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Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis (Review)

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[Intervention Review]

Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis

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ABSTRACT

Background

Cystic fibrosis (CF) is a common, life-shortening, genetic disorder in populations of Northern European descent caused by the mutation of a single gene that codes for the production of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein coordinates the transport of salt (and bicarbonate) across cell surfaces, and the mutation most notably affects the airways. In the lungs of people with CF, the defective protein compromises mucociliary clearance and makes the airway prone to chronic infection and inflammation, damaging the structure of the airways and eventually leading to respiratory failure. In addition, abnormalities in the truncated CFTR protein lead to other systemic complications, including malnutrition, diabetes and subfertility.

Five classes of mutation have been described, depending on the impact of the mutation on the processing of the CFTR protein in the cell. In class I mutations, premature termination codons prevent the production of any functional protein, resulting in severe CF. Therapies targeting class I mutations aim to enable the normal cellular mechanism to read through the mutation, potentially restoring the production of the CFTR protein. This could, in turn, normalise salt transport in the cells and decrease the chronic infection and inflammation that characterises lung disease in people with CF.

This is an update of a previously published review.

Objectives

To evaluate the benefits and harms of ataluren and similar compounds on clinically important outcomes in people with CF with class I mutations (premature termination codons).

Search methods

We searched the Cochrane Cystic Fibrosis Trials Register, which is compiled from electronic database searches and handsearching of journals and conference abstract books. We also searched the reference lists of relevant articles. The last search of the Cochrane Cystic Fibrosis Trials Register was conducted on 7 March 2022.

We searched clinical trial registries maintained by the European Medicines Agency, the US National Institutes of Health and the World Health Organization. The last search of the clinical trials registries was conducted on 4 October 2022.

Selection criteria

Randomised controlled trials (RCTs) of parallel design comparing ataluren and similar compounds (specific therapies for class I mutations) with placebo in people with CF who have at least one class I mutation.

Data collection and analysis

For the included trials, the review authors independently extracted data, assessed the risk of bias and evaluated the certainty of the evidence using GRADE; trial authors were contacted for additional data.

Main results

Our searches identified 56 references to 20 trials; of these, 18 trials were excluded. Both the included parallel RCTs compared ataluren to placebo for 48 weeks in 517 participants (males and females; age range six to 53 years) with CF who had at least one nonsense mutation (a type of class I mutation).

The certainty of evidence and risk of bias assessments for the trials were moderate overall. Random sequence generation, allocation concealment and blinding of trial personnel were well documented; participant blinding was less clear. Some participant data were excluded from the analysis in one trial that also had a high risk of bias for selective outcome reporting. PTC Therapeutics Incorporated sponsored both trials with grant support from the Cystic Fibrosis Foundation, the US Food and Drug Administration's Office of Orphan Products Development and the National Institutes of Health.

The trials reported no difference between treatment groups in terms of quality of life, and no improvement in respiratory function measures. Ataluren was associated with a higher rate of episodes of renal impairment (risk ratio 12.81, 95% confidence interval 2.46 to 66.65; P = 0.002; I^2 = 0%; 2 trials, 517 participants). The trials reported no treatment effect for ataluren for the review's secondary outcomes of pulmonary exacerbation, computed tomography score, weight, body mass index and sweat chloride. No deaths were reported in the trials.

The earlier trial performed a post hoc subgroup analysis of participants not receiving concomitant chronic inhaled tobramycin (n = 146). This analysis demonstrated favourable results for ataluren (n = 72) for the relative change in forced expiratory volume in one second (FEV_1) per cent (%) predicted and pulmonary exacerbation rate. The later trial aimed to prospectively assess the efficacy of ataluren in participants not concomitantly receiving inhaled aminoglycosides, and found no difference between ataluren and placebo in FEV_1 % predicted and pulmonary exacerbation rate.

Authors' conclusions

There is currently insufficient evidence to determine the effect of ataluren as a therapy for people with CF with class I mutations. One trial reported favourable results for ataluren in a post hoc subgroup analysis of participants not receiving chronic inhaled aminoglycosides, but these were not reproduced in the later trial, suggesting that the earlier results may have occurred by chance. Future trials should carefully assess for adverse events, notably renal impairment, and consider the possibility of drug interactions. Cross-over trials should be avoided, given the potential for the treatment to change the natural history of CF.

PLAIN LANGUAGE SUMMARY

Ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for cystic fibrosis

Review question

Can ataluren (and similar compounds specifically targeting class I mutations in cystic fibrosis (CF)) improve the quality of life and lung function of people with CF without having adverse effects?

Key messages

What is CF?

In people with CF, the gene encoding a protein called the cystic fibrosis transmembrane conductance regulator (CFTR) is faulty. This especially affects the airways, causing the airway surface to dry out and making it difficult to clear thick mucus. This leads to progressive infection and damages the lungs, shortening life expectancy.

How will ataluren treat CF?

In people with certain CF genetic mutations where the genetic instructions for producing the CFTR protein are interrupted (known as premature termination codon or class I mutations), ataluren (and similar medicines) may be able to skip over the break in the faulty gene sequence and allow the body to produce a corrected version of the CFTR protein. By correcting the protein, the airway surface should remain hydrated, allowing people with CF to better clear their mucus and so develop fewer lung infections.

What did we want to find out?

We wanted to know whether ataluren can improve the quality of life and lung function of people with CF, and whether it can do so without any side effects. We also wanted to measure the effects on lung infections (need for hospital visits or additional antibiotics), survival, nutritional status (weight, body mass index and height) and whether treatment was cost-effective.

What did we do?

We searched for trials that directly compared drugs such as ataluren to placebo (treatment not containing an active drug) or to a different treatment for these specific genetic mutations in any people with CF.

What did we find?

We found two trials including 517 people (males and females between 6 and 53 years of age) comparing ataluren to a placebo. The trials lasted 48 weeks and everyone taking part in the trials had at least one gene with a class I mutation.

Key results

In people taking ataluren, there was no improvement in clinical outcomes such as quality of life, lung function, exacerbations (flare up of disease), sweat chloride (salt) levels or weight compared with people taking placebo. The trials found that kidney damage was more common in people taking ataluren.

The earlier trial analysed their results in a way not originally planned to see whether the effects of ataluren and placebo were different in people using inhaled tobramycin (an antibiotic) on a long-term basis compared with people not taking the inhaled antibiotic. In people taking ataluren but not using inhaled tobramycin, lung function declined at a slower rate and there were fewer exacerbations than in people in the placebo group also not using inhaled tobramycin. The later trial specifically recruited people not taking tobramycin to see whether this really was an effect of the antibiotic, but the investigators did not find any difference between the ataluren and placebo groups for changes in lung function or exacerbations. This suggests that the earlier results occurred by chance.

There were no deaths and we did not find any differences between ataluren and placebo in side effects or nutritional status. Neither trial reported on hospitalisations, extra courses of antibiotics or cost-effectiveness.

We have not found enough high-quality evidence to determine the effect of ataluren for treating CF. We recommend that future trials are designed and reported clearly so that their results can be included in a systematic review.

What are the limitations of the evidence?

We are moderately confident in our findings, but there is some uncertainty due to how widely the results varied between participants. We are satisfied that everyone taking part had an equal chance of being in either group (ataluren or placebo) and that no one could work out which group the next person would be put into (so that healthier people did not receive the treatment and make the results seem better). We believe that the clinicians running the trials and those taking part in the trials did not know which treatment each person was receiving. We have some concerns about the emphasis the investigators of one trial placed on the results of a comparison they had not planned (the use of long-term inhaled tobramycin). Unfortunately, that trial did not report all its results clearly. Sometimes, the results were reported in a way that meant they could not be used in this review, and sometimes the information was not reported at all. This affected our confidence in the overall results.

Trial funding sources

Both trials were sponsored by PTC Therapeutics Incorporated, who make ataluren. The Cystic Fibrosis Foundation, the US Food and Drug Administration's Office of Orphan Products Development and the US National Institutes of Health also supported the trials.

How up to date is this evidence?

We last searched for evidence on 4 October 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Ataluren versus placebo for people with cystic fibrosis with class I mutations (PTCs)

Ataluren versus placebo for people with cystic fibrosis with class I mutations (PTCs)

Patients or population: adults and children with CF with at least one class I mutation (PTC)

Settings: outpatient

Intervention: oral ataluren 40 mg/kg/day (in divided doses)

Comparison: oral placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Ataluren				
Health-related quality of life: mean change from baseline in CFQ-R respiratory domain score Scale: age-appropriate versions of the CFQ-R questionnaire **Follow-up:** 48 weeks	There was no difference between groups in CFQ-R score. One trial reported that the score was 0.27 points higher in the ataluren group (3.55 points lower to 4.10 points higher). The second trial reported no difference in CFQ-R in either the 6- to 13-year age group or the 14-years-and-over age group.		NA	506 (2 studies)[a,b]	⊕⊕⊕⊕ **High**	Data provided by investigators were analysed via MMRM analysis. The second trial did not present data for analysis and we have reported their results directly from the paper.
Respiratory function: FEV_1 % predicted (relative change from baseline)	The mean (SD) relative change from baseline in the placebo group was -5.5% (12.56%).	The mean relative change from baseline in the ataluren group was 2.97% higher (0.58 lower to 6.52 higher).	NA	203 (1 study)	⊕⊕⊕⊕ **High**	Data provided by investigators were analysed via MMRM analysis.

Follow-up: 48 weeks						We were unable to combine results for this outcome, but we were able to combine the results in one of the subgroup analyses. In the group of participants not receiving chronic inhaled aminoglycosides, the combined data showed no difference between groups (MD 1.84%, 95% CI -0.90 to 4.58; P = 0.19, I^2 = 65%; 2 trials, 399 participants).
Adverse events relating to treatment **Follow-up:** 48 weeks	Acute kidney injury was more common in the ataluren group (RR 12.81, 95% CI 2.46 to 66.65; P = 0.02; 2 trials, 517 participants). Oropharyngeal pain was more common in the ataluren group (RR 0.28, 95% CI 0.10 to 0.83; P = 0.02; 1 trial, 238 participants). There was no difference between groups for any other adverse events relating to treatment, including: diarrhoea; abdominal pain; vomiting; nausea; pyrexia; upper respiratory tract infections; sinusitis; rhinitis; headache; pulmonary exacerbation; cough; haemoptysis; nasopharyngitis; influenza; pharyngitis; and nephrolithiasis.		NA	517 (2 studies)	⊕⊕⊕⊖ **Moderate**[c]	Adverse events were graded by severity (1 to 4); however, details of criteria for grade 1 to 3 classifications were not reported. Adverse events occurring in more than 10% of participants were reported. There was no difference between treatment groups for all other recorded adverse events.
Pulmonary exacerbations: protocol-defined Scale: rate **Follow-up:** 48 weeks	The mean (SD) protocol-defined pulmonary exacerbation rate using modified Fuchs' criteria in the placebo group was 1.78 (2.15).	The mean protocol-defined pulmonary exacerbation rate using modified Fuchs' criteria in the ataluren groups was 0.36 lower (0.89 lower to 0.17 higher).	NA	232 (1 study)	⊕⊕⊕⊕ **High**	Data provided by investigators were analysed via MMRM analysis.
	The mean (SD) protocol-defined pulmonary exacerbation rate using expanded Fuchs' criteria in the placebo group was 1.13 (2.52).	The mean protocol-defined pulmonary exacerbation rate using expanded Fuchs' criteria in the ataluren groups was 0.18 lower (0.66 lower to 0.30 higher).	NA	274 (1 study)	⊕⊕⊕⊕ **High**	

Nutrition and growth: change in weight (kg), BMI (kg/m^2) or height (m) **Follow-up:** 48 weeks	No differences were found between treatment groups for changes in body weight or BMI.		NA	506 (2 studies)	⊕⊕⊕⊕ **High**	Data provided by investigators were analysed via MMRM analysis. One trial reported data for BMI (MD -0.07, 95% CI -0.32 to 0.19); the second trial reported narratively.
Sweat chloride level - change from baseline Scale: mmol/L **Follow-up:** 48 weeks	The mean (SD) change from baseline in the placebo group was -0.6 (10.27) mmol/L.	The mean change from baseline in the ataluren group was 0.70 mmol/L lower (3.41 mmol/L lower to 2.01 mmol/L higher).	NA	194 (1 study)	⊕⊕⊕⊕ **High**	Data provided by investigators were analysed via MMRM analysis.
Mortality rate **Follow-up:** 48 weeks	Both trials reported zero deaths in both treatment groups.		NA	518 (2 studies)	⊕⊕⊕⊕ **High**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
BMI: body mass index;**CF**: cystic fibrosis; **CFQ-R**: Cystic Fibrosis Questionnaire - Revised (Quittner 2009); **CI**: confidence interval; **FEV$_1$**: forced expiratory volume in one second; **ITT**: intention-to-treat; **MD**: mean difference; **MMRM**: mixed-model repeated-measures analysis (based on the average effect across all post-baseline visits); **PTC**: premature termination codon; **RR**: risk ratio; **SD**: standard deviation.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Kerem 2014 stated that 238 participants were randomised, 232 were included in the ITT population and 203 completed the study. It is unclear how many participants were evaluated for the outcome.

bKerem 2014 provided insufficient data to conduct analyses.
cDowngraded due to imprecision demonstrated by wide CIs.

BACKGROUND

A glossary of terms specific to this review can be found in Appendix 1. A more general glossary of terms used in Cochrane systematic reviews can be accessed at Cochrane Glossary.

Description of the condition

Cystic fibrosis (CF) is a common, life-shortening, genetic disorder in populations of Northern European descent (less common in other ethnic groups (Farrell 2018). In the UK, around one in 3000 newborn infants are affected and, in 2013, the median predicted survival was reported as just over 36 years of age (UK CF Trust 2014; Welsh 2001). The condition is caused by the mutation of a single gene, which codes for the production of the cystic fibrosis transmembrane conductance regulator (CFTR) protein (Welsh 2001). After transcription (being produced in the centre of the cell), the protein is transported to the cell membrane, where it has an important role as a chloride channel, coordinating the transport of salt across cell surfaces (Boucher 2007).

Lung disease is the major cause of morbidity and mortality in CF (Davis 2006). In the airways, the CFTR protein does not function correctly, resulting in increased fluid and sodium resorption away from the airway surface; this, in turn, leads to a dehydrated airway surface liquid and compromised clearance of secretions (Boucher 2007). The resulting thick mucus in the airway provides a site for infection. Chronic airway infection and inflammation damage the structure of the airways, eventually resulting in respiratory failure.

Approximately 2000 mutations of the *CFTR* gene have been described. Five classes of mutation have been characterised, depending on the impact of the mutation on the processing of the CFTR protein in the cell (CFMD 2011) (Table 1).

This review focuses on class I mutations, which stop the normal protein-producing mechanisms of the cell, meaning that no significant amounts of CFTR protein are produced. These mutations change the sequence of the *CFTR* gene, with a piece of DNA inserted telling cells to stop producing the protein. The normal process of producing a protein in the cell is called 'transcription', and this is faulty in class I mutations. There are different ways class I mutations cause this effect: they can insert a sequence of DNA that makes no sense (a nonsense mutation) or they can produce a sequence that directs the normal cellular mechanism to stop (a stop codon mutation). Collectively, these different types of mutation are known as premature termination codons (PTCs), but they essentially have the same outcome of no functional protein being produced (Friedman 2014; McElroy 2013; Nicholson 2010).

Class I mutations are seen in approximately 10% of people with CF (with higher proportions seen in the Ashkenazi Jewish population) and result in a severe CF phenotype, with no significant functional protein being synthesised (Kerem 1997; McKone 2006).

Description of the intervention

Advances in the understanding of the molecular genetics of CF have led to the development of novel mutation-specific therapies. One potential strategy has been to correct class I mutations (PTCs) by using drugs that mask the abnormal gene sequence of the mutation and enable the normal cellular mechanism to read through the mutation and produce a full-length protein. The CFTR protein would then be transported normally to the cell membrane, where it might correct the CF salt transport defect.

Previous studies have demonstrated that aminoglycoside antibiotics (e.g. gentamicin) have the ability to read through class I mutations (PTCs), resulting in the expression of full-length CFTR protein and significant changes in the salt-transporting defect towards normal (Clancy 2001; Howard 1996; Wilschanski 2003a). Although gentamicin is widely used as an antibiotic for people with CF, it is not an ideal agent for long-term treatment because of concerns over renal and ototoxicity (Wilschanski 2003a).

High-throughput screening has identified a molecule called ataluren (formerly PTC124), which has potential as an oral class I (PTC) therapy (McElroy 2013; Welch 2007). In the laboratory, ataluren has been shown to have the ability to enable the read through of class I (PTC) mutations (Welch 2007).

How the intervention might work

By correcting the underlying molecular genetic defect, ataluren and related compounds may reverse the abnormal salt transport that characterises CF. This may restore the ability of the airway to prevent airway infection and inflammation and improve respiratory function. In addition, as a systemic treatment, ataluren may have an effect on other parts of the body that are impacted by the CF salt transport defect.

Why it is important to do this review

A number of different mutation-specific therapies are under investigation. These therapies include potentiators, which improve the compromised function of the CFTR protein that has reached the cell membrane (class III and IV mutations), and correctors, which increase the amount of CFTR protein in the cell membrane (class II mutations) (Table 1). Cochrane Reviews assessing both potentiator and corrector therapies have already been published (Skilton 2019; Southern 2020). At present, there are no known trials for therapies specific to class V mutations.

It is important that the randomised controlled trials (RCTs) assessing ataluren or similar compounds are critically appraised. This will allow analysis of the data outlining the benefits and harms of these therapies in people with CF. It is important that funding bodies have a clear evidence base on which to assess novel mutation-specific CF therapies. It is likely that these therapies will represent a significant healthcare resource. In addition, a critical appraisal of included trials will help inform future trial design.

OBJECTIVES

To evaluate the benefits and harms of ataluren and similar compounds on clinically important outcomes in people with CF with class I mutations (premature termination codons).

METHODS

Criteria for considering studies for this review

Types of studies

We included RCTs of parallel design (published or unpublished). We excluded quasi-RCTs due to a greater risk of selection bias. We reviewed cross-over trials individually to evaluate whether data from the first treatment arm could be included; however, because

these therapies aim to correct the underlying gene defect, there is significant potential for longer-term impact on outcomes, and this is not an ideal trial design.

Types of participants

We included trials involving children or adults with CF, of any severity, as confirmed by either the presence of two disease-causing mutations or a combination of a positive sweat test and recognised clinical features of CF. We only included trials in which participants had at least one PTC (nonsense or stop codon) mutation.

Types of interventions

We included trials in which ataluren (or a similar compound for PTC class I mutations) was compared with either placebo or another intervention. We excluded trials that combined therapies for PTC class I mutations with other mutation-specific therapies. No trials comparing different dosing regimens of these therapies were eligible for inclusion based on the aforementioned criteria. In future updates, we will include trials comparing different dosing regimens of therapies for PTC class I mutations if we identify such trials.

Types of outcome measures

Primary outcomes

1. 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 subdomains
2. Measures of respiratory function (litres or per cent (%) predicted for age, sex and height)
   a. Forced expiratory flow rate in one second (FEV_1; relative change from baseline)
   b. FEV_1 (absolute values)
   c. Forced vital capacity (FVC; absolute values and relative change from baseline)
3. Adverse events
   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 effects or those that persist even after treatment is discontinued)

Secondary outcomes

1. Survival
   a. Time to event (death or lung transplant)
   b. Mortality rate
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. Pulmonary exacerbations (either physician- or protocol-defined)
6. Radiological measures of lung disease (assessed using any scoring system)
   a. Chest radiograph score
   b. Computed tomography (CT) score
7. Acquisition of respiratory pathogens
   a. *Pseudomonas aeruginosa*
   b. *Staphylococcus aureus*
   c. *Haemophilus influenzae*
   d. Other significant pathogens
8. Eradication of respiratory pathogens (as defined by trial authors)
   a. *P aeruginosa*
   b. *S aureus*
   c. *H influenzae*
   d. Other significant pathogens
9. Nutrition and growth (measured as relative changes from baseline; including z scores or centiles)
   a. Weight
   b. Body mass index (BMI)
   c. Height
10. Sweat chloride (change from baseline) as a measure of CFTR protein function in sweat glands
11. Cost-effectiveness (cost utility assessed as a comparison of impact on quality of adjusted life years)

Search methods for identification of studies

We searched for all relevant published and unpublished trials without restrictions on language, year or publication status.

Electronic searches

We identified relevant trials from the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register using the term 'drugs that correct stop codon mutations'.

This register has been 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 prospective handsearching of two journals: *Pediatric Pulmonology* and *Journal of Cystic Fibrosis*. We identified unpublished work 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 Cochrane Cystic Fibrosis and Genetic Disorders Group website.

The date of the most recent search was 7 March 2022.

We also searched the following databases and trial registries:

1. US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov; searched 4 October 2022);
2. World Health Organization International Clinical Trials Registry Platform (trialsearch.who.int/; searched 4 October 2022);
3. European Union Clinical Trials Register (www.clinicaltrialsregister.eu; searched 4 October 2022).

For search strategies, please see the table in the appendices (Appendix 2).

Searching other resources

We checked the bibliographies of included trials and any relevant systematic reviews identified for further references to relevant trials. We also contacted the authors of included trials, leaders in the field and companies known to be developing and investigating therapies for PTC class I mutations to identify any trials that may have been missed by these searches.

Data collection and analysis

Selection of studies

Two review authors (AA and Colin Higgins (CH)) independently assessed the suitability of each trial identified by the searches for the first version of this review. Two review authors (AA and IS) independently assessed their suitability for this review update. If any disagreement had arisen on the suitability of a trial for inclusion in the review, we would have attempted to reach a consensus by discussion, failing which, a third author (KS) would have arbitrated.

Data extraction and management

Two authors (AA and CH for the first review; AA and IS for this review update) independently extracted relevant data from the included trials using a standardised data extraction form. If any disagreement had arisen on data extraction, we would have attempted to reach a consensus by discussion, failing which, a third author (KS) would have arbitrated.

We intended to extract QoL scores ideally as relative changes from baseline, calculated as ((measurement at end of treatment - measurement at baseline)/measurement at baseline) x 100. However, data were not reported for this analysis, and, instead, we extracted the absolute change from baseline. We extracted data for FEV_1 (relative change from baseline). The mean and standard error of the mean (SEM) for relative changes from baseline in FEV_1 and FVC were reported at 8, 16, 24, 32, 40 and 48 weeks through graphical representation (Kerem 2014); two review authors (AA and CH) independently estimated these data. Regarding adverse events, we extracted data for severe adverse events (i.e. participants who required discontinuation of therapy). The Kerem trial report presented data for adverse events occurring in more than 10% of participants and the Konstan trial report presented data for adverse events occurring in 5% or more of participants; however, neither report provided information regarding whether treatment required interruption.

With regard to the secondary outcome, pulmonary exacerbations, we extracted the rate of pulmonary exacerbations and noted both protocol-defined and physician-defined rates. For the nutrition and growth outcome, the Kerem trial reported insufficient data for changes from baseline in each treatment arm. Instead, we extracted the difference in change in body weight and BMI between the ataluren and placebo arms. For total lung CT score and sweat chloride concentration, we extracted absolute changes from baseline.

In future updates, if we include trials with different dosing regimens, we will combine the results of all dosing regimens together in a single analysis and subsequently undertake a subgroup analysis to assess the doses individually. We planned to report data as immediate (up to and including one month), medium term (over one month and up to six months) and long term (over six months). We extracted data for up to 48 weeks and estimates at 8, 16, 24, 32 and 40 weeks (when presented) for selected outcomes. Due to the limited data reported by the two included trials, we have only been able to combine data for some outcomes.

Assessment of risk of bias in included studies

Two authors (AA and CH for the first review; AA and IS for this review update) independently assessed the risk of bias for the included trials using the Cochrane risk of bias tool (Higgins 2017). This included assessment of the following methodological aspects of the trials:

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

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

Measures of treatment effect

For binary outcomes, we calculated the treatment effect for each outcome using the risk ratio (RR) and 95% confidence intervals (CIs). However (in a post hoc change), for the analysis of individual adverse events, we have used 99% CIs because the type I error rate (e.g. false positive) is greatly inflated with numerous tests. For continuous outcomes, we calculated the mean change from baseline and standard deviation (SD) for each group. We converted any reported SEMs to SDs. We calculated the mean difference (MD) and 95% CIs. One trial report did not state the number of participants for each time point for the 8-weekly estimates of the relative change from baseline in FEV_1 (as well as the subgroup analysis by chronic inhaled tobramycin use for this outcome) and FVC (Kerem 2014). For these estimated data, because the withdrawal rate was 14% in the ataluren group and 11% in the placebo group, we felt it appropriate to use the respective ITT population for each treatment group and subgroup. For QoL, both studies used the CFQ-R questionnaire, and we intended to calculate the MD and 95% CIs; however, the studies reported insufficient data.

In the included trials, investigators analysed continuous outcomes over 48 weeks via a mixed-model repeated-measures analysis (MMRM) based on the average effect across all post-baseline visits (Kerem 2014; Konstan 2020). Such an analysis is longitudinal and uses all available data at every visit. We have presented week 48 data for the relative change in FEV_1, pulmonary exacerbation rate, total lung CT scores and change in sweat chloride concentration from the MMRM model for the effect at 48 weeks derived from the treatment, by visit term in the model (so data presented as 'up to 48 weeks' are the estimates from the model at the 48-week time point). This also allows for covariate adjustment (baseline value, treatment, visit, treatment-by-visit interaction, baseline-by-visit interaction) and stratification (inhaled antibiotics (yes or no), baseline age (under 18 versus 18 years and over), and baseline per cent predicted FEV_1 (40% up to 65% versus 65% and up to 90%)).

In future updates, if we identify any trials that report time-to-event outcomes, we will use measures of survival analysis and report hazard ratios and 95% CIs between different arms of the trial. Furthermore, if different trials do not report change data, but instead present absolute post-treatment data without baseline data (so it is not possible to calculate change data), we will use absolute post-treatment data instead of change from baseline. However, if the report presents baseline and post-treatment data for any outcome, we will calculate SDs for the change from baseline (e.g. if the CI is available). When there is not enough information available to calculate the SDs for the changes, we aim to impute them from other trials in the review where the data are available and trials are similar (i.e. if the trials used the same measurement scale, had the same degree of measurement error and had the same time periods between baseline and measurement of the final value). If neither of these methods is possible, we will impute a change-from-baseline SD from another trial, making use of an imputed correlation coefficient following methods described in Chapter 23 in the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2022).

Unit of analysis issues

Within this review, we only included results from RCTs of parallel design in which individual trial participants were randomised. We also reviewed cross-over trials on an individual basis. However, we could not extract data from the first arm and, hence, we excluded them. We did not identify any cluster-RCTs. In future updates, we will exclude cluster-RCTs because this is not an appropriate study design for this type of intervention.

Dealing with missing data

In order to allow an ITT analysis, we extracted data on the number of participants with each outcome event, by allocated treatment group, regardless of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up. We recorded the number of participants with outcome data and checked whether this was consistent with the number of originally randomised participants. If any data were missing or unclear, we contacted the primary investigators for clarification. Specifically, we have contacted the authors of one excluded cross-over trial on two occasions, asking whether data are available from the first arm of the trial and, if so, requesting that the investigators share these data with us (Pradal 2002). To date, we have not received a response from the authors. However, if the first-arm data from these trials are made available to us in the future, we will reassess this trial for inclusion. We also contacted the authors of a second cross-over trial and were informed that the data are held by PTC Therapeutics (Sermet-Gaudelus 2010). We did not receive a response to our request for the first-arm data.

Assessment of heterogeneity

We assessed heterogeneity through a visual examination of the combined data presented in the forest plots, and by considering the I^2 statistic (Higgins 2003), together with Chi^2 values and their CIs (Deeks 2019). This approach reflects the likelihood that variations in results across trials are due to heterogeneity rather than chance, and we interpreted the I^2 statistic using the following simple classification:

1. 0% to 40% might not be important;
2. 30% to 60% may represent moderate heterogeneity;
3. 50% to 90% may represent substantial heterogeneity;
4. 75% to 100% may represent considerable heterogeneity.

Assessment of reporting biases

In order to identify selective outcome reporting, where possible we compared outcomes defined in the studies' protocols with those reported in their full publications. We explored the protocols of the included trials (found on the aforementioned clinical trials registries) for evidence of selective reporting bias. In future, if the protocol for an included trial is not available publicly, we will contact the primary investigators, corresponding author(s) or relevant pharmaceutical company for a copy. We also compared outcomes listed in the Methods section of the studies' final papers with those presented in the Results section. For negative findings that were reported either only partially or not at all, we contacted primary investigators for these data, which included: CFQ-R score; weight; BMI; relative change in FVC; adverse events that led to interruption of treatment; grading classification of adverse events; hospitalisations; extra courses of antibiotics; and disruptions to school or work attendance. We did not receive any replies.

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

Data synthesis

We used a random-effects model to analyse the data, regardless of the value of the I^2 statistic.

Subgroup analysis and investigation of heterogeneity

We planned to investigate any heterogeneity that we identified using subgroup analyses of potential confounding factors, if sufficient numbers (at least 10 trials) were available. For this review, we planned that these confounding factors would be:

1. age (children (defined as younger than 18 years of age) versus adults);
2. sex;
3. intervention used.

We did not plan any subgroup analyses by antibiotic use. However, one included trial presented a post hoc subgroup analysis by inhaled tobramycin use, which we have reported in the Results section below (Kerem 2014). Subsequently, a further

trial was conducted that excluded participants who were using long-term inhaled aminoglycosides within the preceding four months (Konstan 2020). This difference in participant baseline characteristics is also a potential confounding factor for future updates.

The analysis in this review is based on aggregate data because we have no individual participant data. We will incorporate such analysis in future updates if these data are available.

Sensitivity analysis

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

Summary of findings and assessment of the certainty of the evidence

We specified in our protocol that we would present three tables: the first for outcomes measured at up to one month; the second for outcomes measured between one and six months; and the third for longer-term outcomes (over six months). We felt that data from previous trials, as well as reviews by Skilton 2019 and Southern 2020, highlight the potential for a rapid response to this type of intervention and planned to present these in the first table. But we were also interested in illustrating evidence of a sustained response in the short to medium term, because we feel this is important for stakeholders. Thus, we aimed to present such data in the second table. At present, data for short- and medium-term outcomes are not available; therefore, we have presented a summary of findings table for longer-term outcomes (Summary of findings 1).

As planned, we have presented the following outcomes in the summary of findings table: QoL, respiratory function measures (FEV_1), adverse events, pulmonary exacerbations, nutrition and growth, and sweat chloride level. In a post hoc change, we have also added the outcome of mortality.

We determined the certainty of the evidence using the GRADE approach, and downgraded evidence in the presence of a high risk of bias in at least one trial, indirectness of the evidence, unexplained heterogeneity or inconsistency, imprecision of results and a high probability of publication bias. We downgraded the evidence by one level if we considered the limitation to be serious and by two levels if we considered it to be very serious. Under the GRADE approach, evidence can be upgraded if a large treatment effect is demonstrated with no obvious biases, or if a dose–response effect exists.

RESULTS

Description of studies

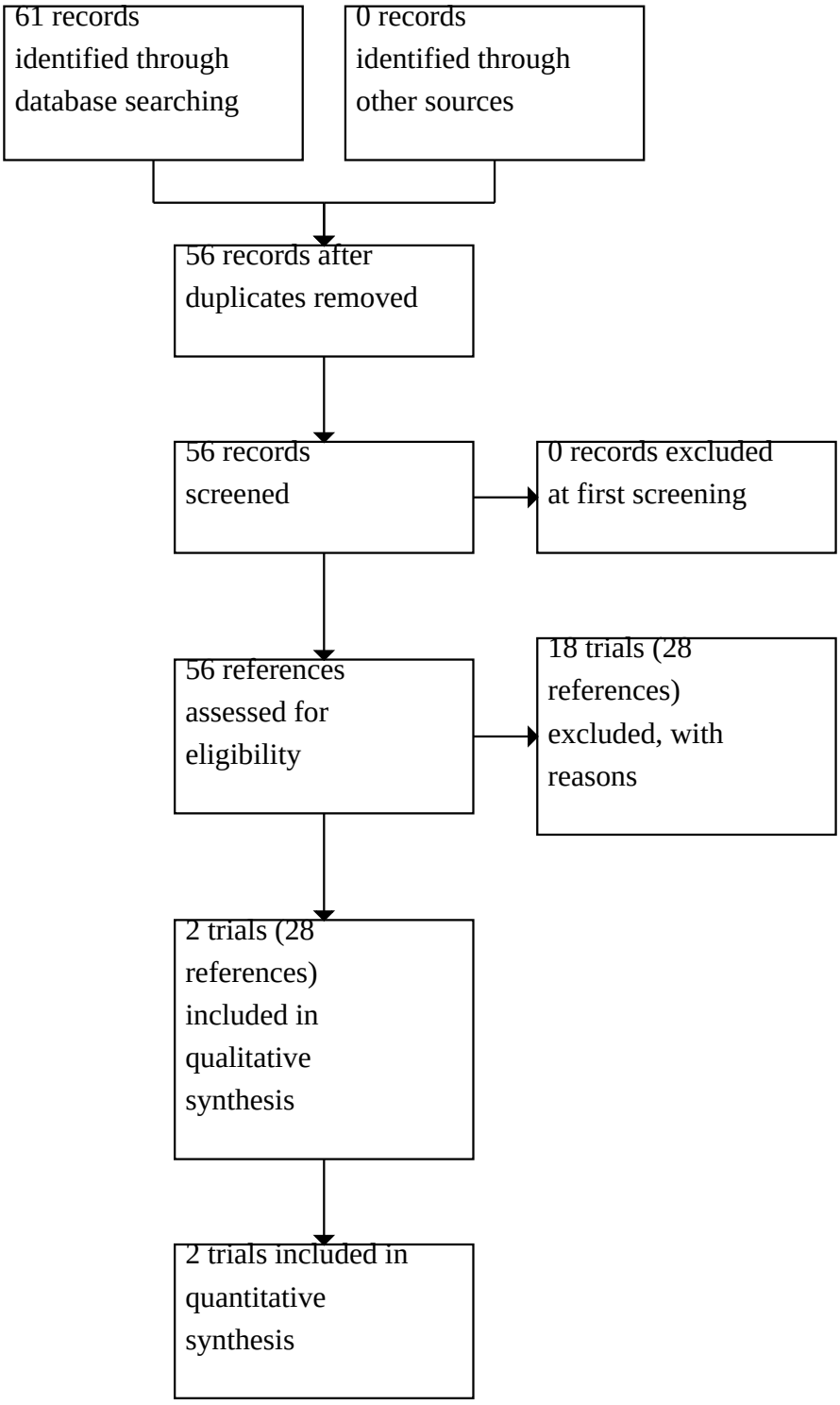
Descriptions of the included and excluded studies are provided in the Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

The search of the Group's Cystic Fibrosis Trials Register identified 44 publications (abstracts and full papers) representing seven trials. The search of the online clinical trials registries identified 13 trials with a single reference each (NCT03670472; NCT04126473; NCT00351078; NCT03256799; NCT03256968; NCT00376428; NCT03624101; NCT04135495; NCT00351078; NCT03256799; NCT03256968; NCT03670472; NCT04126473), as well as four additional references to trials found through the initial search of the Group's register. We did not identify any additional trials by screening references of included trials or by contacting the authors of included trials, leaders in the field or companies known to be developing and investigating ataluren and similar compounds.

We included two trials (28 references) (Kerem 2014; Konstan 2020), and excluded 18 trials (28 references) (Kerem 2008; NCT00234663; NCT00237380; NCT00351078; NCT00376428; NCT01140451; NCT02107859; NCT02456103; NCT03256799; NCT03256968; NCT03624101; NCT03670472; NCT04126473; NCT04135495; Pradal 2002; Romano 2000; Sermet-Gaudelus 2010; Wilschanski 2003b). No trials are listed as ongoing or awaiting classification. The results of the search are shown in the PRISMA diagram (Figure 1).

Figure 1. PRISMA study flow diagram



Included studies

We included two trials (28 references) with 517 participants in total; both trials were available as full-text articles (Kerem 2014; Konstan 2020).

Trial design

Both trials were RCTs of parallel design with two arms, and PTC Therapeutics Incorporated was the responsible funding body. The Cystic Fibrosis Foundation collaborated with both trials. The US Food and Drug Administration's Office of Orphan Products Development and the US National Institutes of Health were also involved in providing grant support to one trial (Kerem 2014).

Both trials were phase III trials, each lasting 48 weeks. Participants in the Kerem 2014 study who completed 48 weeks of treatment were entered into an ongoing open-label extension phase that is planned to last up to 96 weeks (NCT02107859). Participants from this extension trial are not eligible for inclusion in this review because they were not re-randomised to treatment or control.

The included trials were conducted at multiple centres internationally. The Kerem 2014 study recruited participants from 36 sites in 11 countries in North America and Europe, and reported outcome data at time frames ranging from eight to 48 weeks. The Konstan 2020 study recruited participants from 75 sites in 16 countries in North America, South America, Europe and Israel, and reported outcome data at 48 weeks (although the trial registry entry states 88 sites).

Participants

All 517 participants (270 male, 247 female) had a confirmed diagnosis of CF with documentation of the presence of a nonsense mutation in at least one allele of the *CFTR* gene. The trials recruited participants aged six years and over; the mean age was 23 years in the Kerem 2014 study and 22 years in the Konstan 2020 study. Participants were allocated in a 1:1 ratio to either intervention or placebo. Participants were stratified according to age (under 18 years versus 18 years and over), chronic inhaled antibiotic use (yes versus no) and FEV_1% predicted (40% up to 65% versus 65% up to 90%). The Konstan 2020 trial only recruited participants not receiving chronic inhaled aminoglycosides. All participants had a baseline FEV_1 of 40% or over for age, sex and height. Where baseline characteristics were presented, they were similar in the intervention and the placebo arms, with no statistically significant differences between the two arms (Kerem 2014; Konstan 2020).

Interventions

The intervention drug used in both included trials was ataluren (administered as a powdered oral suspension). The trials compared a three-times daily regimen of ataluren (10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening) to placebo. Participants continued on prescribed medications that were approved for CF during the trial period (Kerem 2014; Konstan 2020).

Outcomes

The primary endpoints for both trials was change in FEV_1 % predicted from baseline to week 48, assessed by spirometry. The Kerem 2014 study reported relative change and the Konstan 2020 study reported absolute change in FEV_1 % predicted as the primary endpoint. Both trials used the CFQ-R respiratory domain to measure QoL (Quittner 2009). The Kerem 2014 study reported on the mean change in the score from baseline to week 48 in the supplementary text. Both trials reported on the safety profile of ataluren. The Kerem 2014 study reported on the pulmonary exacerbation rate using the modified Fuchs' definition, whereas the Konstan 2020 study reported on this using the expanded Fuchs' definition. Both trials reported on the change from baseline for BMI, and the Kerem 2014 study also reported on difference between groups for the change in body weight.

The Kerem 2014 study reported on changes in total lung CT scores and subscores. This trial also reported the absolute difference in change in sweat chloride concentration from baseline between the two treatment arms. The Kerem 2014 study also reported nasal potential difference, a tertiary endpoint. We did not include it in this review as it is not yet a validated outcome.

Excluded studies

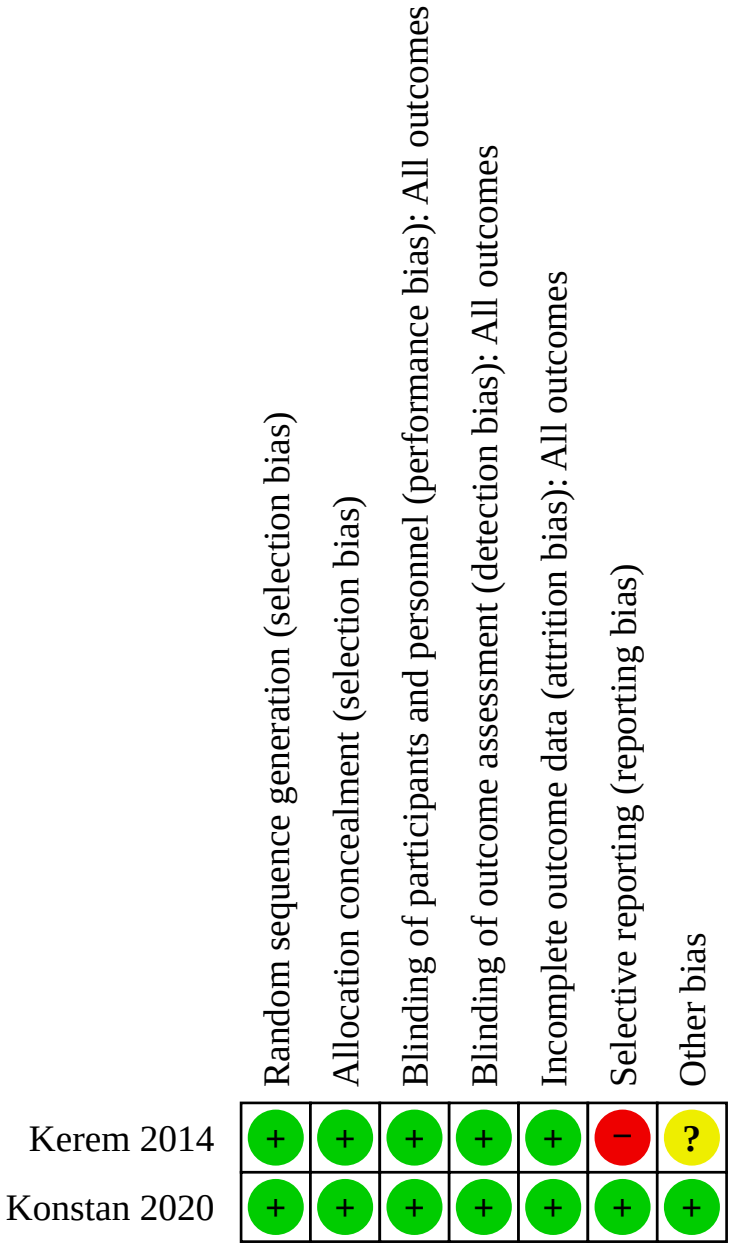
We excluded 18 trials (28 references) (see Characteristics of excluded studies).

One trial was of cross-over design, and we could not extract data from just the first treatment arm (Pradal 2002). We contacted the investigators of this trial requesting the relevant data, but the data have not been made available to us. We excluded one trial because it reported on the mechanism of action of the intervention and not on the clinical benefit (Wilschanski 2003b). A phase II trial did not randomise participants to treatment and entered participants into an open-label extension trial where, again, participants were not randomised to control or treatment (Kerem 2008). Another trial did not randomise participants to treatment and used participants homozygous for deltaF508 mutations as the control group, which was inappropriate for inclusion in this review (Romano 2000). We excluded an open-label extension of the included Kerem 2014 trial, where participants have not been re-randomised and all participants are receiving the same treatment (NCT02107859). Seven trials did not randomise and participants were allocated to a single treatment (NCT00376428; NCT01140451; NCT02456103; NCT03256799; NCT03256968; NCT03624101; NCT04126473). One non-randomised trial assessed dose escalation (NCT04135495), whereas a further three cross-over trials were excluded because they compared dosing regimens and were not placebo-controlled (NCT00234663; NCT00237380; Sermet-Gaudelus 2010). One of these trials also entered participants into an open-label extension trial that was excluded (NCT00351078). One trial was excluded because it was a laboratory-based case-control study (NCT03670472).

Risk of bias in included studies

We present a graphical summary of the risk of bias assessments for the included trials in Figure 2.

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



Allocation

Sequence generation

Both included trials reported that the randomisation code was externally generated using a small block size, stratified by age (under 18 years versus 18 years and over), chronic inhaled antibiotic use (yes versus no), and FEV_1 % predicted (40% up to 65% versus 65% up to 90%). We judged the trials to have a low risk of bias for sequence generation (Kerem 2014; Konstan 2020).

Allocation concealment

Participants in both the included trials were allocated to ataluren or placebo using interactive response technology according to the

concealed randomisation list, and we judged the risk of bias for allocation concealment to be low (Kerem 2014; Konstan 2020).

Blinding

The trials stated that participants were blinded to treatment assignment and that the placebo was identical in appearance to the active drug. Although neither trial referred to the consistency or taste of the orally administered powder for suspension, we judge both trials to have a low risk of bias with regard to the blinding of participants (Kerem 2014; Konstan 2020).

Both trials reported on blinding of trial personnel to treatment assignments, including medical and ancillary staff, the trial investigators and the sponsor (Kerem 2014; Konstan 2020). The trials specifically stated that only designated personnel at the contract research organisation had access to the treatment assignments; therefore, we judged the trials to have a low risk of bias with regard to the blinding of personnel.

Incomplete outcome data

Attrition was low for both trials (less than 15%). In the Kerem 2014 study, there were 116 participants in the ITT population in each treatment arm. In the Konstan 2020 study, there were 138 participants in the ataluren arm and 136 in the placebo arm included in the ITT analysis. We judged there to be a low risk of bias from incomplete outcome data for both trials (Kerem 2014; Konstan 2020).

In the Kerem 2014 trial, 20 participants from the ataluren group and 14 participants from the placebo group withdrew from the trial (P = 0.36). Six participants were excluded prior to week eight because they did not have valid post-baseline spirometry: four from the ataluren group and two from the placebo group. These participants were not included in the ITT population. After week eight, 16 participants from the ataluren group withdrew from the trial. The reasons for exclusion for discontinuation for all participants (ataluren n = 120; placebo = 116) are as follows. Twenty participants in total withdrew from the ataluren group: seven due to an adverse event; one who was lost to follow-up; nine who withdrew consent; one because of investigator decision; one due to protocol non-compliance; and one who withdrew for 'other' reasons. Fourteen participants in total withdrew from the placebo group: two due to an adverse event; nine who withdrew consent; one due to protocol non-compliance; and two for 'other' reasons. The investigators reported the following missing values in % predicted FEV_1 "12% (104/840) in the ataluren treatment group and 9% (73/820) in the placebo group" (Kerem 2014). We identified the following missing data from the ataluren group: one participant's total lung CT score at week 48 and three participants' change from baseline in sweat chloride concentration. In the placebo group, the investigators reported that week 48 FEV_1 data were missing for one participant and that this participant was excluded from the per-protocol population analysis; in addition, we found that data for seven participants for the change from baseline in sweat chloride concentration were missing.

In the Konstan 2020 study, 14 participants from the ataluren group and 13 from the placebo group withdrew from the trial (P = 0.82). Of these withdrawals, five participants (two from the ataluren group and three from the placebo group) were excluded prior to week eight because they did not have valid post-baseline spirometry. These participants were not included in the ITT population. A further 11 participants in each group were withdrawn from the trial after week eight, but reasons were not provided. The investigators reported missing FEV_1 data at 48 weeks for 15 participants in the ataluren group and 21 participants in the placebo group (Konstan 2020).

Selective reporting

The protocols for the included trials were found through online clinical trials registries (NCT00803205; NCT02139306). The following outcomes were included in the Kerem 2014 protocol, but not reported in the full publication: ataluren (PTC124) pharmacokinetics; antibiotic use and hospitalisation due to CF-related symptoms; and disruptions to school or work due to CF-related symptoms. For QoL, weight and BMI, the Kerem 2014 trial reported no significant difference in mean change from baseline between treatment arms, but did not state either baseline and week 48 data or the change from baseline in each group to allow further analysis. Regarding adverse events, the Kerem 2014 trial reported adverse events that occurred in more than 10% of the population and the adverse events that led to discontinuation of treatment. The trial did not report whether an adverse event led to the interruption of treatment (Kerem 2014). By not reporting the aforementioned information, the trial is at high risk of selective outcome reporting.

In the Kerem 2014 trial, investigators undertook a post hoc subgroup analysis of participants depending on their use of chronic inhaled antibiotics; however, they only reported findings for selected outcomes in that subgroup (relative change from baseline in FEV_1, absolute values for FEV_1, pulmonary exacerbation rate and total lung CT scores). The investigators selectively reported data for participants who were or were not receiving inhaled tobramycin, and did not report data for other inhaled antibiotics. Absolute values for FEV_1 at baseline and week 48 were presented for the subgroup of participants who were not receiving chronic inhaled tobramycin, highlighting favourable results for ataluren in this particular group of participants. The trial did not report complete data to allow analysis (i.e. baseline/week 48/change from baseline) of non-significant outcomes, including total lung CT scores by subgroup and relative change from baseline in FEV_1 in participants on long-term inhaled tobramycin, and instead stated that there was no significant difference between treatment arms (Kerem 2014). Due to selectively reporting the findings of the subgroup of participants who were not receiving chronic inhaled tobramycin, we judge the trial to be at high risk of reporting bias.

The Konstan 2020 trial reported on all the protocol outcomes in either the main paper or online. The trial reported on treatment-emergent adverse events occurring in more than 5% of the population and adverse events that led to discontinuation of treatment. The trial did not report whether an adverse event led to the interruption of treatment (Konstan 2020). We therefore judge the trial to be at low risk of bias.

Other potential sources of bias

The baseline characteristics of participants in the treatment arms were similar in both trials. The median rate of compliance was based on trial drug accountability and was reported to be approximately 90% for ataluren and approximately 85% for

placebo in the Kerem 2014 trial, and 96% for ataluren and 95% for placebo in the Konstan 2020 trial.

Kerem 2014 undertook a post hoc subgroup analysis of participants by chronic inhaled antibiotic use. This was not a subgroup that we planned to report on, but we have presented the results directly from the paper within our results below. The rationale for doing this analysis in the trial is not entirely clear; the investigators hypothesised that aminoglycosides, including inhaled tobramycin, interfere with ataluren at a ribosomal level. A post hoc in vitro trial demonstrated that aminoglycosides (tobramycin or gentamicin) reduce ataluren's ability to read through the PTC, and that this effect was not seen with the other tested inhaled antibiotics, colistin or aztreonam (Kerem 2014). There is no further scientific evidence for such an effect. The Konstan 2020 trial was specifically designed with these results in mind and excluded participants receiving chronic inhaled or systemic tobramycin within four weeks prior to screening.

Effects of interventions

See: **Summary of findings 1** Ataluren versus placebo for people with cystic fibrosis with class I mutations (PTCs)

Both of our included studies compared ataluren to placebo (Kerem 2014; Konstan 2020). We have graded the certainty of the evidence of those outcomes included in the summary of findings tables. For the definitions of these gradings, please refer to Summary of findings 1.

Primary outcomes

1. Quality of life

a. Total QoL score

Neither trial reported on total QoL scores.

b. Different subdomains

Both trials reported on the CFQ-R respiratory domain scores, but only one provided data we could analyse (Konstan 2020).

Konstan 2020 reported the change from baseline in CFQ-R respiratory domain scores. There was no statistically significant difference in the mean change from baseline between the two groups at week 48 (MD 0.27, 95% CI -3.55 to 4.10; P = 0.89; 1 trial, 274 participants; Analysis 1.1).

The Kerem 2014 trial did not report absolute data at baseline and week 48; however, it did report on the mean change in CFQ-R respiratory domain scores from baseline to week 48. The reported difference in the mean changes between ataluren and placebo was 2.9 for the age group 6 to 13 years and 0.5 for participants aged 14 and over, neither of which were statistically significant (P = 0.8152 and P = 0.3723, respectively). We were unable to conduct analyses due to the insufficient data provided (Kerem 2014).

2. Respiratory function measures (litres or per cent (%) predicted)

a. FEV_1 (relative change from baseline)

The Kerem 2014 study reported the relative change from baseline in FEV_1 % predicted at up to 48 weeks and presented data in graphical format at 8-weekly intervals (i.e. at 8, 16, 24, 32 and 40 weeks). At up to 48 weeks, both treatment arms showed a decline in mean relative change from baseline in FEV_1 % predicted, but there was no difference between groups (MD 2.97%, 95% CI -0.58 to 6.52; P = 0.10; 1 trial, 203 participants; Analysis 1.2). Using data deduced from the graph (figure 2 in the full paper; Kerem 2014), at 8 weeks, we found a benefit with ataluren versus placebo (estimated MD 3.50%, 95% CI 0.86 to 6.14; P = 0.009; 1 trial, 232 participants; Analysis 1.2). At the remaining time points, the results demonstrated no difference between treatment groups (Analysis 1.2).

Subgroup analysis

In a post hoc subgroup analysis of participants by chronic inhaled antibiotic use, Kerem 2014 reported that, at up to 48 weeks, the subgroup of participants who did not receive chronic inhaled tobramycin experienced a greater mean relative decline from baseline in FEV_1 % predicted in the placebo arm (MD 5.70%, 95% CI 1.71 to 9.69; P = 0.005; 1 trial, 146 participants; Analysis 1.3). In addition, Kerem 2014 showed an estimated benefit with ataluren versus placebo at eight weeks (MD 5.70%, 95% CI 2.21 to 9.19; P = 0.001; 1 trial, 146 participants; Analysis 1.3), at 32 weeks (MD 5.40%, 95% CI 1.08 to 9.72; P = 0.01; 1 trial, 146 participants; Analysis 1.3) and at 40 weeks (MD 4.00%, 95% CI 0.03 to 7.97; P = 0.05; 1 trial, 146 participants; Analysis 1.3). However, there was no treatment difference at week 16 (MD 1.40%, 95% CI -1.94 to 4.74; P = 0.41; 1 trial, 146 participants; Analysis 1.3) and week 24 (MD 1.80%, 95% CI -2.52 to 6.12; P = 0.41; 1 trial, 146 participants; Analysis 1.3) (data estimated from figure 3 in full paper; Kerem 2014).

In the subgroup of participants who were receiving chronic inhaled tobramycin, Kerem 2014 reported no difference at up to 48 weeks (MD -1.60%, 95% CI -8.15 to 4.95; P = 0.63; 1 trial, 86 participants; Analysis 1.4). There was an estimated difference at 24 weeks in the same subgroup of participants that favoured placebo (MD -6.80%, 95% CI -12.35 to -1.25; P = 0.02; 1 trial, 86 participants; Analysis 1.4), but no estimated treatment difference at each of the other 8-weekly time points in this subgroup (Analysis 1.4) (data estimated from figure 3 in full paper; Kerem 2014).

b. FEV_1 absolute values

Both trials reported absolute values for FEV_1 % predicted: Kerem 2014 reported values at baseline and at week 48 and Konstan 2020 reported the absolute mean change from baseline. Kerem 2014 reported no difference in absolute baseline FEV_1 % predicted between the ataluren and placebo groups and no difference in the mean change from baseline at week 48 between the treatment groups (MD 1.76%, 95% CI -0.43 to 3.95; P = 0.12; 1 trial, 203 participants; Analysis 1.5).

Subgroup analysis

In the subgroup analysis of participants not receiving chronic inhaled tobramycin, Kerem 2014 identified a lesser decline in mean absolute change in FEV_1 in the ataluren group compared with the placebo group (MD 3.40%, 95% CI 0.75 to 6.05; Analysis 1.6) in 125 participants not taking chronic inhaled tobramycin (Kerem 2014). No data for mean absolute change in FEV_1 % predicted were reported for participants who were receiving long-term inhaled tobramycin.

Konstan 2020 only recruited participants who were not receiving chronic inhaled aminoglycosides, and found no difference between

groups (n = 274) in the absolute mean change in FEV_1 % predicted (MD 0.59%, 95% CI -1.33 to 2.51; Analysis 1.6).

Combined data at 48 weeks for absolute mean change in FEV_1 % predicted in participants not receiving chronic inhaled aminoglycosides demonstrated no difference between groups (MD 1.84%, 95% CI -0.90 to 4.58; P = 0.19, I^2 = 65%; 2 trials, 399 participants; Analysis 1.6). The studies are very similar, so there is no obvious explanation for this level of heterogeneity.

c. FVC (absolute values and relative change from baseline)

We deduced estimates for the mean relative change from baseline in FVC % predicted at each 8-weekly time point, including week 48, from a graphical representation from the Kerem 2014 study (supplementary figure 1 of the paper; Kerem 2014). There was no estimated difference in the mean relative change from baseline in FVC % predicted at any time point (8, 16, 24, 32, 40 and 48 weeks); end of trial data at 48 weeks are presented in the analysis (MD 1.10%, 95% CI -1.97 to 4.17; P = 0.48; 1 trial, 232 participants; Analysis 1.7).

3. Adverse events

In the Kerem 2014 trial, more participants in the placebo than ataluren group experienced diarrhoea, nausea, pyrexia, upper respiratory tract infections, rhinitis, pulmonary exacerbations, cough, haemoptysis and oropharyngeal pain. Abdominal pain, vomiting, sinusitis, headache and productive cough occurred more frequently in the ataluren group (Kerem 2014).

In the Konstan 2020 trial, more adverse events in total were reported by participants receiving ataluren (905) than by those receiving placebo (768). However, more participants in the placebo group experienced pulmonary exacerbations (including severe exacerbations), influenza, pseudomonal infections and staphylococcal infections, whereas more participants in the ataluren group experienced viral upper respiratory tract infections, sinusitis, nasopharyngitis, rhinitis, pharyngitis, cough, haemoptysis, diarrhoea, abdominal pain, nausea and vomiting, and nephrolithiasis (Konstan 2020).

Regarding specific adverse events, we present details of these in Analysis 1.8. Oropharyngeal pain (as reported by Kerem 2014 only) was less common in the ataluren group (RR 0.28, 99% CI 0.10 to 0.83). In Kerem 2014, a higher number of participants in the ataluren group reported episodes of acute kidney injury (reported terms include renal failure, acute renal failure, renal impairment and hypercreatininaemia; RR 17.70, 99% CI 1.28 to 244.40). In contrast, Konstan 2020 only reported a single incidence of acute renal failure in the ataluren group (although their definition of this is unclear). Combined data suggest a difference in the incidence of acute renal failure between treatment groups, but notably wide 99% CIs (RR 12.81, 99% CI 2.46 to 66.65; P = 0.002, I^2 = 0%; 2 trials, 537 participants; Analysis 1.8). In an open-label extension study of the Kerem study, no participants had clinically significant laboratory abnormalities, including renal function, after 192 weeks of taking ataluren (NCT02107859).

Both studies classified adverse events by severity as grade 1 (mild), grade 2 (moderate), grade 3 (severe) and grade 4 (life-threatening or death); however, they did not specify the criteria for grade 1 to 3 classifications (Kerem 2014; Konstan 2020). It was not possible for us to determine which reported adverse events they would class as mild (therapy does not need to be discontinued) or moderate (therapy is discontinued and the adverse effect ceases). The trials reported on adverse events that required discontinuation of therapy under the heading 'severe (life-threatening or debilitating, or that persist even after treatment is discontinued)'.

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

Individually, neither trial reported differences in grade 1 (mild) adverse events between the ataluren and placebo groups (Kerem 2014: RR 0.88, 95% 0.49 to 1.57; 1 trial, 231 participants; Analysis 1.9, and Konstan 2020: RR 1.43, 95% CI 0.82 to 2.49; 1 trial, 279 participants; Analysis 1.9). Combined data also showed no difference in mild adverse events between groups (RR 1.14, 95% CI 0.77 to 1.70; P = 0.52, I^2 = 30%; 2 trials, 512 participants; Analysis 1.9).

An open-label extension study of the Kerem 2014 study reported four (6.6%) mild adverse events in participants receiving ataluren for 192 weeks (NCT02107859).

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

The trials did not report on adverse events that specifically required interruption of treatment. Neither Kerem 2014 nor Konstan 2020 reported a difference in grade 2 adverse events between the ataluren and placebo groups; combined data also showed no difference (RR 1.09, 95% CI 0.95 to 1.24; P = 0.22, I^2 = 53%; 2 trials, 512 participants; Analysis 1.9). An open-label extension of the Kerem 2014 trial reported 26 (42.6%) moderate adverse events in participants receiving ataluren for 192 weeks (NCT02107859).

c. Severe adverse events (life-threatening or debilitating, or that persist even after treatment is discontinued)

There were no life-threatening events reported in either trial (Kerem 2014; Konstan 2020).

The Kerem 2014 trial reported that eight participants from the ataluren group and three from the placebo group discontinued therapy due to adverse events. Konstan 2020 reported that three participants receiving ataluren and four receiving placebo experienced adverse events that led to discontinuation. No further information was provided regarding the nature of these events.

There was no difference between treatment groups in investigator-defined grade 3 (severe) adverse events for the individual trials (Kerem 2014: RR 0.62, 95% CI 0.37 to 1.03; 1 trial, 233 participants; Analysis 1.9, and Konstan 2020: RR 0.65, 95% CI 0.38 to 1.10; 1 trial, 279 participants; Analysis 1.9; participants may have had more than one adverse event). Combined data showed significantly fewer severe adverse events in participants in the ataluren than placebo groups (RR 0.63, 95% CI 0.44 to 0.92; P = 0.02, I^2 = 0%; 2 trials, 512 participants; Analysis 1.9).

Of note, an open-label extension of the Kerem trial (not included in this review) reported 30 (49.2%) severe and one (1.6%) fatal adverse events in participants receiving ataluren for 192 weeks (NCT02107859).

Secondary outcomes

1. Survival

a. Time to event (death or lung transplant)

Both trials reported zero deaths and did not report on lung transplant (Kerem 2014; Konstan 2020).

b. Mortality rate

The trials reported zero deaths in both treatment groups (Kerem 2014; Konstan 2020).

2. Hospitalisation

No data were reported for hospitalisation in either trial (Kerem 2014; Konstan 2020); one trial listed this outcome in the published protocol, but did not report data in the paper (Kerem 2014).

3. School or work attendance

Neither trial reported on school or work attendance (Kerem 2014; Konstan 2020); one trial listed this outcome in the published protocol, but did not report data in the paper (Kerem 2014).

4. Extra courses of antibiotics

No data were reported specifically for extra courses of antibiotics (Kerem 2014; Konstan 2020). Konstan 2020 reported a pulmonary exacerbation rate, defined as extra courses of antibiotics in combination with four or more of Fuchs' signs and symptoms. Therefore, we do not report these data under this outcome and have presented these data under the following outcome, 'Pulmonary exacerbations'. The second trial listed this outcome in the published protocol, but did not report data in the paper (Kerem 2014).

5. Pulmonary exacerbations

The Kerem 2014 trial reported on both physician-defined (based on the individual physician's judgement) and protocol-defined pulmonary exacerbation rates assessed using modified Fuchs' criteria. These criteria defined a pulmonary exacerbation as four of the following 12 symptoms, with or without treatment with antibiotics: change in sputum; new or increased haemoptysis; increased cough; increased dyspnoea; fatigue; temperature over 38 °C; anorexia; sinus pain; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10% or more from a previously recorded value; or radiographic changes indicative of pulmonary infection (Fuchs 1994). The Konstan 2020 trial reported on protocol-defined pulmonary exacerbation rates assessed using expanded Fuchs' criteria. The expanded Fuch's criteria differ from the modified Fuch's criteria in that they require the use of oral, inhaled or intravenous (IV) antibiotics, or a combination of these, in response to four or more of the above symptoms (Konstan 2020). Thus, we were not able to combine data.

Kerem 2014 reported no treatment difference between the ataluren and placebo groups for either the physician- or protocol-defined pulmonary exacerbation rate at up to 48 weeks (MD -0.02 (95% CI -0.67 to 0.63) and MD -0.36 (95% CI -0.89 to 0.17), respectively; Analysis 1.10). Of those who entered the open-label extension phase of the Kerem trial (all taking ataluren), 68% experienced pulmonary exacerbations (assessed by modified Fuchs' criteria) over 192 weeks (NCT02107859).

Konstan 2020 reported no difference between treatment groups in protocol-defined pulmonary exacerbation rates (no participants in this trial were receiving chronic inhaled aminoglycosides): MD -0.18 (95% CI -0.66 to 0.30; Analysis 1.10).

Subgroup analysis

In the Kerem 2014 subgroup analysis, the investigators reported a lower protocol-defined pulmonary exacerbation rate with ataluren in participants not taking chronic inhaled tobramycin (MD -0.76, 95% CI -1.51 to -0.01) compared to no difference between the ataluren and placebo groups for those receiving chronic inhaled tobramycin (MD 0.36, 95% CI -0.28 to 1.00; Analysis 1.11).

6. Radiological measures of lung disease

a. Chest radiograph score

Neither trial reported on chest radiograph score (Kerem 2014; Konstan 2020).

b. CT score

Kerem 2014 reported on total lung CT scores and subscores at baseline, at the end of treatment (approximately 48 weeks) and the change from baseline. There was no difference in mean change in total lung CT score up to the end of treatment (approximately 48 weeks; MD -0.28, 95% CI -0.68 to 0.12; 1 trial, 203 participants; Analysis 1.12).

Subgroup analysis

Kerem 2014 reported no difference between ataluren and placebo in changes in total lung CT scores in a subgroup analysis according to inhaled tobramycin use (Kerem 2014). Data were not reported for the analysis.

7. Acquisition of respiratory pathogens

The included trials did not report on this outcome (Kerem 2014; Konstan 2020).

8. Eradication of respiratory pathogens

No data were reported for the eradication of respiratory pathogens (Kerem 2014; Konstan 2020).

9. Nutrition and growth

a. Weight

The Kerem 2014 trial reported no difference in the change in body weight between the ataluren and placebo groups over 48 weeks (difference 0.04 kg). Insufficient data were presented for inclusion in our analysis.

b. Body mass index (BMI)

As with weight, the Kerem 2014 trial reported no statistically significant difference in change in BMI between treatment groups over 48 weeks (difference -0.108); further baseline and week 48 data were not reported, precluding any analysis.

Konstan 2020 reported no difference in change in BMI between ataluren and placebo over 48 weeks (MD -0.07, 95% CI -0.32 to 0.19; P = 0.62; 1 trial, 274 participants; Analysis 1.13).

c. Height

Height was not reported in either trial (Kerem 2014; Konstan 2020).

10. Sweat chloride

Kerem 2014 reported no difference in change from baseline in sweat chloride between the ataluren and placebo groups at up to 48 weeks (MD -0.70, 95% CI -3.41 to 2.01; P = 0.61; 1 trial, 194 participants; Analysis 1.14).

11. Cost-effectiveness

The trials did not report on the cost of ataluren treatment for people with CF (Kerem 2014; Konstan 2020).

DISCUSSION

Summary of main results

This review examined whether specific therapies for class I mutations (PTCs) improve clinically relevant outcomes in people with CF. Our search identified 56 references to 20 trials; we excluded 18 trials and included two trials (Kerem 2014; Konstan 2020). The included studies were both RCTs of parallel design and enrolled a total of 517 participants aged six years and over (range six to 53 years old) with documentation of the presence of a nonsense mutation in at least one allele of the *CFTR* gene. The trials compared 40 mg/kg/day (in divided doses) of orally administered ataluren to placebo for a duration of 48 weeks.

The Kerem 2014 trial undertook a post hoc subgroup analysis of participants not receiving chronic inhaled tobramycin (n = 146) that demonstrated favourable results for ataluren. The second included trial was subsequent to the Kerem trial and was designed to prospectively assess the effects of ataluren in participants not receiving chronic tobramycin (Konstan 2020). However, the results from this later trial suggest that the perceived favourable results for ataluren in the subgroup analysis in the earlier trial are likely to have occurred by chance. Some aminoglycosides, including tobramycin and gentamicin, have previously been demonstrated to have the ability to mask the abnormal gene sequence, resulting in significant changes in the salt-transporting defect towards normal (Clancy 2001; Howard 1996; Wilschanski 2003a). The mechanism of action for such aminoglycosides is thought to be similar to that of ataluren, in that they enable read-through of class I mutations (PTCs; Welch 2007). It is possible that in the subgroup of participants in the Kerem 2014 trial receiving chronic inhaled tobramycin, the aminoglycoside may have enabled read-through of the abnormal gene sequence, and therefore they would not benefit further from ataluren.

Results from the two included trials showed that ataluren was no better than placebo for the review's primary or secondary outcome measures at up to 48 weeks (Kerem 2014; Konstan 2020). Neither trial reported a difference in CFQ-R respiratory domain scores between treatment groups (Analysis 1.1). Furthermore, neither trial demonstrated any difference between groups in the improvement in measures of respiratory function at up to 48 weeks (relative or absolute change in FEV_1 % predicted and relative change in FVC % predicted; Analysis 1.2; Analysis 1.3; Analysis 1.4; Analysis 1.5; Analysis 1.6; Analysis 1.7). In the subgroup analysis of participants not on long-term inhaled tobramycin, Kerem 2014 reported a reduction in the decline in FEV_1 over 48 weeks in participants treated with ataluren (n = 72) compared with placebo (n = 74; MD 5.7%, 95% CI 1.71% to 9.69). However, the subsequent Konstan 2020 trial designed to prospectively assess the effects of ataluren in participants not receiving chronic tobramycin showed no reduction in the decline in FEV_1. Combined data at 48 weeks for mean absolute change in FEV_1 in participants not receiving chronic inhaled aminoglycosides demonstrated no difference between groups (MD 1.84, 95% CI -0.90 to 4.58) with considerable heterogeneity (I^2 = 65%; Analysis 1.6). There is no clear explanation for the degree of heterogeneity demonstrated between the two trials.

It was difficult to translate the reported adverse events into the mild, moderate and severe categories proposed in our protocol because the events were not presented according to this characterisation. There were fewer reports of oropharyngeal pain recorded in the ataluren group than the placebo group (RR 0.28, 95% CI 0.10 to 0.83). Ataluren was associated with a higher rate of episodes of acute kidney injury (including reported terms renal failure, acute renal failure, renal impairment and hypercreatininaemia; RR 12.81, 95% CI 2.46 to 66.65). The adverse events profile of ataluren should be interpreted with caution because it is based on small numbers of participants and the trials were not powered to assess this outcome.

Neither trial reported a difference between groups in pulmonary exacerbation rates (either physician- or protocol-defined) or BMI over 48 weeks (Kerem 2014; Konstan 2020). However, in the subgroup of participants not on long-term inhaled tobramycin, those treated with ataluren were seen to have reduced pulmonary exacerbation rates (protocol-defined: MD -0.76, 95% CI -1.51 to -0.01; Kerem 2014), although this was not the case in the Konstan 2020 trial, which was designed to assess the effects of ataluren in participants not receiving chronic tobramycin. Combined data at 48 weeks in participants not receiving chronic inhaled aminoglycosides demonstrated no difference between ataluren and placebo in the rate of protocol-defined pulmonary exacerbation rates (MD -0.35, 95% CI -0.76 to 0.05) with moderate heterogeneity (I^2 = 39%; Analysis 1.11).

One trial reported no difference between groups in sweat chloride concentration or change in total lung CT score over 48 weeks in the ataluren compared with placebo group (Kerem 2014). The second trial reported no difference between groups in body mass index over 48 weeks (Konstan 2020). No deaths were reported in either treatment group by either trial, and the length and size of the trials precluded valid assessment of the impact of ataluren on survival. An open-label extension trial of one of the studies has been completed and, although not eligible for full inclusion due to lack of randomisation and control, it reported one fatality in participants who took ataluren for 192 weeks (NCT02107859).

Neither trial reported on hospitalisations, school or work attendance, extra courses of antibiotics, chest radiograph scores, the acquisition or eradication of respiratory pathogens, height or cost-effectiveness (Kerem 2014; Konstan 2020).

Overall completeness and applicability of evidence

The included trials recruited a mixture of adults and children with CF with nonsense mutations across 124 sites internationally. Participants in the Kerem 2014 trial had a mean age of 23 years, with 32% of participants aged under 18 years. In the Konstan 2020 trial, the mean age was 22 years, with 41% of participants aged under 18 years. Nonsense mutations are a type of class I mutation (PTC), and the results can be assumed to be applicable to individuals with nonsense CF mutations not included in this trial. Of note, however,

is that the trials did not enrol participants aged under six years, pregnant women or those with stop codon mutations (another form of class I mutation (PTCs)). There are no data for outcomes that we considered important for this review: hospitalisation, school or work attendance, extra courses of antibiotics, chest radiograph score, acquisition or eradication of respiratory pathogens and cost-effectiveness.

Certainty of the evidence

Please see the Summary of findings 1.

The trials were RCTs, which represent the highest quality with regard to trial design. The trials included a total of 517 participants and were well powered for one of the review's primary outcomes (change in FEV_1 % predicted). The randomised phase of the trials lasted 48 weeks and participants from the Kerem 2014 trial were entered into an open-label extension trial that lasted a total of 192 weeks (the open-label extension results were not included in this review). We judged the risk of bias to be moderate overall, with well-documented random sequence generation, allocation concealment and blinding of trial personnel. Blinding of participants was less clear, because details of orally administered placebo versus ataluren (e.g. taste and consistency) were not provided. The risk of selective reporting in the Kerem 2014 trial was generally high because the trial did not always report on outcomes outlined in the protocol, present data for all outcomes and report on outcomes that we considered important. The trials were sponsored by the manufacturer of ataluren, PTC Therapeutics Incorportated, and some trial authors declared a financial interest. In the Kerem 2014 trial, eight of 27 authors are employees of PTC Therapeutics Incorportated and hold financial interests in the company; two authors received compensation for consultant services from PTC Therapeutics Incorportated during the trial; and four authors received compensation for travel expenses for meetings related to the trial. One author on the Konstan 2020 trial is an employee of PTC Therapeutics Incorporated; three authors received compensation for consultation services from PTC Therapeutics Incorportated prior to or during the trial (or both); and four authors received compensation for travel expenses for meetings related to the trial.

Overall, we judged the certainty of the evidence to be moderate (Summary of findings 1).

Potential biases in the review process

Two review authors (AA and CH for the first review; AA and IS for this review update) independently applied inclusion and exclusion criteria to references identified through a comprehensive literature search. We then independently extracted data and assessed the risk of bias in the included trials. If any disagreement had arisen as to the risk of bias of the trial, we would have attempted to reach a consensus by discussion, failing which, a third author (KS) would have arbitrated. The analysis was undertaken by one review author (AA). This methodological approach ensured that risks of bias in the review process were kept to a minimum. This review has assessed all available published trial data. We contacted trial authors for relevant unpublished information and individual participant data. None have been made available to date. We are not aware of any unpublished trials, although we have highlighted issues with selective reporting in the included trials.

We planned to include cross-over trials if results from the first treatment arm were available. Independently assessing the only relevant cross-over trial that we identified, we were unable to extract its data and therefore contacted the investigators. Because we did not receive any response from the investigators, we have excluded this trial (Pradal 2002). We are aware that this reduces the number of trials we could include in the review. We acknowledge that the primary outcome for the included trials was relative change in FEV_1 % predicted, and therefore they may not be powered to detect a difference in our other primary outcomes, QoL and adverse events. Therefore, an absence of evidence of a difference in QoL or for the majority of adverse events does not rule out that ataluren may improve QoL or have a higher adverse event profile compared with placebo.

Agreements and disagreements with other studies or reviews

Two trials were eligible for inclusion in this review. In future, should further trials become eligible, we will update this review.

We are not aware of any other published systematic reviews of ataluren and similar compounds (specific therapies for premature termination codon class I mutations) for CF.

AUTHORS' CONCLUSIONS

Implications for practice

There is currently insufficient evidence to determine the effect of ataluren as a therapy for people with cystic fibrosis (CF) with class I mutations. Ataluren was associated with a higher rate of episodes of renal impairment, the degree of which requires further information.

Implications for research

It is important that future trials assess outcomes to determine the long-term use of ataluren in terms of both efficacy and tolerability. Future trials should be powered to detect a difference not only in relative change from baseline in forced expiratory volume in one second (FEV_1), but also in quality of life (QoL) and adverse events, outcomes of significant importance to people with CF. In particular, the clear reporting of adverse events is critical, with particular attention to episodes of renal impairment and nephrolithiasis. Criteria for any grading classifications used when reporting adverse events should be clearly stated.

Given the chronic nature of CF, it is important that the burden of additional treatment to people's current regimen is examined, as well as the potential impact of new therapies on adherence to existing CF medications.

Cross-over trials should be avoided, given the potential for the treatment to change the natural history of CF. Furthermore, future trials should be large enough to enable detailed analysis of the effectiveness of ataluren in population subgroups (e.g. adults and children).

Currently, there are no trials comparing ataluren to treatment with other compounds for class I mutations (premature termination codons (PTCs)) in CF. Further research examining the interaction of tobramycin and ataluren is required; in particular, characterising the potential of tobramycin to cause read-through of PTCs.

The initial promise of other PTC-type agents has not progressed; although a number of targets have been explored by pharmaceutical companies, we are not aware of any active drug development pipelines in this field.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Kerem 2014

Study characteristics	
Methods	2-arm RCT of parallel design Multicentre: 36 sites Duration: 48 weeks
Participants	Participants with CF aged 6 years and over with a nonsense mutation in at least one allele of the *CFTR* gene; 238 participants were enrolled in this study **Age** Treatment group: mean (SD) 22.8 (10.18) years; median (range) 22.0 (6 to 49) years Control group: mean (SD) 23.2 (9.32) years; median (range): 22.0 (8 to 53) years **Age split by group** Treatment group: under 18 years, 38 (32.8%); 18 years and over, 78 (67.2%) Control group: under 18 years, 37 (31.9%); 18 years and over, 79 (68.1%) **Sex** Treatment group: 60 (51.7%) males, 56 (48.3%) females Control group: 58 (50%) males, 58 (50%) females **Body weight** Treatment group: mean (SD) 53.5 (13.94) kg; median (range) 54.4 (21 to 105) kg Control group: mean (SD) 56.0 (13.15) kg; median (range) 57.2 (24 to 93) kg **FEV_1 %predicted at baseline** Treatment group: mean (SD) 62.1 (13.62); median (range) 63.4 (38.4 to 90.3) Control group: mean (SD) 60.2 (15.14); median (range) 59.0 (36.2 to 92.6) **Sweat chloride at baseline (mmol/L)[b]** Treatment group: mean (SD) 100.1 (14.22); median (range) 101.5 (22.5 to 128.0) Control group: mean (SD) 96.6 (15.93); median (range) 100.0 (22.0 to 117.5) **Inhaled antibiotic use at randomisation** Total: treatment group, 64 (55.2%), control group, 63 (53.4%)

Kerem 2014 *(Continued)*

	Aminoglycoside (tobramycin): treatment group 44 (37.9%), control group 42 (35.6%) Colistin: treatment group 30 (25.9%), control group 22 (18.6%) Aztreonam: treatment group 10 (8.3%), control group 8 (6.8%)
Interventions	**Treatment group** (n = 120): ataluren 3 times a day: 10 mg/kg in the morning, 10 mg/kg at midday, 20 mg/kg in the evening **Control group** (n = 118): placebo 3 times a day
Outcomes	**Primary outcome measure** 1. FEV_1[a] **Secondary outcome measures** 1. Pulmonary exacerbation frequency[a] 2. Cough frequency[a] 3. Respiratory health-related quality of life as assessed by the CFQ-R respiratory domain[a] 4. FVC[a] 5. Safety profile[a] 6. Compliance with trial drug administration[a] 7. Ataluren (PTC124) pharmacokinetics 8. Antibiotic use and hospitalisation due to CF-related symptoms 9. Disruptions to school or work due to CF-related symptoms 10. Body weight[a] 11. Markers of lung inflammation 12. Lung computed tomography CF score[a] 13. Nasal transepithelial potential difference 14. Sweat chloride concentration[a]
Notes	PTC Therapeutics Incorporated was the responsible funding body. [a]These outcomes are presented in the review. [b] mmol/L is equivalent to mEq/L.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomisation code was externally generated using a small block size, stratified by age (less than 18 years versus 18 years or older), chronic inhaled antibiotic use (yes versus no), and FEV_1 % predicted (40% to less than 65% versus 65% to 90%).
Allocation concealment (selection bias)	Low risk	Interactive response technology was used to allocate participants to ataluren or placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded to treatment; the appearance of the placebo was described as identical, but details of the consistency and taste of the placebo have not been provided. We still judged this to result in a low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only designated personnel at the contract research organisation had access to the treatment assignments. Medical and ancillary staff, the trial investigators and the sponsor were blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	238 participants were randomised: 120 participants to the ataluren group and 118 participants to the placebo group.

Kerem 2014 *(Continued)*

		4 participants from the ataluren group and 2 from the placebo group were excluded prior to week 8 and were excluded from the ITT population. The ITT population included 116 participants in each treatment arm. 16 participants withdrew from the study in ataluren group and 12 withdrew in the placebo group; 100 participants in the ataluren group and 104 in the placebo group were included in analysis (total = 204). We found minor discrepancies in the number of participants analysed for the following outcome measures: total lung CT score and sweat chloride concentration.
Selective reporting (reporting bias)	High risk	Protocol located on online trials registries database. The following outcomes were listed in the protocol but not published: 1. ataluren (PTC124) pharmacokinetics; 2. antibiotic use and hospitalisation due to CF-related symptoms; 3. disruptions to school or work due to CF-related symptoms. Subgroup analysis of participants not receiving chronic inhaled tobramycin showing significant benefit for ataluren was reported for FEV_1 and pulmonary exacerbations. Results for this subgroup were not reported for each outcome and the results for participants on other inhaled antibiotics were not fully reported.
Other bias	Unclear risk	Similar baseline characteristics and median rate of compliance (approximately 90% for ataluren and approximately 85% for placebo); however, the rationale for the subgroup is not clear and may be flawed, leading to a potential source of bias.

Konstan 2020

Study characteristics	
Methods	Phase III, international, multicentre, randomised, double-blind, placebo-controlled trial of ataluren in participants with nonsense mutation CF not receiving chronic inhaled aminoglycosides
Participants	Participants recruited from 75 sites across 16 countries in North America, Europe and Australasia Inclusion criteria included (but were not limited to): age 6 years and over; sweat chloride > 60 mEq/L; demonstration of a $FEV_1 \geq 40\%$ and $\leq 90\%$ of % predicted; and documentation of the presence of a nonsense mutation in at least 1 allele of the *CFTR* gene 279 participants were enrolled in the trial **Age** Treatment group: mean (SD) 22 (11); range 6 to 52 years Control group: mean (SD) 22 (10.7); range 6 to 52 years **Age split by group** Treatment group: under 18 years, 59 (42.1%); 18 years and over, 81 (57.9%) Control group: under 18 years, 56 (40.3%); 18 years and over, 83 (59.7%) **Sex** Treatment group: 81 (57.9%) males, 59 (42.1%) females

Konstan 2020 *(Continued)*

	Control group: 65 (46.8%) males, 74 (53.2%) females **FEV_1 %predicted at baseline** Treatment group: mean (SD) 63.5 (13.46); range 40 to 88 Control group: mean (SD) 62.2 (14.34); range 40 to 90 **Sweat chloride at baseline (mEq/L)[b]** Treatment group: mean (SD) 100.7 (2.87); range 95 to 120 Control group: mean (SD) 100.0 (2.99); range 93 to 107 **Inhaled antibiotic use at randomisation** Total: treatment group 86 (61.4%). control group 66 (47.5%) Colistimethate: treatment group 60 (42.9%), control group 49 (35.3%) Aztreonam: treatment group 33 (23.6%). control group 22 (15.8%) Tobramycim: treatment group 0, control group 0
Interventions	Ataluren (PTC124) in oral powder for suspension form taken 3 times per day (10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening) for 48 weeks Placebo
Outcomes	**Primary outcome measure** 1. FEV_1 by spirometry[a] **Secondary outcome measures** 1. Rate of pulmonary exacerbations (modified Fuchs' criteria)[a] 2. Respiratory health-related quality of life as assessed by the CFQ-R respiratory domain[a] 3. Body weight and BMI[a] **Other outcome measures** 1. FVC[a] and FEF_{25-75} by spirometry 2. Incidence and duration of pulmonary exacerbations[a] 3. Other health-related quality of life domains as assessed by the CFQ-R[a] 4. Concentrations of liver enzyme tests (AST, ALT, GGT) 5. Faecal calprotectin level 6. New *P aeruginosa* lung infection[a] 7. Safety profile characterised by type, frequency, severity, timing and relationship to study drug of treatment-emergent adverse events, laboratory abnormalities and electrocardiogram abnormalities[a] 8. Trial drug compliance as assessed by quantification of unused trial drug 9. Trough ataluren plasma concentrations Timeframe for all outcomes measures stated to be 48 weeks
Notes	[a]These outcomes are presented in the review. [b]mEq/L is equivalent to mmol/L. [c]Trial registry report states 88 sites, but published paper states 75.

Risk of bias

Bias	Authors' judgement	Support for judgement

Konstan 2020 *(Continued)*

Random sequence generation (selection bias)	Low risk	The randomisation code was externally generated using a small block size (4), stratified by age (less than 18 years versus 18 years and older), chronic inhaled antibiotic use (yes versus no), and FEV_1 % predicted (40% to less than 65% versus 65% to 90%).
Allocation concealment (selection bias)	Low risk	Interactive response technology was used to allocate participants to ataluren or placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All participants were blinded to treatment; the appearance of the placebo was described as identical, but details of the consistency and taste of the placebo have not been provided. We still judged this to result in a low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only designated personnel at the contract research organisation had access to the treatment assignments; medical and ancillary staff, the trial investigators and the sponsor were blinded to treatment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	279 participants were randomised: 140 participants to the ataluren group and 139 participants to the placebo group. 2 participants from the ataluren group and 3 from the placebo group were excluded prior to week 8 and were excluded from the ITT population. The ITT population included 138 participants in the ataluren group and 136 participants in the placebo group, and results were reported on the ITT population. A further 11 participants from each group withdrew after week 8 (meaning the total number of withdrawals was 13 from the ataluren group and 14 from the placebo group). At week 48, there were missing FEV_1 data for 15 participants in the ataluren group and 21 participants in the placebo group.
Selective reporting (reporting bias)	Low risk	The protocol was available online and all outcomes listed in the protocol were reported.
Other bias	Low risk	Similar baseline characteristics and median rate of compliance (95% for ataluren and 95% for placebo).

ALT: alanine aminotransferase
AST: aspartate aminotransferase
BMI: body mass index
CF: cystic fibrosis
CFQ-R: cystic fibrosis questionnaire - revised
CFTR: cystic fibrosis transmembrane conductance regulator
FEF_{25-75}: mid expiratory flow
FEV_1: forced expiratory volume in one second
FVC: forced vital capacity
GGT: gamma-glutamyl transpeptidase
ITT: intention to treat
RCT: randomised controlled trial
SD: standard deviation

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

Study	Reason for exclusion
Kerem 2008	Participants not controlled, randomised or blinded to treatment

Study	Reason for exclusion
NCT00234663	Cross-over trial in which each participant served as their own control for the comparison of 2 different dosing regimens of ataluren
NCT00237380	Cross-over trial in which each participant served as their own control for the comparison of 2 different dosing regimens of ataluren
NCT00351078	Not a randomised controlled trial; participants invited to single allocation safety trial after completing a previous cross-over trial
NCT00376428	Not a randomised controlled trial; compared single agent gentamicin in 2 different populations (individuals with stop codon mutations and in a control group without stop codon mutations)
NCT01140451	Not a randomised controlled trial; participants invited to single allocation safety trial after completing a previous randomised controlled trial
NCT02107859	Not a randomised controlled trial; participants invited to single allocation safety trial after completing a previous randomised controlled trial
NCT02456103	Not a randomised controlled trial; participants invited to single allocation safety trial after completing a previous randomised controlled trial
NCT03256799	Not a randomised controlled trial; participants invited to single allocation of ivacaftor in combination with ataluren
NCT03256968	Not a randomised controlled trial; 1 participant allocated to treatment with ivacaftor in combination with ataluren
NCT03624101	Not a randomised controlled trial; single group assignment
NCT03670472	Laboratory-based case-control study
NCT04126473	Not a randomised controlled trial; participants with cystic fibrosis and at least 1 G542X allele or phenotypically similar nonsense allele invited to single allocation of multiple dose levels of ELX-02 (a eukaryotic ribosomal-selective glycoside) with and without ivacaftor
NCT04135495	Not a randomised controlled trial; phase II dose escalation study
Pradal 2002	Cross-over trial and data from first treatment arm not presented independently; data requested, but no response to date
Romano 2000	Controlled clinical trial: participants were not randomised or blinded to treatment. Controls stated to be participants homozygous for deltaF508 mutations
Sermet-Gaudelus 2010	Cross-over trial in which each participant served as their own control for the comparison of 2 different dosing regimes of ataluren
Wilschanski 2003b	Cross-over trial in which each participant served as their own control. Reported on mechanism of action of the intervention (nasal potential difference and immunofluorescence microscopy of primary human airway cells); this was not relevant to the present review, which is looking at clinical benefit

DATA AND ANALYSES

Comparison 1. Ataluren versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 QoL score (measured using CFQ-R) - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 At 48 weeks	1	274	Mean Difference (IV, Fixed, 95% CI)	0.27 [-3.55, 4.10]
1.2 FEV_1 % predicted - mean relative change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 At up to 8 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	3.50 [0.86, 6.14]
1.2.2 At up to 16 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	1.50 [-1.29, 4.29]
1.2.3 At up to 24 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	1.50 [-1.69, 4.69]
1.2.4 At up to 32 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	2.80 [-0.54, 6.14]
1.2.5 At up to 40 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	2.30 [-1.07, 5.67]
1.2.6 At up to 48 weeks	1	203	Mean Difference (IV, Fixed, 95% CI)	2.97 [-0.58, 6.52]
1.3 FEV_1 % predicted - mean relative change from baseline: subgroup analysis of participants not receiving chronic inhaled tobramycin	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.3.1 At up to 8 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	5.70 [2.21, 9.19]
1.3.2 At up to 16 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	1.40 [-1.94, 4.74]
1.3.3 At up to 24 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	1.80 [-2.52, 6.12]
1.3.4 At up to 32 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	5.40 [1.08, 9.72]
1.3.5 At up to 40 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	4.00 [0.03, 7.97]
1.3.6 At up to 48 weeks	1	146	Mean Difference (IV, Fixed, 95% CI)	5.70 [1.71, 9.69]

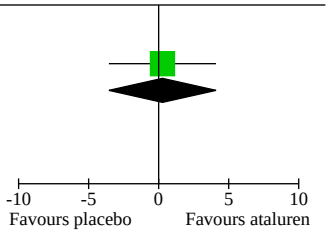
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 FEV_1 % predicted - mean relative change from baseline: subgroup analysis of participants receiving chronic inhaled tobramycin	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 At up to 8 weeks	1	86	Mean Difference (IV, Fixed, 95% CI)	0.30 [-4.02, 4.62]
1.4.2 At up to 16 weeks	1	86	Mean Difference (IV, Fixed, 95% CI)	0.40 [-3.92, 4.72]
1.4.3 At up to 24 weeks	1	86	Mean Difference (IV, Fixed, 95% CI)	-6.80 [-12.35, -1.25]
1.4.4 At up to 32 weeks	1	86	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-7.88, 4.88]
1.4.5 At up to 40 weeks	1	86	Mean Difference (IV, Fixed, 95% CI)	-0.80 [-7.23, 5.63]
1.4.6 At up to 48 weeks	1	86	Mean Difference (IV, Fixed, 95% CI)	-1.60 [-8.15, 4.95]
1.5 FEV_1 % predicted - mean absolute change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.5.1 At up to 48 weeks	1	203	Mean Difference (IV, Fixed, 95% CI)	1.76 [-0.43, 3.95]
1.6 FEV_1 % predicted - mean absolute change from baseline: subgroup of participants not receiving chronic inhaled tobramycin	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.6.1 At up to 48 weeks	2	399	Mean Difference (IV, Random, 95% CI)	1.84 [-0.90, 4.58]
1.7 FVC % predicted - mean relative change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.7.1 At up to 8 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	2.00 [-0.37, 4.37]
1.7.2 At up to 16 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	0.70 [-1.93, 3.33]
1.7.3 At up to 24 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	1.30 [-1.69, 4.29]
1.7.4 At up to 32 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	1.80 [-1.53, 5.13]
1.7.5 At up to 40 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	1.20 [-1.79, 4.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.7.6 At up to 48 weeks	1	232	Mean Difference (IV, Fixed, 95% CI)	1.10 [-1.97, 4.17]
1.8 Specific adverse events (at up to 48 weeks)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.8.1 Diarrhoea	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.48, 1.26]
1.8.2 Abdominal pain	2	517	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.84, 2.45]
1.8.3 Vomiting	2	517	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.81, 2.95]
1.8.4 Nausea	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.56, 1.74]
1.8.5 Pyrexia	1	238	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.47, 1.50]
1.8.6 Viral upper respiratory tract infections	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.66, 1.36]
1.8.7 Sinusitis	2	517	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.70, 1.84]
1.8.8 Rhinitis	2	517	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.61, 1.94]
1.8.9 Upper respiratory tract infection	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.48, 1.26]
1.8.10 Headache	1	238	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.75, 2.65]
1.8.11 Acute kidney injury	2	517	Risk Ratio (M-H, Fixed, 95% CI)	12.81 [2.46, 66.65]
1.8.12 Pulmonary exacerbation	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.84, 1.05]
1.8.13 Cough	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.19]
1.8.14 Haemoptysis	2	517	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.51, 1.41]
1.8.15 Productive cough	1	238	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.49, 2.33]
1.8.16 Oropharyngeal pain	1	238	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.10, 0.83]
1.8.17 Nasopharyngitis	1	279	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.50, 3.05]
1.8.18 Influenza	1	279	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.32, 2.33]
1.8.19 Pharyngitis	1	279	Risk Ratio (M-H, Fixed, 95% CI)	3.48 [0.73, 16.44]
1.8.20 Nephrolithiasis	1	279	Risk Ratio (M-H, Fixed, 95% CI)	6.95 [0.36, 133.32]
1.9 Severity of adverse effects of therapy as graded by trial authors	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.9.1 Grade 1 (mild)	2	512	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.77, 1.70]
1.9.2 Grade 2 (moderate)	2	512	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.95, 1.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.3 Grade 3 (severe)	2	512	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.44, 0.92]
1.9.4 Grade 4 (life-threatening or death)	2	512	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.10 Pulmonary exacerbation rate	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.10.1 Physician-defined pulmonary exacerbation rate	1	232	Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.67, 0.63]
1.10.2 Protocol-defined pulmonary exacerbation rate (as defined by modified Fuchs' criteria) overall	1	232	Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.89, 0.17]
1.10.3 Protocol-defined pulmonary exacerbation rate (as defined by expanded Fuchs' criteria)	1	274	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.66, 0.30]
1.11 Protocol-defined pulmonary exacerbation rate: subgroup analysis by chronic inhaled tobramycin use	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.11.1 Participants not receiving chronic inhaled tobramycin	1	146	Mean Difference (IV, Fixed, 95% CI)	-0.76 [-1.51, -0.01]
1.11.2 Participants receiving chronic inhaled tobramycin	1	86	Mean Difference (IV, Fixed, 95% CI)	0.36 [-0.28, 1.00]
1.12 Total lung computed tomography score - mean change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.12.1 At up to 48 weeks	1	203	Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.68, 0.12]
1.13 Body mass index - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.13.1 At 48 weeks	1	274	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.32, 0.19]
1.14 Sweat chloride level - change from baseline	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.14.1 At up to 48 weeks	1	194	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-3.41, 2.01]

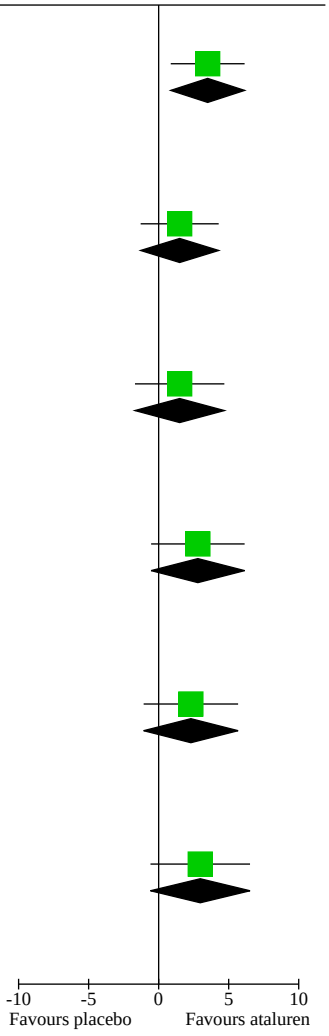
Analysis 1.1. Comparison 1: Ataluren versus placebo, Outcome 1: QoL score (measured using CFQ-R) - change from baseline

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 At 48 weeks								
Konstan 2020	-0.76	16.2	138	-1.032	16.1	136	100.0%	0.27 [-3.55 , 4.10]
Subtotal (95% CI)			**138**			**136**	**100.0%**	**0.27 [-3.55 , 4.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								
Test for subgroup differences: Not applicable								



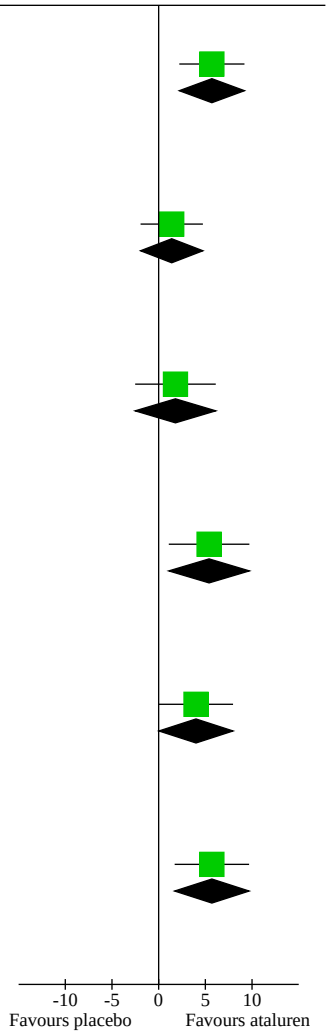
Analysis 1.2. Comparison 1: Ataluren versus placebo, Outcome 2: FEV_1 % predicted - mean relative change from baseline

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 At up to 8 weeks								
Kerem 2014	-1	9.69	116	-4.5	10.77	116	100.0%	3.50 [0.86 , 6.14]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**3.50 [0.86 , 6.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.60 (P = 0.009)								
1.2.2 At up to 16 weeks								
Kerem 2014	-1.4	11.85	116	-2.9	9.69	116	100.0%	1.50 [-1.29 , 4.29]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**1.50 [-1.29 , 4.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
1.2.3 At up to 24 weeks								
Kerem 2014	-2.3	12.92	116	-3.8	11.85	116	100.0%	1.50 [-1.69 , 4.69]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**1.50 [-1.69 , 4.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.92 (P = 0.36)								
1.2.4 At up to 32 weeks								
Kerem 2014	-2.5	14	116	-5.3	11.85	116	100.0%	2.80 [-0.54 , 6.14]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**2.80 [-0.54 , 6.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.64 (P = 0.10)								
1.2.5 At up to 40 weeks								
Kerem 2014	-1.2	15.08	116	-3.5	10.77	116	100.0%	2.30 [-1.07 , 5.67]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**2.30 [-1.07 , 5.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.34 (P = 0.18)								
1.2.6 At up to 48 weeks								
Kerem 2014	-2.53	13.25	100	-5.5	12.56	103	100.0%	2.97 [-0.58 , 6.52]
Subtotal (95% CI)			**100**			**103**	**100.0%**	**2.97 [-0.58 , 6.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.64 (P = 0.10)								



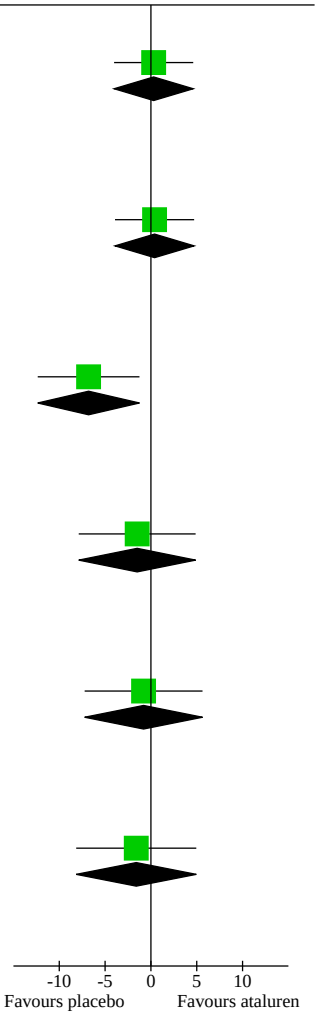
Analysis 1.3. Comparison 1: Ataluren versus placebo, Outcome 3: FEV_1 % predicted - mean relative change from baseline: subgroup analysis of participants not receiving chronic inhaled tobramycin

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.3.1 At up to 8 weeks								
Kerem 2014	0.8	9.33	72	-4.9	12.04	74	100.0%	5.70 [2.21 , 9.19]
Subtotal (95% CI)			**72**			**74**	**100.0%**	**5.70 [2.21 , 9.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.20 (P = 0.001)								
1.3.2 At up to 16 weeks								
Kerem 2014	-0.6	11.03	72	-2	9.46	74	100.0%	1.40 [-1.94 , 4.74]
Subtotal (95% CI)			**72**			**74**	**100.0%**	**1.40 [-1.94 , 4.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								
1.3.3 At up to 24 weeks								
Kerem 2014	-0.6	14.42	72	-2.4	12.04	74	100.0%	1.80 [-2.52 , 6.12]
Subtotal (95% CI)			**72**			**74**	**100.0%**	**1.80 [-2.52 , 6.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.82 (P = 0.41)								
1.3.4 At up to 32 weeks								
Kerem 2014	0	14.42	72	-5.4	12.04	74	100.0%	5.40 [1.08 , 9.72]
Subtotal (95% CI)			**72**			**74**	**100.0%**	**5.40 [1.08 , 9.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.45 (P = 0.01)								
1.3.5 At up to 40 weeks								
Kerem 2014	-0.1	14.42	72	-4.1	9.46	74	100.0%	4.00 [0.03 , 7.97]
Subtotal (95% CI)			**72**			**74**	**100.0%**	**4.00 [0.03 , 7.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.98 (P = 0.05)								
1.3.6 At up to 48 weeks								
Kerem 2014	-0.7	11.93	72	-6.4	12.64	74	100.0%	5.70 [1.71 , 9.69]
Subtotal (95% CI)			**72**			**74**	**100.0%**	**5.70 [1.71 , 9.69]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.80 (P = 0.005)								



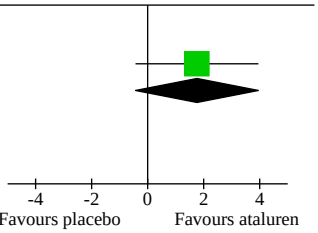
Analysis 1.4. Comparison 1: Ataluren versus placebo, Outcome 4: FEV_1 % predicted - mean relative change from baseline: subgroup analysis of participants receiving chronic inhaled tobramycin

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 At up to 8 weeks								
Kerem 2014	-3.7	11.28	44	-4	9.07	42	100.0%	0.30 [-4.02 , 4.62]
Subtotal (95% CI)			**44**			**42**	**100.0%**	**0.30 [-4.02 , 4.62]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								
1.4.2 At up to 16 weeks								
Kerem 2014	-2.9	11.28	44	-3.3	9.07	42	100.0%	0.40 [-3.92 , 4.72]
Subtotal (95% CI)			**44**			**42**	**100.0%**	**0.40 [-3.92 , 4.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.86)								
1.4.3 At up to 24 weeks								
Kerem 2014	-4.7	12.6	44	2.1	13.61	42	100.0%	-6.80 [-12.35 , -1.25]
Subtotal (95% CI)			**44**			**42**	**100.0%**	**-6.80 [-12.35 , -1.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.40 (P = 0.02)								
1.4.4 At up to 32 weeks								
Kerem 2014	-6.6	15.26	44	-5.1	14.91	42	100.0%	-1.50 [-7.88 , 4.88]
Subtotal (95% CI)			**44**			**42**	**100.0%**	**-1.50 [-7.88 , 4.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
1.4.5 At up to 40 weeks								
Kerem 2014	-3.4	17.25	44	-2.6	12.96	42	100.0%	-0.80 [-7.23 , 5.63]
Subtotal (95% CI)			**44**			**42**	**100.0%**	**-0.80 [-7.23 , 5.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.24 (P = 0.81)								
1.4.6 At up to 48 weeks								
Kerem 2014	-5.6	17.25	44	-4	13.61	42	100.0%	-1.60 [-8.15 , 4.95]
Subtotal (95% CI)			**44**			**42**	**100.0%**	**-1.60 [-8.15 , 4.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.48 (P = 0.63)								



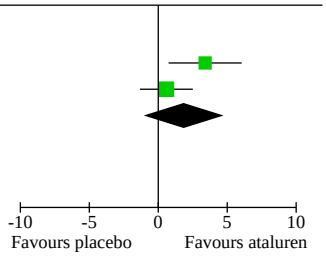
Analysis 1.5. Comparison 1: Ataluren versus placebo, Outcome 5: FEV_1 % predicted - mean absolute change from baseline

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.5.1 At up to 48 weeks								
Kerem 2014	-1.34	8.5	100	-3.1	7.39	103	100.0%	1.76 [-0.43 , 3.95]
Subtotal (95% CI)			**100**			**103**	**100.0%**	**1.76 [-0.43 , 3.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.57 (P = 0.12)								



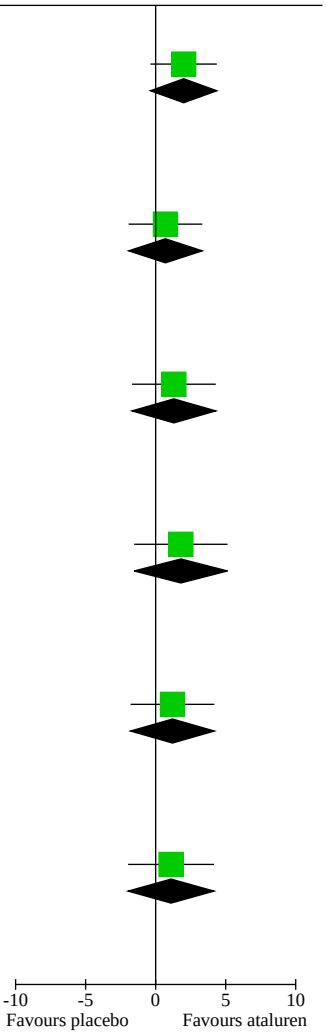
Analysis 1.6. Comparison 1: Ataluren versus placebo, Outcome 6: FEV_1 % predicted - mean absolute change from baseline: subgroup of participants not receiving chronic inhaled tobramycin

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 At up to 48 weeks								
Kerem 2014	-0.3	7.53	62	-3.7	7.58	63	44.5%	3.40 [0.75 , 6.05]
Konstan 2020	-1.4	8.24	138	-1.99	7.94	136	55.5%	0.59 [-1.33 , 2.51]
Subtotal (95% CI)			**200**			**199**	**100.0%**	**1.84 [-0.90 , 4.58]**
Heterogeneity: Tau² = 2.56; Chi² = 2.84, df = 1 (P = 0.09); I² = 65%								
Test for overall effect: Z = 1.32 (P = 0.19)								



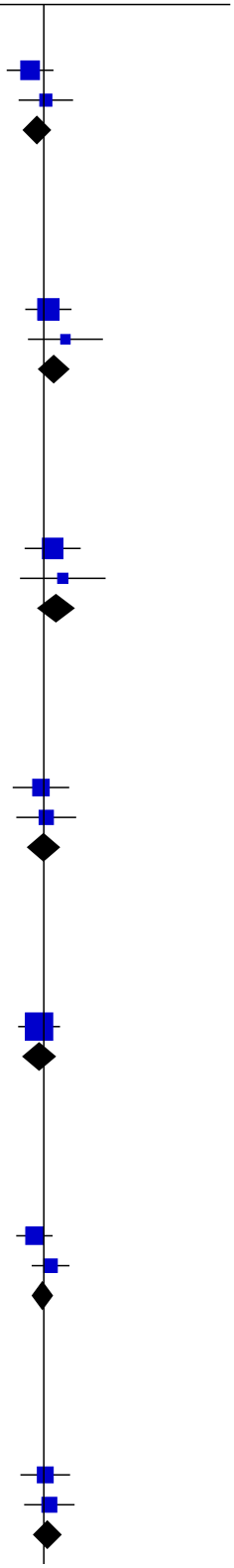
Analysis 1.7. Comparison 1: Ataluren versus placebo, Outcome 7: FVC % predicted - mean relative change from baseline

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 At up to 8 weeks								
Kerem 2014	-0.3	5.39	116	-2.3	11.85	116	100.0%	2.00 [-0.37 , 4.37]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**2.00 [-0.37 , 4.37]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
1.7.2 At up to 16 weeks								
Kerem 2014	-0.8	6.46	116	-1.5	12.92	116	100.0%	0.70 [-1.93 , 3.33]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**0.70 [-1.93 , 3.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
1.7.3 At up to 24 weeks								
Kerem 2014	-0.8	8.62	116	-2.1	14	116	100.0%	1.30 [-1.69 , 4.29]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**1.30 [-1.69 , 4.29]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.85 (P = 0.39)								
1.7.4 At up to 32 weeks								
Kerem 2014	-1.2	8.62	116	-3	16.16	116	100.0%	1.80 [-1.53 , 5.13]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**1.80 [-1.53 , 5.13]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
1.7.5 At up to 40 weeks								
Kerem 2014	-0.5	8.62	116	-1.7	14	116	100.0%	1.20 [-1.79 , 4.19]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**1.20 [-1.79 , 4.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.79 (P = 0.43)								
1.7.6 At up to 48 weeks								
Kerem 2014	-1.5	7.54	116	-2.6	15.08	116	100.0%	1.10 [-1.97 , 4.17]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**1.10 [-1.97 , 4.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								



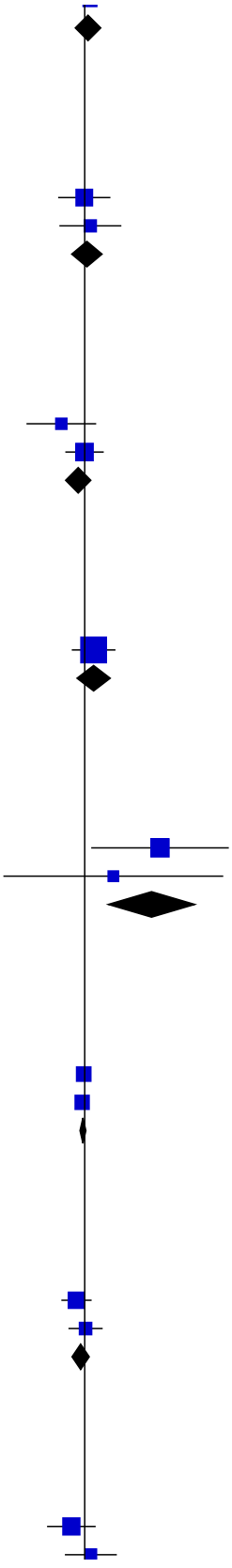
Analysis 1.8. Comparison 1: Ataluren versus placebo, Outcome 8: Specific adverse events (at up to 48 weeks)

Study or Subgroup	Ataluren Events	Ataluren Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 99% CI
1.8.1 Diarrhoea						
Kerem 2014	13	120	21	118	63.7%	0.61 [0.26 , 1.42]
Konstan 2020	13	140	12	139	36.3%	1.08 [0.40 , 2.88]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**0.78 [0.48 , 1.26]**
Total events:	26		33			
Heterogeneity: Chi² = 1.28, df = 1 (P = 0.26); I² = 22%						
Test for overall effect: Z = 1.02 (P = 0.31)						
1.8.2 Abdominal pain						
Kerem 2014	18	120	15	118	75.1%	1.18 [0.51 , 2.72]
Konstan 2020	11	140	5	139	24.9%	2.18 [0.56 , 8.46]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**1.43 [0.84 , 2.45]**
Total events:	29		20			
Heterogeneity: Chi² = 1.00, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
1.8.3 Vomiting						
Kerem 2014	14	120	10	118	71.5%	1.38 [0.50 , 3.79]
Konstan 2020	8	140	4	139	28.5%	1.99 [0.42 , 9.33]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**1.55 [0.81 , 2.95]**
Total events:	22		14			
Heterogeneity: Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.34 (P = 0.18)						
1.8.4 Nausea						
Kerem 2014	11	120	12	118	54.7%	0.90 [0.32 , 2.50]
Konstan 2020	11	140	10	139	45.3%	1.09 [0.37 , 3.22]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**0.99 [0.56 , 1.74]**
Total events:	22		22			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
1.8.5 Pyrexia						
Kerem 2014	18	120	21	118	100.0%	0.84 [0.40 , 1.80]
Subtotal (95% CI)		**120**		**118**	**100.0%**	**0.84 [0.47 , 1.50]**
Total events:	18		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.8.6 Viral upper respiratory tract infections						
Kerem 2014	21	120	29	118	58.1%	0.71 [0.37 , 1.38]
Konstan 2020	27	140	21	139	41.9%	1.28 [0.64 , 2.53]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**0.95 [0.66 , 1.36]**
Total events:	48		50			
Heterogeneity: Chi² = 2.51, df = 1 (P = 0.11); I² = 60%						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.8.7 Sinusitis						
Kerem 2014	15	120	14	118	52.0%	1.05 [0.43 , 2.58]
Konstan 2020	16	140	13	139	48.0%	1.22 [0.49 , 3.04]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**1.13 [0.70 , 1.84]**
Total events:	31		27			



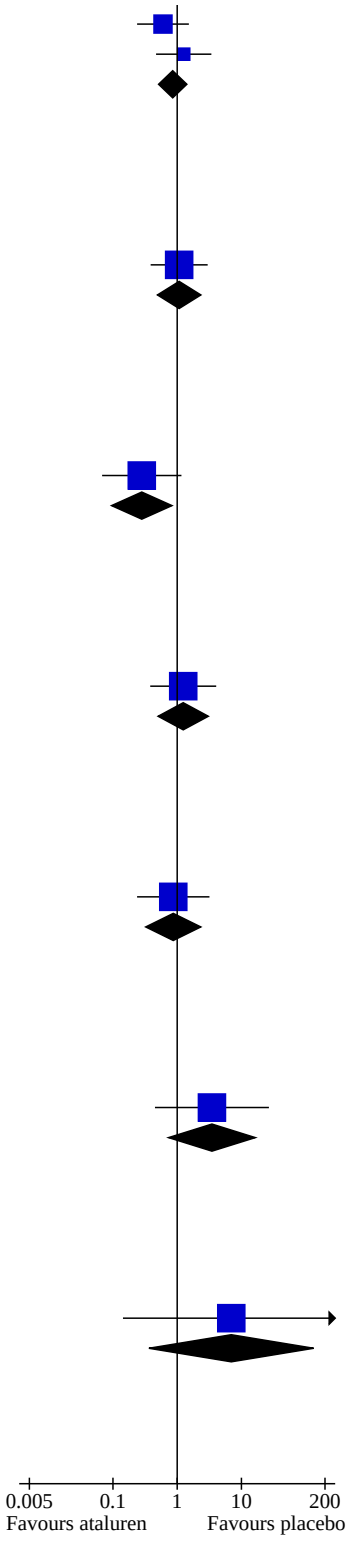
Analysis 1.8. (Continued)

Subtotal (95% CI)		**260**		**257**	**100.0%**	**1.13 [0.70 , 1.84]**
Total events:	31		27			
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
1.8.8 Rhinitis						
Kerem 2014	12	120	12	118	60.1%	0.98 [0.36 , 2.67]
Konstan 2020	10	140	8	139	39.9%	1.24 [0.38 , 4.05]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**1.09 [0.61 , 1.94]**
Total events:	22		20			
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.8.9 Upper respiratory tract infection						
Kerem 2014	5	120	12	118	36.5%	0.41 [0.11 , 1.55]
Konstan 2020	21	140	21	139	63.5%	0.99 [0.48 , 2.07]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**0.78 [0.48 , 1.26]**
Total events:	26		33			
Heterogeneity: Chi² = 2.27, df = 1 (P = 0.13); I² = 56%						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.8.10 Headache						
Kerem 2014	20	120	14	118	100.0%	1.40 [0.61 , 3.23]
Subtotal (95% CI)		**120**		**118**	**100.0%**	**1.40 [0.75 , 2.65]**
Total events:	20		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.29)						
1.8.11 Acute kidney injury						
Kerem 2014	18	120	1	118	66.8%	17.70 [1.28 , 244.40]
Konstan 2020	1	140	0	139	33.2%	2.98 [0.04 , 197.66]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**12.81 [2.46 , 66.65]**
Total events:	19		1			
Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 3.03 (P = 0.002)						
1.8.12 Pulmonary exacerbation						
Kerem 2014	92	120	94	118	50.7%	0.96 [0.81 , 1.15]
Konstan 2020	84	140	92	139	49.3%	0.91 [0.72 , 1.15]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**0.93 [0.84 , 1.05]**
Total events:	176		186			
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 1.19 (P = 0.24)						
1.8.13 Cough						
Kerem 2014	26	120	35	118	58.4%	0.73 [0.41 , 1.30]
Konstan 2020	26	140	25	139	41.6%	1.03 [0.54 , 1.98]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**0.86 [0.62 , 1.19]**
Total events:	52		60			
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%						
Test for overall effect: Z = 0.93 (P = 0.35)						
1.8.14 Haemoptysis						
Kerem 2014	11	120	18	118	62.2%	0.60 [0.24 , 1.52]
Konstan 2020	14	140	11	139	37.8%	1.26 [0.47 , 3.40]



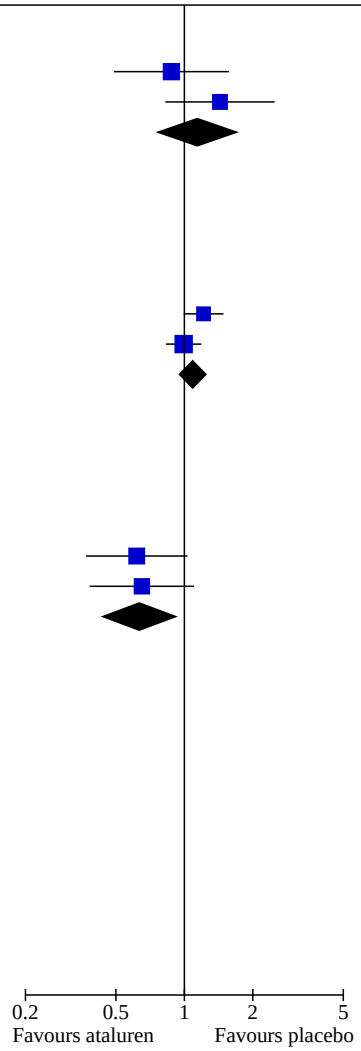
Analysis 1.8. (Continued)

Kerem 2014	11	120	18	118	62.2%	0.60 [0.24 , 1.52]
Konstan 2020	14	140	11	139	37.8%	1.26 [0.47 , 3.40]
Subtotal (95% CI)		**260**		**257**	**100.0%**	**0.85 [0.51 , 1.41]**
Total events:	25		29			
Heterogeneity: Chi² = 1.99, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.62 (P = 0.53)						
1.8.15 Productive cough						
Kerem 2014	12	120	11	118	100.0%	1.07 [0.39 , 2.98]
Subtotal (95% CI)		**120**		**118**	**100.0%**	**1.07 [0.49 , 2.33]**
Total events:	12		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						
1.8.16 Oropharyngeal pain						
Kerem 2014	4	120	14	118	100.0%	0.28 [0.07 , 1.16]
Subtotal (95% CI)		**120**		**118**	**100.0%**	**0.28 [0.10 , 0.83]**
Total events:	4		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
1.8.17 Nasopharyngitis						
Konstan 2020	10	140	8	139	100.0%	1.24 [0.38 , 4.05]
Subtotal (95% CI)		**140**		**139**	**100.0%**	**1.24 [0.50 , 3.05]**
Total events:	10		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.47 (P = 0.64)						
1.8.18 Influenza						
Konstan 2020	7	140	8	139	100.0%	0.87 [0.24 , 3.18]
Subtotal (95% CI)		**140**		**139**	**100.0%**	**0.87 [0.32 , 2.33]**
Total events:	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
1.8.19 Pharyngitis						
Konstan 2020	7	140	2	139	100.0%	3.48 [0.45 , 26.78]
Subtotal (95% CI)		**140**		**139**	**100.0%**	**3.48 [0.73 , 16.44]**
Total events:	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.57 (P = 0.12)						
1.8.20 Nephrolithiasis						
Konstan 2020	3	140	0	139	100.0%	6.95 [0.14 , 337.29]
Subtotal (95% CI)		**140**		**139**	**100.0%**	**6.95 [0.36 , 133.32]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.29 (P = 0.20)						



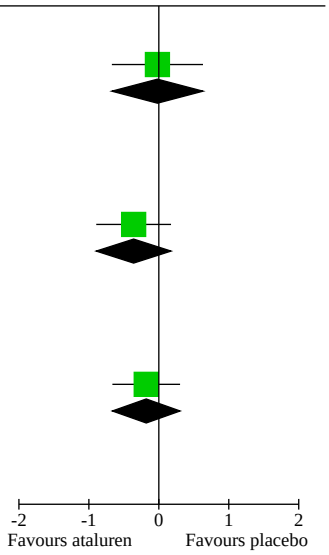
Analysis 1.9. Comparison 1: Ataluren versus placebo, Outcome 9: Severity of adverse effects of therapy as graded by trial authors

Study or Subgroup	Ataluren Events	Ataluren Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.9.1 Grade 1 (mild)						
Kerem 2014	18	118	20	115	52.9%	0.88 [0.49 , 1.57]
Konstan 2020	26	140	18	139	47.1%	1.43 [0.82 , 2.49]
Subtotal (95% CI)		**258**		**254**	**100.0%**	**1.14 [0.77 , 1.70]**
Total events:	44		38			
Heterogeneity: Chi² = 1.44, df = 1 (P = 0.23); I² = 30%						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.9.2 Grade 2 (moderate)						
Kerem 2014	81	118	65	115	42.7%	1.21 [0.99 , 1.49]
Konstan 2020	88	140	88	139	57.3%	0.99 [0.83 , 1.19]
Subtotal (95% CI)		**258**		**254**	**100.0%**	**1.09 [0.95 , 1.24]**
Total events:	169		153			
Heterogeneity: Chi² = 2.14, df = 1 (P = 0.14); I² = 53%						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.9.3 Grade 3 (severe)						
Kerem 2014	19	118	30	115	51.1%	0.62 [0.37 , 1.03]
Konstan 2020	19	140	29	139	48.9%	0.65 [0.38 , 1.10]
Subtotal (95% CI)		**258**		**254**	**100.0%**	**0.63 [0.44 , 0.92]**
Total events:	38		59			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.43 (P = 0.02)						
1.9.4 Grade 4 (life-threatening or death)						
Kerem 2014	0	118	0	115		Not estimable
Konstan 2020	0	140	0	139		Not estimable
Subtotal (95% CI)		**258**		**254**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



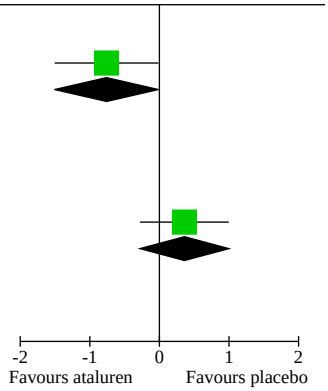
Analysis 1.10. Comparison 1: Ataluren versus placebo, Outcome 10: Pulmonary exacerbation rate

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 Physician-defined pulmonary exacerbation rate								
Kerem 2014	2.26	2.36	116	2.28	2.69	116	100.0%	-0.02 [-0.67 , 0.63]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**-0.02 [-0.67 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.06 (P = 0.95)								
1.10.2 Protocol-defined pulmonary exacerbation rate (as defined by modified Fuchs' criteria) overall								
Kerem 2014	1.42	2	116	1.78	2.15	116	100.0%	-0.36 [-0.89 , 0.17]
Subtotal (95% CI)			**116**			**116**	**100.0%**	**-0.36 [-0.89 , 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.32 (P = 0.19)								
1.10.3 Protocol-defined pulmonary exacerbation rate (as defined by expanded Fuchs' criteria)								
Konstan 2020	0.95	1.4	138	1.13	2.52	136	100.0%	-0.18 [-0.66 , 0.30]
Subtotal (95% CI)			**138**			**136**	**100.0%**	**-0.18 [-0.66 , 0.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.73 (P = 0.47)								



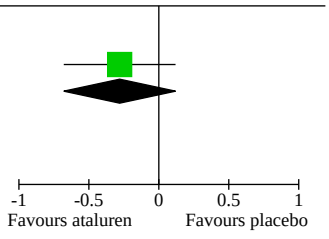
Analysis 1.11. Comparison 1: Ataluren versus placebo, Outcome 11: Protocol-defined pulmonary exacerbation rate: subgroup analysis by chronic inhaled tobramycin use

Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.11.1 Participants not receiving chronic inhaled tobramycin								
Kerem 2014	1.42	2.15	72	2.18	2.44	74	100.0%	-0.76 [-1.51 , -0.01]
Subtotal (95% CI)			**72**			**74**	**100.0%**	**-0.76 [-1.51 , -0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.00 (P = 0.05)								
1.11.2 Participants receiving chronic inhaled tobramycin								
Kerem 2014	1.42	1.74	44	1.06	1.25	42	100.0%	0.36 [-0.28 , 1.00]
Subtotal (95% CI)			**44**			**42**	**100.0%**	**0.36 [-0.28 , 1.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.11 (P = 0.27)								
Test for subgroup differences: Chi^2 = 5.00, df = 1 (P = 0.03), I^2 = 80.0%								

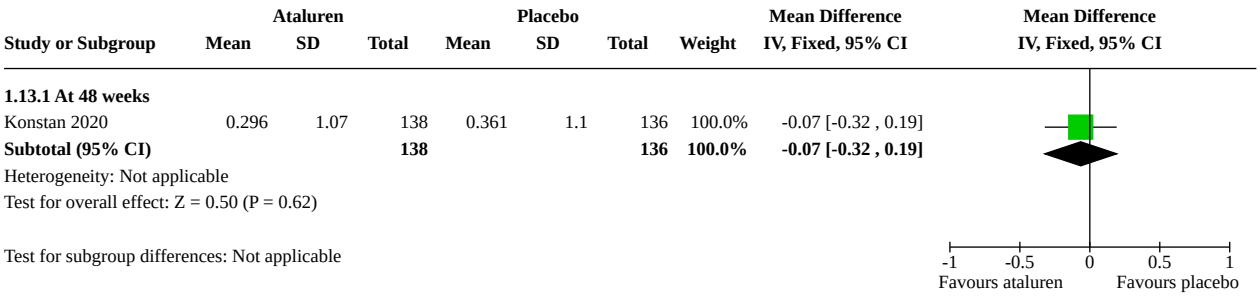


Analysis 1.12. Comparison 1: Ataluren versus placebo, Outcome 12: Total lung computed tomography score - mean change from baseline

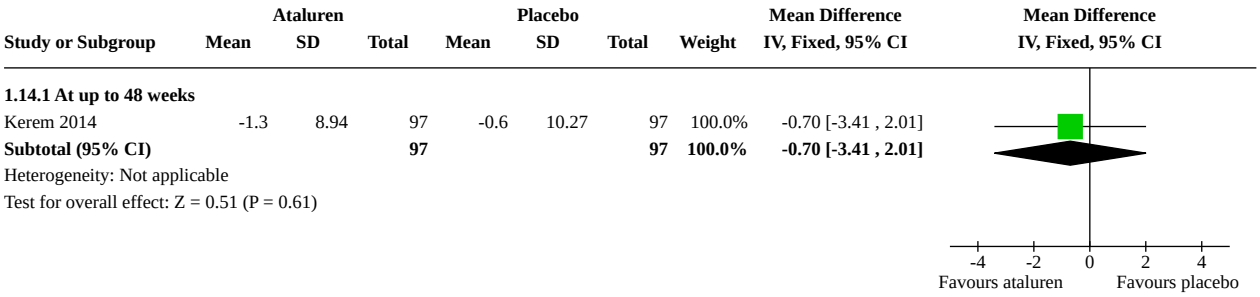
Study or Subgroup	Ataluren Mean	Ataluren SD	Ataluren Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
1.12.1 At up to 48 weeks								
Kerem 2014	0.28	1.34	99	0.56	1.56	104	100.0%	-0.28 [-0.68 , 0.12]
Subtotal (95% CI)			**99**			**104**	**100.0%**	**-0.28 [-0.68 , 0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.37 (P = 0.17)								



Analysis 1.13. Comparison 1: Ataluren versus placebo, Outcome 13: Body mass index - change from baseline



Analysis 1.14. Comparison 1: Ataluren versus placebo, Outcome 14: Sweat chloride level - change from baseline



ADDITIONAL TABLES

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

Class	Example mutation	Impact on CFTR structure and function
I	G542X	Synthesis of CFTR is critically impaired, and no functional protein is produced. This is due to the presence of a premature termination codon in the nucleotide sequence. Individuals have no CFTR function.
II	Phe508del (ΔF508)	A full-length CFTR protein is produced, but is structurally abnormal and destroyed by the cell before it reaches the cell membrane. This is called a defect in the intracellular trafficking pathway. Individuals have no CFTR function under normal conditions.
III	G551D	CFTR is produced and embedded in the cell membrane, but the chloride channel does not respond ('switch on') to normal stimulation from the cell. This means there is no significant ion transport across the membrane. Individuals have no CFTR function.
IV	R347P	CFTR is transported to the outer cell membrane and responds to normal stimulation, but functions at a low level because chloride ions do not cross the channel appropriately. Individuals have some residual CFTR function.
V	A455E	Normal CFTR is produced, but the amount of protein is reduced. Individuals have some residual CFTR function.

CFTR: cystic fibrosis transmembrane conductance regulator

APPENDICES

Appendix 1. Glossary

Term	Explanation
CFTR (cystic fibrosis transmembrane regulator)	A protein that is in the outer membrane of cells. It works by regulating the transport of salt in and out of the cell. Problems with the amount of CFTR in the cell membrane, its structure or the manner in which it functions can lead to altered transport of salt across the cell membrane. In the lungs of people with CF, these problems cause thick airway secretions. Abnormalities of CFTR can also lead to problems in other organs.
CFTR correctors	Drugs or chemicals that work by increasing the amount of CFTR in the cell membrane
CFTR potentiators	Drugs or chemicals that increase the effectiveness of CFTR at transporting salt across the cell membrane
Nonsense mutation	A sequence of DNA that makes no sense, resulting in no functional protein being produced. This is a type of class I mutation (premature termination codon) causing CF.
Phenoytype	The clinical picture resulting from inherited information
Premature termination codon	Also known as a class I mutation; includes nonsense and stop codon mutations
Stop codon mutation	A sequence that directs the normal cellular mechanism to stop, resulting in no functional protein being synthesised. This is a type of class I mutation (premature termination codon) causing CF
Transcription	The first step in protein synthesis. Information in a strand of DNA is copied into a code for the protein, which is then used to construct a protein molecule. The process of transcription is faulty in people with CF with class I mutations

Appendix 2. Electronic search strategies

Database	Search terms	Date searched
US National Institutes of Health (clinicaltrials.gov)	ADVANCED SEARCH FORM Condition or disease: cystic fibrosis Other terms: ataluren OR nonsense OR stop codon Study type: Interventional Studies (Clinical Trials)	4 October 2022
WHO International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int/)	SEARCH 1 (Basic Search Form) cystic fibrosis AND (ataluren OR PTC124) SEARCH 2 (Basic Search Form)	4 October 2022

(Continued)

	cystic fibrosis AND nonsense SEARCH 3 (Basic Search Form) cystic fibrosis AND stop codon	
European Medicines Agency (www.clinicaltrialsregister.eu)	SEARCH 1 (Basic Search Form) cystic fibrosis AND (ataluren OR PTC124) SEARCH 2 (Basic Search Form) cystic fibrosis AND nonsense SEARCH 3 (Basic Search Form) cystic fibrosis AND stop codon	4 October 2022

WHAT'S NEW

Date	Event	Description
2 March 2023	New search has been performed	Searches of the Cochrane Cystic Fibrosis and Genetic Disorders Group's Cystic Fibrosis Trials Register and online trials registries found 22 new references. Included studies We added seven new references to the already included study (Kerem 2014). We added four references to the study that was previously listed as ongoing (with a single reference) and is now included (Konstan 2020). Excluded studies We added two new references to the study previously awaiting assessment (previously with three references) and have now excluded it (Sermet-Gaudelus 2010). We have excluded nine new studies (single reference to each study) (NCT00234663; NCT00237380; NCT00351078; NCT01140451; NCT02456103; NCT03256799; NCT03256968; NCT03670472; NCT04126473).
2 March 2023	New citation required but conclusions have not changed	Despite the addition of one new study, our conclusions have not changed.

HISTORY

Protocol first published: Issue 1, 2016
Review first published: Issue 1, 2017

CONTRIBUTIONS OF AUTHORS

Roles and responsibilities	
TASK	WHO UNDERTOOK THE TASK?
Protocol stage: draft the protocol	AA with comments from all
Review stage: select which trials to include (2 + 1 arbiter)	AA and IS (KS to arbitrate)
Review stage: extract data from trials (2 people)	AA and IS
Review stage: enter data into RevMan	AA
Review stage: carry out the analysis	AA
Review stage: interpret the analysis	AA
Review stage: draft the final review	AA with comments from all
Update stage: update the review	AA, IS and KS

DECLARATIONS OF INTEREST

AA declares no potential conflict of interest.

IS declares no potential conflict of interest.

KS declares no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research, UK

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the analysis of individual adverse events, we have used 99% confidence intervals (CIs) rather than 95% CIs because the type I error rate (e.g. false positive) is greatly inflated with a large number of tests.

INDEX TERMS

Medical Subject Headings (MeSH)

Aminoglycosides; Anti-Bacterial Agents; *Codon, Nonsense; *Cystic Fibrosis [drug therapy] [genetics]; Cystic Fibrosis Transmembrane Conductance Regulator [genetics]; Mutation; Persistent Infection

MeSH check words

Adolescent; Adult; Child; Female; Humans; Male; Middle Aged; Young Adult