor group, median -43.0 mmol/L (P = 0.03) (Accurso 2010). Combined data from the phase 3 G551D trials demonstrated significant reductions in sweat chloride concentration in participants on ivacaftor at 24 weeks, MD -50.19 mmol/L (95% CI -56.20 to -44.18) and 48 weeks, MD -49.74 mmol/L (95% CI -54.61 to -44.87) (Analysis 2.20). Similarly, the ivacaftor group in the R117H trial reported a significant reduction in sweat chloride concentration at 24 weeks, MD -24.00 mmol/L (95% CI -28.01 to -19.99) (Analysis 3.9).

Overall completeness and applicability of evidence

The DISCOVER trial recruited 140 participants homozygous for the F508del mutation, who were a representative sample for people with this mutation aged from 12 years upwards. This trial was included because it evaluated ivacaftor, although on a population with class II mutations in which a minimal amount of CFTR is able to reach the cell surface. In light of the results that failed to reach statistical significance in this population, trials with younger participants with F508del are not appropriate (DISCOVER 2011).

Three trials recruited 238 participants with the G551D mutation representing a significant proportion of all people with this mutation in the countries where the trials were undertaken (Accurso 2010; ENVISION 2013; STRIVE 2011). It can be assumed that the results are applicable to those with the G551D mutation not included in the trials; however, current trials have not enrolled children under six years of age or pregnant women. There are insufficient data for some outcomes, which we considered to be important for this review: school or work attendance; radiological measures of lung disease; acquisition of respiratory pathogens; and cost of treatment. One G551D trial reported on hospitalisations and extra courses of antibiotics (STRIVE 2011).

The R117H trial recruited 69 participants with the R117H mutation. Results are not applicable to individuals with other class IV mutations and the small sample size reduces the applicability of this evidence to people with cystic fibrosis who carry the R117H mutation (KONDUCT 2015).

There is no current evidence to support the use of CFTR potentiators in people with other class III to V mutations (not G551D). While there are trials recruiting people with other class III to V mutations, these have not been included in this review due to their cross-over trial design (KONNECTION 2013; NCT01685801; NCT01784419).

Quality of the evidence

All the included trials were RCTs which represent the highest quality with regards to trial design.

The overall risk of bias across the included trials was judged to be moderate. Random sequence generation, allocation concealment and blinding of trial personnel were well-documented. Blinding

of participants was less clear, as details of ivacaftor and placebo tablets (such as taste, colour and consistency) were not provided. Participant data were excluded from the analysis in four trials (DISCOVER 2011; ENVISION 2013; KONDUCT 2015; STRIVE 2011). The risk of selective reporting was generally high as trials did not always report on outcomes outlined in the protocol, or present data for all outcomes and report on outcomes considered important by the review authors.

The quality of the evidence in this review is judged to be moderate to low, mainly due to risk of bias from incomplete outcome data and selective reporting and imprecision of results, particularly where few individuals have experienced adverse events (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Potential biases in the review process

The review authors conducted a comprehensive literature search of online journal databases using the Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Trials Register and online trials databases (Appendix 1) and also of manual searching of journal conference abstracts. Two authors independently applied the inclusion and exclusion criteria to the resultant literature and extracted relevant trials. The authors independently extracted data and assessed the risk of bias of the included trials. If they failed to reach a consensus on the risk of bias in a trial, a third author (KWS) arbitrated. The initial analyses were undertaken by one review author (SP) and checked for appropriateness by the review statistician (KD). MS completed the analysis for the update of the review. This methodological approach ensured that risks of bias in the review process were kept to a minimum.

This review has assessed all available published trial data. Trial authors were contacted for relevant unpublished information and individual participant data. To date, a protocol synopsis and summary of product characteristics have been provided with regards to information requested for the R117H trial (KONDUCT 2015). We are not aware of any unpublished trials, although we have highlighted issues with selective reporting in the included trials.

Agreements and disagreements with other studies or reviews

We are aware of one other published review of ivacaftor for people with CF which included the phase 3 G551D trials and data from the open-label extensions to these trials (Whiting 2014). In line with this Cochrane Review, the Whiting review also concluded that ivacaftor has a clinically relevant impact on people with CF with the G551D mutation. We identified disagreements between the two reviews concerning the methodological quality and risk of bias assessments for the phase 3 G551D trials, although both reviews have used the Cochrane risk of bias tool. In the Whiting review, the authors judged the risk of bias for all methodological aspects of the adult phase 3 G551D trial to be low; whereas we judged this trial to have an unclear risk of detection bias and high risks of attrition bias and selective reporting bias (STRIVE 2011). With regards to the paediatric phase 3 G551D trial, disagreements were identified for participant and outcome assessor blinding, incomplete outcome data and selective reporting. The Whiting review judged this trial to have a low risk of detection bias, performance bias and selective outcome reporting bias and an unclear risk of attrition bias; while we judged the trial to have an

unclear risk of detection and performance bias and a high risk of attrition bias and selective outcome reporting bias ([ENVISION 2013](#)). The overall methodological quality of the phase 3 G551D trials was assessed to be higher in the Whiting review than in this review.

AUTHORS' CONCLUSIONS

Implications for practice

The F508del trial demonstrated no evidence to support the use of ivacaftor in those with the F508del mutation ([DISCOVER 2011](#)). The two G551D phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes at 24 and 48 weeks in children (over six years of age) and adults with cystic fibrosis (CF) and the G551D mutation ([ENVISION 2013](#); [STRIVE 2011](#)). The R117H trial demonstrated an improvement in the respiratory domain of the CFQ-R but no improvement in respiratory function ([KONDUCT 2015](#)). These trials were judged to have a moderate risk of bias.

Implications for research

Ivacaftor is the first intervention that corrects the underlying molecular defect in CF. It has demonstrated effectiveness in people with a class III mutation (G551D) and some effectiveness with class IV mutations (R117H) and has the potential to be used for other class III and IV mutations. Phase 3 trials examining ivacaftor in combination with a CFTR corrector (lumacaftor) in class II mutations (F508del) have been assessed in a separate Cochrane Review ([Southern 2018](#)).

As new mutation-specific therapies emerge, it is important that the lessons learnt from this review are taken on board, in particular with respect to trial design (cross-over trials are not appropriate given the potential for the therapies under consideration to

fundamentally change the natural history of the condition), selective reporting and the details of participant blinding. It is important that these trials examine valid outcomes that are relevant to people with CF and their families.

With novel therapies and approaches, such as ivacaftor, the reporting of adverse events is critical and this should be undertaken in a robust and consistent manner. Valid post-market surveillance is also essential.

In view of the cost implications for this therapy, ongoing health economic evaluations are required.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Accurso 2010

Methods	3-arm RCT of parallel design.
	Multicentre: 13 centres reported.

Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis (Review)

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Accurso 2010 (Continued)

Duration: 28 days.

Participants

Adults with CF with a G551D-CFTR mutation on at least 1 allele. Total of 19 participants were enrolled in Part 2 of this trial.

Gender n (%)

Total cohort: 10 (53) males; Treatment group 1: 3 (38) males; Treatment group 2: 4 (57) males; Control group: 3 (75) males.

White race n (%)

Total cohort: 19 (100); Treatment group 1: 8 (100); Treatment group 2: 7 (100); Control group: 4 (100).

Age median (range)

Total cohort: 21 (18 - 42) years; Treatment group 1: 23 (18 - 40) years; Treatment group 2: 21 (20 - 38) years; Control group: 24 (18 - 42) years.

BMI median (range)

Total cohort: 22 (20 - 25); Treatment group 1: 22 (20 - 23); Treatment group 2: 23 (20 - 25); Control group: 22 (21 - 23).

CFTR Genotype n (%)

G551D/F508del

Total cohort: 16 (84); Treatment group 1: 7 (88); Treatment group 2: 5 (71); Control group: 4 (100).

G551D/3849+10kbC→T

Total cohort: 1 (5); Treatment group 1: 0 (0); Treatment group 2: 1 (14) Control group: 0 (0).

G551D/621+1G→T

Total cohort: 1 (5); Treatment group 1: 1 (12); Treatment group 2: 0 (0); Control group: 0 (0).

G551D/G542X

Total cohort: 1 (5); Treatment group 1: 0 (0); Treatment group 2: 1 (14); Control group: 0 (0).

FEV₁ % predicted

Median (range)

Total cohort: 69 (40 - 122); Treatment group 1: 65 (42 - 122); Treatment group 2: 76 (40 - 106); Control group: 77 (53 - 112).

40% to <70% n (%)

Total cohort: 10 (53); Treatment group 1: 5 (62); Treatment group 2: 3 (43); Control group: 2 (50).

70% to <90% n (%)

Total cohort: 5 (26); Treatment group 1: 2 (25); Treatment group 2: 3 (43); Control group: 0 (0).

≥90% value n (%)

Total cohort: 4 (21); Treatment group 1: 1 (12); Treatment group 2: 1 (14); Control group: 2 (50).

Sweat chloride (mmol/L) mean (range)

Total cohort: 95.5 (84.8 - 115.8); Treatment group 1: 100.1 (86.8 - 112.5); Treatment group 2: 97.3 (84.8 - 115.8); Control group: 93.8 (88.0 - 109.5).

CFQ-R respiratory domain (points) mean (range)

Accurso 2010 (Continued)

Total cohort: 72.2 (16.7 - 88.9); Treatment group 1: 69.4 (16.7 - 88.9); Treatment group 2: 72.2 (61.1 - 83.3); Control group: 80.6 (38.9 - 83.3).

Interventions	<p>Treatment Group 1: VX-770 150 mg 2x daily (n = 8).</p> <p>Treatment Group 2; VX-770 250 mg 2x daily (n = 7).</p> <p>Control: placebo 2x daily (n = 4).</p>
Outcomes	<p>Primary outcome:</p> <p>1. Safety and adverse effects*</p> <p>Secondary outcomes:</p> <p>1. CFTR ion channel function.</p> <p>2. Change in QoL from baseline*</p> <p>3. Relative change from baseline in FEV₁*</p> <p>4. Relative change from baseline in FVC* and relative change from baseline in FEF₂₅₋₇₅</p> <p>5. Change from baseline in sweat chloride concentration.*</p>
Notes	<p>This was a 2-part trial; part 1 was of cross-over design and so not included in this review. We only present details of the second part which was of parallel design.</p> <p>The responsible funding body was Vertex Pharmaceuticals Incorporated.</p> <p>* These outcomes are presented in the review.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list generated by a statistician not otherwise associated with the trial.
Allocation concealment (selection bias)	Low risk	Participants assigned to a treatment arm using an Interactive Voice Response system according to a concealed randomisation list. This ensured the outcome assessors and participants were unaware of their allocation.
Blinding (performance bias and detection bias) All outcomes	Low risk	All trial personnel were blinded to participants' treatment. Exceptions to this were the laboratory staff and clinical pharmacist who prepared the medication. These trial personnel were not otherwise involved in the trial.
Blinding of participants	Unclear risk	All participants received the same number of tablets to maintain trial and personnel blinding. However, there is no report on details of the tablets (e.g. colour, size, taste).
Incomplete outcome data (attrition bias) All outcomes	Low risk	All together, 20 participants were randomised. 1 of 5 placebo participants withdrew due to withdrawal of consent prior to dosing (5% of total participants). All other participants were accounted for in the analysis.
Selective reporting (reporting bias)	High risk	The change from baseline in weight, although not reported as an outcome, was measured at day 1, 3, 14, 21 and 28. It was not reported in the publication.
Other bias	Low risk	Similar baseline characteristics and high adherence rate (100% [range, 92.6 - 100]).

DISCOVER 2011

Methods	<p>2-part RCT, both parts of parallel design. Participants who met set out criteria by the end of part A were eligible to proceed to part B of the trial.</p> <p>In part A, participants were randomly assigned to the intervention or control group in a 4:1 ratio respectively.</p> <p>Multicentre: 34 sites.</p> <p>Duration: part A lasted 16 weeks with part B, an open label extension, lasting up to 96 weeks.</p>
Participants	<p>140 participants randomised to treatment or placebo in a ratio of 4:1 (treatment group n = 112; placebo n = 28).</p> <p>Gender n (%)</p> <p>Treatment group: 58 (52) males; Placebo group: 16 (57) males.</p> <p>Age years, mean (SD)/median (range)</p> <p>Treatment group: 22.8 (10.3)/19.5 (12 - 52); Placebo group: 25.0 (8.4)/24.0 (12 - 39).</p> <p>CFTR Genotype</p> <p>All homozygous for the F508del-CFTR mutation.</p> <p>Height cm, median (range)</p> <p>Treatment group: 164.0 (139.0 - 189.6); Placebo group: 170.7 (145.6 - 184.0).</p> <p>Weight kg, median (range)</p> <p>Treatment group: 55.9 (35.1 - 99.8); Placebo group: 64.9 (44.2 - 100.3).</p> <p>BMI kg/m², median (range)</p> <p>Treatment group: 20.4 (15.7 - 31.6); Placebo group: 21.5 (17.9 - 40.8).</p> <p>Sweat chloride mmol/L, mean (SD)/median (range)</p> <p>Treatment group: 101.4 (10.3)/101.0 (79.5 - 135.5); Placebo group: 102.4 (7.9)/101.5 (91.0 - 122.0).</p> <p>FEV₁ % predicted, mean (SD)/median (range)</p> <p>Treatment group: 79.7 (22.7)/79.0 (40 - 129); Placebo group: 74.8 (24.1)/67.0 (43 - 127).</p>
Interventions	<p>Part A</p> <p>Treatment group: 150 mg of VX-770 (ivacaftor) 2x daily (n = 112).</p> <p>Control group: placebo (n = 28).</p> <p>Part B</p> <p>Treatment group: 150 mg of VX-770 2x daily.</p> <p>Control group: placebo.</p>
Outcomes	<p>Primary outcomes</p> <ol style="list-style-type: none"> 1. Adverse events, clinical laboratory values, ECGs, vital signs and physical examination.* 2. Absolute change in FEV₁ % predicted from baseline through 16 weeks.*

DISCOVER 2011 (Continued)

Secondary outcomes

1. Change from baseline through week 16 in sweat chloride concentration.*
2. Change from baseline through week 16 in weight.*
3. Participant reported health using the disease-specific CFQ-R through week 16.*

Notes

The responsible funding body was Vertex Pharmaceuticals Incorporated.

* These outcomes are presented in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomised to a treatment group (ivacaftor or placebo) in a 1:1 ratio using a randomisation code produced by Vertex.
Allocation concealment (selection bias)	Low risk	2 statisticians were involved. The trial statistician was blinded whereas the other was unblinded and not associated with the trial. The unblinded statistician generated the final randomisation list that was provided to the Interactive Voice Response/Interactive Web Response System.
Blinding (performance bias and detection bias) All outcomes	Low risk	All site personnel including the investigator, the trial monitor, and the Vertex trial team were blinded. Laboratory personnel or their designee were unblinded to the bio-analysis results, but remained blinded to treatment assignment. A clinical pharmacologist not involved in the conduct of the trial reviewed the bio-analysis results on an ongoing basis, but remained blinded to the participant's identity number and treatment assignment.
Blinding of participants	Unclear risk	The participants were 'blinded.' There is no report on details of the tablets (e.g. colour, size, taste).
Incomplete outcome data (attrition bias) All outcomes	High risk	8 withdrawals were reported in the ivacaftor group and 2 in the placebo group. Analyses were performed on all randomised participants who received at least 1 dose of the trial drug (ivacaftor n = 112 and placebo n = 28), as shown in table 3 of the full paper. However, when assessing the results on clinicaltrials.gov , the number in the ivacaftor group is presented as 111 instead of 112 for the outcomes change from baseline in sweat chloride and absolute change from baseline in FEV ₁ , suggesting an ITT analysis was not conducted.
Selective reporting (reporting bias)	High risk	The protocol for this trial was not available. There are no data for the change from baseline in FEV ₁ at day 15 or week 8. In addition no data were reported for the outcome measures FVC or FEF ₂₅₋₇₅ at 16 weeks. 1 withdrawal from the trial was due to "early termination per sponsor decision" and no additional information was provided. The author was approached for information on these missing data.
Other bias	Low risk	Similar baseline characteristics.

ENVISION 2013

Methods

2-arm RCT of parallel design. Participants were randomly assigned in a 1:1 ratio.

Multicentre: 29 centres reported.

ENVISION 2013 (Continued)

Duration: 48 weeks.

Participants

52 children enrolled onto this trial (control n = 26, intervention n = 26). Children aged 6 to 11 years were eligible for inclusion

Gender n (%)

Total cohort: 25 (48) males; Treatment group: 9 (35) males; Control group: 16 (62) males.

Age years, mean (range)

Total cohort: 8.9 (range 6 - 12); Treatment group: 8.9 (range 6 - 12); Control group: 8.9 (range 6 - 12).

CFTR Genotype
NB Participants with at least one G551D allele were eligible.

 44 participants had the *G551D/F508del* genotype. 8 participants had the *G551D-CFTR* mutation on one allele and a non-*F508del-CFTR* mutation on the second allele

Height cm, mean (range)

Total cohort: 133.8 (110.5 - 168.6); Treatment group: 134.9 (115.0 - 168.6); Control group: 132.6 (110.5 - 155.8).

Weight kg, mean (range)

Total cohort: 30.9 (17.8 - 62.6); Treatment group: 31.8 (18.8 - 62.6); Control group: 30.0 (17.8 - 46.3).

FEV₁ % predicted
Participants with baseline FEV₁ 40% - 105% of the predicted value for persons of their age, sex and height were eligible.
Mean (range)

Total cohort: 84.2 (44.0 - 133.8); Treatment group: 84.7 (52.4 - 133.8); Control group: 83.7 (44.0 - 116.3).

< 70%, n (%)

Total cohort: 12 (23); Treatment group: 4 (15); Control group: 8 (31).

> 70% to < 90%, n (%)

Total cohort: 18 (35); Treatment group: 12 (46); Control group: 6 (23).

> 90%, n (%)

Total cohort: 22 (42); Treatment group: 10 (38); Control group: 12 (46).

Sweat chloride mmol/L, mean (range)

Total cohort: 104.6 (54.0 - 128.0); Treatment group: 104.3 (54.0 - 128.0); Control group: 104.8 (92.0 - 121.0).

CFQ-R score for respiratory domain, mean (range)
Child version

Total cohort: 79 (25.0 - 100.0); Treatment group: 78 (33.3 - 100.0); Control group: 80 (25.0 - 100.0).

Parent/caregiver version

Total cohort: 81 (33.3 - 100.0); Treatment group: 81 (33.3 - 100.0); Control group: 81 (38.9 - 100.0).

Interventions
48-week RCT

ENVISION 2013 (Continued)

Treatment: VX-770 also known as ivacaftor 150 mg 2x daily (n = 26).

Control: placebo (n = 26).

Open-label extension

Treatment: VX-770 also known as ivacaftor 150 mg 2x daily.

Control: placebo.

Outcomes	<p>Primary Outcome</p> <p>1. Absolute change from baseline through week 24 in % predicted FEV₁ *</p> <p>Secondary outcomes</p> <p>Absolute changes from baseline in:</p> <ol style="list-style-type: none"> 1. % predicted FEV₁ (through week 48);* 2. weight (at weeks 24 and 48);* 3. concentrations of sweat chloride (a measure of CFTR function) (at weeks 24 and 48);* 4. participant-reported respiratory symptoms as assessed by the respiratory domain of the child version of the CFQ-R (at weeks 24 and 48);* 5. safety.*
Notes	<p>The responsible funding body was Vertex Pharmaceuticals Incorporated.</p> <p>* These outcomes are presented in the review.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants randomised in a 1:1 ratio, however method not reported.
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double blind. It is not stated how attending researchers were blinded.
Blinding of participants	Unclear risk	Described as double blind. It is not stated how participants were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>In the paediatric phase 3 G551D trial 4/52 participants (7.7%) withdrew from the total trial population. All 4 participants withdrew from the placebo group.</p> <p>In the analysis of the following outcomes participant data were excluded:</p> <ul style="list-style-type: none"> • absolute change from baseline in % predicted FEV₁ (1 participant excluded from placebo group) • change from baseline in sweat chloride concentration (6 participants excluded) • CFQ-R respiratory domain child version (1 participant excluded from placebo group).

ENVISION 2013 (Continued)

		A modified intention-to-treat analysis (not per protocol) was employed, where data were excluded from the analysis (ENVISION 2013).
Selective reporting (reporting bias)	High risk	At each visit (days 1, 15 and weeks 8, 16, 24, 32, 40 and 48) participant FVC measurements were recorded. These results were not published in the full text, nor made available upon request. Data for the relative change from baseline in FEV ₁ (an important outcome in such a trial) were not reported at 48 weeks.
Other bias	Low risk	Similar baseline characteristics and high adherence rate.

KONDUCT 2015

Methods	Phase 3, double-blind, RCT of parallel design. Multicentre: 31 centres reported. Duration: 24 weeks with an open-label extension phase for up to 104 weeks. Participants were not re-randomised for the extension phase.
Participants	69 participants aged 6 years or older with CF with at least 1 allele of the R117H-CFTR mutation were enrolled. Total: control n = 35, intervention n = 34; 6 - 11 years control n = 8, intervention n = 9; ≥ 18 years control n = 26, intervention n = 24. Age years, mean (SD) Overall: treatment group: 29.2 (16.6); placebo group: 32.7 (17.4). 6 - 11 years: treatment group 8.8 (1.9); placebo group 9 (1.6). ≥ 18 years: treatment group 37.5 (12.1); placebo group 40.6 (12.6). Gender n (%) Overall: treatment group 19 (56%) females; placebo group 20 (57%) females. 6 - 11 years: treatment group 5 (56%) females; placebo group 3 (38%) females. ≥ 18 years: treatment group 13 (54%); placebo group 16 (62%). Weight kg, mean (SD) Overall: treatment group: 66.1 (25.5); placebo group: 62.8 (25.4). 6 - 11 years: treatment group 32.9 (13.3); placebo group 34.0 (9.1). ≥ 18 years: treatment group 77.9 (16.7); placebo group 71.7 (22.5). BMI kg/m², mean (SD) Overall: treatment group: 24.5 (6.3); placebo group: 23.1 (6). 6 - 11 years: treatment group 17.6 (3.3); placebo group 17.1 (2.4). ≥ 18 years: treatment group 26.9 (5.2); placebo group 24.9 (5.7). FEV₁ % predicted, mean (SD) <i>Participants with baseline FEV₁ 40% to 90% (for participants aged 12 years or older) or 40% to 105% (for participants aged 6 to 11 years) of the predicted value for age, sex, and height were eligible.</i> Overall: treatment group: 75.7 (19.3); placebo group: 70.2 (18.9). 6 - 11 years: treatment group 97.5 (8.6); placebo group 94.0 (8.4).

KONDUCT 2015 (Continued)

≥ 18 years: treatment group 67.0 (15.4); placebo group 62.3 (14.4).

FEV₁ % predicted, n (%)

<70%

Overall: treatment group: 13 (38%); placebo group: 15 (43%).

6 - 11 years: treatment group 0; placebo group 0.

≥ 18 years: treatment group 13 (54%); placebo group 15 (58%).

≥ 70 to ≤ 90%

Overall: treatment group: 14 (41%); placebo group: 14 (40%).

6 - 11 years: treatment group 3 (33%); placebo group 2 (25%).

≥ 18 years: treatment group 10 (42%); placebo group 11 (42%).

> 90%

Overall: treatment group: 7 (21%); placebo group: 6 (17%).

6 - 11 years: treatment group 6 (67%); placebo group 6 (75%).

≥ 18 years: treatment group 1 (4%); placebo group 0.

Sweat chloride n/mmol/l, mean (SD)

Overall: treatment group: 32/67.3 (23.5); placebo group: 35/73.4 (19.7).

6 - 11 years: treatment group 8/64.2 (22.6); placebo group 8/74.7 (28.6).

≥ 18 years: treatment group 23/69.3 (24.1); placebo group 26/73.0 (17.3).

CFQ-R score for respiratory domain, n/score, mean (SD)

Overall: treatment group: 33/75.3 (20.1); placebo group: 34/66.4 (24.4).

6 - 11 years: treatment group 8/92.7 (7.0); placebo group 7/91.7 (6.8).

≥ 18 years: treatment group 24/68.4 (19.1); placebo group 26/59.2 (23.2).

CFTR genotype (Arg117His/Phe508del), mean (SD)

Overall: treatment group: 28 (82%); placebo group: 25 (71%).

6 - 11 years: treatment group 8 (89%); placebo group 6 (75%).

≥ 18 years: treatment group 19 (79%); placebo group 19 (73%).

Interventions	Ivacaftor 150 mg orally 2x daily for 24 weeks.
Outcomes	<p>Primary outcome:</p> <p>1. absolute change from baseline in % predicted FEV₁ (through 24 weeks).</p> <p>Secondary outcomes:</p> <p>1. change from baseline in BMI (through 24 weeks);</p> <p>2. change from baseline in sweat chloride (through 24 weeks);</p> <p>3. change from baseline in the respiratory domain of the CFQ-R (through 24 weeks);</p> <p>4. time to first pulmonary exacerbation (through 24 weeks);</p> <p>5. number of participants with adverse events and serious adverse events (through 24 weeks).</p>
Notes	The responsible funding body was Vertex Pharmaceuticals Incorporated.

KONDUCT 2015 (Continued)

* These outcomes are presented in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were assigned to receive placebo or ivacaftor (1:1) via a randomisation specification and randomisation code. The code list was sent to the IVRS.
Allocation concealment (selection bias)	Low risk	A masked biostatistician created the randomisation specification and dummy randomisation code, this was then approved by an unmasked biostatistician not associated with the trial, prior to generating the final randomisation list. An unblinded quality check biostatistician reviewed and approved final randomisation list. The biostatistician not associated with the trial provided the final list to IVRS.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double blinded. Other than the biostatisticians, it is not stated which trial personnel were blinded or how they were blinded.
Blinding of participants	Unclear risk	Described as double blinded. There is no report on details of the tablets (e.g. colour, size, taste).
Incomplete outcome data (attrition bias) All outcomes	Low risk	In total, 69 participants were randomised. 2 withdrew from the intervention group with reasons given. A full analysis set included all randomised participants who received at least 1 dose of trial drug.
Selective reporting (reporting bias)	High risk	<p>No protocol was available online to compare outcomes in the protocol with those published. The author was approached for further information and a protocol synopsis provided. This showed the following tertiary outcomes which were reported in the protocol but no with no published results.</p> <ol style="list-style-type: none"> 1. PK parameter estimates of ivacaftor and metabolites, M1 and M6, derived from plasma concentration-time data 2. Change from baseline in nonrespiratory domains of the CFQ-R 3. Change from baseline in weight 4. Change from baseline in height 5. CF-related complications (pancreatitis or distal ileal obstruction syndrome) 6. Change from baseline in inflammatory mediators 7. Change from baseline in qualitative microbiological cultures 8. Change from baseline in IRT 9. Change from baseline in fecal elastase-1
Other bias	Low risk	<p>Similar baseline characteristics.</p> <p>There were only 2 participants between 12 - 17 years of age so no age subgroup statistical analysis were performed for this group. They were included in overall analysis. No comment was made regarding the reason for low enrolment in this age group.</p>

STRIVE 2011

Methods	<p>2-arm RCT of parallel design.</p> <p>Multicentre international trial with participants from Europe, North America and Australia.</p>
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STRIVE 2011 (Continued)

Duration: up to 48 weeks.

Participants

Total of 167 participants recruited: treatment group n = 84; control group n = 83.

 Participants (at least 12 years of age) were stratified according to age (< 18 years versus ≥18 years) and pulmonary function (under 70% versus 70% and over of the predicted FEV₁).

Gender, n (%)

Total cohort: 77 (48) males; Treatment group: 39 (47) males; Control group: 38 (49) males.

Non-Hispanic or white, n (%)

Total cohort: 158 (98); Treatment group: 81 (98); Control group: 77 (99).

Geographic distribution, n (%)
North America

Total cohort: 100 (62); Treatment group: 50 (60); Control group: 50 (64).

Europe

Total cohort: 42 (26); Treatment group: 23 (28); Control group: 19 (24).

Australia

Total cohort: 19 (12); Treatment group: 10 (12); Control group: 9 (12).

Age years, mean (range)

Total cohort: 25.5 (12 - 53); Treatment group: 26.2 (12 - 53); Control group: 24.7(12 - 53).

Age distribution, n (%)
Under 18 years

Total cohort: 36 (22); Treatment group: 19 (23); Control group: 17 (22).

18 years and over

Total cohort: 125 (78); Treatment group: 64 (77); Control group: 61 (78).

Height cm, mean (range)

Total cohort: 167.1 (142.2 - 189.8); Treatment group: 167.7 (142.8 - 185.0); Control group: 166.5 (142.2 - 189.8).

Weight kg, mean (range)

Total cohort: 61.5 (30.2 - 109.9); Treatment group: 61.7(30.2 - 107.2); Control group: 61.2(31.9 - 109.9).

BMI, mean (range)

Total cohort: 21.8 (14.8 - 38.9); Treatment group: 21.7 (14.8 - 38.9); Control group: 21.9 (15.2 - 38.6).

Positive for *Pseudomonas aeruginosa*, n (%)

Total cohort: 122 (76); Treatment group: 64 (77); Control group: 57 (73).

CFTR Genotype
Non-G551D-CFTR allele n (%), NB Only participants with at least 1 G551D allele were eligible.
Class I

Total cohort: 21 (13); Treatment group: 10 (12); Control group: 11 (14).

STRIVE 2011 (Continued)

Class II

Total cohort: 132 (82); Treatment group: 70 (84); Control group: 62 (79).

Class III

Total cohort: 1 (1); Treatment group: 0; Control group: 1 (1).

Class IV

Total cohort: 4 (2); Treatment group: 2 (2); Control group: 2 (3).

Class V

Total cohort: 1 (1); Treatment group: 0; Control group: 1 (1).

Unknown

Total cohort: 2(1); Treatment group: 1(1); Control group: 1(1).

FEV₁ % predicted, mean (range)

NB Only participants with baseline FEV₁ 40% - 90% of the predicted value for persons of their age, sex and height were eligible.

Total cohort: 63.6 (31.6 - 98.2); Treatment group: 63.5 (37.3 - -98.2); Control group: 63.7 (31.6 - 97.1).

FEV₁ distribution, n (%)
Under 70% of predicted value

Total cohort: 94 (58); Treatment group: 49 (59); Control group: 45 (58).

70% and over of predicted value

Total cohort: 67 (42); Treatment group: 34 (41); Control group: 33 (42).

Sweat chloride mmol/L, mean (range)

Total cohort: 100.2 (58.0 - 128.0); Treatment group: 100.4 (74.5 - 128.0); Control group: 100.1 (58.0 - 121.5).

Interventions
48-week RCT

Treatment: VX-770 also known as ivacaftor 150 mg 2x daily (n = 83).

Control: placebo (n = 78).

Open-label extension

Treatment: VX-770 also known as ivacaftor 150 mg 2x daily.

Control: placebo.

Outcomes
Primary outcome

1. Absolute change from baseline through week 24 in % predicted FEV₁.*

Secondary outcomes

1. Change from baseline through week 48 in % predicted FEV₁.*

2. Time to the first pulmonary exacerbation through week 24 and week 48. *

3. Participant-reported health using the disease-specific CFQ-R.*

STRIVE 2011 (Continued)

4. Change in weight from baseline to week 24 and week 48. *
5. Change from baseline in the concentration of sweat chloride through week 24 and week 48.*

Tertiary endpoints

1. Number and duration of pulmonary exacerbations.*
2. Total number of days of hospitalisation for pulmonary exacerbations.*
3. Need for antibiotic therapy for sinopulmonary signs or symptoms.*

Notes * These outcomes are presented in the review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Eligible participants were randomised to a treatment group (ivacaftor or placebo) in a 1:1 ratio using a randomisation code produced by Vertex.
Allocation concealment (selection bias)	Low risk	2 biostatisticians involved in randomisation process; 1 blinded trial statistician and 1 unblinded statistician not involved in the trial. The statistician not associated with the trial generated the final randomisation list that was provided to an Interactive Voice Response System.
Blinding (performance bias and detection bias) All outcomes	Low risk	All site personnel including the investigator, the trial monitor, and the Vertex trial team were blinded. Laboratory personnel or their designee were unblinded to the bio-analysis results, but remained blinded to treatment assignment. A clinical pharmacologist not involved in the conduct of the trial reviewed the bio-analysis results on an ongoing basis, but remained blinded to the participant's identity number and treatment assignment.
Blinding of participants	Unclear risk	All participants were stated to have been blinded, however, details of the tablets have not been provided (e.g. colour, size, taste).
Incomplete outcome data (attrition bias) All outcomes	High risk	167 participants were randomised - 83 participants to the placebo group and 84 participants to the ivacaftor group. 10 participants withdrew from the placebo group and 6 participants withdrew from the ivacaftor group. 78 participants in the placebo group and 83 participants in the ivacaftor group (total n = 161) were included in the analysis. The review authors found a minor discrepancy in the number of participants analysed for the outcomes measures: change from baseline in CFQ-R respiratory domain scores (total analysed n = 151) and the change from baseline in sweat chloride concentration (total analysed n = 152) (STRIVE 2011).
Selective reporting (reporting bias)	High risk	<p>Protocol provided. The following tertiary outcomes were reported in the protocol, but results for these outcomes were not published.</p> <ol style="list-style-type: none"> 1. Change from baseline in oxygen saturation through weeks 24 and 48. 2. Change from baseline in EuroQol Questionnaire (EQ-5D) through weeks 24 and 48. 3. Outpatient sick visits to the clinic or hospital for CF-related complications through weeks 24 and 48. <p>In addition to this, results were only reported for CFQ-R domains where improvements were seen in the ivacaftor group.</p>
Other bias	Low risk	Similar baseline characteristics.

STRIVE 2011 (Continued)

The responsible funding body was Vertex Pharmaceuticals Incorporated.

ALT: alanine transaminase
 AST: aspartate transaminase
 BMI: body mass index
 CF: cystic fibrosis
 CFQ-R: cystic fibrosis questionnaire - revised
 CFTR: cystic fibrosis transmembrane regulator
 ECG: electro-cardiogram
 FEF₂₅₋₇₅: forced expiratory flow at 25-75% of the pulmonary volume
 FEV₁: forced expiratory volume at one second
 FVC: forced vital capacity
 IRT: immunoreactive trypsinogen
 ITT: intention to treat
 IVRS: interactive voice response system
 MRI: magnetic resonance image
 PK: pharmacokinetic
 QoL: quality of life
 RCT: randomised controlled trial
 ULN: upper limit of normal

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Accurso 2013	Secondary analysis on trials of cross-over design.
ALBATROSS 2017	Intervention to correct molecular defect, not a potentiator.
Altes 2011	Trial of cross-over design.
ARRIVAL 2018	Single-arm interventional study, no comparison to placebo.
Berkers 2017	Trial of cross-over design.
Chadwick 1998	Intervention to correct molecular defect, not a potentiator.
Clancy 2012	Intervention to correct molecular defect, not a potentiator.
Davies 2012	Trial of cross-over design.
Davies 2016	Single-arm interventional trial.
Edgeworth 2017	Trial of cross-over design.
EudraCT Number: 2014-000817-30	Single-arm interventional study. Intervention was not with CFTR potentiator.
EudraCT Number: 2016-001440-18	Observational study. Intervention was not with CFTR potentiator.
EudraCT Number: 2016-001619-19	Trial of cross-over design. Intervention was not CFTR potentiator.
EUudraCT Number: 2016-001785-29	Intervention used antibiotic therapy rather than CFTR potentiator.

Study	Reason for exclusion
FLAMINGO 2017	Intervention to correct molecular defect, not a potentiator.
Horsley 2018	Intervention to correct molecular defect, not a potentiator.
Hubert 2018	Retrospective cohort design.
Kerem 2014	Intervention for stop codon mutations.
KONNECTION 2013	Trial of cross-over design.
McCarty 2002	Intervention to correct molecular defect, not a potentiator.
McGarry 2015	Trial of cross-over design.
NCT01549314	Prospective cohort study design.
NCT01685801	Trial of cross-over design.
NCT01784419	Trial of cross-over design.
NCT01863238	Prospective cohort study design.
NCT01946412	Single-arm interventional study.
NCT02039986	Prospective cohort study design.
NCT02141464	Prospective cohort study design.
NCT02310789	Single-arm interventional study. Enrolled healthy participants only.
NCT02311140	Prospective cohort study design.
NCT02323100	Intervention was glycerol phenylbutyrate corrector therapy, not a potentiator.
NCT02443688	Intervention was with anti-inflammatory drug rather than CFTR potentiator.
NCT02445053	Prospective cohort study design.
NCT02690519	Single-arm interventional trial design.
NCT02707562	Single-arm interventional trial design.
NCT02709109	Trial of cross-over design.
NCT02718495	Intervention was with a CFTR amplifier versus placebo.
NCT02722057	Cohort study design.
NCT02724527	Compared another mutation-specific therapy (corrector) with placebo.
NCT02742519	Trial of cross-over design.
NCT02759562	Intervention was with a monoclonal antibody rather than CFTR potentiator.
NCT02934698	Single-arm interventional study.

Study	Reason for exclusion
NCT03068312	Trial of cross-over design.
NCT03256799	Single-arm interventional study. Intervention was not CFTR potentiator.
NCT03256968	Single-arm interventional study. Intervention was not CFTR potentiator.
NCT03258424	Intervention was with a CFTR amplifier versus placebo.
NCT03277196	Non-randomised, intervention compared to observational arm, not placebo.
NCT03390985	Prospective cohort study design.
NCT03474042	Intervention was with CFTR corrector versus placebo.
NCT03652090	Cohort study design. Intervention was a cell sampling procedure.
PERSIST 2014	Single-arm interventional study.
Pradal 2002	Intervention for stop codon mutations.
RIO-CF 2017	Intervention was a soluble guanylate cyclase stimulator, not a potentiator.
Romano 2000	Intervention for stop codon mutations.
Rubenstein 1998	Intervention to correct molecular defect, not a potentiator.
Rubenstein 2006	Intervention to correct molecular defect, not a potentiator.
Seliger 2015	Observational trial.
Sermet-Gaudelus 2010	Intervention for stop codon mutations.
TOPIC 2018	Participants with CF were excluded.
Wilschanski 2003	Intervention for stop codon mutations.
Wilschanski 2008	Intervention for stop codon mutations.
Zeitlin 2002	Intervention to correct molecular defect, not a potentiator.

CFTR: cystic fibrosis transmembrane regulator

Characteristics of studies awaiting assessment *[ordered by study ID]*

Kazani 2016

Methods	RCT, double-blind. Phase 2. Parallel design. Duration: 2 weeks (with follow-up to Day 42).
Participants	Eligibility criteria (Part 3)

Kazani 2016 (Continued)

Confirmed diagnosis of CF.

Heterozygous with one allele represented as any CFTR mutation and the other allele must represent a class III, IV, V, VI CFTR mutation.

Aged over 18 years.

BMI: 15 - 35 kg/m².

FEV₁ 40% - 100% .

Oxygen saturation > 90% on room air.

2016 abstract describes an interim analysis of 40 participants who were enrolled into Part 3 of the trial. According to the clinicaltrials.gov record, 49 participants with CF with a class III, IV, V, or VI mutation on one allele and any other CFTR mutation on the other allele were randomised and all completed the trial.

Randomised: overall n = 49; intervention 1 n = 6; intervention 2 (multiple mutations) n = 12, intervention 2 (homozygous for F508del) n = 19; control group n = 12.

Age, mean (SD): intervention 1 - 39.3 (5.47) years; intervention 2 (multiple mutations) - 32.7 (13.77) years, intervention 2 (homozygous for F508del) - 27 (5.44) years; control - 27.9 (6.37) years.

Gender split: overall - 30 males, 19 females; intervention 1 - 5 males, 1 female; intervention 2 (multiple mutations) - 7 males, 5 females, intervention 2 (homozygous for F508del) - 10 males, 9 females; control - 8 males, 4 females.

Interventions

Intervention 1 (n = 4): QBW251 150 mg twice daily (oral capsule).

Intervention 2 (n = 12): QBW251 450 mg twice daily (oral capsule).

Control (n = 10): placebo (oral capsule).

Outcomes

Primary outcomes

1. Change in LCI
2. Adverse events

Secondary outcomes

1. Change in FEV₁
2. Change in CFQR reported outcomes
3. Change in sweat chloride

Notes

Only part 3 of trial which includes people with CF is eligible to be included in review. Parts 1 and 2 enrolled healthy participants.

The trial has been terminated, but some results are posted on clinicaltrials.gov.

Sponsor is Novartis.

Uttamsingh 2016

Methods

RCT, double-blind.

Phase 1.

Parallel design.

Uttamsingh 2016 (Continued)

Duration: 7 days.

Participants	40 participants (each cohort enrolled 10 new participants; 8 participants received active drug and 2 received placebo (4:1 randomisation)).
Interventions	<p>Intervention 1: CTP-656 75 mg once daily.</p> <p>Intervention 2: CTP-656 150 mg once daily.</p> <p>Intervention 3: CTP-656 225 mg once daily.</p> <p>Control: placebo.</p> <p>All participants were dosed under fed conditions; a high-fat breakfast was provided on Day 1 through Day 7 approximately 30 minutes prior to dosing. Dose escalation was initiated only after safety and tolerability were found to support proceeding to the higher dose.</p>
Outcomes	PK blood samples were collected at several time points post-dose on Day 1 and Day 7, and at 12 and 24 hours post-dose on Day 2 through Day 6. The plasma concentrations of CTP-656 and its metabolites, D-M1 and D-M6 were analysed by LC-MS/MS. The steady-state PK profiles for CTP-656, D-M1 and D-M6 were evaluated for the 3 dose cohorts.
Notes	<p>The author was approached for further information.</p> <p>Drug initially developed by Concert Pharmaceuticals Inc. before being sold to Vertex for further development in 2017 and being re-named VX-561.</p>

BMI: body mass index

CF: cystic fibrosis

CFQ-R: cystic fibrosis questionnaire-revised

CFTR: cystic fibrosis transmembrane regulator

 FEV₁: forced expiratory volume at one second

LCI: lung clearance index

LC-MS/MS: liquid chromatography with mass spectrometry

PK: pharmacokinetic

RCT: randomised controlled trial

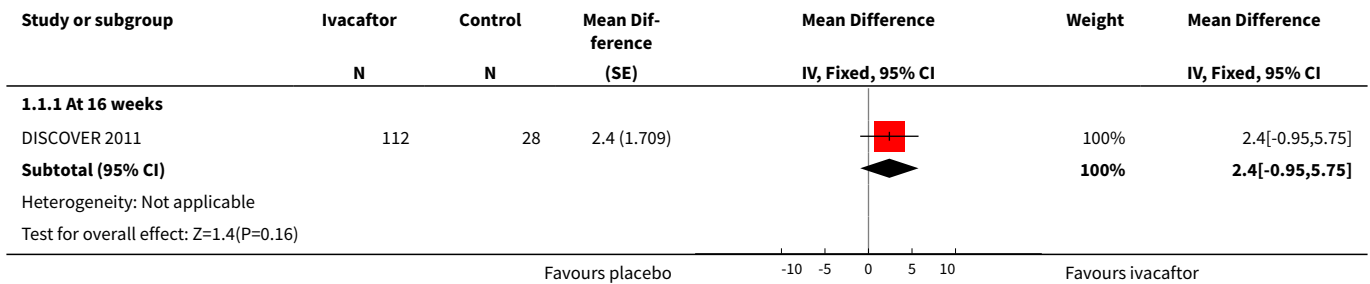
DATA AND ANALYSES
Comparison 1. Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV ₁ - relative change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 At 16 weeks	1	140	Mean Difference (Fixed, 95% CI)	2.4 [-0.95, 5.75]
2 Adverse effects	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 Pulmonary exacerbation	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.44 [0.14, 1.41]
2.2 Upper respiratory tract infection	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.18, 11.10]

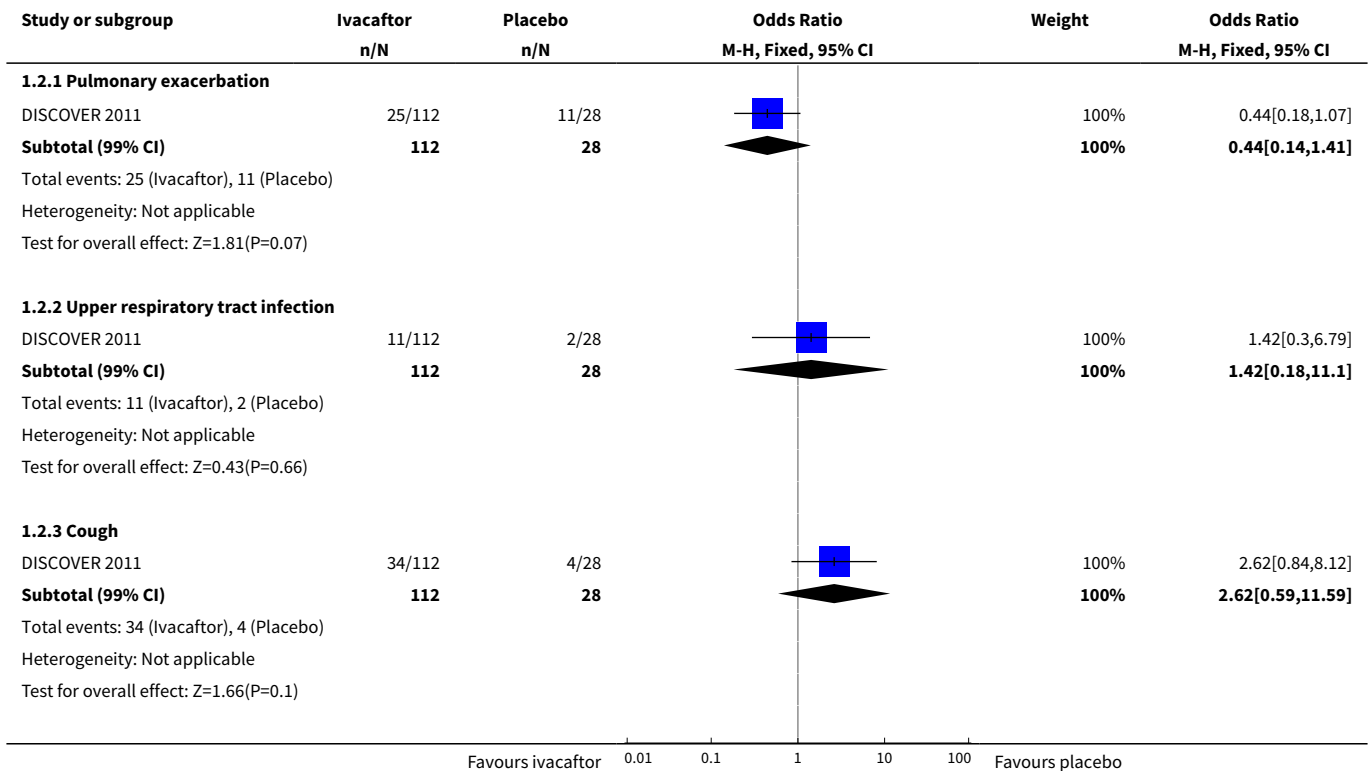
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Cough	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.62 [0.59, 11.59]
2.4 Productive cough	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.36 [0.15, 37.71]
2.5 Headache	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.42 [0.18, 11.10]
2.6 Nasal congestion	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.71 [0.22, 13.09]
2.7 Sinusitis	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.08 [0.13, 33.75]
2.8 Oropharyngeal pain	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.14, 4.90]
2.9 Upper abdominal pain	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.8 [0.11, 29.87]
2.10 Nausea	1	140	Odds Ratio (M-H, Fixed, 95% CI)	2.65 [0.17, 41.76]
2.11 Diarrhea	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.74 [0.08, 6.49]
2.12 Contact dermatitis	1	140	Odds Ratio (M-H, Fixed, 95% CI)	3.48 [0.08, 158.51]
2.13 Rash	1	140	Odds Ratio (M-H, Fixed, 95% CI)	5.23 [0.12, 228.54]
2.14 Fatigue	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.12, 4.45]
2.15 Pyrexia	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.14, 9.20]
2.16 Increase in C-reactive protein	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.53 [0.09, 26.08]
3 Severity of adverse effects of therapy with regards to study drug interruption (moderate) or discontinuation (severe)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Adverse effect requiring study drug interruption (moderate)	1	140	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.06, 27.62]
3.2 Adverse effect requiring study drug discontinuation (severe)	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.06, 2.25]
4 FEV₁ % predicted - absolute change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 At 16 weeks	1	140	Mean Difference (Fixed, 95% CI)	1.70 [-0.65, 4.05]
5 Antibiotic treatment of sinopulmonary signs or symptoms	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 At 16 weeks	1	140	Odds Ratio (M-H, Fixed, 95% CI)	0.56 [0.24, 1.30]
6 Weight (kg) - change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only

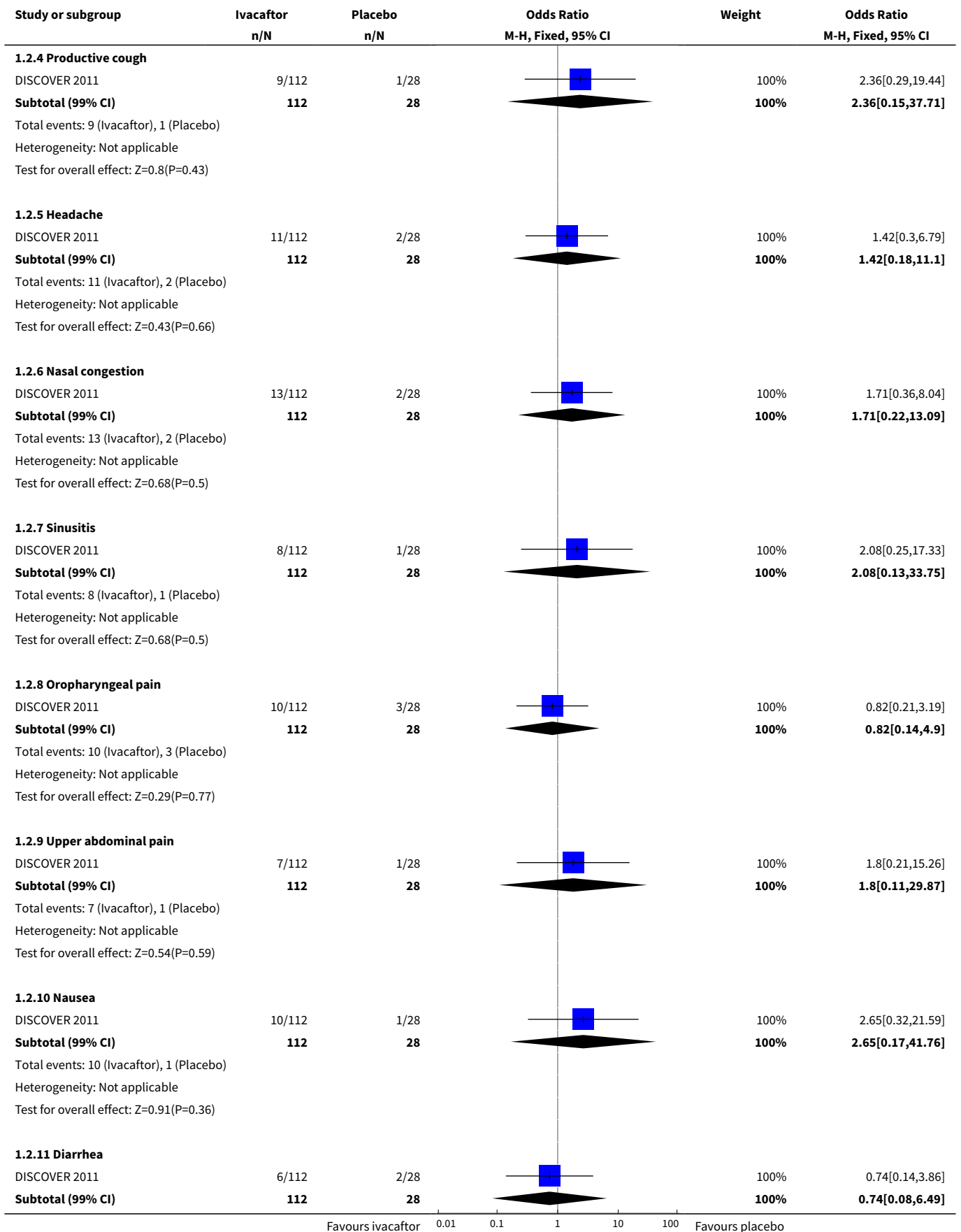
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 At 16 weeks	1	140	Mean Difference (Fixed, 95% CI)	-0.2 [-1.18, 0.78]
7 Sweat chloride concentration - change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
7.1 At 16 weeks	1	140	Mean Difference (Fixed, 95% CI)	-2.9 [-5.60, -0.20]

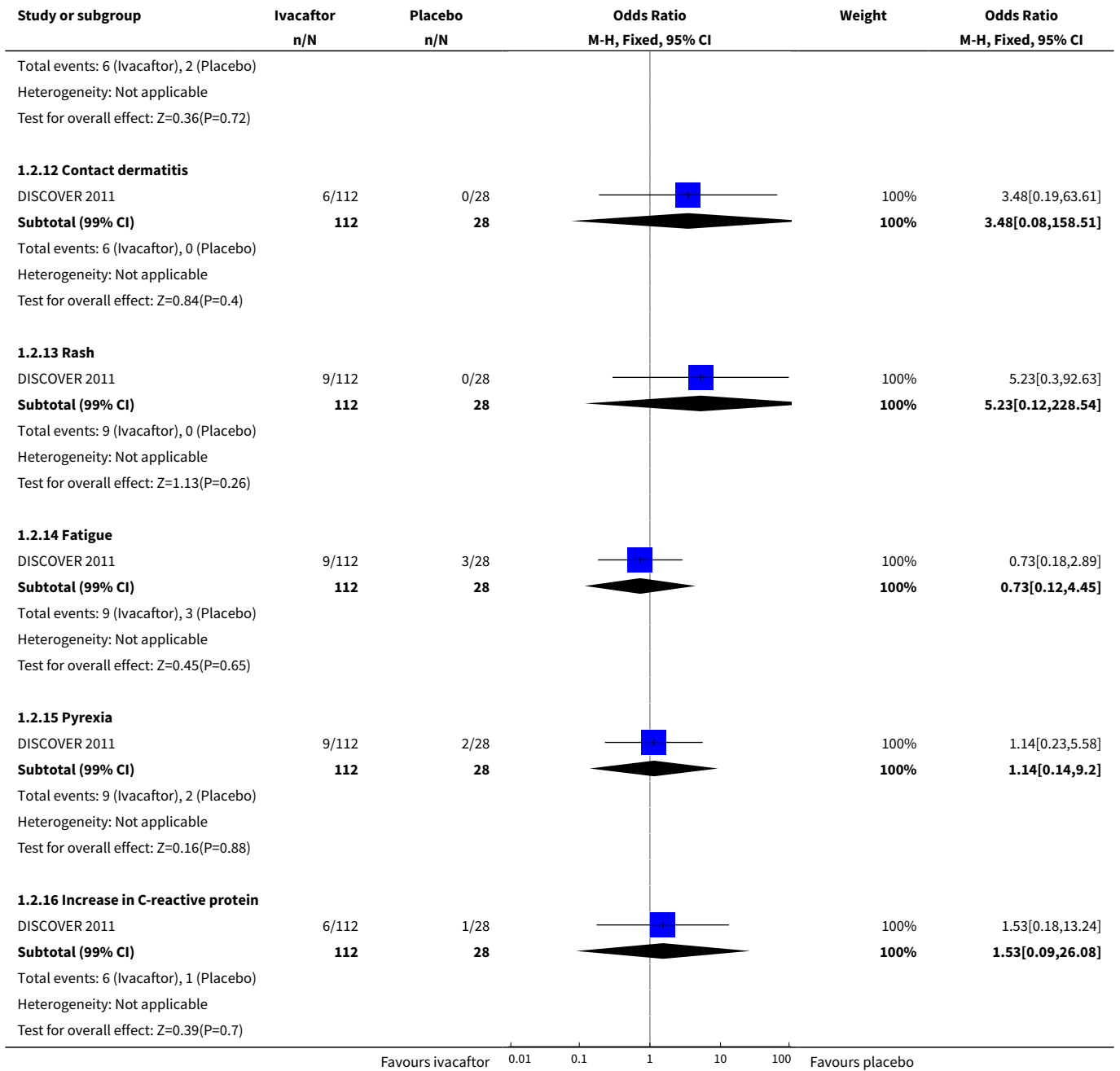
Analysis 1.1. Comparison 1 Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation, Outcome 1 FEV₁ - relative change from baseline.



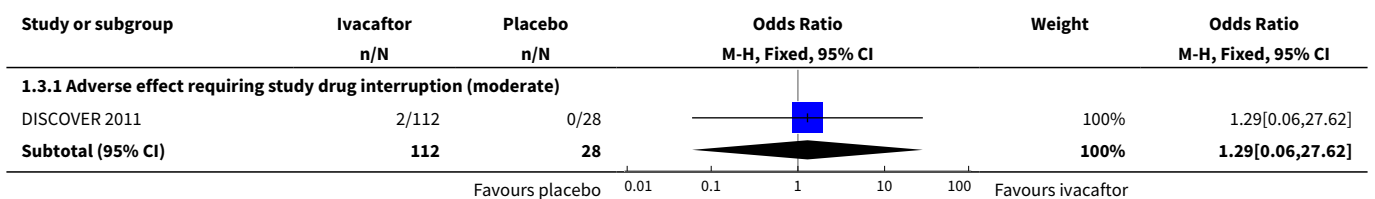
Analysis 1.2. Comparison 1 Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation, Outcome 2 Adverse effects.

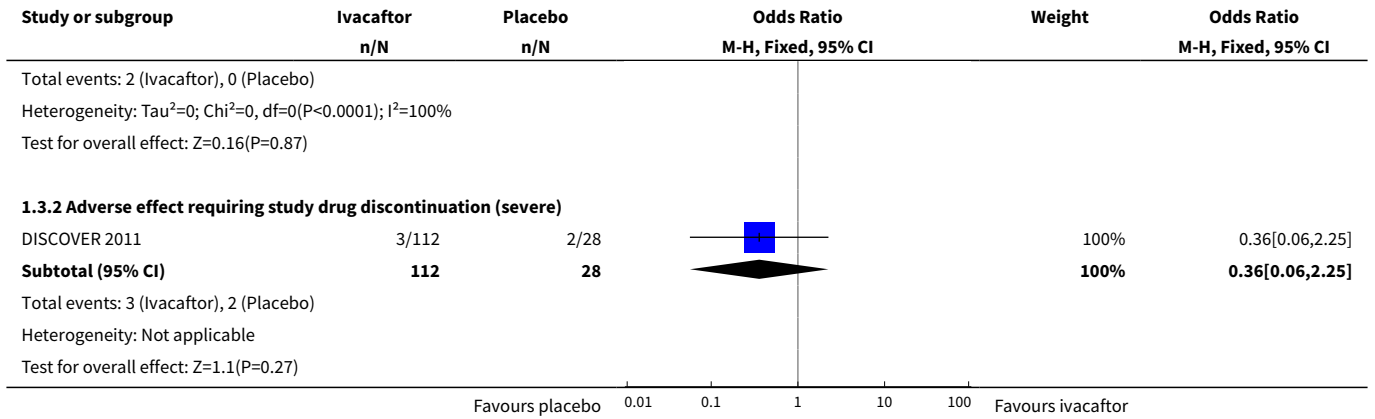




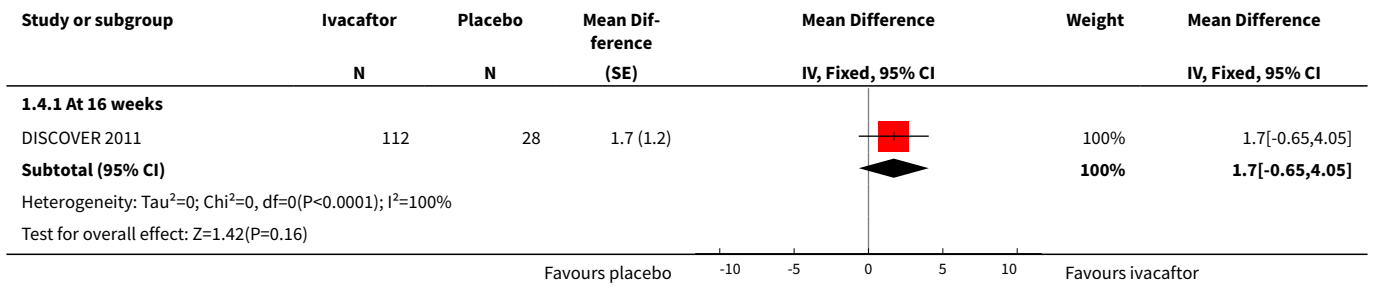


Analysis 1.3. Comparison 1 Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation, Outcome 3 Severity of adverse effects of therapy with regards to study drug interruption (moderate) or discontinuation (severe).

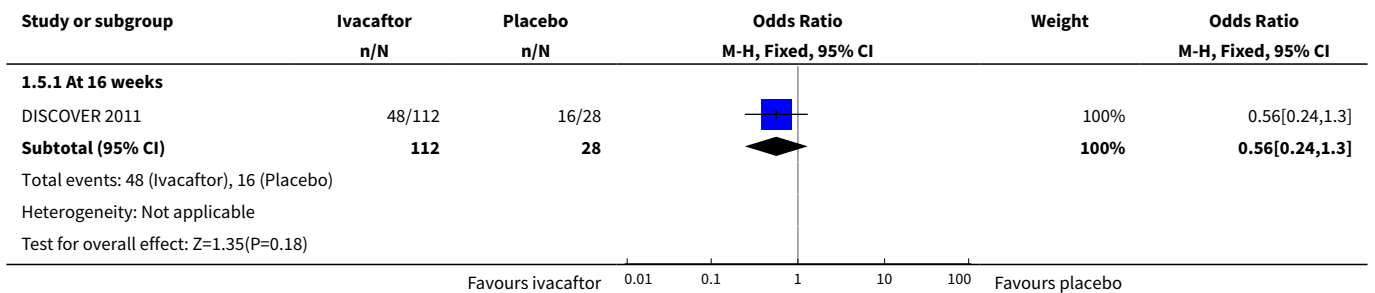




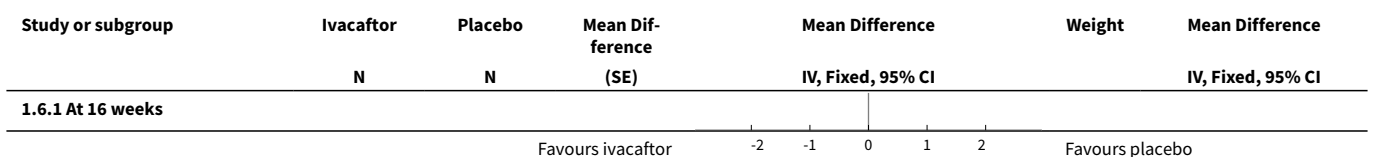
Analysis 1.4. Comparison 1 Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation, Outcome 4 FEV₁ % predicted - absolute change from baseline.

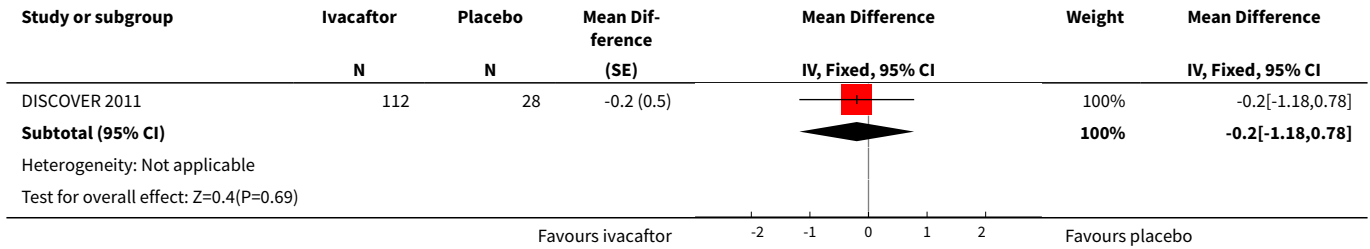


Analysis 1.5. Comparison 1 Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation, Outcome 5 Antibiotic treatment of sinopulmonary signs or symptoms.

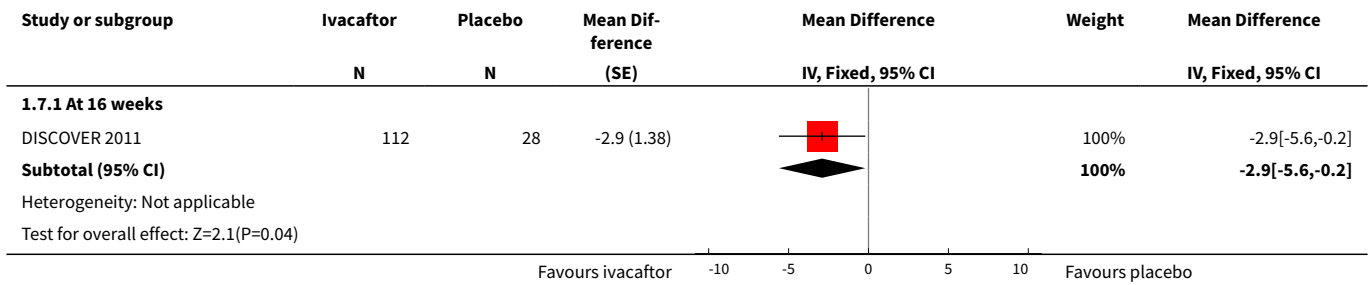


Analysis 1.6. Comparison 1 Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation, Outcome 6 Weight (kg) - change from baseline.





Analysis 1.7. Comparison 1 Ivacaftor (VX-770) versus placebo in people with the F508del CFTR mutation, Outcome 7 Sweat chloride concentration - change from baseline.



Comparison 2. Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CFQ-R score (respiratory domain, child version) - adjusted change from baseline	2		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 At 24 weeks	2	51	Mean Difference (Fixed, 95% CI)	6.1 [-1.35, 13.55]
1.2 At 48 weeks	1	51	Mean Difference (Fixed, 95% CI)	5.1 [-1.56, 11.76]
2 CFQ-R score (respiratory domain score, parent/care-giver version) - adjusted change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 At 24 weeks	1	52	Mean Difference (Fixed, 95% CI)	5.9 [0.41, 11.39]
2.2 At 48 weeks	1	52	Mean Difference (Fixed, 95% CI)	4.9 [-0.39, 10.19]
3 CFQ-R score (respiratory domain score, pooled) - absolute change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 At 24 weeks	1	151	Mean Difference (Fixed, 95% CI)	8.1 [4.77, 11.43]
3.2 At 48 weeks	1	151	Mean Difference (Fixed, 95% CI)	8.6 [5.27, 11.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 FEV ₁ - mean relative change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
4.1 24 weeks	1	161	Mean Difference (Fixed, 95% CI)	16.9 [13.60, 20.20]
4.2 48 weeks	1	161	Mean Difference (Fixed, 95% CI)	16.8 [13.50, 20.10]
5 Adverse events occurring in greater than or equal to 5% of trial participants	2		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
5.1 Pulmonary exacerbation	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.64 [0.30, 1.33]
5.2 Cough	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.57 [0.27, 1.19]
5.3 Productive Cough	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.81 [0.29, 2.24]
5.4 Pulmonary function test decreased	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.29 [0.07, 1.14]
5.5 Wheezing	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.12 [0.28, 4.52]
5.6 Rales	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.86 [0.28, 2.69]
5.7 Oropharyngeal pain	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.26 [0.52, 3.05]
5.8 Nasal congestion	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.39 [0.55, 3.53]
5.9 Nasopharyngitis	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.32 [0.46, 3.76]
5.10 Upper respiratory tract infection	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.91 [0.74, 4.90]
5.11 Bronchitis	1	52	Odds Ratio (M-H, Fixed, 99% CI)	1.57 [0.13, 18.48]
5.12 Otitis media	1	52	Odds Ratio (M-H, Fixed, 99% CI)	4.55 [0.23, 89.19]
5.13 Rhinorrhoea	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.65 [0.17, 2.45]
5.14 Sinusitis	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.75 [0.21, 2.68]
5.15 Ear Infection	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.18 [0.00, 10.67]
5.16 Pharyngitis streptococcal	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
5.17 Rhinitis	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.86 [0.40, 8.70]
5.18 Viral Infection	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.36 [0.04, 3.24]
5.19 Sinus Headache	1	161	Odds Ratio (M-H, Fixed, 99% CI)	1.44 [0.26, 8.01]
5.20 Headache	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.60 [0.66, 3.92]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.21 Dizziness	1	161	Odds Ratio (M-H, Fixed, 99% CI)	10.55 [0.69, 162.40]
5.22 Pyrexia	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.96 [0.35, 2.60]
5.23 Fatigue	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.83 [0.23, 3.07]
5.24 Abdominal pain upper	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.87 [0.26, 2.91]
5.25 Abdominal pain	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.29 [0.46, 3.59]
5.26 Constipation	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.34 [0.06, 2.05]
5.27 Diarrhea	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.36 [0.45, 4.11]
5.28 Vomiting	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.58 [0.20, 1.68]
5.29 Nausea	2	213	Odds Ratio (M-H, Fixed, 99% CI)	1.13 [0.37, 3.40]
5.30 Gastroesophageal reflux disease	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
5.31 Weight decreased	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.46 [0.05, 4.42]
5.32 Aspartate aminotransferase increased	2	213	Odds Ratio (M-H, Fixed, 99% CI)	2.02 [0.40, 10.31]
5.33 Alanine aminotransferase increased	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.83 [0.21, 3.31]
5.34 Eosinophil count increased	1	52	Odds Ratio (M-H, Fixed, 99% CI)	3.26 [0.15, 69.97]
5.35 C-reactive protein increased	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.74 [0.12, 4.37]
5.36 Blood glucose increased	1	166	Odds Ratio (M-H, Fixed, 99% CI)	1.71 [0.25, 11.72]
5.37 Hypoglycaemia	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.69 [0.09, 5.18]
5.38 white blood cell count decreased	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
5.39 Bacteria sputum Identified	2	213	Odds Ratio (M-H, Fixed, 99% CI)	2.02 [0.39, 10.32]
5.40 Joint Sprain	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.10 [0.00, 4.71]
5.41 Breath Sounds abnormal	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.35 [0.05, 2.49]
5.42 Arthralgia	1	161	Odds Ratio (M-H, Fixed, 99% CI)	1.34 [0.28, 6.44]
5.43 Myalgia	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.44 Back pain	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.94 [0.17, 5.03]
5.45 Neck pain	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
5.46 Haemoptysis	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.51 [0.16, 1.65]
5.47 Respiratory tract congestion	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.71 [0.18, 2.86]
5.48 Sinus Congestion	1	161	Odds Ratio (M-H, Fixed, 99% CI)	1.97 [0.39, 10.10]
5.49 Dyspnoea	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.36 [0.04, 3.24]
5.50 Pleuritic pain	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.44 [0.27, 21.87]
5.51 Respiration abnormal	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.46 [0.05, 4.42]
5.52 Pharyngeal erythema	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
5.53 Culture throat positive	1	51	Odds Ratio (M-H, Fixed, 99% CI)	2.17 [0.09, 55.58]
5.54 Rash	2	213	Odds Ratio (M-H, Fixed, 99% CI)	2.03 [0.58, 7.06]
5.55 Acne	1	161	Odds Ratio (M-H, Fixed, 99% CI)	1.95 [0.30, 12.62]
5.56 Lymphadenopathy	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.48 [0.02, 12.25]
5.57 Excoriation	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.48 [0.02, 12.25]
5.58 Neutrophil count decreased	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
5.59 Forced expiratory volume decreased	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
5.60 Seasonal allergy	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.48 [0.02, 12.25]
5.61 Allergic rhinitis	1	52	Odds Ratio (M-H, Fixed, 99% CI)	5.41 [0.09, 312.04]
6 All adverse events	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
6.1 Cardiac Murmur	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.2 Chest discomfort	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.08 [0.00, 6.60]
6.3 Pulmonary exacerbation	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.4 Upper respiratory tract infection	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.5 Respiratory tract congestion	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.6 Cough	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.09 [0.04, 30.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.7 Cough decreased	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.8 Productive cough	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.21 [0.00, 11.63]
6.9 Sputum abnormal	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.10 Sputum decreased	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.11 Sputum discolored	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.12 Increased upper airway secretion	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.13 Increased bronchial secretion	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.14 Rhonchi	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.15 Headache	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.16 Tension headache	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.17 Sinus headache	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.18 Sinusitis	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.19 Chronic sinusitis	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.08 [0.00, 6.60]
6.20 Sinus congestion	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.21 Nasal congestion	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.22 Nasal oedma	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.23 Nasal dryness	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.24 Nasal turbinate abnormality	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.25 Nasal septum disorder	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.26 Mucosal erosion	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.27 Epistaxis	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.28 Oral candidiasis	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.29 Pharyngeal oedema	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.30 Pharyngeal erythema	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.31 Pharyngolaryngeal pain	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.32 Tonsillar hypertrophy	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.08 [0.00, 6.60]
6.33 Abdominal distension	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.08 [0.00, 6.60]
6.34 Upper abdominal pain	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.35 Decreased appetite	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.08 [0.00, 6.60]
6.36 Nausea	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.37 Vomiting	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.38 Diarrhoea	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.46 [0.01, 16.23]
6.39 Flatulence	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.08 [0.00, 6.60]
6.40 Pyuria	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.41 White blood cells in urine	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.42 Rash	1	19	Odds Ratio (M-H, Fixed, 99% CI)	1.67 [0.02, 114.48]
6.43 Contact dermatitis	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.08 [0.00, 6.60]
6.44 Erythema	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.45 Excoriation	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.46 Pruritis	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.47 Genital pruritis (female)	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.48 Vulvovaginal mycotic infection	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.49 Photosensitivity reaction	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.50 Allergy to arthropod bite	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.51 Skin laceration	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.52 Injection site oedema	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.53 Fatigue	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.54 Somnolence	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.55 Joint crepitation	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
6.56 Lymphadenopathy	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.57 Blood creatinine increased	1	19	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.01, 78.14]
7 Severity of adverse effects of therapy with regards to study drug interruption (moderate) or discontinuation (severe)	3		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Adverse effect requiring study drug interruption (moderate)	2	213	Odds Ratio (M-H, Random, 95% CI)	1.18 [0.14, 9.92]
7.2 Adverse effect requiring study drug discontinuation (severe)	3	232	Odds Ratio (M-H, Random, 95% CI)	0.25 [0.04, 1.57]
8 Serious adverse events	3		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
8.1 Haemoptysis	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.23 [0.01, 4.14]
8.2 Hypoglycaemia	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.18 [0.00, 10.12]
8.3 Complete atrioventricular block	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.4 Pulmonary exacerbation	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.34 [0.13, 0.88]
8.5 Gastroesophageal reflux	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.6 Pancreatic pseudocyst	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.7 Pancreatitis	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.8 Vomiting	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.9 Abdominal pain	1	52	Odds Ratio (M-H, Fixed, 99% CI)	3.12 [0.04, 222.22]
8.10 Constipation	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.32 [0.00, 22.86]
8.11 Weight decreased	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.12 Anaphylactic shock	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.13 Catheter related complication	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.14 Implant site infection	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.15 Influenza	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.16 Pseudomonal lung infection	2	213	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.02, 6.34]

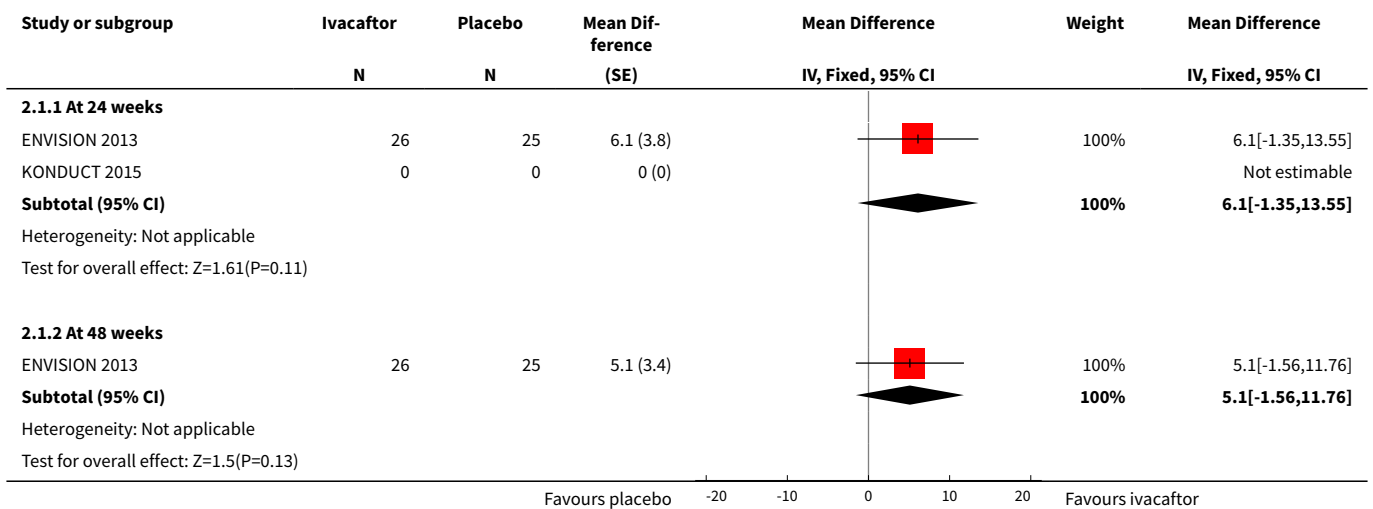
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.17 Pneumonia	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.18 Sinusitis	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.19 Cough	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.20 Pleuritic pain	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.21 Pulmonary embolism	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.22 Respiratory distress	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.23 Productive cough	1	52	Odds Ratio (M-H, Fixed, 99% CI)	1.0 [0.02, 41.06]
8.24 Respiratory failure	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.25 Pulmonary function test decreased	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.32 [0.00, 22.86]
8.26 Lung consolidation	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.32 [0.00, 22.86]
8.27 Myringitis bullous	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.28 Hepatic enzyme increased	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.29 Cervix carcinoma	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.30 Musculoskeletal chest pain	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.31 Pain in extremity	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.32 Spontaneous abortion	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.33 Haematuria	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.34 IgA nephropathy	1	161	Odds Ratio (M-H, Fixed, 99% CI)	2.85 [0.04, 195.35]
8.35 Nephrolithiasis	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.36 Renal Colic	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.37 Testicular torsion	1	161	Odds Ratio (M-H, Fixed, 99% CI)	0.31 [0.00, 21.17]
8.38 Pyrexia	1	52	Odds Ratio (M-H, Fixed, 99% CI)	3.12 [0.04, 222.22]
8.39 Muscle strain	1	52	Odds Ratio (M-H, Fixed, 99% CI)	3.12 [0.04, 222.22]
8.40 Hepatic enzyme increased	1	52	Odds Ratio (M-H, Fixed, 99% CI)	3.12 [0.04, 222.22]
8.41 Adjustment disorder	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.32 [0.00, 22.86]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.42 Anxiety	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.32 [0.00, 22.86]
8.43 Affective disorder	1	52	Odds Ratio (M-H, Fixed, 99% CI)	0.32 [0.00, 22.86]
8.44 Conversion disorder	1	52	Odds Ratio (M-H, Fixed, 99% CI)	3.12 [0.04, 222.22]
9 The number of G551D participants who developed episodes of pulmonary exacerbation	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 At 1 month	1	19	Odds Ratio (M-H, Fixed, 95% CI)	1.67 [0.07, 41.64]
9.2 At 48 weeks	2	213	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.36, 1.12]
10 Time to first pulmonary exacerbation	1		Hazard Ratio (Fixed, 95% CI)	Subtotals only
10.1 At 24 weeks	1	161	Hazard Ratio (Fixed, 95% CI)	0.46 [0.28, 0.76]
10.2 At 48 weeks	1	161	Hazard Ratio (Fixed, 95% CI)	0.46 [0.29, 0.73]
11 Maximum liver function test abnormalities in adolescents/adults at 48 weeks	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 2x to 3x ULN AST	1	161	Odds Ratio (M-H, Fixed, 95% CI)	1.97 [0.57, 6.84]
11.2 2x to 3x ULN ALT	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.77 [0.23, 2.63]
11.3 2x to 3x ULN Bilirubin	1	161	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [0.17, 21.39]
11.4 3x to 5x ULN AST	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.04, 5.21]
11.5 3x to 5x ULN ALT	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.88]
11.6 3x to 5x ULN Bilirubin	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.7 5x to 8x ULN AST	1	161	Odds Ratio (M-H, Fixed, 95% CI)	2.85 [0.11, 71.12]
11.8 5x to 8x ULN ALT	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.01, 7.71]
11.9 5x to 8x ULN Bilirubin	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.10 8x AST	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.94 [0.06, 15.28]
11.11 8x ALT	1	161	Odds Ratio (M-H, Fixed, 95% CI)	6.83 [0.35, 134.32]
11.12 8x Bilirubin	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Duration of hospitalisation for pulmonary exacerbation	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

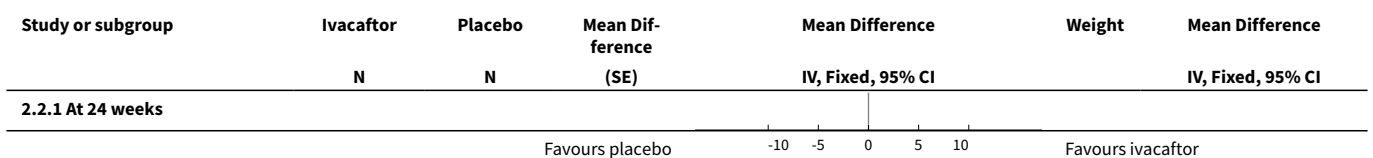
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 At 48 weeks	1	161	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-3.74, 3.28]
13 Number of hospitalisations for pulmonary exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 At 48 weeks	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.37 [0.16, 0.81]
14 FEV ₁ (% predicted) - mean absolute change from baseline	2		Mean Difference (Fixed, 95% CI)	Subtotals only
14.1 24 weeks	2	213	Mean Difference (Fixed, 95% CI)	10.80 [8.91, 12.69]
14.2 48 weeks	2	213	Mean Difference (Fixed, 95% CI)	10.44 [8.56, 12.32]
15 FEV ₁ (litres) - mean absolute change from baseline	2		Mean Difference (Random, 95% CI)	Subtotals only
15.1 24 weeks	2	212	Mean Difference (Random, 95% CI)	0.33 [0.17, 0.49]
15.2 48 weeks	2	212	Mean Difference (Random, 95% CI)	0.31 [0.11, 0.50]
16 Change from baseline through week 24 in percent of predicted FEV ₁ according to subgroup	1		Mean Difference (Fixed, 95% CI)	Subtotals only
16.1 Subgroup 1: Baseline FEV ₁ of less than or equal to 90% predicted	1	30	Mean Difference (Fixed, 95% CI)	14.9 [7.30, 22.50]
16.2 Subgroup 2: Baseline FEV ₁ of more than 90% predicted	1	21	Mean Difference (Fixed, 95% CI)	6.9 [-3.80, 17.60]
16.3 Subgroup 3: North America	1	26	Mean Difference (Fixed, 95% CI)	5.8 [-2.60, 14.20]
16.4 Subgroup 4: Europe	1	11	Mean Difference (Fixed, 95% CI)	24.60 [6.40, 42.80]
16.5 Subgroup 5: Australia	1	14	Mean Difference (Fixed, 95% CI)	4.2 [-3.70, 12.10]
16.6 Subgroup 6: Male	1	24	Mean Difference (Fixed, 95% CI)	5.2 [-2.20, 12.60]
16.7 Subgroup 7: Female	1	27	Mean Difference (Fixed, 95% CI)	13.8 [4.20, 23.40]
17 Number of pulmonary exacerbations requiring intravenous antibiotics	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
17.1 At 48 weeks	1	161	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.18, 0.64]

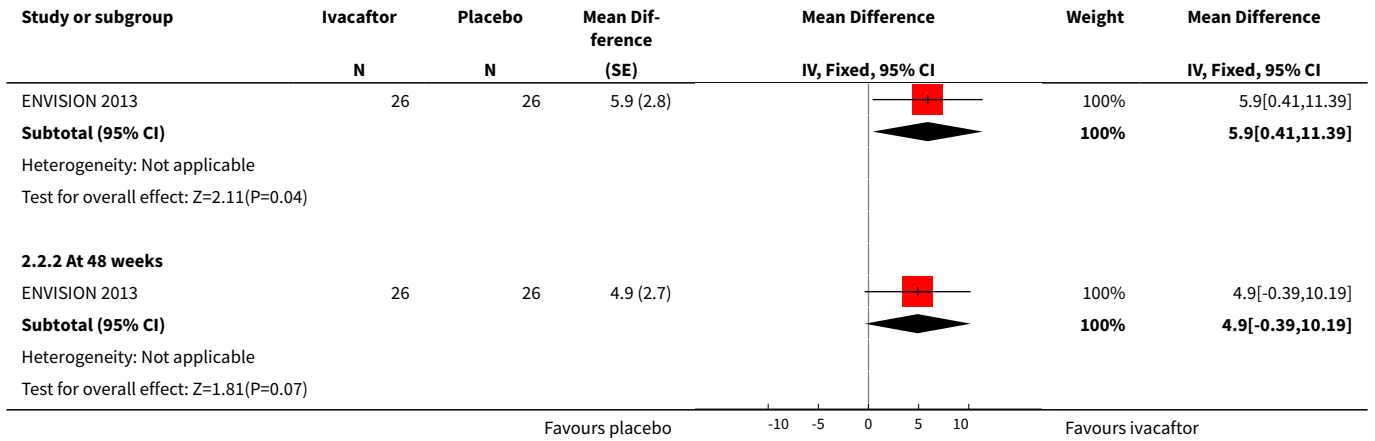
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18 Days with intravenous antibiotics administered for pulmonary exacerbations	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
18.1 At 48 weeks	1	161	Mean Difference (IV, Fixed, 95% CI)	-4.35 [-10.51, 1.81]
19 Weight - change from baseline (kg)	2		Mean Difference (Fixed, 95% CI)	Subtotals only
19.1 At 24 weeks	2	213	Mean Difference (Fixed, 95% CI)	2.37 [1.68, 3.06]
19.2 at 48 weeks	2	213	Mean Difference (Fixed, 95% CI)	2.75 [1.74, 3.75]
20 Sweat chloride level - change from baseline	2		Mean Difference (Random, 95% CI)	Subtotals only
20.1 At 24 weeks	2	213	Mean Difference (Random, 95% CI)	-50.19 [-56.20, -44.18]
20.2 At 48 weeks	2	213	Mean Difference (Random, 95% CI)	-49.74 [-54.61, -44.87]

Analysis 2.1. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 1 CFQ-R score (respiratory domain, child version) - adjusted change from baseline.

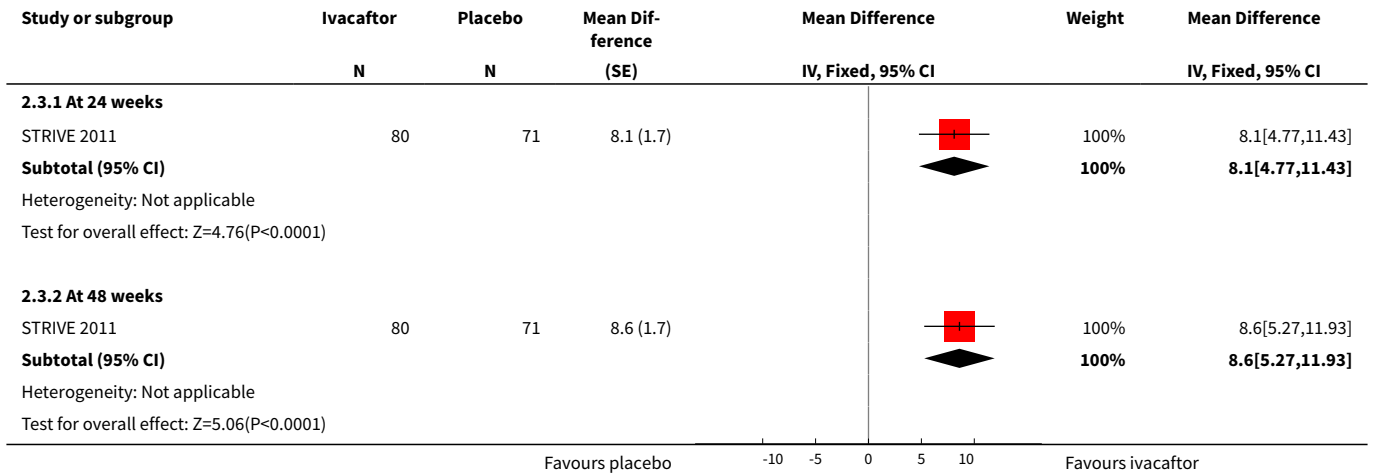


Analysis 2.2. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 2 CFQ-R score (respiratory domain score, parent/caregiver version) - adjusted change from baseline.

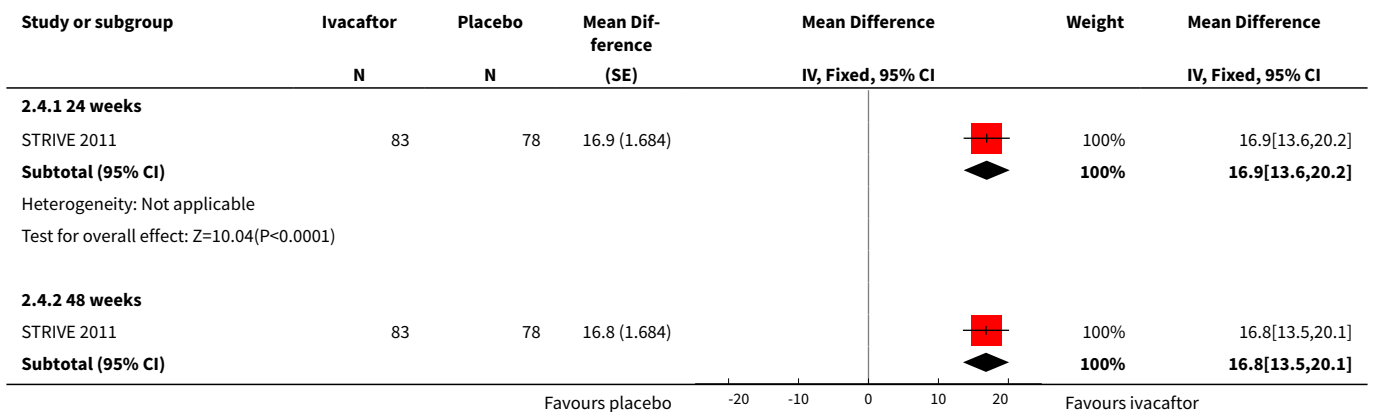


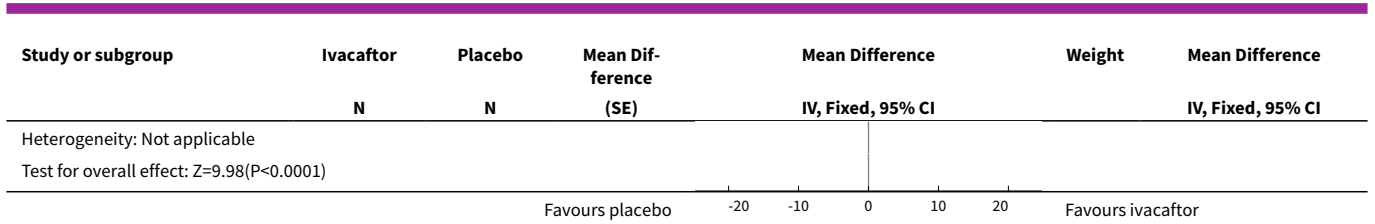


Analysis 2.3. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 3 CFQ-R score (respiratory domain score, pooled) - absolute change from baseline.

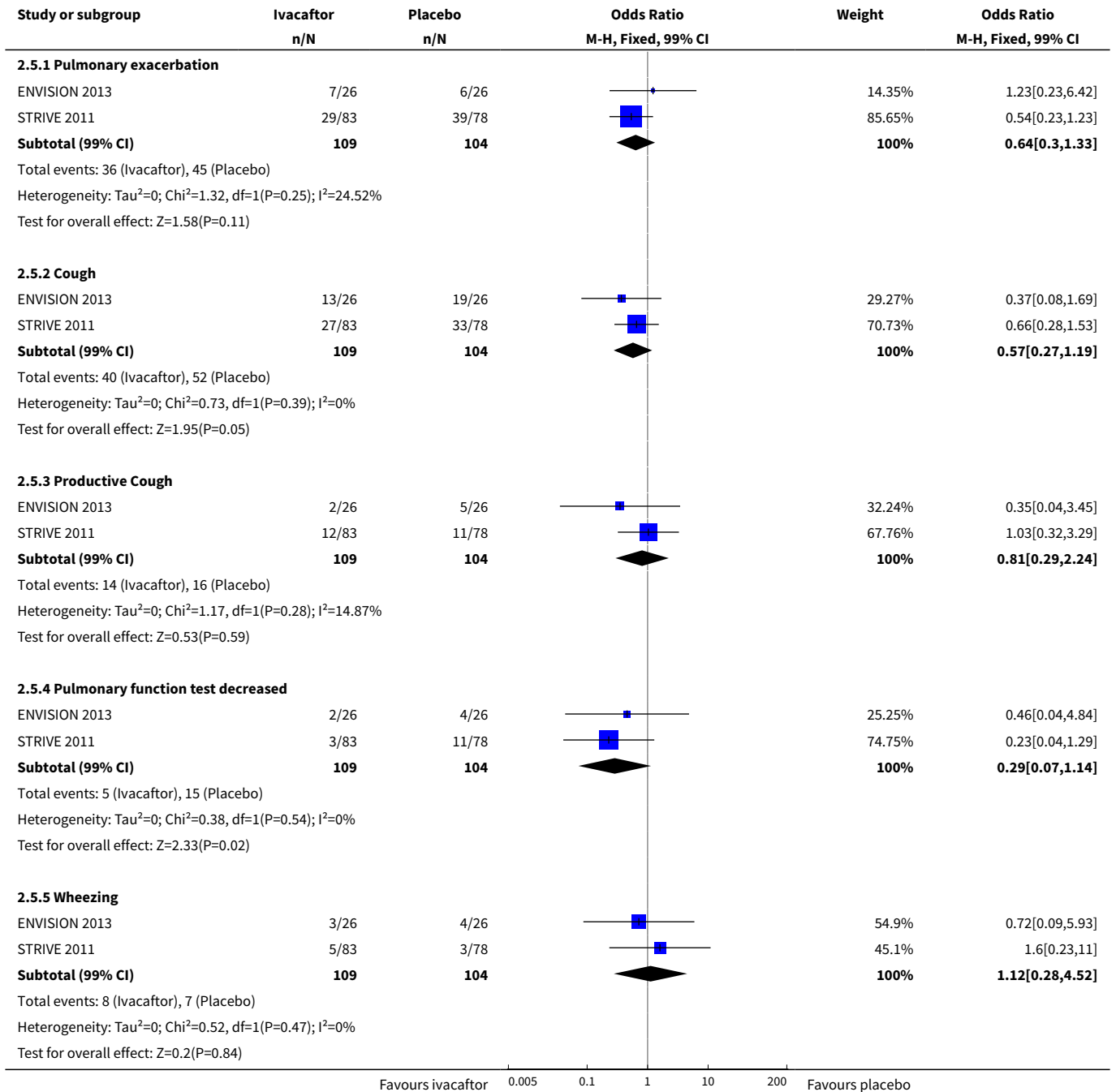


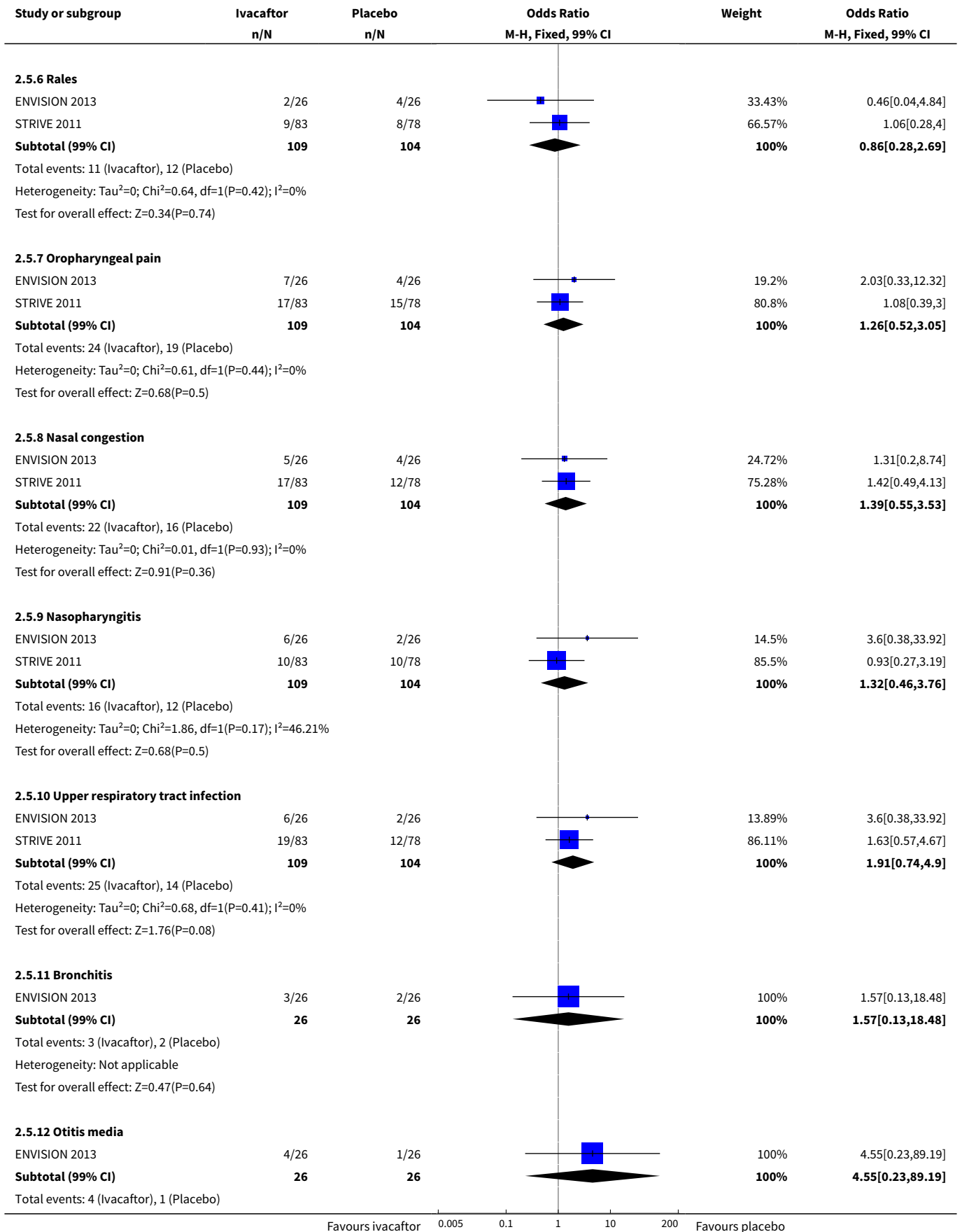
Analysis 2.4. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 4 FEV₁ - mean relative change from baseline.

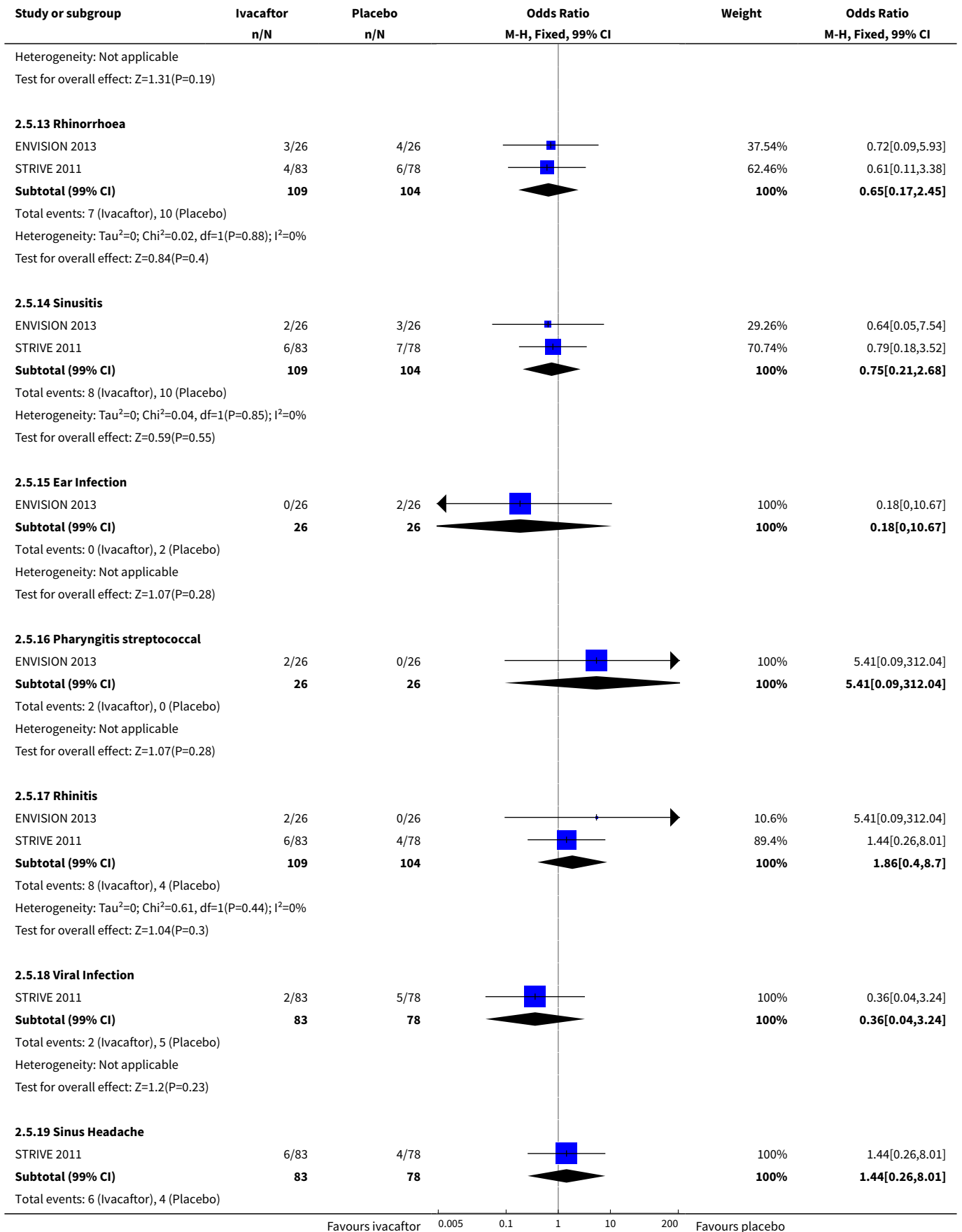


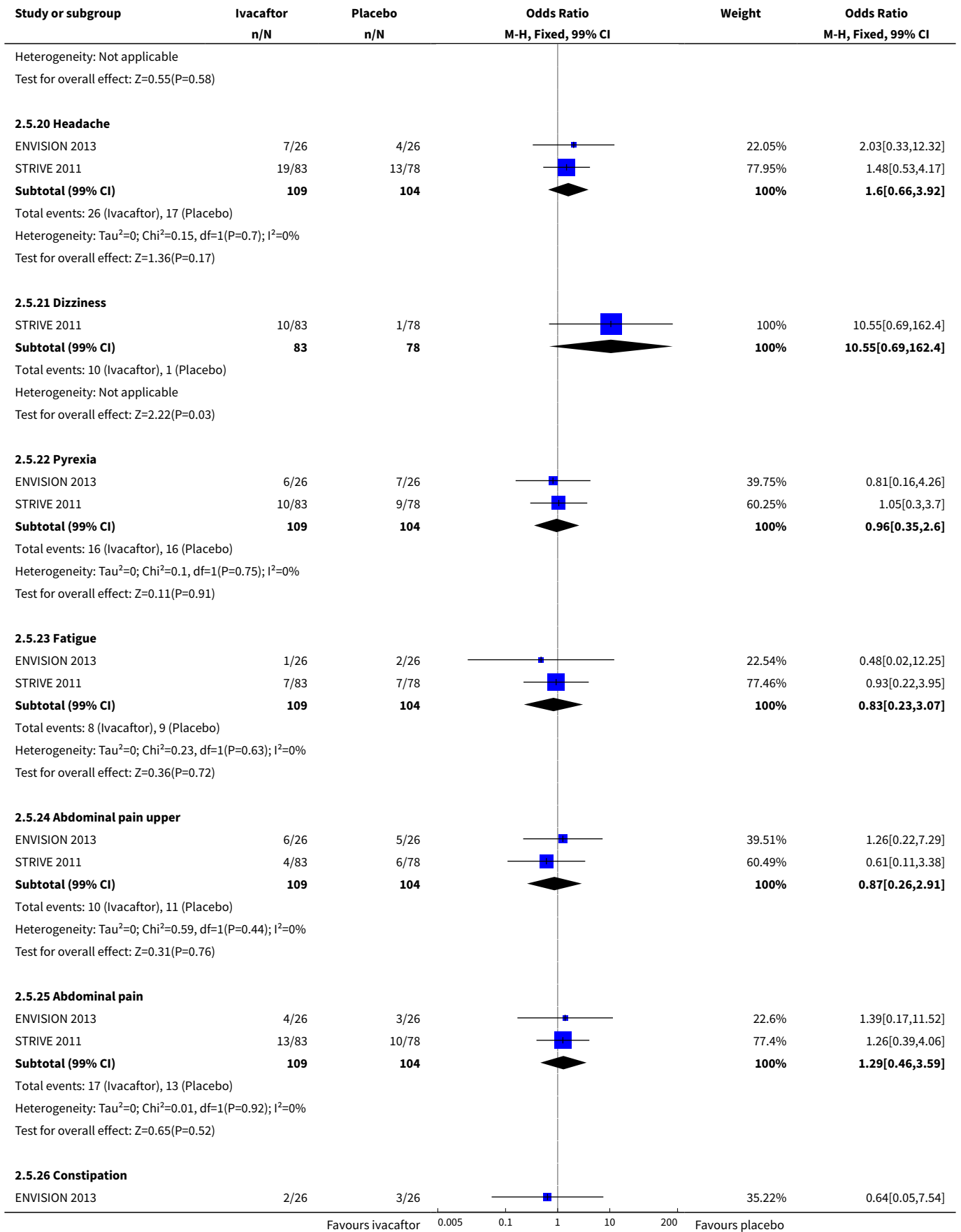


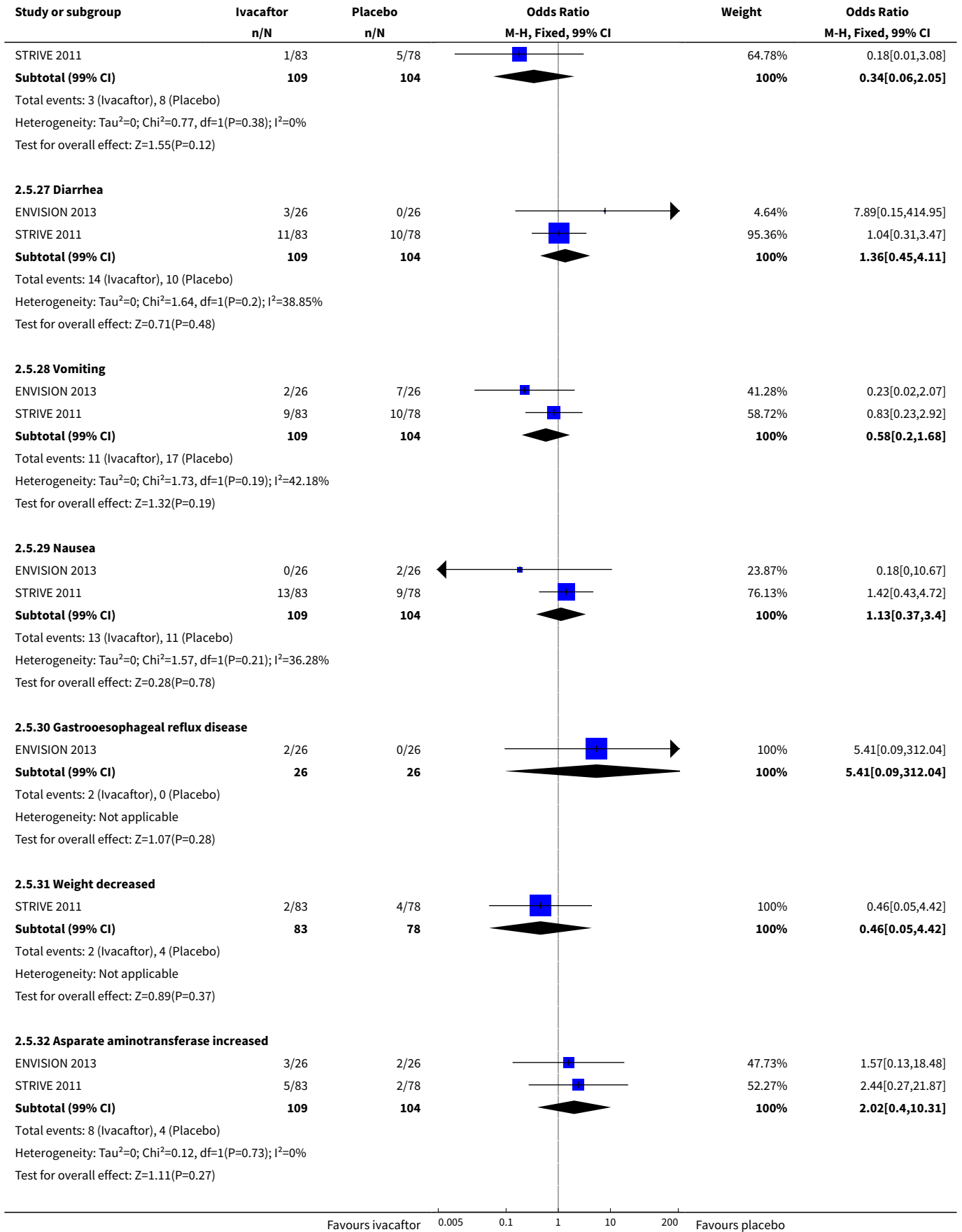
Analysis 2.5. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 5 Adverse events occurring in greater than or equal to 5% of trial participants.

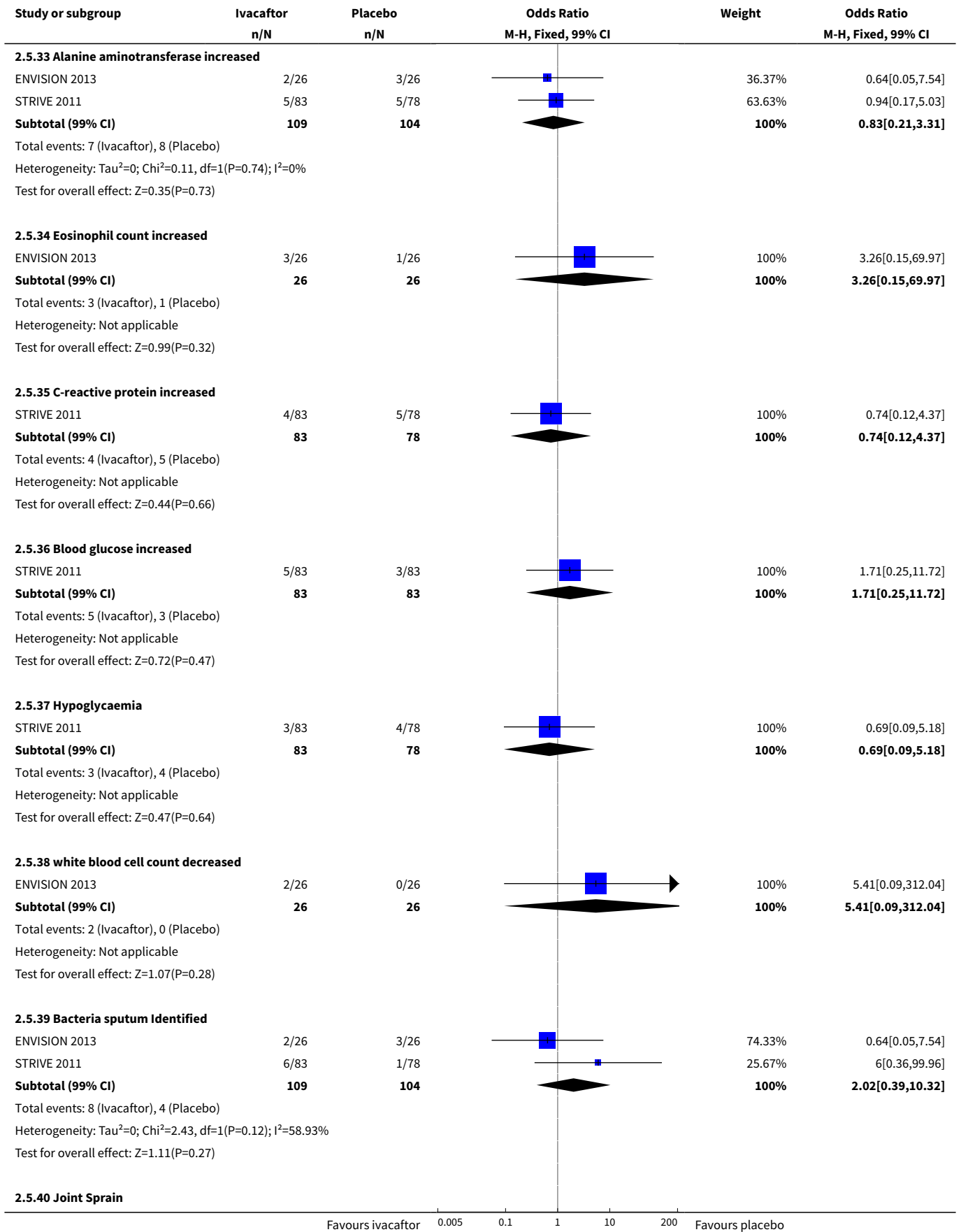


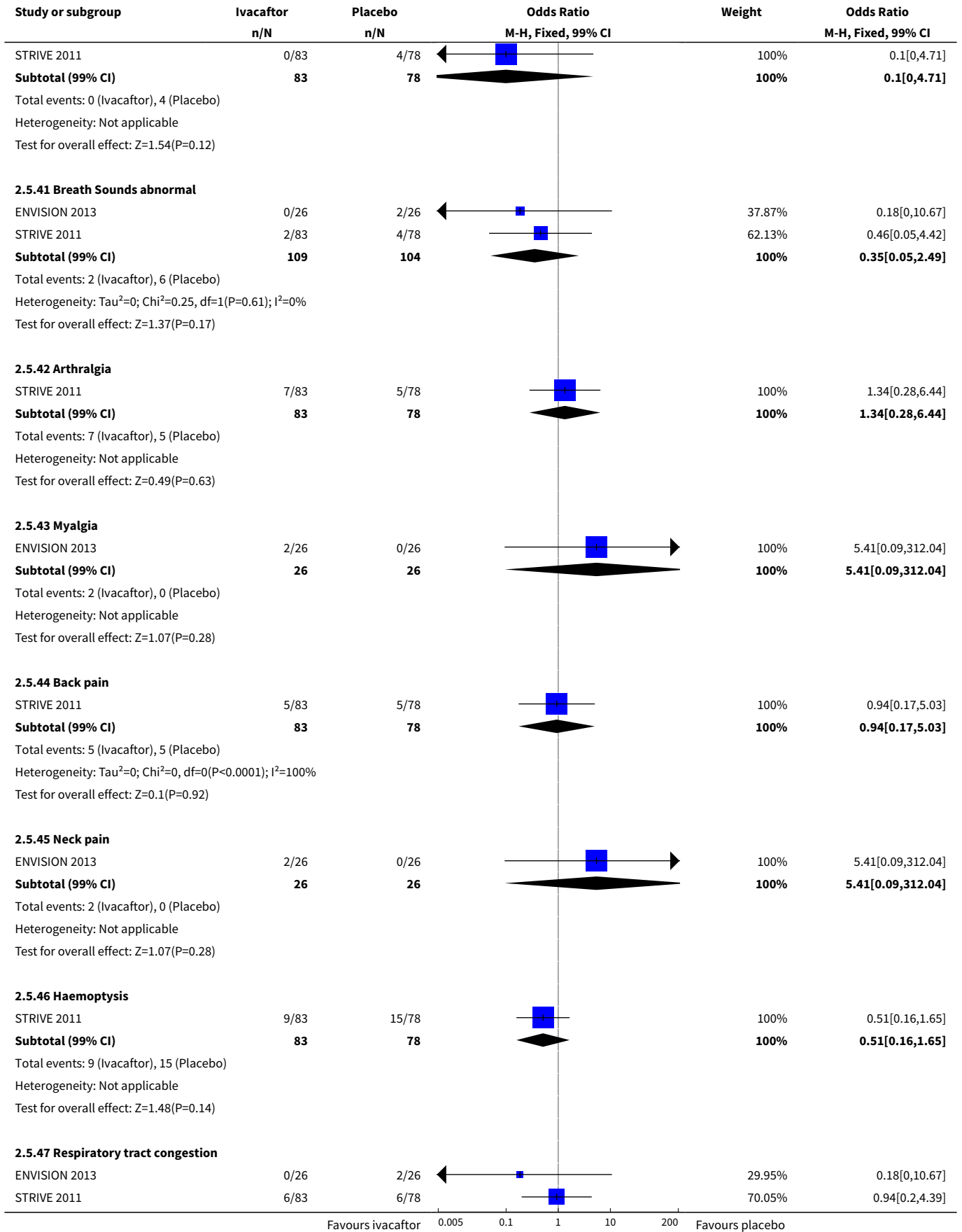


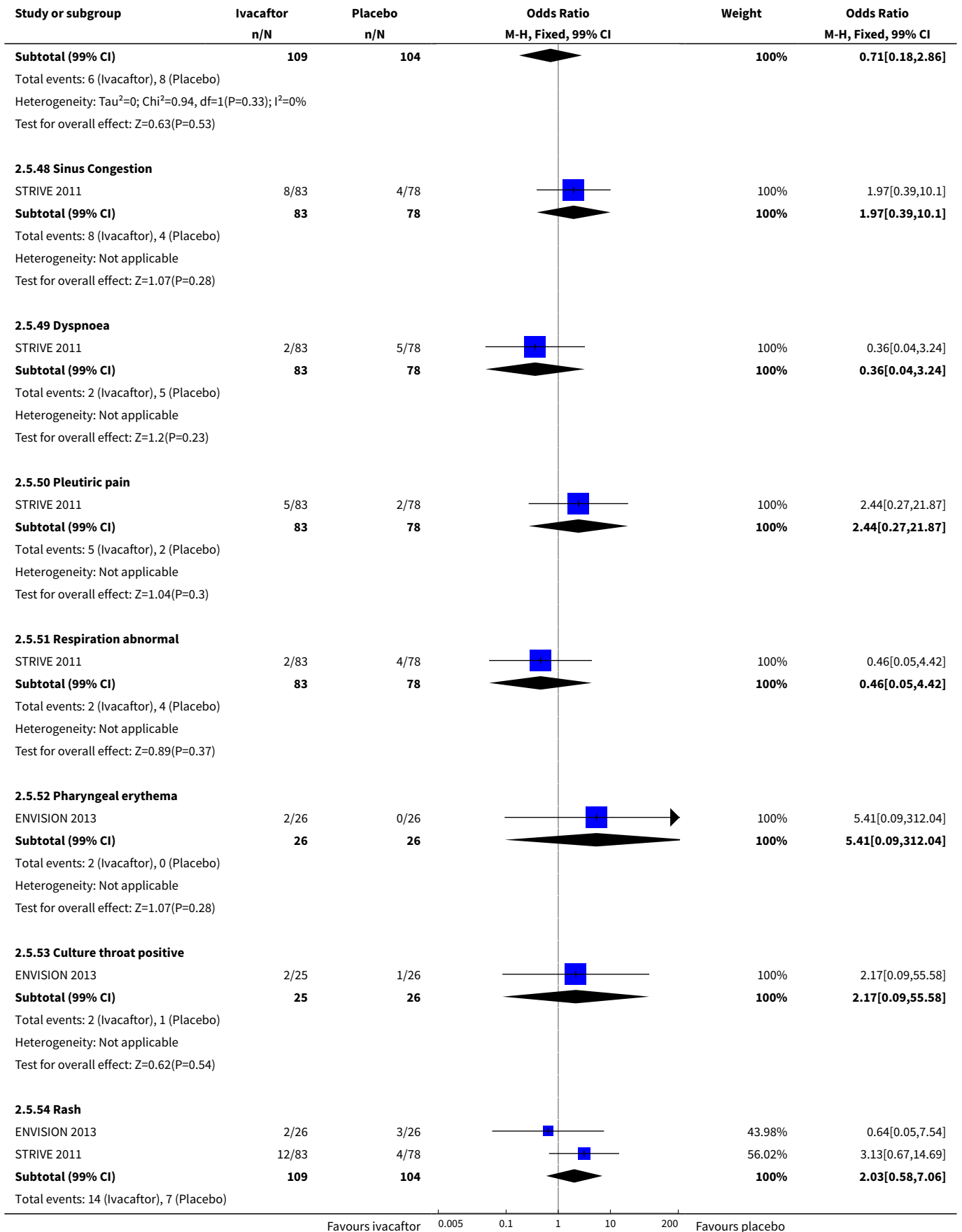


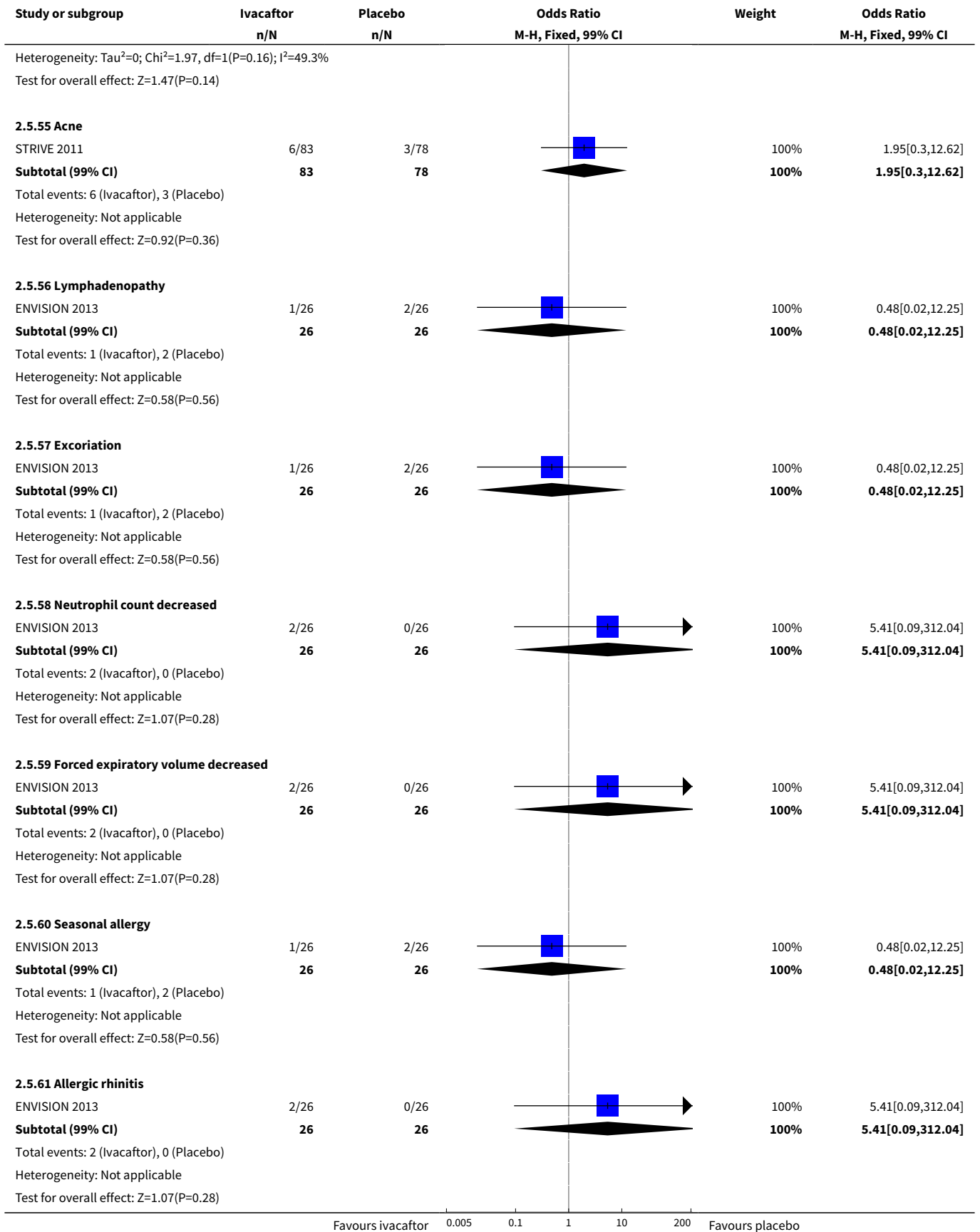




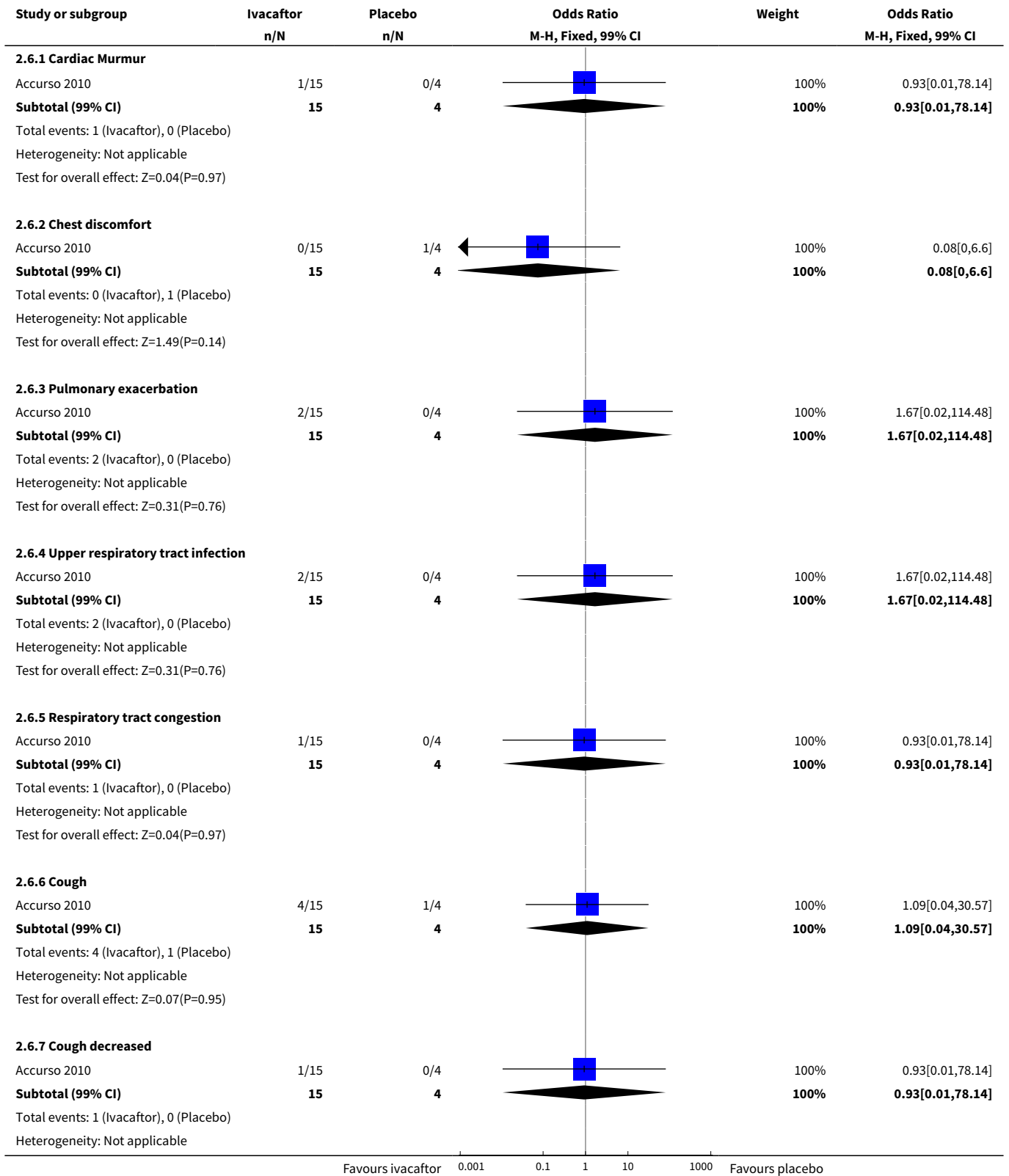


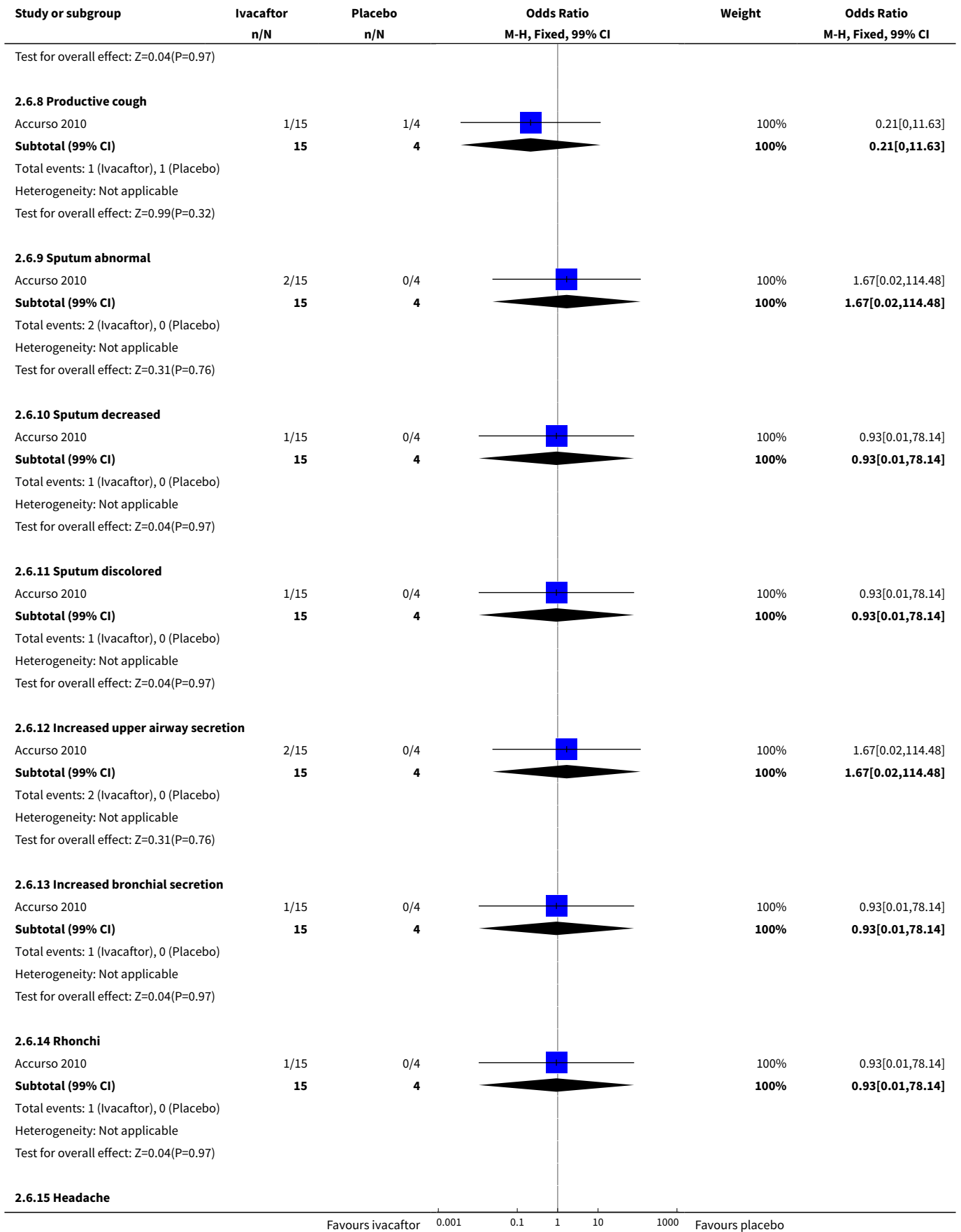


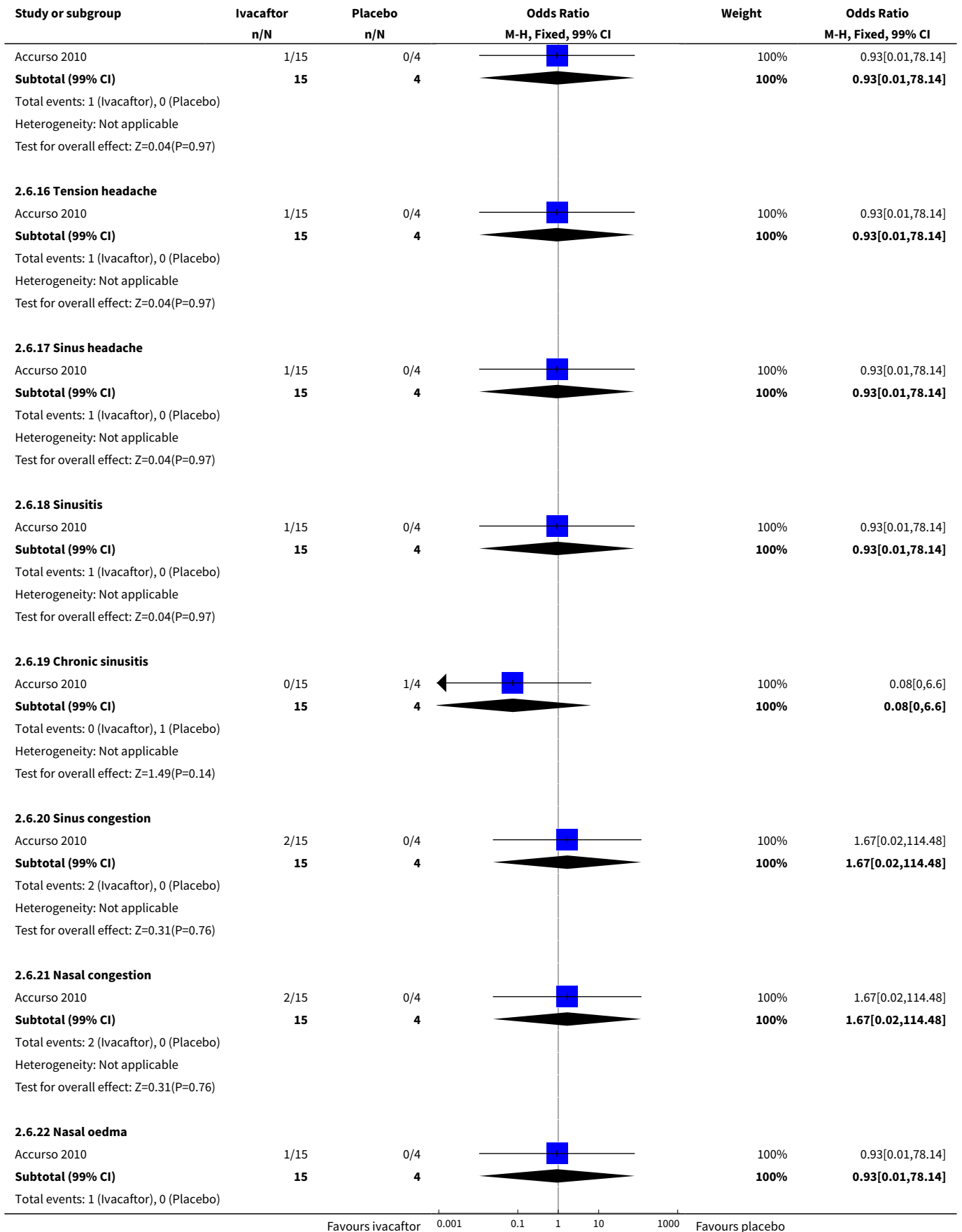


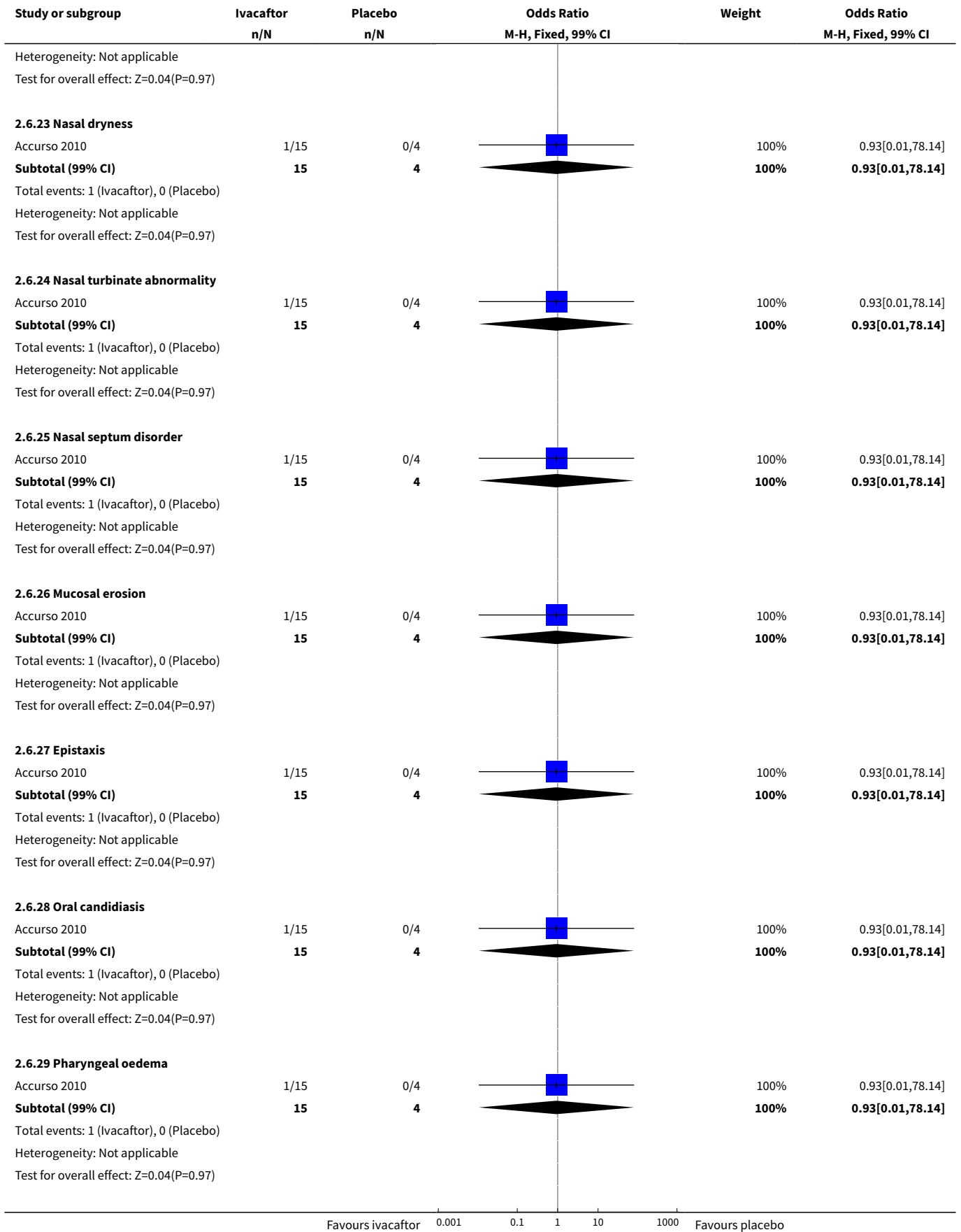


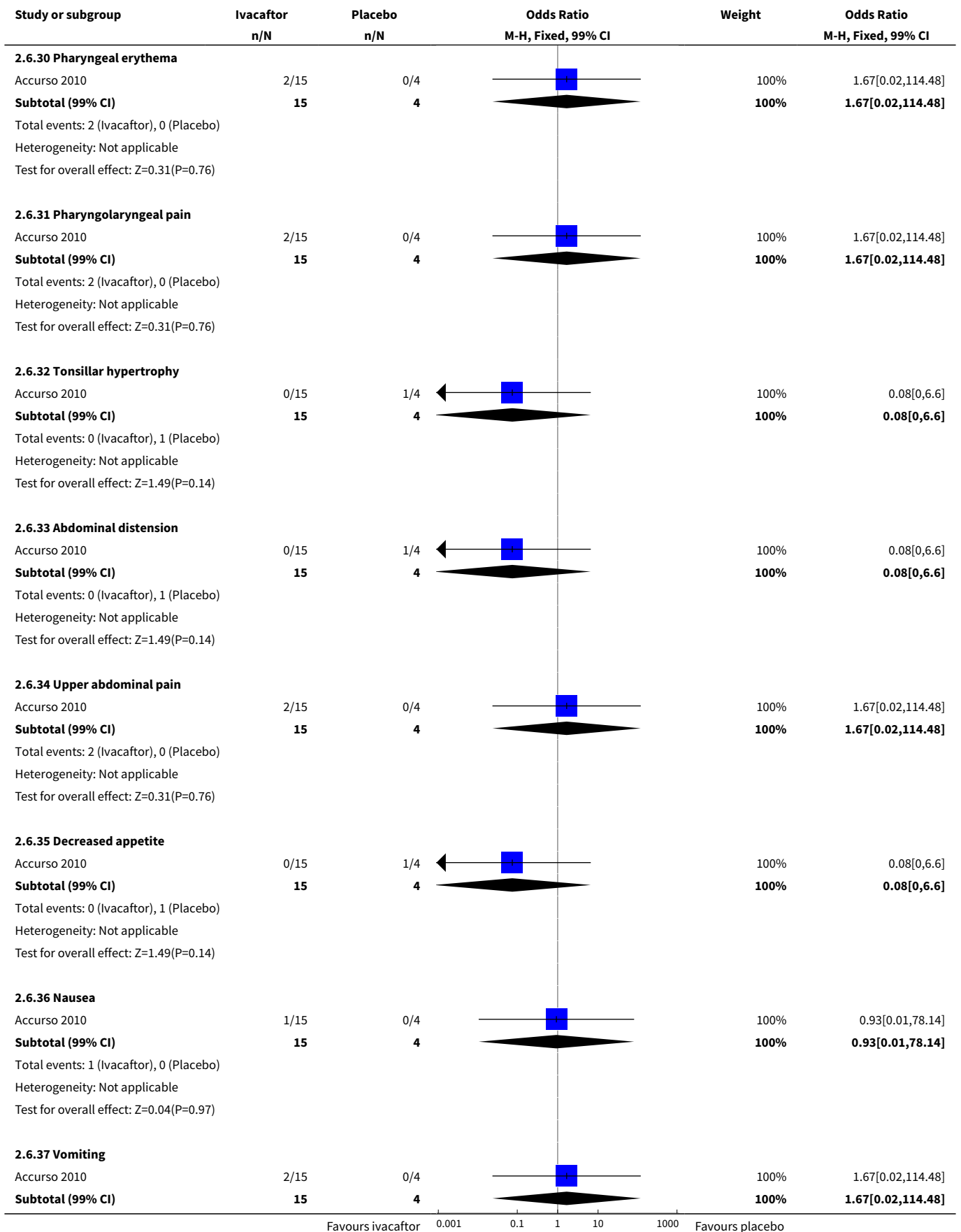
Analysis 2.6. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 6 All adverse events.

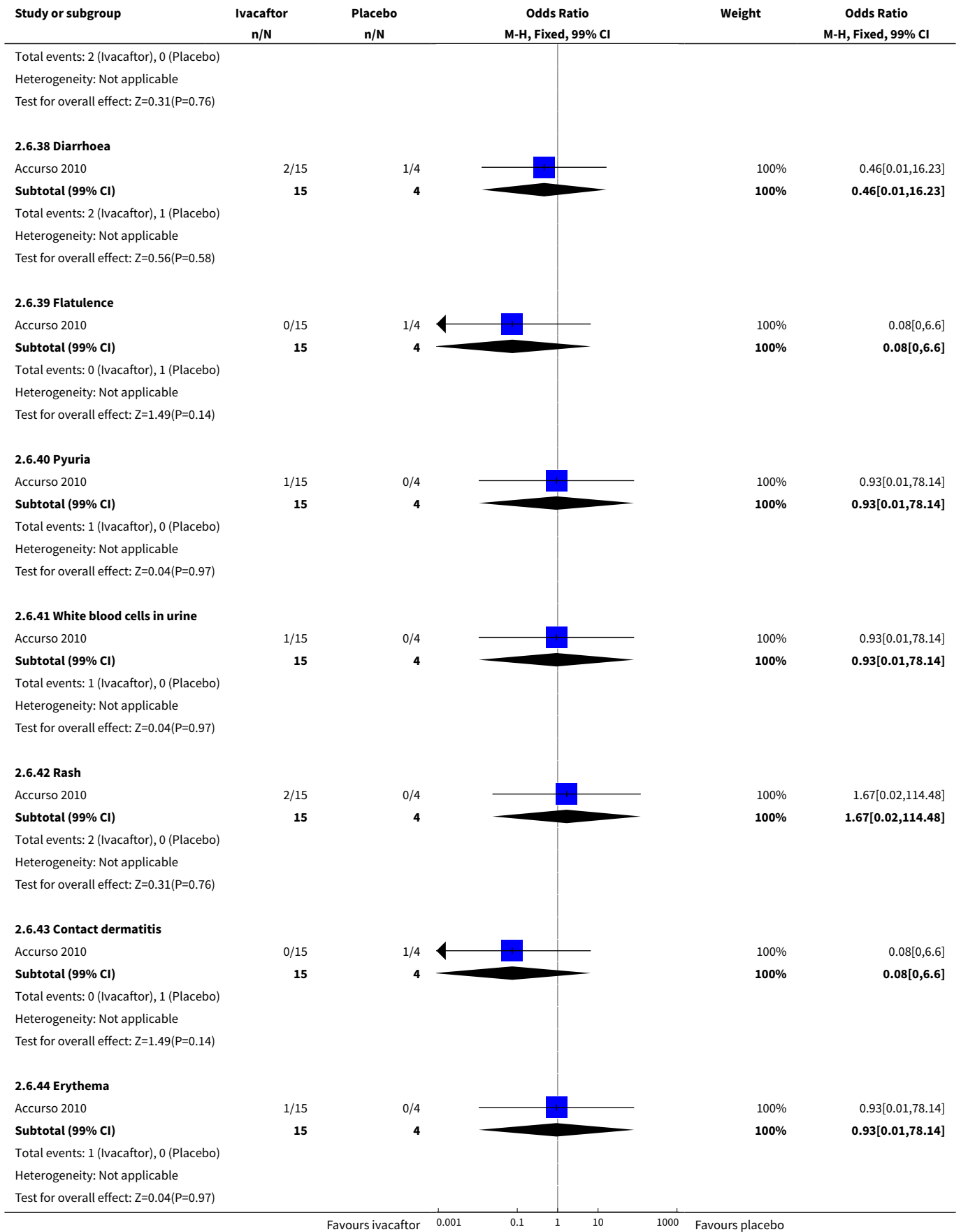


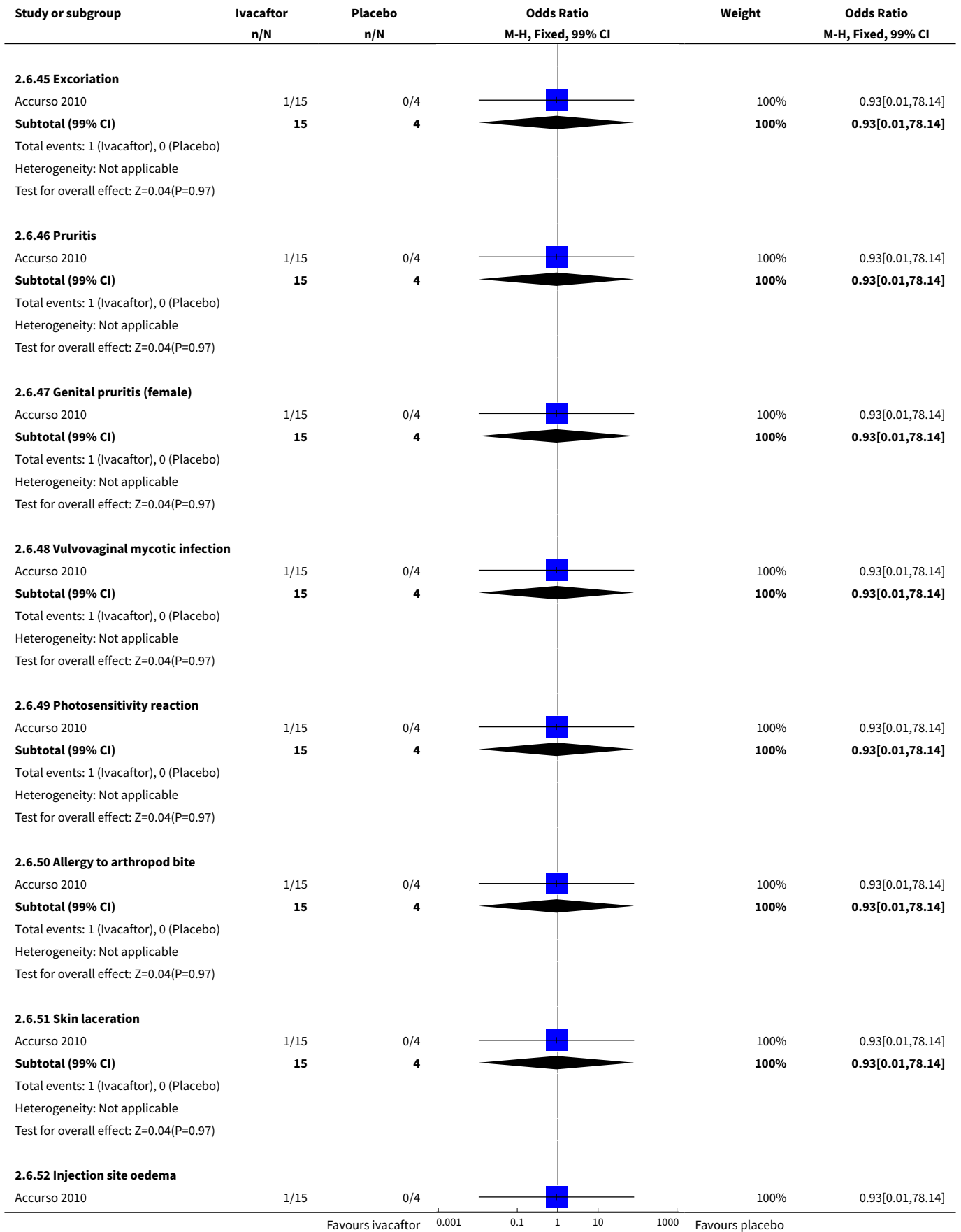


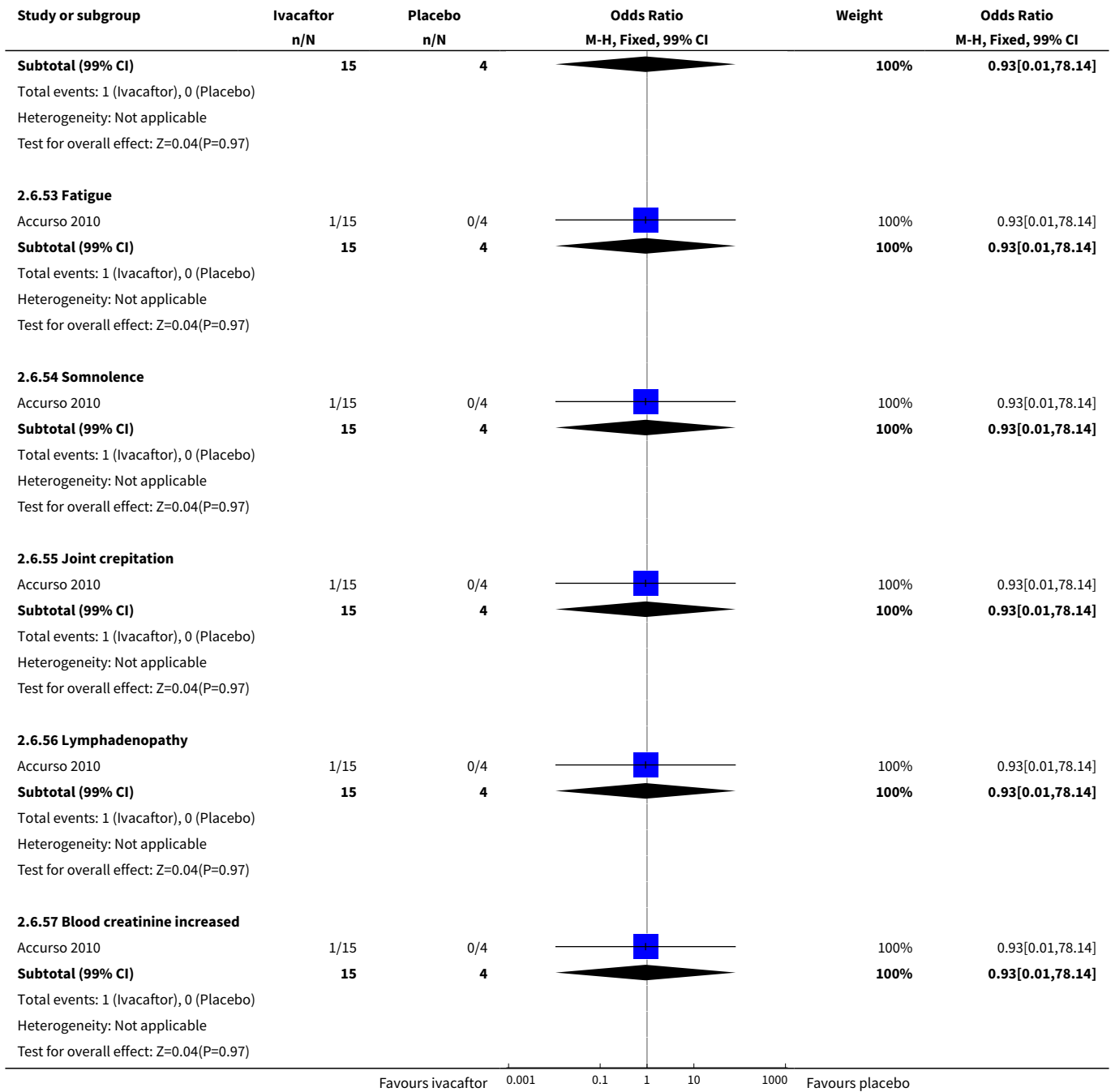




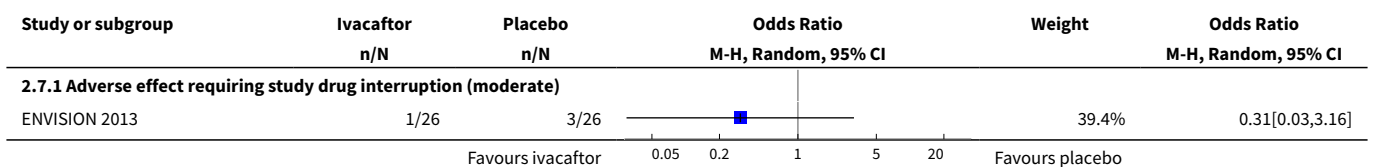


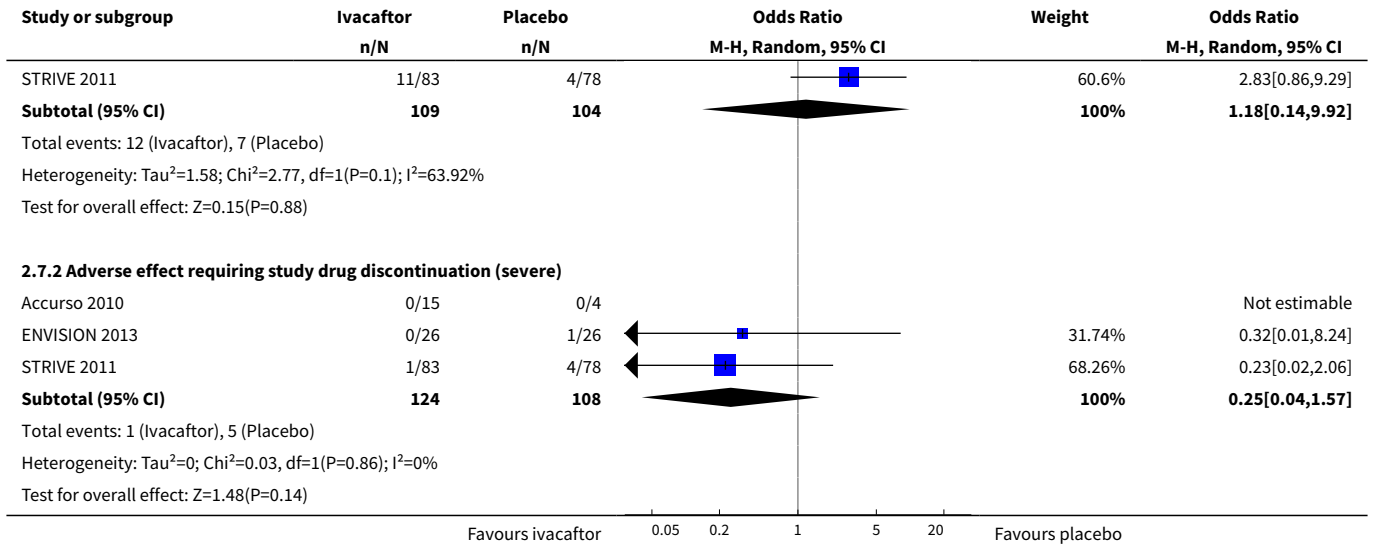




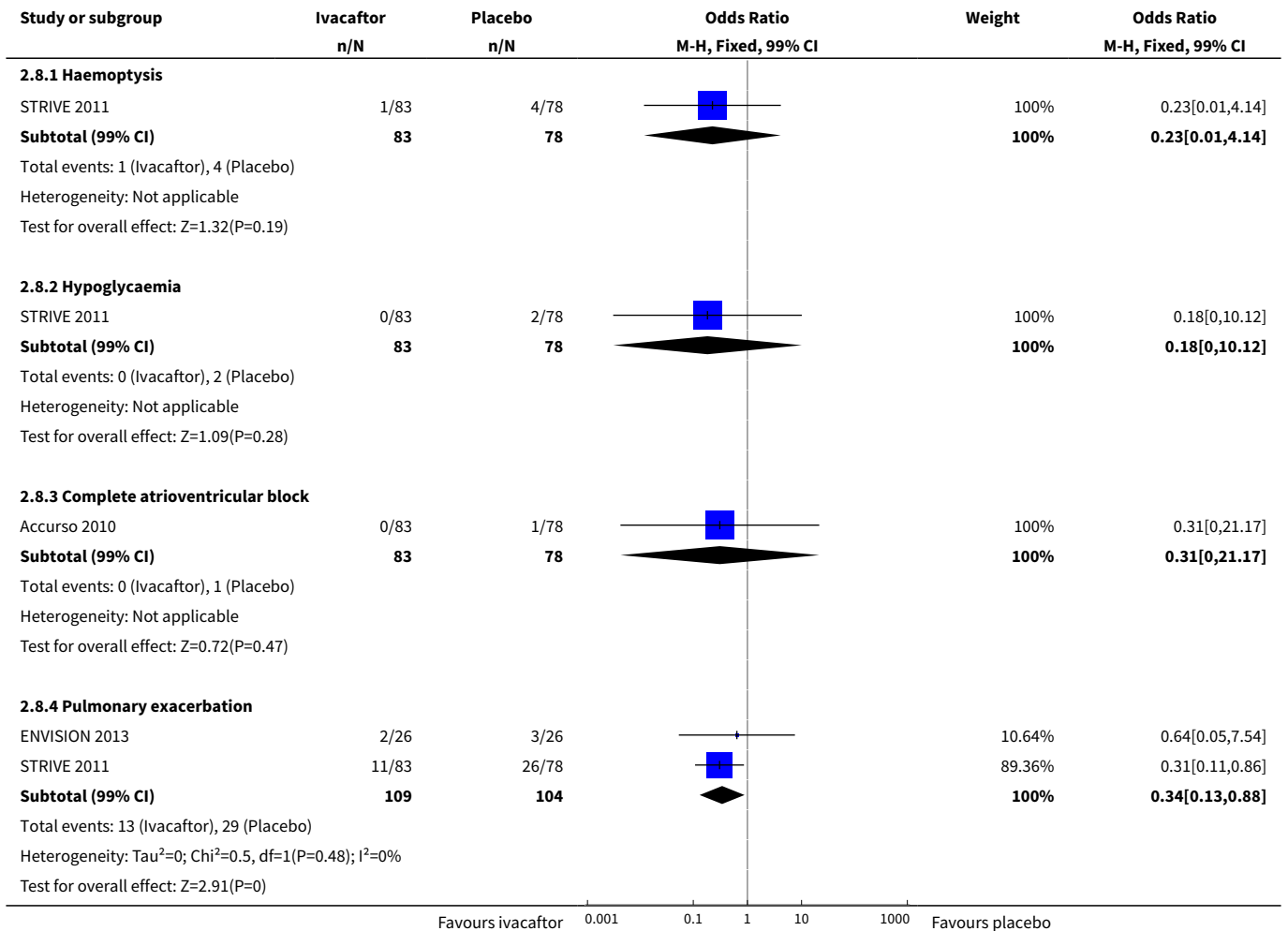


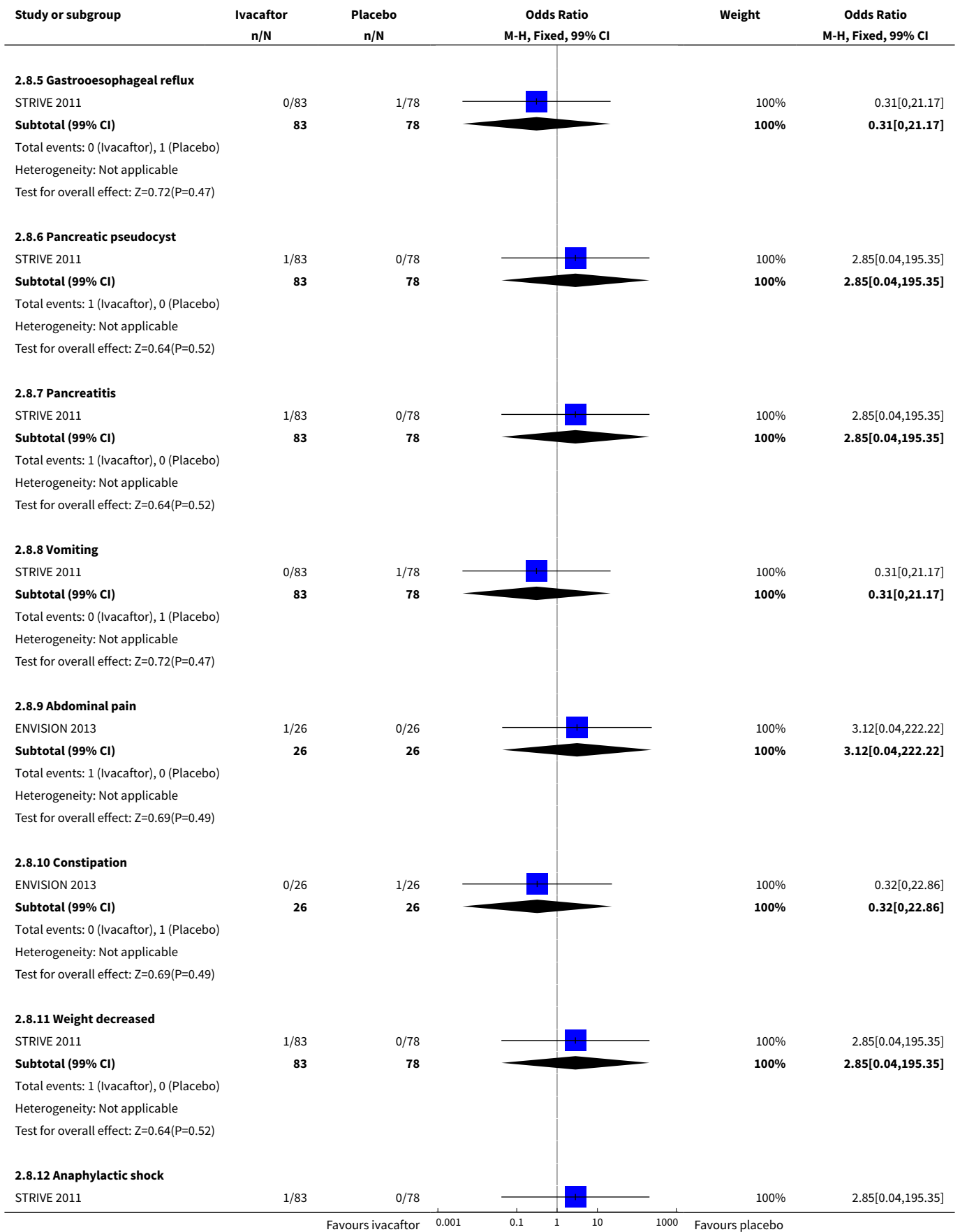
Analysis 2.7. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 7 Severity of adverse effects of therapy with regards to study drug interruption (moderate) or discontinuation (severe).

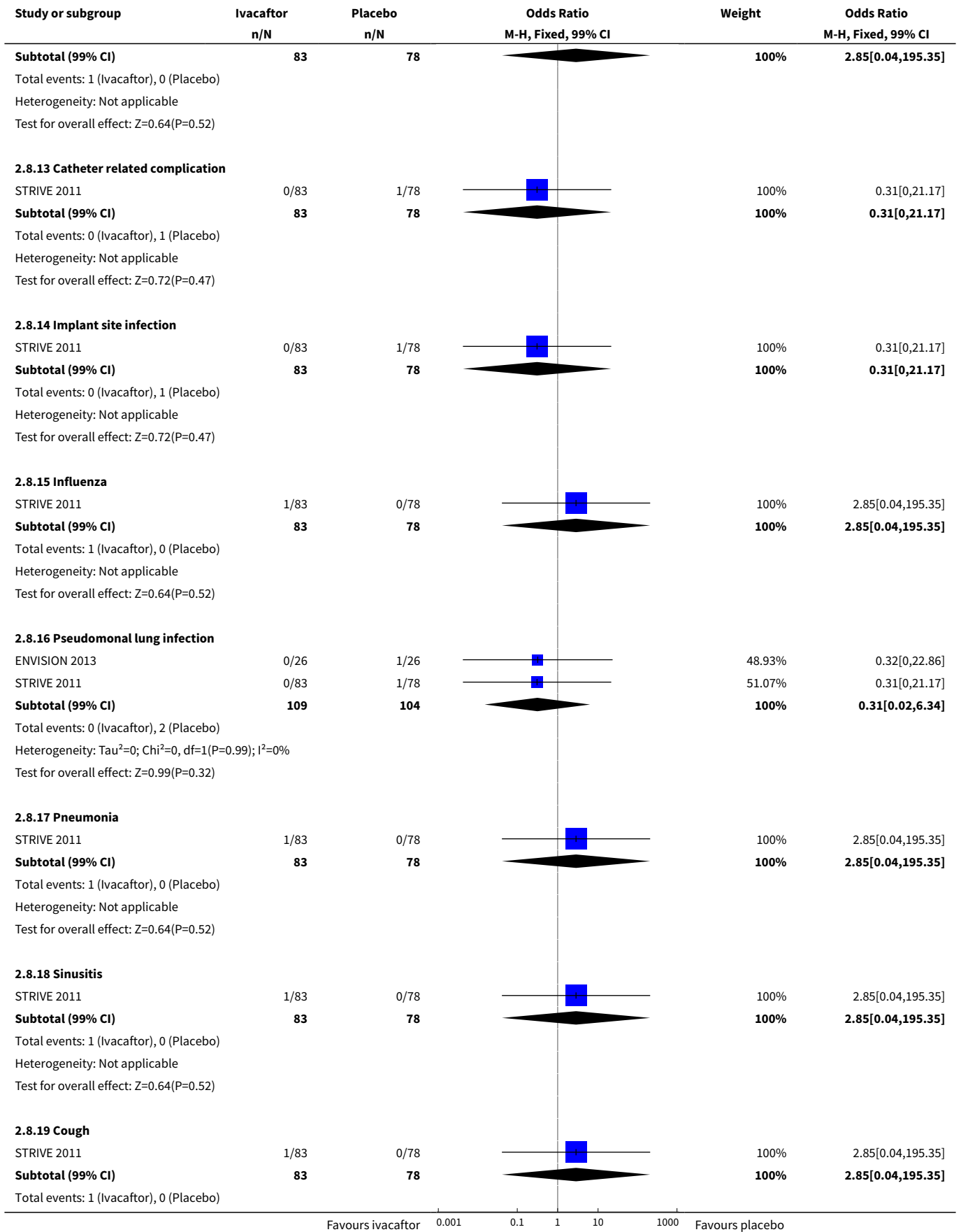


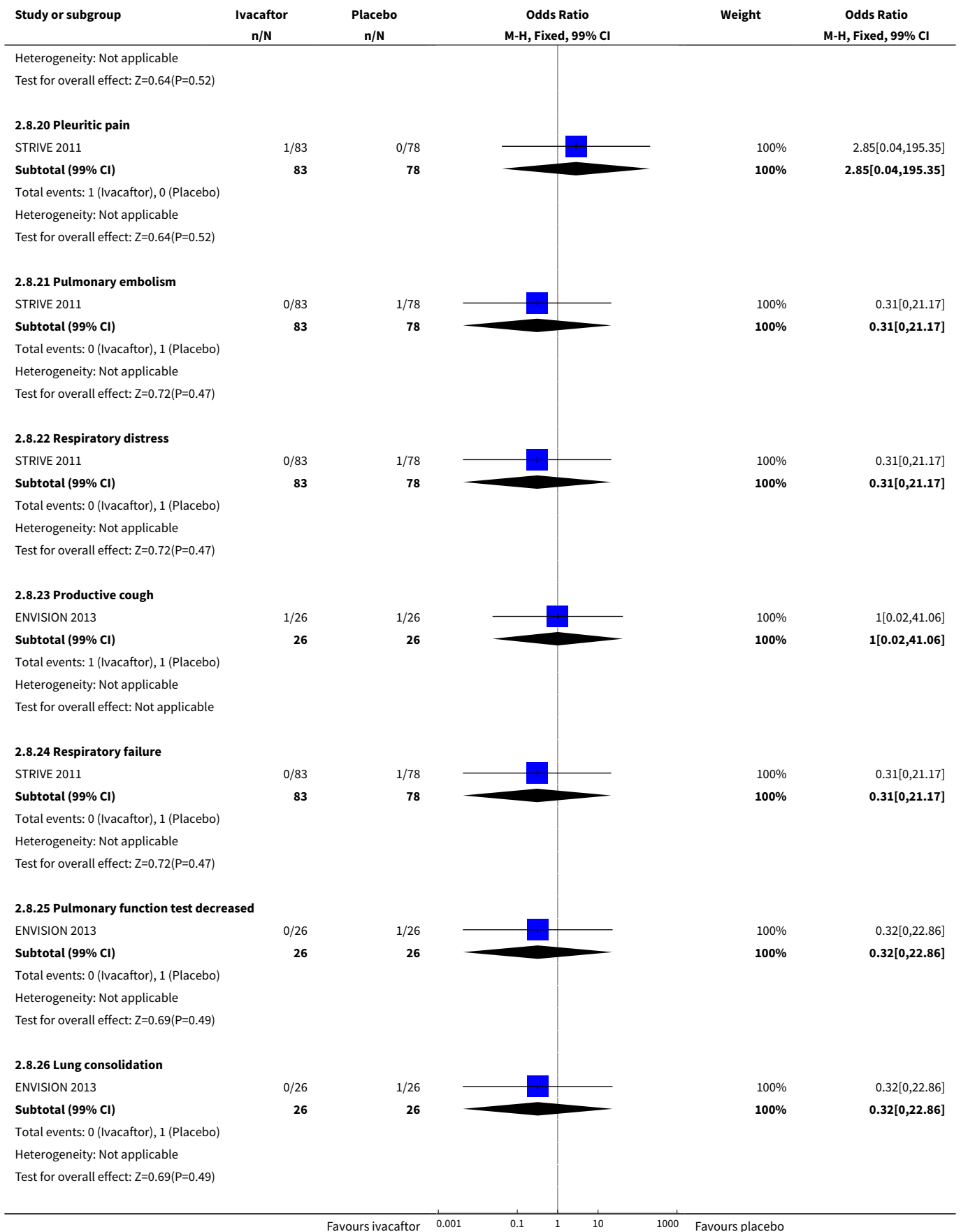


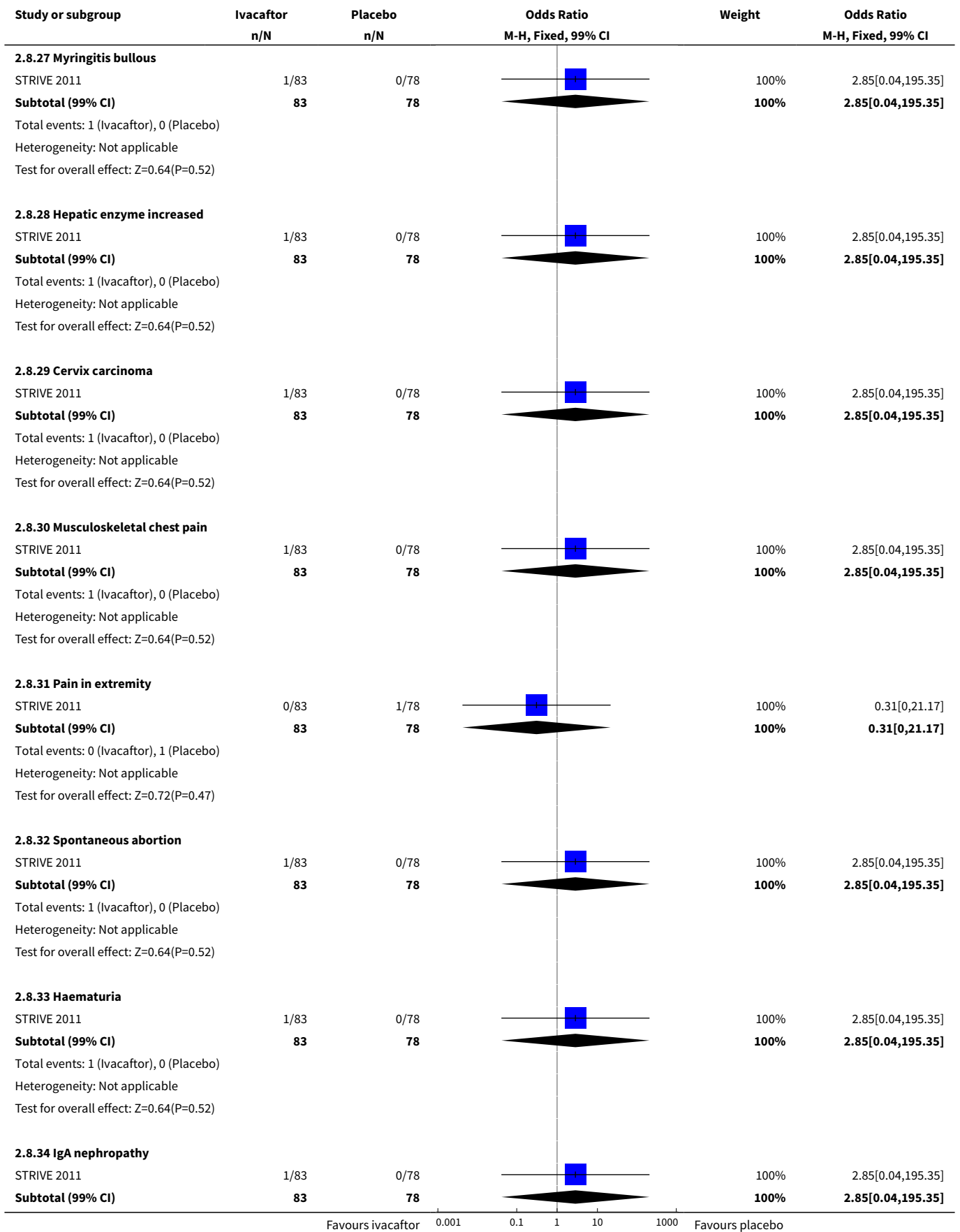
Analysis 2.8. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 8 Serious adverse events.

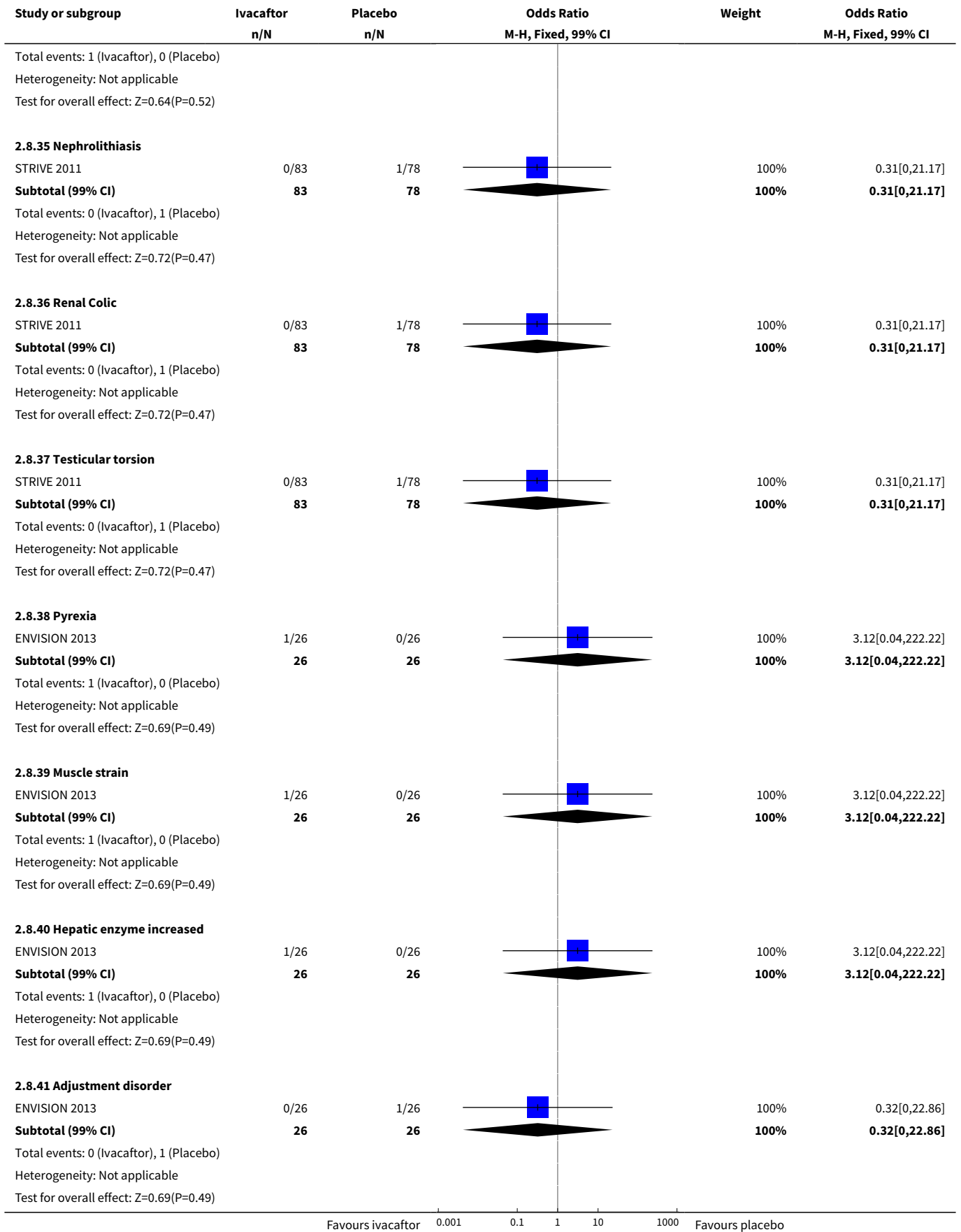


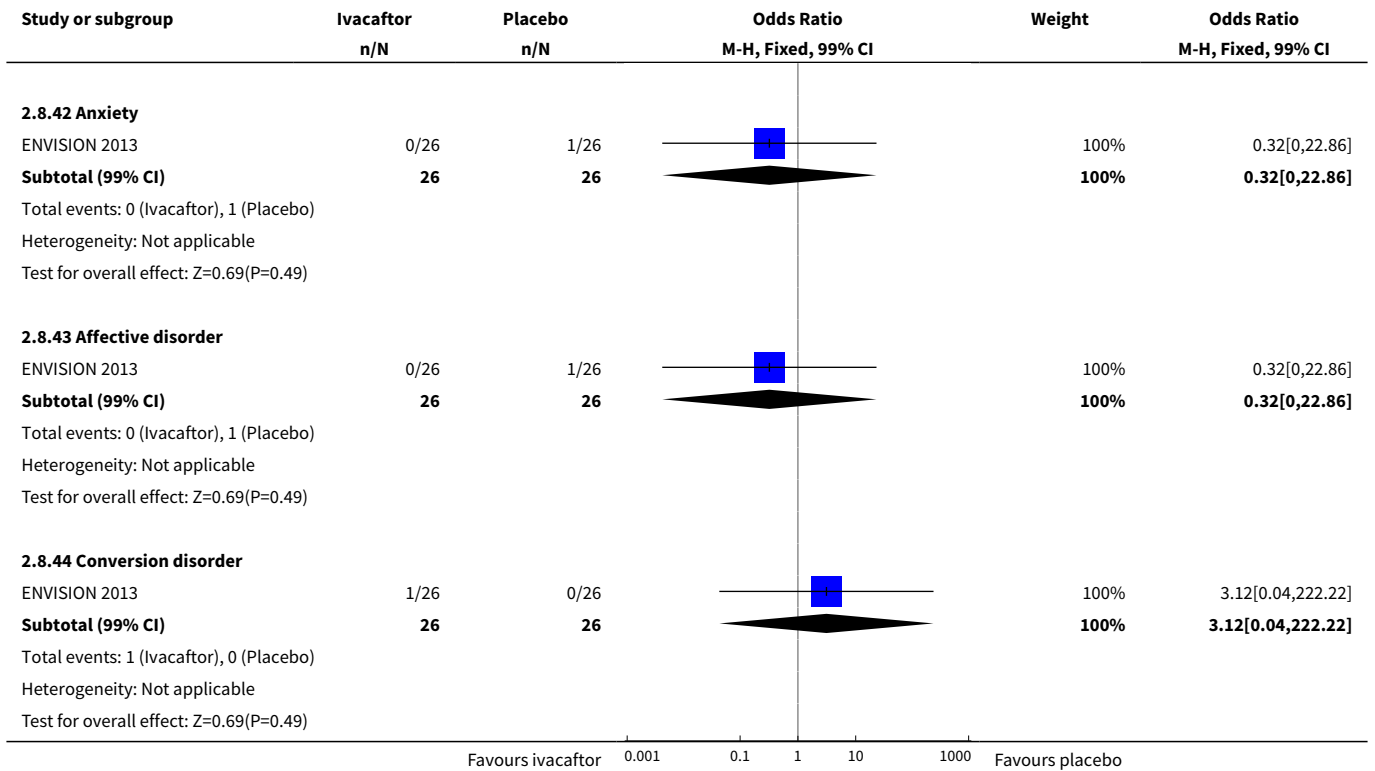




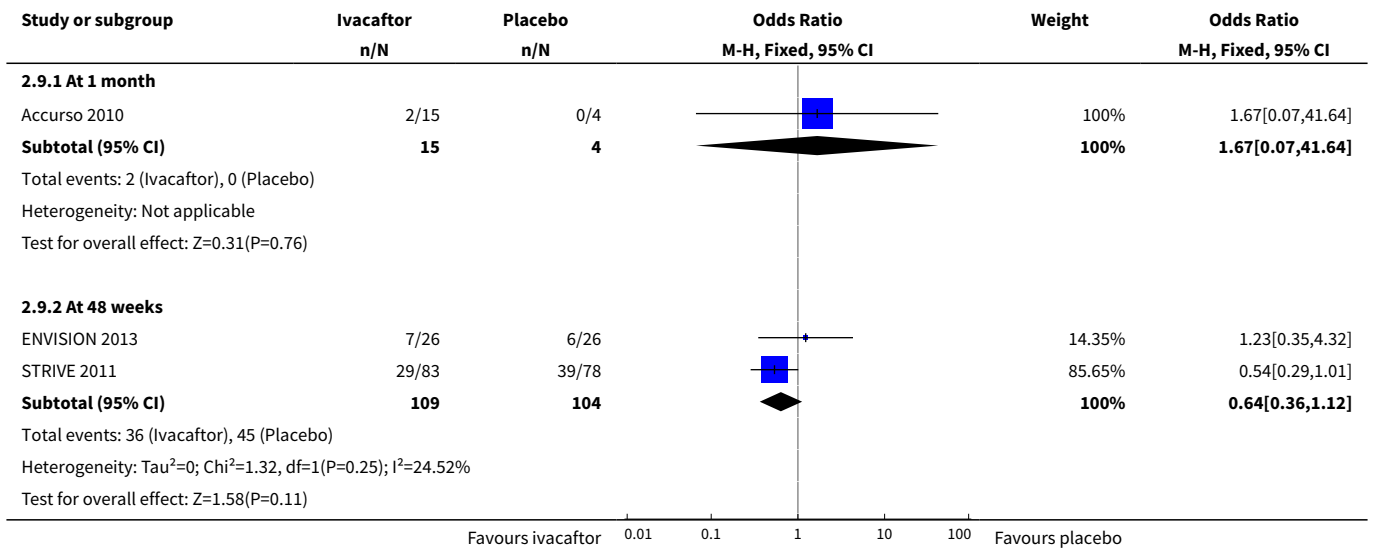




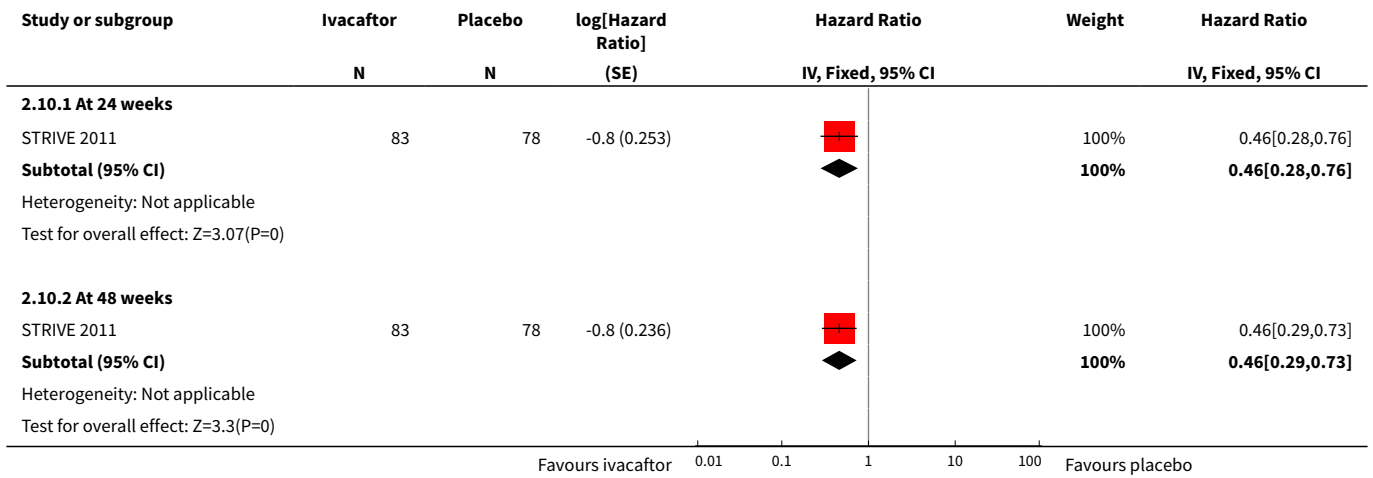




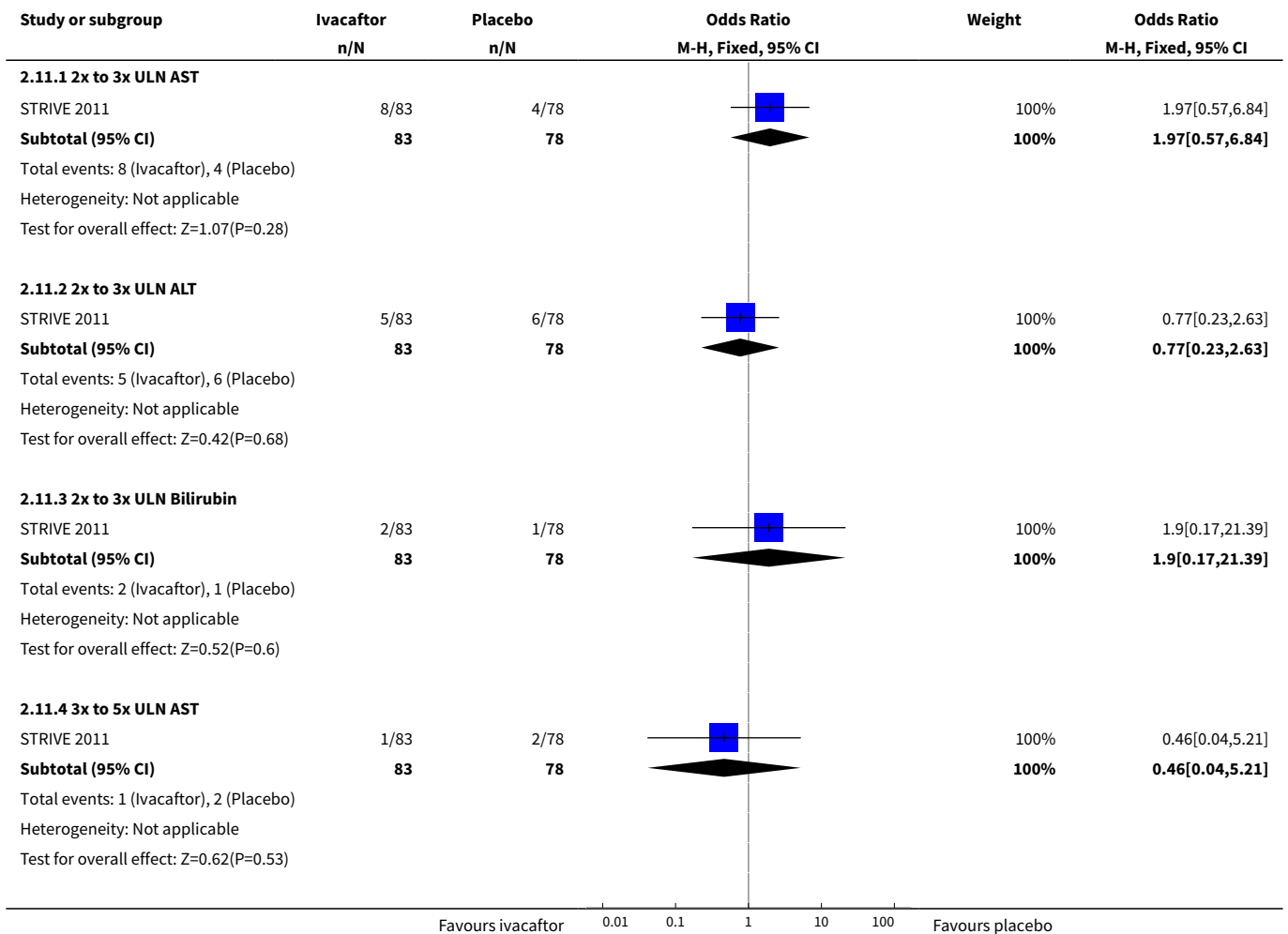
Analysis 2.9. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 9 The number of G551D participants who developed episodes of pulmonary exacerbation.

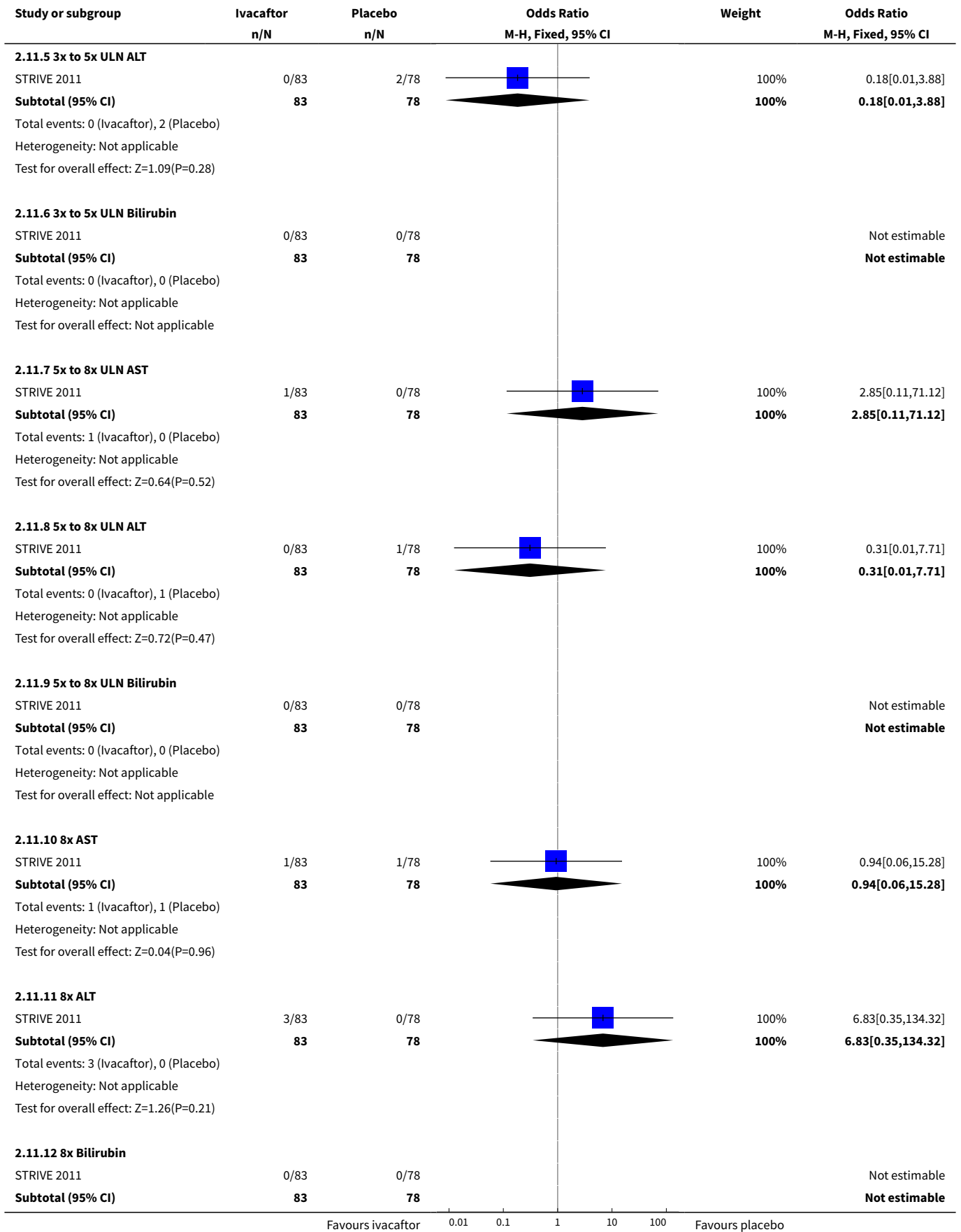


Analysis 2.10. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 10 Time to first pulmonary exacerbation.



Analysis 2.11. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 11 Maximum liver function test abnormalities in adolescents/adults at 48 weeks.





Study or subgroup	Ivacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 0 (Ivacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 2.12. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 12 Duration of hospitalisation for pulmonary exacerbation.

Study or subgroup	Ivacaftor		Placebo		Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
	N	Mean(SD)	N	Mean(SD)			
2.12.1 At 48 weeks							
STRIVE 2011	83	3.9 (13.6)	78	4.2 (8.7)		100%	-0.23[-3.74,3.28]
Subtotal ***	83		78			100%	-0.23[-3.74,3.28]

Heterogeneity: Not applicable
Test for overall effect: Z=0.13(P=0.9)

Analysis 2.13. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 13 Number of hospitalisations for pulmonary exacerbations.

Study or subgroup	Ivacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
2.13.1 At 48 weeks					
STRIVE 2011	11/83	23/78		100%	0.37[0.16,0.81]
Subtotal (95% CI)	83	78		100%	0.37[0.16,0.81]

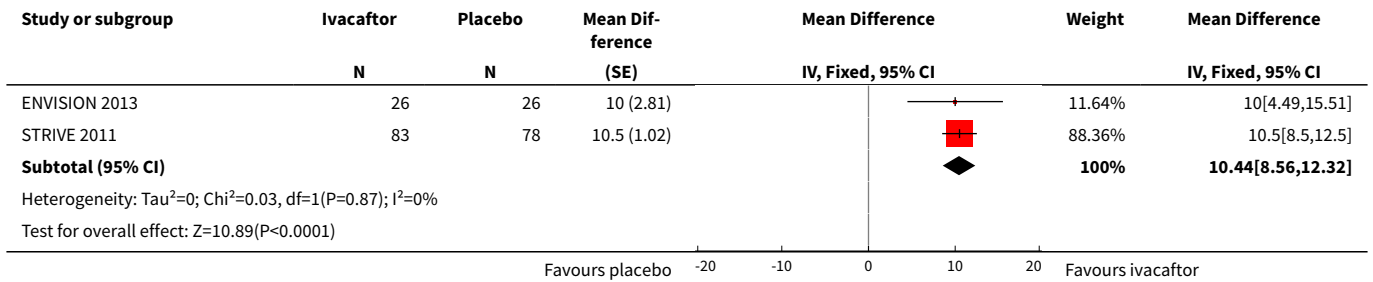
Total events: 11 (Ivacaftor), 23 (Placebo)
Heterogeneity: Not applicable
Test for overall effect: Z=2.47(P=0.01)

Analysis 2.14. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 14 FEV₁ (% predicted) - mean absolute change from baseline.

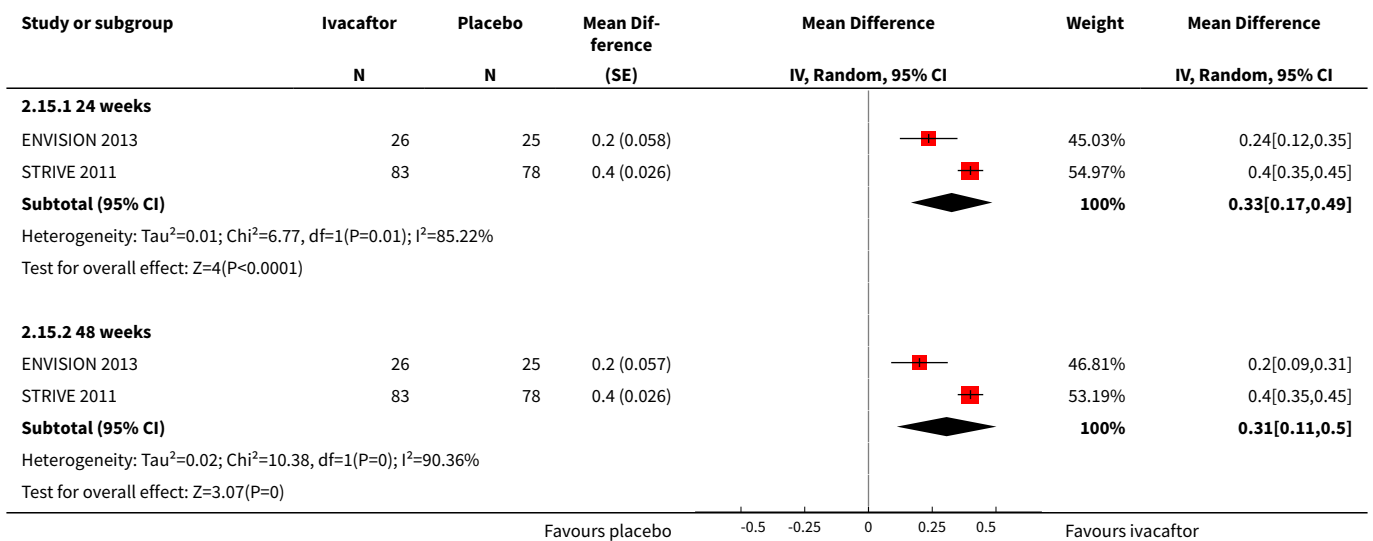
Study or subgroup	Ivacaftor	Placebo	Mean Dif- ference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
	N	N				
2.14.1 24 weeks						
ENVISION 2013	26	26	12.5 (2.98)		10.49%	12.5[6.66,18.34]
STRIVE 2011	83	78	10.6 (1.02)		89.51%	10.6[8.6,12.6]
Subtotal (95% CI)					100%	10.8[8.91,12.69]

Heterogeneity: Tau²=0; Chi²=0.36, df=1(P=0.55); I²=0%
Test for overall effect: Z=11.19(P<0.0001)

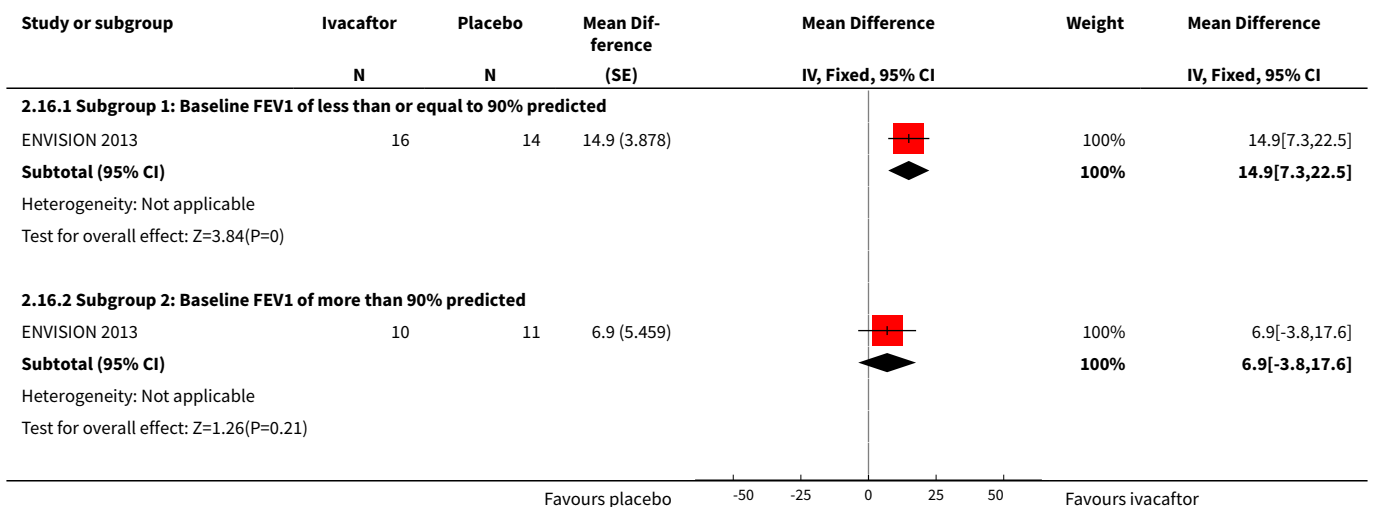
2.14.2 48 weeks						
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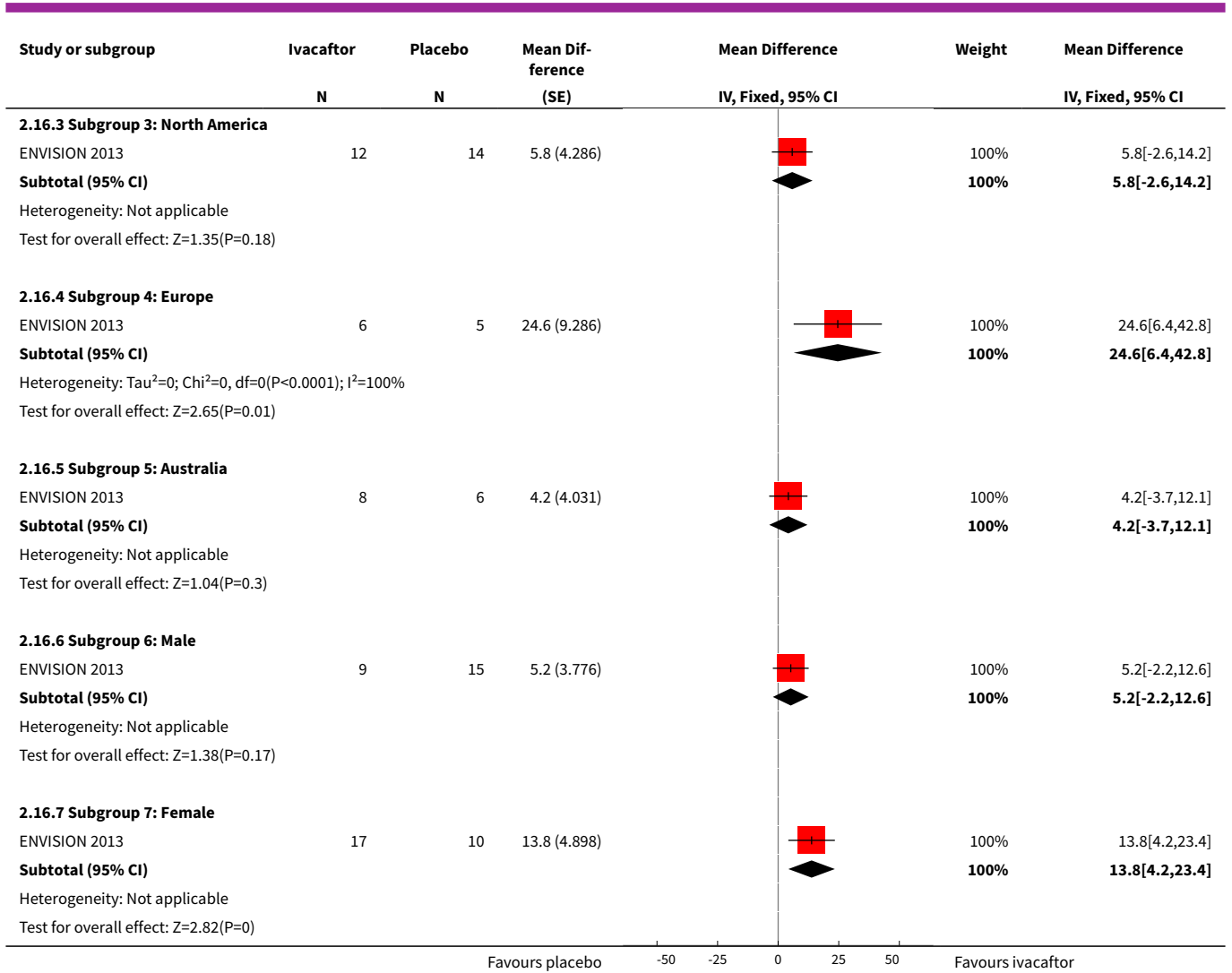


Analysis 2.15. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 15 FEV₁ (litres) - mean absolute change from baseline.

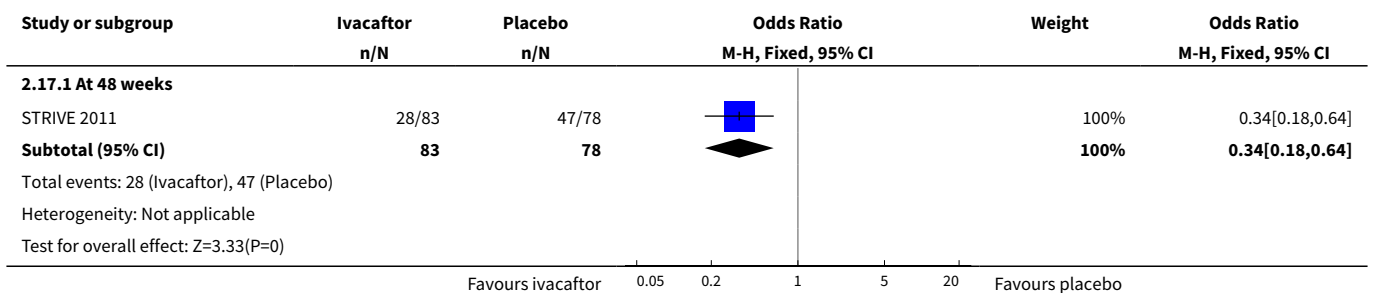


Analysis 2.16. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 16 Change from baseline through week 24 in percent of predicted FEV₁ according to subgroup.

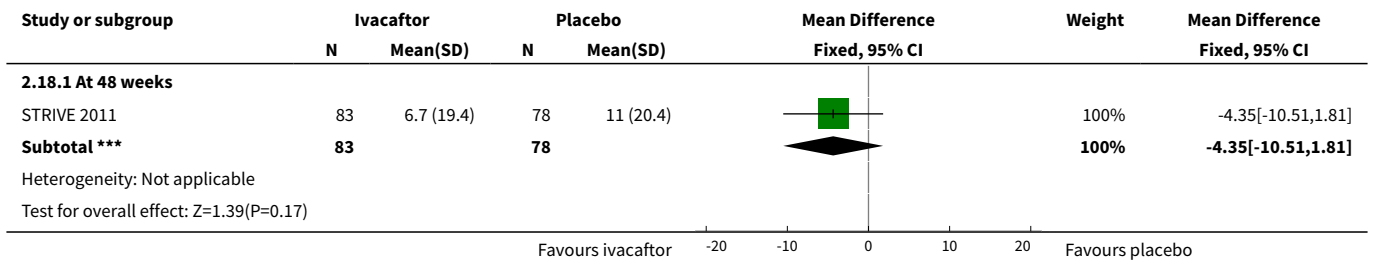




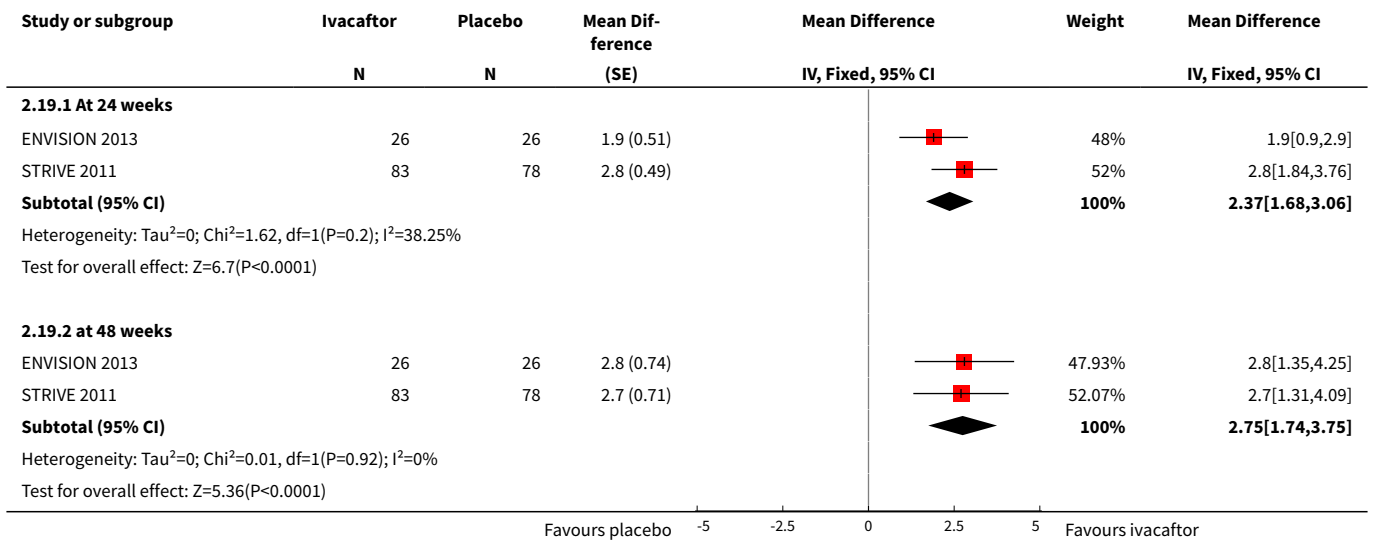
Analysis 2.17. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 17 Number of pulmonary exacerbations requiring intravenous antibiotics.



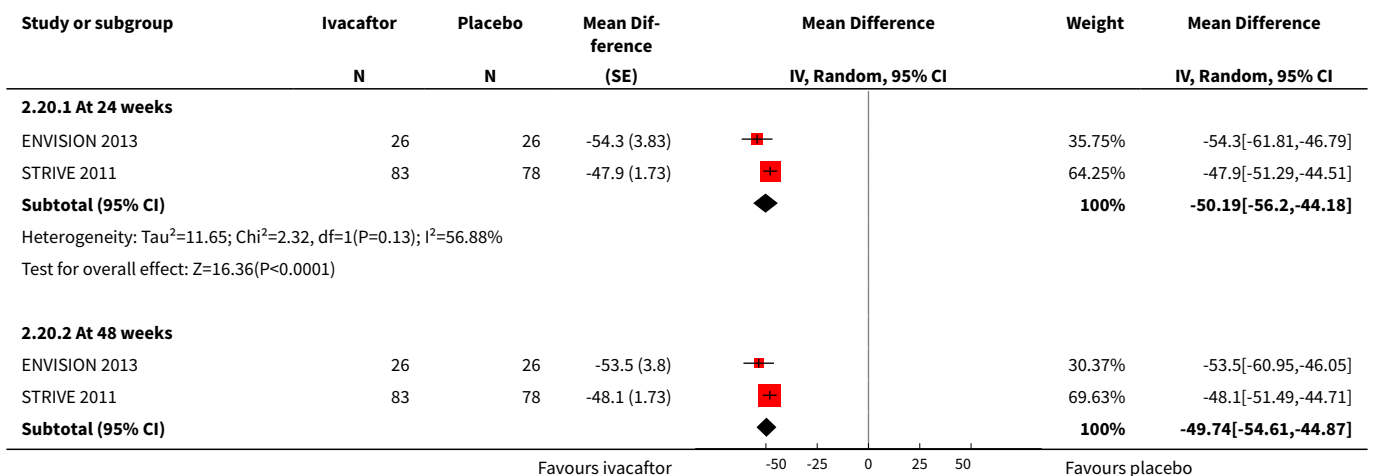
Analysis 2.18. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 18 Days with intravenous antibiotics administered for pulmonary exacerbations.

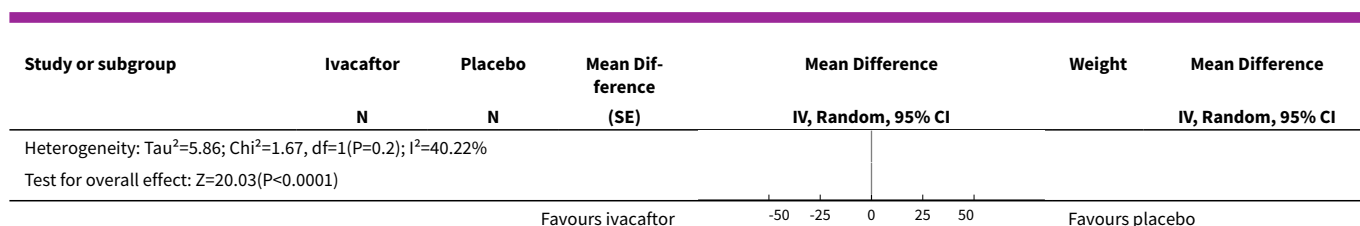


Analysis 2.19. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 19 Weight - change from baseline (kg).



Analysis 2.20. Comparison 2 Ivacaftor (VX-770) versus placebo in people with at least one G551D CFTR mutation, Outcome 20 Sweat chloride level - change from baseline.



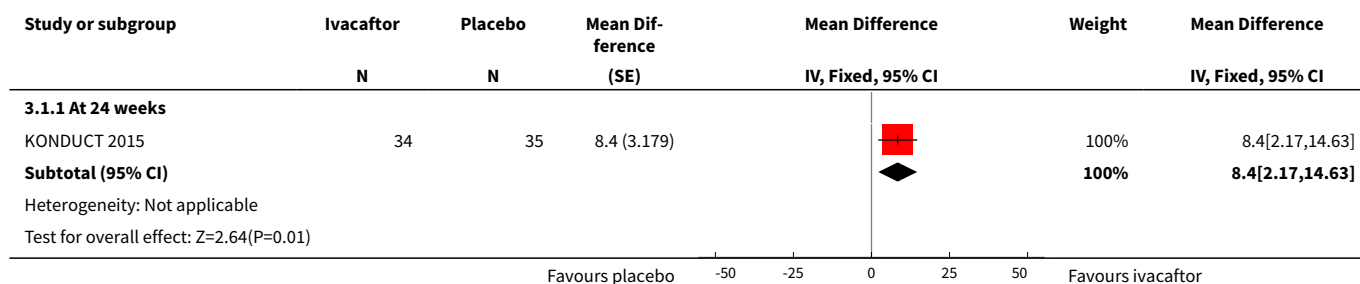


Comparison 3. Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation

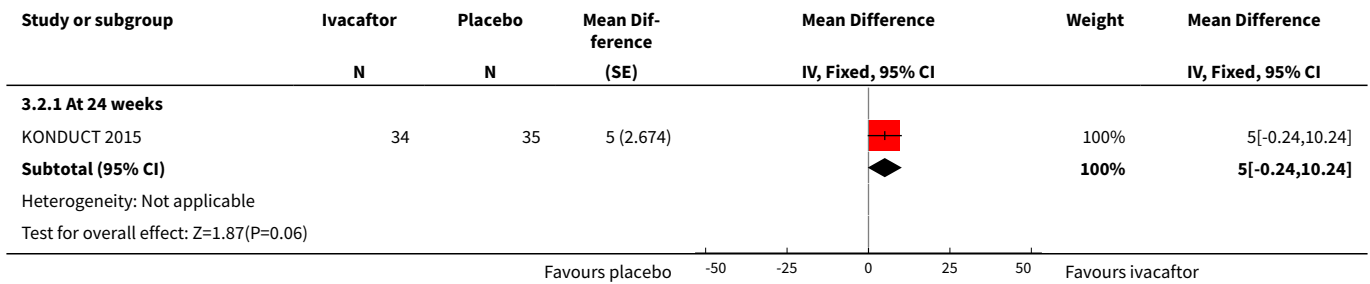
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CFQ-R score (respiratory domain score, pooled) - absolute change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 At 24 weeks	1	69	Mean Difference (Fixed, 95% CI)	8.4 [2.17, 14.63]
2 FEV₁ relative change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 At 24 weeks	1	69	Mean Difference (Fixed, 95% CI)	5.0 [-0.24, 10.24]
3 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 Any adverse event	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.18 [0.01, 3.96]
3.2 Serious adverse event	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.16, 2.52]
3.3 Adverse event leading to discontinuation	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Adverse events in > 15% of participants	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Pulmonary exacerbation	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.35, 2.44]
4.2 Cough	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.42, 3.47]
4.3 Headache	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.35, 4.69]
4.4 Increased sputum	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.33, 5.47]
4.5 Nasal congestion	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.33, 5.47]
4.6 Oropharyngeal pain	1	69	Odds Ratio (M-H, Fixed, 95% CI)	2.84 [0.51, 15.79]
4.7 Diarrhoea	1	69	Odds Ratio (M-H, Fixed, 95% CI)	1.34 [0.33, 5.47]
4.8 Abdominal pain	1	69	Odds Ratio (M-H, Fixed, 95% CI)	10.48 [0.54, 202.47]
4.9 Wheezing	1	69	Odds Ratio (M-H, Fixed, 95% CI)	4.53 [0.48, 42.82]
4.10 Cystic fibrosis lung pathogen colonisation	1	69	Odds Ratio (M-H, Fixed, 95% CI)	3.29 [0.32, 33.31]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Summary of pulmonary exacerbations	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 All pulmonary exacerbations	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.81 [0.30, 2.19]
5.2 Number of hospitalisations for pulmonary exacerbation	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.62]
5.3 Number of pulmonary exacerbations requiring intravenous antibiotics	1	69	Odds Ratio (M-H, Fixed, 95% CI)	0.30 [0.06, 1.62]
6 Time to first pulmonary exacerbation	1		Hazard Ratio (Fixed, 95% CI)	Subtotals only
6.1 At 24 weeks	1	69	Hazard Ratio (Fixed, 95% CI)	0.93 [0.42, 2.08]
7 FEV₁ predicted % absolute change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
7.1 At 24 weeks	1	69	Mean Difference (Fixed, 95% CI)	2.1 [-1.13, 5.33]
8 BMI absolute change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
8.1 At 24 weeks	1	69	Mean Difference (Fixed, 95% CI)	0.26 [-1.57, 2.09]
9 Sweat chloride concentration - change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
9.1 At 24 weeks	1	69	Mean Difference (Fixed, 95% CI)	-22.00 [-28.01, -19.99]

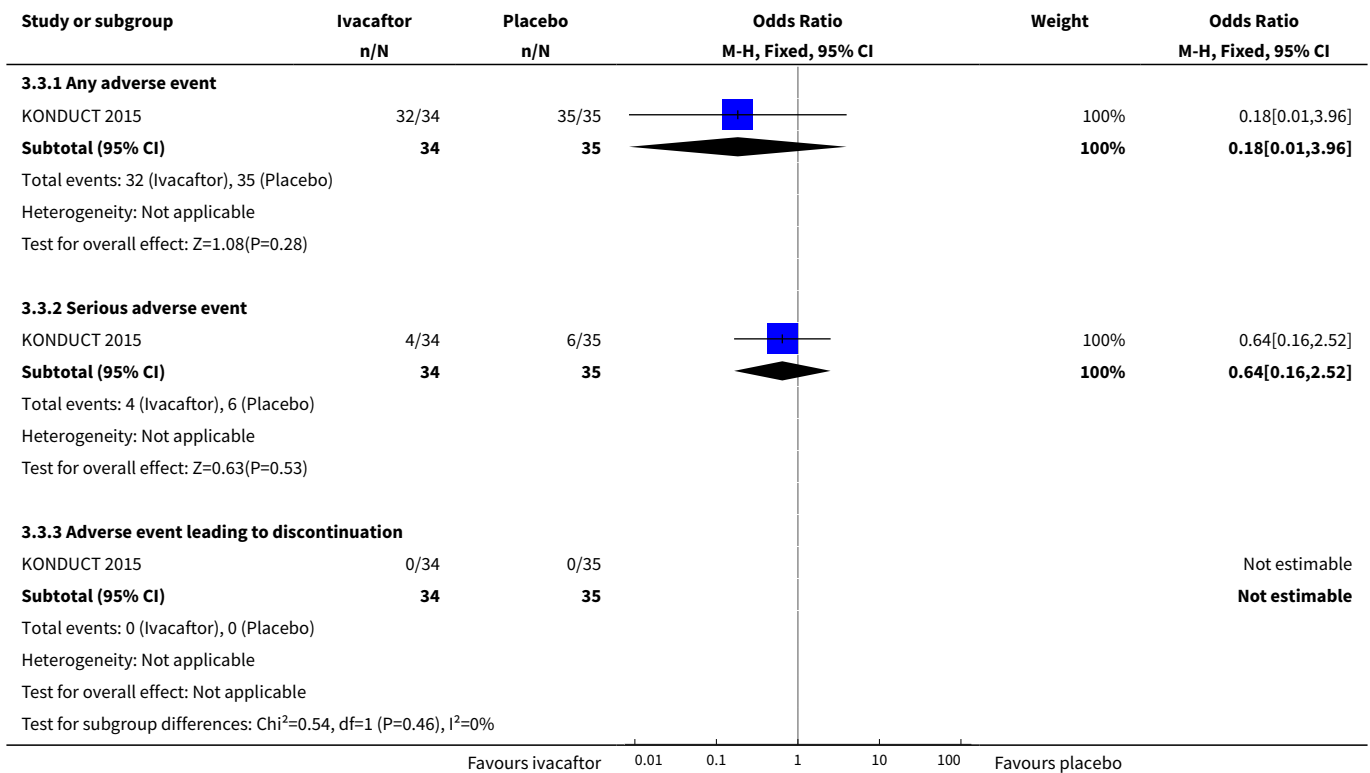
Analysis 3.1. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 1 CFQ-R score (respiratory domain score, pooled) - absolute change from baseline.



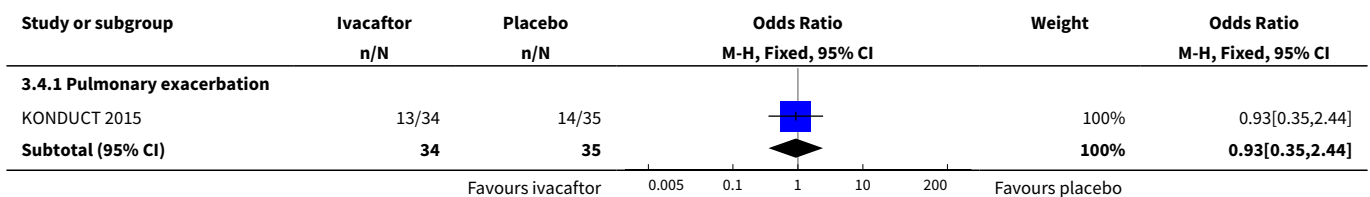
Analysis 3.2. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 2 FEV₁ relative change from baseline.

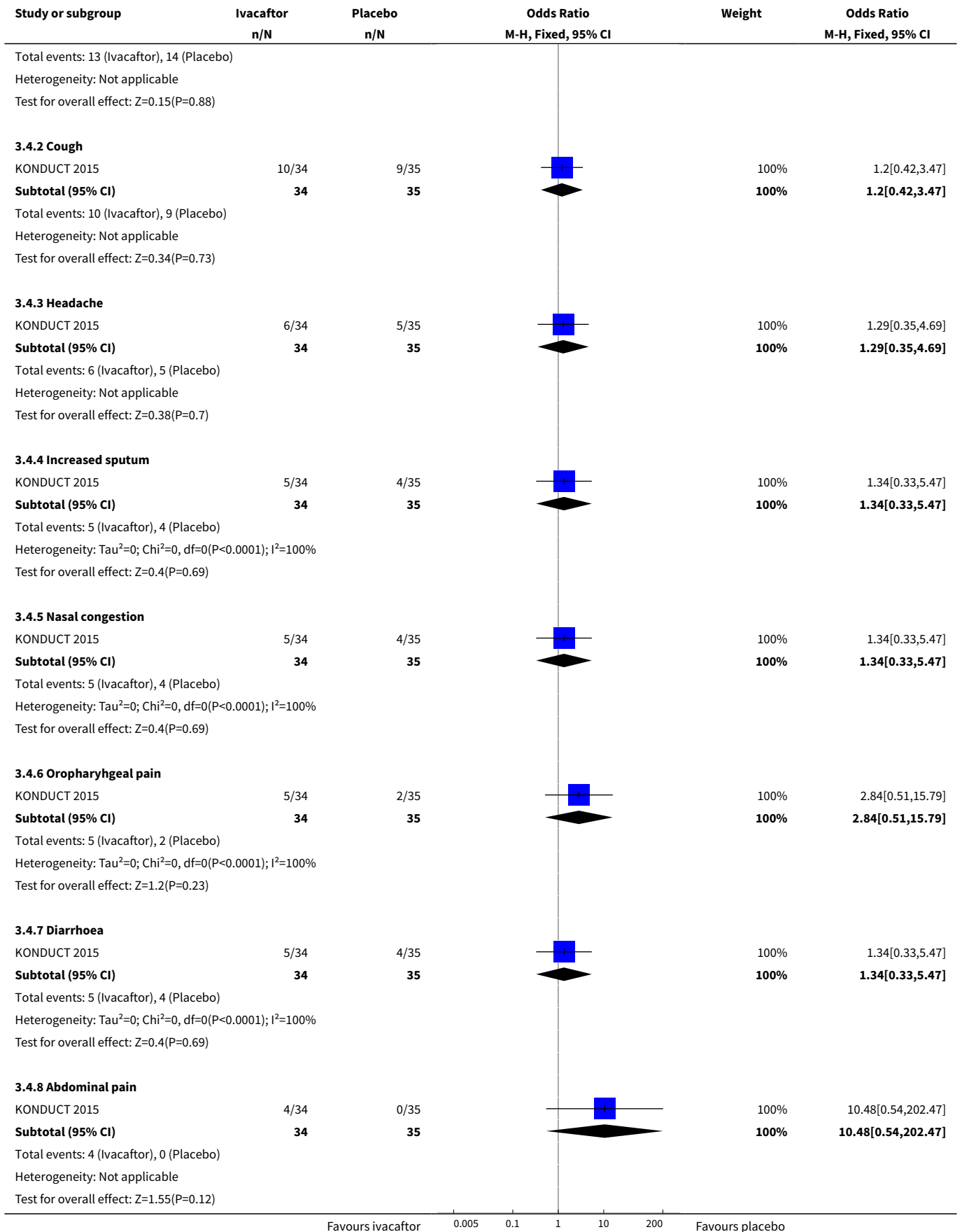


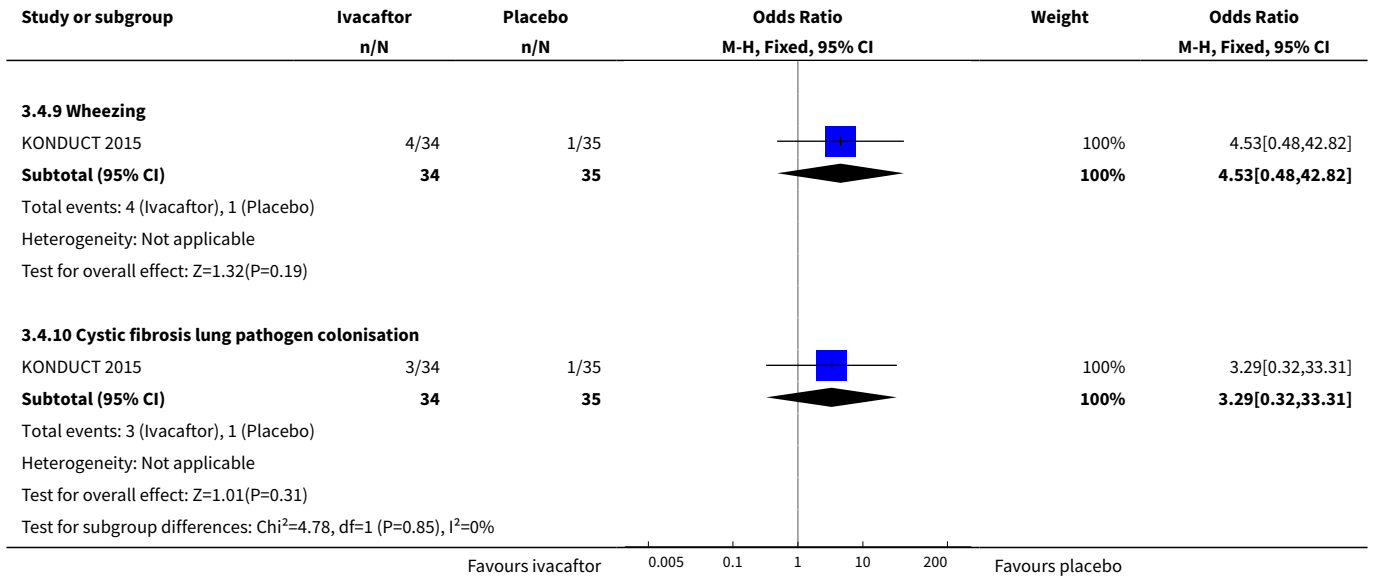
Analysis 3.3. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 3 Adverse events.



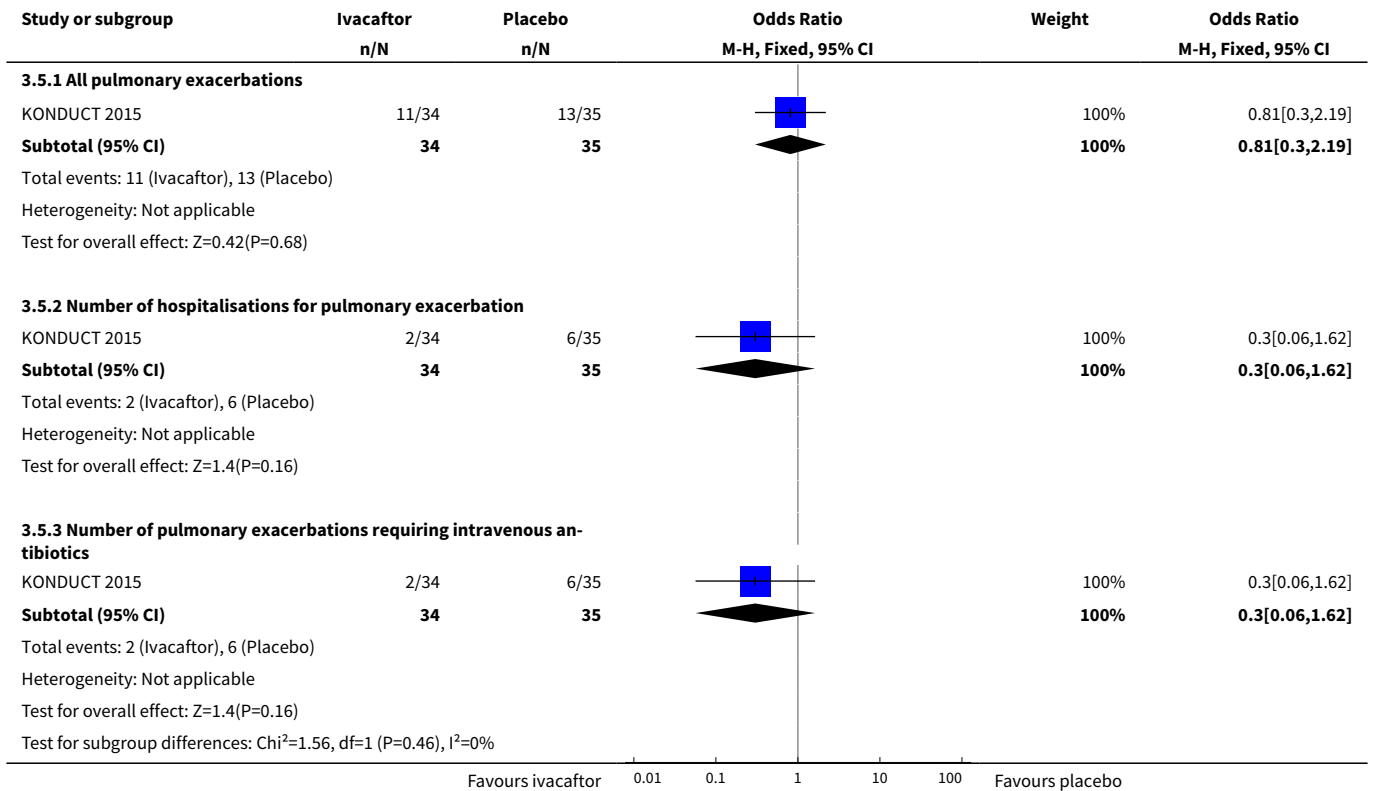
Analysis 3.4. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 4 Adverse events in > 15% of participants.



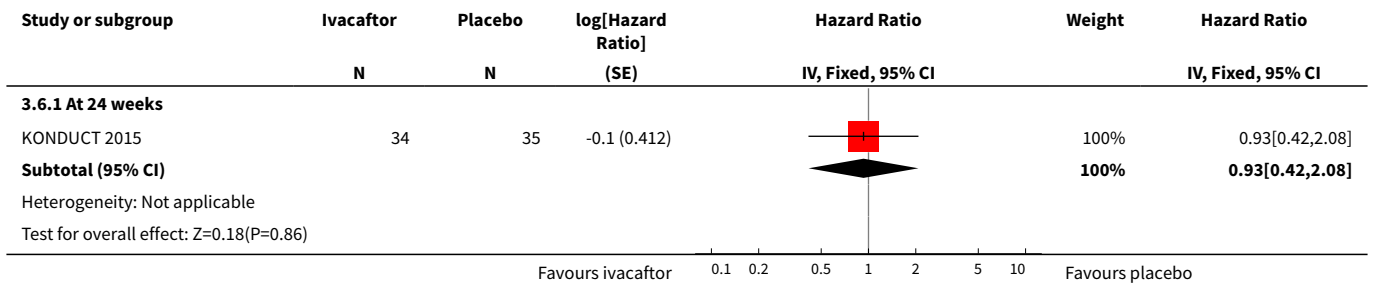




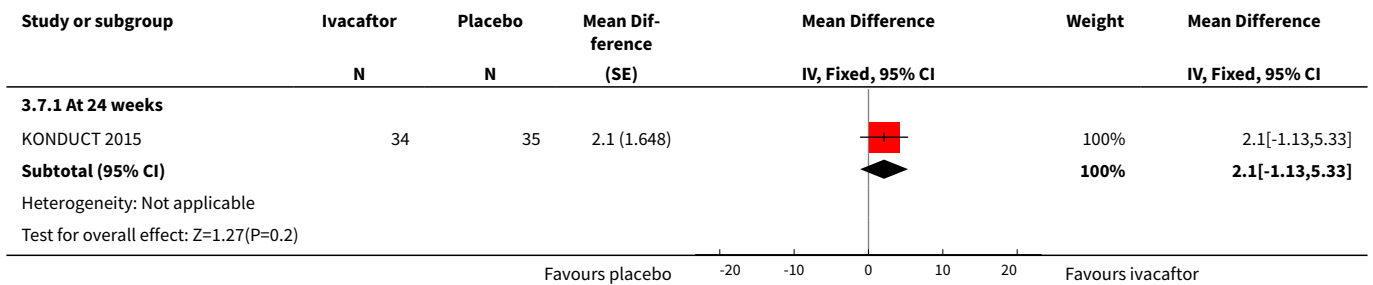
Analysis 3.5. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 5 Summary of pulmonary exacerbations.



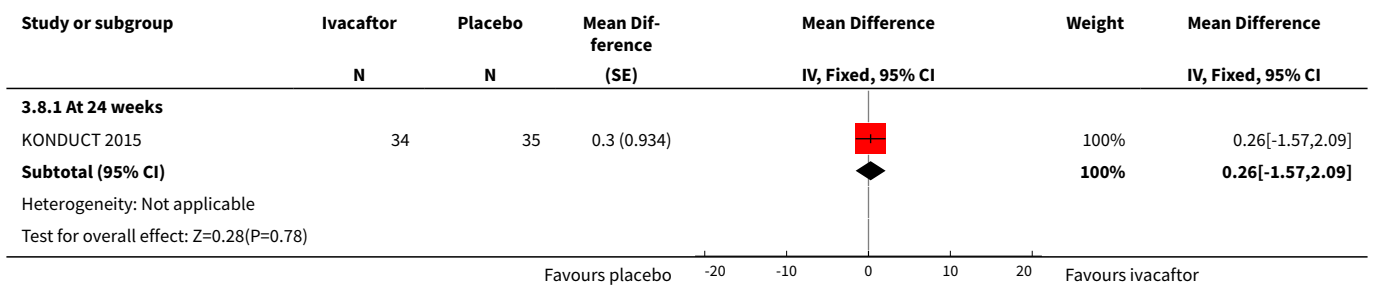
Analysis 3.6. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 6 Time to first pulmonary exacerbation.



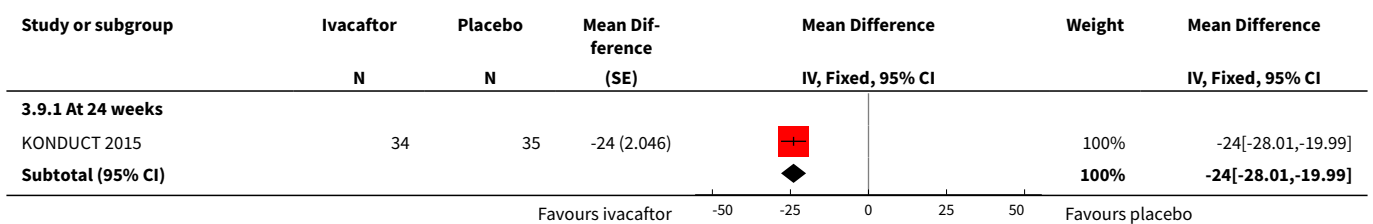
Analysis 3.7. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 7 FEV₁ predicted % absolute change from baseline.

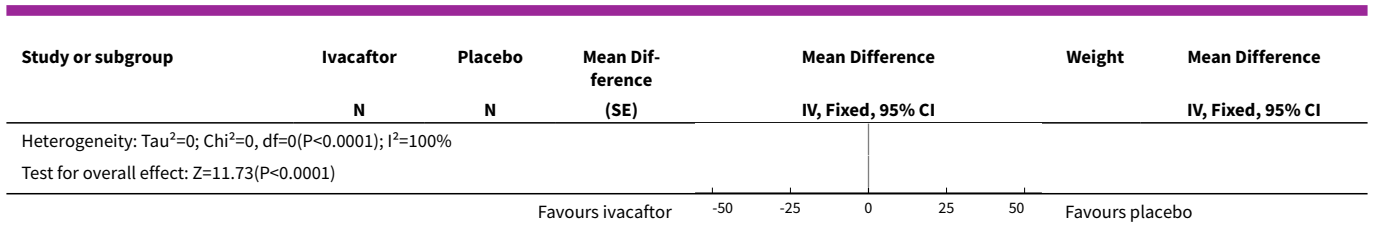


Analysis 3.8. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 8 BMI absolute change from baseline.



Analysis 3.9. Comparison 3 Ivacaftor (VX-770) versus placebo in people with at least one R117H CFTR mutation, Outcome 9 Sweat chloride concentration - change from baseline.





ADDITIONAL TABLES

Table 1. Classes of mutations affecting CFTR production, structure, and function

Class	Example mutation	Impact on CFTR structure and function
I	G542X	Synthesis of CFTR is critically impaired, and no functional protein is produced. This is due to the presence of a premature stop codon in the nucleotide sequence. Individuals have minimal CFTR function.
II	ΔF508	A full length of CFTR is produced, but this is structurally abnormal and destroyed by the cell before it reaches the cell membrane. This is called a defect in the intracellular trafficking pathway. Minimal amounts of CFTR can escape being destroyed and be transported to the cell membrane. However here, class II CFTR products display defective ion transport. Individuals have minimal CFTR function.
III	G551D	CFTR is produced and embedded in the cell membrane, but the chloride channel does not respond ('switch on') to normal stimulation from the cell. This means there is no significant ion transport across the protein. Individuals have some residual CFTR function.
IV	R347P	CFTR is transported to the outer cell membrane, and responds to normal stimulation, but functions at a low level because chloride ions do not cross the channel appropriately. Individuals have some residual CFTR function.
V	A455E	Normal CFTR is produced, but the amount of protein is reduced. Individuals have some residual CFTR function.

CFTR: cystic fibrosis transmembrane conductance regulator

Table 2. CFQ-R domain scores in the phase 2 G551D study at 4 weeks (median (range))

Domain	Day 14			Day 28		
	Placebo (n = 4)	VX-770 150 mg (n = 8)	VX-770 250 mg (n = 7)	Placebo (n = 4)	VX-770 150 mg (n = 8)	VX-770 250 mg (n = 7)
Body image	0 (-11.1 to 22.2)	0 (-22.2 to 0)	0 (-11.1 to 22.2)	-5.6 (-11.1 to 22.2)	0 (-22.2 to 11.1)	0 (-11.1 to 44.4)
Digestive symptoms	-5.6 (-22.2 to 0)	0 (0 to 22.2)	0 (-11.1 to 22.2)	0 (-22.0 to 0)	5.6 (0 to 22.2)	0 (-11.1 to 33.3)
Eating disturbances	0 (-11.1 to 11.1)	0 (0 to 11.1)	0 (-11.1 to 0)	-5.6 (-11.1 to 0)	0	0 (-11.1 to 0)

Table 2. CFQ-R domain scores in the phase 2 G551D study at 4 weeks (median (range)) (Continued)
 (0 to 0)

Emotional functioning	13.3 (-6.7 to 20.0)	0 (-26.7 to 0)	0 (-20.0 to 26.7)	3.3 (0 to 20.0)	0 (-6.7 to 6.7)	6.7 (-6.7 to 20.0)
Health perceptions	5.6 (-11.1 to 11.1)	0 (-22.2 to 22.2)	0 (-33.3 to 11.1)	0 (-11.1 to 11.1)	0 (-22.2 to 22.2)	0 (-11.1 to 11.1)
Physical functioning	0 (0 to 4.2)	2.1 (-4.2 to 16.7)	4.2 (0 to 8.3)	2.1 (0 to 4.2)	4.2 (-8.3 to 25.0)	0 (0 to 12.5)
Respiratory symptoms	2.8 (-5.6 to 11.1)	5.6 (0 to 16.7)	5.6 (-11.1 to 11.1)	2.8 (-5.6 to 11.1)	8.3 (0 to 16.7)	11.1 (-5.6 to 33.3)
Role	0 (0 to 8.3)	0 (-8.3 to 8.3)	0 (0 to 8.3)	0 (0 to 0)	0 (-8.3 to 8.3)	0 (-8.3 to 8.3)
Social	2.8 (-5.6 to 5.6)	0 (-44.4 to 11.1)	-5.6 (-16.7 to 5.6)	2.8 (-11.1 to 5.6)	0 (-11.1 to 5.6)	0 (-16.7 to 11.1)
Treatment burden	0 (-11.1 to 11.1)	-5.6 (-22.2 to 11.1)	0 (-22.2 to 22.2)	0 (0 to 0)	-5.6 (-22.2 to 11.1)	0 (-22.2 to 11.1)
Vitality	4.2 (-16.7 to 8.3)	4.2 (-8.3 to 16.7)	0 (-8.3 to 16.7)	-8.3 (-16.7 to 0)	0 (-16.7 to 25.0)	0 (0 to 16.7)
Weight	0 (0 to 33.3)	0 (0 to 33.3)	0 (-33.3 to 33.3)	0 (0 to 33.3)	0 (0 to 33.3)	0 (-33.3 to 33.3)

CFQ-R: Cystic Fibrosis Questionnaire-Revised

Table 3. Outcomes for age subgroups in R117H study at 24 weeks

	Overall		6 - 11 years		≥18 years	
	Treatment difference	P value	Treatment difference	P value	Treatment difference	P value
Quality of life (CFQ-R) - respiratory domain (pooled)	8.4	0.009	-6.1	0.19	12.6	0.002
% predicted FEV ₁ - absolute change from baseline	2.1	0.20	-6.3	0.03	5.0	0.01
% predicted FEV ₁ - relative change from baseline	5.0	0.06	-6.8	0.04	0.2	0.008
BMI - absolute change from baseline	0.26	0.78	-0.18	0.87	0.31	0.78
Sweat chloride - absolute change from baseline	-24.0	<0.0001	-27.6	<0.001	-21.9	<0.001

Treatment difference was adjusted for age and % predicted FEV₁

BMI: body mass index

CFQ-R: cystic fibrosis questionnaire - revised

FEV₁: forced expiratory volume in one second

Table 4. Absolute change in FEV₁ % predicted amongst pre-defined subgroups in the adult phase 3 G551D study at 48 weeks.

Subgroup	Treatment effect	P value
Baseline percent of predicted FEV ₁ of less than 70%	10.6	< 0.001
Baseline percent of predicted FEV ₁ of greater or equal to 70%	10.3	< 0.001
Participants from North America	9.0	< 0.001
Participants from Europe	9.9	< 0.001
Participants from Australia	11.9	0.008
Male	11.0	< 0.001
Female	11.6	< 0.001
Less than 18 years	11.4	0.005
Greater than or equal to 18 years	9.9	< 0.001

The treatment effect represents the difference between the ivacaftor group and the placebo group with respect to the absolute change from baseline through week 48.

FEV₁: forced expiratory volume at one second

Table 5. Change from baseline in sweat chloride concentration in FEV₁ responders and FEV₁ non-responders in the phase 3 G551D studies

	Paediatric phase 3 G551D study (ENVISION 2013)		Adult phase 3 G551D study (STRIVE 2011)	
	Treatment difference (mmol/L)	P value	Treatment difference (mmol/L)	P value
Minimal responders (less than 5% point improvement)	-55.8	<0.0001	-46.1	< 0.0001
FEV ₁ responders (5% point improvement)	-53.9	<0.0001	-49.7	< 0.0001

FEV₁: forced expiratory volume at one second

APPENDICES

Appendix 1. Glossary

Term	Explanation
CFTR (cystic fibrosis trans-membrane regulator)	A protein which is in the outer membrane of cells. It works by regulating transport of salt in and out of the cell. Problems with the amount of CFTR in the cell membrane, its structure, or the manner in which it functions can lead to altered transport of salt across the cell membrane. In the lungs of people with CF, these problems cause thick airway secretions. Abnormalities of CFTR can also lead to problems in other organs.
CFTR correctors	Drugs or chemicals which work by increasing the amount of CFTR in the cell membrane.
CFTR potentiators	Drugs or chemicals which increase the effectiveness of CFTR at transporting salt across the cell membrane.
CFTR stop-codon therapies	Drugs or chemicals which help the cell to synthesise CFTR. They specifically work in people with CF in whom the basic defect happens because CFTR which is made is too short, and so functions abnormally.

Appendix 2. Electronic search strategies

Database / Resource	Search terms	Date last searched
European Medicines Agency (www.clinicaltrialsregister.eu/)	cystic fibrosis AND ivacaftor	13 April 2018
US National Institute of Health trials database (clinicaltrials.gov/)	cystic fibrosis AND ivacaftor	13 April 2018
WHO ICTRP (apps.who.int/trialsearch/)	cystic fibrosis AND ivacaftor	13 April 2018

WHAT'S NEW

Date	Event	Description
18 December 2018	New citation required and conclusions have changed	<p>One new trial was included (KONDUCT 2015). An improvement in the respiratory domain of the CFQ-R was demonstrated but no improvement in respiratory function.</p> <p>Three authors have stepped down from the review (Kerry Dwan, Carlos Echevarria and Michael Schechter) and two new authors have joined the team (Mica Skilton and Ashma Krishan).</p>
18 December 2018	New search has been performed	<p>One trial has been included from the previous ongoing studies section (KONDUCT 2015).</p> <p>A search of the Cochrane Cystic Fibrosis and Genetic Disorders Review Group's Cystic Fibrosis Register identified 99 new references (45 trials) which were potentially eligible for inclusion in this review.</p>

Date	Event	Description
		<p>There were 14 references to already included trials: two references were added to the Accurso trial (Accurso 2010); six references were added to the Ramsey trial (STRIVE 2011); three references were added to the Davies trial (ENVISION 2013); and three references which are linked to both the Davies and Ramsey trials were also added (ENVISION 2013; STRIVE 2011).</p> <p>A further four references were identified and added to already excluded trials: three references to the Kerem trial (Kerem 2014); one reference to the Davies trial (Davies 2012). There were 29 references to 10 new trials identified, all were excluded (AL-BATROSS 2017; Berkers 2017; Davies 2016; Edgeworth 2017; FLAMINGO 2017; Horsley 2018; McGarry 2015; NCT02323100; RIO-CF 2017; Seliger 2015).</p> <p>Two new references were added to studies awaiting classification (Kazani 2016; Uttamsingh 2016).</p> <p>A search of two clinical trials registries identified 33 new relevant trials, all of which were excluded.</p> <p>In a post hoc change, corrector and potentiator combination therapy trials have not been referenced in the review, meaning the remaining 52 references identified have not been listed.</p>

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO WILL UNDERTAKE THE TASK?
<i>Protocol stage:</i> draft the protocol	IS with comments from all
<i>Review stage:</i> select which trials to include (2 + 1 arbiter)	IS, SP, MS
<i>Review stage:</i> extract data from trials (at least 2 people)	IS, SP, CE
<i>Review stage:</i> enter data into RevMan	SP, KD
<i>Review stage:</i> carry out the analysis	SP, KD
<i>Review stage:</i> interpret the analysis	IS, SP, KD
<i>Review stage:</i> draft the final review	SP with comments from all
<i>Update stage:</i> update the review	MS, IS, SP, AK

DECLARATIONS OF INTEREST

Mica Skilton declares no potential conflict of interest.

Ian Sinha declares no potential conflict of interest.

Sanjay Patel declares no potential conflict of interest.

Kevin Southern declares no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

This systematic review was supported by the National Institute for Health Research, via Cochrane Infrastructure funding to the Cochrane Cystic Fibrosis and Genetic Disorders Group.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Full review 2016

We have made several changes since the protocol stage.

- The title has been changed from 'Mutation-specific therapies that potentiate cystic fibrosis transmembrane conductance regulator (CFTR) function in cystic fibrosis' to the current title of this review.
- We decided to only include trials that compare a CFTR potentiator to a placebo or other intervention. Trials comparing a CFTR potentiator alongside another CFTR modulator will be published in a different review.
- For the primary outcome of survival, in a post hoc change, mortality data were also considered.
- We have decided to add cost of treatment as a secondary outcome of interest.
- In a post hoc change, we have edited the methods section that 99% confidence intervals will be used to analyse separate adverse events. This is the most appropriate statistical approach for considering adverse events individually.
- We have added a Summary of Findings table based on the most clinically important outcomes, in line with the outcomes to be reported in the ongoing review of CFTR correctors ([Southern 2018](#)).

Update 2018

- In a post hoc change, corrector and potentiator combination therapy trials have not been referenced in the review, meaning the 39 references to combination therapy identified in the 2018 searches have not been listed as excluded studies

INDEX TERMS

Medical Subject Headings (MeSH)

Age Factors; Aminophenols [adverse effects] [*therapeutic use]; Chloride Channel Agonists [adverse effects] [*therapeutic use]; Clinical Trials, Phase II as Topic; Clinical Trials, Phase III as Topic; Cystic Fibrosis [*drug therapy] [*genetics]; Cystic Fibrosis Transmembrane Conductance Regulator [drug effects] [*genetics]; Forced Expiratory Volume [drug effects]; Molecular Targeted Therapy [methods]; Mucociliary Clearance; Mutation [*genetics]; Quality of Life; Quinolones [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans