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Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis (Review)

Southern KW, Patel S, Sinha IP, Nevitt SJ

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[Intervention Review]

Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis

Kevin W Southern[1], Sanjay Patel[2], Ian P Sinha[1], Sarah J Nevitt[3]

[1]Department of Women's and Children's Health, University of Liverpool, Liverpool, UK. [2]Stepping Hill Hopsital, Stockport NHS Foundation Trust, Stockport, UK. [3]Department of Biostatistics, University of Liverpool, Liverpool, UK

Contact address: Kevin W Southern, Department of Women's and Children's Health, University of Liverpool, Alder Hey Children's NHS Foundation Trust, Eaton Road, Liverpool, Merseyside, L12 2AP, UK. kwsouth@liverpool.ac.uk.

A B S T R A C T

Background

Cystic fibrosis (CF) is a common life-shortening condition caused by mutation in the gene that codes for that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein, which functions as a salt transporter. F508del, the most common *CFTR* mutation that causes CF, is found in up to 80% to 90% of people with CF. In people with this mutation, a full length of protein is transcribed, but recognised as misfolded by the cell and degraded before reaching the cell membrane, where it needs to be positioned to effect transepithelial salt transport. This severe mutation is associated with no meaningful CFTR function. A corrective therapy for this mutation could positively impact on an important proportion of the CF population.

Objectives

To evaluate the effects of CFTR correctors on clinically important outcomes, both benefits and harms, in children and adults with CF and class II *CFTR* mutations (most commonly F508del).

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Cystic Fibrosis Trials Register. We also searched reference lists of relevant articles and online trials registries. Most recent search: 24 February 2018.

Selection criteria

Randomised controlled trials (RCTs) (parallel design) comparing CFTR correctors to placebo in people with CF with class II mutations. We also included RCTs comparing CFTR correctors combined with CFTR potentiators to placebo.

Data collection and analysis

Two authors independently extracted data, assessed risk of bias and quality of the evidence using the GRADE criteria. Study authors were contacted for additional data.

Main results

We included 13 RCTs (2215 participants), lasting between 1 day and 24 weeks. Additional safety data from an extension study of two lumacaftor-ivacaftor studies were available at 96 weeks (1029 participants). We assessed monotherapy in seven RCTs (317 participants) (4PBA (also known as Buphenyl), CPX, lumacaftor or cavosonstat) and combination therapy in six RCTs (1898 participants) (lumacaftor-ivacaftor or tezacaftor-ivacaftor) compared to placebo. Twelve RCTs recruited individuals homozygous for F508del, one RCT recruited participants with one F508del mutation and a second mutation with residual function.

Risk of bias varied in its impact on the confidence we have in our results across different comparisons. Some findings were based on single RCTs that were too small to show important effects. For five RCTs, results may not be applicable to all individuals with CF due to age limits of recruited populations (i.e. adults only, children only) or non-standard design of converting from monotherapy to combination therapy.

Monotherapy versus placebo

No deaths were reported and there were no clinically relevant improvements in quality of life in any RCT. There was insufficient evidence available from individual studies to determine the effect of any of the correctors examined on lung function outcomes.

No placebo-controlled study of monotherapy demonstrated a difference in mild, moderate or severe adverse effects; however, it is difficult to assess the clinical relevance of these events with the variety of events and the small number of participants.

Combination therapy versus placebo

No deaths were reported during any RCT (moderate- to high-quality evidence). The quality of life scores (respiratory domain) favoured combination therapy (both lumacaftor-ivacaftor and tezacaftor-ivacaftor) compared to placebo at all time points. At six months lumacaftor (600 mg once daily or 400 mg once daily) plus ivacaftor improved Cystic Fibrosis Questionnaire (CFQ) scores by a small amount compared with placebo (mean difference (MD) 2.62 points (95% confidence interval (CI) 0.64 to 4.59); 1061 participants; high-quality evidence). A similar effect size was observed for twice-daily lumacaftor (200 mg) plus ivacaftor (250 mg) although the quality of evidence was low (MD 2.50 points (95% CI 0.10 to 5.10)). The mean increase in CFQ scores with twice-daily tezacaftor (100 mg) and ivacaftor (150 mg) was approximately five points (95% CI 3.20 to 7.00; 504 participants; moderate-quality evidence). Lung function measured by relative change in forced expiratory volume in one second (FEV_1) % predicted improved with both combination therapies compared to placebo at six months, by 5.21% with once daily lumacaftor-ivacaftor (95% CI 3.61 to 6.80; 504 participants; high-quality evidence) and by 2.40% with twice-daily lumacaftor-ivacaftor (95% CI 0.40% to 4.40%; 204 participants; low-quality evidence). One study reported an increase in FEV_1 with tezacaftor-ivacaftor of 6.80% (95% CI 5.30 to 8.30%; 520 participants; moderate-quality evidence).

More participants receiving the lumacaftor-ivacaftor combination reported early transient breathlessness, odds ratio 2.05 (99% CI 1.10 to 3.83; 739 participants; high-quality evidence). In addition, participants allocated to the 400 mg twice-daily dose of lumacaftor-ivacaftor experienced a rise in blood pressure over the 120-week period of the initial studies and the follow-up study of 5.1 mmHg (systolic blood pressure) and 4.1 mmHg (diastolic blood pressure) (80 participants; high-quality evidence). These adverse effects were not reported in the tezacaftor-ivacaftor studies.

The rate of pulmonary exacerbations decreased for participants receiving and additional therapies to ivacaftor compared to placebo: lumacaftor 600 mg hazard ratio (HR) 0.70 (95% CI 0.57 to 0.87; 739 participants); lumacaftor 400 mg, HR 0.61 (95% CI 0.49 to 0.76; 740 participants); and tezacaftor, HR 0.64 (95% CI, 0.46 to 0.89; 506 participants) (moderate-quality evidence).

Authors' conclusions

There is insufficient evidence that monotherapy with correctors has clinically important effects in people with CF who have two copies of the F508del mutation.

Combination therapies (lumacaftor-ivacaftor and tezacaftor-ivacaftor) each result in similarly small improvements in clinical outcomes in people with CF; specifically improvements quality of life (moderate-quality evidence), in respiratory function (high-quality evidence) and lower pulmonary exacerbation rates (moderate-quality evidence). Lumacaftor-ivacaftor is associated with an increase in early transient shortness of breath and longer-term increases in blood pressure (high-quality evidence). These adverse effects were not observed for tezacaftor-ivacaftor. Tezacaftor-ivacaftor has a better safety profile, although data are not available for children younger than 12 years. In this age group, lumacaftor-ivacaftor had an important impact on respiratory function with no apparent immediate safety concerns, but this should be balanced against the increase in blood pressure and shortness of breath seen in longer-term data in adults when considering this combination for use in young people with CF.

P L A I N   L A N G U A G E   S U M M A R Y

CFTR correctors, a therapy for cystic fibrosis targeted at specific mutations

Review question

We looked at drugs (or combination of drugs) that aim to correct the basic defect for the commonest mutation (F508del) that causes cystic fibrosis (CF). We assessed the impact on clinical outcomes that are important to people with CF (e.g., survival, quality of life, lung function and safety).

Background

The CF gene makes a protein that has important function in many parts of the body by helping the movement of salts across cells. People with CF are either not able to make this protein or make a protein that is defective. A common mutation of the CF gene is F508del and over 80% of people with CF have at least one copy of this gene variant. When the CF gene is affected by F508del, a full length of protein is made

but it is not able to move through the cell correctly. Laboratory experiments suggest that if this protein can be transported to the cell wall then it may be able to function, restore salt movement and correct the chronic problems experienced by people with CF. We examined a number of agents that might correct the F508del mutation.

Search date

Evidence is current to: 24 February 2018.

Study characteristics

We included 13 studies (2215 children and adults with CF) which lasted between 1 day and 24 weeks (with an extension study of two studies up to 96 weeks). Seven studies (317 participants) looked at single agents (monotherapy: 4PBA (also known as Buphenyl), CPX, lumacaftor and cavosonstat) versus placebo (a dummy treatment containing no active medicine) and six recent studies (1898 participants) assessed combination therapy (lumacaftor-ivacaftor or tezacaftor-ivacaftor) versus placebo. In 12 studies participants had two copies of the F508del mutation and in one study they had one F508del mutation and a second different mutation.

Key results

Monotherapy versus placebo

These studies did not report any deaths or any clinically relevant improvements in quality of life scores. There was not enough evidence to show an effect on lung function. Side effects were reported in all studies, but it is difficult to assess their relevance due to the range of effects and the small number of participants in the studies.

Combination therapy versus placebo

No deaths were reported in either the lumacaftor-ivacaftor or tezacaftor-ivacaftor studies in people with two copies of the F508del mutation and there were improvements in quality of life and lung function. Rates of pulmonary exacerbations (a flare up of symptoms) were also lower. Neither combination therapy was associated with severe side effects, although people on lumacaftor-ivacaftor regularly experienced shortness of breath for one to two weeks at the start of treatment, which usually resolved without further intervention. Of more concern was that in longer studies some people receiving lumacaftor-ivacaftor experienced a rise in blood pressure; of these, two people (out of more than 500 who received the combination in these studies) discontinued lumacaftor-ivacaftor treatment because of high blood pressure. These side effects were not reported for the tezacaftor-ivacaftor combination. Tezacaftor-ivacaftor therapy has not yet been assessed in children with CF younger than 12 years of age.

Quality of the evidence

We judged the overall quality of the evidence for the outcomes measured to vary from low to high. Study design was generally poorly reported, which did not allow us to make clear judgements on any potential bias, but we had fewer concerns with the six larger and more recent studies. We did find that some results were omitted from the analysis or not reported in seven studies. Some findings were based on single studies that were too small to show important effects and for five studies the results may not be applicable to all individuals with CF due to the ages of people recruited into the studies (i.e. adults only, children only) or an unusual design used in which people receive monotherapy and then combination therapy.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Summary of findings - Lumacaftor monotherapy compared to placebo

Lumacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor

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	Lumacaftor				
Survival Follow-up: 14 to 28 days	No deaths reported.	No deaths reported.	NA	147 (2 studies)	⊕⊕⊝⊝ **low**[1]	
Quality of life - total score Follow-up: 14 to 28 days	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 14 to 28 days	There was a statistically significant decrease in the CFQ-R respiratory domain in the 50 mg lumacaftor group compared to placebo. No differences were found in the other dose groups (25 mg, 100 mg, 200 mg) compared to placebo.		NA	85 (1 study)	⊕⊕⊝⊝ **low**[1]	A higher score indicates a better outcome.
FEV_1 % predicted: relative change from baseline Follow-up: 14 to 28 days	Outcome not reported.				NA	
FEV_1 % predicted: absolute change from baseline Follow-up: 14 to 28 days	The mean change from baseline was 1.7% predicted.	The mean change from baseline was	NA	61 (1 study)	⊕⊕⊕⊝ **moderate**[2]	

			1.90% predicted lower (4.13 lower to 0.33 higher).	
Adverse events Follow-up: 14 to 28 days	There were no statistically significant differences between groups in terms of participants experiencing any specific adverse event. In 1 of the studies, 1 participant from each of the lumacaftor arms - 1 participant in each of the discontinued the study drug due to respiratory adverse effects. No participants discontinued from the placebo group.	NA	115 (2 studies)	⊕⊖⊖⊖ **very low**[1,2,3]
Time to first pulmonary exacerbation Follow-up: 14 to 28 days	Outcome not reported (see comment).		NA	Time to first pulmonary exacerbation was not reported. There was no statistically significant difference between groups in the number of participants experiencing pulmonary exacerbations.

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

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval, **EQ-5D-3L**: 5-Dimension-3 Level, **FEV$_1$**: forced expiratory volume at one second; **MD**: mean difference.

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

1. Downgraded twice due to risk of bias: in one study data were selectively reported and often presentation of data did not allow for inclusion in analysis (Clancy 2012). There are also incomplete outcome data in the study with participants unaccounted for in analysis.
2. Downgraded once due to indirectness: design of the study means that monotherapy treatment was measured for only 14 days before a combination therapy phase was started (Boyle 2014).
3. Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide (Analysis 1.2; Analysis 1.3).

Summary of findings 2.   Summary of findings - Cavosonstat compared with placebo for cystic fibrosis

Cavosonstat compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: cavosonstat 200 mg

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	Cavosonstat				
Survival Follow-up: 28 days	No deaths reported.	No deaths reported.	NA	26 (1 study)	⊕⊕⊖⊖ **low**[1,2]	
Quality of life: total score Follow-up: NA	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: 28 days	The mean absolute change from baseline in CFQ-R respiratory domain was -4.6 points in the placebo group.	The mean absolute change from baseline in CFQ-R respiratory domain was 3.80 higher (11.30 lower to 18.90 higher) in the Cavosonstat group than the placebo group.	NA	26 (1 study)	⊕⊖⊖⊖ **very low**[1,2,3]	A higher score indicates a better outcome.
FEV$_1$ % predicted: relative change from baseline Follow-up: NA	Outcome not reported.				NA	
FEV$_1$ % predicted: absolute change from baseline Follow-up: 28 days	There were no treatment-related changes in FEV$_1$ (% predicted) compared to placebo.		NA	26 (1 study)	⊕⊕⊖⊖ **low**[1,2]	A graphical figure of change from baseline in FEV$_1$ (% predicted) is provided but numerical data cannot be extract-

				ed to include in analysis due to overlapping lines.
Adverse events: occurring in at least 10% of cavosonstat treated participants Follow-up: 28 days	There was no statistically significant difference between groups in terms of cough, pulmonary exacerbation, chest discomfort and fatigue.	NA	26 (1 study)	⊕⊝⊝⊝ **very low**[1,2,4]
Time to first pulmonary exacerbation Follow-up: NA	Outcome not reported.			NA

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **NA**: not applicable.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to potential risk of bias: unclear details related to methodological design and some unbalanced baseline characteristics.
2. Downgraded once due to indirectness: adults only were recruited into the study, therefore, results are not applicable to children.
3. Downgraded once due to imprecision: wide CIs around the result.
4. Downgraded once due to imprecision: very wide CIs around results (due to small event numbers).

Summary of findings 3.   Summary of findings - Lumacaftor plus ivacaftor (once daily) compared with placebo for cystic fibrosis (short term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (600 mg once daily or 400 mg once daily) plus ivacaftor (250 mg twice daily)

Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)	Relative effect	No of Participants	Quality of the evidence	Comments

	Assumed risk	Corresponding risk	(95% CI)	(studies)	(GRADE)	
	Placebo	Lumacaftor plus ivacaftor				
Survival Follow-up: 6 months	No deaths reported.	No deaths reported.	NA	1108 (2 studies)	⊕⊕⊕⊕ **high**	
Quality of life - (Euro-Qol) EQ-5D-3L Index Score (total score): absolute change from baseline Follow-up: 6 months	The mean absolute change from baseline ranged from 0.0006 to 0.0017 points.	The mean absolute change from baseline was 0.00 points higher (0.01 lower to 0.01 higher).	NA	1061 (2 studies)	⊕⊕⊕⊕ **high**	A higher score indicates a better outcome.
Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 6 months	The mean absolute change from baseline ranged from 1.1 to 2.81 points.	The mean absolute change from baseline was 2.62 points higher (0.64 higher to 4.59).	NA	1076 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	A higher score indicates a better outcome. There was also a statistically significant difference between groups at 28 days, MD 3.70 points (95% CI 1.81 to 5.58).
FEV$_1$ % predicted: relative change from baseline Follow-up: 6 months	The mean relative change from baseline ranged from -0.34% to 0%.	The mean relative change from baseline was 5.21% higher (3.61% higher to 6.80% higher).	NA	1072 (2 studies)	⊕⊕⊕⊕ **high**	
FEV$_1$ % predicted: absolute change from baseline Follow-up: 6 months	The mean absolute change from baseline ranged from -0.44 to -0.15% predicted.	The mean absolute change from baseline was 3.07% predicted higher (2.17 higher to 3.97 higher).	NA	1072 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	There was also a statistically significant difference between groups at 28 days, MD 2.37% predicted (95% CI 1.52 to 3.22).
Adverse events	Cough was statistically significantly more common in the placebo group compared to the lumacaftor-ivacaftor group.		NA	1108	⊕⊕⊕⊕ **high**	

Follow-up: 6 months	Dyspnoea was statistically significantly more comment in the lumacaftor-ivacaftor group compared to the placebo group. There were no statistically significant differences between groups in terms of number of participants experiencing adverse events, serious adverse events or other adverse events. Long-term open-label follow-up data of the 2 studies showed a statistically significant increase in early transient shortness of breath. In participants allocated a 400 mg twice-daily dose, there was a statistically significant rise in blood pressure.	(2 studies)		
Time to first pulmonary exacerbation Follow-up: 6 months	Time to first pulmonary exacerbation was statistically significantly longer in both in the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily and the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily groups	NA	1108 (2 studies)	⊕⊕⊕⊝ **moderate**[1]	Presentation of data did not allow an analysis of the lumacaftor doses pooled.

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

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **EQ-5D-3L**: 5-Dimension-3 Level; **EuroQol**: Euro Quality of Life Scale; **FEV$_1$**: forced expiratory volume at one second; **MD**: mean difference.

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

1. Downgraded once due to risk of bias from selective reporting: data contributing to analyses were extrapolated from published graphs or estimated. We have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update and this judgement will be reconsidered.

Summary of findings 4.   Summary of findings - Lumacaftor plus ivacaftor (twice daily) compared with placebo for cystic fibrosis (short term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily)

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				
Survival Follow-up: 24 weeks	No deaths reported.	No deaths reported.	NA	204 (1 study)	⊕⊕⊕⊝ **moderate**[1]	
Quality of life - total score Follow-up: 24 weeks	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life - CFQ-R respiratory domain: absolute change from baseline Follow-up: 24 weeks	See comment.	The mean change in the CFQ-R respiratory domain was 2.50 points higher in the lumacaftor-ivacaftor group compared to the placebo group, ranging from 0.10 lower to 5.10 higher.	NA	204 (1 study)	⊕⊕⊝⊝ **low**[1,2]	A higher score indicates a better outcome. Data were analysed via a MMRM. Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24.
FEV$_1$ % predicted: relative change from baseline Follow-up: 24 weeks	Outcome not reported.				NA	Relative change from baseline in FEV$_1$ was listed in the methods of the study but no numerical results were presented. if numerical data becomes available at a later date, it will be included in an update of this review.
FEV$_1$ % predicted: absolute change from baseline Follow-up: 24 weeks	See comment.	The mean change in FEV$_1$ % predicted was 2.40 higher in the lumacaftor-ivacaftor group compared to the placebo group, ranging from 0.40 higher to 4.40 higher.	NA	204 (1 study)	⊕⊕⊝⊝ **low**[1,2]	Data were analysed via a MMRM. Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24.

Adverse events Follow-up: 24 weeks	There was no statistically significant difference between the groups in terms of productive cough, nasal congestion, oropharyngeal pain, upper abdominal pain, rhinorrhoea, increased sputum, cough, pyrexia, headache, upper respiratory tract infection, abdominal pain, nausea, vomiting, fatigue and respiratory events (such as wheezing, dyspnoea, asthma and chest discomfort).	NA	204 (1 study)	⊕⊕⊖⊖ **low**[2,3]
Time to first pulmonary exacerbation Follow-up: 24 weeks	Outcome not reported.		NA	Time to first pulmonary exacerbation was listed in the methods of the study but no numerical results were presented. If numerical data become available at a later date, they will be included in an update of this review.

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CFQ-R: Cystic Fibrosis Questionnaire-Revised; **CI**: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second; **MMRM**: mixed model for repeated measures; **NA**: not applicable.

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

1. Downgraded once due to indirectness: children aged 6 - 11 years were recruited in this study, therefore, results are not applicable to other age groups.
2. Downgraded once due to risk of bias from selective reporting: limited data available which is adjusted for all visits. Further graphical data were available in the publication but could not be accurately extracted. We have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update and this judgement will be reconsidered
3. Downgraded once due to imprecision; few events occurred therefore CIs for occurrence of specific events are very wide (Analysis 11.4).

Summary of findings 5.   Summary of findings - Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis (immediate term)

Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: lumacaftor (200 mg) plus ivacaftor (150 mg or 250 mg twice daily)[1]

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	**Lumacaftor plus ivacaftor**[1]				
Survival Follow-up: 21 days[1]	No deaths reported.	No deaths reported.	NA	62 (1 study)	⊕⊕⊕⊖ **moderate**[2]	
Quality of life: total score Follow-up: 21 days[1]	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life: respiratory domain Follow-up: 21 days[1]	Outcome not reported.				NA	A higher score indicates a better outcome.
FEV$_1$ % predicted: relative change from baseline Follow-up: 21 days[1]	Outcome not reported.				NA	
FEV$_1$ % predicted: absolute change from baseline Follow-up: 21 days[1]	The mean change from baseline was 0.3.	The mean change from baseline was 1.57% predicted higher (-2.13 lower to 5.27 higher).	NA	59 (1 study)	⊕⊕⊕⊖ **moderate**[2]	

Adverse events Follow-up: 21 days[1]	There were no statistically significant differences between groups in terms of participants experiencing: cough, oropharyngeal pain, nasal congestion, dizziness, a prolonged prothrombin time, and upper respiratory tract infection.	NA	61 (1 study)	⊕⊕⊖⊖ **low**[2,3]	
Time to first pulmonary exacerbation Follow-up: 21 days[1]	Outcome not reported (see comment).		NA		Time to first pulmonary exacerbation was not reported. There was no statistically significant difference between groups in the number of participants experiencing pulmonary exacerbations.

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

CI: confidence interval; **FEV$_1$**: forced expiratory volume at 1 second.

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. The design of the study was 14 days of lumacaftor monotherapy (200 mg once daily) then a dose of ivacaftor (150 mg or 250 mg once daily) was added on for 7 days of combination therapy. Results presented in this table are from the combination treatment period only.
2. Downgraded once due to indirectness: design of the study means that combination treatment was measured for only 7 days and prior lumacaftor monotherapy phase (see footnote 1) may have influenced results of the combination phase.
3. Downgraded once due to imprecision: few events occurred therefore CIs for occurrence of specific events are very wide (Analysis 12.2).

Summary of findings 6.   Summary of findings - tezacaftor plus ivacaftor compared with placebo or ivacaftor alone

Tezacaftor plus ivacaftor compared with placebo or ivacaftor alone for cystic fibrosis

Patient or population: adults and children with cystic fibrosis

Settings: outpatients

Intervention: tezacaftor (100 mg daily) plus ivacaftor (150 mg twice daily)

Comparison: placebo (i.e. tezacaftor placebo) or ivacaftor (150 mg twice daily)

Outcomes	**Illustrative comparative risks* (95% CI)**	**Relative effect**	**No of Participants**	**Quality of the evidence**	**Comments**

	Assumed risk	Corresponding risk	(95% CI)	(studies)	(GRADE)	
	Placebo or ivacaftor alone	**Tezacaftor plus ivacaftor**				
Survival Follow-up: up to 24 weeks	No deaths reported.	No deaths reported.	NA	522 (2 studies)	⊕⊕⊕⊝ **moderate**[1,2]	
Quality of life: total score Follow-up: NA	Outcome not reported.				NA	A higher score indicates a better outcome.
Quality of life: CFQ-R respiratory domain: absolute change from baseline Follow-up: up to 24 weeks	See comment.	The mean absolute change from baseline in CFQ-R respiratory domain score in the tezacaftor-ivacaftor group was 5.10 points higher (3.20 higher to 7.00 higher) than the placebo group (result from 1 study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊝ **moderate**[1, 2]	A higher score indicates a better outcome Difference in absolute change from baseline calculated by least-squares regression, hence assumed risk not presented. The mean absolute change from baseline in CFQ-R respiratory domain score in the tezacaftor plus ivacaftor group was also statistically significantly higher than the placebo group at 4 weeks: MD 5.10 (95% CI 2.99 to 7.21) The second study (n = 18) showed that the treatment effect of tezacaftor-ivacaftor versus placebo was 6.81 points of CFQ-R respiratory domain (P = 0.2451) up to day 28.

FEV$_1$ % predicted: relative change from baseline Follow-up: up to 24 weeks	See comment.	The mean relative change from baseline in FEV$_1$ % predicted in the tezacaftor-ivacaftor group was 6.80% higher (5.30% higher to 8.30% higher) than the placebo group (result from 1 study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]	Difference in relative change from baseline calculated by least-squares regression, hence assumed risk not presented. The second study (n = 18) showed no statistically significant difference between groups in mean relative change from baseline in FEV$_1$ % predicted MD 3.72 (95% CI -7.77 to 15.21).
FEV$_1$ % predicted: absolute change from baseline Follow-up: up to 24 weeks	See comment	The mean absolute change from baseline in FEV$_1$ % predicted in the tezacaftor plus ivacaftor group was 4.00 % predicted higher (3.10 higher to 4.90 higher) than the placebo group (result from one study with 510 individuals).	NA	522 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]	Difference in absolute change from baseline calculated by least-squares regression, hence assumed risk not presented. The mean absolute change from baseline in FEV$_1$ % predicted in the tezacaftor-ivacaftor group was also statistically significantly higher than the placebo group at 4 weeks, MD 3.59 (95% CI 2.40 to 4.78), 2 studies, n = 528, I^2 =0%.
Adverse events: most commonly occurring events (occurring in at least 10% of participants) Follow-up: up to 24 weeks	The most commonly occurring adverse events in both groups were cough and pulmonary exacerbation. There were no statistically significant differences between groups (99% confidence intervals) in the number of participants experiencing cough, pulmonary exacerbation, headache, nasal congestion or nasopharyngitis, increased sputum, haemoptysis, pyrexia, oropharyngeal pain, nausea or fatigue.		NA	527 (2 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Time to first pulmonary exacerbation	The hazard ratio for pulmonary exacerbation in the tezacaftor plus–ivacaftor group, as compared with the placebo group was 0.64 (95% CI 0.46 to 0.89).		NA	504 (1 study)	⊕⊕⊕⊖ **moderate**[1,2]	A hazard ratio below 1 favours the tezacaftor-ivacaftor group.

Follow-up: up to 24 weeks

*The basis for the **assumed risk** is the control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **NA**: not applicable.

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: we are very uncertain about the estimate.

1. Downgraded once due to indirectness: 1 study recruited individuals over the age of 12 (Taylor-Cousar 2017) and 1 study recruited individuals over the age of 18 with one F508del mutation and one G551D mutation (Donaldson 2018). Therefore, results are not applicable to children under the age of 12 and some results are not applicable to individuals homozygous for F508del.

2. One study has some unclear details related to methodological design and had unbalanced treatment group sizes and baseline characteristics (Donaldson 2018). However, this study contributed a small proportion of the evidence of this comparison (n = 18, 3% of evidence) compared to the second study in the comparison (n = 509, 97% of evidence, overall low risk of bias) (Taylor-Cousar 2017). Therefore, no downgrading is made due to potential risks of bias in the smaller study.

BACKGROUND

Description of the condition

Cystic fibrosis (CF) is the most common inherited life-shortening illness with a prevalence of 1 in 2000 at birth in Northern Europeans (Bobadilla 2002) and varying prevalence in other populations depending on ethnic composition. The affected gene codes for a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) (Riordan 1989; Southern 1997). CFTR protein is transported to the outer cell membrane, where it has a role in the transport of salts (anions, chloride and bicarbonate) in and out of the cell (Rogan 2011). This role is important in all epithelial cells; particularly those lining the airways, pancreatic ducts, sweat gland, bile ducts in the liver and vas deferens.

In the lungs of people with CF (pwCF), defective salt transport leads to a reduction in airway surface liquid volume. This, in turn, leads to compromised mucociliary clearance, which makes the airway susceptible to infection, which initiates a cycle of inflammation, chronic infection and progressive lung damage. Eventually this causes respiratory failure, which is the commonest cause of premature death for pwCF. In addition to the airway problems, the abnormal transepithelial salt transport can lead to complications in other organs. This can result in malnutrition and diabetes (through pancreatic damage), salt depletion (through excess loss in sweat) and subfertility.

Over 2000 mutations have been identified in the CFTR gene. These mutations are classified according to the impact they have on the synthesis, processing, or function of the CFTR gene (CFMD 2013). Classes of CFTR mutation are described in more detail in the additional tables (Table 1) (Rowntree 2003; Southern 2007). Most CFTR mutations are associated with a complete loss of CFTR protein and result in a classical CF phenotype. Some CFTR mutations are associated with residual function and these tend to be associated with less severe phenotype, e.g. patients may be pancreatic sufficient and not require pancreatic replacement therapy.

The commonest CF causing mutation, F508del (also known as ΔF508 or phe508del), is found in the majority of pwCF (up to 80% to 90% of some populations, e.g. pwCF from a Northern European heritage). For individuals with F508del, a full length of protein is transcribed but recognised as misfolded by the cell and is degraded before reaching the cell membrane, where it needs to be positioned to effect transepithelial salt transport. Hence this is a severe mutation associated with no meaningful CFTR function. This type of mutation is called a class II mutation (or trafficking defect) and much research has explored masking the molecular defect, bypassing the cellular mechanisms and enabling the F508del protein to traffic to the cell membrane, where it may have some normal salt transport capability.

Description of the intervention

Increasing understanding of how different mutations affect the production, structure, and function of CFTR has led to the concept of mutation-specific therapies (Table 1). For class II mutations a full length of protein is produced, but recognised as abnormal by the cell and degraded before reaching the cell membrane. This is called a defect in intracellular trafficking. Scientists have recognised that certain laboratory manoeuvres can affect this process, e.g. reducing

cell temperature, and the trafficking defect can be overcome (Colledge 1995). In such circumstances the F508del protein may reach the cell membrane, where it has some ability to transport salt. This has lead to the search for molecules that can overcome the F508del trafficking defect and these drugs have been called 'correctors'.

Two distinct scientific 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 overcome the intracellular trafficking defect.

These approaches have resulted in the identification of small molecules that may be taken orally, and have been examined in phase 1 and phase 2 clinical trials (Rubenstein 1997; Van Goor 2011).

How the intervention might work

Correction of the basic CF defect may lead to normalisation of airway surface liquid, and correction of mucociliary clearance, reducing the susceptibility to airway infection and inflammation.

In addition to correctors, other drugs which aim to treat the CFTR defect are also under investigation. These include potentiators for class III and IV mutations, which enhance the function of mutated CFTR protein embedded in the cell membrane by increasing the time the CFTR salt channel remains open and therapies for class I mutations, which act to prevent structural abnormalities of CFTR that occur when premature stop codons terminate protein synthesis. Cochrane Reviews assessing these interventions are published (Aslam 2017; Patel 2015).

If correctors are successful at facilitating the F508del protein to reach the cell membrane, it may still have sub-optimal function. It is possible that CFTR correctors may need to be combined with other agents, such as potentiators to achieve a clinical benefit pwCF who have the F508del mutation. This review examines both correctors on their own and in combination with other agents.

Why it is important to do this review

CFTR correctors are novel therapies and it is important that randomised controlled trials (RCTs) are conducted and critically appraised. This will provide clear evidence to assess the benefits and harms of CFTR correctors. 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. In addition, critical appraisal of studies will help inform future study design.

New therapies that correct the F508del mutation will have a positive impact on an important proportion of the CF population (Southern 1997). Given the number of pwCF who will be prescribed this treatment, there will be an important healthcare cost. Experience from other licensed agents that correct the underlying CF defect, suggests that these costs may be considerable (NICE 2016).

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This review aims to collate evidence from RCTs that have evaluated the benefits and harms of CFTR correctors in pwCF and class II CFTR mutations.

OBJECTIVES

To evaluate the effects of CFTR correctors on clinically important outcomes, both benefits and harms, in children and adults with CF and class II CFTR mutations (most commonly F508del).

METHODS

Criteria for considering studies for this review

Types of studies

We have included RCTs of parallel design (published or unpublished). We have not included quasi-RCTs. Additionally, we have not included cross-over studies as we do not feel this study design is appropriate given that the intervention aims to correct the underlying defect. If the intervention is effective it will have an important impact on the course of the disease. This has been established from the data from trials examining ivacaftor for people with class III mutations.

Types of participants

We have included studies involving children or adults with CF, as confirmed either by the presence of two disease-causing mutations, or by a combination of positive sweat test and recognised clinical features of CF. We have included studies that include participants with any level of disease severity. Participants should have at least one class II mutation.

Types of interventions

A CFTR corrector is defined as a drug which aims to increase the amount of CFTR expressed at the epithelial cell apical membrane, by reducing or preventing degradation of CFTR by normal intracellular mechanisms. The main mutation targeted by this approach is F508del.

We have included studies in which CFTR correctors are compared with either placebo or another intervention. We have also included studies in which CFTR correctors are administered alongside another class of drug that also aims to improve CFTR function (e.g. potentiators).

Types of outcome measures

Primary outcomes

1. Survival
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. Physiological measures of lung function (L or per cent (%) predicted for age, sex and height)
   a. forced expiratory flow rate at one second (FEV_1) (relative change from baseline)
   b. FEV_1 absolute values (rather than change from baseline)
   c. forced vital capacity (FVC) (absolute values and change from baseline)
   d. lung clearance index (LCI) (post hoc change)
   e. other relevant physiological measures of lung function

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
2. Hospitalisation
   a. number of days
   b. number of episodes
   c. time to next hospitalisation
3. School or work attendance (i.e. number of days missed)
4. 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
5. Sweat chloride (change from baseline) as a measure of CFTR function
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 pathogen clinically relevant in CF
8. Eradication of respiratory pathogens (as defined by study authors)
   a. *P aeruginosa*
   b. *S aureus*
   c. *H influenzae*
   d. other pathogen clinically relevant in CF
9. Nutrition and growth (measured as relative change from baseline) (including z scores or centiles)
   a. weight
   b. body mass index (BMI)
   c. height

Search methods for identification of studies

We searched for all relevant published and unpublished studies without restrictions on language (we did not exclude studies reported in a language other than English), year or publication status.

Electronic searches

We identified relevant studies from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register using the terms: 'drugs that correct defects in CFTR transcription, translation or processing'. Relevant studies have been tagged with these terms for indexing purposes in the Group's Cystic Fibrosis Trials Register.

The Cystic Fibrosis Trials Register 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 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 Cystic Fibrosis and Genetic Disorders Group website.

Date of the most recent search: 24 February 2018.

We also searched clinical trial registries maintained by the European Medicines Agency, the US National Institutes of Health (NIH) and the WHO; further details are presented in the appendices (Appendix 1).

Date of the most recent search: 25 January 2018.

Searching other resources

We screened references of included studies to identify additional potentially relevant studies. We also contacted authors of included studies, leaders in the field, and companies known to be developing and investigating CFTR correctors, to identify any studies which may have been missed by this search. We recorded response rates from this contact process below (Results of the search).

Data collection and analysis

Selection of studies

Two authors (IS and SP or IS and KWS) independently assessed the suitability of each potential study identified by the search. If disagreement arose on the suitability of a study for inclusion in the review, we attempted to reach a consensus by discussion, failing which, a third author arbitrated.

Data extraction and management

Two authors (IS and SP or IS and SJN) independently extracted relevant data from each included study. If disagreement arose on data extraction, we attempted to reach a consensus by discussion, failing which, a third author (KWS) arbitrated. Two authors (SP and SN) entered the data into RevMan for analysis.

If studies had reported data on our primary outcome (survival), we planned to report these as a binary outcome or a time-to-event outcome. We planned on extracting QoL scores as relative change from baseline ((measurement at end of treatment - measurement at baseline) / measurement at baseline) x 100). We extracted data presented as post-treatment values or change from baseline when this was not possible.

With regards to the secondary outcome 'Extra courses of antibiotics', we planned to extract data as time-to-the-next course of antibiotics and the total number of courses of antibiotics. We noted whether episodes of pulmonary exacerbations were physician-defined or protocol-defined. If studies reported baseline and post-treatment sweat chloride concentration values, we calculated the relative change from baseline values ((measurement at end of treatment - measurement at baseline) / measurement at baseline) x 100).

We reported data as immediate (up to and including one month), short-term (over one month and up to six months) and longer-term (over six months).

We attempted to extract the most precise data as possible for each outcome; extraction of tabulated data was preferred. If data were presented only graphically, two authors (SP and SJN) estimated the relevant data from graphs and compared estimations for accuracy.

Assessment of risk of bias in included studies

Two authors (IS and SP or IS and SJN) assessed the risk of bias for each study using the Cochrane risk of bias tool (Higgins 2011a). This includes assessment of the following methodological aspects of the included studies:

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 (e.g. the influence of funding sources or industry on trial characteristics and presented results).

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 study, 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% confidence intervals (CIs) or 99% CIs for analysis of separate adverse events.

For continuous outcomes, we calculated the mean change from baseline for each group or the mean post-intervention values and standard deviation (SD) for each group. We converted standard errors (SEs) to SDs. We produced a pooled estimate of treatment effect by calculating the mean difference (MD) and 95% CIs.

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 studies 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 and had the same time periods between baseline and final value measurement). 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 section 16.1.3.2 in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011b)).

Where time-to-event data were reported (e.g. survival time, time to next hospitalisation, time to first exacerbation), we reported a hazard ration (HR) and 95% CIs.

When reporting on outcomes we used the following subheadings to describe the time points: immediate (up to and including one month); short term (over one month and up to six months); and longer term (over six months).

Unit of analysis issues

Within this review, we only included results from RCTs of parallel design in which individual study participants are randomised. We have not included cross-over studies as we do not feel this study design is appropriate given that the intervention aims to correct the underlying defect. If the intervention is effective it will have an important impact on the course of the disease. This has been established from the data from trials examining ivacaftor for people with class III mutations (Patel 2015).

In one included study, continuous outcomes were analysed via a mixed model repeated measures analysis (MMRM) based on the average effect across the measured time points (Ratjen 2017). Such an analysis is longitudinal and uses all available data at every visit and allows adjustment for covariates such as the baseline measurement of the outcome. All analyses were also adjusted for baseline weight (less than 25 kg versus 25 kg or over) and baseline FEV_1 (% predicted - less than 90% versus 90% or above). Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24. Within this review, results are entered into the analysis via generic inverse variance and are not pooled with other studies, due to the different approaches to analysis.

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. If any data were missing or unclear, we contacted the primary investigators for clarification.

Assessment of heterogeneity

We assessed heterogeneity through visual examination of the combined data presented in the forest plots, and by considering overlap of study-specific CIs, and the I^2 statistic (Higgins 2003) together with Chi² values (Deeks 2011). The I^2 statistic reflects the likelihood that variation of results across studies are due to heterogeneity rather than by chance, and we interpreted this statistic using the following simple 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.

Assessment of reporting biases

In order to identify selective outcome reporting, where possible, we have compared outcomes described in the study protocol with those reported in the publication. We have requested protocols for specific studies from the primary investigators and recorded the proportion of protocols that were available to us. If a protocol was not available, we searched for information about outcomes from 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 reported negative findings either only partially, or not at all, we contacted primary investigators for these data.

We would have assessed publication bias by constructing and assessing the symmetry of a funnel plot. This would have been possible if we included more than 10 studies in a meta-analysis in the review. We would have plotted the number of participants in the study against a measure of treatment effect. If the funnel plot was asymmetrical, we would consider whether this was due to publication bias, or whether methodology or small sample size caused results of certain studies to show exaggerated treatment effects.

Data synthesis

As we intended to assess different CFTR correctors within this review, we assumed that there would not be a single common true effect. We also anticipated participants in each study would vary due to different eligibility criteria. Therefore, regardless of I^2 value, we intended to use a random-effects model to analyse data from studies.

As the review progressed, we included a number of early-phase studies of interventions (which were ultimately not taken forward) in addition to large Phase 3 studies of combination therapies; therefore, we felt it more appropriate to employ separate comparisons within the review. As only a relatively small number of studies were included in each comparison (and when meta-analysis was undertaken), it was considered more appropriate to employ a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

We would have investigated any heterogeneity that we identified using subgroup analyses of potential confounding factors, if

sufficient numbers (at least 10 studies included in a meta-analysis) were available. For this review, 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 study investigators and such information was not available within published reports, we did not undertake a subgroup analysis on the basis of disease severity. We may incorporate such an analysis in future updates of this review.

Sensitivity analysis

In future updates of this review, if sufficient data are available, we will examine the impact of bias on the results by comparing meta-analyses including and excluding studies 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 study personnel.

Summary of findings and quality of the evidence (GRADE)

In a post hoc change from protocol, we have presented six summary of findings tables (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6).

We have presented two tables under the comparison of 'Correctors (monotherapy) compared to placebo;' where lumacaftor monotherapy is compared to placebo (Summary of findings for the main comparison). We have presented lumacaftor results only rather than other correctors in the table for this comparison due to the relevance of this particular treatment at the time of writing (NICE 2016). A further table is also provided for cavosonstat compared to placebo (Summary of findings 2).

We have presented four tables under the comparison of 'Correctors plus potentiators in combination therapy compared to placebo':

- lumacaftor (600 mg once daily or 400 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo reporting short-term results (one month to six months) (Summary of findings 3);
- lumacaftor (200 mg twice daily) and ivacaftor (250 mg twice daily) versus placebo reporting immediate-term results (up to one month (Summary of findings 4);
- lumacaftor (200 mg) plus ivacaftor (150 mg or 250 mg twice daily) versus placebo reporting immediate-term results (up to one month) (Summary of findings 5).
- tezacaftor (100 mg once daily) and ivacaftor (150 mg twice daily) versus placebo or ivacaftor (150 mg twice daily alone) (Summary of findings 6).

Tables were presented separately for lumacaftor plus ivacaftor under this comparison due to the differences in doses, measurement times and approaches to analysis.

The following outcomes were reported in all tables (chosen based on relevance to clinicians and consumers): survival, QoL (total score), QoL (respiratory domain), FEV_1 (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 sub-domains 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 sub-domains 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 study, 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.

R E S U L T S

Description of studies

Results of the search

The search of specified databases identified 98 unique references corresponding to 38 studies. No further studies were identified from contacting CF researchers or from screening relevant references. There were 13 studies (80 references) which met the eligibility criteria for inclusion in this review (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; PROGRESS 2017; McCarty 2002; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002). The results from two of these studies were jointly reported in 15 papers (TRAFFIC 2015; TRANSPORT 2015).

We excluded 11 studies (17 references) (Berkers 2014; Chadwick 1998; Lebecque 2011; Leonard 2012; Chilvers 2017; NCT01899105; Nick 2014; Rowe 2017; Rubenstein 2006; Sumner 2014; Ziady 2015).

We identified 13 relevant ongoing studies (Meijer 2016; NCT02070744; NCT02323100; NCT02412111; NCT02589236; NCT02718495; NCT02730208; NCT02951195; NCT03093714; NCT03150719; NCT03224351; NCT03227471; NCT03258424) and one study is listed as awaiting classification pending further information (Hunt 2017)

Results of the online electronic searches are displayed in a PRISMA diagram (Figure 1).

Figure 1. PRISMA study flow diagram

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Figure 1. (Continued)

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        │ 10 trials included   │
        │ in quantitative      │
        │ synthesis            │
        │ (meta-analysis).     │
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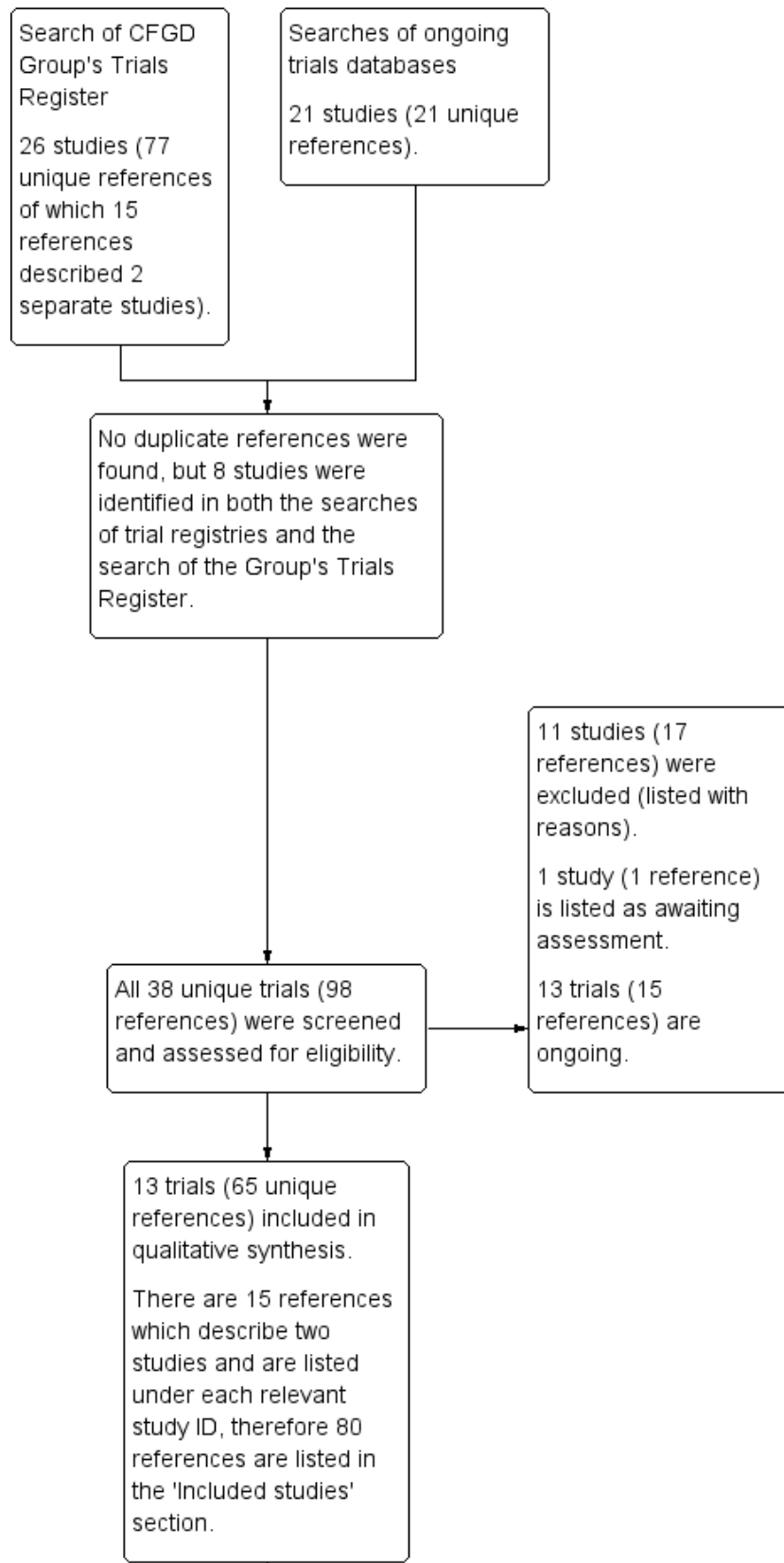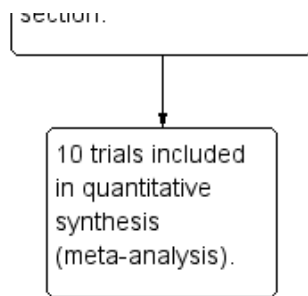
Included studies

Study design

The 13 included studies ranged from Phase 1 to Phase 3 RCTs, and all employed a parallel study design (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; PROGRESS 2017; McCarty 2002; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002). The PROGRESS study was an extension study of the TRAFFIC and TRANSPORT studies included in the review (TRAFFIC 2015; TRANSPORT 2015), but with participants in the placebo group from the initial trials randomised to receive the active treatment at one of two doses (PROGRESS 2017).

A total of 2215 randomised participants were included in this review. Study sample sizes ranged from 18 participants (Rubenstein 1998) to 563 participants (TRANSPORT 2015). One study was composed of three cohorts - cohort 1 (n = 62), cohort 2 (n = 109) and cohort 3 (n = 15); any reference to this study is to participants randomised to cohort 1 only, since data for the placebo participants from cohorts 2 and 3 were pooled, undoing the effects of randomisation and rendering them ineligible for inclusion in this review (Boyle 2014). In the Phase 2 study of tezacaftor-ivacaftor, only data from the heterozygous population are included (n = 18), as the placebo groups in the homozygous arms of the trial were pooled (Donaldson 2018).

The duration of the included studies ranged from 1 day (Phase 1 single-dose testing) (McCarty 2002) to 24 weeks (Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015) with an extension of two of these studies of 96 weeks (PROGRESS 2017).

Two studies were undertaken at single centres (Rubenstein 1998; Zeitlin 2002), but the remaining studies were conducted at multiple centres, ranging from at four (McCarty 2002) to 191 sites (PROGRESS 2017). Five studies were conducted in the USA only (Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002), four in North America and Europe (Clancy 2012; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017) and the remainder across North America, Europe and Australia (Boyle 2014; PROGRESS 2017; TRAFFIC 2015; TRANSPORT 2015).

Full texts were available for 12 studies (Boyle 2014; Clancy 2012; Donaldson 2017; Donaldson 2018; PROGRESS 2017; McCarty 2002; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002) and one as an online summary on Clinicaltrials.gov (Donaldson 2014).

Participants

One study recruited pwCF with one F508del mutation (the other mutation was classified as residual function (ivacaftor responsive)) (Donaldson 2018). All remaining studies recruited participants who were homozygous for F508del.

One study recruited children between the ages of 6 to 11 years (Ratjen 2017), five studies recruited adolescents and adults (PROGRESS 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015) and the remaining studies recruited only adults (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; McCarty 2002; Zeitlin 2002).

Interventions

Monotherapy

The included studies examined the effects of 4-Phenylbutyrate (4PBA) (Rubenstein 1998; Zeitlin 2002), 8-cyclopentyl-1, 3-dipropylxanthine (CPX) (McCarty 2002), N6022 (Donaldson 2014), cavosonstat (N91115) (Donaldson 2017), lumacaftor monotherapy (Boyle 2014; Clancy 2012), lumacaftor-ivacaftor combination therapy (Boyle 2014; PROGRESS 2017; Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015) and tezacaftor-ivacaftor combination therapy (Donaldson 2018; Taylor-Cousar 2017).

Two studies compared 4PBA to placebo (Rubenstein 1998; Zeitlin 2002). In the earlier study, participants received either 19 g of 4PBA (split into three daily doses) or placebo for one week (Rubenstein 1998). The subsequent Phase 2 study examined the effects 4PBA given at either 20 g (n = 6), 30 g (n = 6) or 40 g (n = 3), given in three daily doses for one week (Zeitlin 2002).

One study compared escalating doses of CPX to placebo (McCarty 2002). Participants were randomised to receive single doses of either placebo (n = 8) or 1 mg (n = 4), 3 mg (n = 4), 10 mg (n = 4), 30 mg (n = 4), 100 mg (n = 5), 300 mg (n = 4) or 1000 mg (n = 4) of CPX.

One study compared sequential ascending doses of N6022 to placebo (Donaldson 2014). Participants were randomised to receive placebo (n = 19) or the active drug (intravenous solution of N6022 in normal saline) at a dose of either 5 mg (n = 10), 10 mg (n = 9), 20 mg (n = 9), 40 mg (n = 19). Both treatments were administered by infusion pump over one to eight minutes once per day for seven days.

The study of cavosonstat included both healthy volunteers and pwCF (Donaldson 2017). Those with CF were randomised to receive 50 mg placebo (n = 12) or cavosonstat at different doses (50 mg (n = 12), 100 mg (n = 13), or 200 mg (n = 14)) twice daily for 28 days.

One included study compared lumacaftor monotherapy at escalating doses of 25 mg (n = 18), 50 mg (n = 18), 100 mg (n = 17) and 200 mg (n =19), to placebo (n = 17) for 28 days (Clancy 2012).

Combination therapy

Five studies have evaluated lumacaftor-ivacaftor combination therapy (Boyle 2014; PROGRESS 2017; Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015). In one cohort of a Phase 2 study, participants received 200 mg lumacaftor once daily for 14 days, followed by seven days of 200 mg lumacaftor once daily plus either 150 mg (n = 20) or 250 mg (n = 21) of ivacaftor twice daily (day 15 to 21), or placebo (Boyle 2014). In one Phase 3 study, children received either a combination of lumacaftor 200 mg plus ivacaftor 250 mg every 12 hours or placebo for 24 weeks (Ratjen 2017). Two Phase 3, three-arm studies (TRAFFIC and TRANSPORT) also compared lumacaftor-ivacaftor combination therapy to placebo. In these studies, two separate doses of lumacaftor (600 mg once daily and 400 mg twice daily) were combined with twice daily 250 mg of ivacaftor. The placebo group received lumacaftor-matched placebo every 12 hours in combination with ivacaftor-matched placebo every 12 hours (TRAFFIC 2015; TRANSPORT 2015). A long-term extension study (96 weeks) randomised those in the placebo groups of the TRAFFIC and TRANSPORT studies to one of the two lumacaftor-ivacaftor combination doses; those already receiving an active treatment continued with their existing treatment (PROGRESS 2017).

Two studies have evaluated tezacaftor-ivacaftor combination therapy (Donaldson 2018; Taylor-Cousar 2017). A Phase 2 study included a dose-escalation arm, a comparison of various doses of tezacaftor-ivacaftor in people homozygous for F508del, and a comparison of tezacaftor-ivacaftor against ivacaftor alone in people with one F508del mutation and one G551D mutation (Donaldson 2018). The Phase 3 study compared a combination of tezacaftor 100 mg plus ivacaftor 150 mg every 12 hours to a matched placebo for 24 weeks (Taylor-Cousar 2017).

Outcomes

Lung function using FEV$_1$ was reported in 11 studies (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; PROGRESS 2017; McCarty 2002; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). One study additionally reported LCI (Ratjen 2017). Eight studies reported QoL, all of which utilised the respiratory domain of the CFQ-R (Clancy 2012; Donaldson 2017; Donaldson 2018; PROGRESS 2017; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

Reporting of the pre-specified secondary outcomes in this review varied across studies. All included studies monitored the adverse effects of therapy, but the manner in which these safety outcomes were analysed and reported varied considerably. Five studies reported outcomes relating to pulmonary exacerbations (PROGRESS 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). No studies specifically reported on rates of hospitalisation. Eight studies reported changes in sweat chloride, as a marker of CFTR function (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; Zeitlin 2002). No studies reported radiological outcomes. Two studies reported microbiological outcomes (Taylor-Cousar 2017; Zeitlin 2002). Five studies reported BMI (PROGRESS

2017; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

Funding sources

Eight studies were funded by pharmaceutical companies (Donaldson 2014; Donaldson 2017; PROGRESS 2017; McCarty 2002; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). Three studies were funded jointly by pharmaceutical companies and other sources (Boyle 2014; Clancy 2012; Donaldson 2018). Two studies were not funded by pharmaceutical companies at all: one was funded by the Cystic Fibrosis Foundation (CFF) (Zeitlin 2002), and one jointly by the CFF and the NIH (Rubenstein 1998).

Further information about the studies is presented in the tables (Characteristics of included studies).

Excluded studies

We excluded 11 studies in total. Six studies were of cross-over design (Berkers 2014; Lebecque 2011; Leonard 2012; NCT01899105; Nick 2014; Rowe 2017), two studies were single-assignment studies, i.e. participants were not randomised to different study arms (Chilvers 2017; Rubenstein 2006), one study was not randomised (Chadwick 1998), one study was a pre-clinical laboratory study (Ziady 2015) and the remaining study was of general gene therapy and not a mutation-specific therapy (Sumner 2014).

Ongoing studies

There are 13 studies listed as ongoing (Meijer 2016; NCT02070744; NCT02323100; NCT02412111; NCT02589236; NCT02718495; NCT02730208; NCT02951195; NCT03093714; NCT03150719; NCT03224351; NCT03227471; NCT03258424).

Monotherapy

Five ongoing clinical studies are currently evaluating four monotherapy correctors. One study is comparing doses of a corrector known as (R)-roscovitine to placebo in adults with CF with either one or two copies of the F508del mutation (Meijer 2016). A second study is comparing GPBA to placebo in people who are homozygous for F508del (NCT02323100). A third is comparing a corrector called FDL 169 to placebo in people who are homozygous for F508del (NCT03093714). Two studies are evaluating PTI 428 (a particular type of CFTR corrector called an amplifier, which augment the actions of other CFTR modulators) (NCT02718495; NCT03258424).

Combination therapy

Four ongoing studies are evaluating the safety and efficacy of tezacaftor-ivacaftor in pwCF; three of these are in people homozygous for F508del (NCT02070744; NCT02730208; NCT03150719), and one in heterozygous people who have one copy of the F508del mutation and one mutation that has been demonstrated to be responsive to ivacaftor therapy (NCT02412111). One of the studies is in people who have previously been taking lumacaftor-ivacaftor but were not able to continue due to an adverse event or drug reaction (NCT03150719).

Three ongoing placebo-controlled studies are evaluating triple combination therapies, each adding a drug to a tezacaftor-ivacaftor combination therapy in pwCF (NCT02951195; NCT03224351; NCT03227471). One study is evaluating VX152 in combination with tezacaftor-ivacaftor in people homozygous for F508del

(NCT02951195). Two studies are evaluating triple therapies, both in people who are homozygous for F508del and people with one F508del mutation and a minimal function mutation that is unlikely to respond to tezacaftor-ivacaftor, one of these is evaluating VX-659 (NCT03224351) and the second is evaluating VX-445 (NCT03227471).

A Phase 2 placebo-controlled study is assessing the efficacy of cavosonstat when added to pre-existing lumacaftor-ivacaftor therapy in adults with CF who are homozygous for the F508del-CFTR mutation (NCT02589236).

Studies awaiting classification

One study is currently awaiting classification until further information is available (Hunt 2017). In this RCT, 18 adults (11 females) with CF who were homozygous for the F508del mutation, and who were all receiving lumacaftor-ivacaftor combination therapy were randomised to four weeks of either 40 mg sildenafil three times daily or matched placebo. Outcomes measured include sweat chloride, FEV_1 % predicted, BMI, exhaled nitric oxide, CFQ-R, nasal potential difference and LCI. This study was described in an abstract presented at a conference in 2017 and we will further evaluate for inclusion once the full publication is available.

Risk of bias in included studies

We have summarised our risk of bias judgements in the figures (Figure 2; Figure 3).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
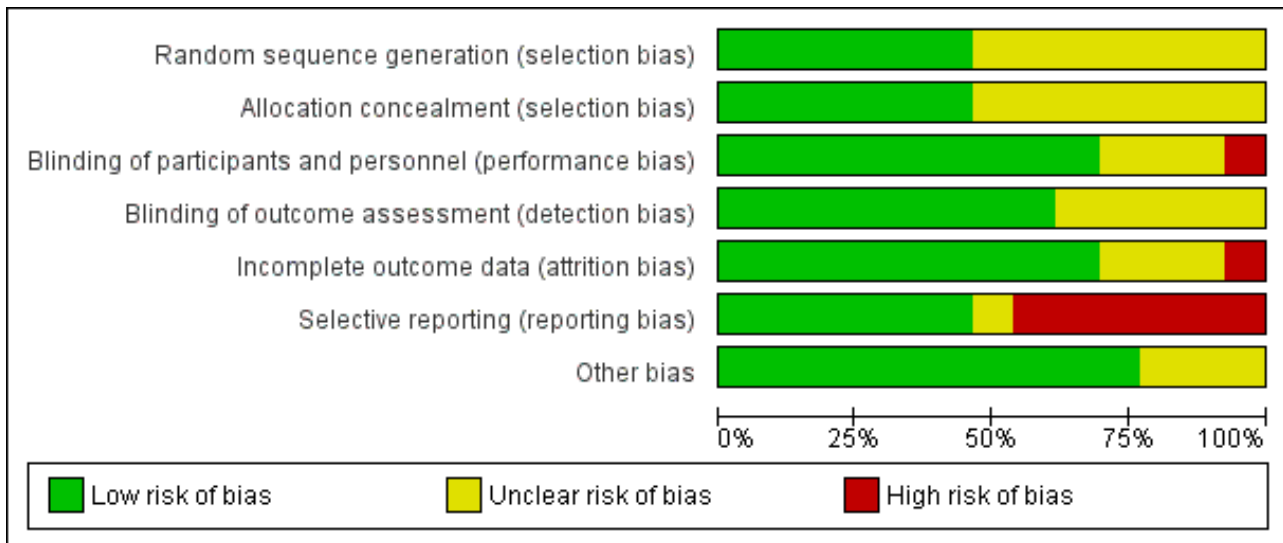
Allocation

Sequence generation

We judged six studies to have a low risk of bias (Boyle 2014; PROGRESS 2017; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). Of these, one study used a computer-generated randomisation schedule developed by an independent party (Boyle 2014), and the others randomised participants via an interactive web response system (PROGRESS 2017; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). As none of the remaining seven included studies reported details of random sequence generation we have judged the risk of bias as unclear (Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

Allocation concealment

We judged six studies to have a low risk of bias (Boyle 2014; PROGRESS 2017; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). In the phase 2 lumacaftor-ivacaftor study, site pharmacists dispensed drugs on the basis of an interactive voice response system, making it unlikely that participants or study personnel would have been aware of group assignments prior to recruitment into the study (Boyle 2014). The remaining lumacaftor-ivacaftor studies, and the tezacaftor-ivacaftor study also employed an interactive web response system to allocate participants to treatment groups (PROGRESS 2017; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). Methods to conceal group allocation were not reported by the remaining seven studies, who also failed to report on random sequence generation, so we judged these as having an unclear risk of bias (Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

Blinding

Eight studies were judged to have a low risk of performance and detection bias (Boyle 2014; Donaldson 2014; Donaldson 2017; Donaldson 2018; PROGRESS 2017; Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015). In the Boyle study, drug doses were prepared by an independent unmasked pharmacist and dispensed by site pharmacists who were masked to treatment assignment. Site investigators and the study sponsor were also masked to treatment assignment and to sweat chloride levels - data that could have potentially disclosed treatment assignment. Participant blinding was maintained by placebo which was matched to intervention by the quantity of tablets and by size, colour, coating and packaging (Boyle 2014). In the Donaldson study, participants, care givers, investigators and outcome assessors were double-blinded via intravenous administration of placebo (saline) using the same volume as the active drug groups (Donaldson 2014). In the two Phase 3 lumacaftor-ivacaftor studies and the extension study, the participants and study team remained blinded to the treatment assignments and the placebo was matched in appearance and packaging to the active intervention. The online protocol further stated that all site personnel, including the investigator, the site monitor and the study team would remain blinded to treatment group (PROGRESS 2017; TRAFFIC 2015; TRANSPORT 2015). In the paediatric lumacaftor-ivacaftor study, double blinding was achieved by using placebo tablets visually identical to the test product (Ratjen 2017).

In the pilot 4PBA, CPX and the lumacaftor monotherapy studies, there was insufficient information about how participant, study personnel or outcome assessor blinding was maintained and so we judged these three studies to have an unclear risk of performance and detection bias (Clancy 2012; McCarty 2002; Rubenstein 1998).

Participants from the three intervention groups (20 g, 30 g and 40 g) in the Phase 2 4PBA study had different dosing schedules and were given a different number of tablets. Therefore this study was judged to have a high risk of performance bias. Also in this study, there were insufficient data on blinding of outcome assessors and we therefore judged it to have an unclear risk of detection bias (Zeitlin 2002).

Incomplete outcome data

We judged nine studies to have a low risk of bias due to incomplete outcome data (Donaldson 2014; Donaldson 2018; PROGRESS 2017;

McCarty 2002; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

Three studies were judged to have an unclear risk of attrition bias (Boyle 2014; Donaldson 2017; Zeitlin 2002). In the phase 2 lumacaftor-ivacaftor study, one out of 62 participants withdrew (1.6%) due to an adverse effect, demonstrating a low withdrawal rate. However, in the analysis only participants for whom data were available were included. Although these participants were excluded because of insufficient data rather than for reasons that could potentially lead to the exclusion of participants with unfavourable characteristics, e.g. adverse effects, we judged this study as having an unclear risk of attrition bias because it was unclear how these exclusions would have affected the balance between groups in baseline characteristics (Boyle 2014). The cavosonstat study was judged as having an unclear risk of bias in this domain because two out of 51 participants are unaccounted for in the final analysis, but it is unlikely that these would affect the overall findings (Donaldson 2017). In the phase 2 4PBA study, all 19 randomised participants completed the final study visit, but risk of attrition bias was unclear because there was no report of how many of these participants were included in the analysis (Zeitlin 2002). We approached the primary author to clarify this, but did not receive any additional information.

We judged the study of lumacaftor monotherapy to have a high risk of attrition bias (Clancy 2012). Although only four out of 89 (5%) participants withdrew from the study due to adverse events (demonstrating a low withdrawal rate), data for a number of outcomes were excluded from the analysis. A total of 42 participants were excluded from reports of adverse events; nine participants were excluded from reports on change from baseline in sweat chloride concentration (demonstrated by figure 1b in the full-text article) and four participants were excluded from the information on CFQ-R domain scores. Our judgement of a high risk of attrition bias was due firstly to the high level of excluded participant data and secondly to the lack of reasons for the exclusion of these participant data. The study's lead investigator was approached for clarification, but we have received no response to date (Clancy 2012).

Selective reporting

Where study protocols were not available, or there were missing outcome data, we approached the studies' primary authors for additional information.

We judged six studies to have a low risk of reporting bias (Boyle 2014; Donaldson 2017; Donaldson 2018; PROGRESS 2017; McCarty 2002; Rubenstein 1998). For the Phase 2 lumacaftor-ivacaftor study, the protocol was not available, but outcomes were presented on the NIH trials registry (clinicaltrials.gov/); we did not identify any missing outcomes for the included cohort (Boyle 2014). For the pilot 4PBA and CPX studies, protocols were not available and planned outcomes were not listed on ongoing online trials databases (McCarty 2002; Rubenstein 1998). So, we compared the outcomes reported in the 'Methods' sections to the outcomes reported in the 'Results' sections of the publications and did not identify any missing outcomes (McCarty 2002; Rubenstein 1998). For the extension study of TRAFFIC and TRANSPORT, we compared the list of outcomes provided on the NIH trials registry (clinicaltrials.gov/) to the results reported in the published paper; all listed outcomes were reported (PROGRESS 2017).

One study was judged to be at unclear risk of bias from selective outcome reporting (Donaldson 2014). Only limited results were available from the NIH trials registry (clinicaltrials.gov/) and it was unclear if all relevant information has been made available.

We judged six studies to have a high risk of bias from selective outcome reporting (Clancy 2012; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002). The protocol for the Clancy lumacaftor study was not available, but the planned outcomes were listed on the NIH trials registry (clinicaltrials.gov/). We compared these outcomes to those reported in the 'Results' section of the published paper and ascertained that no data were reported for $FEF_{25-75\%}$ or FVC at 28 days (Clancy 2012). The study protocol for the phase 2 4PBA study was not available and planned outcomes were not listed on ongoing online trials databases (Zeitlin 2002). We compared the outcomes reported in the 'Methods' section of the paper to the outcomes reported in the 'Results' section and identified that data were not reported for the change from baseline in FEV_1 or microbiology scores at day seven (Zeitlin 2002).

In the two Phase 3 lumacaftor-ivacaftor studies, pre-specified data were reported on the NIH trials registry (TRAFFIC 2015; TRANSPORT 2015). In these studies, data for the outcomes; absolute change from baseline in FEV_1 and relative change from baseline in FEV_1 were combined at 16 and 24 weeks. Combination of this data was not pre-specified and the primary author was contacted from clarification. Furthermore, some results had to be extrapolated from graphical figures and some additional data were only reported on clinicaltrials.gov for outcomes not reported in the final paper. Also, investigators state that they measured FVC (which was not listed as an end-point) and do not report this in the joint paper (TRAFFIC 2015; TRANSPORT 2015).

In the paediatric combination study, several outcomes which were listed in the methods of the full publication and also on the ClinicalTrials.gov entry for this study were not reported in the results section of the paper (Ratjen 2017). These outcomes include $LCI_{5.0}$, weight, height and time to first pulmonary exacerbation.

In the tezacaftor-ivacaftor combination study, a number of outcomes were recorded according to the study protocol but were not reported in the published paper (Taylor-Cousar 2017). These outcomes were the CF respiratory symptom diary, duration of daily physical activity (number of minutes), the Pittsburgh Sleep Quality Index (PSQI), SF-12 health survey, sputum microbiology, the time-to-first and number of days with an exacerbation, the time to first hospitalisation and the number of days hospitalised with exacerbation, the number of exacerbations requiring IV therapy, the time to the first IV therapy and the number of days on IV therapy.

Other potential sources of bias

We judged there to be a low risk of other bias due to no statistically significant difference between baseline characteristics in six studies (PROGRESS 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002) and due to well-matched baseline characteristics in a further four studies (Boyle 2014; Clancy 2012; Donaldson 2014; Ratjen 2017). Futhermore, in both the TRAFFIC and TRANSPORT studies adherence to treatment was high with similar compliance rates across the different treatment groups (TRAFFIC 2015; TRANSPORT 2015).

In the remaining three studies, there was insufficient detail about baseline characteristics or an apparent imbalance in baseline characteristics, leading to an unclear risk of bias (Donaldson 2017; Donaldson 2018; McCarty 2002).

Effects of interventions

See: **Summary of findings for the main comparison** Summary of findings - Lumacaftor monotherapy compared to placebo; **Summary of findings 2** Summary of findings - Cavosonstat compared with placebo for cystic fibrosis; **Summary of findings 3** Summary of findings - Lumacaftor plus ivacaftor (once daily) compared with placebo for cystic fibrosis (short term); **Summary of findings 4** Summary of findings - Lumacaftor plus ivacaftor (twice daily) compared with placebo for cystic fibrosis (short term); **Summary of findings 5** Summary of findings - Lumacaftor plus ivacaftor compared with placebo for cystic fibrosis (immediate term); **Summary of findings 6** Summary of findings - tezacaftor plus ivacaftor compared with placebo or ivacaftor alone

As described above, we identified two types of intervention relevant for this review. The first group of studies examined single agents that aimed to correct the F508del trafficking defect (commonly referred to as "correctors"). The second group of studies examined a combination of various correctors with ivacaftor (a drug known to potentiate the function of the CFTR in the membrane). As these interventions have different potential mechanisms of action, we present the results separately for 'Correctors (monotherapy) compared to placebo' and 'Correctors plus potentiators (combination therapy) compared to placebo'. Results are summarised for all doses reported separately and for treatment doses combined where appropriate. 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.

Correctors (monotherapy) compared to placebo

Seven studies with 317 participants contributed to this comparison (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

Two studies (n = 37) compared 4PBA to placebo (Rubenstein 1998; Zeitlin 2002), one study (n = 66) compared N6022 to placebo (Donaldson 2014), one study (n = 37) compared CPX to placebo (McCarty 2002) and two studies (n = 151) compared varying doses of lumacaftor alone to placebo (Boyle 2014; Clancy 2012). One study (n = 26) compared cavosonstat 200 mg (twice daily) to placebo (Donaldson 2017). We only present this dose comparison (200 mg) from this early-phase study as this is the only dose that is being studied further and other doses are not relevant to current clinical practice. Participants in one study (n = 64) received lumacaftor monotherapy for 14 days followed by combination therapy with ivacaftor for seven days, therefore this study contributes to both comparisons of this review (Boyle 2014).

Important results for this comparison are summarised in the tables (Summary of findings for the main comparison; Summary of findings 2).

Primary outcomes

1. Survival

No deaths were reported during any of the included studies (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

2. QoL

a. Total QoL score

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

b. Different sub-domains

i. Immediate term (up to and including one month)

Lumacaftor versus placebo

The study by Clancy (n = 89) reported on the change from baseline scores for all CFQ-R domains at 28 days (Table 2). We have presented these absolute change from baseline scores as we were unable to calculate the relative change from baseline in CFQ-R scores since baseline CFQ-R scores were not reported. Furthermore, no SDs or CIs were reported to allow calculation of SDs for entry into the analysis (Clancy 2012).

Participants in the 25 mg group reported statistically significantly lower CFQ-R scores for the role domain (MD -8.15) and respiratory domain (MD -9.75) compared participants in the placebo group. Participants in the 50 mg lumacaftor group reported statistically significantly lower CFQ-R scores for the eating domain (MD -9.4), health perceptions domain (MD -12.0), respiratory domain (MD -10.85) and treatment burden domain (MD -8.42) compared to participants assigned to placebo. Participants in the 200 mg group reported statistically significantly lower CFQ-R scores for the role domain (P < 0.05) compared participants in the placebo group (Clancy 2012).

Cavosonstat versus placebo

Donaldson (n = 51) also reported data for both the respiratory and eating domains of the CFQ-R at 28 days, but neither result showed any difference between cavosonstat and placebo groups (Analysis 2.1; Analysis 2.2) (Donaldson 2017).

ii. Short term (over one month and up to and including six months)

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

3. Physiological measures of lung function

a. FEV$_1$ (relative change from baseline)

i. Immediate term (up to and including one month)

Lumacaftor versus placebo

The study by Clancy (n = 89) reported the mean relative change from baseline in FEV$_1$ after 28 days of treatment with escalating doses of lumacaftor, but did not present the corresponding SDs precluding analysis (Clancy 2012). No statistically significant differences were reported between the placebo group and the different lumacaftor dose groups: 25 mg, MD -2.53% predicted; 50 mg, MD -2.22%

predicted; 100 mg, MD 0.25% predicted; and 200 mg, MD 0.40% predicted. No SDs or CIs were reported to allow calculation of SDs for entry into the analysis (Clancy 2012).

Cavosonstat versus placebo

Donaldson (n = 51) presents data for cavosonstat versus placebo pictorially in the graph (supplementary tables), but overlapping SD lines render these data difficult to extract. The paper reports that no treatment-related changes in FEV_1 were seen with cavosonstat compared to placebo (Donaldson 2017).

N6022 versus placebo

The study by Donaldson (n = 66) reported the mean relative change from baseline in FEV_1 % predicted after seven days of treatment with sequential ascending doses of N6022 (5 mg, 10 mg, 20 mg or 40 mg per day) (Donaldson 2014). No statistically significant differences were reported between the placebo group and any of the N6022 dose groups (Analysis 3.1).

ii. Short term (over one month and up to and including six months)

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

b. FEV_1 (absolute values)

i. Immediate term (up to and including one month)

Lumacaftor versus placebo

The Phase 2 study (n = 62) reported on the absolute change from baseline in FEV_1 after lumacaftor monotherapy (day 14) (Boyle 2014); there was no statistically significant difference between treatment groups, MD -1.90 (95% CI -4.13 to 0.33) (Analysis 1.1) (moderate-quality evidence).

Cavosonstat versus placebo

As previously stated, Donaldson (n = 51) reported that no treatment-related changes in FEV_1 were seen with cavosonstat compared to placebo (Donaldson 2017) (low-quality evidence).

ii. Short term (over one month and up to and including six months)

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

c. FVC

Data for this outcome were not reported by six studies (Boyle 2014; Clancy 2012; Donaldson 2014; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

Cavosonstat versus placebo

Similarly, to FEV_1, Donaldson (n = 51) reported that no treatment-related changes in FVC were seen with cavosonstat compared to placebo (Donaldson 2017).

Secondary outcomes

1. Adverse effects

Adverse effects of therapy were reported by all included studies (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002). The extent and type of adverse event reporting varied between studies.

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

In Phase 2 trials of potential correctors (CPX, 4PBA, N6022, lumacaftor and cavosonstat), there was no evidence of a statistically significant increase in adverse event reporting compared to placebo (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002). However, a large number of events were reported and it is difficult to assess the clinical relevance of these events with the small number of participants in the trials. Further details are given below.

Lumacaftor versus placebo

Adverse events occurring in more than one participant in any lumacaftor dose treatment group in the lumacaftor study by Clancy are presented in the additional tables (Table 3) (Clancy 2012). We have combined the total number of participants with adverse events occurring in the 100 mg and 200 mg lumacaftor groups and compared this to the number of participants experiencing adverse effects in the placebo group (Analysis 1.2). Adverse event data for participants receiving a lower dose (25 or 50 mg of lumacaftor) were not included as there was no evidence of efficacy. The most commonly reported side effect was cough; there was no statistically significant difference in the number of participants who reported cough between the participants assigned to either 100 mg or 200 mg lumacaftor and those assigned to placebo, OR 1.28 (99% CI 0.28 to 5.92) (Analysis 1.2) (Clancy 2012).

Data for 14 days of lumacaftor monotherapy (200 mg once daily) demonstrated no statistically significant differences between participants treated with lumacaftor therapy and placebo in the number of participants experiencing cough, oropharyngeal pain, nasal congestion, dizziness, a prolonged prothrombin time, and upper respiratory tract infection (Analysis 1.3) (Boyle 2014) (very low-quality evidence).

Cavosonstat versus placebo

In the cavosonstat study, there was no statistically significant difference in cough, pulmonary exacerbation, chest discomfort, fatigue in the treatment group compared to placebo (Analysis 2.3) (Donaldson 2017) (very low-quality evidence). All adverse events observed in this study were reported to be 'mild or moderate' in severity.

N6022 versus placebo

The number of Grade 1 (mild) adverse events across all N6022 doses and placebo were reported (Donaldson 2014). There was no statistically significant difference between any of the N6022 doses and placebo in terms of the number of mild adverse events, specific events were not reported (Analysis 3.2).

CPX versus placebo

Participants received a single dose of the assigned CPX dose level (1 mg, 3 mg, 10 mg, 30 mg, 100 mg, 300 mg or 1000 mg) (McCarty 2002). Adverse events were recorded on the day of dosing (day one), day two and followed up one week post-dosing. Adverse effects that occurred in more than 3% of participants are shown in the additional tables (Table 4). Combined data from all CPX groups versus placebo demonstrated that the following events were less common in the placebo group: abdominal pain, OR 0.45 (99% CI 0.01 to 24.92); asthenia, OR 0.65 (99% CI 0.01 to 39.69); headache, OR 0.33 (99% CI 0.01 to 17.72); pain, OR 0.45 (99% CI 0.01 to 24.92); diarrhoea, OR 0.65 (99% CI 0.01 to 39.69); lung disease, OR 0.45 (99% CI 0.01 to 24.92); and rhinitis, OR 0.45 (99% CI 0.01 to 24.92) (Analysis 4.1). Dizziness was more common amongst participants in the placebo group, OR 9.33 (99% CI 0.32 to 268.92) (Analysis 4.1). The difference between CPX groups (combined data) and placebo was not statistically significant for any adverse event (McCarty 2002).

4PBA versus placebo

In the pilot 4PBA study (n = 18) (Rubenstein 1998), the differences between groups in the number of participants who reported episodes of bad taste in their mouth and diarrhoea were not statistically significant, OR 0.44 (99% CI 0.01 to 13.44) and OR 3.35 (99% CI 0.04 to 267.31) respectively (Analysis 5.1).

In the Phase 2 4PBA study (n = 19), participants randomised to the 20 g cohort reported episodes of transient nausea, headache, sleepiness and body odour after the initial dose; the transient nausea, sleepiness and headache resolved with a dose of Tylenol® (acetaminophen). No numerical data were reported regarding adverse events, therefore no data can be entered into analysis for this study (Zeitlin 2002).

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

None of the participants in the Phase 2 lumacaftor-ivacaftor study, the pilot 4PBA study or the CPX study the required study drug interruption for the adverse effects of therapy (Boyle 2014; McCarty 2002; Rubenstein 1998).

Lumacaftor versus placebo

There were no statistically significant differences in terms of any lumacaftor dose compared to placebo in the number of adverse events requiring study drug discontinuation up to day 28 (Analysis 1.4) (Clancy 2012).

Cavosonstat versus placebo

In the cavosonstat study, there was no statistically significant difference in cough, pulmonary exacerbation, chest discomfort, fatigue in the treatment group compared to placebo (Analysis 2.3) (Donaldson 2017) (very low-quality evidence). All adverse events observed in this study were reported to be 'mild or moderate' in severity.

N6022 versus placebo

The number of Grade 2 (moderate) adverse events across all N6022 doses and placebo were reported (Donaldson 2014). There was no statistically significant differences between any of the N6022 doses and placebo in terms of the number of Grade 2 adverse events; specific events were not reported (Analysis 3.3).

4PBA versus placebo

In the phase 4 4PBA study, participants who were discontinued from a particular study dose were assigned a reduced dose and this is discussed under severe adverse effects (Zeitlin 2002).

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

None of the participants from the CPX study or the cavosonstat study required study drug termination (Rubenstein 1998; Donaldson 2017).

Lumacaftor versus placebo

In the Clancy study, adverse effects in eight participants were considered severe: fatigue (n = 1); sinus congestion (n = 1); musculoskeletal discomfort (n = 1); cough (n = 2); and pulmonary exacerbation (n = 3). It is not stated which arm these participants were randomised to. Four out of 89 participants (5%) - one participant from each of the lumacaftor arms - discontinued the study drug due to respiratory adverse effects. No participants discontinued from the placebo group (Clancy 2012).

N6022 versus placebo

The number of Grade 3 or above (serious or life-threatening) adverse events across all N6022 doses and placebo were reported (Donaldson 2014). There was no statistically significant differences between any of the N6022 doses and placebo in terms of the number of Grade 3 or above adverse events (Analysis 3.4). The events were as follows: one participant with appendicitis in the 5 mg/day N6022 group and three participants with a pulmonary exacerbation of CF one each in the placebo, 5 mg/day and 40 mg/day N6022 groups.

4PBA versus placebo

None of the participants from the pilot 4PBA study required study drug termination (McCarty 2002). In the Phase 2 4PBA study, none of the participants in the 20 g group required study drug termination (Zeitlin 2002). "Several" participants (exact number not stated) in the 30 g group reported episodes of transient nausea, headache, sleepiness and transient visual disturbances after the initial dose. Two participants from the 30 g cohort required dose reduction to 20 g due to headache (n = 1) and for an unknown reason (n = 1). One participant who started in this group had to discontinue medication after developing acute distal intestinal obstruction syndrome on day two, but was replaced by another participant. The three participants assigned 40 g of 4PBA reported episodes of nausea, headache and visual disturbances and one participant reported cramp in hands and fingers. One participant tolerated the dose whilst splitting the 40 g into six daily doses, one participant had a dose reduction to 30 g daily and another participant in this group was discontinued from the study due to intolerable symptoms (nausea, headache and visual disturbances). The 40 g cohort was terminated early following analysis of the data by the safety monitoring committee (Zeitlin 2002).

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

Lumacaftor versus placebo

Two studies also reported on the number of participants who experienced episodes of pulmonary exacerbations described as adverse events (Boyle 2014; Clancy 2012). Results are presented in the analyses and described below (see 'Extra courses of antibiotics') (Analysis 1.2; Analysis 1.3).

N6022 versus placebo

Donaldson reported on "none serious" adverse events on each dose of N6022 and placebo (Donaldson 2014). Due to the small numbers of participants experiencing different adverse events, these results are not entered into analysis and are reported in the additional tables (Table 5).

2. Hospitalisation

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

3. School or work attendance

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017 McCarty 2002; Rubenstein 1998; Zeitlin 2002).

4. Extra courses of antibiotics

a. Time-to the next course of antibiotics

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

b. Total number of courses of antibiotics

Lumacaftor versus placebo

In the lumacaftor study (n = 89), pulmonary exacerbations were physician-defined and there was no statistically significant difference in the frequency of participants who developed pulmonary exacerbations between those in the lumacaftor groups and the placebo group, OR 1.50 (99% CI 0.16 to 14.31) (Analysis 1.2) (Clancy 2012).

In the Boyle study (n = 62), it was unclear whether the reported exacerbations were protocol-defined or physician-defined. At day 14, exacerbations were more common in participants receiving 200 mg lumacaftor once daily in comparison to participants receiving placebo, OR 2.72 (99% CI 0.05 to 156.17) (Analysis 1.3). However, the difference between groups was not statistically significant (Boyle 2014).

5. Sweat chloride (change from baseline) as a measure of CFTR function

All included studies reported on sweat chloride concentration (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

i. Immediate (up to one month)

Lumacaftor versus placebo

In the Clancy study (n = 89), data at seven days demonstrated small reductions in the change from baseline in sweat chloride concentration compared to placebo for the participants taking 25 mg lumacaftor, MD 1.7 mmol/L; 50 mg lumacaftor, MD -1.5 mmol/

L; 100 mg lumacaftor, MD -0.1mmol/L; and 200 mg lumacaftor, MD -4.4 mmol/L (Clancy 2012). No SDs or CIs were reported to allow the inclusion of these results into the analysis (Clancy 2012). At 28 days, participants in the 25 mg lumacaftor group demonstrated a marginal increase in sweat chloride concentration compared to placebo, MD 0.1 mmol/L and those in the 50 mg lumacaftor group demonstrated a decreased sweat chloride concentration compared to placebo, MD -4.61 mmol/L (Clancy 2012). These differences were not statistically significant and no SDs or CIs were reported for inclusion of these results into the analysis (Clancy 2012). Data at one month demonstrated statistically significant reductions in sweat chloride concentration compared to placebo for participants in the once daily 100 mg lumacaftor group, MD -6.13 mmol/L (95% CI -12.25 to -0.01) and once daily 200 mg lumacaftor group, MD -8.21 (95% CI -14.30 to -2.12) (Analysis 1.5) (Clancy 2012).

Boyle reported that at day 14, there was a small reduction in sweat chloride concentration reported in participants taking 200 mg lumacaftor once daily compared to placebo, MD -2.75 mmol/L (95% CI -7.65 to 2.15) which was not statistically significant (Analysis 1.6) (Boyle 2014). Results for up to 21 days (monotherapy and combination therapy) are reported above (see 'Correctors plus potentiators in combination therapy compared to placebo').

Cavosonstat versus placebo

There was no statistically significant difference in sweat chloride concentration between cavosonstat and placebo at 28 days (n = 51), MD -3.30 mmol/L (95% CI -9.13 to 2.53) (Analysis 2.4) (Donaldson 2017).

CPX versus placebo

In the CPX study (n = 37), McCarty reported post-treatment sweat chloride concentration values at the end of treatment on day one (McCarty 2002). The baseline sweat chloride values in the CPX group and the placebo group appear to have been pooled. By calculating the values for relative change from baseline, we have assumed that the baseline sweat chloride value represents the baseline sweat chloride concentration value for each arm. At the end of treatment on day one, there were no statistically significant differences in sweat chloride concentration between the placebo group and the 1 mg CPX group, MD 12.8%; the 3 mg CPX group, MD 7.5%; the 10 CPX mg group, MD 11.3%; the 30 CPX mg group, MD 5.4%; the 100 CPX mg group, MD 5.1%; the 300 CPX mg group, MD 14.7%; and the 1000 CPX mg group, MD -8.2%. No SDs or CIs were reported to allow calculation of SDs for entry into the analysis (McCarty 2002).

4BPA versus placebo

In the pilot 4PBA study by Rubenstein (n = 18), there was no statistically significant difference in sweat chloride concentration at one week between participants in the 4PBA group and the placebo group (P = 0.387). Data were plotted on a graph and could not be extracted with accuracy (Rubenstein 1998).

The Phase 2 4PBA study by Zeitlin reported post-treatment sweat chloride concentration values at day two, day three, day four and day seven; we calculated the relative change from baseline values at each time-point. There was no statistically significant difference in sweat chloride concentration between the 20 g 4PBA group and the placebo group after two days of treatment, MD -7.8%; three days, MD -4.9%; four days, MD -3.3% and seven days, MD -8.7%.

Furthermore, there was no statistically significant difference in sweat chloride concentration between the 30 g 4PBA group and the placebo group after two days of treatment, MD -25.9%; three days, MD 0.5%; four days, MD -6.4% and seven days, MD -3.9% (Zeitlin 2002). No SDs or CIs were reported to allow calculation of SDs for entry into the analysis. Due to insufficient reporting of data by both 4PBA studies, we were unable to include the results in the analysis (Rubenstein 1998; Zeitlin 2002).

6. Radiological measures of lung disease

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

7. Acquisition of respiratory pathogens

Data for the acquisition of *S aureus*, *H influenzae* or any other clinically relevant pathogens except *P aeruginosa*, were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

a. P aeruginosa

This was a pre-defined outcome of interest in the Phase 1/2 4PBA study, but no study results were reported (Zeitlin 2002). Data for this outcome were not reported the other studies (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998).

8. Eradication of respiratory pathogens

Data for this outcome were not reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

9. Nutrition and growth

No data for this outcome, either in terms of weight, BMI or height, were reported by any study (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002).

Correctors plus potentiators (combination therapy) compared to placebo

Six studies with 1898 participants contributed to the efficacy results in this comparison (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). A further study contributed additional safety data to this comparison (see below) (PROGRESS 2017).

Four studies with 1376 participants compared lumacaftor plus ivacaftor to placebo (Boyle 2014; Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015) and two studies with 522 participants compared tezacaftor plus ivacaftor to placebo or ivacaftor alone (i.e. tezacaftor placebo) (Donaldson 2018; Taylor-Cousar 2017).

Two three-arm studies (n = 1108) compared 600 mg once daily lumacaftor plus 250 mg twice daily ivacaftor to 400 mg twice daily lumacaftor plus 250 mg twice daily ivacaftor and to placebo (TRAFFIC 2015; TRANSPORT 2015). One study (n = 64) compared lumacaftor 200 mg once daily plus 150 mg or 250 mg twice daily ivacaftor to placebo (Boyle 2014). Participants in this study received lumacaftor monotherapy for 14 days followed by

combination therapy with ivacaftor for seven days, therefore this study contributes to both comparisons of this review (Boyle 2014).

The paediatric combination study (n = 204) compared 200 mg lumacaftor twice daily plus 250mg ivacaftor twice daily to placebo for 24 weeks (Ratjen 2017). Primary and secondary outcomes of this study were analysed via a mixed model for repeated measures (MMRM), further details of this analysis approach are provided in the tables (Characteristics of included studies). Results provided by this model can be interpreted as treatment effect averaged from each study visit until week 24.

The PROGRESS study was an extension to the TRAFFIC and TRANSPORT studies (TRAFFIC 2015; TRANSPORT 2015), in which participants from the original placebo groups were randomised to one of the two interventions (PROGRESS 2017). Due to the overlap of participants in these three studies, we have not included efficacy data for the PROGRESS study under a comparison of lumacaftor (plus ivacaftor) doses. We have included safety data from this study as these are important longer-term results for participants on this intervention; results for the PROGRESS study are presented in the tables for information (PROGRESS 2017; Table 6; Table 7).

One study (n = 510) compared a combination of tezacaftor 100 mg plus ivacaftor 150 mg every 12 hours to a matched placebo for 24 weeks (Taylor-Cousar 2017) and one study compared tezacaftor (100 mg per day) plus ivacaftor (150 mg twice daily) against placebo (150 mg twice daily ivacaftor alone) in people with one F508del mutation and one G551D mutation (Donaldson 2018).

Important results for this comparison are summarised in the tables (Summary of findings 3; Summary of findings 4; Summary of findings 5; Summary of findings 6).

Primary outcomes

1. Survival

No deaths were reported during any of the included studies (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015) (high to moderate-quality evidence).

2. QoL

Five studies reported on QoL (Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

a. Total QoL score

Lumacaftor plus ivacaftor versus placebo

Two studies reported QoL according to the Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score at six months (TRAFFIC 2015; TRANSPORT 2015). This information was not reported in the primary journal article, but is available from the study record on ClinicalTrials.gov (TRAFFIC 2015; TRANSPORT 2015).

There was no statistically significant improvement in the absolute change from baseline of EQ-5D-3L index score between the lumacaftor 600 mg once daily plus 250 mg ivacaftor twice daily group and placebo group, MD 0.00 (95% CI -0.01 to 0.02) (Analysis 6.1), or the lumacaftor 400 mg twice daily plus 250 mg ivacaftor twice daily group and placebo group, MD 0.00 (95% CI -0.01 to 0.02) (Analysis 7.1), or when the two lumacaftor doses were pooled at six

months, MD 0.00 (95% CI -0.01 to 0.01) (Analysis 8.1) (high-quality evidence).

b. QoL sub-domains

i. Immediate term (up to and including one month)

Lumacaftor plus ivacaftor versus placebo

In the TRAFFIC and TRANSPORT studies (n = 1108), at 28 days participants in the both the lumacaftor 600 mg once daily plus 250 mg ivacaftor twice daily group and the lumacaftor 400 mg twice daily plus 250 mg ivacaftor twice daily group experienced statistically significantly higher absolute changes from baseline in the CFQ-R respiratory domain compared to the placebo group, MD 3.32 (95% CI 1.13 to 5.51) (Analysis 6.2) and MD 4.13 (95% CI 1.94 to 6.31) (Analysis 7.2), respectively (TRAFFIC 2015; TRANSPORT 2015). There was also a statistically significantly higher absolute change from baseline in the CFQ-R respiratory domain compared to the placebo group when the two lumacaftor doses were pooled, MD 3.70 (95% CI 1.81 to 5.58) (Analysis 8.2).

Tezacaftor plus ivacaftor versus control

Taylor-Cousar (n = 510) reported on the CFQ-R respiratory domain at four weeks (Taylor-Cousar 2017) and found a statistically significant difference in favour of the treatment group, MD 5.10 (95% CI 2.99 to 7.21) (Analysis 13.1).

Donaldson (n= 18) presents the within-group change from baseline to Day 28 for the CFQ-R respiratory domain and at the end of the study the difference in treatment effect between tezacaftor-ivacaftor and placebo was 6.81 points (P = 0.2451) (Donaldson 2018). These data were extrapolated and we have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update.

ii. Short term (over one month and up to and including six months)

Lumacaftor plus ivacaftor versus placebo

In the two studies (n = 1108) (TRAFFIC 2015; TRANSPORT 2015), the statistically significant difference in the absolute change from baseline in the CFQ-R respiratory domain was maintained to six months in the 600 mg lumacaftor group compared to placebo, MD 3.04 (95% CI 0.76 to 5.32) (Analysis 6.2), but not in the 400 mg lumacaftor group compared to placebo, MD 2.18 (95% CI -0.11 to 4.47) (Analysis 7.2). There was a statistically significantly higher absolute change from baseline in the CFQ-R respiratory domain compared to the placebo group when the two lumacaftor doses were pooled, MD 2.62 (95% CI 0.64 to 4.59) (Analysis 8.2) (moderate-quality evidence). These data were extrapolated and we have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update.

The EQ-5D-3L Visual Analog Scale (VAS) domain score was also reported at six months in two studies (TRAFFIC 2015; TRANSPORT 2015). Participants in the both the lumacaftor 600 mg group and the lumacaftor 400 mg group experienced statistically significantly higher absolute changes from baseline in the EQ-5D-3L VAS domain compared to the placebo group, MD 2.24 (95% CI 0.18 to 4.31) (Analysis 6.3) and MD 2.30 (95% CI 0.25 to 4.36) (Analysis 7.3) respectively. There was also a statistically significantly higher

absolute change from baseline in the EQ-5D-3L VAS domain compared to the placebo group when the two lumacaftor doses were pooled, MD 2.28 (95% CI 0.50 to 4.06) (Analysis 8.3). This information was not reported in the primary journal article, but is available from the study record on ClinicalTrials.gov (TRAFFIC 2015; TRANSPORT 2015). Immediate-term data for this domain have been requested from the study investigators and any unpublished information we receive will be included in a future update.

The paediatric combination study also reported the absolute change from baseline (up to and including 24 weeks) of the CFQ-R respiratory domain (Ratjen 2017). The change within the lumacaftor plus ivacaftor group was higher compared to the placebo group, but this difference did not reach statistical significance, MD 2.50 (95% CI -0.10 to 5.10) (Analysis 11.1) (low-quality evidence). Additional results at earlier time points (day 15, week 4, and week 16) were published graphically in the full study publication, but the graphical plots were too small to allow for accurate extraction of data (Ratjen 2017). Numerical data for these time points have been requested from the study investigators and any unpublished information we receive will be included in a future update.

Investigators in this study also list the absolute change in Treatment Satisfaction Questionnaire for Medication (TSQM) domains as a secondary outcome of the study, but results for this outcome are not presented (Ratjen 2017). Numerical data for this outcome have also been requested from the study investigators and any unpublished information we receive will be included in a future update.

Tezacaftor plus ivacaftor versus control

Taylor-Cousar (n = 510) also reported on the CFQ-R respiratory domain at 24 weeks (Taylor-Cousar 2017); there was a statistically significant difference in favour of tezacaftor-ivacaftor, MD 5.10 (95% CI 3.20 to 7.00) (Analysis 13.1) (moderate-quality evidence).

3. Physiological measures of lung function

a. FEV$_1$ (relative change from baseline)

i. Immediate term (up to and including one month)

Lumacaftor plus ivacaftor versus placebo

Immediate-term data for this domain have been requested from the investigators of two studies (TRAFFIC 2015; TRANSPORT 2015). Any unpublished information we receive will be included in a future update.

Tezacaftor plus ivacaftor versus control

There was no statistically significant difference between tezacaftor plus ivacaftor compared to ivacaftor alone at four weeks (n = 504), MD 3.72 (95% CI -7.77 to 15.21) (Analysis 13.2) (Donaldson 2018).

ii. Short term (over one month and up to and including six months)

Lumacaftor plus ivacaftor versus placebo

At six months, participants in the TRAFFIC and TRANSPORT studies (n = 1108) in the both the lumacaftor 600 mg group and the lumacaftor 400 mg group experienced statistically significantly higher relative changes from baseline in FEV$_1$ (% predicted) compared to the placebo group, MD 5.63 (95% CI 3.80 to 7.47)

(Analysis 6.4) and MD 4.77 (95% CI 2.93 to 6.61) (Analysis 7.4) respectively (TRAFFIC 2015; TRANSPORT 2015). There was also a statistically significantly higher relative change from baseline in FEV_1 (% predicted) compared to the placebo group when the two lumacaftor doses were pooled, MD 5.21 (95% CI 3.61 to 6.80) (Analysis 8.4) (high-quality evidence).

Tezacaftor plus ivacaftor versus control

At 24 weeks, a statistically significantly higher relative change from baseline in FEV_1 (% predicted) compared to the placebo group in the tezacaftor-ivacaftor study (n = 510), MD 6.80 (95% CI 5.30 to 8.30) (Analysis 13.2) (Taylor-Cousar 2017) (moderate-quality evidence).

b. FEV_1 absolute values

i. Immediate term (up to and including one month)

Lumacaftor plus ivacaftor versus placebo

In two studies (n = 1108), participants in the both the lumacaftor 600 mg group and the lumacaftor 400 mg group experienced statistically significantly higher absolute changes from baseline in FEV_1 (% predicted) at 28 days compared to the placebo group, MD 2.32 (95% CI 1.34 to 3.31) (Analysis 6.5) and MD 2.42 (95% CI 1.43 to 3.40) (Analysis 7.5), respectively (TRAFFIC 2015; TRANSPORT 2015). There was also a statistically significantly higher absolute change from baseline in FEV_1 compared to the placebo group when the two lumacaftor doses were pooled, MD 2.37 (95% CI 1.52 to 3.22) (Analysis 8.5). These data were extrapolated and we have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update.

The Phase 2 lumacaftor-ivacaftor study (n = 62) reported on the absolute change from baseline in FEV_1 after lumacaftor monotherapy (day 14) and lumacaftor (200 mg daily) and ivacaftor (150 mg or 250 mg twice daily) combination therapy (day 21) (Boyle 2014). Results for lumacaftor monotherapy are discussed above (see 'Correctors (monotherapy) compared to placebo').

Small, but non-statistically significant improvements in FEV_1 were reported at day 21 for participants treated with 200 mg lumacaftor once daily (day 1 to 21) and either 150 mg ivacaftor twice daily (day 15 to 21), MD 2.80 (95% CI -1.39 to 6.99) (Analysis 9.1) or 250 mg ivacaftor twice daily (day 15 to 21), MD 0.20 (95% CI -4.20 to 4.60) (Analysis 10.1) respectively and when ivacaftor doses were combined, MD 1.57 (95% CI -2.13 to 5.27) (Analysis 12.1) (Boyle 2014) (moderate-quality evidence).

Tezacaftor plus ivacaftor versus control

At four weeks, there was a statistically significantly higher absolute change from baseline in FEV_1 (% predicted) compared to the control groups in the two tezacaftor-ivacaftor studies (n = 528), pooled MD 3.59 (95% CI 2.40 to 4.78) (Analysis 13.3) (Taylor-Cousar 2017).

ii. Short term (over one month and up to and including six months)

Lumacaftor plus ivacaftor versus placebo

In the TRAFFIC and TRANSPORT studies (n = 1108), at six months the statistically significant difference in absolute changes from baseline in FEV_1 (% predicted) were maintained in the both the lumacaftor

600 mg group and the lumacaftor 400 mg groups, MD 3.34 (95% CI 2.30 to 4.38) (Analysis 6.5) and MD 2.80 (95% CI 1.75 to 3.84) (Analysis 7.5) respectively (TRAFFIC 2015; TRANSPORT 2015). There was also a statistically significantly higher absolute change from baseline in FEV_1 (% predicted) compared to the placebo group when the two lumacaftor doses were pooled, MD 3.07 (95% CI 2.17 to 3.97) (Analysis 8.5) (moderate-quality evidence).

In the paediatric combination study, investigators reported a statistically significantly higher absolute change from baseline in FEV_1 (% predicted) in the lumacaftor plus ivacaftor group compared to the placebo group up to and including 24 weeks (n = 204) (Ratjen 2017), MD 2.40 (95% CI 0.40 to 4.40) (Analysis 11.2) (low-quality evidence). Additional results at earlier time points (day 15, week 4, and week 16) were published graphically in the study report, but the graphical plots were too small to allow for accurate extraction of data (Ratjen 2017). Numerical data for these time points have been requested from the study investigators and any unpublished information we receive will be included in a future update. Investigators in this study also reported early post-drug dose declines in FEV_1 (% predicted) at day one in the lumacaftor plus ivacaftor group (Ratjen 2017). A markedly smaller decline was observed post-dose at day 15, and no decline was observed by week 16. These data are not available for all participants so are not entered into analysis for this review; instead these results are presented in the additional tables (Table 8).

Tezacaftor plus ivacaftor versus control

At 24 weeks, there was a statistically significantly higher absolute change from baseline in FEV_1 (% predicted) compared to the placebo group in the tezacaftor-ivacaftor study, MD 4.00 (95% CI 3.10 to 4.90) (Analysis 13.3) (Taylor-Cousar 2017) (moderate-quality evidence).

c. FVC (absolute values and change from baseline)

Data for this outcome were not reported by any study in this comparison (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). However, it is stated in the protocol of the TRAFFIC and TRANSPORT studies that FVC data was collected (although not considered as an outcome). Any recorded data relevant to this outcome has been requested from the study investigators and any unpublished information we receive will be included in a future update.

d. LCI

Lumacaftor plus ivacaftor versus placebo

Only one study (n = 204) reported this outcome and its primary outcome was $LCI_{2.5}$, i.e. the number of lung volume turnovers required to reach 2.5% of starting tracer gas concentration (Ratjen 2017). There was a statistically significantly larger reduction in $LCI_{2.5}$ in the lumacaftor plus ivacaftor group compared to the placebo group up to and including 24 weeks, MD -1.10 (95% CI -1.40 to -0.80) (Analysis 11.3). Additional results at earlier time points (day 15, week 4, and week 16) were published graphically in the full study report, but the graphical plots were too small to allow for accurate extraction of data (Ratjen 2017). Numerical data for these time points have been requested from the study investigators and any unpublished information we receive will be included in a future update.

Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis (Review)

The study investigators also list LCI$_{5.0}$ as a secondary outcome of the study, i.e. number of lung volume turnovers required to reach 5% of starting tracer gas concentration (Ratjen 2017). However, results for this outcome are not presented. Numerical data for this outcome have been requested from the study investigators and any unpublished information we receive will be included in a future update.

Secondary outcomes

1. Adverse events

Adverse events were reported by all studies examining combination therapies (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). The type and extent of adverse event reporting was not consistent across studies making comparison between different treatment regimens and interventions a challenge. For the Phase 3 studies a common adverse events was defined by the researchers as one that occurred in more than 10% of participants.

Lumacaftor plus ivacaftor versus placebo

The TRAFFIC and TRANSPORT studies reported no statistically significant differences in the number of participants experiencing adverse events during the study, either by lumacaftor dose or when lumacaftor doses were pooled, OR 1.00 (99% CI 0.37 to 2.71) (Analysis 6.6), OR 0.77 (99% CI 0.30 to 1.96) (Analysis 7.6) and OR 0.87 (99% CI 0.38 to 2.02) (Analysis 8.6), respectively (TRAFFIC 2015; TRANSPORT 2015) (high-quality evidence).

In the paediatric lumacaftor-ivacaftor study the overall rate of reporting of adverse events was lower than for the TRAFFIC and TRANSPORT studies with a similar profile, including increased reporting of chest tightness on starting the lumacaftor-ivacaftor intervention compared to placebo (Ratjen 2017). The studies also reported no statistically significant difference between the lumacaftor plus ivacaftor group compared to placebo in the number of participants experiencing adverse events during the study, OR 0.60 (99% CI 0.09 to 4.08) (Analysis 11.4) (low-quality evidence).

Tezacaftor plus ivacaftor versus control

For the tezacaftor-ivacaftor studies, we present the most common adverse events which occurred in at least 10% of participants in either study (Analysis 13.4). Further less commonly occurring adverse events are presented in the original trial reports; none of which showed any difference between groups (Donaldson 2018; Taylor-Cousar 2017) (moderate-quality evidence).

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

Lumacaftor plus ivacaftor versus placebo

Boyle reported data for lumacaftor-ivacaftor combination therapy at 21 days (day 14 to 21) (Boyle 2014). The combined analysis showed no statistically significant differences between participants treated with lumacaftor-ivacaftor combination therapy and placebo in the number of participants experiencing cough, oropharyngeal pain, nasal congestion, dizziness, a prolonged prothrombin time, and upper respiratory tract infection (Analysis 9.2; Analysis 10.2; Analysis 12.2) (low-quality evidence).

For participants in the TRAFFIC and TRANSPORT studies receiving the lumacaftor-ivacaftor therapy, the most regularly reported adverse events were respiratory in nature (e.g. chest tightness) (TRAFFIC 2015; TRANSPORT 2015). Most respiratory adverse events occurred shortly after starting lumacaftor-ivacaftor therapy and for those who continued with the intervention they were reported to be transient in nature. Dyspnoea was statistically significantly more common in the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily group compared to placebo, OR 2.05 (99% CI 1.10 to 3.83) (Analysis 6.6) and when lumacaftor doses were combined, OR 1.90 (99% CI 1.08 to 3.35) (Analysis 8.6). Cough was statistically significantly less common in the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily group compared to placebo, OR 0.58 (99% CI 0.39 to 0.88) (Analysis 7.6) and when lumacaftor doses were combined, OR 0.65 (99% CI 0.46 to 0.92) (Analysis 8.6).

There were no statistically significant differences between lumacaftor 600 mg once daily, lumacaftor 400 mg twice daily plus 250 mg ivacaftor twice daily or lumacaftor doses combined compared to placebo in terms of the number of participants experiencing other adverse events: infective pulmonary exacerbation, headache, haemoptysis, diarrhoea, abnormal respiration, increased sputum, nasopharyngitis, oropharyngeal pain, abdominal pain, fatigue, nausea, pyrexia, nasal congestion, upper respiratory tract infection (Analysis 6.6; Analysis 7.6, Analysis 8.6).

In the TRAFFIC and TRANSPORT studies, in seven participants receiving lumacaftor-ivacaftor therapy abnormal liver function (elevated liver enzyme) results led to a temporary discontinuation of the intervention, after which liver function improved (to baseline in six participants). Treatment was re-started in six of these participants; in one participant abnormal liver function was associated with hepatitis E infection (TRAFFIC 2015; TRANSPORT 2015).

For the paediatric lumacaftor-ivacaftor study, the number of treatment-emergent adverse events with an incidence over 10% were reported (Ratjen 2017). Productive cough, nasal congestion, oropharyngeal pain, upper abdominal pain, rhinorrhoea and increased sputum were observed more frequently in the lumacaftor-ivacaftor group compared to the placebo group, but there was no statistically significant difference between the groups (Analysis 11.4). There was also no statistically significant differences between the groups in terms of cough, pyrexia, headache, upper respiratory tract infection, abdominal pain, nausea, vomiting, fatigue and respiratory events (such as wheezing, dyspnoea, asthma and chest discomfort) (Analysis 11.4).

Tezacaftor plus ivacaftor versus control

There were no statistically significant differences between tezacaftor-ivacaftor and control groups (99% confidence intervals) in the number of participants experiencing cough, pulmonary exacerbation, headache, nasal congestion or nasopharyngitis, increased sputum, haemoptysis, pyrexia, oropharyngeal pain, nausea or fatigue (Analysis 13.4) (Donaldson 2018; Taylor-Cousar 2017). Taylor-Cousar specified respiratory compromise on initiation as an adverse event in light of the reports from the TRAFFIC and TRANSPORT studies, but there was no increased reporting of this event (Taylor-Cousar 2017).

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

Lumacaftor plus ivacaftor versus placebo

None of the participants in the Phase 2 lumacaftor-ivacaftor study required study drug interruption for the adverse effects of therapy (Boyle 2014). It was not stated in the TRAFFIC and TRANSPORT studies whether study drug interruption for the adverse effects of therapy was required for any participants (TRAFFIC 2015; TRANSPORT 2015). The combined safety data demonstrated similar rates of serious adverse event reporting for participants receiving placebo (28.6%) and those receiving the lumacaftor-ivacaftor combination therapy (17.3% to 22.8%); however, the characteristics of these events were different (Analysis 6.6; Analysis 7.6; Analysis 8.6).

In two studies, 14 participants on lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily and 17 participants on lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily discontinued the study due to adverse events. In total 31 of 738 (4.2%) of participants receiving lumacaftor-ivacaftor discontinued compared to six of 370 (1.6%) participants receiving placebo (TRAFFIC 2015; TRANSPORT 2015). The differences in the discontinuation rates in the treatment groups were not statistically significant compared to placebo at the 1% statistical significance level to allow for multiple analyses related to adverse events, OR 2.38 (99% CI 0.67 to 8.50) (Analysis 6.6), OR 2.91 (99% CI 0.85 to 10.03) (Analysis 7.6) and OR 2.65 (99% CI 0.83 to 8.45) (Analysis 8.6) respectively.

In the same studies, 84 participants on lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily, 64 participants on lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily and 106 participants on placebo experienced at least one 'serious' adverse event (TRAFFIC 2015; TRANSPORT 2015). A 'serious' adverse event was defined as "death, life threatening adverse experience, in-patient hospitalization/prolongation of hospitalization, persistent/significant disability or incapacity, congenital anomaly/birth defect, important medical event". The following adverse events, which occurred on more than one occasion, were reported to have resulted in discontinuation of the lumacaftor-ivacaftor therapy: elevated serum creatinine kinase level (n = 4), haemoptysis (n = 3), bronchospasm (n = 2), dyspnoea (n = 2), pulmonary exacerbation (n = 2) (see below), and rash (n = 2). One participant developed hypertension and discontinued the study (not included in the initial reports of this study); other reasons for discontinuation were not recorded (TRAFFIC 2015; TRANSPORT 2015).

There was no statistically significant difference between the number of adverse events between participants on lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily compared to placebo, OR 0.73 (99% CI 0.47 to 1.13) (Analysis 6.6). Statistically significantly fewer participants experienced serious adverse events on lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily compared to placebo, OR 0.52 (99% CI 0.33 to 0.83) (Analysis 7.6); this was also true when lumacaftor doses were combined, OR 0.62 (99% CI 0.42 to 0.91) (Analysis 8.6).

For the paediatric study of lumacaftor-ivacaftor, there was no statistically significant difference reported between groups in the number of serious adverse events reported, OR 1.18 (99% CI 0.38 to 3.63) (Analysis 11.4). There were 13 participants who had serious adverse events in the lumacaftor plus ivacaftor group; these were considered to be treatment-related in two participants (one drug interaction and one obstructive airways disorder). In the placebo group, 11 participants had serious adverse events; these were considered to be treatment-related in three participants (one distal

intestinal obstruction syndrome, two elevated aminotransferases) (Ratjen 2017). In this study six out of 103 participants discontinued, three due to adverse events. One participant discontinued due to an early respiratory event, a second due to persistently abnormal liver function tests and the reasons for the remaining four who discontinued were not recorded (Ratjen 2017).

In the longer-term follow-up study to the TRAFFIC and TRANSPORT studies (PROGRESS), in which participants were randomised to two different lumacaftor-ivacaftor dose regimens, the paper reported that 7% of the participants withdrew because of adverse events during the 96 week-study period; in one participant this was due to hypertension (PROGRESS 2017).

Tezacaftor plus ivacaftor versus control

In the Phase 3 tezacaftor-ivacaftor study, seven out of 251 participants receiving tezacaftor-ivacaftor discontinued compared to eight out of 258 participants in the placebo group (Taylor-Cousar 2017). Reasons for discontinuation in the tezacaftor-ivacaftor group included abdominal pain (n = 2), raised serum creatinine phosphokinase (n = 1), raised liver enzymes (n = 1) and a generalised tonic-clonic seizure (n = 1).

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

Lumacaftor plus ivacaftor versus placebo

For trials evaluating lumacaftor-ivacaftor, there were no adverse events reported, that in our assessment, were life-threatening or debilitating. When treatments were discontinued the reported adverse events resolved (Boyle 2014; Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015).

Tezacaftor plus ivacaftor versus control

In the large tezacaftor-ivacaftor study (n = 510) one life-threatening adverse event (haemoptysis) was reported in a participant in the tezacaftor-ivacaftor treatment group (Taylor-Cousar 2017).

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

All studies reported on the number of participants who experienced episodes of pulmonary exacerbations described as adverse events (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). Results are presented in the analyses (Analysis 6.6; Analysis 7.6; Analysis 8.6; Analysis 9.2; Analysis 10.2; Analysis 12.2; Analysis 11.4; Analysis 13.4) and described below (see 'Extra courses of antibiotics').

Lumacaftor plus ivacaftor versus placebo

After a second participant on lumacaftor-ivacaftor was withdrawn with hypertension, the researchers for the TRAFFIC and TRANSPORT and PROGRESS studies reported the blood pressure measurements for the participants over the total study period (PROGRESS 2017; TRAFFIC 2015; TRANSPORT 2015). Average blood pressure data were presented from participants over the total 120-week study period of TRAFFIC and TRANSPORT and PROGRESS for participants who continued on lumacaftor-ivacaftor, but only for those who received the 400 mg twice daily dose, as this was the dose for which the company received a product licence (PROGRESS 2017). There was a statistically significant mean (SE) increase in

systolic blood pressure of 5.1 (1.5) mm Hg and in diastolic blood pressure of 4.1 (1.2) mm Hg (n = 80) (PROGRESS 2017).

2. Hospitalisation

Data for this outcome were reported in two lumacaftor-ivacaftor studies (TRAFFIC 2015; TRANSPORT 2015) and for the tezacaftor-ivacaftor study (Taylor-Cousar 2017), but not by the remaining studies in this comparison (Boyle 2014; Donaldson 2018; Ratjen 2017).

Lumacaftor plus ivacaftor versus placebo

Excerbations were protocol-defined in the TRAFFIC and TRANSPORT studies as exacerbations leading to hospitalisation or treatment with intravenous antibiotics (TRAFFIC 2015; TRANSPORT 2015). We present information relating to events leading to hospitalisation here and information relating to all pulmonary exacerbations below (see 'Extra courses of antibiotics').

The study publications reported on the rate of events per participant leading to hospitalisation over 48 weeks, graphically pooled across both studies (TRAFFIC 2015; TRANSPORT 2015). We estimate that the event rate per participant over 48 weeks in the placebo group was 0.45. The corresponding event rate in the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily group was 0.27 (equal to a 39% decrease compared to the placebo group, P = 0.003). In the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily the event rate was 0.18 (equal to a 61% decrease compared to the placebo group, P < 0.001). The presentation of data did not allow us to estimate the rate over the two lumacaftor doses combined. These data were extrapolated and we have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update.

Tezacaftor plus ivacaftor versus control

The rate of pulmonary exacerbations that led to hospitalisation or treatment with intravenous antibiotic agents (or both) was also lower in the tezacaftor–ivacaftor group than in the placebo group (0.29 versus 0.54 events per year; rate ratio, 0.53; 95% CI, 0.34 to 0.82) (Taylor-Cousar 2017).

3. School or work attendance

Data for this outcome were not reported by any study (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

4. Extra courses of antibiotics

Excerbations were protocol-defined in two studies as exacerbations leading to hospitalisation or treatment with intravenous antibiotics (TRAFFIC 2015; TRANSPORT 2015). Therefore we present information relating to pulmonary exacerbations (as well as information specifically relating to antibiotic use) here. In the other studies, it was unclear whether reported exacerbations were protocol-defined or physician-defined (Boyle 2014; Ratjen 2017).

a. Time-to the next course of antibiotics

The paediatric combination study listed the time to first pulmonary exacerbation as a secondary outcome of the study, but results for this outcome are not presented (Ratjen 2017). Numerical data for this outcome have been requested from the trial investigators and

any unpublished information we receive will be included in a future update.

Lumacaftor plus ivacaftor versus placebo

In the TRAFFIC and TRANSPORT studies, when compared to placebo the time-to-first pulmonary exacerbation was statistically significantly longer in both in the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily group, hazard ratio (HR) 0.70 (95% CI 0.57 to 0.87) (Analysis 6.7) and the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily group, HR 0.61 (95% CI 0.49 to 0.76) (Analysis 7.7) (both moderate-quality evidence). Similarly, the rate of exacerbations was statistically significantly lower in both the active intervention groups compared to placebo; the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily group, rate ratio 0.70 (95% CI 0.57 to 0.87) (Analysis 6.8) and the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily group, rate ratio 0.61 (95% CI 0.49 to 0.76) (Analysis 7.8). This information was not reported in the primary journal article, but is available from the study record on ClinicalTrials.gov (TRAFFIC 2015; TRANSPORT 2015). Information regarding time to first pulmonary exacerbation was reported only as a hazard ratio and P value; the SE used in this analysis was estimated using the methods of Parmar (Parmar 1998).

Tezacaftor plus ivacaftor versus control

The time-to-first pulmonary exacerbation was statistically significantly longer in the tezacaftor-ivacaftor group compared to the placebo group, HR 0.64 (95% CI, 0.46 to 0.89) (Taylor-Cousar 2017) (Analysis 13.5) (moderate-quality evidence).

b. Total number of courses of antibiotics

Lumacaftor plus ivacaftor versus placebo

In two studies, both the lumacaftor 600 mg once daily plus 250 mg ivacaftor twice daily and 400 mg twice daily plus 250 mg ivacaftor twice daily groups experienced statistically significantly fewer pulmonary exacerbations than the placebo group, OR 0.66 (99% CI 0.45 to 0.97) (Analysis 6.6) and OR 0.57 (99% CI 0.39 to 0.84) (Analysis 7.6), respectively (TRAFFIC 2015; TRANSPORT 2015). This statistically significant difference was also observed for the two lumacaftor doses combined compared to placebo, OR 0.62 (99% CI 0.44 to 0.86) (Analysis 8.6).

These studies also reported the rate of events per participant leading to intravenous antibiotic treatment over 48 weeks graphically pooled across the two studies (TRAFFIC 2015; TRANSPORT 2015). These data were extrapolated and we have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update.

We estimate that the event rate per participant over 48 weeks in the placebo group was 0.58. The corresponding event rate in the lumacaftor 600 mg once daily plus ivacaftor 250 mg twice daily group was 0.32 (equal to a 45% decrease compared to the placebo group, P < 0.001) and in the lumacaftor 400 mg twice daily plus ivacaftor 250 mg twice daily was 0.18 (equal to a 56% decrease compared to the placebo group, P < 0.001).

The presentation of data did not allow us to estimate the time to first pulmonary exacerbation or rate of exacerbations over the two lumacaftor doses combined. These data were extrapolated

and we have requested confirmation of the exact data from the study investigators. Any unpublished information we receive will be included in a future update.

Data from the Phase 2 lumacaftor-ivacaftor study on the number of exacerbations were reported at day 21 (Boyle 2014). These data demonstrated no statistically significant differences between treatment groups from participants receiving 200 mg lumacaftor once daily plus either 150 mg or 250 mg of ivacaftor twice daily or ivacaftor doses combined compared to placebo, OR 2.22 (99% CI 0.08 to 58.11) (Analysis 9.2), OR 1.05 (99% CI 0.03 to 44.10) (Analysis 10.2) and OR 1.62 (99% CI 0.08 to 34.55) (Analysis 12.2), respectively.

There were no statistically significance differences between treatment groups in the number of pulmonary exacerbations experienced in the paediatric combination study, OR 1.11 (99% CI 0.44 to 2.81) (Ratjen 2017) (Analysis 11.4).

Tezacaftor plus ivacaftor versus control

The larger study (n = 510) also reported rate of pulmonary exacerbations that led to hospitalisation or treatment with intravenous antibiotic agents (or both); see secondary outcome 'Hospitalisation' above for further details (Taylor-Cousar 2017).

5. Sweat chloride (change from baseline) as a measure of CFTR function

Lumacaftor plus ivacaftor versus placebo

Two studies did not report this outcome (TRAFFIC 2015; TRANSPORT 2015).

Boyle reported that following lumacaftor (day 1 to 21) and ivacaftor (day 15 to 21) combination therapy, data at 21 days demonstrated reductions in sweat chloride concentration in the 150 mg ivacaftor group, MD -5.00 mmol/L (95% CI -11.60 to 1.60) (Analysis 9.3) and 250 mg ivacaftor group, MD -10.90 mmol/L (95% CI -17.60 to -4.20) (Analysis 10.3), the latter of which was statistically significant (Boyle 2014). There was also a statistically significant reduction in sweat chloride concentration when ivacaftor doses were combined MD -7.95 (95% CI -13.81 to -2.09) (Analysis 12.3)

The paediatric combination study reported a statistically significantly greater absolute reduction in sweat chloride concentration from baseline in the lumacaftor plus ivacaftor group compared to the placebo group, up to and including four weeks, MD -20.80 (95% CI -23.40 to -18.20) (Analysis 11.5). Additional results (at time points day 15, week 16, and week 24) were published graphically in the study publication, but the graphical plots were too small to allow for accurate extraction of data (Ratjen 2017). Numerical data for these time points have been requested from the study investigators and any unpublished information we receive will be included in a future update.

Tezacaftor plus ivacaftor versus control

There was a statistically significant reduction in sweat chloride concentration in the tezacaftor-ivacaftor groups at four weeks compared to the control groups, pooled MD -9.24 mmol/L (95% CI -11.12 to -7.35) (Analysis 13.6) (Donaldson 2018; Taylor-Cousar 2017); this was maintained at 24 weeks in the Taylor-Cousar study, MD -10.10 mmol/L (95% CI -11.40 to -8.80) (Analysis 13.6) (Taylor-Cousar 2017).

6. Radiological measures of lung disease (assessed using any scoring system)

Data for this outcome were not reported by any study (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

7. Acquisition of respiratory pathogens

No study reported on the acquisition of any respiratory pathogens (*P aeruginosa*, *S aureus*, *H influenzae*, or any other clinically relevant pathogen in CF) (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

8. Eradication of respiratory pathogens

Data for this outcome were not reported by any study (Boyle 2014; Donaldson 2018; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

9. Nutrition and growth

a. Weight

Lumacaftor plus ivacaftor versus placebo

Data for this outcome were reported by three studies (Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015).

Two studies presented results for the absolute change from baseline in weight (kg) at six months (TRAFFIC 2015; TRANSPORT 2015). Participants in both the lumacaftor 600 mg once daily plus 250 mg ivacaftor twice daily group and the 400 mg twice daily plus 250 mg ivacaftor twice daily group experienced a statistically significantly higher absolute weight gain from baseline compared to the placebo group, MD 0.80 kg (95% CI 0.42 to 1.18) (Analysis 6.9) and MD 0.65 kg (95% CI 0.27 to 1.03) (Analysis 7.9), respectively. There was also a statistically significantly higher absolute weight gain from baseline compared to the placebo group when the two lumacaftor doses were pooled, MD 0.72 kg (95% CI 0.39 to 1.05) (Analysis 8.7).

The paediatric combination study listed absolute change in weight and absolute change in weight-for-age z score as a secondary outcome of the study, but results for this outcome are not presented (Ratjen 2017). Numerical data for this outcome have been requested from the study investigators and any unpublished information we receive will be included in a future update.

b. BMI

Data for the absolute change from baseline in BMI were reported by four studies (Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015); one study additionally reported absolute change in BMI-for-age z score (Ratjen 2017).

i. Immediate term (up to and including one month)

Lumacaftor plus ivacaftor versus placebo

At 28 days, there was no statistically significant difference in the absolute change in BMI from baseline between the lumacaftor 600 mg once daily plus 250 mg ivacaftor twice daily and placebo groups, MD 0.01 (95% CI -0.07 to 0.09) (Analysis 6.10) or the lumacaftor 400 mg twice daily plus 250 mg ivacaftor twice daily and placebo groups, MD 0.02 (95% CI -0.06 to 0.10) (Analysis 7.10). There was also no statistically significant difference in absolute change in BMI from

baseline compared to the placebo group when the two lumacaftor doses were pooled, MD 0.02 (95% CI -0.05 to 0.08) (Analysis 8.8).

Tezacaftor plus ivacaftor versus control

There was no statistically significant difference between tezacaftor-ivacaftor and placebo in terms of change from baseline in BMI in the Taylor-Cousar study at four weeks, MD -0.03 (95% CI -0.13 to 0.07) (Analysis 13.7) (Taylor-Cousar 2017).

ii. Short term (over one month and up to and including six months)

Lumacaftor plus ivacaftor versus placebo

Despite no immediate differences between treatment groups, at six months participants in the both the lumacaftor 600 mg once daily plus 250 mg ivacaftor twice daily and 400 mg twice daily plus 250 mg ivacaftor twice daily groups experienced a statistically significantly higher absolute change in BMI from baseline compared to the placebo group, MD 0.29 (95% CI 0.16 to 0.43) (Analysis 6.10) and MD 0.25 (95% CI 0.12 to 0.39) (Analysis 7.10) respectively. There was also a statistically significantly higher absolute change in BMI from baseline compared to the placebo group when the two lumacaftor doses were pooled; MD 0.27 (95% CI 0.16 to 0.39) (Analysis 8.8)

At six months Rajten reported no statistically significant difference between groups in the absolute change in BMI or the absolute change in BMI-for-age z score, MD 0.10 (95% CI -0.10 to 0.30) (Analysis 11.6) and MD 0.00 (95% CI -0.10 to 0.10) (Analysis 11.7) respectively. Additional results for BMI at earlier time points (day 15, week 4, and week 16) were published graphically in the full paper, but the graphical plots were too small to allow for accurate extraction of data (Ratjen 2017). Numerical data for these time points have been requested from the study investigators and any unpublished information we receive will be included in a future update.

Tezacaftor plus ivacaftor versus control

There was no statistically significant difference between tezacaftor-ivacaftor and placebo in terms of change from baseline in BMI in the Taylor-Cousar study at 24 weeks, MD -0.06 (95% CI -0.08 to 0.20) (Analysis 13.7) (Taylor-Cousar 2017).

c. Height

Lumacaftor plus ivacaftor versus placebo

This outcome was not reported in three studies (Boyle 2014; TRAFFIC 2015; TRANSPORT 2015). One study listed the absolute change in height and absolute change in height-for-age z score as a secondary outcome of the study, but results for this outcome are not presented (Ratjen 2017). Numerical data for this outcome have been requested from the study investigators and any unpublished information we receive will be included in a future update.

DISCUSSION

The class II mutation of the *CFTR* gene, F508del, is prevalent (particularly in the Northern European population) and is the commonest cause of CF. A therapy that corrects the F508del molecular defect would potentially have a profound impact on the field of CF, providing a therapeutic option for many pwCF.

Summary of main results

We identified 13 eligible RCTs evaluating correctors for pwCF and class II CFTR mutations (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; Donaldson 2018; PROGRESS 2017; McCarty 2002; Ratjen 2017; Rubenstein 1998; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015; Zeitlin 2002). Seven studies examined monotherapy of a number of different correctors (Boyle 2014; Clancy 2012; Donaldson 2014; Donaldson 2017; McCarty 2002; Rubenstein 1998; Zeitlin 2002). Seven studies (including the multi-arm Boyle trial) examined combination therapy of either lumacaftor-ivacaftor or tezacaftor-ivacaftor (Boyle 2014; Donaldson 2018; PROGRESS 2017; Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015). Four of these were well-powered Phase 3 studies that enrolled pwCF (including one of children aged 6 to 11 years) with two copies of the F508del mutation (F508del homozygotes) (Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANSPORT 2015).

Monotherapy versus placebo

Early phase trials evaluated various potential molecules 4PBA (Rubenstein 1998; Zeitlin 2002), CPX (McCarty 2002), N6022 (Donaldson 2014), cavosonstat (Donaldson 2017) and lumacaftor (Clancy 2012; Boyle 2014). There was no statistically significant impact on clinical outcomes (including sweat chloride) with either 4BPA, CPX or N6022 and phase 3 studies of these drugs were not conducted. In one small Phase 1 study of cavosonstat monotherapy, there was a reduction in sweat chloride of -4.1 mmol (P = 0.032) at the highest dose (200 mg), and there were no important safety concerns (Donaldson 2017); and we have identified an ongoing study of this agent (NCT02589236). There was a modest improvement in sweat chloride with lumacaftor alone compared with placebo after four weeks, MD -8.21 mmol/L (95% CI -14.30 to -2.12) (Clancy 2012), but not sufficient to warrant investigation of this agent as monotherapy in later phase studies. Although there was not a statistically significant increase in adverse events the size of the studies was not sufficient to provide confidence on the safety profiles of these agents.

Combination therapy versus placebo

Early phase studies of lumacaftor combined with ivacaftor demonstrated a greater magnitude of effect with a reduction in sweat chloride of MD -10.9 mmol/L (95% CI -17.6 to -4.2) compared to lumacaftor monotherapy (Boyle 2014). The efficacy and safety of the lumacaftor-ivacaftor combination therapy were examined in two multicentre placebo-controlled RCTs, enrolling over 1000 adults and young pwCF, homozygous for F508del (TRAFFIC 2015; TRANSPORT 2015). In participants allocated to the lumacaftor-ivacaftor combination, combined trial data demonstrated no difference with regards to change in a generic measure of QoL (measured by the EQ-5L-3D tool). There was a statistically significant improvement in the respiratory domain of the CF-specific QoL measure (CFQ-R) at 24 weeks, MD 2.62 (95% CI 0.64 to 4.59). An improvement of four points on this scale is considered the minimal clinically important difference (MCID) for this outcome measure (Quittner 2009; Ramsey 2011).

With respect to respiratory function (as measured by % predicted FEV_1), there were statistically significant differences from baseline in favour of the lumacaftor-ivacaftor combination over placebo in both relative change, MD 5.21 (95% CI 3.61 to 6.80) and absolute

change, MD 3.07 (95% CI 2.17 to 3.97). Improvement in FEV_1 is considered an important surrogate measure for pwCF. The European Medicines Agency (EMA) has suggested that "as FEV_1 is linked to mortality, any statistically significant difference between placebo and active treatment is potentially clinically relevant" (EMA 2012). In the study protocol, the MCID in absolute change in FEV_1 used to calculate the sample sizes for the TRAFFIC and TRANSPORT was 5% (TRAFFIC 2015; TRANSPORT 2015). This magnitude of improvement in respiratory function was not achieved with the lumacaftor-ivacaftor combination. In a post hoc change to the protocol, the primary outcome for TRAFFIC and TRANSPORT was altered from absolute change from baseline in FEV_1 at 24 weeks to an average of the FEV_1 values at 16 and 24 weeks.

A number of important secondary outcomes were reported that were included in this review. In the TRAFFIC and TRANSPORT studies, pulmonary exacerbations were reported more frequently in participants allocated to placebo compared to those receiving lumacaftor-ivacaftor combination therapy (TRAFFIC 2015; TRANSPORT 2015); pulmonary exacerbations are a challenging outcome to record accurately, but one that is important to pwCF. Additionally, BMI improved in participants allocated to the lumacaftor-ivacaftor combination therapy after 24 weeks (Analysis 1.10; Analysis 2.10; Analysis 3.8). Data on school or work attendance, acquisition or eradication of microbial pathogens, or radiological outcomes were not reported.

Overall the safety data reported for the lumacaftor-ivacaftor combination were reassuring, but there was clear evidence of increased reporting of early respiratory compromise, OR 2.05 (99% CI 1.1 to 3.8) (TRAFFIC 2015; TRANSPORT 2015). The aetiology of this event is unclear and it was reported to settle after a few weeks if the intervention was continued (TRAFFIC 2015; TRANSPORT 2015). Two participants were withdrawn because of hypertension (including one in the follow-up study (PROGRESS 2017)). For participants (n = 80) receiving 400 mg twice a day of lumacaftor there was a statistically significant mean (SE) increase in systolic blood pressure of 5.1 (1.5) mm Hg and in diastolic blood pressure of 4.1 (1.2) mm Hg (PROGRESS 2017).

For the children (aged 6 to 11 years) enrolled in the Phase 3 study of lumacaftor-ivacaftor combination therapy, the safety profile reported was similar to the TRAFFIC and TRANSPORT studies, including transient early respiratory compromise and infrequent elevation in serum transaminases (liver enzymes) (Ratjen 2017). The efficacy data for this study are discussed below in the section on applicability.

The efficacy outcomes (primary and secondary) for the tezacaftor-ivacaftor Phase 3 study were very similar to those reported with lumacaftor-ivacaftor (Taylor-Cousar 2017). After 24 weeks the participants allocated to tezacaftor-ivacaftor had a 4.0% improvement in their absolute change in FEV_1 compared to those who received placebo (Analysis 12.1). There was no increased reporting of adverse events, in particular the early transient dyspnoea reported with the lumacaftor-ivacaftor combination, and no increased withdrawals of tezacaftor-ivacaftor participants compared to those receiving placebo.

Overall completeness and applicability of evidence

Monotherapy versus placebo

The single-agent studies have enrolled participants with two copies of the F508del mutation. These studies have not been taken forward on larger more representative populations in Phase 3 studies. New agents (such as cavosonstat) are currently being assessed in early phase studies (Donaldson 2017).

Combination therapy versus placebo

The Phase 3 studies of both lumacaftor and tezacaftor combined with ivacaftor have examined this therapy for people with two copies of the F508del mutation (F508del homozygotes) (Ratjen 2017; Taylor-Cousar 2017; TRAFFIC 2015; TRANS{ORT 2015). There have been no Phase 3 studies for pwCF who are compound heterozygotes of F508del with another CF-causing mutation. One cross-over study has examined compound heterozygotes who have F508del with a ivacaftor-sensitive residual function mutation, to evaluate any potential additive impact of tezacaftor on the recognised ivacaftor benefit (Rowe 2017). We excluded this study because of concerns over study design, in particular carryover effects of an intervention (ivacaftor) that has been shown to correct the basic defect in CF.

The Phase 3 studies of both the lumacaftor and ivacaftor combination therapy are well-powered and provide clear statistical evidence of improvement in clinical outcomes, even if these are limited in magnitude compared to the changes anticipated in the protocols and to those reported for individuals with G551D receiving ivacaftor (Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015). These Phase 3 studies were conducted across a large number of CF centres in North America, Europe and Australia, and the results are applicable to pwCF who are homozygous for F508del in these regions with mild to moderate lung disease.

The Phase 3 studies of lumacaftor-ivacaftor enrolled children and adults (age range 6 to 64 years) (Ratjen 2017; TRAFFIC 2015; TRANSPORT 2015)). For lumacaftor-ivacaftor, results were consistent across age groups, although for the study of 6 to 11 year olds the absolute change in FEV_1 was less marked, MD 2.4% (95% CI 0.4 to 4.4) (Ratjen 2017). The primary outcome for the study on children was change in LCI; although this measure is a well-validated research outcome assessing respiratory function, it is not yet routinely used in clinical practice. The children allocated to lumacaftor-ivacaftor demonstrated a statistically significant reduction in LCI compared to those receiving placebo, least squares mean difference -1.09 (95% CI -1.43 to -0.75). Although this difference is statistically significant, it is difficult to assess the clinical relevance of this result for young pwCF.

The tezacaftor-ivacaftor study enrolled adults and young pwCF (from 12 years and with a mean age of approximately 26 years) (Taylor-Cousar 2017).

This review has examined evidence for efficacy and safety. We have not included outcomes relating to cost-effectiveness.

Quality of the evidence

Monotherapy versus placebo

The quality of the evidence of the early phase studies included in this review were difficult to appraise and interpret due to limited

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Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis (Review)

reporting and complex study design, including numerous dose regimens. For the early phase studies of 4PBA, CPX an N6022; relevant outcome data to this review were limited and the risk of bias for various domains was difficult to judge.

The quality of the evidence from a short-term study of cavosonstat compared to placebo was low to very low due to concerns over unclear methodological design, indirectness (lack of applicability of results to children) and limited outcome data resulting in wide CIs around effect sizes (Summary of findings 2).

Combination therapy versus placebo

The studies included in this review were difficult to appraise and interpret due to very complex study designs that incorporated several drug doses.

We judged the quality of the evidence from the three large multicentre RCTs of lumacaftor-ivacaftor combination therapy to be moderate to high (Summary of findings 3). Not all outcomes were reported in the final study publication; some were available in the online supplement, some were extrapolated from graphical figures and others were available on the NIH database (ClinicalTrials.gov). Although the time-point for assessment of the primary outcome changed after the data had been collected, from FEV_1 at 24 weeks to an aggregate of 16 and 24 weeks (which was in fact a larger treatment effect), we did not judge this to reflect a high risk of bias. This was because the results at 24 weeks were also statistically significant, and the amended protocol states that "This change was made during final review by senior management. It is important to note that this change was made based on theoretical considerations alone. No data analysis was used to support this change and, in fact, the spirometry data were maintained at the designated vendor and were not available to any Vertex personnel".

We judged the quality of the evidence from an additional large multicentre RCT of lumacaftor-ivacaftor combination therapy to be moderate to low (Summary of findings 4). The study recruited children aged 6 to 11 years, so results are not applicable to other age groups. Not all outcomes were reported in the final study report and additional data could not be extracted from graphical figures. Furthermore the analysis approach taken within this review adjusted for earlier time points in the analysis at 24 weeks, therefore results should be interpreted as the treatment effect averaged from each study visit until week 24.

We judged the quality of the evidence from two tezacaftor-ivacaftor combination therapy studies (including one large multicentre RCT) to be of moderate quality (Summary of findings 6); results are not applicable to children under the age of 12 and some results are not applicable to individuals homozygous for F508del. Furthermore, in the large tezacaftor-ivacaftor combination study, a number of outcomes which were not presented in the summary of findings table of this review were recorded according to the study protocol, but not presented in the published study report (Taylor-Cousar 2017).

We judged the quality of the evidence from a small, very short-term study of lumacaftor-ivacaftor combination therapy and from a small study of lumacaftor monotherapy to be very low to moderate due to concerns over incomplete outcome data, selective reporting and limited outcome data resulting in wide CIs around effect sizes (Summary of findings for the main comparison; Summary of findings 5).

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 the ongoing online trials databases (Appendix 1) and also of manual searching of journal conference abstracts. Two authors individually applied the inclusion and exclusion criteria to the identified studies and excluded studies that were not relevant. Included studies were appraised more thoroughly and data extracted independently using a pre-determined form. The authors assessed the risk of bias of the included studies and if they failed to reach a consensus on the risk of bias, a third author (KWS) arbitrated. The analyses were undertaken by two review authors (SP, IS) and checked for appropriateness by the review statistician (SN). This approach minimized the risks of bias in the review process.

None of the authors have received direct or indirect payments from the companies responsible for the development of any agents included in this review; however, KWS has attended and has organised educational events that have received financial support from Vertex, the company that has developed and is evaluating some of the agents included in this review.

Not all results were reported in a format from which they could be accurately extracted, and so we have had to extrapolate data for several important outcomes from graphs and figures. We are awaiting confirmation from Vertex that these estimates are accurate.

This review has assessed all available published study data. Study authors were contacted for relevant unpublished information and individual participant data. None have been made available to date. We are not aware of any unpublished trials.

Agreements and disagreements with other studies or reviews

The National Institute for Health and Care Excellence (NICE) in the UK has undertaken a health technology appraisal for lumacaftor-ivacaftor which was published on 27 July 2016 (NICE 2016). The appraisal included the TRAFFIC, TRANSPORT and PROGRESS studies (PROGRESS 2017; TRAFFIC 2015; TRANSPORT 2015); the report concluded that the quality of these studies was generally good and that the results were generalisable to a UK population with mild-moderate disease severity. The evidence review group (ERG) noted that there were statistically significant effects on key outcomes compared with standard care alone, but it was unclear how clinically significant the effects were. Adverse event data were recorded as per the published papers, but withdrawals due to hypertension and the overall increase in blood pressure in participants receiving 400 mg twice a day were not recorded. In addition, the ERG examined a detailed cost-effectiveness assessment (including an estimate of incremental cost-effectiveness ratio) and concluded, on that basis, that lumacaftor-ivacaftor is not recommended, within its marketing authorisation, for treating CF in people 12 years and older who are homozygous for F508del mutation of the CFTR gene.

An evaluation of the safety of lumacaftor and ivacaftor highlighted the finding of "transaminitis" (raised transaminases) in ivacaftor

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and combination studies (Talamo Guervara 2017). In addition, the review reported non-congenital cataracts identified in pre-clinical studies and in children taking ivacaftor and combined therapy. The review also highlighted that lumacaftor is a strong inducer of the liver enzyme, cytochrome P3A and the implications for co-prescribing of drugs metabolised through this route.

AUTHORS' CONCLUSIONS

Implications for practice

Data from the Phase 3 studies of both lumacaftor and tezacaftor combined with ivacaftor suggest that these compounds are influencing the basic defect associated with the F508del mutation; with small but consistent and statistically significant improvements in key clinical outcomes. The size of these studies and the low- to moderate-quality evidence from the studies gives us good confidence in the validity of these results. Overall the drugs appeared well-tolerated, but there were some important adverse effects, in particular with the lumacaftor-ivacaftor combination. The adverse events noted with lumacaftor-ivacaftor were not recorded in the tezacaftor-ivacaftor study and, from the available data, this combination appears to have a better safety profile.

From our appraisal of the available data, the combination of lumacaftor or tezacaftor with ivacaftor can be considered for the management of people with cystic fibrosis (pwCF) homozygous for F508del, with mild to moderate lung disease. These results cannot be translated automatically to pwCF with more severe lung disease. This agrees with the NICE appraisal of lumacaftor-ivacaftor, although the evidence review group did not support the routine use of lumacaftor-ivacaftor on the basis of their detailed cost-effectiveness assessment (NICE 2016). Lumacaftor-ivacaftor (trade name, Orkambi™) has been approved for use in other countries, including the USA, Canada and Germany. It is useful to compare the results of the available studies of correctors with studies examining ivacaftor for pwCF with one class 3 mutation (G551D). The absolute change in forced expiratory volume in one second (FEV_1) after ivacaftor therapy compared to placebo was 16.9% (95% confidence interval 13.6 to 20.2) (Patel 2015).

The evidence from this systematic review demonstrates that tezacaftor-ivacaftor for treating pwCF with two F508del mutations and mild to moderate lung disease results in similar clinical benefit but with an improved safety profile compared to lumacaftor-ivacaftor.

In children younger than 12 years of age, there are no data to assess tezacaftor-ivacaftor. In a study of lumacaftor-ivacaftor in children aged 6 to 11 years, there was some evidence of clinical efficacy (decreasing lung clearance index (LCI) value), but the clinical relevance of these changes is not clear. The reports of increased

adverse events for lumacaftor-ivacaftor in this age group and in older pwCF should be taken into account when considering this intervention for this age group until further data or an alternative agent (e.g., tezacaftor-ivacaftor) is available.

Implications for research

It is important that post-market surveillance is undertaken for all agents that correct the F508del mutation. It is clear that lumacaftor-ivacaftor is associated with a number of important adverse effects, some of which necessitated the withdrawal of therapy. Although tezacaftor-ivacaftor appears to have a more favourable safety profile there are no data in children and close monitoring is required for all individuals on this drug combination.

Evidence of efficacy for the population of pwCF who have two copies of the F508del mutation cannot be automatically translated to pwCF who have one copy of F508del or another class II mutation (such as G85E) and research strategies need to be developed that assess impact on these individuals. Small numbers of potential participants for these studies makes this a challenge.

As new mutation-specific therapies emerge, it is important that lessons learnt from this review are taken on board. Investigators should report clearly on methodological approaches to reduce the risk of bias, in particular with regards to random sequence generation, allocation concealment and blinding; they should also ensure that randomisation is maintained when analysing data. It is important that future studies examine and clearly report on outcomes relevant to pwCF and their families.

With novel therapies and approaches, reporting of adverse events is critical and this should be undertaken in a robust, comprehensive and consistent manner.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Boyle 2014

Methods	Phase 2 placebo-controlled RCT with 3 different cohorts. Only cohort 1 was included in this review (n = 62). (The following information will refer to cohort 1 only - see 'Notes'.)
	Parallel design.
	Multicentre study conducted at 69 different sites in North America, Europe and Australia.
	Duration: Cohort 1 lasted 21 days.

Participants	**Mutation**: participants homozygous for F508del mutation.
	Age: participants in Cohort 1 have a mean age of 29.1 years.
	Gender split: 50% of participants are male
	Lung function: all participants in Cohort 1 have a FEV_1 ≥ 40% of predicted normal for age, gender, and height and a mean (range) predicted FEV_1 of 66.9% (32.8 - 117.1).
	Sweat chloride levels: participants in Cohort 1 have a mean (range) level of 101.9 mmol/L (87.5 - 121.0).
Interventions	**Intervention 1**: lumacaftor (also known as VX-809, a CFTR corrector) alone.
	Intervention 2: lumacaftor in combination with ivacaftor (also known as VX-770, a CFTR potentiator).
	Intervention 3: placebo.
	Cohort 1 (n = 62)
	Study drug participants: 200 mg lumacaftor once daily for 14 days; then from day 15, participants continue to take 200 mg of lumacaftor in addition to either 150 mg or 250 mg of ivacaftor twice daily until day 21.
	Placebo participants: placebo for 21 days.
Outcomes	**Primary outcomes**
	1. Change in sweat chloride when ivacaftor is administered in combination with lumacaftor*
	2. Safety and tolerability assessments based on adverse events, plasma samples (haematology, clinical chemistry, coagulation), urinalysis, ECGs, and vital signs*
	Secondary outcomes
	1. Change in % predicted FEV_1*
	2. Change in sweat chloride of increasing doses of lumacaftor administered alone*
	3. PK parameters (including exposure, concentration and half-life) of lumacaftor and metabolite in plasma in the presence and absence of ivacaftor
	4. PK parameters (including exposure, concentration and half-life) of ivacaftor and metabolites in plasma in the presence of lumacaftor
Funding source	Vertex Pharmaceuticals, and the Cystic Fibrosis Foundation Therapeutics Development Network.
Notes	* denotes outcomes relevant to this review.
	Only data from Cohort 1 were included in this review. This was because data for placebo participants from Cohorts 2 and 3 were pooled, although randomisation in these cohorts occurred separately. This meant that the effects of randomisation in these cohorts were undone. Data for participants in Cohorts 2 and 3 were excluded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random sequence was generated by a computer by an independent party.

Boyle 2014 *(Continued)*

Allocation concealment (selection bias)	Low risk	"Site pharmacists dispensed drugs on the basis of an interactive voice response system".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drug doses were prepared by an independent unmasked pharmacist and dispensed by site pharmacists who were masked to treatment assignment. Participant blinding was maintained by placebo which was matched to intervention by the quantity of tablets and by size, colour, coating and packaging.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Site investigators and the study sponsor were also masked to treatment assignment and to sweat chloride levels - data that could have potentially disclosed treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participant data were excluded from the analysis due to insufficient data, e.g. participants were excluded from the analysis of sweat chloride concentration if insufficient amount of sweat were provided. We judged this trial as having an unclear risk of attrition bias because it was unclear how these exclusions would have affected the balance between groups in baseline characteristics.
Selective reporting (reporting bias)	Low risk	We compared the outcomes reported on the US NIH trials registry (www.clinicaltrials.gov) to the outcomes reported in the results of the published paper as the protocol was not available. No selective outcome reporting was identified.
Other bias	Low risk	Similar baseline characteristics.

Clancy 2012

Methods	Phase 2a placebo-controlled RCT. Parallel design. Multicentre study conducted at 25 study locations over North America and Europe. Duration: 28 days.
Participants	**Mutation**: all 89 randomised participants had a confirmed diagnosis of CF and all but 1 were homozygous for the F508del mutation. **Age**: median (range) age of 26 (18 - 54) years. **Gender split**: 60% of the participants were males. **Lung function**: a baseline FEV_1 > 40% predicted was an eligibility criteria; but scores ranged from 34.2 to 126.3 with a median of 71. **Sweat chloride levels**: 103.5 (66.0 - 129.0) mmol/L. **Nutritional status**: median (range) baseline BMI of 22 (16 - 34).
Interventions	**Intervention** 1: placebo (n = 17). **Intervention 2**: lumacaftor (VX-809) 25 mg once daily (n = 18). **Intervention 3**: lumacaftor 50 mg once daily (n = 18). **Intervention 4**: lumacaftor 100 mg once daily (n = 17). **Intervention 5**: lumacaftor 200 mg once daily (n = 19).
Outcomes	**Primary outcome**

Clancy 2012 *(Continued)*

1. Evaluation of safety and tolerability of lumacaftor based on adverse events*, haematology, clinical chemistry, urinalysis, ECGs, vital signs, and physical examinations

Secondary outcomes

1. Evaluation of the pharmacodynamic impact of lumacaftor on CFTR function

2. Change from baseline in sweat chloride concentration*

3. Nasal potential difference (optional)

4. Spirometry* (FEV_1, $FEF_{25-75\%}$, FVC)

5. Change from baseline in CFQ-R score*

Funding source	Vertex Pharmaceuticals, and grants from the NIH.
Notes	* denotes outcomes relevant to this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was insufficient information on how participant or study personnel blinding were maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information on how outcome assessor blind was maintained.
Incomplete outcome data (attrition bias) All outcomes	High risk	In the adverse events table, the total number of participants shown (n = 45) is less than the total number of participants randomised (n = 89). In Figure 1B the number of participants analysed in the outcome 'Change from baseline in sweat chloride' (n = 63) is less than the total number of participants randomised to the intervention (n = 72). Therefore, 9 participants have been unaccounted for. In the table of results of total CFQ-R scores, 1 participant appears to be excluded from each of the treatment groups.
Selective reporting (reporting bias)	High risk	No results have been presented for $FEF_{25-75\%}$ or FVC despite being stated as an outcome.
Other bias	Low risk	Baseline characteristics well matched except for the less severe lung disease in 25 mg and placebo groups.

Donaldson 2014

Methods	Double-blind, placebo-controlled RCT.

Donaldson 2014 *(Continued)*

	Parallel design.
	Duration: 7 days.
	Multicentre: 17 sites in USA.
Participants	66 participants.
	Mean (SD) age: 29 (8) years.
	Gender split: 40 female and 26 male.
	Disease severity: mean (SD) % predicted FEV_1 70 (21)%, and mean (SD) sweat chloride 101 (11) mmol/L.
	There were no statistically significant differences among the treatment groups at baseline.
Interventions	**Intervention**: 4 sequential ascending doses of N6022 were assessed (5, 10, 20, and 40 mg/day) given by intravenous infusion once daily.
	Control: placebo (normal saline).
Outcomes	**Primary outcome**
	Safety and tolerability (over 7 treatment days and 7 days of follow-up)*
	Secondary outcomes
	Change from baseline in % predicted FEV_1 (at Day 7)*
	Change from baseline in biomarkers of CFTR Function measured as sweat chloride mEq/L (at Day 7)
Funding source	Sponsored by Nivalis Therapeutics.
Notes	* denotes outcomes relevant to this review.
	4 sequential ascending doses of N6022 were assessed (5, 10, 20, and 40 mg/day) followed by a confirmatory cohort of participants at the highest dose. An independent Data Monitoring Committee adjudicated dose escalation at the completion of each cohort after review of unblinded safety data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (participant, caregiver, investigator, outcomes assessor) achieved with intravenous administration of placebo (saline) using the same volume as the active drug groups.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind (participant, caregiver, investigator, outcomes assessor) achieved with intravenous administration of placebo (saline) using the same volume as the active drug groups.
Incomplete outcome data (attrition bias)	Low risk	All randomised participants completed the 7 days of follow-up.

Donaldson 2014 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Unclear risk	No full text publication of the study available. Limited results (without any statistical analysis) available on the ongoing trials database (www.clinicaltrials.gov). Unclear if all relevant information has been made available.
Other bias	Low risk	Baseline characteristics across the 5 treatment groups seem fairly well-balanced despite small numbers in each group.

Donaldson 2017

Methods	Phase 1 double-blind RCT.
	Parallel design.
	Duration: 28 days treatment.
	Multicentre (10 centres).
Participants	51 adults with CF randomised.
	Mutation: CF homozygous for the F508del-CFTR mutation.
	Age: over 18 years.
	Gender: 32 out of 51 participants were female.
	Lung function: FEV_1 ≥ 40% of predicted normal for age, gender, and height (Hankinson standards). pre- or post-bronchodilator value, at screening.
	Sweat chloride: ≥ 60 mEq/L.
Interventions	**Intervention**: cavosonstat 2x daily 50 mg, 100 mg, or 200 mg.
	Control: placebo 2x daily.
Outcomes	**Primary outcome** (no prespecified sample size)
	Safety (AE and SAE) *
	Secondary outcomes (at 28 days)
	Sweat chloride *
	FEV_1*
	*CFQ-R
Funding source	Sponsored by Nivalis Therapeutics.
Notes	* Denotes an outcome relevant to this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of method.

Allocation concealment (selection bias)	Unclear risk	No description of method.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Likely low risk as double-blind and placebo-controlled but further information about this aspect of methodology not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely low risk as double-blind and placebo-controlled but further information about this aspect of methodology not described.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants unaccounted for in analysis, but unlikely to have affected result.
Selective reporting (reporting bias)	Low risk	Likely low risk - all outcomes reported, but they appear to have been measured at other time-points that are not reported (7 days and 14 days).
Other bias	Unclear risk	"Approximately two-thirds of CF subjects were female; however, there was a greater proportion of males in the 200 mg BID dose group. Other baseline characteristics were similar across the treatment groups." Unclear if this gender imbalance may have influenced the results.

Donaldson 2018

Methods	Double-blind, placebo-controlled Phase 2 RCT, which included a dose-ranging arm.
	Parallel design.
	Duration: 28 days treatment followed by 28 days observation.
	Multicentre.
Participants	**Mutation**: participants homozygous for F508del mutation, and heterozygous participants with 1 F508del mutation and 1 G551D mutation. Only the 18 heterozygous participants are included in the analysis of this review (this is because the placebo participants in the homozygous arms of the trial were pooled, and this was judged to negate the effects of randomisation).
	Age: heterozygous participants - active drug arm mean (SD) age 26.6 (7.0) years, placebo arm mean (SD) age 34.5 (7.6) years.
	Gender split: heterozygous participants - active drug arm 6/14 (43%) participants female; placebo arm 3/4 (75%) female.
	Lung function, mean (SD): heterozygous participants - active drug arm baseline FEV_1 59.1 (16.6)% predicted, placebo arm baseline FEV_1 62.6 (12.7)% predicted.
	Sweat chloride levels, mean (SD): heterozygous participants - active drug arm baseline 52.9 (19.6); placebo arm baseline 56.7 (22.1).
Interventions	**Intervention**: tezacaftor 100 mg/day and ivacaftor 150 mg.
	Control: ivacaftor 150 mg (heterozygous arm only).
Outcomes	**Primary outcome** Safety through day 56*

Donaldson 2018 *(Continued)*

Secondary outcomes

Absolute change in FEV_1 at day 28*

Relative change in FEV_1 at day 28*

Change in CFQ-R respiratory domain (day 28)*

Funding source	Vertex Pharmaceuticals and grants from the NIH.
Notes	* Denotes outcomes relevant to this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method not described.
Allocation concealment (selection bias)	Unclear risk	Method not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched placebo - double-blind RCT.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Matched placebo - double-blind RCT.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised participants included in analysis.
Selective reporting (reporting bias)	Low risk	All outcomes appear to have been reported.
Other bias	Unclear risk	Baseline characteristics of heterozygous participants somewhat imbalanced across groups (e.g. sex, age, FEV_1). However, this imbalance may be due to small numbers (active drug arm n = 14 and placebo arm n = 4) and unclear if the imbalance has influenced results.

McCarty 2002

Methods	Phase 1, placebo-controlled RCT. Parallel design. Multicentre conducted at 4 sites in North America. Duration: single-dose assessment. Participants were monitored for 2 days followed up at 1 week.
Participants	**Mutation**: all 37 participants were homozygous for the F508del mutation and were described as having mild CF. **Age**: 18 years or over; age range 18 - 38 years.

McCarty 2002 *(Continued)*

Gender split: 21 males and 16 females.

Lung function: participants were eligible if they had a baseline $FEV_1 \geq 60\%$ predicted and had not endured pulmonary colonisation by a drug resistant organism within 12 months of screening.

Interventions	**Intervention 1**: placebo. **Intervention 2**: CPX in the following escalating doses: 1 mg CPX; 3 mg CPX; 10 mg CPX; 30 mg CPX; 100 mg CPX; 300 mg CPX; 1000 mg CPX.
Outcomes	**Primary outcome** 1. Safety profile of CPX including occurrence of adverse events* **Secondary outcomes** 1. Nasal potential difference values 2. Sweat chloride values (mEq/L) * 3. Analysis of blood haemoglobin and serum potassium
Funding source	SciClone Pharmaceuticals, and grants from the NIH.
Notes	* denotes outcomes relevant to this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Not stated.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There was insufficient information on how participant or study personnel blinding were maintained.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information on how outcome assessor blind was maintained.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No report of withdrawals and all originally randomised participants were included in the analysis.
Selective reporting (reporting bias)	Low risk	Protocol not available and outcomes not reported on the ongoing online database (www.clinicaltrials.gov). Reported results corresponded to outcomes listed in methods section.
Other bias	Unclear risk	Unclear whether baseline characteristics were well matched.

PROGRESS 2017

Methods	Phase 3 RCT. Double-blinded rollover study (participants on active treatment continued their treatment, participants on placebo were randomised to 1 of the 2 active interventions). Parallel design. Multicentre: 191 sites in 15 countries across North America, Australia and Europe Duration: 96 weeks.
Participants	**Mutation**: homozygous or heterozygous for the F508del mutation. **Age**: 12 years and older. **Gender**: both males and females. Confirmed diagnosis of CF. Participants have previously participated in TRAFFIC or TRANSPORT and completed 24 weeks of treatment.
Interventions	**Intervention 1**: 600 mg lumacaftor once daily + 250 mg ivacaftor every 12 hours (continued treatment). **Intervention 2**: 600 mg lumacaftor once daily + 250 mg ivacaftor every 12 hours (rolled over from placebo). **Intervention 3**: 400 mg lumacaftor every 12 hours + 250 mg ivacaftor every 12 hours (continued treatment). **Intervention 4**: 400 mg lumacaftor every 12 hours + 250 mg ivacaftor every 12 hours (rolled over from placebo).
Outcomes	**Primary outcome measure** Treatment cohorts: safety of long-term treatment based on AEs, clinical laboratory values (serum chemistry, haematology, coagulation studies, and urinalysis), standard digital ECGs, vital signs, and pulse oximetry at 100 weeks **Secondary outcome measures** 1. Absolute change from baseline in % predicted FEV_1 at 96 weeks 2. Relative change from baseline in % predicted FEV_1 at 96 weeks 3. Absolute change from baseline in CFQ-R respiratory domain score at 96 weeks 4. Absolute change from baseline in BMI at 100 weeks 5. Number of pulmonary exacerbations starting from the previous study through 96 weeks 8. Event of having at least 1 pulmonary exacerbation in the current study through 96 weeks
Funding source	Sponsored by Vertex Pharmaceuticals Inc.
Notes	Long-term extension of the TRAFFIC and TRANSPORT studies in which participants receiving an active treatment continued with this treatment and those receiving placebo were randomised to receive 1 of the 2 active treatments from the TRAFFIC and TRANSPORT. Additional analyses were conducted comparing participants receiving 400 mg lumacaftor every 12 hours + 250 mg ivacaftor every 12 hours to an observational registry cohort of matched controls. These analyses are not reported in this review.

Risk of bias

PROGRESS 2017 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Only the placebo groups from the previous studies were randomised. Participants randomly assigned (in a 1:1:1 ratio) to 1 of 3 study groups; the randomisation was established by an interactive web response system. Randomisation was stratified according to age (< 18 years versus ≥ 18 years), sex, and pulmonary function (% predicted FEV_1 at screening, < 70 versus ≥ 70).
Allocation concealment (selection bias)	Low risk	Only the placebo groups from the previous studies were randomised. The randomisation was established by an interactive web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	These were double-blind studies in which the participant and study team remained blinded to the treatment assignments. Interventions were matched in appearance and packaging.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	These were double-blind studies in which the participant and study team remained blinded to the treatment assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates reported, all participants randomised who received at least 1 dose of study medication were included in analysis. Missing data were investigated in sensitivity analyses.
Selective reporting (reporting bias)	Low risk	All listed outcomes reported in the results.
Other bias	Low risk	A 'rate of change' analysis showed that baseline characteristics across the groups were well balanced.

Ratjen 2017

Methods	Phase 3, placebo-controlled RCT. Parallel design. Multicentre: 54 sites in 9 countries (USA, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK). Duration: 24 weeks.
Participants	**Mutation**: all participants were homozygous for the F508del-CFTR mutation. **Age**: eligibility criteria 6 - 11 years, mean (SD) age was 8.8 (1.6) years. **Gender split**: 83 males and 121 females. **Lung function**: participants must have a FEV_1 (% predicted) of 70 or more, and $LCI_{2.5}$ of 7.5 or more.
Interventions	**Intervention**: lumacaftor 200 mg every 12 hours in combination with ivacaftor 250 mg every 12 hours. **Control**: matched placebo.
Outcomes	**Primary outcome** Mean absolute change in $LCI_{2.5}$ from baseline at all study visits up to and including week 24*

Ratjen 2017 *(Continued)*

Secondary outcomes

Absolute change in BMI up to and including week 24*

Absolute change in CFQ-R respiratory domain score up to and including week 24*

Absolute change in $LCI_{5.0}$ up to and including week 24*

Absolute change in sweat chloride up to and including week 24*

Absolute change in FEV_1 (% predicted) up to and including week 24*

Relative change in FEV_1 (% predicted) up to and including week 24*

Absolute change in BMI-for-age z score up to and including week 24*

Absolute change in weight up to and including week 24*

Absolute change in weight-for-age z score up to and including week 24*

Absolute change in height up to and including week 24*

Absolute change in height-for-age z score up to and including week 24*

Absolute change in TSQM domains up to and including week 24

Time-to-first pulmonary exacerbation up to and including week 24

Event of having at least 1 pulmonary exacerbation up to and including week 24

Number of pulmonary exacerbations up to and including week 24

Number of participants with adverse events and serious adverse events up to week 24*

Funding source	Vertex Pharmaceuticals.
Notes	* denotes outcomes relevant to this review.
	Analyses were performed as the absolute change from baseline (including all measurements up to and including week 24, both on-treatment measurements and measurements after treatment discontinuation) - was based on a MMRM, adjusted for the baseline measurement of the outcome, baseline weight (less than 25 kg versus 25 kg or over and baseline FEV_1 (% predicted) (less than 90% compared to 90% or more), with treatment-by-visit interaction as fixed effects, participant as a random effect.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation was performed via an interactive web response system, stratified by baseline weight and FEV_1 (% predicted).
Allocation concealment (selection bias)	Low risk	Randomisation was performed centrally via the interactive web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinding was achieved by using placebo tablets visually identical to the test product.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	It was not stated whether outcome assessment was blinded.

Ratjen 2017 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were reported and an ITT approach was taken to analysis, with all randomised participants who received at least 1 dose of the study drug included in analysis (1 participant in each group was randomised but did not receive the study drug).
Selective reporting (reporting bias)	High risk	Several outcomes which are listed in the methods (e.g. LCI$_{5.0}$, time-to-first pulmonary exacerbation, absolute change in TSQM domains) but are not presented in the results.
Other bias	Low risk	Baseline characteristics were similar across the 2 groups.

Rubenstein 1998

Methods	A pilot, placebo-controlled RCT. Parallel design. Single centre. Duration: 1 week.
Participants	**Mutation**: homozygous for F508del mutation. **Age, mean (SD)**: participants were eligible if 14 years or older, placebo group 24.8 (4.9) years; intervention group: 22.3 (5.9) years. **Gender split**: placebo group 4 males and 5 females; intervention group 5 males and 4 females. **Lung function**: baseline mean (SD) FVC % predicted placebo group: 65.5 (18.6); intervention group 73.4 (20.3). Baseline mean (SD) FEV$_1$ % predicted placebo group 47.5 (22.1); intervention group 57.8 (27.2).
Interventions	18 participants were allocated to either intervention or placebo group (9 participants in each group). **Intervention 1**: placebo. **Intervention 2**: sodium 4-phenylbutyrate (also known as Buphenyl or 4PBA) 19 g, orally administered, in 3 daily doses of 6 g, 6 g, and 7 g.
Outcomes	1. Changes from baseline in nasal potential difference in 1 week 2. Change from baseline in sweat chloride in 1 week* 3. 4BPA metabolites in plasma and urine after 1 week 4. Side effects*
Funding source	NIH and Cystic Fibrosis Foundation.
Notes	* denotes outcomes relevant to this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study article states that "randomization and blinding were performed by the Johns Hopkins Hospital Investigational Drug Pharmacy" but exact method of randomisation has not been described.

Rubenstein 1998 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Study article states that "randomization and blinding were performed by the Johns Hopkins Hospital Investigational Drug Pharmacy" but exact method of allocation concealment has not been described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind. Study article states that "randomization and blinding were performed by the Johns Hopkins Hospital Investigational Drug Pharmacy" but exact method of blinding has not been described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Described as double-blind. Study article states that "randomization and blinding were performed by the Johns Hopkins Hospital Investigational Drug Pharmacy" but exact method of blinding has not been described.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were analysed with 9 participants each group, equivalent to the number originally randomised.
Selective reporting (reporting bias)	Low risk	Protocol not available and outcome not presented on the ongoing trials database (www.clinicaltrials.gov/). Outcomes reported in the 'methods' were reported in the 'results' so selective reporting bias is low.
Other bias	Low risk	"... baseline characteristics between the groups were similar with respect to age, gender, pancreatic sufficiency, and baseline pulmonary function."

Taylor-Cousar 2017

Methods	Placebo-controlled RCT.
	Parallel design.
	Duration: 24 weeks.
	Multicentre in North America and Europe.
Participants	510 participants diagnosed with CF.
	Age: inclusion criteria 12 years and older, 23% were aged 12 - 18 years.
	Mutation: homozygous for F508del.
	Gender: 49% female.
	Mean FEV$_1$ at baseline: 60% (9.4% had baseline FEV$_1$ < 40% predicted, 2% had baseline FEV$_1$ > 90% predicted).
	Mean baseline sweat chloride: 100.5.
	Mean BMI: 21.
Interventions	**Intervention**: 100 mg tezacaftor 1x daily and 150 mg ivacaftor 2x daily.
	Control: placebo.
Outcomes	**Primary outcome**
	Absolute change in FEV$_1$ % predicted (from baseline through week 24)
	Secondary outcomes

Taylor-Cousar 2017 *(Continued)*

Relative change in FEV_1 % predicted (from baseline through week 24)

Number of pulmonary exacerbations (through week 24)

Absolute change in BMI (from baseline at week 24)

Absolute change in CFQ-R respiratory domain score (from baseline through week 24)

Safety and tolerability assessments based on AEs, clinical laboratory values (i.e., haematology, serum chemistry, coagulation studies, vitamin levels, lipid panel, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry

Time-to-first pulmonary exacerbation (through week 24)

Absolute change in sweat chloride (from baseline through week 24)

Absolute change in BMI z score (from baseline at week 24 (in participants under 20 years of age at time of screening))

Absolute change in body weight (from baseline at week 24)

PK parameters of VX-661, M1-661, M2-661, ivacaftor, and M1-ivacaftor

Absolute change in CFRSD severity score (from baseline through week 24)

Absolute change in duration of physical activity during the day (from baseline through week 24)

Absolute change in duration of sleep time and sleep quality during the night (from baseline through week 24)

Absolute change in PSQI score (from baseline through week 24 (in participants under 18 years of age))

Absolute change in QoL assessment (SF-12) physical, mental, and utility component scores (at weeks 12 and 24)

Absolute change in inflammatory mediators (from baseline at week 24)

Absolute change in sputum microbiology (from baseline at week 24)

Absolute change in serum IRT (from baseline at week 24)

Funding source	Vertex Pharmaceuticals.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Statistician separate to study team produced a list of randomisation codes and allocations assigned via web-based interactive system (information provided in online protocol).
Allocation concealment (selection bias)	Low risk	Web-based interactive system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Matched placebo - all relevant people blinded (participants and study personnel).
Blinding of outcome assessment (detection bias)	Low risk	Matched placebo - all relevant people blinded (participants and study personnel).

Taylor-Cousar 2017 *(Continued)*

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant who was randomised but did not receive the trial intervention was excluded from efficacy and safety analyses. A further 5 participants who were randomised and received the trial intervention were found to have an ineligible or unconfirmed CFTR genotype were excluded from efficacy analyses. Small numbers of excluded participants (up to 6 out of 510) unlikely to have introduced bias.
Selective reporting (reporting bias)	High risk	The following outcomes were measured (according to the protocol), but not reported. • CF respiratory symptom diary • Number of minutes of physical activity daily • PSQI • SF12 • Sputum microbiology • Various outcome analyses related to exacerbation (number of days with exacerbation, time-to-first exacerbation, time to first hospitalisation, number of days hospitalised with exacerbation, number of exacerbations requiring IV therapy, number of days on IV therapy, time to first IV therapy)
Other bias	Low risk	Final manuscript written with the assistance of medical writers funded by the sponsor, however, this is unlikely to have introduced bias.

TRAFFIC 2015

Methods	Double-blind, placebo-controlled Phase 3 RCT. Parallel design. Multicentre: 90 sites in North America, Australia and Europe. Estimated sample size: 559. Duration: 24 weeks.
Participants	549 participants with a confirmed diagnosis of CF and stable disease (as judged by the investigator). **Mean age (range)**: treatment arm 1 24.7 (12 - 54) years; treatment arm 2 25.5 (12 - 57) years; placebo 25.0 (12 to 64 years). **Gender**: 295 (54%) males; 254 (46%) females. **Mutation**: homozygous for the F508del mutation. **Lung function**: FEV_1 between ≥ 40% and ≤ 90% of predicted normal for age, sex, and height.
Interventions	**Intervention 1** (n = 183): 600 mg of lumacaftor 1x daily and 250 mg of ivacaftor every 12 hours. **Intervention 2** (n = 182): 400 mg of lumacaftor every 12 hours and 250 mg of ivacaftor every 12 hours. **Intervention 3** (n = 184): lumacaftor-matched placebo every 12 hours in combination with ivacaftor-matched placebo every 12 hours.
Outcomes	**Primary outcome measure** Absolute change in % predicted FEV_1 (% predicted) at 24 weeks

TRAFFIC 2015 *(Continued)*

Secondary outcome measures

1. Relative change in % predicted FEV_1 (% predicted) at 24 weeks

2. Absolute change in BMI at 24 weeks

3. Number of pulmonary exacerbations at 24 weeks

4. Absolute change in CFQ-R respiratory domain score at 24 weeks

5. Absolute change in BMI z score at 24 weeks

6. Absolute change in body weight at 24 weeks

7. Time-to-first pulmonary exacerbation at 24 weeks

8. Event of having at least 1 pulmonary exacerbation through week 24

9. Absolute change in EuroQol 3 Level (EQ 5D 3L) at 24 weeks

10. Absolute change in TSQM domains at 24 weeks

11. Safety and tolerability assessments based on adverse events, clinical laboratory values (haematology, serum chemistry, coagulation studies, and urinalysis), standard digital ECGs, ambulatory ECGs, vital signs, and pulse oximetry up to 28 weeks

12. PK parameters of lumacaftor, M28 lumacaftor, ivacaftor, M1 ivacaftor, and M6 ivacaftor at 16 weeks

Funding source	Sponsored by Vertex Pharmaceuticals Inc.
Notes	Known as TRAFFIC study.
	The TRAFFIC and TRANSPORT studies were identical with the following exceptions: TRAFFIC included ambulatory ECG screening at days 1 and 15 in approximately 165 participants in the USA; TRANSPORT included additional pharmacokinetics assessments performed in approximately 28 adolescents in the USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned (in a 1:1:1 ratio) to 1 of 3 study groups; the randomisation was established by an interactive web response system.
		Randomisation was stratified according to age (< 18 years versus ≥ 18 years), sex, and pulmonary function (% predicted FEV_1 (% predicted) at screening, < 70 versus ≥ 70).
Allocation concealment (selection bias)	Low risk	The randomisation was established by an interactive web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	These were double-blind studies in which the participant and study team remained blinded to the treatment assignments. Placebo was matched in appearance and packaging.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	These were double-blind studies in which the participant and study team remained blinded to the treatment assignments.
Incomplete outcome data (attrition bias)	Low risk	Correct number of participants included in the analysis (i.e. those who received at least one dose of the study drug – ITT).

TRAFFIC 2015 *(Continued)*

All outcomes		Prior to first dose 10 out of 559 participants withdrew: 2 withdrew from treatment arm 1; 5 withdrew from treatment arm 2; 3 withdrew from placebo group.
		Post first dose 25 out of 549 participants withdrew (with reasons): 11 from treatment arm 1; 10 withdrew from treatment arm 2; 4 withdrew from placebo group.
Selective reporting (reporting bias)	High risk	Additional data available on www.clinicaltrials.gov for outcomes not reported in the final paper such as:
		1. absolute change in EQ-5D-3L score from baseline at week 24;
		2. absolute change in TSQM domains from baseline at week 24;
		3. time to first exacerbation;
		4. event of having at least one pulmonary exacerbation.
		Some results had to be extrapolated from graphical figures, we await confirmation from the study sponsor of the accuracy of the results.
		Investigators state that they measured FVC (which was not listed as an endpoint) and do not report this in the joint paper.
Other bias	Low risk	Adherence to study treatment was high and the mean compliance rate (determined by site personnel and ongoing study drug count) was similar across lumacaftor-ivacaftor and placebo groups (99.1% versus 98.5%).

TRANSPORT 2015

Methods	Double-blind, placebo-controlled Phase 3 RCT. Parallel design. Multicentre: 82 sites in North America, Australia and Europe. Estimated sample size: 563. Duration: 24 weeks.
Participants	559 participants with confirmed diagnosis of CF and with stable disease (as judged by the investigator). **Mean age** (range): treatment arm 1 24.3 (12 - 48) years; treatment arm 2 25.0 (12 - 54) years; placebo 25.7 (12 - 55) years. **Gender**: 268 (48%) males; 291 (52%) females. **Mutation**: homozygous for the F508del mutation. **Lung function**: FEV_1 (% predicted) between ≥ 40% and ≤ 90% of predicted normal for age, sex, and height.
Interventions	**Intervention 1**: 600 mg of lumacaftor 1x daily and 250 mg of ivacaftor every 12 hours for 24 weeks. **Intervention 2**: 400 mg of lumacaftor every 12 hours and 250 mg of ivacaftor every 12 hours for 24 weeks. **Intervention 3**: placebo.
Outcomes	**Primary outcome measure**

Absolute change in % predicted FEV_1 (% predicted) at 24 weeks

Secondary outcome measures

1**.** Relative change in % predicted FEV_1 (% predicted) at 24 weeks

2. Absolute change in BMI at 24 weeks

3. Number of pulmonary exacerbations at 24 weeks

4. Absolute change in CFQ-R respiratory domain score at 24 weeks

5. Absolute change in BMI z score at 24 weeks

6. Absolute change in body weight at 24 weeks

7. Time-to-first pulmonary exacerbation at 24 weeks

8. Event of having at least 1 pulmonary exacerbation at week 24

9. Absolute change in EQ 5D 3L at 24 weeks

10. Absolute change in TSQM domains at 24 weeks

11. Safety and tolerability assessments based on adverse events, clinical laboratory values (haematology, serum chemistry, coagulation studies, and urinalysis), standard digital ECGs, ambulatory ECGs, vital signs, and pulse oximetry up to 28 weeks

12. PK parameters of lumacaftor, M28 lumacaftor, ivacaftor, M1 ivacaftor, and M6 ivacaftor at 16 weeks

Funding source	Sponsored by Vertex Pharmaceuticals Inc.
Notes	Known as TRANSPORT study.
	The TRAFFIC and TRANSPORT studies were identical with the following exceptions: TRAFFIC included ambulatory ECG screening at days 1 and 15 in approximately 165 participants in the USA; TRANSPORT included additional pharmacokinetics assessments performed in approximately 28 adolescents in the USA.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomly assigned (in a 1:1:1 ratio) to 1 of 3 study groups; the randomisation was established by an interactive web response system.
		Randomisation was stratified according to age (< 18 years versus ≥ 18 years), sex, and pulmonary function (% predicted FEV_1 (% predicted) at screening, < 70 versus ≥ 70).
Allocation concealment (selection bias)	Low risk	The randomisation was established by an interactive web response system.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	These were double-blind studies in which the participant and study team remained blinded to the treatment assignments. Placebo was matched in appearance and packaging.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	These were double-blind studies in which the participant and study team remained blinded to the treatment assignments.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Correct number of participants included in the analysis (i.e. those who received at least one dose of the study drug – ITT).
		Prior to first dose 4 out of 563 participants withdrew: 2 withdrew from treatment arm 1; 2 withdrew from treatment arm 2; none withdrew from placebo group.
		Post first dose 29 out of 559 participants withdrew (with reasons): 9 from treatment arm 1; 15 withdrew from treatment arm 2; 5 withdrew from placebo group.
Selective reporting (reporting bias)	High risk	Additional data available on www.clinicaltrials.gov for outcomes not reported in the final paper such as:
		1. absolute change in EQ-5D-3L score from baseline at week 24;
		2. absolute change in TSQM domains from baseline at week 24;
		3.. time to first exacerbation;
		4. event of having at least 1 pulmonary exacerbation.
		Some results had to be extrapolated from graphical figures, we await confirmation from the study sponsor of the accuracy of the results.
		Investigators state that they measured FVC (which was not listed as an endpoint) and do not report this in the joint paper.
Other bias	Low risk	Adherence to study treatment was high and the mean compliance rate (determined by site personnel and ongoing study drug count) was similar across lumacaftor-ivacaftor and placebo groups (99.1% versus 98.5%).

Zeitlin 2002

Methods	Phase 1/2 placebo-controlled RCT.
	Parallel design.
	Single centre.
	Duration: 1 week.
	This study follows on from a pilot study (see above) (Rubenstein 1998).
Participants	19 participants were supposed to be randomised in a 3:1 ratio to either study drug or placebo. Randomisation to 40 g group discontinued due to safety reasons; therefore 6 participants were allocated to the 20 g and 30 g groups, 3 to the 40 g group and 4 to the placebo group. It is unclear why only 4 participants were randomised to the placebo group.
	Mutation: all participants were homozygous for the F508del mutation.
	Age: mean (SD) age of 28.5 years.
	Gender split: 12 males and 7 females.
	Lung function: mean (SD) FEV_1 % predicted of 63.7 (17.0).
	Nutritional status: mean (SD) weight 62.6 (17.0) kg.
Interventions	**Intervention 1**: placebo.

Zeitlin 2002 *(Continued)*

> **Intervention 2**: 4-phenylbutyrate (4PBA) 20 g.
>
> **Intervention 3**: 4-phenylbutyrate (4PBA) 30 g.
>
> **Intervention 4**: 4-phenylbutyrate (4PBA) 40 g.
>
> All active interventions split into 3 daily doses.

Outcomes	1. Nasal epithelial chloride transport measured by nasal potential difference
	2. Adverse events*
	3. Absolute values in sweat chloride concentrations
	4. Hepatic enzyme profile 5. Uric acid levels
	6. Change from baseline in pulmonary function (% predicted FEV_1 (% predicted))
	7. Semi-quantitative scoring of sputum microbiology
Funding source	Cystic Fibrosis Foundation.
Notes	* denotes outcomes relevant to this review.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated as randomised but it is not clear how this was conducted.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Escalation to the next dose level was preceded by an examination of the safety profile of the preceding dose. Therefore, study personnel would have been aware of treatment allocation. Also between the 3 intervention groups, participants received a different number of tablets and had different dosage schedules: • 20 g daily dose was divided into 13 tablets to be taken in the morning and afternoon and 14 tablets to be taken in the evening; • 30 g daily dose was divided into 20 tablets to be taken in the morning, afternoon and evening; • 40 g daily dose was initially prescribed as 27 tablets to be taken in the morning and afternoon and 26 tablets to be taken in the evening. Therefore it is unlikely that study personnel blinding and participant blinding was maintained throughout the study.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	There was insufficient information on how outcome assessor blind was maintained.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All 19 participants completed the final study visit, but it is unclear how many participants were used in the analysis.

| Selective reporting (reporting bias) | High risk | Protocol not available. Pulmonary function or microbiology scores at day 7 not reported. |
| Other bias | Low risk | "There were no significant differences in gender, baseline age, weight, or FEV_1 (% predicted) among participants in the four groups." |

AE: adverse event
BMI: body mass index
CF: cystic fibrosis
CFQ-R: Cystic Fibrosis Questionnaire-Revised
CFRSD: Cystic Fibrosis Respiratory Symptom Diary
CPX: 8-cyclopentyl-1, 3-dipropylxanthine
ECG: electrocardiograms
EQ 5D 3L: EuroQol 3 Level
$FEF_{25-75\%}$: forced expiratory flow
FEV_1: forced expiratory volume in one second
FVC: forced vital capacity
IRT: immunoreactive trypsinogen
ITT: intention to treat
IV: intravenous
LCI: lung clearance index
mEq/L: millequivalents/L
MMRM: mixed effects model for repeated measurements
NIH: National Institutes of Health
PK: pharmacokinetic
PSQI: Pittsburgh Sleep Quality Index
QoL: quality of life
RCT: randomised controlled trial
SAE: serious adverse event
TSQM: Treatment Satisfaction Questionnaire for Medication

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

Study	Reason for exclusion
Berkers 2014	Cross-over study with participants with gating defects and not a class II defect.
Chadwick 1998	Investigators informed review authors that study was not randomised.
Chilvers 2017	Single-group assignment.
Lebecque 2011	Cross-over design.
Leonard 2012	Cross-over design.
NCT01899105	Cross-over design.
Nick 2014	Cross-over study assessing CFTR mutations eligible for treatment with ivacaftor (not relevant to this review).
Rowe 2017	Cross-over design.
Rubenstein 2006	Participants were not randomised.
Sumner 2014	Gene therapy study, not a mutation-specific therapy.

Study	Reason for exclusion
Ziady 2015	Laboratory study conducted within cells donated by CF and non-CF donors. Not a study of people with CF.

CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator

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

Hunt 2017

Methods	Randomised placebo-controlled trial.
	Duration: 4-week treatment period.
Participants	18 adults with mild to moderate CF who were homozygous for the f508-del mutation, and who were receiving lumacaftor-ivacaftor combination therapy.
	Baseline characteristics:
	Mean (SD) age: 28.7 (6.6) years.
	Gender split: 65% (11/18) were female.
	Mean (SD) % predicted FEV$_1$: 85.2 (12.9)%.
	Mean (SD) BMI: 23.2 (6.6).
Interventions	**Intervention**: 40 mg sildenafil 3x daily.
	Control: matched placebo.
Outcomes	Sweat chloride, % predicted FEV$_1$, BMI, exhaled nitric oxide, CFQR, nasal potential difference, LCI.
Notes	Presented as a poster at the 31st Annual North American Cystic Fibrosis Conference, Indianapolis, November 2017.
	Supported by NIH/NHLBI and NIH/NCRR Colorado CTSI Grant Number UL1 RR025780.
	NCT01132482.

BMI: body mass index
CF: cystic fibrosis
CFQR: cystic fibrosis questionnaire - revised
FEV$_1$: forced expiratory volume in one second
LCI: lung clearance index

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

Meijer 2016

Trial name or title	Evaluation of (R)-Roscovitine Safety and Effects in Subjects With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation (ROSCO-CF)
Methods	Phase 2, dose-ranging, multicentre, double-blind, placebo-controlled RCT.
	Duration: 3 months.

Meijer 2016 *(Continued)*

	Multicentre study conducted in France.
Participants	36 adults with CF carrying 2 CF-causing mutations with at least 1 F508del-CFTR mutation and chronically infected with *Pseudomonas aeruginosa.*
Interventions	Roscovitine 200 mg or 400 mg compared to placebo.
Outcomes	**Primary outcome measure** Safety of increasing doses of roscovitine **Secondary outcome measures** Change in the concentration of *P aeruginosa* Change in the concentration (CFU/mL) of *P aeruginosa* in the sputum at each visit from V1 (screening) up to V7 (completion visit) PK parameters: Cmax, time to reach Cmax, AUC (AUCt and AUCInf), half-life (t1/2) for roscovitine and its M3 metabolite Pro- and anti-inflammatory cytokines Change in C-reactive protein at each visit from V1 (screening) up to V7 (completion) Change in CFQ-R at each visit from V1 up to V8 (safety follow-up) Change in BMI at each visit from V1 (screening) up to V7 (completion visit) Change in FEV_1 at each visit from V1 (screening) up to V7 (completion visit) Change in sweat chloride concentration at V2, V3, V5 and V7 (Completion) Change in nasal potential difference at V1 (screening) and V6 (for participants included in Paris Cochin CF Center) Pain questionnaire
Starting date	February 2016.
Contact information	Principle investigator: Dr Gilles Rault (gilles.rault@perharidy.fr).
Notes	Estimated study completion date: October 2017. Estimated primary completion date: August 2017 (Final data collection date for primary outcome measure).

NCT02070744

Trial name or title	Study to Evaluate Safety and Efficacy of VX-661 in Combination With Ivacaftor in Subjects With Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation
Methods	Double-blind, placebo-controlled, 3-part Phase 2 RCT. Parallel design. Multicentre: 20 sites. Sample size: expected to enrol 40 participants. Duration: 12 weeks of treatment.
Participants	Age: 18 years or older. Gender: both male and female. Mutation: homozygous for the F508del mutation.

NCT02070744 *(Continued)*

Lung function: $FEV_1 \geq 40\%$ and $\leq 90\%$ of predicted normal for age, sex, and height.

Participants must have stable CF disease as judged by the investigator.

Interventions	**Experimental Group 1** Treatment: VX-661 + ivacaftor (every 12 hours schedule). Control: VX-661 placebo + ivacaftor placebo (every 12 hours schedule). **Experimental Group 2** Treatment: VX-661 + ivacaftor (once daily and schedule). Control: VX-661 placebo + ivacaftor placebo (once daily and schedule).
Outcomes	**Primary outcome measure** 1. Safety as determined by AEs, physical examination, clinical laboratory values, standard digital ECGs, vital signs and pulse oximetry at 16 weeks **Secondary outcome measures** 1. Absolute change in % predicted FEV_1 at 12 weeks 2. Relative change in % predicted FEV_1 at 12 weeks 3. Absolute change in body weight at 12 weeks 4. Absolute change in BMI at 12 weeks 5. Absolute change in the respiratory domain of the CFQ-R at 12 weeks 6. PK parameters estimates of VX-661 and ivacaftor and their respective metabolites, derived from plasma concentration-time data at 16 weeks 7. Absolute change in sweat chloride at 12 weeks
Starting date	March 2014.
Contact information	No contact information provided.
Notes	This study is listed as completed but no results are available on www.clinicaltrials.gov. Sponsored by Vertex Pharmaceuticals Inc.

NCT02323100

Trial name or title	Glycerol Phenylbutyrate Corrector Therapy For CF (Cystic Fibrosis) (GPBA)
Methods	Double-blind, placebo-controlled, 3-part Phase 2 RCT. Parallel design. Multicentre: 3 sites. Sample size: expected to enrol 36 participants. Duration: 7 days of treatment.
Participants	**Inclusion criteria** Age/gender: male or female ≥ 18 years of age. Mutation: homozygous for F508del, and taking pancreatic enzyme replacement therapy.

NCT02323100 *(Continued)*

Lung function: FEV_1 > 30% of predicted normal for age, gender, and height (Hankinson standards).

Interventions	Low-dose glycerol phenylbutyrate versus high-dose glycerol phenylbutyrate versus placebo.
Outcomes	**Primary outcome** Change in average measurement of nasal potential difference between day 7 and baseline (at 7 days) **Secondary outcomes** Change from baseline in other nasal potential difference measures (baseline potential difference, change in amiloride, low chloride, and low chloride plus isoproterenol) (at 4 days, 7 days and 14 days) Change from baseline in sodium and chloride transport Change from baseline in average sweat chloride measurement (at 4 days, 7 days and 14 days) Change from baseline in sweat chloride Safety and tolerability (standard safety and tolerability lab values) (at 14 days)
Starting date	December 2017.
Contact information	Britany Zeglin (bzeglin1@jhmi.edu).
Notes	

NCT02412111

Trial name or title	A Phase 3 Study of VX-661 in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Who Have One F508del-CFTR Mutation and a Second Mutation That Has Been Demonstrated to be Clinically Responsive to Ivacaftor
Methods	Double-blind, placebo-controlled Phase 2 RCT. Parallel design. Multicentre: 68 centres. Sample size: expected to enrol 156 participants. Duration: unclear duration of treatment.
Participants	Age: 12 years and older Mutation: heterozygous for F508del-CFTR mutation and a second CFTR allele with a gating defect that is clinically demonstrated to be ivacaftor responsive Lung function: FEV_1 ≥ 40% and ≤ 90% of predicted.
Interventions	This study is evaluating VX-661 in combination with ivacaftor versus placebo with ivacaftor **GROUP 1**: morning VX-661 100 mg/ivacaftor 150 mg fixed-dose tablet with ivacaftor matching placebo tablet; evening ivacaftor 150 mg tablet. **GROUP 2**: morning VX-661/ivacaftor matching placebo tablet plus ivacaftor 150 mg tablet; evening ivacaftor 150 mg tablet.

Outcomes	**Primary outcome**
	Absolute change in % predicted FEV_1 (from baseline through week 8)
	Secondary outcomes
	Relative change in **%** predicted FEV_1 (from baseline through week 8)
	Absolute change in sweat chloride (from baseline through week 8)
	Absolute change in CFQ-R respiratory domain score (from baseline through week 8)
	Number of participants with AEs and serious AEs (up to 4 weeks after receiving last dose)
	PK parameters of VX-661, M1-661, ivacaftor, and M1-ivacaftor
Starting date	June 2015.
Contact information	Sponsored by Vertex Pharmaceuticals - no contact details given.
Notes	

NCT02589236

Trial name or title	Study of Cavosonstat (N91115) in Patients With CF Homozygous for the F508del-CFTR Mutation (SNO-6)
Methods	Double-blind, placebo-controlled, parallel RCT.
Participants	Participants must have been treated with lumacaftor-ivacaftor for at least 8 weeks prior to day 1.
	Age: 18 years and older.
	FEV_1: 40% - 85% predicted.
Interventions	Group 1: cavosonstat 200 mg 2x daily.
	Group 2: cavosonstat 400 mg 2x daily.
	Group 3: placebo.
Outcomes	**Primary outcome**
	Absolute change in FEV_1 % predicted (from baseline to 12 weeks)
	Secondary outcomes
	Relative change in FEV_1 % predicted (from baseline to 12 weeks)
	Absolute change in sweat chloride (from baseline to 12 weeks)
	Absolute change in CFQ-R (respiratory symptom scale) (from baseline to 16 weeks)
	Absolute change in BMI (from baseline to 12 weeks)
	Absolute change in Patient Global Impression of Change (patient-reported outcome journal) (from baseline to 12 weeks)
	Incidence of treatment-emergent AEs (including clinical laboratory values, ECG, pulmonary exacerbations, or vital sign changes) (from baseline to 16 weeks)
	Number of pulmonary exacerbations (up to 12 weeks)

NCT02589236 *(Continued)*

Starting date	November 2015.
Contact information	
Notes	

NCT02718495

Trial name or title	Study Assessing PTI-428 Safety, Tolerability, and Pharmacokinetics in Subjects With Cystic Fibrosis
Methods	Quadruple-blind, placebo-controlled, parallel design 3-arm Phase 2 RCT.
	Multicentre: 29 centres
	Sample size: expected to enrol 136 participants.
	Duration: 28 days of treatment.
	Part A has 2 groups: the 1st group will enrol adults with CF into a single ascending dose treatment group; the 2nd group will enrol adults with CF, including those on background treatment with ORKAMBI® and those not on a CFTR modulator into a multiple ascending dose treatment group.
	Part B will enrol adults with CF currently on stable ORKAMBI® background therapy for a minimum of 3 months into a Phase II treatment group consisting of 2 cohorts.
	Part C will enrol adults with CF, including those on background treatment with KALYDECO® and those not on a CFTR modulator, into a Phase II treatment group consisting of 3 cohorts.
Participants	Age: 18 years and older. Mutation: not specified.
	Lung function: FEV_1 40% - 90% predicted.
Interventions	PTI-428 versus placebo.
Outcomes	**Primary outcome**
	Safety and tolerability as assessed by adverse events, pulmonary function tests, safety labs (haematology, chemistry, and urinalysis, ECGs, physical examinations, and vital signs)
	Secondary outcomes PK and pharmacodynamic parameters
	Change in FEV_1
	Change in sweat chloride
	Change in weight
	Change in CFQ-R
	Change in nasal epithelial CFTR mRNA and protein expression
Starting date	November 2017.
Contact information	
Notes	

NCT02730208

Trial name or title	A Phase 2, Randomized, Placebo-Controlled, Double-blind Study to Evaluate the Effect of VX-661 in Combination With Ivacaftor on Chest Imaging Endpoints in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the F508del CFTR Mutation
Methods	Placebo-controlled, double-blind Phase 2 RCT.
Participants	12 years and older.
	Homozygous for F508del CFTR mutation.
	Stable CF disease as judged by the investigator.
	FEV_1 ≥ 40% and ≤ 90% of predicted; ≥ 70% of predicted normal for age, sex, and height during screening.
Interventions	**Group 1**: morning dose VX-661 100 mg/ivacaftor 150 mg and an evening dose (approximately 12 hours after the morning dose) ivacaftor 150 mg.
	Group 2: placebo.
Outcomes	**Primary outcome**
	Change in CT imaging score (from baseline to week 72)
	Secondary outcomes
	Safety and tolerability assessments including number of participants with AEs and serious AEs (up to week 72)
Starting date	September 2016.
Contact information	Unclear of individual to contact - study conducted by Vertex Pharmaceuticals.
Notes	

NCT02951195

Trial name or title	A Study Evaluating the Safety of VX-152 Combination Therapy in Adults With Cystic Fibrosis
Methods	Double-blind, placebo and active-controlled, parallel group, multicentre Phase 2 RCT.
Participants	**Inclusion criteria**
	Body weight ≥ 35 kg.
	Sweat chloride value ≥ 60 mmol/L from test results obtained during screening.
	CFTR genotype: Cohorts 1A, 1B, 1C are heterozygous for F508del and a minimal function mutation known or predicted not to respond to tezacaftor and/or ivacaftor; Cohorts 2A, 2B are homozygous for F508del.
	FEV_1 ≥ 40% and ≤ 90% of predicted normal for age, sex, and height at the screening visit.
	Stable CF disease as judged by the investigator.
Interventions	**Initial cohort**: VX-152 100 mg administered every 12 hours, tezacaftor 100 mg 1x daily, ivacaftor 150 mg every 12 hours versus placebo (i.e. no active VX-152, tezacaftor, or ivacaftor).

	Subsequent cohorts: same combination with different doses of VX-152, adjusted as the study progresses.
Outcomes	**Primary outcome** AEs and serious AEs (up to 8 weeks) **Secondary outcomes** Absolute change in sweat chloride concentrations (from baseline to day 15) Absolute change in % predicted FEV_1 (from baseline to day 15) Relative change in % predicted FEV_1 (from baseline to day 15) Absolute change in CFQ-R respiratory domain score (from baseline to day 15) PK and pharmacodynamic parameters
Starting date	November 2016.
Contact information	Vertex Pharmaceuticals (medicalinfo@vrtx.com).
Notes	

NCT03093714

Trial name or title	A Study to Evaluate Safety, PK and PD of FDL169 in Cystic Fibrosis Subjects
Methods	Multicentre (14 sites), placebo-controlled, dose-escalation RCT.
Participants	**Inclusion criteria** Male and female participants with CF. Age 18 and above on the date of informed consent. Weight ≥ 40 kg. Homozygous for the F508del-CFTR mutation.
Interventions	**Group 1**: FDL 169 test formulation at 3 doses (dose escalation). **Group 2**: placebo.
Outcomes	**Primary outcome** Treatment-emergent AEs (up to 28 days) **Secondary outcomes** PK parameters
Starting date	August 2017.
Contact information	Jingwen Chai, Flatley Discovery Laboratory (jingwen.chai@flatleydiscoverylab.com).
Notes	

NCT03150719

Trial name or title	A Study to Evaluate Safety, Efficacy, and Tolerability of TEZ/IVA in Orkambi® (Lumacaftor/Ivacaftor) - Experienced Subjects With Cystic Fibrosis (CF)
Methods	Double-blind, placebo-controlled, 3-part Phase 3b RCT.
	Parallel design.
	Multicentre: 32 centres.
	Sample size: expected to enrol 90 participants.
	Duration: 28 days of treatment.
Participants	Age: 12 years and older.
	Mutation: homozygous for F508del mutation.
	Lung function: $FEV_1 \geq 25\%$ and $\leq 90\%$ of predicted.
Interventions	**Group 1**: tezacaftor 100 mg plus ivacaftor 150 mg fixed-dose combination tablet in the morning plus ivacaftor 150 mg tablet in the evening.
	Group 2: placebo.
Outcomes	**Primary outcome**
	Respiratory AEs (at day 56)
	Secondary outcomes
	Absolute change in % predicted FEV_1 (from baseline to the average of the day 28 and day 56 measurements)
	Relative change in % predicted FEV_1 (from baseline to the average of the day 28 and day 56 measurements)
	Absolute change in CFQ-R respiratory domain score % predicted FEV_1 (from baseline to the average of the day 28 and day 56 measurements)
	Tolerability (defined as the number and proportion of study participants who discontinue treatment) (up to day 56)
	AEs and serious AEs (AEs, abnormal laboratory values, vital signs or pulse oximetry) (safety follow-up (up to 28 days after last dose of study drug))
Starting date	April 2017.
Contact information	Vertex Pharmaceuticals (medicalinfo@vrtx.com).
Notes	

NCT03224351

Trial name or title	A Study Evaluating the Safety and Efficacy of VX-659 Combination Therapy in Subjects With Cystic Fibrosis
Methods	Double-blind, placebo- and tezacaftor-ivacaftor (TEZ/IVA)-controlled, parallel design, 3-part, multicentre Phase 2 RCT.

NCT03224351 *(Continued)*

Participants	**Inclusion criteria**
	Body weight ≥ 35 kg.
	CFTR genotype: Part 1 and Part 3 - heterozygous for F508del and an MF mutation (F/MF); Part 2 - homozygous for F508del (F/F).
	FEV_1 value ≥ 40% and ≤ 90% of predicted mean for age, sex, and height.
Interventions	Group 1: VX-659 4x daily with tezacaftor and ivacaftor for 4 weeks (80 mg, 240 mg, or 400 mg).
	Group 2: placebo.
Outcomes	**Primary outcome**
	Safety and tolerability as assessed by number of participants with AEs and serious AEs (up to 20 weeks)
	Absolute change in FEV_1 % predicted (from baseline to day 29)
	Secondary outcomes
	Absolute change in sweat chloride concentrations (from baseline through day 29)
	Relative change in FEV_1 % predicted
	Absolute change in CFQ-R respiratory domain score (from baseline at day 29)
	PK and pharmacodynamic parameters
Starting date	August 2017.
Contact information	Vertex Pharmaceuticals (medicalinfo@vrtx.com).
Notes	

NCT03227471

Trial name or title	A Study of VX-445 in Healthy Subjects and Subjects With Cystic Fibrosis
Methods	First-in-human, proof-of-concept RCT.
	Parallel design.
	Multicentre: 38 centres
	Sample size: expected to enrol 224 participants.
	Duration: 4 weeks of treatment.
	The study includes 6 parts, of which the first 3 are conducted in healthy participants, and the last 3 in people with CF.
Participants	**Inclusion criteria**
	Age: 18 years and older.
	Mutation: heterozygous for F508del and an MF mutation (F/MF), or Homozygous for F508del (F/F).
	Lung function: FEV_1 value ≥ 40% and ≤ 90% of predicted mean for age, sex, and height.
Interventions	**Group 1**: VX-445 in triple combination with tezacaftor and VX-561 for 4 weeks.

	Group 2: placebo.
Outcomes	**Primary outcomes**
	Safety and tolerability as assessed by number of participants with AEs and serious AEs
	Absolute change in FEV_1 % predicted (Parts D, E, and F only) (from baseline through day 29)
	Secondary outcomes
	Absolute change in sweat chloride concentrations (from baseline through day 29)
	Relative change in FEV_1 % predicted (from baseline through day 29)
	Absolute change in CFQ-R respiratory domain score (from baseline through day 29)
Starting date	January 2017.
Contact information	Vertex Pharmaceuticals (medicalinfo@vrtx.com).
Notes	

NCT03258424

Trial name or title	Study Assessing PTI-428 Safety, Tolerability, and Pharmacokinetics in Subjects With Cystic Fibrosis on KALYDECO® as Background Therapy
Methods	Phase 1 placebo-controlled RCT.
	Parallel design.
	2 centres.
	Sample size: expected to enrol 16 participants.
	Duration: 14 days of treatment.
Participants	**Inclusion criteria**
	Age: 18 years and older.
	Mutation: taking ivacaftor but no specific mutations specified as eligible/ineligible.
	Lung function: FEV_1 40% - 90% predicted.
Interventions	Group 1: 1x daily dosing of PTI-428.
	Group 2: placebo for 14 days.
	All participants continue on ivacaftor.
Outcomes	**Primary outcome**
	Safety and tolerability as assessed by adverse events, safety labs, ECGs, physical examinations, and vital signs (at day 21)
	Secondary outcomes
	t1/2 of multiple oral doses (change from baseline to day 21)
	Tmax of multiple oral doses (change from baseline to day 21)
	Cmax of multiple oral doses (change from baseline to day 21)
	AUC0-t of multiple oral doses (change from baseline to day 21)
	Other outcomes
	Nasal epithelial mRNA and protein expression over time (change from baseline to day 21)

	Sweat chloride (change from baseline to day 21) FEV_1 (change from baseline to day 21) Weight (change from baseline to day 21)
Starting date	July 2017.
Contact information	Proteostasis Clinical Trials (pticlinicaltrials@proteostasis.com).
Notes	

AE: adverse event
AUC: area under the curve
BMI: body mass index
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
CFU: colony forming units
CFQ-R: Cystic Fibrosis Questionnaire-Revised
Cmax: maximum concentration
CT: computer tomography
ECG: electrocardiograms
FEV_1: forced expiratory volume in one second
PK: pharmacokinetic
RCT: randomised controlled trial
TSQM: Treatment Satisfaction Questionnaire for Medication

DATA AND ANALYSES

Comparison 1.   Lumacaftor versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV_1 % predicted (absolute change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 14 days	1	61	Mean Difference (IV, Fixed, 95% CI)	-1.90 [-4.13, 0.33]
2 Adverse effects: 100 mg and 200 mg lumacaftor groups (combined data) versus placebo	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
2.1 Cough	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.28 [0.28, 5.92]
2.2 Headache	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.13 [0.16, 8.04]
2.3 Rales	1	53	Odds Ratio (M-H, Fixed, 99% CI)	3.2 [0.18, 57.82]
2.4 Productive cough	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.79 [0.27, 11.98]

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2.5 Dyspnoea	1	53	Odds Ratio (M-H, Fixed, 99% CI)	3.2 [0.18, 57.82]
2.6 Pulmonary exacerbation	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.5 [0.16, 14.31]
2.7 Fatigue	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.21 [0.12, 12.09]
2.8 Fever	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.5 [0.16, 14.31]
2.9 Nasal congestion	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.58 [0.07, 4.93]
2.10 Wheezing	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.13 [0.01, 2.91]
2.11 Diarrhoea	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.27 [0.02, 3.31]
2.12 Oropharyngeal pain	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.27 [0.02, 3.31]
2.13 Upper respiratory tract infection	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.45 [0.07, 31.52]
2.14 Sinus congestion	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.21 [0.01, 5.55]
2.15 Respiration abnormal	1	53	Odds Ratio (M-H, Fixed, 99% CI)	4.85 [0.10, 243.04]
2.16 Haemoptysis	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.44 [0.03, 6.54]
2.17 Constipation	1	53	Odds Ratio (M-H, Fixed, 99% CI)	2.54 [0.04, 147.25]
2.18 Abdominal pain	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.46 [0.01, 18.95]
2.19 Myalgia	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.46 [0.01, 18.95]
2.20 Post-tussive vomiting	1	53	Odds Ratio (M-H, Fixed, 99% CI)	2.54 [0.04, 147.25]
2.21 Nausea	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.48 [0.02, 106.10]
2.22 Nasopharyngitis	1	53	Odds Ratio (M-H, Fixed, 99% CI)	3.66 [0.07, 193.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.23 Dizziness	1	53	Odds Ratio (M-H, Fixed, 99% CI)	3.66 [0.07, 193.30]
2.24 Back pain	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.48 [0.02, 106.10]
2.25 Upper abdominal pain	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.45 [0.07, 31.52]
2.26 Sputum abnormal	1	53	Odds Ratio (M-H, Fixed, 99% CI)	1.48 [0.02, 106.10]
2.27 Epistaxis	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.94 [0.04, 24.27]
2.28 C-reactive protein increased	1	53	Odds Ratio (M-H, Fixed, 99% CI)	2.54 [0.04, 147.25]
2.29 Paranasal sinus hypersecretion	1	53	Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
2.30 Lung hyperinflation	1	53	Odds Ratio (M-H, Fixed, 99% CI)	2.54 [0.04, 147.25]
3 Adverse effects: 200 mg lumacaftor group versus placebo at 14 days	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
3.1 Cough	1	62	Odds Ratio (M-H, Fixed, 99% CI)	3.43 [0.19, 60.73]
3.2 Pulmonary exacerbation	1	62	Odds Ratio (M-H, Fixed, 99% CI)	2.72 [0.05, 156.17]
3.3 Oropharyngeal pain	1	62	Odds Ratio (M-H, Fixed, 99% CI)	2.72 [0.05, 156.17]
3.4 Nasal congestion	1	62	Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
3.5 Dizziness	1	62	Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
3.6 Prothrombin time prolonged	1	62	Odds Ratio (M-H, Fixed, 99% CI)	1.59 [0.02, 113.01]
3.7 Upper respiratory tract infection	1	62	Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4 Adverse effects requiring study drug discontinuation at day 28	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 25 mg lumacaftor	1	35	Odds Ratio (M-H, Fixed, 95% CI)	3.0 [0.11, 78.81]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 50 mg lumacaftor	1	35	Odds Ratio (M-H, Fixed, 95% CI)	3.0 [0.11, 78.81]
4.3 100 mg lumacaftor	1	34	Odds Ratio (M-H, Fixed, 95% CI)	3.18 [0.12, 83.76]
4.4 200 mg lumacaftor	1	36	Odds Ratio (M-H, Fixed, 95% CI)	2.84 [0.11, 74.42]
5 Change from baseline in sweat chloride concentration after 28 days [mmol/L]	1		Mean Difference (Fixed, 95% CI)	Subtotals only
5.1 100 mg lumacaftor	1	34	Mean Difference (Fixed, 95% CI)	-6.13 [-12.25, -0.01]
5.2 200 mg lumacaftor	1	36	Mean Difference (Fixed, 95% CI)	-8.21 [-14.30, -2.12]
6 Sweat chloride concentration (mmol/L) (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 At 14 days	1	51	Mean Difference (IV, Fixed, 95% CI)	-2.75 [-7.65, 2.15]

Analysis 1.1. Comparison 1 Lumacaftor versus placebo, Outcome 1 FEV$_1$ % predicted (absolute change from baseline).

Study or subgroup	Lumacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.1.1 At 14 days							
Boyle 2014	40	-0.2 (4.3)	21	1.7 (4.2)		100%	-1.9[-4.13,0.33]
Subtotal ***	**40**		**21**			**100%**	**-1.9[-4.13,0.33]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.67(P=0.1)							

Favours placebo -100 -50 0 50 100 Favours lumacaftor

Analysis 1.2. Comparison 1 Lumacaftor versus placebo, Outcome 2 Adverse effects: 100 mg and 200 mg lumacaftor groups (combined data) versus placebo.

Study or subgroup	Lumacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
1.2.1 Cough					
Clancy 2012	17/36	7/17		100%	1.28[0.28,5.92]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.28[0.28,5.92]**
Total events: 17 (Lumacaftor), 7 (Placebo)					
Heterogeneity: Not applicable					

Favours lumacaftor 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	Lumacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
Test for overall effect: Z=0.41(P=0.68)					
1.2.2 Headache					
Clancy 2012	7/36	3/17		100%	1.13[0.16,8.04]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.13[0.16,8.04]**
Total events: 7 (Lumacaftor), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.16(P=0.88)					
1.2.3 Rales					
Clancy 2012	6/36	1/17		100%	3.2[0.18,57.82]
Subtotal (99% CI)	**36**	**17**		**100%**	**3.2[0.18,57.82]**
Total events: 6 (Lumacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
1.2.4 Productive cough					
Clancy 2012	10/36	3/17		100%	1.79[0.27,11.98]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.79[0.27,11.98]**
Total events: 10 (Lumacaftor), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					
1.2.5 Dyspnoea					
Clancy 2012	6/36	1/17		100%	3.2[0.18,57.82]
Subtotal (99% CI)	**36**	**17**		**100%**	**3.2[0.18,57.82]**
Total events: 6 (Lumacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.04(P=0.3)					
1.2.6 Pulmonary exacerbation					
Clancy 2012	6/36	2/17		100%	1.5[0.16,14.31]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.5[0.16,14.31]**
Total events: 6 (Lumacaftor), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.64)					
1.2.7 Fatigue					
Clancy 2012	5/36	2/17		100%	1.21[0.12,12.09]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.21[0.12,12.09]**
Total events: 5 (Lumacaftor), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.21(P=0.83)					
1.2.8 Fever					
Clancy 2012	6/36	2/17		100%	1.5[0.16,14.31]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.5[0.16,14.31]**
Total events: 6 (Lumacaftor), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.46(P=0.64)					
1.2.9 Nasal congestion					

Favours lumacaftor 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	Lumacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
Clancy 2012	4/36	3/17		100%	0.58[0.07,4.93]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.58[0.07,4.93]**

Total events: 4 (Lumacaftor), 3 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

Test for overall effect: Z=0.65(P=0.52)

1.2.10 Wheezing

Clancy 2012	1/36	3/17		100%	0.13[0.01,2.91]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.13[0.01,2.91]**

Total events: 1 (Lumacaftor), 3 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=1.68(P=0.09)

1.2.11 Diarrhoea

Clancy 2012	2/36	3/17		100%	0.27[0.02,3.31]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.27[0.02,3.31]**

Total events: 2 (Lumacaftor), 3 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

Test for overall effect: Z=1.34(P=0.18)

1.2.12 Oropharyngeal pain

Clancy 2012	2/36	3/17		100%	0.27[0.02,3.31]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.27[0.02,3.31]**

Total events: 2 (Lumacaftor), 3 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

Test for overall effect: Z=1.34(P=0.18)

1.2.13 Upper respiratory tract infection

Clancy 2012	3/36	1/17		100%	1.45[0.07,31.52]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.45[0.07,31.52]**

Total events: 3 (Lumacaftor), 1 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.31(P=0.75)

1.2.14 Sinus congestion

Clancy 2012	1/36	2/17		100%	0.21[0.01,5.55]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.21[0.01,5.55]**

Total events: 1 (Lumacaftor), 2 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

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

1.2.15 Respiration abnormal

Clancy 2012	4/36	0/17		100%	4.85[0.1,243.04]
Subtotal (99% CI)	**36**	**17**		**100%**	**4.85[0.1,243.04]**

Total events: 4 (Lumacaftor), 0 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=1.04(P=0.3)

1.2.16 Haemoptysis

Clancy 2012	2/36	2/17		100%	0.44[0.03,6.54]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.44[0.03,6.54]**

Total events: 2 (Lumacaftor), 2 (Placebo)

Favours lumacaftor 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	Lumacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=0.78(P=0.43)					
1.2.17 Constipation					
Clancy 2012	2/36	0/17		100%	2.54[0.04,147.25]
Subtotal (99% CI)	**36**	**17**		**100%**	**2.54[0.04,147.25]**
Total events: 2 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
1.2.18 Abdominal pain					
Clancy 2012	1/36	1/17		100%	0.46[0.01,18.95]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.46[0.01,18.95]**
Total events: 1 (Lumacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
1.2.19 Myalgia					
Clancy 2012	1/36	1/17		100%	0.46[0.01,18.95]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.46[0.01,18.95]**
Total events: 1 (Lumacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.54(P=0.59)					
1.2.20 Post-tussive vomiting					
Clancy 2012	2/36	0/17		100%	2.54[0.04,147.25]
Subtotal (99% CI)	**36**	**17**		**100%**	**2.54[0.04,147.25]**
Total events: 2 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
1.2.21 Nausea					
Clancy 2012	1/36	0/17		100%	1.48[0.02,106.1]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.48[0.02,106.1]**
Total events: 1 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.2.22 Nasopharyngitis					
Clancy 2012	3/36	0/17		100%	3.66[0.07,193.3]
Subtotal (99% CI)	**36**	**17**		**100%**	**3.66[0.07,193.3]**
Total events: 3 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.84(P=0.4)					
1.2.23 Dizziness					
Clancy 2012	3/36	0/17		100%	3.66[0.07,193.3]
Subtotal (99% CI)	**36**	**17**		**100%**	**3.66[0.07,193.3]**
Total events: 3 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.84(P=0.4)					

Favours lumacaftor 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	Lumacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
1.2.24 Back pain					
Clancy 2012	1/36	0/17		100%	1.48[0.02,106.1]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.48[0.02,106.1]**
Total events: 1 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.2.25 Upper abdominal pain					
Clancy 2012	3/36	1/17		100%	1.45[0.07,31.52]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.45[0.07,31.52]**
Total events: 3 (Lumacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.31(P=0.75)					
1.2.26 Sputum abnormal					
Clancy 2012	1/36	0/17		100%	1.48[0.02,106.1]
Subtotal (99% CI)	**36**	**17**		**100%**	**1.48[0.02,106.1]**
Total events: 1 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.24(P=0.81)					
1.2.27 Epistaxis					
Clancy 2012	2/36	1/17		100%	0.94[0.04,24.27]
Subtotal (99% CI)	**36**	**17**		**100%**	**0.94[0.04,24.27]**
Total events: 2 (Lumacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
1.2.28 C-reactive protein increased					
Clancy 2012	2/36	0/17		100%	2.54[0.04,147.25]
Subtotal (99% CI)	**36**	**17**		**100%**	**2.54[0.04,147.25]**
Total events: 2 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
1.2.29 Paranasal sinus hypersecretion					
Clancy 2012	0/36	0/17			Not estimable
Subtotal (99% CI)	**36**	**17**			**Not estimable**
Total events: 0 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.2.30 Lung hyperinflation					
Clancy 2012	2/36	0/17		100%	2.54[0.04,147.25]
Subtotal (99% CI)	**36**	**17**		**100%**	**2.54[0.04,147.25]**
Total events: 2 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					

Favours lumacaftor   0.001   0.1   1   10   1000   Favours placebo

Analysis 1.3. Comparison 1 Lumacaftor versus placebo, Outcome 3
Adverse effects: 200 mg lumacaftor group versus placebo at 14 days.

Study or subgroup	Lumacaftor group	Placebo group	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
1.3.1 Cough					
Boyle 2014	6/41	1/21		100%	3.43[0.19,60.73]
Subtotal (99% CI)	**41**	**21**		**100%**	**3.43[0.19,60.73]**
Total events: 6 (Lumacaftor group), 1 (Placebo group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.1(P=0.27)					
1.3.2 Pulmonary exacerbation					
Boyle 2014	2/41	0/21		100%	2.72[0.05,156.17]
Subtotal (99% CI)	**41**	**21**		**100%**	**2.72[0.05,156.17]**
Total events: 2 (Lumacaftor group), 0 (Placebo group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.3.3 Oropharyngeal pain					
Boyle 2014	2/41	0/21		100%	2.72[0.05,156.17]
Subtotal (99% CI)	**41**	**21**		**100%**	**2.72[0.05,156.17]**
Total events: 2 (Lumacaftor group), 0 (Placebo group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.64(P=0.52)					
1.3.4 Nasal congestion					
Boyle 2014	0/41	0/21			Not estimable
Subtotal (99% CI)	**41**	**21**			**Not estimable**
Total events: 0 (Lumacaftor group), 0 (Placebo group)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.5 Dizziness					
Boyle 2014	0/41	0/21			Not estimable
Subtotal (99% CI)	**41**	**21**			**Not estimable**
Total events: 0 (Lumacaftor group), 0 (Placebo group)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
1.3.6 Prothrombin time prolonged					
Boyle 2014	1/41	0/21		100%	1.59[0.02,113.01]
Subtotal (99% CI)	**41**	**21**		**100%**	**1.59[0.02,113.01]**
Total events: 1 (Lumacaftor group), 0 (Placebo group)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					
1.3.7 Upper respiratory tract infection					
Boyle 2014	0/41	0/21			Not estimable
Subtotal (99% CI)	**41**	**21**			**Not estimable**
Total events: 0 (Lumacaftor group), 0 (Placebo group)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours lumacaftor 0.001 0.1 1 10 1000 Favours placebo

Analysis 1.4. Comparison 1 Lumacaftor versus placebo, Outcome 4 Adverse effects requiring study drug discontinuation at day 28.

Study or subgroup	Lumacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.4.1 25 mg lumacaftor					
Clancy 2012	1/18	0/17		100%	3[0.11,78.81]
Subtotal (95% CI)	**18**	**17**		**100%**	**3[0.11,78.81]**
Total events: 1 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
1.4.2 50 mg lumacaftor					
Clancy 2012	1/18	0/17		100%	3[0.11,78.81]
Subtotal (95% CI)	**18**	**17**		**100%**	**3[0.11,78.81]**
Total events: 1 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
1.4.3 100 mg lumacaftor					
Clancy 2012	1/17	0/17		100%	3.18[0.12,83.76]
Subtotal (95% CI)	**17**	**17**		**100%**	**3.18[0.12,83.76]**
Total events: 1 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.69(P=0.49)					
1.4.4 200 mg lumacaftor					
Clancy 2012	1/19	0/17		100%	2.84[0.11,74.42]
Subtotal (95% CI)	**19**	**17**		**100%**	**2.84[0.11,74.42]**
Total events: 1 (Lumacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.63(P=0.53)					

Favours lumacaftor 0.01 0.1 1 10 100 Favours placebo

Analysis 1.5. Comparison 1 Lumacaftor versus placebo, Outcome 5 Change from baseline in sweat chloride concentration after 28 days [mmol/L].

Study or subgroup	Lumacaftor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 100 mg lumacaftor						
Clancy 2012	17	17	-6.1 (3.123)		100%	-6.13[-12.25,-0.01]
Subtotal (95% CI)					**100%**	**-6.13[-12.25,-0.01]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.96(P=0.05)						
1.5.2 200 mg lumacaftor						
Clancy 2012	19	17	-8.2 (3.107)		100%	-8.21[-14.3,-2.12]
Subtotal (95% CI)					**100%**	**-8.21[-14.3,-2.12]**
Heterogeneity: Not applicable						

Favours lumacaftor -20 -10 0 10 20 Favours placebo

Study or subgroup	Lumacaftor	Placebo	Mean Dif-ference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Test for overall effect: Z=2.64(P=0.01)						

Favours lumacaftor   -20   -10   0   10   20   Favours placebo

Analysis 1.6. Comparison 1 Lumacaftor versus placebo, Outcome 6 Sweat chloride concentration (mmol/L) (change from baseline).
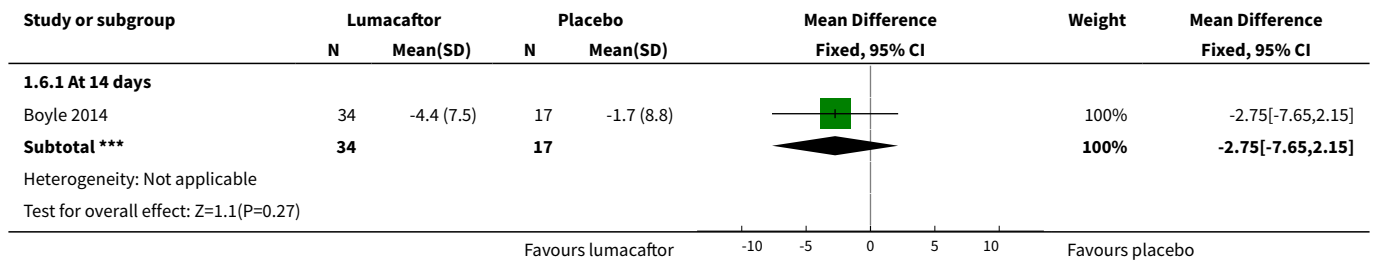
Study or subgroup	Lumacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
1.6.1 At 14 days							
Boyle 2014	34	-4.4 (7.5)	17	-1.7 (8.8)		100%	-2.75[-7.65,2.15]
Subtotal ***	**34**		**17**			**100%**	**-2.75[-7.65,2.15]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							

Favours lumacaftor   -10   -5   0   5   10   Favours placebo

Comparison 2. Cavosonstat (N91115) (200 mg twice daily) versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 CFQR respiratory domain: absolute change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 28 days	1	24	Mean Difference (IV, Fixed, 95% CI)	3.8 [-11.30, 18.90]
2 CFQR eating domain: absolute change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 28 days	1	24	Mean Difference (IV, Fixed, 95% CI)	2.4 [-2.75, 7.55]
3 Adverse events occurring in > 10% of participants	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
3.1 Cough	1	26	Odds Ratio (M-H, Fixed, 99% CI)	1.05 [0.13, 8.17]
3.2 Pulmonary exacerbation	1	26	Odds Ratio (M-H, Fixed, 99% CI)	0.26 [0.00, 20.03]
3.3 Chest discomfort	1	26	Odds Ratio (M-H, Fixed, 99% CI)	5.0 [0.08, 308.20]
3.4 Fatigue	1	26	Odds Ratio (M-H, Fixed, 99% CI)	3.0 [0.13, 71.47]
4 Sweat chloride	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 At 28 days	1	24	Mean Difference (IV, Fixed, 95% CI)	-3.30 [-9.13, 2.53]

Analysis 2.1. Comparison 2 Cavosonstat (N91115) (200 mg twice daily) versus placebo, Outcome 1 CFQR respiratory domain: absolute change from baseline.

Study or subgroup	Cavosonstat 200mg		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
2.1.1 At 28 days							
Donaldson 2017	12	-0.8 (16.6)	12	-4.6 (20.9)		100%	3.8[-11.3,18.9]
Subtotal ***	**12**		**12**			**100%**	**3.8[-11.3,18.9]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.49(P=0.62)							

Favours placebo -100 -50 0 50 100 Favours cavosonstat
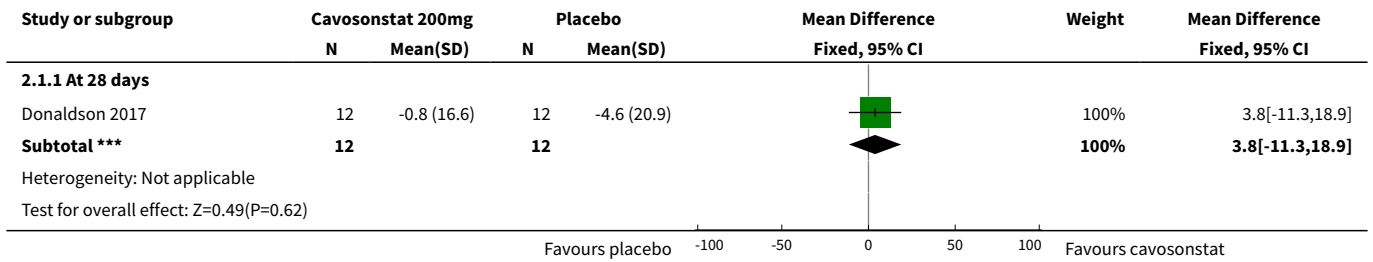
Analysis 2.2. Comparison 2 Cavosonstat (N91115) (200 mg twice daily) versus placebo, Outcome 2 CFQR eating domain: absolute change from baseline.

Study or subgroup	Cavosonstat 200mg		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
2.2.1 At 28 days							
Donaldson 2017	12	2.4 (7.8)	12	0 (4.7)		100%	2.4[-2.75,7.55]
Subtotal ***	**12**		**12**			**100%**	**2.4[-2.75,7.55]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.91(P=0.36)							

Favours placebo -10 -5 0 5 10 Favours cavosonstat
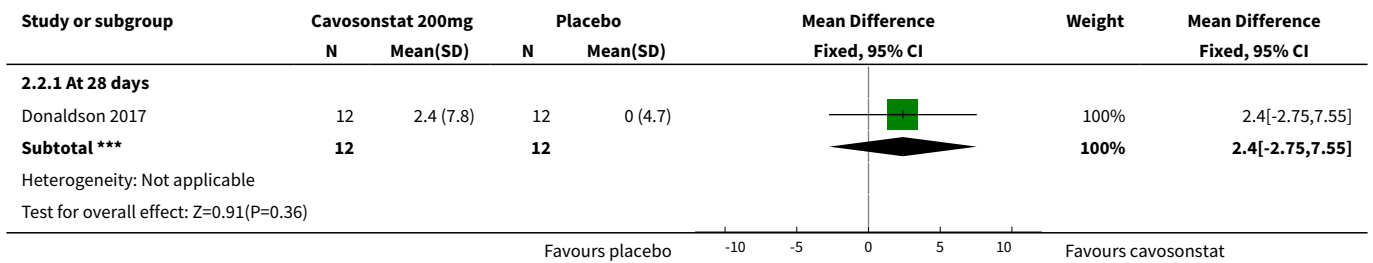
Analysis 2.3. Comparison 2 Cavosonstat (N91115) (200 mg twice daily) versus placebo, Outcome 3 Adverse events occurring in > 10% of participants.

Study or subgroup	Cavoson-stat 200mg	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
2.3.1 Cough					
Donaldson 2017	6/14	5/12		100%	1.05[0.13,8.17]
Subtotal (99% CI)	**14**	**12**		**100%**	**1.05[0.13,8.17]**
Total events: 6 (Cavosonstat 200mg), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					
2.3.2 Pulmonary exacerbation					
Donaldson 2017	0/14	1/12		100%	0.26[0,20.03]
Subtotal (99% CI)	**14**	**12**		**100%**	**0.26[0,20.03]**
Total events: 0 (Cavosonstat 200mg), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					
2.3.3 Chest discomfort					
Donaldson 2017	2/14	0/12		100%	5[0.08,308.2]
Subtotal (99% CI)	**14**	**12**		**100%**	**5[0.08,308.2]**
Total events: 2 (Cavosonstat 200mg), 0 (Placebo)					

Favours lumacaftor 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	Cavoson-stat 200mg	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					
2.3.4 Fatigue					
Donaldson 2017	3/14	1/12		100%	3[0.13,71.47]
Subtotal (99% CI)	**14**	**12**		**100%**	**3[0.13,71.47]**
Total events: 3 (Cavosonstat 200mg), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.89(P=0.37)					

Favours lumacaftor 0.001 0.1 1 10 1000 Favours placebo

Analysis 2.4. Comparison 2 Cavosonstat (N91115) (200 mg twice daily) versus placebo, Outcome 4 Sweat chloride.

Study or subgroup	Cavosonstat 200mg		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
2.4.1 At 28 days							
Donaldson 2017	12	-4.1 (5)	12	-0.8 (9)		100%	-3.3[-9.13,2.53]
Subtotal ***	**12**		**12**			**100%**	**-3.3[-9.13,2.53]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.11(P=0.27)							

Favours cavosonstat -100 -50 0 50 100 Favours placebo

Comparison 3.   N6022 versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 FEV$_1$ % predicted (relative change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 5 mg/day N6022	1	29	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-5.31, 1.31]
1.2 10 mg/day N6022	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.7 [-4.73, 1.33]
1.3 20 mg/day N6022	1	28	Mean Difference (IV, Fixed, 95% CI)	-2.2 [-5.28, 0.88]
1.4 40 mg/day N6022	1	38	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-3.06, 1.06]
2 Treatment-emergent adverse events (mild)	1		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 5 mg/day N6022	1	29	Odds Ratio (M-H, Fixed, 95% CI)	0.48 [0.10, 2.30]

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
2.2 10 mg/day N6022	1	28	Odds Ratio (M-H, Fixed, 95% CI)	1.45 [0.28, 7.64]
2.3 20 mg/day N6022	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.58 [0.12, 2.88]
2.4 40 mg/day N6022	1	38	Odds Ratio (M-H, Fixed, 95% CI)	1.25 [0.34, 4.59]
3 Treatment-emergent adverse events (moderate)	1	123	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.41, 2.04]
3.1 5 mg/day N6022	1	29	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.18, 4.90]
3.2 10 mg/day N6022	1	28	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.20, 5.87]
3.3 20 mg/day N6022	1	28	Odds Ratio (M-H, Fixed, 95% CI)	2.71 [0.53, 13.85]
3.4 40 mg/day N6022	1	38	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.04, 1.48]
4 Treatment-emergent adverse events (serious / severe)	1	123	Odds Ratio (M-H, Fixed, 95% CI)	1.37 [0.35, 5.41]
4.1 5 mg/day N6022	1	29	Odds Ratio (M-H, Fixed, 95% CI)	4.5 [0.35, 57.11]
4.2 10 mg/day N6022	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.02, 17.51]
4.3 20 mg/day N6022	1	28	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.02, 17.51]
4.4 40 mg/day N6022	1	38	Odds Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 17.25]

Analysis 3.1. Comparison 3 N6022 versus placebo, Outcome 1 FEV_1 % predicted (relative change from baseline).

Study or subgroup	N6022 N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.1.1 5 mg/day N6022							
Donaldson 2014	10	-0.5 (4.7)	19	1.5 (3.4)		100%	-2[-5.31,1.31]
Subtotal ***	**10**		**19**			**100%**	**-2[-5.31,1.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.18(P=0.24)							
3.1.2 10 mg/day N6022							
Donaldson 2014	9	-0.2 (4)	19	1.5 (3.4)		100%	-1.7[-4.73,1.33]
Subtotal ***	**9**		**19**			**100%**	**-1.7[-4.73,1.33]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.1(P=0.27)							
3.1.3 20 mg/day N6022							
Donaldson 2014	9	-0.7 (4.1)	19	1.5 (3.4)		100%	-2.2[-5.28,0.88]
Subtotal ***	**9**		**19**			**100%**	**-2.2[-5.28,0.88]**
Heterogeneity: Not applicable							

Favours placebo -5 -2.5 0 2.5 5 Favours N6022

Study or subgroup	N6022		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Test for overall effect: Z=1.4(P=0.16)							
3.1.4 40 mg/day N6022							
Donaldson 2014	19	0.5 (3)	19	1.5 (3.4)		100%	-1[-3.06,1.06]
Subtotal ***	19		19			100%	**-1[-3.06,1.06]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.95(P=0.34)							

Favours placebo -5 -2.5 0 2.5 5 Favours N6022

Analysis 3.2. Comparison 3 N6022 versus placebo, Outcome 2 Treatment-emergent adverse events (mild).

Study or subgroup	N6022	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
3.2.1 5 mg/day N6022					
Donaldson 2014	4/10	11/19		100%	0.48[0.1,2.3]
Subtotal (95% CI)	10	19		100%	**0.48[0.1,2.3]**
Total events: 4 (N6022), 11 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.91(P=0.36)					
3.2.2 10 mg/day N6022					
Donaldson 2014	6/9	11/19		100%	1.45[0.28,7.64]
Subtotal (95% CI)	9	19		100%	**1.45[0.28,7.64]**
Total events: 6 (N6022), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.44(P=0.66)					
3.2.3 20 mg/day N6022					
Donaldson 2014	4/9	11/19		100%	0.58[0.12,2.88]
Subtotal (95% CI)	9	19		100%	**0.58[0.12,2.88]**
Total events: 4 (N6022), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.66(P=0.51)					
3.2.4 40 mg/day N6022					
Donaldson 2014	12/19	11/19		100%	1.25[0.34,4.59]
Subtotal (95% CI)	19	19		100%	**1.25[0.34,4.59]**
Total events: 12 (N6022), 11 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.33(P=0.74)					

Favours N6022 0.01 0.1 1 10 100 Favours placebo

Analysis 3.3. Comparison 3 N6022 versus placebo, Outcome 3 Treatment-emergent adverse events (moderate).

Study or subgroup	N6022	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
3.3.1 5 mg/day N6022					

Favours N6022 0.01 0.1 1 10 100 Favours placebo

Study or subgroup	N6022 n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Donaldson 2014	3/10	6/19		23.08%	0.93[0.18,4.9]
Subtotal (95% CI)	**10**	**19**		**23.08%**	**0.93[0.18,4.9]**

Total events: 3 (N6022), 6 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.09(P=0.93)

3.3.2 10 mg/day N6022

Donaldson 2014	3/9	6/19		20.49%	1.08[0.2,5.87]
Subtotal (95% CI)	**9**	**19**		**20.49%**	**1.08[0.2,5.87]**

Total events: 3 (N6022), 6 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.09(P=0.93)

3.3.3 20 mg/day N6022

Donaldson 2014	5/9	6/19		13.66%	2.71[0.53,13.85]
Subtotal (95% CI)	**9**	**19**		**13.66%**	**2.71[0.53,13.85]**

Total events: 5 (N6022), 6 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

Test for overall effect: Z=1.2(P=0.23)

3.3.4 40 mg/day N6022

Donaldson 2014	2/19	6/19		42.77%	0.25[0.04,1.48]
Subtotal (95% CI)	**19**	**19**		**42.77%**	**0.25[0.04,1.48]**

Total events: 2 (N6022), 6 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=1.53(P=0.13)

Total (95% CI)	**47**	**76**		**100%**	**0.92[0.41,2.04]**

Total events: 13 (N6022), 24 (Placebo)

Heterogeneity: Tau²=0; Chi²=3.77, df=3(P=0.29); I²=20.47%

Test for overall effect: Z=0.22(P=0.83)

Test for subgroup differences: Chi²=3.76, df=1 (P=0.29), I²=20.28%

Favours N6022 0.01 0.1 1 10 100 Favours placebo

Analysis 3.4. Comparison 3 N6022 versus placebo, Outcome 4 Treatment-emergent adverse events (serious / severe).

Study or subgroup	N6022 n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
3.4.1 5 mg/day N6022					
Donaldson 2014	2/10	1/19		16.23%	4.5[0.35,57.11]
Subtotal (95% CI)	**10**	**19**		**16.23%**	**4.5[0.35,57.11]**

Total events: 2 (N6022), 1 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=1.16(P=0.25)

3.4.2 10 mg/day N6022

Donaldson 2014	0/9	1/19		27.95%	0.65[0.02,17.51]
Subtotal (95% CI)	**9**	**19**		**27.95%**	**0.65[0.02,17.51]**

Favours N6022 0.01 0.1 1 10 100 Favours placebo

Study or subgroup	N6022 n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Total events: 0 (N6022), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.8)					
3.4.3 20 mg/day N6022					
Donaldson 2014	0/9	1/19		27.95%	0.65[0.02,17.51]
Subtotal (95% CI)	**9**	**19**		**27.95%**	**0.65[0.02,17.51]**
Total events: 0 (N6022), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.26(P=0.8)					
3.4.4 40 mg/day N6022					
Donaldson 2014	1/19	1/19		27.87%	1[0.06,17.25]
Subtotal (95% CI)	**19**	**19**		**27.87%**	**1[0.06,17.25]**
Total events: 1 (N6022), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**47**	**76**		**100%**	**1.37[0.35,5.41]**
Total events: 3 (N6022), 4 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.28, df=3(P=0.73); I²=0%					
Test for overall effect: Z=0.45(P=0.65)					
Test for subgroup differences: Chi²=1.28, df=1 (P=0.73), I²=0%					

Favours N6022   0.01   0.1   1   10   100   Favours placebo

Comparison 4. CPX versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Adverse events occurring in more than 3% of participants in all treatment groups (combined data) versus placebo	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
1.1 Abdominal pain	1	37	Odds Ratio (M-H, Fixed, 99% CI)	0.45 [0.01, 24.92]
1.2 Asthenia	1	37	Odds Ratio (M-H, Fixed, 99% CI)	0.65 [0.01, 39.69]
1.3 Headache	1	37	Odds Ratio (M-H, Fixed, 99% CI)	0.33 [0.01, 17.72]
1.4 Pain	1	37	Odds Ratio (M-H, Fixed, 99% CI)	0.45 [0.01, 24.92]
1.5 Diarrhoea	1	37	Odds Ratio (M-H, Fixed, 99% CI)	0.65 [0.01, 39.69]
1.6 Dizziness	1	37	Odds Ratio (M-H, Fixed, 99% CI)	9.33 [0.32, 268.92]
1.7 Lung disease	1	37	Odds Ratio (M-H, Fixed, 99% CI)	0.45 [0.01, 24.92]
1.8 Rhinitis	1	37	Odds Ratio (M-H, Fixed, 99% CI)	0.45 [0.01, 24.92]

Analysis 4.1. Comparison 4 CPX versus placebo, Outcome 1 Adverse events occurring in more than 3% of participants in all treatment groups (combined data) versus placebo.

Study or subgroup	CPX n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
4.1.1 Abdominal pain					
McCarty 2002	0/8	3/29		100%	0.45[0.01,24.92]
Subtotal (99% CI)	**8**	**29**		**100%**	**0.45[0.01,24.92]**
Total events: 0 (CPX), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					
4.1.2 Asthenia					
McCarty 2002	0/8	2/29		100%	0.65[0.01,39.69]
Subtotal (99% CI)	**8**	**29**		**100%**	**0.65[0.01,39.69]**
Total events: 0 (CPX), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					
4.1.3 Headache					
McCarty 2002	0/8	4/29		100%	0.33[0.01,17.72]
Subtotal (99% CI)	**8**	**29**		**100%**	**0.33[0.01,17.72]**
Total events: 0 (CPX), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					
4.1.4 Pain					
McCarty 2002	0/8	3/29		100%	0.45[0.01,24.92]
Subtotal (99% CI)	**8**	**29**		**100%**	**0.45[0.01,24.92]**
Total events: 0 (CPX), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					
4.1.5 Diarrhoea					
McCarty 2002	0/8	2/29		100%	0.65[0.01,39.69]
Subtotal (99% CI)	**8**	**29**		**100%**	**0.65[0.01,39.69]**
Total events: 0 (CPX), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.79)					
4.1.6 Dizziness					
McCarty 2002	2/8	1/29		100%	9.33[0.32,268.92]
Subtotal (99% CI)	**8**	**29**		**100%**	**9.33[0.32,268.92]**
Total events: 2 (CPX), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.71(P=0.09)					
4.1.7 Lung disease					
McCarty 2002	0/8	3/29		100%	0.45[0.01,24.92]
Subtotal (99% CI)	**8**	**29**		**100%**	**0.45[0.01,24.92]**
Total events: 0 (CPX), 3 (Placebo)					
Heterogeneity: Not applicable					

Favours CPX 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	CPX n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
Test for overall effect: Z=0.52(P=0.6)					
4.1.8 Rhinitis					
McCarty 2002	0/8	3/29		100%	0.45[0.01,24.92]
Subtotal (99% CI)	**8**	**29**		**100%**	**0.45[0.01,24.92]**
Total events: 0 (CPX), 3 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.52(P=0.6)					

Favours CPX 0.001 0.1 1 10 1000 Favours placebo

Comparison 5. 4PBA versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Adverse effects after 1 week	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
1.1 Bad taste in mouth	1	18	Odds Ratio (M-H, Fixed, 99% CI)	0.44 [0.01, 13.44]
1.2 Diarrhoea	1	18	Odds Ratio (M-H, Fixed, 99% CI)	3.35 [0.04, 267.31]
2 Participants requiring study drug termination or a reduced dosage	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.1 30 g 4PBA	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 5.1. Comparison 5 4PBA versus placebo, Outcome 1 Adverse effects after 1 week.

Study or subgroup	4PBA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
5.1.1 Bad taste in mouth					
Rubenstein 1998	1/9	2/9		100%	0.44[0.01,13.44]
Subtotal (99% CI)	**9**	**9**		**100%**	**0.44[0.01,13.44]**
Total events: 1 (4PBA), 2 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.62(P=0.53)					
5.1.2 Diarrhoea					
Rubenstein 1998	1/9	0/9		100%	3.35[0.04,267.31]
Subtotal (99% CI)	**9**	**9**		**100%**	**3.35[0.04,267.31]**
Total events: 1 (4PBA), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.71(P=0.48)					

Favours 4PBA 0.002 0.1 1 10 500 Favours placebo

Analysis 5.2. Comparison 5 4PBA versus placebo, Outcome 2 Participants requiring study drug termination or a reduced dosage.

Study or subgroup	4PBA n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
5.2.1 30 g 4PBA				
Zeitlin 2002	2/6	0/4		5[0.18,136.32]

Favours 4PBA 0.001 0.1 1 10 1000 Favours placebo

Comparison 6. Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Quality of life - Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 6 months	2	715	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.01, 0.02]
2 Quality of life - CFQ-R respiratory domain (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 28 days	2	739	Mean Difference (IV, Fixed, 95% CI)	3.32 [1.13, 5.51]
2.2 At 6 months	2	725	Mean Difference (IV, Fixed, 95% CI)	3.04 [0.76, 5.32]
3 Quality of life - EQ-5D-3L VAS Score (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 6 months	2	712	Mean Difference (IV, Fixed, 95% CI)	2.24 [0.18, 4.31]
4 FEV_1 % predicted (relative change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 At 6 months	2	720	Mean Difference (IV, Fixed, 95% CI)	5.63 [3.80, 7.47]
5 FEV_1 % predicted (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 At 28 days	2	739	Mean Difference (IV, Fixed, 95% CI)	2.32 [1.34, 3.31]
5.2 At 6 months	2	720	Mean Difference (IV, Fixed, 95% CI)	3.34 [2.30, 4.38]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Adverse events by end of study (at 6 months)	2		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
6.1 Any adverse event	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.00 [0.37, 2.71]
6.2 Discontinuation due to an adverse event	2	739	Odds Ratio (M-H, Fixed, 99% CI)	2.38 [0.67, 8.50]
6.3 At least 1 serious adverse event	2	739	Odds Ratio (M-H, Fixed, 99% CI)	0.73 [0.47, 1.13]
6.4 Infective pulmonary exacerbation	2	739	Odds Ratio (M-H, Fixed, 99% CI)	0.66 [0.45, 0.97]
6.5 Cough	2	739	Odds Ratio (M-H, Fixed, 99% CI)	0.72 [0.49, 1.08]
6.6 Headache	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.00 [0.59, 1.68]
6.7 Haemoptysis	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.04 [0.60, 1.81]
6.8 Diarrhoea	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.18 [0.61, 2.28]
6.9 Abnormal respiration	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.91 [0.94, 3.88]
6.10 Increased sputum	2	739	Odds Ratio (M-H, Fixed, 99% CI)	0.74 [0.44, 1.24]
6.11 Dyspnoea	2	739	Odds Ratio (M-H, Fixed, 99% CI)	2.05 [1.10, 3.83]
6.12 Nasopharyngitis	2	739	Odds Ratio (M-H, Fixed, 99% CI)	0.55 [0.27, 1.10]
6.13 Oropharyngeal pain	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.52 [0.80, 2.89]
6.14 Abdominal pain	2	739	Odds Ratio (M-H, Fixed, 99% CI)	0.80 [0.39, 1.62]
6.15 Fatigue	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.03 [0.51, 2.08]
6.16 Nausea	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.04 [0.51, 2.11]
6.17 Pyrexia	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.03 [0.54, 1.98]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.18 Nasal congestion	2	739	Odds Ratio (M-H, Fixed, 99% CI)	0.73 [0.39, 1.35]
6.19 Upper respiratory tract infection	2	739	Odds Ratio (M-H, Fixed, 99% CI)	1.21 [0.54, 2.70]
7 Time to first pulmonary exacerbation	2	739	Hazard Ratio (Fixed, 95% CI)	0.70 [0.57, 0.87]
8 Rate of exacerbations	2	739	Rate Ratio (Fixed, 95% CI)	0.70 [0.57, 0.87]
9 Weight (kg) (absolute change from base-line)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 At 6 months	2	725	Mean Difference (IV, Fixed, 95% CI)	0.80 [0.42, 1.18]
10 BMI (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 At 28 days	2	739	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.07, 0.09]
10.2 At 6 months	2	725	Mean Difference (IV, Fixed, 95% CI)	0.29 [0.16, 0.43]

Analysis 6.1.   Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 1 Quality of life - Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
6.1.1 At 6 months							
TRAFFIC 2015	175	0 (0.1)	179	0 (0.1)		44.96%	0.01[-0.01,0.03]
TRANSPORT 2015	178	0 (0.1)	183	0 (0.1)		55.04%	-0[-0.02,0.02]
Subtotal ***	**353**		**362**			**100%**	**0[-0.01,0.02]**
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.54); I²=0%							
Test for overall effect: Z=0.17(P=0.86)							

Favours placebo   -0.05 -0.025   0   0.025 0.05   Favours lumacaftor-ivacaftor
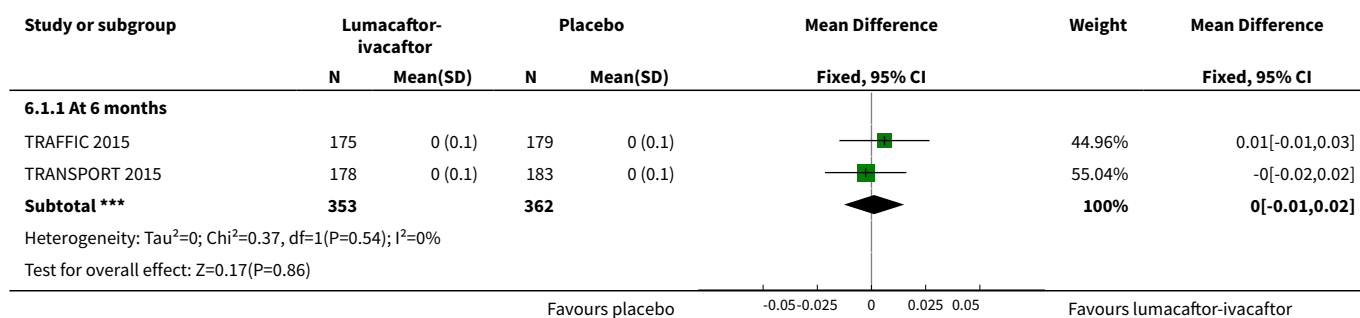
Analysis 6.2.   Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 2 Quality of life - CFQ-R respiratory domain (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
6.2.1 At 28 days							

Favours placebo   -20   -10   0   10   20   Favours lumacaftor-ivacaftor

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
TRAFFIC 2015	183	4 (15.2)	184	3 (14.5)		51.7%	1[-2.04,4.04]
TRANSPORT 2015	185	6.8 (15.3)	187	1 (15.7)		48.3%	5.8[2.65,8.95]
Subtotal ***	368		371			100%	3.32[1.13,5.51]
Heterogeneity: Tau²=0; Chi²=4.62, df=1(P=0.03); I²=78.36%							
Test for overall effect: Z=2.97(P=0)							
6.2.2 At 6 months							
TRAFFIC 2015	176	5 (15.6)	184	1.1 (15.7)		49.57%	3.88[0.64,7.12]
TRANSPORT 2015	180	5 (15.6)	185	2.8 (15.7)		50.43%	2.21[-1,5.42]
Subtotal ***	356		369			100%	3.04[0.76,5.32]
Heterogeneity: Tau²=0; Chi²=0.51, df=1(P=0.47); I²=0%							
Test for overall effect: Z=2.61(P=0.01)							

Favours placebo -20 -10 0 10 20 Favours lumacaftor-ivacaftor

Analysis 6.3. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 3 Quality of life - EQ-5D-3L VAS Score (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
6.3.1 At 6 months							
TRAFFIC 2015	173	3.5 (13.7)	180	1.4 (13.8)		51.9%	2.1[-0.77,4.97]
TRANSPORT 2015	177	5.7 (14.4)	182	3.3 (14.4)		48.1%	2.4[-0.58,5.38]
Subtotal ***	350		362			100%	2.24[0.18,4.31]
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.89); I²=0%							
Test for overall effect: Z=2.13(P=0.03)							

Favours placebo -5 -2.5 0 2.5 5 Favours lumacaftor-ivacaftor
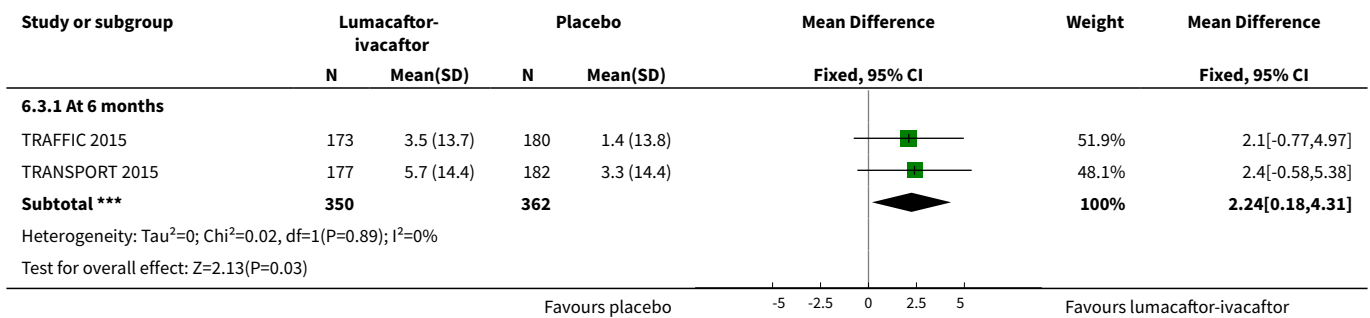
Analysis 6.4. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 4 FEV$_1$ % predicted (relative change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
6.4.1 At 6 months							
TRAFFIC 2015	176	6.4 (12.1)	180	-0.3 (12.2)		52.51%	6.73[4.2,9.26]
TRANSPORT 2015	181	4.4 (12.9)	183	0 (13)		47.49%	4.42[1.76,7.08]
Subtotal ***	357		363			100%	5.63[3.8,7.47]
Heterogeneity: Tau²=0; Chi²=1.52, df=1(P=0.22); I²=34.15%							
Test for overall effect: Z=6.02(P<0.0001)							

Favours placebo -10 -5 0 5 10 Favours lumacaftor-ivacaftor
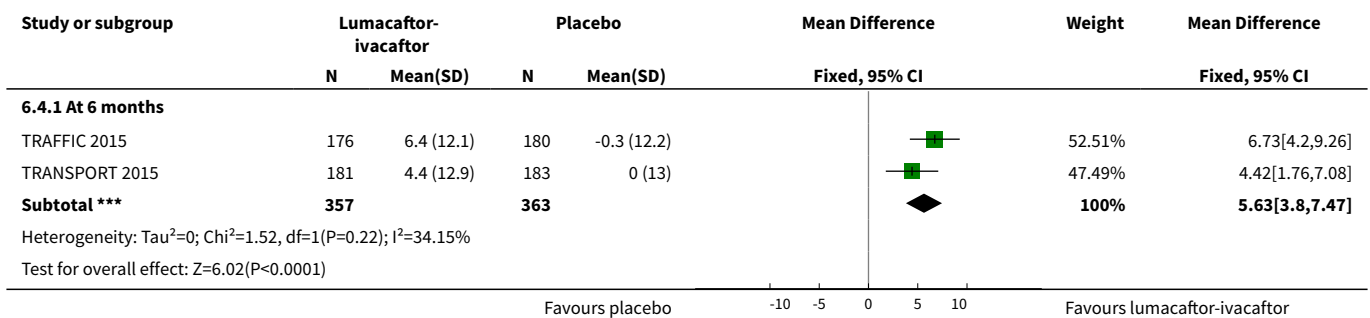
Analysis 6.5. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 5 FEV$_1$ % predicted (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
6.5.1 At 28 days							
TRAFFIC 2015	183	2.5 (7.6)	184	0 (7.6)		40.1%	2.5[0.94,4.06]
TRANSPORT 2015	185	2.5 (6.2)	187	0.3 (6.3)		59.9%	2.2[0.93,3.47]
Subtotal ***	**368**		**371**			**100%**	**2.32[1.34,3.31]**
Heterogeneity: Tau²=0; Chi²=0.09, df=1(P=0.77); I²=0%							
Test for overall effect: Z=4.62(P<0.0001)							
6.5.2 At 6 months							
TRAFFIC 2015	176	3.6 (7)	180	-0.4 (7)		51.41%	4.03[2.58,5.48]
TRANSPORT 2015	181	2.5 (7.3)	183	-0.1 (7.3)		48.59%	2.61[1.11,4.11]
Subtotal ***	**357**		**363**			**100%**	**3.34[2.3,4.38]**
Heterogeneity: Tau²=0; Chi²=1.78, df=1(P=0.18); I²=43.84%							
Test for overall effect: Z=6.28(P<0.0001)							

Favours placebo   -5   -2.5   0   2.5   5   Favours lumacaftor-ivacaftor

Analysis 6.6. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 6 Adverse events by end of study (at 6 months).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
6.6.1 Any adverse event					
TRAFFIC 2015	175/184	174/183		63.69%	1.01[0.29,3.49]
TRANSPORT 2015	181/186	181/186		36.31%	1[0.19,5.21]
Subtotal (99% CI)	**370**	**369**		**100%**	**1[0.37,2.71]**
Total events: 356 (Lumacaftor-ivacaftor), 355 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0%					
Test for overall effect: Z=0.01(P=0.99)					
6.6.2 Discontinuation due to an adverse event					
TRAFFIC 2015	8/184	4/183		66.47%	2.03[0.41,10.08]
TRANSPORT 2015	6/186	2/186		33.53%	3.07[0.37,25.56]
Subtotal (99% CI)	**370**	**369**		**100%**	**2.38[0.67,8.5]**
Total events: 14 (Lumacaftor-ivacaftor), 6 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%					
Test for overall effect: Z=1.76(P=0.08)					
6.6.3 At least 1 serious adverse event					
TRAFFIC 2015	33/184	49/183		49.36%	0.6[0.31,1.15]
TRANSPORT 2015	51/186	57/186		50.64%	0.85[0.47,1.54]
Subtotal (99% CI)	**370**	**369**		**100%**	**0.73[0.47,1.13]**
Total events: 84 (Lumacaftor-ivacaftor), 106 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.09, df=1(P=0.3); I²=8.66%					
Test for overall effect: Z=1.87(P=0.06)					
6.6.4 Infective pulmonary exacerbation					

Favours lumacaftor-ivacaftor   0.1   0.2   0.5   1   2   5   10   Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
TRAFFIC 2015	65/184	87/183		51.03%	0.6[0.35,1.05]
TRANSPORT 2015	80/186	95/186		48.97%	0.72[0.42,1.24]
Subtotal (99% CI)	**370**	**369**		**100%**	**0.66[0.45,0.97]**
Total events: 145 (Lumacaftor-ivacaftor), 182 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.37, df=1(P=0.54); I²=0%					
Test for overall effect: Z=2.77(P=0.01)					

6.6.5 Cough

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
TRAFFIC 2015	52/184	66/183		47.93%	0.7[0.39,1.25]
TRANSPORT 2015	69/186	82/186		52.07%	0.75[0.43,1.29]
Subtotal (99% CI)	**370**	**369**		**100%**	**0.72[0.49,1.08]**
Total events: 121 (Lumacaftor-ivacaftor), 148 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.05, df=1(P=0.82); I²=0%					
Test for overall effect: Z=2.09(P=0.04)					

6.6.6 Headache

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
TRAFFIC 2015	28/184	25/183		43.44%	1.13[0.53,2.44]
TRANSPORT 2015	30/186	33/186		56.56%	0.89[0.44,1.82]
Subtotal (99% CI)	**370**	**369**		**100%**	**1[0.59,1.68]**
Total events: 58 (Lumacaftor-ivacaftor), 58 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.35, df=1(P=0.55); I²=0%					
Test for overall effect: Z=0.01(P=0.99)					

6.6.7 Haemoptysis

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
TRAFFIC 2015	22/184	24/183		49.28%	0.9[0.4,2.03]
TRANSPORT 2015	30/186	26/186		50.72%	1.18[0.56,2.5]
Subtotal (99% CI)	**370**	**369**		**100%**	**1.04[0.6,1.81]**
Total events: 52 (Lumacaftor-ivacaftor), 50 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.41, df=1(P=0.52); I²=0%					
Test for overall effect: Z=0.2(P=0.84)					

6.6.8 Diarrhoea

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
TRAFFIC 2015	16/184	13/183		42.56%	1.25[0.46,3.39]
TRANSPORT 2015	20/186	18/186		57.44%	1.12[0.46,2.72]
Subtotal (99% CI)	**370**	**369**		**100%**	**1.18[0.61,2.28]**
Total events: 36 (Lumacaftor-ivacaftor), 31 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%					
Test for overall effect: Z=0.63(P=0.53)					

6.6.9 Abnormal respiration

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
TRAFFIC 2015	26/184	9/183		39.2%	3.18[1.13,8.96]
TRANSPORT 2015	14/186	13/186		60.8%	1.08[0.39,3.03]
Subtotal (99% CI)	**370**	**369**		**100%**	**1.91[0.94,3.88]**
Total events: 40 (Lumacaftor-ivacaftor), 22 (Placebo)					
Heterogeneity: Tau²=0; Chi²=3.62, df=1(P=0.06); I²=72.38%					
Test for overall effect: Z=2.34(P=0.02)					

6.6.10 Increased sputum

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
TRAFFIC 2015	15/184	23/183		36.47%	0.62[0.25,1.52]
TRANSPORT 2015	40/186	47/186		63.53%	0.81[0.43,1.53]
Subtotal (99% CI)	**370**	**369**		**100%**	**0.74[0.44,1.24]**

Favours lumacaftor-ivacaftor 0.1 0.2 0.5 1 2 5 10 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI

Total events: 55 (Lumacaftor-ivacaftor), 70 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.4, df=1(P=0.52); I²=0%

Test for overall effect: Z=1.5(P=0.13)

6.6.11 Dyspnoea

TRAFFIC 2015	22/184	14/183		50.04%	1.64[0.65,4.13]
TRANSPORT 2015	33/186	15/186		49.96%	2.46[1.05,5.76]
Subtotal (99% CI)	370	369		100%	2.05[1.1,3.83]

Total events: 55 (Lumacaftor-ivacaftor), 29 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.69, df=1(P=0.41); I²=0%

Test for overall effect: Z=2.96(P=0)

6.6.12 Nasopharyngitis

TRAFFIC 2015	9/184	20/183		50.77%	0.42[0.14,1.22]
TRANSPORT 2015	14/186	20/186		49.23%	0.68[0.26,1.73]
Subtotal (99% CI)	370	369		100%	0.55[0.27,1.1]

Total events: 23 (Lumacaftor-ivacaftor), 40 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.74, df=1(P=0.39); I²=0%

Test for overall effect: Z=2.22(P=0.03)

6.6.13 Oropharyngeal pain

TRAFFIC 2015	24/184	10/183		32.82%	2.6[0.95,7.12]
TRANSPORT 2015	20/186	20/186		67.18%	1[0.42,2.37]
Subtotal (99% CI)	370	369		100%	1.52[0.8,2.89]

Total events: 44 (Lumacaftor-ivacaftor), 30 (Placebo)

Heterogeneity: Tau²=0; Chi²=3.43, df=1(P=0.06); I²=70.82%

Test for overall effect: Z=1.69(P=0.09)

6.6.14 Abdominal pain

TRAFFIC 2015	11/184	12/183		38.09%	0.91[0.3,2.75]
TRANSPORT 2015	15/186	20/186		61.91%	0.73[0.29,1.83]
Subtotal (99% CI)	370	369		100%	0.8[0.39,1.62]

Total events: 26 (Lumacaftor-ivacaftor), 32 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.15, df=1(P=0.7); I²=0%

Test for overall effect: Z=0.83(P=0.41)

6.6.15 Fatigue

TRAFFIC 2015	17/184	19/183		65.02%	0.88[0.36,2.17]
TRANSPORT 2015	13/186	10/186		34.98%	1.32[0.43,4.05]
Subtotal (99% CI)	370	369		100%	1.03[0.51,2.08]

Total events: 30 (Lumacaftor-ivacaftor), 29 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.54, df=1(P=0.46); I²=0%

Test for overall effect: Z=0.12(P=0.9)

6.6.16 Nausea

TRAFFIC 2015	9/184	11/183		40.88%	0.8[0.24,2.64]
TRANSPORT 2015	20/186	17/186		59.12%	1.2[0.49,2.93]
Subtotal (99% CI)	370	369		100%	1.04[0.51,2.11]

Total events: 29 (Lumacaftor-ivacaftor), 28 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.47, df=1(P=0.49); I²=0%

Test for overall effect: Z=0.13(P=0.9)

Favours lumacaftor-ivacaftor   0.1 0.2   0.5   1   2   5   10   Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
6.6.17 Pyrexia					
TRAFFIC 2015	12/184	12/183		36.85%	0.99[0.34,2.95]
TRANSPORT 2015	23/186	22/186		63.15%	1.05[0.46,2.39]
Subtotal (99% CI)	**370**	**369**		**100%**	**1.03[0.54,1.98]**
Total events: 35 (Lumacaftor-ivacaftor), 34 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%					
Test for overall effect: Z=0.12(P=0.91)					
6.6.18 Nasal congestion					
TRAFFIC 2015	9/184	25/183		59.03%	0.33[0.11,0.92]
TRANSPORT 2015	24/186	19/186		40.97%	1.3[0.56,3.02]
Subtotal (99% CI)	**370**	**369**		**100%**	**0.73[0.39,1.35]**
Total events: 33 (Lumacaftor-ivacaftor), 44 (Placebo)					
Heterogeneity: Tau²=0; Chi²=7.17, df=1(P=0.01); I²=86.04%					
Test for overall effect: Z=1.33(P=0.18)					
6.6.19 Upper respiratory tract infection					
TRAFFIC 2015	16/184	10/183		48.89%	1.65[0.56,4.83]
TRANSPORT 2015	8/186	10/186		51.11%	0.79[0.23,2.77]
Subtotal (99% CI)	**370**	**369**		**100%**	**1.21[0.54,2.7]**
Total events: 24 (Lumacaftor-ivacaftor), 20 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.31, df=1(P=0.25); I²=23.76%					
Test for overall effect: Z=0.61(P=0.54)					

Favours lumacaftor-ivacaftor 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 6.7. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 7 Time to first pulmonary exacerbation.

Study or subgroup	Lumacaftor-ivacaftor	Placebo	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
TRAFFIC 2015	183	184	-0.4 (0.16)		46.78%	0.69[0.51,0.95]
TRANSPORT 2015	185	187	-0.3 (0.15)		53.22%	0.72[0.53,0.96]
Total (95% CI)					**100%**	**0.7[0.57,0.87]**
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.88); I²=0%						
Test for overall effect: Z=3.2(P=0)						

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

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Analysis 6.8. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 8 Rate of exacerbations.

Study or subgroup	Lumacaftor-ivacaftor	Placebo	log[Rate Ratio]	Rate Ratio	Weight	Rate Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
TRAFFIC 2015	183	184	-0.3 (0.168)		43.2%	0.72[0.52,1]
TRANSPORT 2015	185	187	-0.4 (0.147)		56.8%	0.69[0.52,0.92]
Total (95% CI)					**100%**	**0.7[0.57,0.87]**
Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.86); I²=0%						
Test for overall effect: Z=3.19(P=0)						

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Analysis 6.9. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 9 Weight (kg) (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
6.9.1 At 6 months							
TRAFFIC 2015	178	1.3 (2.7)	184	0.9 (2.7)		45.91%	0.41[-0.15,0.97]
TRANSPORT 2015	180	1.6 (2.5)	183	0.4 (2.5)		54.09%	1.13[0.61,1.65]
Subtotal ***	**358**		**367**			**100%**	**0.8[0.42,1.18]**
Heterogeneity: Tau²=0; Chi²=3.39, df=1(P=0.07); I²=70.46%							
Test for overall effect: Z=4.1(P<0.0001)							

Favours placebo -2 -1 0 1 2 Favours lumacaftor-ivacaftor

Analysis 6.10. Comparison 6 Lumacaftor (600 mg once daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 10 BMI (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
6.10.1 At 28 days							
TRAFFIC 2015	183	0.1 (0.6)	184	0.1 (0.5)		46.5%	0.03[-0.08,0.14]
TRANSPORT 2015	185	0.1 (0.5)	187	0.1 (0.6)		53.5%	-0.01[-0.12,0.1]
Subtotal ***	**368**		**371**			**100%**	**0.01[-0.07,0.09]**
Heterogeneity: Tau²=0; Chi²=0.25, df=1(P=0.62); I²=0%							
Test for overall effect: Z=0.22(P=0.83)							
6.10.2 At 6 months							
TRAFFIC 2015	178	0.4 (0.9)	184	0.2 (0.9)		47.06%	0.16[-0.03,0.35]
TRANSPORT 2015	180	0.5 (0.9)	183	0.1 (0.9)		52.94%	0.41[0.23,0.59]
Subtotal ***	**358**		**367**			**100%**	**0.29[0.16,0.43]**
Heterogeneity: Tau²=0; Chi²=3.38, df=1(P=0.07); I²=70.38%							
Test for overall effect: Z=4.3(P<0.0001)							

Favours placebo -0.5 -0.25 0 0.25 0.5 Favours lumacaftor-ivacaftor

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Comparison 7. Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life - Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 6 months	2	708	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.01, 0.02]
2 Quality of life - CFQ-R respiratory domain (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 28 days	2	740	Mean Difference (IV, Fixed, 95% CI)	4.13 [1.94, 6.31]
2.2 At 6 months	2	720	Mean Difference (IV, Fixed, 95% CI)	2.18 [-0.11, 4.47]
3 Quality of life - EQ-5D-3L VAS Score (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 6 months	2	710	Mean Difference (IV, Fixed, 95% CI)	2.30 [0.25, 4.36]
4 FEV_1 % predicted (relative change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 At 6 months	2	715	Mean Difference (IV, Fixed, 95% CI)	4.77 [2.93, 6.61]
5 FEV_1 % predicted (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 At 28 days	2	740	Mean Difference (IV, Fixed, 95% CI)	2.42 [1.43, 3.40]
5.2 At 6 months	2	715	Mean Difference (IV, Fixed, 95% CI)	2.80 [1.75, 3.84]
6 Adverse events by end of study (at 6 months)	2		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
6.1 Any adverse event	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.77 [0.30, 1.96]
6.2 Discontinuation due to an adverse event	2	738	Odds Ratio (M-H, Fixed, 99% CI)	2.91 [0.85, 10.03]
6.3 At least 1 serious adverse event	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.52 [0.33, 0.83]
6.4 Infective pulmonary exacerbation	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.57 [0.39, 0.84]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
6.5 Cough	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.58 [0.39, 0.88]
6.6 Headache	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.00 [0.59, 1.68]
6.7 Haemoptysis	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.00 [0.58, 1.74]
6.8 Diarrhoea	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.51 [0.80, 2.85]
6.9 Abnormal respiration	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.50 [0.71, 3.14]
6.10 Increased sputum	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.73 [0.44, 1.22]
6.11 Dyspnea	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.75 [0.93, 3.32]
6.12 Nasopharyngitis	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.23 [0.68, 2.21]
6.13 Oropharyngeal pain	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.78 [0.38, 1.63]
6.14 Abdominal pain	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.03 [0.53, 2.01]
6.15 Fatigue	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.19 [0.60, 2.35]
6.16 Nausea	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.74 [0.91, 3.34]
6.17 Pyrexia	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.97 [0.50, 1.87]
6.18 Nasal congestion	2	738	Odds Ratio (M-H, Fixed, 99% CI)	0.51 [0.26, 1.02]
6.19 Upper respiratory tract infection	2	738	Odds Ratio (M-H, Fixed, 99% CI)	1.94 [0.93, 4.08]
7 Time to first pulmonary exacerbation	2	740	Hazard Ratio (Fixed, 95% CI)	0.61 [0.49, 0.76]
8 Rate of exacerbations	2	740	Rate Ratio (Fixed, 95% CI)	0.61 [0.49, 0.76]
9 Weight (kg) (absolute change from base-line)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
9.1 At 6 months	2	723	Mean Difference (IV, Fixed, 95% CI)	0.65 [0.27, 1.03]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
10 BMI (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
10.1 At 28 days	2	740	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.06, 0.10]
10.2 At 6 months	2	723	Mean Difference (IV, Fixed, 95% CI)	0.25 [0.12, 0.39]

Analysis 7.1. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 1 Quality of life - Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
7.1.1 At 6 months							
TRAFFIC 2015	170	0 (0.1)	179	0 (0.1)		45.08%	0.01[-0.01,0.03]
TRANSPORT 2015	176	0 (0.1)	183	0 (0.1)		54.92%	-0[-0.02,0.02]
Subtotal ***	346		362			100%	0[-0.01,0.02]
Heterogeneity: Tau²=0; Chi²=0.52, df=1(P=0.47); I²=0%							
Test for overall effect: Z=0.53(P=0.6)							

Favours placebo   -0.05 -0.025   0   0.025   0.05   Favours lumacaftor-ivacaftor

Analysis 7.2. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 2 Quality of life - CFQ-R respiratory domain (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
7.2.1 At 28 days							
TRAFFIC 2015	182	5 (15.1)	184	3 (14.5)		51.7%	2[-1.04,5.04]
TRANSPORT 2015	187	7.4 (15.3)	187	1 (15.7)		48.3%	6.4[3.25,9.55]
Subtotal ***	369		371			100%	4.13[1.94,6.31]
Heterogeneity: Tau²=0; Chi²=3.88, df=1(P=0.05); I²=74.25%							
Test for overall effect: Z=3.7(P=0)							
7.2.2 At 6 months							
TRAFFIC 2015	172	2.6 (15.6)	184	1.1 (15.7)		49.33%	1.5[-1.76,4.76]
TRANSPORT 2015	179	5.7 (15.6)	185	2.8 (15.7)		50.67%	2.85[-0.37,6.07]
Subtotal ***	351		369			100%	2.18[-0.11,4.47]
Heterogeneity: Tau²=0; Chi²=0.33, df=1(P=0.56); I²=0%							
Test for overall effect: Z=1.87(P=0.06)							

Favours placebo   -5   -2.5   0   2.5   5   Favours lumacaftor-ivacaftor

Analysis 7.3. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 3 Quality of life - EQ-5D-3L VAS Score (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
7.3.1 At 6 months							
TRAFFIC 2015	171	2.8 (13.3)	180	1.4 (13.8)		52.38%	1.4[-1.44,4.24]
TRANSPORT 2015	177	6.6 (14.4)	182	3.3 (14.4)		47.62%	3.3[0.32,6.28]
Subtotal ***	**348**		**362**			**100%**	**2.3[0.25,4.36]**
Heterogeneity: Tau²=0; Chi²=0.82, df=1(P=0.37); I²=0%							
Test for overall effect: Z=2.2(P=0.03)							

Favours placebo   -5   -2.5   0   2.5   5   Favours lumacaftor-ivacaftor
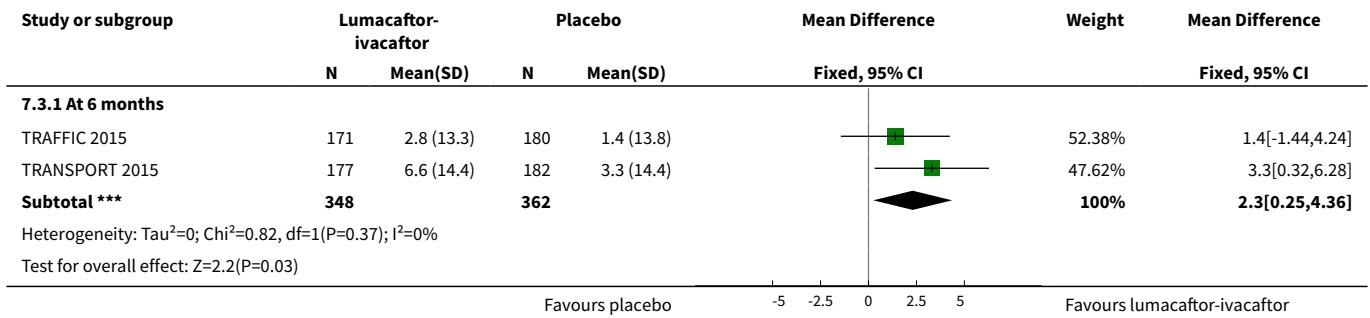
Analysis 7.4. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 4 FEV₁ % predicted (relative change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
7.4.1 At 6 months							
TRAFFIC 2015	172	4 (12.1)	180	-0.3 (12.2)		52.26%	4.33[1.79,6.87]
TRANSPORT 2015	180	5.3 (12.9)	183	0 (13)		47.74%	5.25[2.59,7.91]
Subtotal ***	**352**		**363**			**100%**	**4.77[2.93,6.61]**
Heterogeneity: Tau²=0; Chi²=0.24, df=1(P=0.62); I²=0%							
Test for overall effect: Z=5.08(P<0.0001)							

Favours placebo   -10   -5   0   5   10   Favours lumacaftor-ivacaftor
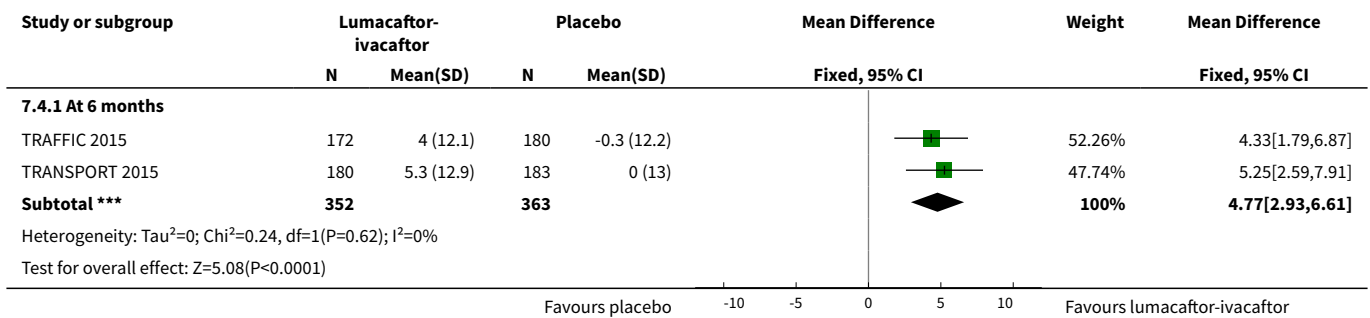
Analysis 7.5. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 5 FEV₁ % predicted (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
7.5.1 At 28 days							
TRAFFIC 2015	182	2.3 (7.6)	184	0 (7.6)		40.1%	2.3[0.74,3.86]
TRANSPORT 2015	187	2.8 (6.3)	187	0.3 (6.3)		59.9%	2.5[1.23,3.77]
Subtotal ***	**369**		**371**			**100%**	**2.42[1.43,3.4]**
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.85); I²=0%							
Test for overall effect: Z=4.81(P<0.0001)							
7.5.2 At 6 months							
TRAFFIC 2015	172	2.2 (7)	180	-0.4 (7)		51.17%	2.6[1.14,4.06]
TRANSPORT 2015	180	2.9 (7.2)	183	-0.1 (7.3)		48.83%	3[1.5,4.5]
Subtotal ***	**352**		**363**			**100%**	**2.8[1.75,3.84]**
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.71); I²=0%							
Test for overall effect: Z=5.24(P<0.0001)							

Favours placebo   -5   -2.5   0   2.5   5   Favours lumacaftor-ivacaftor

Analysis 7.6. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 6 Adverse events by end of study (at 6 months).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
7.6.1 Any adverse event					
TRAFFIC 2015	174/182	174/183		44.01%	1.13[0.31,4.05]
TRANSPORT 2015	177/187	181/186		55.99%	0.49[0.12,2.06]
Subtotal (99% CI)	**369**	**369**		**100%**	**0.77[0.3,1.96]**
Total events: 351 (Lumacaftor-ivacaftor), 355 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.24, df=1(P=0.26); I²=19.59%					
Test for overall effect: Z=0.72(P=0.47)					
7.6.2 Discontinuation due to an adverse event					
TRAFFIC 2015	6/182	4/183		67.15%	1.53[0.28,8.23]
TRANSPORT 2015	11/187	2/186		32.85%	5.75[0.78,42.43]
Subtotal (99% CI)	**369**	**369**		**100%**	**2.91[0.85,10.03]**
Total events: 17 (Lumacaftor-ivacaftor), 6 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.75, df=1(P=0.19); I²=42.72%					
Test for overall effect: Z=2.23(P=0.03)					
7.6.3 At least 1 serious adverse event					
TRAFFIC 2015	33/182	49/183		45.62%	0.61[0.31,1.17]
TRANSPORT 2015	31/187	57/186		54.38%	0.45[0.23,0.86]
Subtotal (99% CI)	**369**	**369**		**100%**	**0.52[0.33,0.83]**
Total events: 64 (Lumacaftor-ivacaftor), 106 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.69, df=1(P=0.41); I²=0%					
Test for overall effect: Z=3.64(P=0)					
7.6.4 Infective pulmonary exacerbation					
TRAFFIC 2015	67/182	87/183		46.87%	0.64[0.37,1.11]
TRANSPORT 2015	65/187	95/186		53.13%	0.51[0.3,0.88]
Subtotal (99% CI)	**369**	**369**		**100%**	**0.57[0.39,0.84]**
Total events: 132 (Lumacaftor-ivacaftor), 182 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.59, df=1(P=0.44); I²=0%					
Test for overall effect: Z=3.71(P=0)					
7.6.5 Cough					
TRAFFIC 2015	48/182	66/183		45.69%	0.64[0.35,1.14]
TRANSPORT 2015	56/187	82/186		54.31%	0.54[0.31,0.95]
Subtotal (99% CI)	**369**	**369**		**100%**	**0.58[0.39,0.88]**
Total events: 104 (Lumacaftor-ivacaftor), 148 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.25, df=1(P=0.62); I²=0%					
Test for overall effect: Z=3.41(P=0)					
7.6.6 Headache					
TRAFFIC 2015	29/182	25/183		42.85%	1.2[0.56,2.56]
TRANSPORT 2015	29/187	33/186		57.15%	0.85[0.42,1.74]
Subtotal (99% CI)	**369**	**369**		**100%**	**1[0.59,1.68]**
Total events: 58 (Lumacaftor-ivacaftor), 58 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.71, df=1(P=0.4); I²=0%					
Test for overall effect: Z=0(P=1)					

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Weight	Odds Ratio M-H, Fixed, 99% CI
7.6.7 Haemoptysis					
TRAFFIC 2015	30/182	24/183		46.2%	1.31[0.61,2.81]
TRANSPORT 2015	20/187	26/186		53.8%	0.74[0.33,1.67]
Subtotal (99% CI)	**369**	**369**		**100%**	**1[0.58,1.74]**
Total events: 50 (Lumacaftor-ivacaftor), 50 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.74, df=1(P=0.19); I²=42.64%					
Test for overall effect: Z=0(P=1)					
7.6.8 Diarrhoea					
TRAFFIC 2015	24/182	13/183		41.26%	1.99[0.78,5.04]
TRANSPORT 2015	21/187	18/186		58.74%	1.18[0.49,2.83]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.51[0.8,2.85]**
Total events: 45 (Lumacaftor-ivacaftor), 31 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.1, df=1(P=0.29); I²=9.13%					
Test for overall effect: Z=1.68(P=0.09)					
7.6.9 Abnormal respiration					
TRAFFIC 2015	14/182	9/183		41.29%	1.61[0.52,5.01]
TRANSPORT 2015	18/187	13/186		58.71%	1.42[0.53,3.77]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.5[0.71,3.14]**
Total events: 32 (Lumacaftor-ivacaftor), 22 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.05, df=1(P=0.83); I²=0%					
Test for overall effect: Z=1.4(P=0.16)					
7.6.10 Increased sputum					
TRAFFIC 2015	25/182	23/183		33.2%	1.11[0.5,2.46]
TRANSPORT 2015	29/187	47/186		66.8%	0.54[0.28,1.07]
Subtotal (99% CI)	**369**	**369**		**100%**	**0.73[0.44,1.22]**
Total events: 54 (Lumacaftor-ivacaftor), 70 (Placebo)					
Heterogeneity: Tau²=0; Chi²=3.08, df=1(P=0.08); I²=67.5%					
Test for overall effect: Z=1.58(P=0.11)					
7.6.11 Dyspnea					
TRAFFIC 2015	17/182	14/183		50.22%	1.24[0.47,3.29]
TRANSPORT 2015	31/187	15/186		49.78%	2.27[0.96,5.35]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.75[0.93,3.32]**
Total events: 48 (Lumacaftor-ivacaftor), 29 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.42, df=1(P=0.23); I²=29.55%					
Test for overall effect: Z=2.26(P=0.02)					
7.6.12 Nasopharyngitis					
TRAFFIC 2015	26/182	20/183		49.14%	1.36[0.6,3.08]
TRANSPORT 2015	22/187	20/186		50.86%	1.11[0.48,2.58]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.23[0.68,2.21]**
Total events: 48 (Lumacaftor-ivacaftor), 40 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.2, df=1(P=0.65); I²=0%					
Test for overall effect: Z=0.91(P=0.36)					
7.6.13 Oropharyngeal pain					
TRAFFIC 2015	11/182	10/183		33.43%	1.11[0.35,3.55]
TRANSPORT 2015	13/187	20/186		66.57%	0.62[0.24,1.62]

Favours lumacaftor-ivacaftor   0.01   0.1   1   10   100   Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
Subtotal (99% CI)	**369**	**369**		**100%**	**0.78[0.38,1.63]**
Total events: 24 (Lumacaftor-ivacaftor), 30 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1, df=1(P=0.32); I²=0.22%					
Test for overall effect: Z=0.85(P=0.39)					
7.6.14 Abdominal pain					
TRAFFIC 2015	23/182	12/183		35.52%	2.06[0.79,5.38]
TRANSPORT 2015	10/187	20/186		64.48%	0.47[0.17,1.32]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.03[0.53,2.01]**
Total events: 33 (Lumacaftor-ivacaftor), 32 (Placebo)					
Heterogeneity: Tau²=0; Chi²=7.29, df=1(P=0.01); I²=86.29%					
Test for overall effect: Z=0.13(P=0.9)					
7.6.15 Fatigue					
TRAFFIC 2015	17/182	19/183		65.33%	0.89[0.36,2.2]
TRANSPORT 2015	17/187	10/186		34.67%	1.76[0.61,5.1]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.19[0.6,2.35]**
Total events: 34 (Lumacaftor-ivacaftor), 29 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.59, df=1(P=0.21); I²=36.92%					
Test for overall effect: Z=0.66(P=0.51)					
7.6.16 Nausea					
TRAFFIC 2015	14/182	11/183		41.75%	1.3[0.44,3.82]
TRANSPORT 2015	32/187	17/186		58.25%	2.05[0.9,4.68]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.74[0.91,3.34]**
Total events: 46 (Lumacaftor-ivacaftor), 28 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.75, df=1(P=0.39); I²=0%					
Test for overall effect: Z=2.19(P=0.03)					
7.6.17 Pyrexia					
TRAFFIC 2015	17/182	12/183		34.97%	1.47[0.53,4.04]
TRANSPORT 2015	16/187	22/186		65.03%	0.7[0.29,1.7]
Subtotal (99% CI)	**369**	**369**		**100%**	**0.97[0.5,1.87]**
Total events: 33 (Lumacaftor-ivacaftor), 34 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.02, df=1(P=0.16); I²=50.54%					
Test for overall effect: Z=0.13(P=0.9)					
7.6.18 Nasal congestion					
TRAFFIC 2015	11/182	25/183		56.92%	0.41[0.15,1.08]
TRANSPORT 2015	13/187	19/186		43.08%	0.66[0.25,1.73]
Subtotal (99% CI)	**369**	**369**		**100%**	**0.51[0.26,1.02]**
Total events: 24 (Lumacaftor-ivacaftor), 44 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.81, df=1(P=0.37); I²=0%					
Test for overall effect: Z=2.51(P=0.01)					
7.6.19 Upper respiratory tract infection					
TRAFFIC 2015	17/182	10/183		50.24%	1.78[0.61,5.17]
TRANSPORT 2015	20/187	10/186		49.76%	2.11[0.75,5.94]
Subtotal (99% CI)	**369**	**369**		**100%**	**1.94[0.93,4.08]**
Total events: 37 (Lumacaftor-ivacaftor), 20 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.08, df=1(P=0.77); I²=0%					

Favours lumacaftor-ivacaftor   0.01   0.1   1   10   100   Favours placebo

<table>
<thead>
<tr><th>Study or subgroup</th><th>Lumacaftor-ivacaftor</th><th>Placebo</th><th colspan="2">Odds Ratio</th><th>Weight</th><th>Odds Ratio</th></tr>
<tr><th></th><th>n/N</th><th>n/N</th><th colspan="2">M-H, Fixed, 99% CI</th><th></th><th>M-H, Fixed, 99% CI</th></tr>
</thead>
<tbody>
<tr><td colspan="7">Test for overall effect: Z=2.31(P=0.02)</td></tr>
</tbody>
</table>

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Analysis 7.7. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 7 Time to first pulmonary exacerbation.

Study or subgroup	Lumacaftor-ivacaftor	Placebo	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
TRAFFIC 2015	182	184	-0.4 (0.16)		50%	0.69[0.5,0.95]
TRANSPORT 2015	187	187	-0.6 (0.16)		50%	0.53[0.39,0.73]
Total (95% CI)					**100%**	**0.61[0.49,0.76]**
Heterogeneity: Tau²=0; Chi²=1.32, df=1(P=0.25); I²=24.03%						
Test for overall effect: Z=4.41(P<0.0001)						

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Analysis 7.8. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 8 Rate of exacerbations.

Study or subgroup	Lumacaftor-ivacaftor	Placebo	log[Rate Ratio]	Rate Ratio	Weight	Rate Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
TRAFFIC 2015	182	184	-0.4 (0.171)		44.47%	0.66[0.47,0.93]
TRANSPORT 2015	187	187	-0.6 (0.153)		55.53%	0.57[0.42,0.76]
Total (95% CI)					**100%**	**0.61[0.49,0.76]**
Heterogeneity: Tau²=0; Chi²=0.49, df=1(P=0.49); I²=0%						
Test for overall effect: Z=4.36(P<0.0001)						

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Analysis 7.9. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 9 Weight (kg) (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
7.9.1 At 6 months							
TRAFFIC 2015	176	1.2 (2.7)	184	0.9 (2.7)		45.78%	0.3[-0.26,0.86]
TRANSPORT 2015	180	1.4 (2.5)	183	0.4 (2.5)		54.22%	0.94[0.42,1.46]
Subtotal ***	**356**		**367**			**100%**	**0.65[0.27,1.03]**
Heterogeneity: Tau²=0; Chi²=2.68, df=1(P=0.1); I²=62.7%							
Test for overall effect: Z=3.32(P=0)							

Favours placebo -2 -1 0 1 2 Favours lumacaftor-ivacaftor

Analysis 7.10. Comparison 7 Lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 10 BMI (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
7.10.1 At 28 days							
TRAFFIC 2015	182	0.1 (0.6)	184	0.1 (0.5)		53.11%	0.04[-0.07,0.15]
TRANSPORT 2015	187	0.1 (0.6)	187	0.1 (0.6)		46.89%	0[-0.11,0.11]
Subtotal ***	**369**		**371**			**100%**	**0.02[-0.06,0.1]**
Heterogeneity: Tau²=0; Chi²=0.26, df=1(P=0.61); I²=0%							
Test for overall effect: Z=0.54(P=0.59)							
7.10.2 At 6 months							
TRAFFIC 2015	176	0.3 (0.9)	184	0.2 (0.9)		46.71%	0.13[-0.07,0.33]
TRANSPORT 2015	180	0.4 (0.9)	183	0.1 (0.9)		53.29%	0.36[0.18,0.54]
Subtotal ***	**356**		**367**			**100%**	**0.25[0.12,0.39]**
Heterogeneity: Tau²=0; Chi²=2.84, df=1(P=0.09); I²=64.74%							
Test for overall effect: Z=3.71(P=0)							

Favours placebo   -0.5 -0.25   0   0.25 0.5   Favours lumacaftor-ivacaftor

Comparison 8. Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life - Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 6 months	2	1061	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.01, 0.01]
2 Quality of life - CFQ-R respiratory domain (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 At 28 days	2	1108	Mean Difference (IV, Fixed, 95% CI)	3.70 [1.81, 5.58]
2.2 At 6 months	2	1076	Mean Difference (IV, Fixed, 95% CI)	2.62 [0.64, 4.59]
3 Quality of life - EQ-5D-3L VAS Score (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 6 months	2	1060	Mean Difference (IV, Fixed, 95% CI)	2.28 [0.50, 4.06]
4 FEV$_1$ % predicted (relative change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 At 6 months	2	1072	Mean Difference (IV, Fixed, 95% CI)	5.21 [3.61, 6.80]
5 FEV$_1$ % predicted (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 At 28 days	2	1108	Mean Difference (IV, Fixed, 95% CI)	2.37 [1.52, 3.22]
5.2 At 6 months	2	1072	Mean Difference (IV, Fixed, 95% CI)	3.07 [2.17, 3.97]
6 Adverse events by end of study (at 6 months)	2		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
6.1 Any adverse event	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.87 [0.38, 2.02]
6.2 Discontinuation due to an adverse event	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	2.65 [0.83, 8.45]
6.3 At least 1 serious adverse event	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.62 [0.42, 0.91]
6.4 Infective pulmonary exacerbation	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.62 [0.44, 0.86]
6.5 Cough	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.65 [0.46, 0.92]
6.6 Headache	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.00 [0.64, 1.57]
6.7 Haemoptysis	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.02 [0.63, 1.65]
6.8 Diarrhea	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.34 [0.76, 2.37]
6.9 Abnormal respiration	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.70 [0.89, 3.26]
6.10 Increased sputum	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.73 [0.47, 1.14]
6.11 Dyspnea	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.90 [1.08, 3.35]
6.12 Nasopharyngitis	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.87 [0.51, 1.50]
6.13 Oropharyngeal pain	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.14 [0.63, 2.06]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.14 Abdominal pain	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.91 [0.51, 1.65]
6.15 Fatigue	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.11 [0.61, 2.03]
6.16 Nausea	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.38 [0.76, 2.51]
6.17 Pyrexia	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.00 [0.57, 1.76]
6.18 Nasal congestion	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	0.62 [0.36, 1.07]
6.19 Upper respiratory tract infection	2	1108	Odds Ratio (M-H, Fixed, 99% CI)	1.57 [0.79, 3.11]
7 Weight (kg) (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 At 6 months	2	1081	Mean Difference (IV, Fixed, 95% CI)	0.72 [0.39, 1.05]
8 BMI (absolute change from baseline)	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
8.1 At 28 days	2	1108	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.05, 0.08]
8.2 At 6 months	2	1081	Mean Difference (IV, Fixed, 95% CI)	0.27 [0.16, 0.39]

Analysis 8.1.   Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 1 Quality of life - Euro Quality of Life Scale (EuroQol) 5-Dimension-3 Level (EQ-5D-3L) Index Score (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.1.1 At 6 months							
TRAFFIC 2015	345	0 (0.1)	179	0 (0.1)		45.11%	0.01[-0.01,0.03]
TRANSPORT 2015	354	0 (0.1)	183	0 (0.1)		54.89%	-0[-0.02,0.01]
Subtotal ***	**699**		**362**			**100%**	**0[-0.01,0.01]**
Heterogeneity: Tau²=0; Chi²=0.59, df=1(P=0.44); I²=0%							
Test for overall effect: Z=0.4(P=0.69)							

Favours placebo   -0.1 -0.05   0   0.05   0.1   Favours lumacaftor-ivacaftor
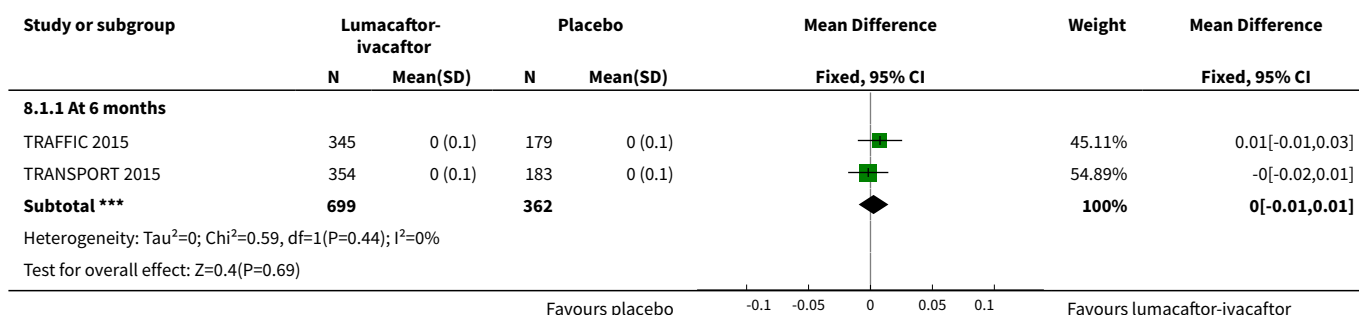
Analysis 8.2. **Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 2 Quality of life - CFQ-R respiratory domain (absolute change from baseline).**

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.2.1 At 28 days							
TRAFFIC 2015	365	4.5 (15.2)	184	3 (14.5)		52.28%	1.5[-1.11,4.11]
TRANSPORT 2015	372	7.1 (15.3)	187	1 (15.7)		47.72%	6.1[3.37,8.84]
Subtotal ***	**737**		**371**			**100%**	**3.7[1.81,5.58]**
Heterogeneity: Tau²=0; Chi²=5.69, df=1(P=0.02); I²=82.43%							
Test for overall effect: Z=3.83(P=0)							
8.2.2 At 6 months							
TRAFFIC 2015	348	3.8 (15.7)	184	1.1 (15.7)		49.47%	2.7[-0.1,5.51]
TRANSPORT 2015	359	5.3 (15.6)	185	2.8 (15.7)		50.53%	2.53[-0.25,5.31]
Subtotal ***	**707**		**369**			**100%**	**2.62[0.64,4.59]**
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.93); I²=0%							
Test for overall effect: Z=2.6(P=0.01)							

Favours placebo -50 -25 0 25 50 Favours lumacaftor-ivacaftor

Analysis 8.3. **Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 3 Quality of life - EQ-5D-3L VAS Score (absolute change from baseline).**

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.3.1 At 6 months							
TRAFFIC 2015	344	3.2 (13.5)	180	1.4 (13.8)		52.06%	1.75[-0.72,4.22]
TRANSPORT 2015	354	6.2 (14.4)	182	3.3 (14.4)		47.94%	2.85[0.27,5.43]
Subtotal ***	**698**		**362**			**100%**	**2.28[0.5,4.06]**
Heterogeneity: Tau²=0; Chi²=0.36, df=1(P=0.55); I²=0%							
Test for overall effect: Z=2.5(P=0.01)							

Favours placebo -100 -50 0 50 100 Favours lumacaftor-ivacaftor
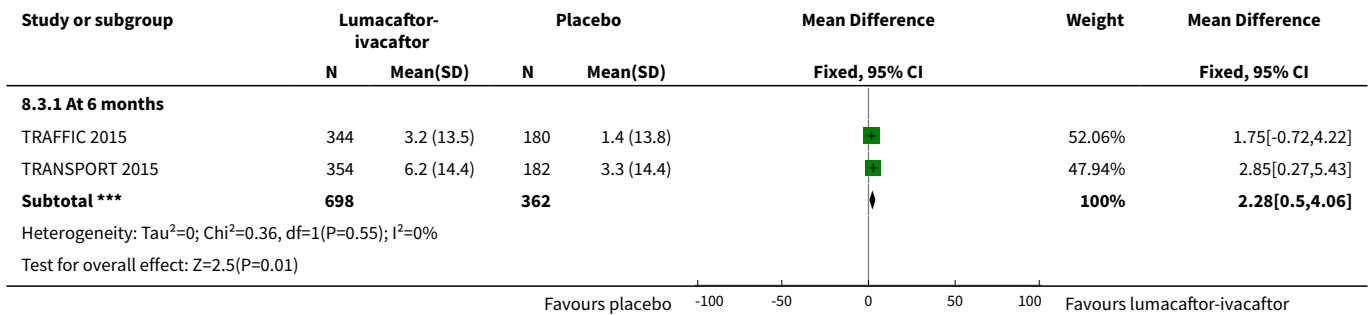
Analysis 8.4. **Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 4 FEV$_1$ % predicted (relative change from baseline).**

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.4.1 At 6 months							
TRAFFIC 2015	348	5.2 (12.2)	180	-0.3 (12.2)		52.35%	5.54[3.35,7.74]
TRANSPORT 2015	361	4.8 (12.9)	183	0 (13)		47.65%	4.83[2.53,7.14]
Subtotal ***	**709**		**363**			**100%**	**5.21[3.61,6.8]**
Heterogeneity: Tau²=0; Chi²=0.19, df=1(P=0.66); I²=0%							
Test for overall effect: Z=6.41(P<0.0001)							

Favours placebo -100 -50 0 50 100 Favours lumacaftor-ivacaftor

Analysis 8.5. Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 5 FEV$_1$ % predicted (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.5.1 At 28 days							
TRAFFIC 2015	365	2.4 (7.6)	184	0 (7.6)		40.1%	2.4[1.05,3.75]
TRANSPORT 2015	372	2.7 (6.3)	187	0.3 (6.3)		59.9%	2.35[1.25,3.45]
Subtotal ***	**737**		**371**			**100%**	**2.37[1.52,3.22]**
Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.96); I²=0%							
Test for overall effect: Z=5.45(P<0.0001)							
8.5.2 At 6 months							
TRAFFIC 2015	348	2.9 (7)	180	-0.4 (7)		51.25%	3.32[2.06,4.59]
TRANSPORT 2015	361	2.7 (7.2)	183	-0.1 (7.3)		48.75%	2.8[1.51,4.1]
Subtotal ***	**709**		**363**			**100%**	**3.07[2.17,3.97]**
Heterogeneity: Tau²=0; Chi²=0.32, df=1(P=0.57); I²=0%							
Test for overall effect: Z=6.66(P<0.0001)							

Favours placebo   -10 -5 0 5 10   Favours lumacaftor-ivacaftor

Analysis 8.6. Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 6 Adverse events by end of study (at 6 months).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
8.6.1 Any adverse event					
TRAFFIC 2015	349/366	174/183		52.59%	1.06[0.36,3.15]
TRANSPORT 2015	358/373	181/186		47.41%	0.66[0.17,2.55]
Subtotal (99% CI)	**739**	**369**		**100%**	**0.87[0.38,2.02]**
Total events: 707 (Lumacaftor-ivacaftor), 355 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.5, df=1(P=0.48); I²=0%					
Test for overall effect: Z=0.42(P=0.67)					
8.6.2 Discontinuation due to an adverse event					
TRAFFIC 2015	14/366	4/183		66.82%	1.78[0.41,7.81]
TRANSPORT 2015	17/373	2/186		33.18%	4.39[0.63,30.56]
Subtotal (99% CI)	**739**	**369**		**100%**	**2.65[0.83,8.45]**
Total events: 31 (Lumacaftor-ivacaftor), 6 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.93, df=1(P=0.33); I²=0%					
Test for overall effect: Z=2.16(P=0.03)					
8.6.3 At least 1 serious adverse event					
TRAFFIC 2015	66/366	49/183		47.43%	0.6[0.35,1.05]
TRANSPORT 2015	82/373	57/186		52.57%	0.64[0.38,1.07]
Subtotal (99% CI)	**739**	**369**		**100%**	**0.62[0.42,0.91]**
Total events: 148 (Lumacaftor-ivacaftor), 106 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.04, df=1(P=0.84); I²=0%					
Test for overall effect: Z=3.24(P=0)					
8.6.4 Infective pulmonary exacerbation					

Favours lumacaftor-ivacaftor   0.01 0.1 1 10 100   Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
TRAFFIC 2015	132/366	87/183		48.9%	0.62[0.39,1]
TRANSPORT 2015	145/373	95/186		51.1%	0.61[0.38,0.97]
Subtotal (99% CI)	**739**	**369**		**100%**	**0.62[0.44,0.86]**
Total events: 277 (Lumacaftor-ivacaftor), 182 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.93); I²=0%					
Test for overall effect: Z=3.76(P=0)					
8.6.5 Cough					
TRAFFIC 2015	100/366	66/183		46.78%	0.67[0.4,1.1]
TRANSPORT 2015	125/373	82/186		53.22%	0.64[0.4,1.03]
Subtotal (99% CI)	**739**	**369**		**100%**	**0.65[0.46,0.92]**
Total events: 225 (Lumacaftor-ivacaftor), 148 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.88); I²=0%					
Test for overall effect: Z=3.21(P=0)					
8.6.6 Headache					
TRAFFIC 2015	57/366	25/183		43.15%	1.17[0.6,2.27]
TRANSPORT 2015	59/373	33/186		56.85%	0.87[0.47,1.61]
Subtotal (99% CI)	**739**	**369**		**100%**	**1[0.64,1.57]**
Total events: 116 (Lumacaftor-ivacaftor), 58 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.68, df=1(P=0.41); I²=0%					
Test for overall effect: Z=0.01(P=0.99)					
8.6.7 Haemoptysis					
TRAFFIC 2015	52/366	24/183		47.75%	1.1[0.55,2.17]
TRANSPORT 2015	50/373	26/186		52.25%	0.95[0.49,1.86]
Subtotal (99% CI)	**739**	**369**		**100%**	**1.02[0.63,1.65]**
Total events: 102 (Lumacaftor-ivacaftor), 50 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.14, df=1(P=0.7); I²=0%					
Test for overall effect: Z=0.12(P=0.91)					
8.6.8 Diarrhea					
TRAFFIC 2015	40/366	13/183		41.93%	1.6[0.68,3.78]
TRANSPORT 2015	41/373	18/186		58.07%	1.15[0.53,2.48]
Subtotal (99% CI)	**739**	**369**		**100%**	**1.34[0.76,2.37]**
Total events: 81 (Lumacaftor-ivacaftor), 31 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.55, df=1(P=0.46); I²=0%					
Test for overall effect: Z=1.33(P=0.18)					
8.6.9 Abnormal respiration					
TRAFFIC 2015	40/366	9/183		40.26%	2.37[0.89,6.32]
TRANSPORT 2015	32/373	13/186		59.74%	1.25[0.52,3.01]
Subtotal (99% CI)	**739**	**369**		**100%**	**1.7[0.89,3.26]**
Total events: 72 (Lumacaftor-ivacaftor), 22 (Placebo)					
Heterogeneity: Tau²=0; Chi²=1.58, df=1(P=0.21); I²=36.72%					
Test for overall effect: Z=2.11(P=0.04)					
8.6.10 Increased sputum					
TRAFFIC 2015	40/366	23/183		34.83%	0.85[0.42,1.75]
TRANSPORT 2015	69/373	47/186		65.17%	0.67[0.39,1.17]
Subtotal (99% CI)	**739**	**369**		**100%**	**0.73[0.47,1.14]**

Favours lumacaftor-ivacaftor   0.01   0.1   1   10   100   Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI

Total events: 109 (Lumacaftor-ivacaftor), 70 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.47, df=1(P=0.5); I²=0%

Test for overall effect: Z=1.81(P=0.07)

8.6.11 Dyspnea

TRAFFIC 2015	39/366	14/183		50.14%	1.44[0.62,3.33]
TRANSPORT 2015	64/373	15/186		49.86%	2.36[1.08,5.14]
Subtotal (99% CI)	739	369		100%	1.9[1.08,3.35]

Total events: 103 (Lumacaftor-ivacaftor), 29 (Placebo)

Heterogeneity: Tau²=0; Chi²=1.24, df=1(P=0.27); I²=19.5%

Test for overall effect: Z=2.91(P=0)

8.6.12 Nasopharyngitis

TRAFFIC 2015	35/366	20/183		50%	0.86[0.4,1.85]
TRANSPORT 2015	36/373	20/186		50%	0.89[0.42,1.89]
Subtotal (99% CI)	739	369		100%	0.87[0.51,1.5]

Total events: 71 (Lumacaftor-ivacaftor), 40 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.95); I²=0%

Test for overall effect: Z=0.64(P=0.52)

8.6.13 Oropharyngeal pain

TRAFFIC 2015	35/366	10/183		33.14%	1.83[0.7,4.75]
TRANSPORT 2015	33/373	20/186		66.86%	0.81[0.37,1.74]
Subtotal (99% CI)	739	369		100%	1.14[0.63,2.06]

Total events: 68 (Lumacaftor-ivacaftor), 30 (Placebo)

Heterogeneity: Tau²=0; Chi²=2.98, df=1(P=0.08); I²=66.47%

Test for overall effect: Z=0.59(P=0.55)

8.6.14 Abdominal pain

TRAFFIC 2015	34/366	12/183		36.82%	1.46[0.59,3.58]
TRANSPORT 2015	25/373	20/186		63.18%	0.6[0.27,1.34]
Subtotal (99% CI)	739	369		100%	0.91[0.51,1.65]

Total events: 59 (Lumacaftor-ivacaftor), 32 (Placebo)

Heterogeneity: Tau²=0; Chi²=3.65, df=1(P=0.06); I²=72.57%

Test for overall effect: Z=0.39(P=0.69)

8.6.15 Fatigue

TRAFFIC 2015	34/366	19/183		65.19%	0.88[0.41,1.92]
TRANSPORT 2015	30/373	10/186		34.81%	1.54[0.58,4.06]
Subtotal (99% CI)	739	369		100%	1.11[0.61,2.03]

Total events: 64 (Lumacaftor-ivacaftor), 29 (Placebo)

Heterogeneity: Tau²=0; Chi²=1.32, df=1(P=0.25); I²=24.42%

Test for overall effect: Z=0.45(P=0.65)

8.6.16 Nausea

TRAFFIC 2015	23/366	11/183		41.31%	1.05[0.4,2.78]
TRANSPORT 2015	52/373	17/186		58.69%	1.61[0.75,3.44]
Subtotal (99% CI)	739	369		100%	1.38[0.76,2.51]

Total events: 75 (Lumacaftor-ivacaftor), 28 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.8, df=1(P=0.37); I²=0%

Test for overall effect: Z=1.38(P=0.17)

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
8.6.17 Pyrexia					
TRAFFIC 2015	29/366	12/183		35.91%	1.23[0.49,3.07]
TRANSPORT 2015	39/373	22/186		64.09%	0.87[0.42,1.81]
Subtotal (99% CI)	**739**	**369**		**100%**	**1[0.57,1.76]**
Total events: 68 (Lumacaftor-ivacaftor), 34 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.57, df=1(P=0.45); I²=0%					
Test for overall effect: Z=0.01(P=0.99)					
8.6.18 Nasal congestion					
TRAFFIC 2015	20/366	25/183		57.98%	0.37[0.16,0.82]
TRANSPORT 2015	37/373	19/186		42.02%	0.97[0.45,2.08]
Subtotal (99% CI)	**739**	**369**		**100%**	**0.62[0.36,1.07]**
Total events: 57 (Lumacaftor-ivacaftor), 44 (Placebo)					
Heterogeneity: Tau²=0; Chi²=5.06, df=1(P=0.02); I²=80.23%					
Test for overall effect: Z=2.27(P=0.02)					
8.6.19 Upper respiratory tract infection					
TRAFFIC 2015	33/366	10/183		49.57%	1.71[0.66,4.48]
TRANSPORT 2015	28/373	10/186		50.43%	1.43[0.54,3.8]
Subtotal (99% CI)	**739**	**369**		**100%**	**1.57[0.79,3.11]**
Total events: 61 (Lumacaftor-ivacaftor), 20 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.12, df=1(P=0.73); I²=0%					
Test for overall effect: Z=1.7(P=0.09)					

Favours lumacaftor-ivacaftor   0.01   0.1   1   10   100   Favours placebo

Analysis 8.7.   Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 7 Weight (kg) (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.7.1 At 6 months							
TRAFFIC 2015	354	1.3 (2.7)	184	0.9 (2.7)		45.96%	0.36[-0.13,0.84]
TRANSPORT 2015	360	1.5 (2.5)	183	0.4 (2.5)		54.04%	1.04[0.59,1.48]
Subtotal ***	**714**		**367**			**100%**	**0.72[0.39,1.05]**
Heterogeneity: Tau²=0; Chi²=4.04, df=1(P=0.04); I²=75.26%							
Test for overall effect: Z=4.29(P<0.0001)							

Favours placebo   -5   -2.5   0   2.5   5   Favours lumacaftor-ivacaftor

Analysis 8.8. Comparison 8 Lumacaftor (600 mg once daily or 400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 8 BMI (absolute change from baseline).

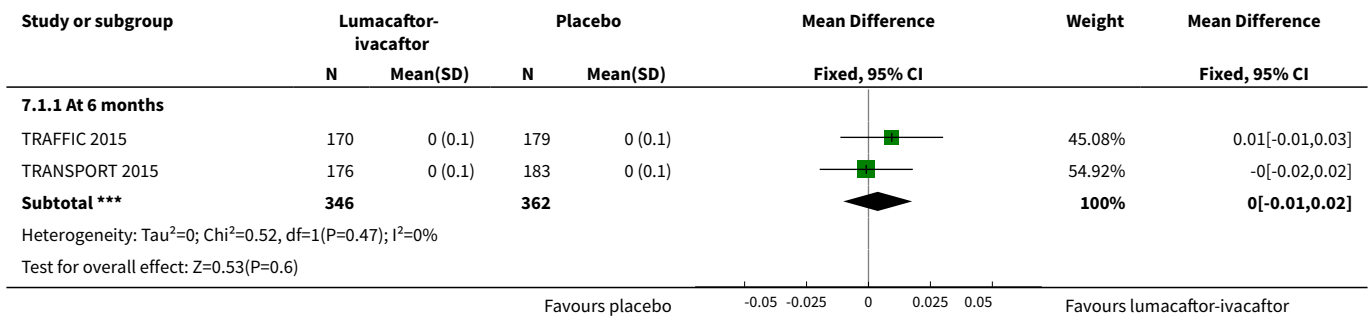| Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
8.8.1 At 28 days							
TRAFFIC 2015	365	0.1 (0.6)	184	0.1 (0.5)		51.98%	0.03[-0.06,0.13]
TRANSPORT 2015	372	0.1 (0.5)	187	0.1 (0.6)		48.02%	-0[-0.1,0.09]
Subtotal ***	**737**		**371**			**100%**	**0.02[-0.05,0.08]**
Heterogeneity: Tau²=0; Chi²=0.35, df=1(P=0.56); I²=0%							
Test for overall effect: Z=0.47(P=0.64)							
8.8.2 At 6 months							
TRAFFIC 2015	354	0.3 (0.9)	184	0.2 (0.9)		46.95%	0.15[-0.02,0.31]
TRANSPORT 2015	360	0.5 (0.9)	183	0.1 (0.9)		53.05%	0.39[0.23,0.54]
Subtotal ***	**714**		**367**			**100%**	**0.27[0.16,0.39]**
Heterogeneity: Tau²=0; Chi²=4.14, df=1(P=0.04); I²=75.84%							
Test for overall effect: Z=4.63(P<0.0001)							

Favours placebo -2 -1 0 1 2 Favours lumacaftor-ivacaftor

Comparison 9. Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (150 mg twice daily) for days 15 to 21 versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV$_1$ % predicted (absolute change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 14 days (before addition of ivacaftor)	1	41	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-4.39, 0.79]
1.2 At 21 days	1	41	Mean Difference (IV, Fixed, 95% CI)	2.80 [-1.39, 6.99]
2 Adverse events occurring in 10% or more participants (from days 15 - 21)	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
2.1 Cough	1	41	Odds Ratio (M-H, Fixed, 99% CI)	1.06 [0.14, 8.09]
2.2 Pulmonary Exacerbation	1	41	Odds Ratio (M-H, Fixed, 99% CI)	2.22 [0.08, 58.11]
2.3 Oropharyngeal pain	1	41	Odds Ratio (M-H, Fixed, 99% CI)	0.5 [0.02, 13.07]
2.4 Nasal congestion	1	41	Odds Ratio (M-H, Fixed, 99% CI)	0.5 [0.02, 13.07]
2.5 Dizziness	1	41	Odds Ratio (M-H, Fixed, 99% CI)	5.81 [0.10, 341.36]
2.6 Prothrombin time prolonged	1	41	Odds Ratio (M-H, Fixed, 99% CI)	5.81 [0.10, 341.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7 Upper respiratory tract infection	1	41	Odds Ratio (M-H, Fixed, 99% CI)	5.81 [0.10, 341.36]
3 Sweat chloride concentration (mmol/L) (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 14 days (before addition of ivacaftor)	1	34	Mean Difference (IV, Fixed, 95% CI)	-3.10 [-8.58, 2.38]
3.2 At 21 days	1	33	Mean Difference (IV, Fixed, 95% CI)	-5.0 [-11.61, 1.61]

Analysis 9.1. Comparison 9 Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (150 mg twice daily) for days 15 to 21 versus placebo, Outcome 1 FEV$_1$ % predicted (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
9.1.1 At 14 days (before addition of ivacaftor)							
Boyle 2014	20	-0.1 (4.3)	21	1.7 (4.2)		100%	-1.8[-4.39,0.79]
Subtotal ***	**20**		**21**			**100%**	**-1.8[-4.39,0.79]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.36(P=0.17)							
9.1.2 At 21 days							
Boyle 2014	20	3.1 (6.7)	21	0.3 (7)		100%	2.8[-1.39,6.99]
Subtotal ***	**20**		**21**			**100%**	**2.8[-1.39,6.99]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.31(P=0.19)							

Favours placebo -100 -50 0 50 100 Favours lumacaftor-ivacaftor

Analysis 9.2. Comparison 9 Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (150 mg twice daily) for days 15 to 21 versus placebo, Outcome 2 Adverse events occurring in 10% or more participants (from days 15 - 21).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
9.2.1 Cough					
Boyle 2014	4/20	4/21		100%	1.06[0.14,8.09]
Subtotal (99% CI)	**20**	**21**		**100%**	**1.06[0.14,8.09]**
Total events: 4 (Lumacaftor-ivacaftor), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.08(P=0.94)					
9.2.2 Pulmonary Exacerbation					
Boyle 2014	2/20	1/21		100%	2.22[0.08,58.11]

Favours lumacaftor-ivacaftor 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
Subtotal (99% CI)	**20**	**21**		**100%**	**2.22[0.08,58.11]**

Total events: 2 (Lumacaftor-ivacaftor), 1 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.63(P=0.53)

9.2.3 Oropharyngeal pain

Boyle 2014	1/20	2/21		100%	0.5[0.02,13.07]
Subtotal (99% CI)	**20**	**21**		**100%**	**0.5[0.02,13.07]**

Total events: 1 (Lumacaftor-ivacaftor), 2 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.55(P=0.58)

9.2.4 Nasal congestion

Boyle 2014	1/20	2/21		100%	0.5[0.02,13.07]
Subtotal (99% CI)	**20**	**21**		**100%**	**0.5[0.02,13.07]**

Total events: 1 (Lumacaftor-ivacaftor), 2 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.55(P=0.58)

9.2.5 Dizziness

Boyle 2014	2/20	0/21		100%	5.81[0.1,341.36]
Subtotal (99% CI)	**20**	**21**		**100%**	**5.81[0.1,341.36]**

Total events: 2 (Lumacaftor-ivacaftor), 0 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

Test for overall effect: Z=1.11(P=0.27)

9.2.6 Prothrombin time prolonged

Boyle 2014	2/20	0/21		100%	5.81[0.1,341.36]
Subtotal (99% CI)	**20**	**21**		**100%**	**5.81[0.1,341.36]**

Total events: 2 (Lumacaftor-ivacaftor), 0 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

Test for overall effect: Z=1.11(P=0.27)

9.2.7 Upper respiratory tract infection

Boyle 2014	2/20	0/21		100%	5.81[0.1,341.36]
Subtotal (99% CI)	**20**	**21**		**100%**	**5.81[0.1,341.36]**

Total events: 2 (Lumacaftor-ivacaftor), 0 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%

Test for overall effect: Z=1.11(P=0.27)

Favours lumacaftor-ivacaftor 0.001 0.1 1 10 1000 Favours placebo

Analysis 9.3. Comparison 9 Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (150 mg twice daily) for days 15 to 21 versus placebo, Outcome 3 Sweat chloride concentration (mmol/L) (change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
9.3.1 At 14 days (before addition of ivacaftor)							
Boyle 2014	17	-4.8 (7.4)	17	-1.7 (8.8)		100%	-3.1[-8.58,2.38]

Favours lumacaftor-ivacaftor -100 -50 0 50 100 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Subtotal ***	**17**		**17**		◆	**100%**	**-3.1[-8.58,2.38]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.11(P=0.27)							
9.3.2 At 21 days							
Boyle 2014	17	-6.7 (9.5)	16	-1.7 (9.8)	▉	100%	-5[-11.61,1.61]
Subtotal ***	**17**		**16**		◆	**100%**	**-5[-11.61,1.61]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.48(P=0.14)							

Favours lumacaftor-ivacaftor -100 -50 0 50 100 Favours placebo

Comparison 10.   Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (250 mg twice daily) for days 15 to 21 versus placebo

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 FEV$_1$ % predicted (absolute change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 14 days (before addition of ivacaftor)	1	41	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-4.66, 0.66]
1.2 At 21 days	1	39	Mean Difference (IV, Fixed, 95% CI)	0.2 [-4.20, 4.60]
2 Adverse events occurring in 10% or more participants (from days 15 - 21)	1	287	Odds Ratio (M-H, Fixed, 99% CI)	0.93 [0.26, 3.33]
2.1 Cough	1	41	Odds Ratio (M-H, Fixed, 99% CI)	0.22 [0.01, 4.52]
2.2 Pulmonary Exacerbation	1	41	Odds Ratio (M-H, Fixed, 99% CI)	1.05 [0.03, 44.10]
2.3 Oropharyngeal pain	1	41	Odds Ratio (M-H, Fixed, 99% CI)	1.06 [0.07, 15.89]
2.4 Nasal congestion	1	41	Odds Ratio (M-H, Fixed, 99% CI)	1.68 [0.14, 20.50]
2.5 Dizziness	1	41	Odds Ratio (M-H, Fixed, 99% CI)	3.31 [0.05, 239.61]
2.6 Prothrombin time prolonged	1	41	Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
2.7 Upper respiratory tract infection	1	41	Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
3 Sweat chloride concentration (mmol/L) (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 At 14 days (before addition of ivacaftor)	1	34	Mean Difference (IV, Fixed, 95% CI)	-2.40 [-6.00, 3.20]
3.2 At 21 days	1	33	Mean Difference (IV, Fixed, 95% CI)	-10.9 [-17.60, -4.20]

Analysis 10.1. Comparison 10 Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (250 mg twice daily) for days 15 to 21 versus placebo, Outcome 1 FEV$_1$ % predicted (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
10.1.1 At 14 days (before addition of ivacaftor)							
Boyle 2014	20	-0.3 (4.5)	21	1.7 (4.2)		100%	-2[-4.66,0.66]
Subtotal ***	**20**		**21**			**100%**	**-2[-4.66,0.66]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.48(P=0.14)							
10.1.2 At 21 days							
Boyle 2014	18	0.5 (7)	21	0.3 (7)		100%	0.2[-4.2,4.6]
Subtotal ***	**18**		**21**			**100%**	**0.2[-4.2,4.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.09(P=0.93)							

Favours placebo -100 -50 0 50 100 Favours lumacaftor-ivacaftor
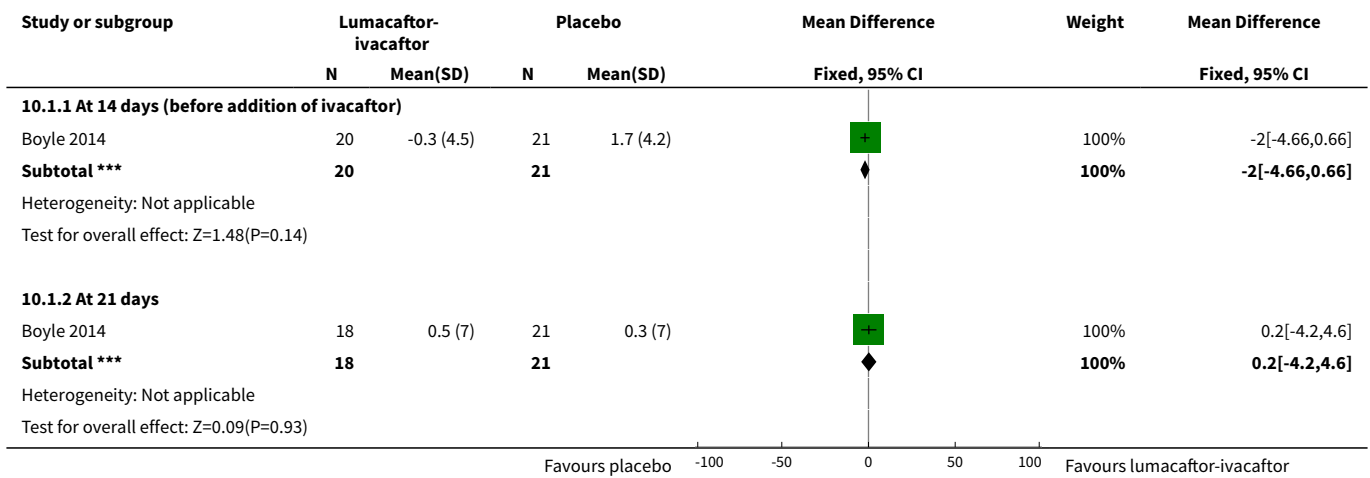
Analysis 10.2. Comparison 10 Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (250 mg twice daily) for days 15 to 21 versus placebo, Outcome 2 Adverse events occurring in 10% or more participants (from days 15 - 21).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
10.2.1 Cough					
Boyle 2014	1/20	4/21		43.6%	0.22[0.01,4.52]
Subtotal (99% CI)	**20**	**21**		**43.6%**	**0.22[0.01,4.52]**
Total events: 1 (Lumacaftor-ivacaftor), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.28(P=0.2)					
10.2.2 Pulmonary Exacerbation					
Boyle 2014	1/20	1/21		10.9%	1.05[0.03,44.1]
Subtotal (99% CI)	**20**	**21**		**10.9%**	**1.05[0.03,44.1]**
Total events: 1 (Lumacaftor-ivacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
10.2.3 Oropharyngeal pain					

Favours lumacaftor-ivacaftor 0.001 0.1 1 10 1000 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
Boyle 2014	2/20	2/21		20.65%	1.06[0.07,15.89]
Subtotal (99% CI)	**20**	**21**		**20.65%**	**1.06[0.07,15.89]**
Total events: 2 (Lumacaftor-ivacaftor), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.05(P=0.96)					
10.2.4 Nasal congestion					
Boyle 2014	3/20	2/21		19.51%	1.68[0.14,20.5]
Subtotal (99% CI)	**20**	**21**		**19.51%**	**1.68[0.14,20.5]**
Total events: 3 (Lumacaftor-ivacaftor), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.53(P=0.6)					
10.2.5 Dizziness					
Boyle 2014	1/20	0/21		5.33%	3.31[0.05,239.61]
Subtotal (99% CI)	**20**	**21**		**5.33%**	**3.31[0.05,239.61]**
Total events: 1 (Lumacaftor-ivacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.72(P=0.47)					
10.2.6 Prothrombin time prolonged					
Boyle 2014	0/20	0/21			Not estimable
Subtotal (99% CI)	**20**	**21**			**Not estimable**
Total events: 0 (Lumacaftor-ivacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
10.2.7 Upper respiratory tract infection					
Boyle 2014	0/20	0/21			Not estimable
Subtotal (99% CI)	**20**	**21**			**Not estimable**
Total events: 0 (Lumacaftor-ivacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (99% CI)	**140**	**147**		**100%**	**0.93[0.26,3.33]**
Total events: 8 (Lumacaftor-ivacaftor), 9 (Placebo)					
Heterogeneity: Tau²=0; Chi²=2.46, df=4(P=0.65); I²=0%					
Test for overall effect: Z=0.14(P=0.89)					
Test for subgroup differences: Chi²=2.45, df=1 (P=0.65), I²=0%					

Favours lumacaftor-ivacaftor 0.001 0.1 1 10 1000 Favours placebo

Analysis 10.3. Comparison 10 Lumacaftor (200 mg once daily) for 21 days plus ivacaftor (250 mg twice daily) for days 15 to 21 versus placebo, Outcome 3 Sweat chloride concentration (mmol/L) (change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
10.3.1 At 14 days (before addition of ivacaftor)							
Boyle 2014	17	-4.1 (7.8)	17	-1.7 (8.8)		100%	-2.4[-8,3.2]

Favours lumacaftor-ivacaftor -100 -50 0 50 100 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Subtotal ***	17		17			100%	-2.4[-8,3.2]
Heterogeneity: Not applicable							
Test for overall effect: Z=0.84(P=0.4)							
10.3.2 At 21 days							
Boyle 2014	17	-12.6 (9.8)	16	-1.7 (9.8)		100%	-10.9[-17.6,-4.2]
Subtotal ***	17		16			100%	-10.9[-17.6,-4.2]
Heterogeneity: Not applicable							
Test for overall effect: Z=3.19(P=0)							

Favours lumacaftor-ivacaftor   -100 -50 0 50 100   Favours placebo

Comparison 11.   Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Quality of life - CFQ-R respiratory domain (absolute change from baseline)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 up to and including week 24	1	204	Mean Difference (Fixed, 95% CI)	2.5 [-0.10, 5.10]
2 FEV$_1$ % predicted (absolute change from baseline)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 up to and including 24 weeks	1	204	Mean Difference (Fixed, 95% CI)	2.4 [0.40, 4.40]
3 LCI$_{2.5}$ (absolute change from baseline)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 up to and including 24 weeks	1	204	Mean Difference (Fixed, 95% CI)	-1.1 [-1.40, -0.80]
4 Treatment-emergent adverse events with incidence > 10% in any treatment group	1		Odds Ratio (M-H, Fixed, 99% CI)	Totals not selected
4.1 Any adverse event	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.2 Any serious adverse event	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.3 Cough	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.4 Pulmonary exacerbation	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.5 Productive cough	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.6 Nasal congestion	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.7 Oropharyngeal pain	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.8 Pyrexia	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.9 Upper abdominal pain	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.10 Headache	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.11 Upper respiratory tract infection	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.12 Sputum increased	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.13 Abdominal pain	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.14 Nausea	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.15 Rhinorrhoea	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.16 Vomiting	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.17 Fatigue	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
4.18 Respiratory events	1		Odds Ratio (M-H, Fixed, 99% CI)	0.0 [0.0, 0.0]
5 Sweat chloride concentration (absolute change from baseline)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
5.1 up to and including 4 weeks	1	204	Mean Difference (Fixed, 95% CI)	-20.8 [-23.40, -18.20]
6 BMI (absolute change from baseline)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
6.1 up to and including 24 weeks	1	204	Mean Difference (Fixed, 95% CI)	0.1 [-0.10, 0.30]
7 BMI for age z-score (absolute change from baseline)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
7.1 up to and including 24 weeks	1	204	Mean Difference (Fixed, 95% CI)	0.0 [-0.10, 0.10]

Analysis 11.1. Comparison 11 Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 1 Quality of life - CFQ-R respiratory domain (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
11.1.1 up to and including week 24						
Ratjen 2017	103	101	2.5 (1.327)		100%	2.5 [-0.1, 5.1]
Subtotal (95% CI)					**100%**	**2.5 [-0.1, 5.1]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.88(P=0.06)						

Favours placebo -10 -5 0 5 10 Favours lumacaftor-ivacaftor
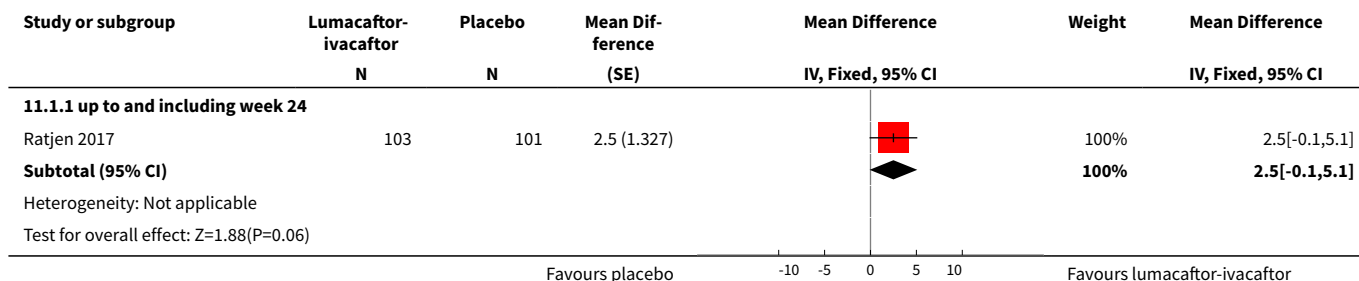
Analysis 11.2. Comparison 11 Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 2 FEV$_1$ % predicted (absolute change from baseline).

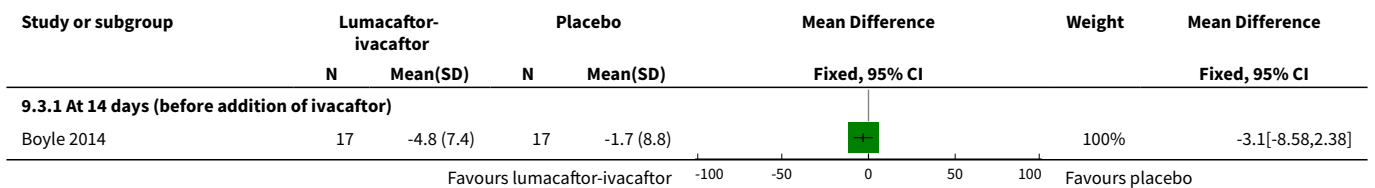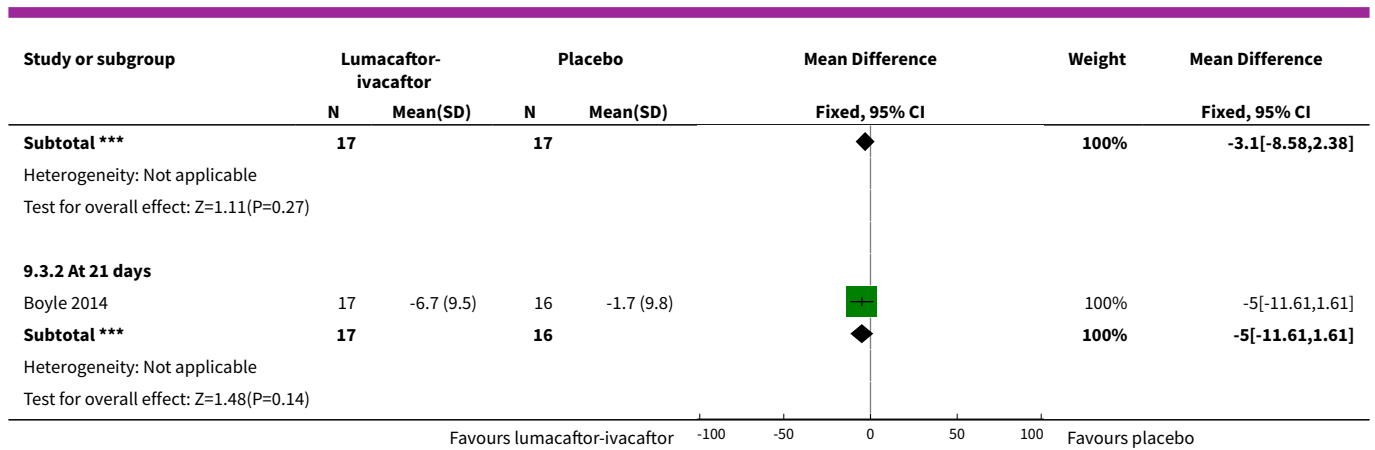| Study or subgroup	Lumacaftor-ivacaftor	Placebo	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
11.2.1 up to and including 24 weeks						
Ratjen 2017	103	101	2.4 (1.02)		100%	2.4[0.4,4.4]
Subtotal (95% CI)					**100%**	**2.4[0.4,4.4]**
Heterogeneity: Not applicable						
Test for overall effect: Z=2.35(P=0.02)						

Favours placebo   -5   -2.5   0   2.5   5   Favours lumacaftor-ivacaftor
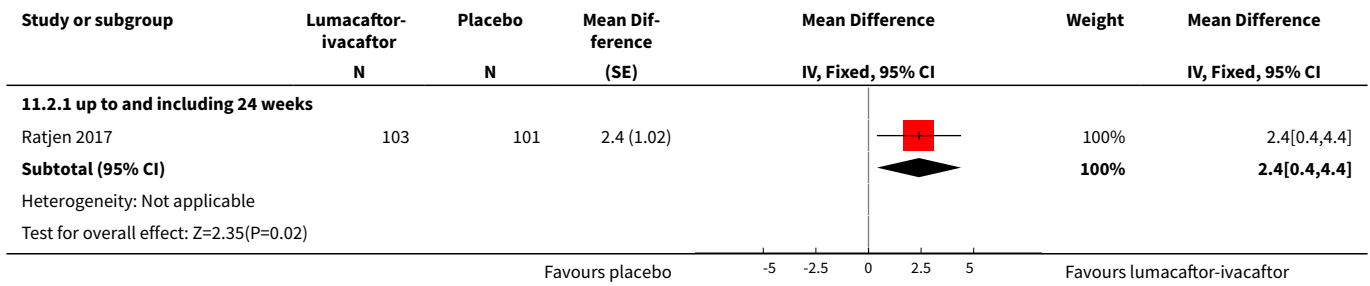
Analysis 11.3. Comparison 11 Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 3 LCI$_{2.5}$ (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
11.3.1 up to and including 24 weeks						
Ratjen 2017	103	101	-1.1 (0.153)		100%	-1.1[-1.4,-0.8]
Subtotal (95% CI)					**100%**	**-1.1[-1.4,-0.8]**
Heterogeneity: Not applicable						
Test for overall effect: Z=7.18(P<0.0001)						

Favours lumacaftor-ivacaftor   -2   -1   0   1   2   Favours placebo
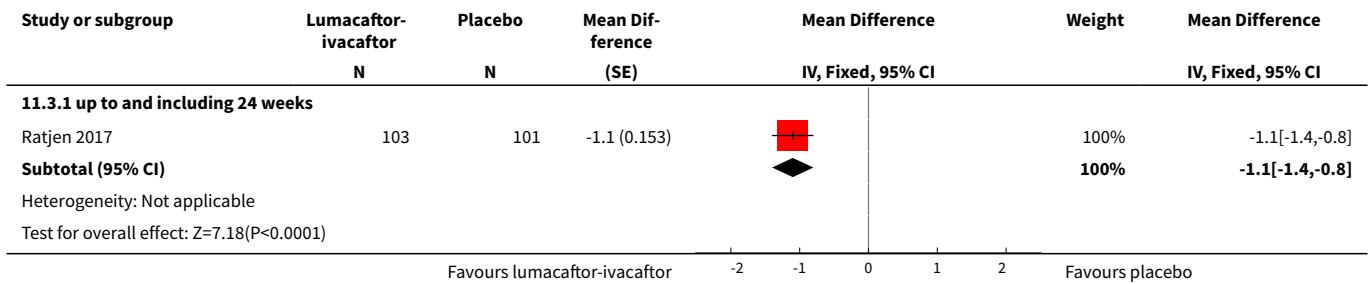
Analysis 11.4. Comparison 11 Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 4 Treatment-emergent adverse events with incidence > 10% in any treatment group.

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI	M-H, Fixed, 99% CI
11.4.1 Any adverse event				
Ratjen 2017	98/103	98/101		0.6[0.09,4.08]
11.4.2 Any serious adverse event				
Ratjen 2017	13/103	11/101		1.18[0.38,3.63]
11.4.3 Cough				
Ratjen 2017	46/103	47/101		0.93[0.45,1.91]
11.4.4 Pulmonary exacerbation				
Ratjen 2017	20/103	18/101		1.11[0.44,2.81]
11.4.5 Productive cough				
Ratjen 2017	18/103	6/101		3.35[0.94,11.98]
11.4.6 Nasal congestion				
Ratjen 2017	17/103	8/101		2.3[0.71,7.4]

Favours lumacaftor-ivacaftor   0.01   0.1   1   10   100   Favours placebo

Study or subgroup	Lumacaftor-ivacaftor n/N	Placebo n/N	Odds Ratio M-H, Fixed, 99% CI	Odds Ratio M-H, Fixed, 99% CI
11.4.7 Oropharyngeal pain				
Ratjen 2017	15/103	10/101		1.55[0.51,4.75]
11.4.8 Pyrexia				
Ratjen 2017	15/103	20/101		0.69[0.26,1.81]
11.4.9 Upper abdominal pain				
Ratjen 2017	13/103	7/101		1.94[0.55,6.88]
11.4.10 Headache				
Ratjen 2017	13/103	9/101		1.48[0.45,4.81]
11.4.11 Upper respiratory tract infection				
Ratjen 2017	13/103	10/101		1.31[0.42,4.15]
11.4.12 Sputum increased				
Ratjen 2017	11/103	2/101		5.92[0.79,44.39]
11.4.13 Abdominal pain				
Ratjen 2017	10/103	10/101		0.98[0.29,3.29]
11.4.14 Nausea				
Ratjen 2017	10/103	9/101		1.1[0.32,3.81]
11.4.15 Rhinorrhoea				
Ratjen 2017	10/103	5/101		2.06[0.48,8.89]
11.4.16 Vomiting				
Ratjen 2017	10/103	10/101		0.98[0.29,3.29]
11.4.17 Fatigue				
Ratjen 2017	9/103	11/101		0.78[0.23,2.65]
11.4.18 Respiratory events				
Ratjen 2017	19/103	13/101		1.53[0.56,4.19]

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Analysis 11.5. Comparison 11 Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 5 Sweat chloride concentration (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor N	Placebo N	Mean Difference (SE)	Mean Difference IV, Fixed, 95% CI	Weight	Mean Difference IV, Fixed, 95% CI
11.5.1 up to and including 4 weeks						
Ratjen 2017	103	101	-20.8 (1.327)		100%	-20.8[-23.4,-18.2]
Subtotal (95% CI)					100%	**-20.8[-23.4,-18.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=15.68(P<0.0001)						

Favours lumacaftor-ivacaftor -100 -50 0 50 100 Favours placebo

Analysis 11.6. Comparison 11 Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 6 BMI (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
11.6.1 up to and including 24 weeks						
Ratjen 2017	103	101	0.1 (0.102)		100%	0.1[-0.1,0.3]
Subtotal (95% CI)					**100%**	**0.1[-0.1,0.3]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.98(P=0.33)						

Favours placebo -2 -1 0 1 2 Favours lumacaftor-ivacaftor
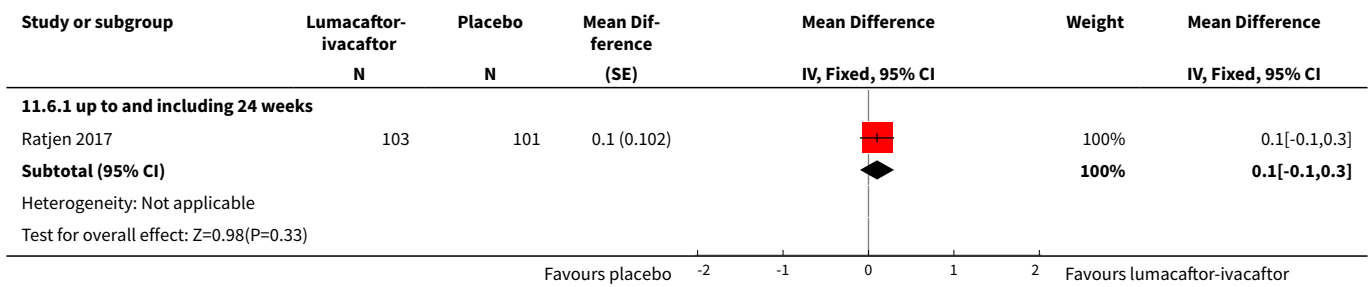
Analysis 11.7. Comparison 11 Lumacaftor (200 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo, Outcome 7 BMI for age z-score (absolute change from baseline).
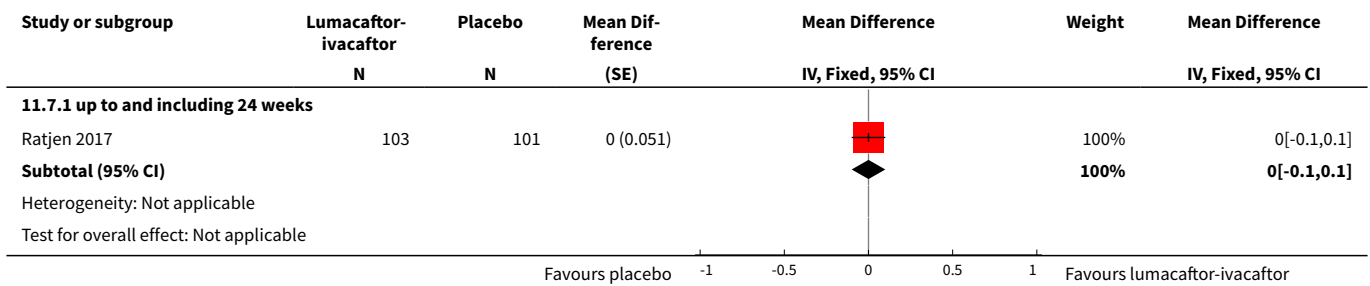
Study or subgroup	Lumacaftor-ivacaftor	Placebo	Mean Difference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
11.7.1 up to and including 24 weeks						
Ratjen 2017	103	101	0 (0.051)		100%	0[-0.1,0.1]
Subtotal (95% CI)					**100%**	**0[-0.1,0.1]**
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						

Favours placebo -1 -0.5 0 0.5 1 Favours lumacaftor-ivacaftor

Comparison 12. Lumacaftor (200 mg once daily monotherapy for 14 days) plus ivacaftor (150 mg or 250 mg twice daily for days 15 to 21) for 21 days

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 FEV$_1$ % predicted (absolute change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 At 21 days	1	59	Mean Difference (IV, Fixed, 95% CI)	1.57 [-2.13, 5.27]
2 Adverse events occurring in 10% or more participants (from days 15 - 21)	1		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
2.1 Cough	1	61	Odds Ratio (M-H, Fixed, 99% CI)	0.61 [0.09, 4.01]
2.2 Pulmonary exacerbation	1	61	Odds Ratio (M-H, Fixed, 99% CI)	1.62 [0.08, 34.55]
2.3 Oropharyngeal pain	1	61	Odds Ratio (M-H, Fixed, 99% CI)	0.77 [0.07, 9.03]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2.4 Nasal congestion	1	61	Odds Ratio (M-H, Fixed, 99% CI)	1.06 [0.10, 11.04]
2.5 Dizziness	1	61	Odds Ratio (M-H, Fixed, 99% CI)	4.01 [0.08, 209.72]
2.6 Prothrombin time prolonged	1	61	Odds Ratio (M-H, Fixed, 99% CI)	2.79 [0.05, 160.31]
2.7 Upper respiratory tract infection	1	61	Odds Ratio (M-H, Fixed, 99% CI)	2.79 [0.05, 160.31]
3 Sweat chloride concentration (mmol/L) (change from baseline)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 At 21 days	1	50	Mean Difference (IV, Fixed, 95% CI)	-7.95 [-13.81, -2.09]

Analysis 12.1. Comparison 12 Lumacaftor (200 mg once daily monotherapy for 14 days) plus ivacaftor (150 mg or 250 mg twice daily for days 15 to 21) for 21 days, Outcome 1 FEV$_1$ % predicted (absolute change from baseline).

Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
12.1.1 At 21 days							
Boyle 2014	38	1.9 (6.9)	21	0.3 (7)		100%	1.57[-2.13,5.27]
Subtotal ***	**38**		**21**			**100%**	**1.57[-2.13,5.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.83(P=0.41)							

Favours placebo -100 -50 0 50 100 Favours lumacaftor-ivacaftor

Analysis 12.2. Comparison 12 Lumacaftor (200 mg once daily monotherapy for 14 days) plus ivacaftor (150 mg or 250 mg twice daily for days 15 to 21) for 21 days, Outcome 2 Adverse events occurring in 10% or more participants (from days 15 - 21).

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
12.2.1 Cough					
Boyle 2014	5/40	4/21		100%	0.61[0.09,4.01]
Subtotal (99% CI)	**40**	**21**		**100%**	**0.61[0.09,4.01]**
Total events: 5 (Lumacaftor-ivacaftor), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.68(P=0.5)					
12.2.2 Pulmonary exacerbation					

Favours lumacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Study or subgroup	Lumacaftor-ivacaftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
Boyle 2014	3/40	1/21		100%	1.62[0.08,34.55]
Subtotal (99% CI)	**40**	**21**		**100%**	**1.62[0.08,34.55]**
Total events: 3 (Lumacaftor-ivacaftor), 1 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.41(P=0.68)					
12.2.3 Oropharyngeal pain					
Boyle 2014	3/40	2/21		100%	0.77[0.07,9.03]
Subtotal (99% CI)	**40**	**21**		**100%**	**0.77[0.07,9.03]**
Total events: 3 (Lumacaftor-ivacaftor), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.27(P=0.78)					
12.2.4 Nasal congestion					
Boyle 2014	4/40	2/21		100%	1.06[0.1,11.04]
Subtotal (99% CI)	**40**	**21**		**100%**	**1.06[0.1,11.04]**
Total events: 4 (Lumacaftor-ivacaftor), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					
12.2.5 Dizziness					
Boyle 2014	3/40	0/21		100%	4.01[0.08,209.72]
Subtotal (99% CI)	**40**	**21**		**100%**	**4.01[0.08,209.72]**
Total events: 3 (Lumacaftor-ivacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.9(P=0.37)					
12.2.6 Prothrombin time prolonged					
Boyle 2014	2/40	0/21		100%	2.79[0.05,160.31]
Subtotal (99% CI)	**40**	**21**		**100%**	**2.79[0.05,160.31]**
Total events: 2 (Lumacaftor-ivacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.51)					
12.2.7 Upper respiratory tract infection					
Boyle 2014	2/40	0/21		100%	2.79[0.05,160.31]
Subtotal (99% CI)	**40**	**21**		**100%**	**2.79[0.05,160.31]**
Total events: 2 (Lumacaftor-ivacaftor), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.51)					

Favours lumacaftor-ivacaftor   0.01   0.1   1   10   100   Favours placebo

Analysis 12.3. Comparison 12 Lumacaftor (200 mg once daily monotherapy for 14 days) plus ivacaftor (150 mg or 250 mg twice daily for days 15 to 21) for 21 days, Outcome 3 Sweat chloride concentration (mmol/L) (change from baseline).
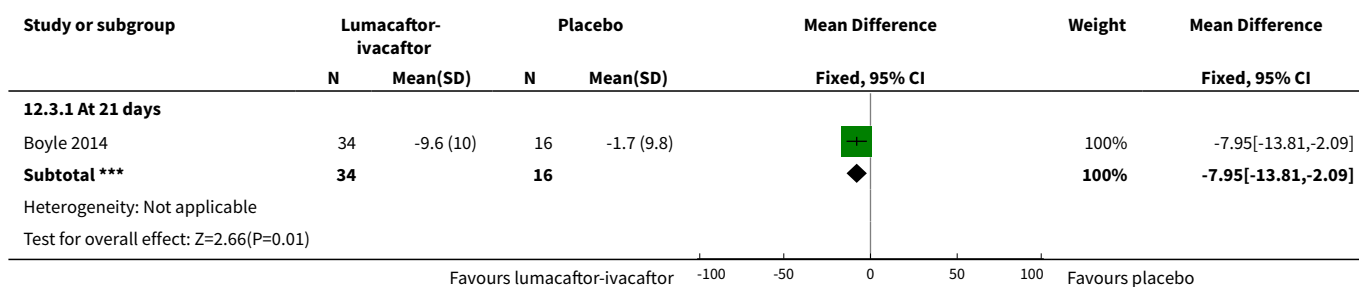
Study or subgroup	Lumacaftor-ivacaftor		Placebo		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
12.3.1 At 21 days							
Boyle 2014	34	-9.6 (10)	16	-1.7 (9.8)		100%	-7.95[-13.81,-2.09]
Subtotal ***	**34**		**16**			**100%**	**-7.95[-13.81,-2.09]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.66(P=0.01)							

Favours lumacaftor-ivacaftor   -100   -50   0   50   100   Favours placebo

Comparison 13. Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 CFQ-R respiratory domain (absolute change from baseline)	1		Mean Difference (Fixed, 95% CI)	Subtotals only
1.1 At 4 weeks	1	504	Mean Difference (Fixed, 95% CI)	5.1 [2.99, 7.21]
1.2 At 24 weeks	1	504	Mean Difference (Fixed, 95% CI)	5.1 [3.20, 7.00]
2 FEV_1 % predicted (relative change from baseline)	2		Mean Difference (Fixed, 95% CI)	Subtotals only
2.1 At week 4	1	18	Mean Difference (Fixed, 95% CI)	3.72 [-7.77, 15.21]
2.2 At week 24	1	504	Mean Difference (Fixed, 95% CI)	6.80 [5.30, 8.30]
3 FEV_1 % predicted (absolute change from baseline)	2		Mean Difference (Fixed, 95% CI)	Subtotals only
3.1 At week 4	2	522	Mean Difference (Fixed, 95% CI)	3.59 [2.40, 4.78]
3.2 At week 24	1	504	Mean Difference (Fixed, 95% CI)	4.0 [3.10, 4.90]
4 Most common adverse events (occurring in at least 10% of participants in either group)	2		Odds Ratio (M-H, Fixed, 99% CI)	Subtotals only
4.1 Cough	2	527	Odds Ratio (M-H, Fixed, 99% CI)	0.70 [0.43, 1.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Pulmonary exacerbation	2	527	Odds Ratio (M-H, Fixed, 99% CI)	0.71 [0.44, 1.16]
4.3 Headache	2	527	Odds Ratio (M-H, Fixed, 99% CI)	1.26 [0.68, 2.35]
4.4 Nasal congestion or nasopharyngitis	2	527	Odds Ratio (M-H, Fixed, 99% CI)	1.09 [0.59, 2.02]
4.5 Increased sputum	1	509	Odds Ratio (M-H, Fixed, 99% CI)	0.86 [0.46, 1.63]
4.6 Haemoptysis	2	527	Odds Ratio (M-H, Fixed, 99% CI)	0.74 [0.37, 1.49]
4.7 Pyrexia	2	527	Odds Ratio (M-H, Fixed, 99% CI)	0.89 [0.44, 1.79]
4.8 Oropharyngeal pain	1	509	Odds Ratio (M-H, Fixed, 99% CI)	0.76 [0.35, 1.63]
4.9 Fatigue	2	527	Odds Ratio (M-H, Fixed, 99% CI)	0.51 [0.23, 1.15]
4.10 Nausea	2	527	Odds Ratio (M-H, Fixed, 99% CI)	1.36 [0.60, 3.12]
5 Time to first pulmonary exacerbation	1		Hazard Ratio (Fixed, 95% CI)	Subtotals only
6 Sweat chloride change from baseline	2		Mean Difference (Fixed, 95% CI)	Subtotals only
6.1 At 4 weeks	2	522	Mean Difference (Fixed, 95% CI)	-9.24 [-11.12, -7.35]
6.2 At 24 weeks	1	504	Mean Difference (Fixed, 95% CI)	-10.1 [-11.40, -8.80]
7 BMI change from baseline	1		Mean Difference (Fixed, 95% CI)	Subtotals only
7.1 At 4 weeks	1	504	Mean Difference (Fixed, 95% CI)	-0.03 [-0.13, 0.07]
7.2 At 24 weeks	1	504	Mean Difference (Fixed, 95% CI)	0.06 [-0.08, 0.20]

Analysis 13.1. Comparison 13 Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone, Outcome 1 CFQ-R respiratory domain (absolute change from baseline).

Study or subgroup	Teza-caftor-iva-caftor	Placebo	Mean Dif-ference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
13.1.1 At 4 weeks						
Taylor-Cousar 2017	248	256	5.1 (1.077)		100%	5.1[2.99,7.21]
Subtotal (95% CI)					**100%**	**5.1[2.99,7.21]**
Heterogeneity: Not applicable						
Test for overall effect: Z=4.73(P<0.0001)						
13.1.2 At 24 weeks						
Taylor-Cousar 2017	248	256	5.1 (0.969)		100%	5.1[3.2,7]
Subtotal (95% CI)					**100%**	**5.1[3.2,7]**
Heterogeneity: Not applicable						
Test for overall effect: Z=5.26(P<0.0001)						

Favours placebo -10 -5 0 5 10 Favours tezacaftor-ivacaftor
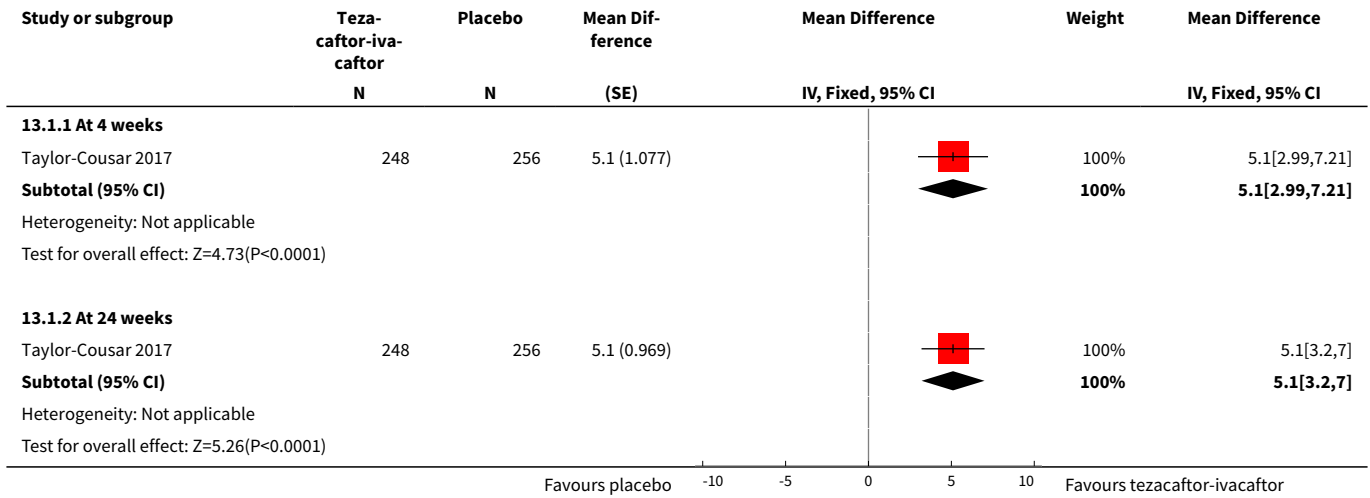
Analysis 13.2. Comparison 13 Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone, Outcome 2 FEV_1 % predicted (relative change from baseline).

Study or subgroup	Teza-caftor-iva-caftor	Placebo	Mean Dif-ference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
13.2.1 At week 4						
Donaldson 2018	14	4	3.7 (5.862)		100%	3.72[-7.77,15.21]
Subtotal (95% CI)					**100%**	**3.72[-7.77,15.21]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.63(P=0.53)						
13.2.2 At week 24						
Taylor-Cousar 2017	248	256	6.8 (0.765)		100%	6.8[5.3,8.3]
Subtotal (95% CI)					**100%**	**6.8[5.3,8.3]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%						
Test for overall effect: Z=8.89(P<0.0001)						

Favours placebo -100 -50 0 50 100 Favours tezacaftor-ivacaftor

Analysis 13.3. Comparison 13 Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone, Outcome 3 FEV_1 % predicted (absolute change from baseline).
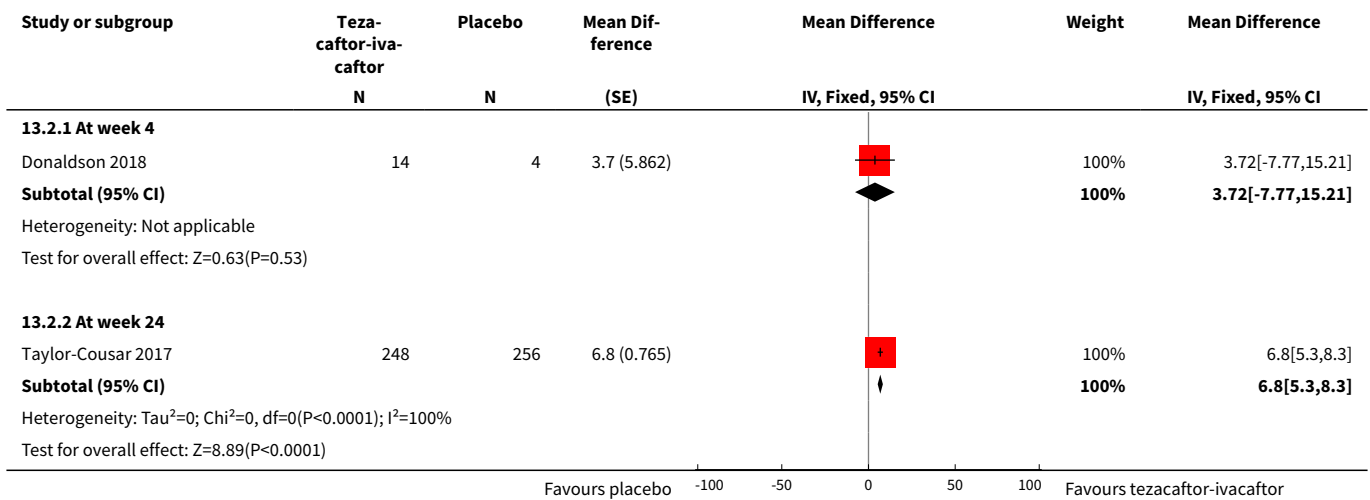
Study or subgroup	Teza-caftor-iva-caftor	Placebo	Mean Dif-ference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
13.3.1 At week 4						
Donaldson 2018	14	4	3.2 (3.725)		2.65%	3.2[-4.1,10.5]
Taylor-Cousar 2017	248	256	3.6 (0.614)		97.35%	3.6[2.4,4.8]

Favours placebo -5 -2.5 0 2.5 5 Favours tezacaftor-ivacaftor

Study or subgroup	Teza-caftor-iva-caftor	Placebo	Mean Dif-ference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Subtotal (95% CI)					100%	3.59[2.4,4.78]

Heterogeneity: Tau²=0; Chi²=0.01, df=1(P=0.92); I²=0%

Test for overall effect: Z=5.92(P<0.0001)

13.3.2 At week 24

| Taylor-Cousar 2017 | 248 | 256 | 4 (0.459) | | 100% | 4[3.1,4.9] |
| Subtotal (95% CI) | | | | | 100% | 4[3.1,4.9] |

Heterogeneity: Not applicable

Test for overall effect: Z=8.71(P<0.0001)

Favours placebo -5 -2.5 0 2.5 5 Favours tezacaftor-ivacaftor
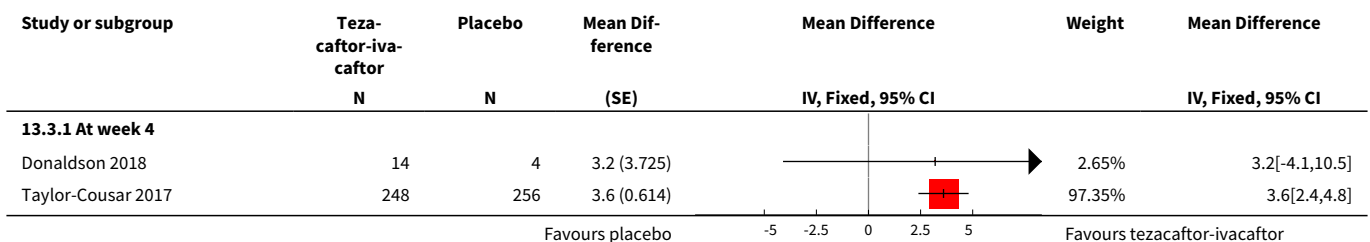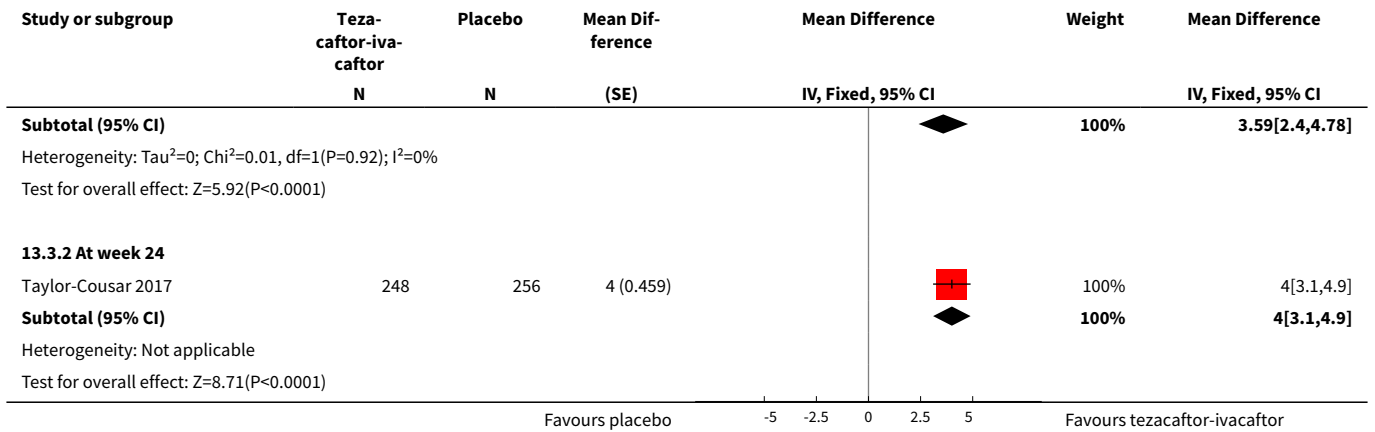

Analysis 13.4.   Comparison 13 Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone, Outcome 4 Most common adverse events (occurring in at least 10% of participants in either group).

Study or subgroup	Tezacaftor-iva-caftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI
13.4.1 Cough					
Donaldson 2018	2/14	0/4		0.97%	1.8[0.03,124.22]
Taylor-Cousar 2017	66/251	88/258		99.03%	0.69[0.42,1.14]
Subtotal (99% CI)	265	262		100%	0.7[0.43,1.15]

Total events: 68 (Tezacaftor-ivacaftor), 88 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.34, df=1(P=0.56); I²=0%

Test for overall effect: Z=1.85(P=0.06)

13.4.2 Pulmonary exacerbation					
Donaldson 2018	2/14	1/4		1.97%	0.5[0.01,17.69]
Taylor-Cousar 2017	75/251	96/258		98.03%	0.72[0.44,1.17]
Subtotal (99% CI)	265	262		100%	0.71[0.44,1.16]

Total events: 77 (Tezacaftor-ivacaftor), 97 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.07, df=1(P=0.79); I²=0%

Test for overall effect: Z=1.8(P=0.07)

13.4.3 Headache					
Donaldson 2018	1/14	0/4		2.19%	1[0.01,84.25]
Taylor-Cousar 2017	44/251	37/258		97.81%	1.27[0.68,2.37]
Subtotal (99% CI)	265	262		100%	1.26[0.68,2.35]

Total events: 45 (Tezacaftor-ivacaftor), 37 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.89); I²=0%

Test for overall effect: Z=0.97(P=0.33)

13.4.4 Nasal congestion or nasopharyngitis					
Donaldson 2018	1/14	1/4		4.32%	0.23[0,12.59]
Taylor-Cousar 2017	42/251	39/258		95.68%	1.13[0.6,2.11]
Subtotal (99% CI)	265	262		100%	1.09[0.59,2.02]

Total events: 43 (Tezacaftor-ivacaftor), 40 (Placebo)

Heterogeneity: Tau²=0; Chi²=1.02, df=1(P=0.31); I²=2%

Favours tezacaftor-ivacaftor 0.001 0.1 1 10 1000 Favours placebo

Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis (Review)

Study or subgroup	Tezacaftor-iva-caftor	Placebo	Odds Ratio	Weight	Odds Ratio
	n/N	n/N	M-H, Fixed, 99% CI		M-H, Fixed, 99% CI

Test for overall effect: Z=0.36(P=0.72)

13.4.5 Increased sputum

| Taylor-Cousar 2017 | 36/251 | 42/258 | | 100% | 0.86[0.46,1.63] |
| Subtotal (99% CI) | 251 | 258 | | 100% | 0.86[0.46,1.63] |

Total events: 36 (Tezacaftor-ivacaftor), 42 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.61(P=0.54)

13.4.6 Haemoptysis

Donaldson 2018	1/14	0/4		2.13%	1[0.01,84.25]
Taylor-Cousar 2017	26/251	35/258		97.87%	0.74[0.36,1.5]
Subtotal (99% CI)	265	262		100%	0.74[0.37,1.49]

Total events: 27 (Tezacaftor-ivacaftor), 35 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.86); I²=0%

Test for overall effect: Z=1.1(P=0.27)

13.4.7 Pyrexia

Donaldson 2018	1/14	0/4		2.35%	1[0.01,84.25]
Taylor-Cousar 2017	28/251	32/258		97.65%	0.89[0.44,1.8]
Subtotal (99% CI)	265	262		100%	0.89[0.44,1.79]

Total events: 29 (Tezacaftor-ivacaftor), 32 (Placebo)

Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.95); I²=0%

Test for overall effect: Z=0.43(P=0.67)

13.4.8 Oropharyngeal pain

| Taylor-Cousar 2017 | 22/251 | 29/258 | | 100% | 0.76[0.35,1.63] |
| Subtotal (99% CI) | 251 | 258 | | 100% | 0.76[0.35,1.63] |

Total events: 22 (Tezacaftor-ivacaftor), 29 (Placebo)

Heterogeneity: Not applicable

Test for overall effect: Z=0.93(P=0.35)

13.4.9 Fatigue

Donaldson 2018	1/14	0/4		2.3%	1[0.01,84.25]
Taylor-Cousar 2017	16/251	31/258		97.7%	0.5[0.22,1.14]
Subtotal (99% CI)	265	262		100%	0.51[0.23,1.15]

Total events: 17 (Tezacaftor-ivacaftor), 31 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.16, df=1(P=0.69); I²=0%

Test for overall effect: Z=2.14(P=0.03)

13.4.10 Nausea

Donaldson 2018	2/14	0/4		3.73%	1.8[0.03,124.22]
Taylor-Cousar 2017	23/251	18/258		96.27%	1.35[0.58,3.13]
Subtotal (99% CI)	265	262		100%	1.36[0.6,3.12]

Total events: 25 (Tezacaftor-ivacaftor), 18 (Placebo)

Heterogeneity: Tau²=0; Chi²=0.03, df=1(P=0.86); I²=0%

Test for overall effect: Z=0.96(P=0.34)

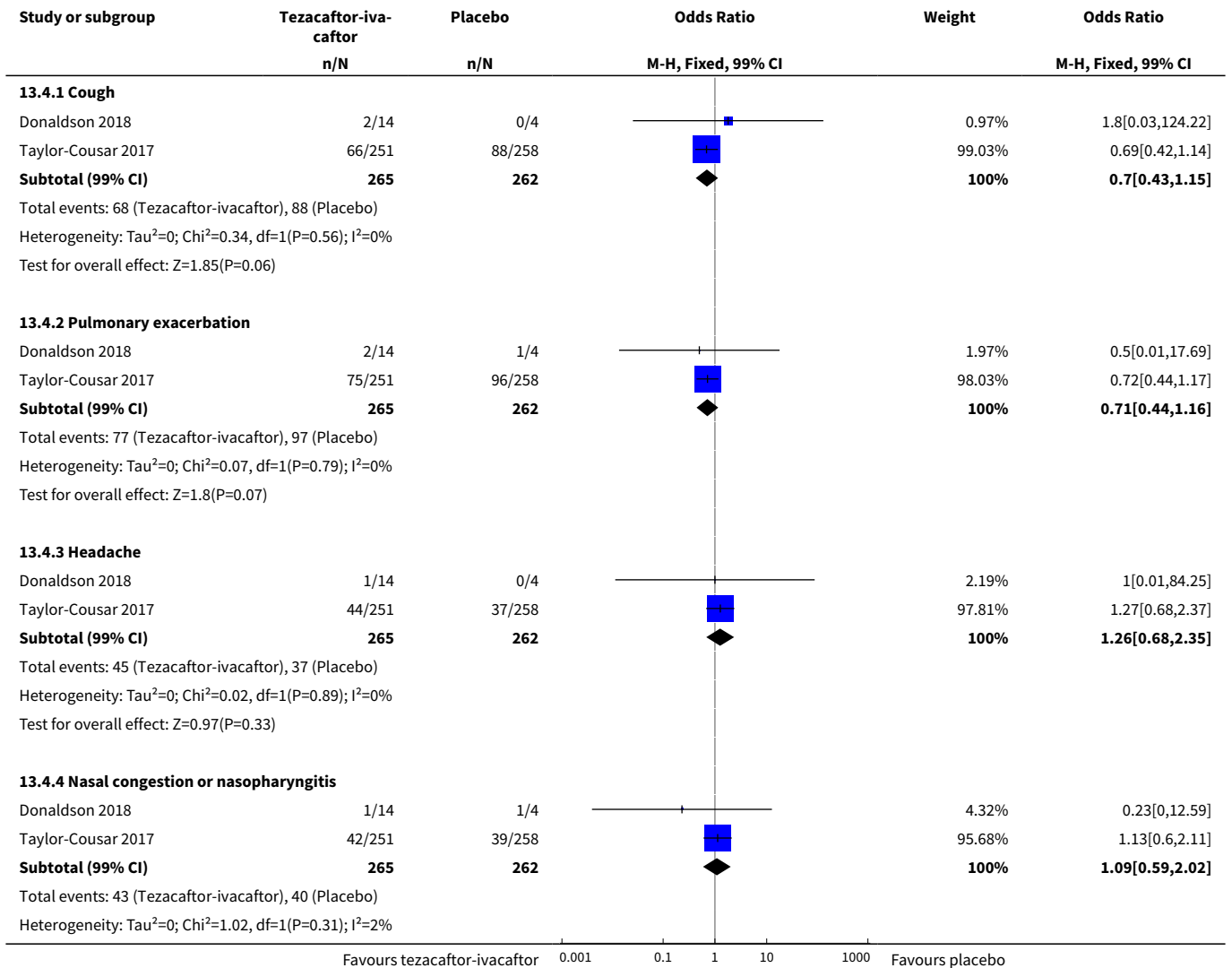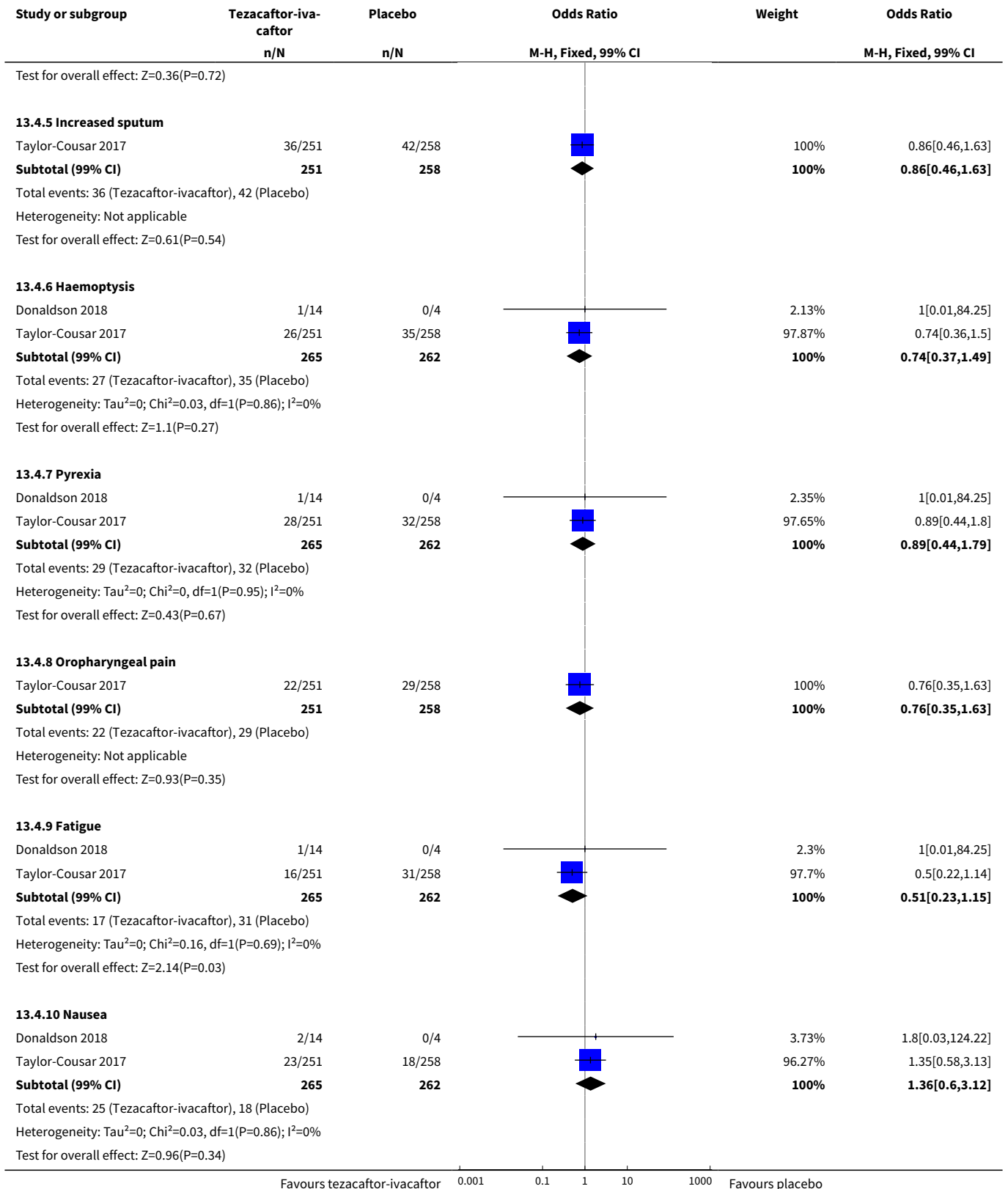Favours tezacaftor-ivacaftor   0.001   0.1   1   10   1000   Favours placebo

Analysis 13.5. Comparison 13 Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone, Outcome 5 Time to first pulmonary exacerbation.

Study or subgroup	Teza-caftor-iva-caftor	Placebo	log[Hazard Ratio]	Hazard Ratio	Weight	Hazard Ratio
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
Taylor-Cousar 2017	248	258	-0.4 (0.169)		0%	0.64[0.46,0.89]

Favours tezacaftor-ivacaftor 0.01 0.1 1 10 100 Favours placebo

Analysis 13.6. Comparison 13 Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone, Outcome 6 Sweat chloride change from baseline.

Study or subgroup	Teza-caftor-iva-caftor	Placebo	Mean Dif-ference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
13.6.1 At 4 weeks						
Donaldson 2018	14	4	-17.2 (7.424)		1.68%	-17.2[-31.75,-2.65]
Taylor-Cousar 2017	248	256	-9.1 (0.97)		98.32%	-9.1[-11,-7.2]
Subtotal (95% CI)					100%	**-9.24[-11.12,-7.35]**
Heterogeneity: Tau²=0; Chi²=1.17, df=1(P=0.28); I²=14.57%						
Test for overall effect: Z=9.6(P<0.0001)						
13.6.2 At 24 weeks						
Taylor-Cousar 2017	248	256	-10.1 (0.663)		100%	-10.1[-11.4,-8.8]
Subtotal (95% CI)					100%	**-10.1[-11.4,-8.8]**
Heterogeneity: Not applicable						
Test for overall effect: Z=15.23(P<0.0001)						

Favours tezacaftor-ivacaftor -100 -50 0 50 100 Favours placebo

Analysis 13.7. Comparison 13 Tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone, Outcome 7 BMI change from baseline.

Study or subgroup	Teza-caftor-iva-caftor	Placebo	Mean Dif-ference	Mean Difference	Weight	Mean Difference
	N	N	(SE)	IV, Fixed, 95% CI		IV, Fixed, 95% CI
13.7.1 At 4 weeks						
Taylor-Cousar 2017	248	256	-0 (0.05)		100%	-0.03[-0.13,0.07]
Subtotal (95% CI)					100%	**-0.03[-0.13,0.07]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.6(P=0.55)						
13.7.2 At 24 weeks						
Taylor-Cousar 2017	248	256	0.1 (0.071)		100%	0.06[-0.08,0.2]
Subtotal (95% CI)					100%	**0.06[-0.08,0.2]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.84(P=0.4)						

Favours placebo -1 -0.5 0 0.5 1 Favours tezacaftor-ivacaftor

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	F508del	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. Small amounts of CFTR do reach the cell membrane; however here, they display defective ion transport, demonstrating that the phe508del mutation is more than just a processing defect. 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 meaningful ion transport across the protein. Individuals have minimal 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 regulator

Table 2. Change from baseline CFQ-R domain scores at 28 days (Clancy 2012)

	Lumacaftor				Placebo
Domain	25 mg (n = 17)	50 mg (n = 17)	100 mg (n = 16)	200 mg (n =18)	(n = 17)
Body	-0.21	-1.63	2.61	0.06	-1.34
Digestion	2.28	-0.72	0.25	2.58	4.62
Eating	-3.66	-7.27*	3.24	-2.58	2.11
Emotion	-3.22	-1.36	3.49	-2.62	4.86
Health Perceptions	-2.84	-6.97*	-0.44	-1.9	5.03
Physical	-5.97	-7.38*	-3.46	-0.98	1.23
Respiratory	-5.22	-6.32*	-1.29	2.22	4.53
Role	-5.94*	-4.6	1.1	-6.53*	2.21
Social	0	-1.01	0.47	-2.64	-0.55
Treatment Burden	4.19	-5.96*	1.42	-0.68	2.46

Table 2.   Change from baseline CFQ-R domain scores at 28 days (Clancy 2012) *(Continued)*

Vitality	-4.65	-7.23*	-1.52	0.73	-2.18
Weight	5.41	2.18	8.83	-4.19	0.3

*statistically significant results versus placebo are highlighted by stars

Table 3.   Frequency of adverse effects occurring in more than one participant in any VX-809 treatment group (Clancy 2012)

	Placebo	Lumacaftor				Total
	n (%)	n (%)				n (%)
Adverse effect n (%)	(n = 17)	25 mg (n = 18)	50 mg (n = 18)	100 mg (n = 17)	200 mg (n = 18)	(n = 45)*
Cough	7 (41.2)	10 (55.6)	6 (33.3)	7 (41.2)	10 (52.6)	40 (88.9)
Headache	3 (17.6)	4 (22.2)	5 (27.8)	2 (11.8)	5 (26.3)	19 (42.2)
Rales	1 (5.9)	6 (33.3)	2 (11.1)	3 (17.6)	3 (15.8)	15 (33.3)
Productive cough	3 (17.6)	2 (11.1)	0 (0.0)	4 (23.5)	6 (31.6)	15 (17.8)
Dyspnoea	1 (5.9)	5 (27.8)	3 (16.7)	2 (11.8)	4 (21.1)	15 (33.3)
Pulmonary exacerbation*	2 (11.8)	4 (22.2)	2 (11.1)	2 (11.8)	4 (21.1)	14 (31.1)
Fatigue	2 (11.8)	3 (16.7)	3 (16.7)	2 (11.8)	3 (15.8)	13 (28.9)
Fever	2 (11.8)	2 (11.1)	1 (5.6)	1 (5.9)	5 (26.3)	11 (24.4)
Nasal congestion	3 (17.6)	2 (11.1)	1 (5.6)	2 (11.8)	2 (10.5)	10 (22.2)
Wheezing	3 (17.6)	1 (5.6)	4 (22.2)	1 (5.9)	0 (0.0)	9 (20.0)
Diarrhoea	3 (17.6)	3 (16.7)	1 (5.6)	2 (11.8)	0 (0.0)	9 (20)
Oropharyngeal pain	3 (17.6)	0 (0.0)	3 (16.7)	0 (0.0)	2 (10.5)	8 (17.8)
Upper respiratory tract infection	1 (5.9)	2 (11.1)	1 (5.6	3 (17.6)	0 (0.0)	7 (15.6)
Sinus congestion	2 (11.8)	1 (5.6)	2 (11.1)	0 (0.0)	1 (5.3)	6 (13.3)
Respiration abnormal	0 (0.0)	1 (5.6)	1 (5.6)	0 (0.0)	4 (21.1)	6 (13.3)
Haemoptysis	2 (11.8)	1 (5.6)	1 (5.6)	0 (0.0)	2 (10.5)	6 (13.3)
Constipation	0 (0.0)	2 (11.1)	2 (11.1)	1 (5.9)	1 (5.3)	6 (13.3)
Abdominal pain	1 (5.9)	3 (16.7)	1 (5.6)	0 (0.0)	1 (5.3)	6 (13.3)
Myalgia	1 (5.9)	0 (0.0)	3 (16.7)	0 (0.0)	1 (5.3)	5 (11.1)

Table 3.   Frequency of adverse effects occurring in more than one participant in any VX-809 treatment group (Clancy 2012) *(Continued)*

Post-tussive vomiting	0 (0.0)	0 (0.0)	2 (11.1)	1 (5.9)	1 (5.3)	4 (8.9)
Nausea	0 (0.0)	3 (16.7)	0 (0.0)	0 (0.0)	1 (5.3)	4 (8.9)
Nasopharyngitis	0 (0.0)	1 (5.6)	0 (0.0)	1 (5.9)	2 (10.5)	4 (8.9)
Dizziness	0 (0.0)	1 (5.6)	0 (0.0)	2 (11.8)	1 (5.3)	4 (8.9)
Back pain	0 (0.0)	2 (11.1)	1 (5.6)	0 (0.0)	1 (5.3)	4 (8.9)
Abdominal pain upper	1 (5.9)	0 (0.0)	0 (0.0)	1 (5.9)	2 (10.5)	4 (8.9)
Sputum abnormal	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	1 (5.3)	3 (6.7)
Epistaxis	1 (5.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (10.5)	3 (6.7)
C-reactive protein increased	0 (0.0)	1 (5.6)	0 (0.0)	2 (11.8)	0 (0.0)	3 (6.7)
Paranasal sinus hypersecretion	0 (0.0)	2 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.4)
Lung hyperinflation	0 (0.0)	0 (0.0)	0 (0.0)	2 (11.8)	0 (0.0)	2 (4.4)

* Unclear why the total number of participants in the study is shown to be 45. The author has been contacted for clarification.

| Adverse effects, n | Placebo | CPX | | | | | | |
	(n = 8)	1 mg (n = 4)	3 mg (n = 4)	10 mg (n = 4)	30 mg (n = 4)	100 mg (n = 5)	300 mg (n = 4)	1000 mg (n = 4)
Abdominal pain	0	0	0	0	0	1	1	1
Asthenia	0	0	0	0	0	0	1	1
Headache	0	0	0	2	1	0	1	0
Pain	0	0	0	1	0	0	2	0
Diarrhoea	0	0	0	0	0	1	1	0
Dizziness	2	0	0	1	0	0	0	0
Lung Disease	0	0	0	1	0	0	0	2
Rhinitis	0	2	0	1	0	0	0	2

CPX: 8-cyclopentyl-1, 3-dipropylxanthine

Table 5. Adverse events (non-serious) reported in Donaldson 2014 (N6022 versus placebo)

	Placebo	N6022				Total
Adverse events, n	(n = 19)	5 mg (n = 10)	10 mg (n = 9)	20 mg (n = 9)	40 mg (n = 19)	(n = 66)
Lymphadenopathy	1	0	0	0	0	1
Chest tightness	1	2	0	0	2	5
Atrioventricular block second degree	0	0	1	0	0	1
Nodal rhythm	0	0	0	1	0	1
Supraventricular extrasystoles	0	0	0	1	0	1
Supraventricular tachycardia	0	0	1	0	0	1
Ventricular extrasystoles	1	0	0	0	0	1
Ventricular tachycardia	0	0	0	1	0	1
Diarrhoea	2	0	1	0	0	3
Nausea	1	1	0	0	1	3
Vomiting	0	0	0	0	2	2
Flatulence	0	0	1	0	0	1
Parosmia	0	0	0	2	0	2
Night sweats	0	0	2	0	0	2
Fatigue	1	1	0	0	2	4
Pyrexia	0	1	0	0	2	3
Infective pulmonary exacerbations of CF	1	1	0	0	1	3
Upper respiratory tract infection	1	0	0	0	0	1
Headache	1	1	1	2	1	6
Cough	7	3	1	3	2	16
Increased bronchial secretion	3	2	2	2	1	10
Nasal congestion	1	3	0	0	1	5
Rales	0	3	0	1	0	4
Total participants with at least one adverse event, n (%)	18 (95%)	9 (90%)	9 (100%)	9 (100%)	15 (79%)	60 (91%)

CF: cystic fibrosis

Table 6. Adverse events with an incidence of ≥ 0.20 events per patient-year in Konstan 2017

Event	Lumacaftor 400 mg twice daily/ivacaftor 250 twice daily (n = 340)	Placebo transitioned to lumacaftor 400 mg twice daily/ivacaftor 250 mg twice daily (n = 176)	Lumacaftor 600 mg once daily/ivacaftor 250 mg twice daily (n = 335)	Placebo transitioned to lumacaftor 600 mg once daily/ ivacaftor 250 mg twice daily (n = 178)
Total exposure in patient-years	570	290	570	300
Infective pulmonary exacerbation	0.980	1.035	1.157	1.080
Cough	0.510	0.573	0.627	0.609
Haemoptysis	0.266	0.200	0.235	0.239
Increased sputum	0.208	0.207	0.224	0.175
Nasopharyngitis	0.194	0.169	Not reported	Not reported
Headache	0.140	0.107	0.129	0.101
Dyspnoea	0.124	0.166	0.117	0.128
Pyrexia	0.114	0.152	0.148	0.148
Upper respiratory tract infection	0.129	0.131	Not reported	Not reported
Diarrhoea	0.093	0.145	0.111	0.101
Abnormal respiration	0.077	0.128	0.088	0.145
Nausea	0.072	0.104	Not reported	Not reported
Fatigue	0.084	0.090	Not reported	Not reported
Abdominal pain	0.087	0.066	0.087	0.084
Oropharyngeal pain	Not reported	Not reported	0.101	0.081
Nasal congestion	Not reported	Not reported	0.104	0.091
Rhinitis	Not reported	Not reported	0.064	0.030
Any adverse event: n (%)	333 (97.9)	176 (100)	331 (98.8)	177 (99.4)
Any serious adverse event: n (%)	143 (42.1)	89 (50.6)	156 (46.6)	77 (43.3)
Any treatment emergent respiratory event: n (%)	99 (29)	67 (38)	102 (30)	67 (38)

Table 7. Secondary efficacy outcomes reported in Konstan 2017

Outcome	Lumacaftor 400 mg twice daily/ivacaftor 250 mg twice daily (n = 340)	Placebo transitioned to lumacaftor 400 mg twice daily/ivacaftor 250 mg twice daily (n = 176)	Lumacaftor 600 mg once daily/ivacaftor 250 mg twice daily (n = 335)	Placebo transitioned to lumacaftor 600 mg once daily/ivacaftor 250 mg twice daily (n = 178)
FEV_1 (% predicted):[1] Week 72	0.5 (95% CI –0.4 to 1.5) P = 0.2806	1.5 (95% CI 0.2, 2.9) P = 0.0254	1.2 (95% CI 0.3 to 2.2) P = 0.0127	1.9 (95% CI 0.6 to 3.2) P = 0.0037
FEV_1 (% predicted):[1] Week 96	0.5 (95% CI –0.7 to 1.6) P = 0.4231	0.8 (95% CI –0.8, 2.3) P = 0.3495	0.0 (95% CI -1.1 to 1.1) P = 0.9682	1.6 (95% CI -0.1 to 3.2) P = 0.0632
FEV_1 (% predicted):[2] Week 72	0.9 (95% CI 0.0 to 1.9) P = 0.0500	1.9 (95% CI 0.6 to 3.2) P = 0.0040	1.7 (95% CI 0.8 to 2.7) P = 0.0003	2.2 (95% CI 1.0 to 3.5) P = 0.0005
FEV_1 (% predicted):[2] Week 96	1.1 (95% CI 0.0 to 2.2) P = 0.0535	1.1 (95% CI –0.5 to 2.6) P = 0.1696	0.7 (95% CI -0.4 to 1.8) P = 0.1966	2.0 (95% CI 0.4 to 3.6) P = 0.0149
FEV_1 (% predicted):[1] Relative change Week 72	1.4 (95% CI –0.3 to 3.2) P = 0.1074	2.6 (95% CI 0.2 to 5.0) P = 0.0332	2.4 (95% CI 0.6 to 4.1) P = 0.0080	3.8 (95% CI 1.4 to 6.1) P = 0.0017
FEV_1 (% predicted):[1] Relative change Week 96	1.2 (95% CI –0·8 to 3·3) P = 0·2372	1·1 (95% CI –1·7 to 3·9) P = 0·4415	0.1 (95% CI -1.9 to 2.1) P = 0.9297	3.6 (95% CI 0.6 to 6.6) P = 0.0172
BMI Week 72	0.69 (95% CI 0.56 to 0.81) P < 0.0001	0.62 (95% CI 0.45 to 0.79) P < 0.0001	0.72 (95% CI 0.60 to 0.84) P < 0.0001	0.52 (95% CI 0.36 to 0.69) P < 0.0001
BMI Week 96	0.96 (95% CI 0.81 to 1.11) P < 0.0001	0.76 (95% CI 0.56 to 0.97) P < 0.0001	0.81 (95% CI 0.66 to 0.95) P < 0.0001	0.55 (95% CI 0.34 to 0.76) P < 0.0001
CFQ-R respiratory domain Week 72	5.7 (95% CI 3.8 to 7.5) P < 0.0001	3.3 (95% CI 0.7 to 5.9) P = 0.0124	3.2 (95% CI 1.4 to 5.1) P = 0.0007	3.3 (95% CI 0.7 to 5.8) P = 0.0116
CFQ-R respiratory domain Week 96	3.5 (95% CI 1.3 to 5.8) P = 0·0018	0.5 (95% CI –2·7 to 3.6) P = 0·7665	1.1 (95% CI -1.1 to 3.2) P = 0.3339	2.0 (95% CI -1.1 to 5.1) P = 0.2033
Pulmonary exacerbations: events per patient year	0.65 (95% CI 0.56 to 0.75)	0.69 (95% CI 0·56 to 0.85)	0.80 (95% CI 0.70 to 0.92)	0.76 (95% CI 0.62 to 0.93)

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Table 7. Secondary efficacy outcomes reported in Konstan 2017 *(Continued)*

Pulmonary exacerbations: events requiring hospital admission per patient year	0.24 (95% CI 0.19 to 0.29)	0.30 (95% CI 0.22 to 0.40)	0.31 (95% CI 0.25 to 0.38)	0.35 (95% CI 0.26 to 0.47)
Pulmonary exacerbations: events requiring IV antibiotics per patient year	0.32 (95% CI 0.26 to 0.38)	0.37 (95% CI 0.29 to 0.49)	0.38 (95% CI 0.32 to 0.46)	0.42 (95% CI 0.33 to 0.54)

BMI: body mass index
CFQ-R: cystic fibrosis questionnaire-revised
CI: confidence interval
FEV_1: forced expiratory volume at one second
IV: intravenous
Unless otherwise stated, all outcomes reported are the mean (95% CI) absolute change from baseline. P values correspond to the within-group change compared to baseline.
1. Calculated using Wang-Hankinson equations.
2. Calculated using Global Lungs Initiative equations.

Table 8. Acute changes in FEV_1 (% predicted) following study drug administration in Ratjen 2017

	Lumacaftor plus ivacaftor mean (SD)	Placebo mean (SD)
Day 1, ≤ 2 hours post dose	n = 91 -5.5 (8.2)	n = 97 -0.1 (5.1)
Day 1, 4 to 6 hours post dose	n = 92 -7.7 (7.3)	n = 96 -1.4 (7.1)
Day 1, 24 hours post dose	n = 38 -4.1 (10.1)	n = 44 -1.7 (6.8)
Day 15, ≤ 2 hours post dose	n = 88 -1.4 (7.0)	n = 87 0.9 (5.5)
Day 15, 4 to 6 hours post dose	n = 86 -1.3 (6.4)	n = 87 0.1 (5.2)
Week 16, ≤ 2 hours post dose	n = 33 1.7 (4.8)	n = 42 0.8 (5.8)
Week 16, 4 to 6 hours post dose	n = 33 0.5 (7.4)	n = 42 0.6 (7.1)
Week 24, ≤ 2 hours post dose	n = 25	n = 23

Table 8. Acute changes in FEV$_1$ (% predicted) following study drug administration in Ratjen 2017 *(Continued)*

	0.3 (4.1)	0.0 (3.4)
Week 24, 4 to 6 hours post dose	n = 24	n = 24
	-2.8 (4.0)	0.1 (4.3)

SD: standard deviation

APPENDICES

Appendix 1. Electronic search strategies

Database/resource	Date searched	Seach strategy
US National Institutes of Health database (clinicaltrials.gov/)	25 January 2018	Cystic fibrosis AND (VX OR corrector)
WHO ICTRP (www.who.int/ictrp/en/)	25 January 2018	Cystic fibrosis AND (VX OR corrector)
European Medicines Agency (www.clinicaltrialsregister.eu/)	25 January 2018	Cystic fibrosis AND (VX OR corrector)

WHAT'S NEW

Date	Event	Description
28 August 2018	Amended	Wording in Background section of the Abstract revised with regard to the populations where CF occurs.

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	**WHO WILL UNDERTAKE THE TASK?**
Protocol stage: draft the protocol	IS, SP with comments from all
Review stage: select which trials to include (2 + $_1$ arbiter)	IS, SP (+ KWS)
Review stage: extract data from trials (2 people)	IS, SP
Review stage: enter data into RevMan	SP, SJN

Review stage: carry out the analysis	SP, SJN
Review stage: interpret the analysis	IS, SP, SJN
Review stage: draft the final review	IS, SP with comments from all
Update stage: update the review	SP

DECLARATIONS OF INTEREST

Dr Ian Sinha declares no potential conflict of interest.

Dr Sanjay Patel declares no potential conflict of interest.

Professor Kevin Southern has attended and has organised educational events that have received financial support from Vertex, the company that has developed and is evaluating some of the agents included in this review.

Dr Sarah J Nevitt declares no potential conflict of interest.

SOURCES OF SUPPORT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Lung clearance index (LCI) was added as an outcome due to the increasing use of this outcome as a measure of lung function in the younger population.

We have added a statement to 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.

Originally, we intended to combine all studies included in the review using a random-effects approach to meta-analysis. However, due to the substantial differences in the designs and interventions employed within the studies, we considered it more appropriate to make separate comparisons within the review, and where small numbers of studies of a similar design and intervention were pooled in meta-analysis, a fixed-effect approach was appropriate.

In line with current Cochrane guidance, we have included summary of findings tables for all comparisons.

INDEX TERMS

Medical Subject Headings (MeSH)

*Mutation; Aminophenols [therapeutic use]; Aminopyridines [therapeutic use]; Benzodioxoles [therapeutic use]; Cystic Fibrosis [*genetics] [*therapy]; Cystic Fibrosis Transmembrane Conductance Regulator [*drug effects] [*genetics]; Drug Combinations; Genetic Therapy [*methods]; Indoles [therapeutic use]; Phenylbutyrates [therapeutic use]; Quinolones [therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans