UNIVERSITY OF LIVERPOOL

Systematic evaluation of F508del variant specific therapies for people with cystic fibrosis

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Abstract

Introduction: Cystic fibrosis (CF) is caused by abnormal variants of the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, of which F508del, is the commonest. The F508del protein is degraded before reaching the cell membrane. Therapy to correct this defect would benefit many people with CF (pwCF).

Objectives: To evaluate the use of CFTR corrector medications on clinically important pre-defined outcomes for pwCF with class II *CFTR* variants (most commonly F508del) of any age.

Methods: We searched the Cochrane Cystic Fibrosis and Genetic Disorders Cystic Fibrosis Trials Register, reference lists of relevant articles and online trials registries. The most recent search was conducted on 31st December 2021. We searched for randomised controlled trials (RCTs) of parallel design comparing CFTR correctors to control in pwCF with class II variants and contacted authors for additional data. Two authors then independently extracted data, assessed risk of bias and evidence quality (GRADE).

Results: A total of 34 RCTs were included (4713 participants); eight monotherapy RCTs (4PBA, CPX, lumacaftor, cavosonstat and FDL 169), fifteen dual-therapy RCTs (lumacaftor-ivacaftor or tezacaftor-ivacaftor) and eleven triple-therapy RCTs (elexacaftor-tezacaftor-ivacaftor, VX-659- tezacaftor-ivacaftor, VX-440-tezacaftor-ivacaftor and VX-152-tezacaftor-ivacaftor). For monotherapy trials, there were no clinically relevant improvements in quality of life (QoL) or lung function. Across all of the lumacaftor doses, there were significantly lower cystic fibrosis questionnaire-revised (CFQ-R) scores in all domains when compared to placebo. There was a significant improvement in the absolute change in FEV_1 % predicted found in the 400 mg dose of FDL169 compared to placebo, though it was unclear whether this was clinically significant, mean difference (MD) 4.68 % predicted (95% confidence interval (CI) 0.12 to 9.24). For the dual therapy data, there were small but significant improvements in QoL and lung function. At six months, in four studies looking at tezacaftor-ivacaftor, the pooled data demonstrated a statistically significant increase in the CFQ-R

respiratory domain score, MD 2.89 (95% CI 2.48 to 3.29). Pooled data from three studies looking at lumacaftor-ivacaftor demonstrated statistically significant improvements in both the relative and absolute changes in FEV_1 at six months, MD 5.12 (95% CI 3.57 to 6.67) and 3.08 (95% CI 2.20 to 3.97) respectively. For lumacaftor-ivacaftor some participants experienced transient dyspnoea and an overall rise in blood pressure was noted. For triple therapy, there were improvements in QoL scores and respiratory function (FEV_1). In 175 participants with F508del/F508del, elexacaftor-tezacaftor-ivacaftor improved QoL respiratory scores (MD 15.90 (95% CI 11.74 to 20.06)) and absolute change in FEV_1 (MD 10.20 (95% CI 8.26 to 12.14)) compared to control through six months.

Conclusions: There is no evidence to support corrector monotherapy use and limited evidence to support dual therapy. There were significant and clinically relevant differences found across outcomes in the triple therapy studies, with improved safety profile. More research is needed into assessing these therapies in paediatric patients and the longer-term safety profiles of these new therapies, but these early results suggest this will be a transformational intervention for pwCF with class II *CFTR* gene variants.

Dedication

To my dad, in loving memory.

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My intercalated year has been a particular highlight of my university experience so far and I would like to sincerely thank my supervisors, Professor Kevin Southern and Professor Ian Sinha, for guiding me with my project and providing countless hours of support. I'm very grateful for the opportunities that this year has brought, and it has been their expertise and advice that has truly enriched my degree.

I would also like to thank Nikki Jahnke, Tracey Remmington and Natalie Hall for their advice and help with navigating the Cochrane database, and for being so generous of their time in doing so.

I am very grateful for the continuous guidance received from Dr Jared Murphy, who has regularly offered support with my project from start to finish.

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List of abbreviations

BMI	Body mass index
CF	Cystic fibrosis
CFQ-R	Cystic fibrosis questionnaire-revised
CFRD	Cystic fibrosis related diabetes
CFTR	Cystic fibrosis transmembrane conductance regulator
CI	Confidence interval
FEV_1	Forced expiratory volume after one second
FVC	Forced vital capacity
GRADE	Grading of recommendations assessment, development and evaluation
LCI	Lung clearance index
MD	Mean difference
MF	Minimal function
mg	Milligrams
NBS	Newborn screening
NICE	National Institute for Health and Care Excellence
NSAIDs	Non-steroidal anti-inflammatory drugs

OR	Odds ratio
$ppFEV_1$	Percent predicted forced expiratory volume after one second
pwCF	People with cystic fibrosis
QoL	Quality of life
RCT	Randomised controlled trial
WHO	World health organisation

1. Variant nomenclature and overview of MPhil

The term “variant” will be used instead of “mutation” throughout this thesis, as it is no longer considered to be an acceptable term.

There has been a change in the way variants are described; instead of describing variants by their impact on the protein that is produced, using the legacy system, the Human Genome Variation Society (HGVS) system is now used. The HGVS system describes variants by their changes to the genetic code.[1] Throughout this thesis, variants will be referred to by their HGVS name first, followed by their legacy name in brackets; the legacy name will then be used throughout the rest of the thesis.

My MPhil project this year has formed part of an ongoing process of evaluating all of the available data for a Cochrane systematic review. As part of my project, I have updated a Cochrane systematic review on corrector therapies and evaluated all of the studies within this review, alongside the studies that I have identified for inclusion. The newly identified results of the Cochrane systematic review are presented in this thesis, alongside the relevant summaries of data from the previous update of the review.[2]

2. Introduction

2.1. What is cystic fibrosis?

Cystic fibrosis (CF) is an autosomal recessive genetic condition that mainly affects the lungs and gastrointestinal organs, such as the pancreas and liver.[3] In Caucasians, CF is the most common life-limiting inherited disease[4] and in the United Kingdom in 2019, there were 10655 people living with the condition.[5]

CF is caused by a variant affecting the cystic fibrosis transmembrane conductance regulator (CFTR) protein. This protein is responsible for effective chloride ion secretion and increased sodium ion absorption via sodium channels throughout cells at various epithelial surfaces in the body. When defective, this leads to abnormal water transport from cells, resulting in viscous secretions.[3] Within the respiratory system, the maintenance of airway surface liquid (ASL) plays an important role in mucociliary clearance; however, in CF, these homeostatic mechanisms are impaired. This results in dehydrated and, due to abnormal CFTR bicarbonate transport, acidic ASL. Consequently, patients with CF are particularly susceptible to recurrent bacterial infections.[6] In addition to the pulmonary complications of CF (which account for more than 90% of deaths in patients), patients are also at risk of pancreatic insufficiency and diabetes mellitus, amongst other conditions described later.[7]

2.2. Newborn screening

All babies are screened for CF using the heel prick test when they are five days old. This was introduced in 2003 in Scotland and, since 2007, all babies born throughout the UK have been screened. Following a positive screening result, a sweat test is performed to confirm the diagnosis.[8, 9] Without newborn screening (NBS), the diagnosis of CF is delayed, leading to worse clinical outcomes due to persistent nutritional and growth deficiencies.[10] In a study completed in Poland, the average time of a CF diagnosis in patients who had been referred to a centre due to occurrence of symptoms suggesting the disease (before the introduction of NBS in Poland) was 45.25 months from birth. The average time of a CF diagnosis in patients who were diagnosed based on the level of sweat chloride,

in addition to evidence of CFTR dysfunction, was 1.59 months from birth. Earlier diagnoses allow for the earlier introduction of appropriate treatment, leading to better clinical outcomes.[11]

2.3. Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) variants

As an autosomal recessive condition, people with CF (pwCF) have a disease causing variant in both copies of the *CFTR* gene in each cell, inheriting one copy from each parent.[12] There are 401 CF-causing variants.[13]

2.3.1. Classification of *CFTR* variants

The different classes of *CFTR* variants are[14, 15]:

- Class 1: Reduced or absent CFTR expression. Class 1 variants result in premature termination codons and include frameshift, splicing or nonsense sequences.
- Class 2: Abnormal folding and maturation defect of the CFTR protein. The CFTR protein formed is targeted by the endoplasmic reticulum control system in the cell, leading to degradation and a reduced number of proteins reaching the cell surface.
- Class 3: Protein regulation defect. Class 3 variants allow for the CFTR protein to reach the cell surface, however there is a reduced open probability of the channel, resulting in no chloride ion flow. These are also known as gating variants.
- Class 4: Reduced conductance. Class 4 variants result in proteins with disrupted ion conduction pores.
- Class 5: Significantly reduced amount of protein at cell surface membrane. Class 5 variants allow the CFTR protein to reach the cell surface membrane, however the abundance of the protein is reduced due to splicing or promoter abnormalities.
- Class 6: Reduction of stability within the membrane. Class 6 variants lead to increased plasma membrane turnover due to increased instability of the channel. Overall, this leads to reduced expression of the protein at the membrane.[16]

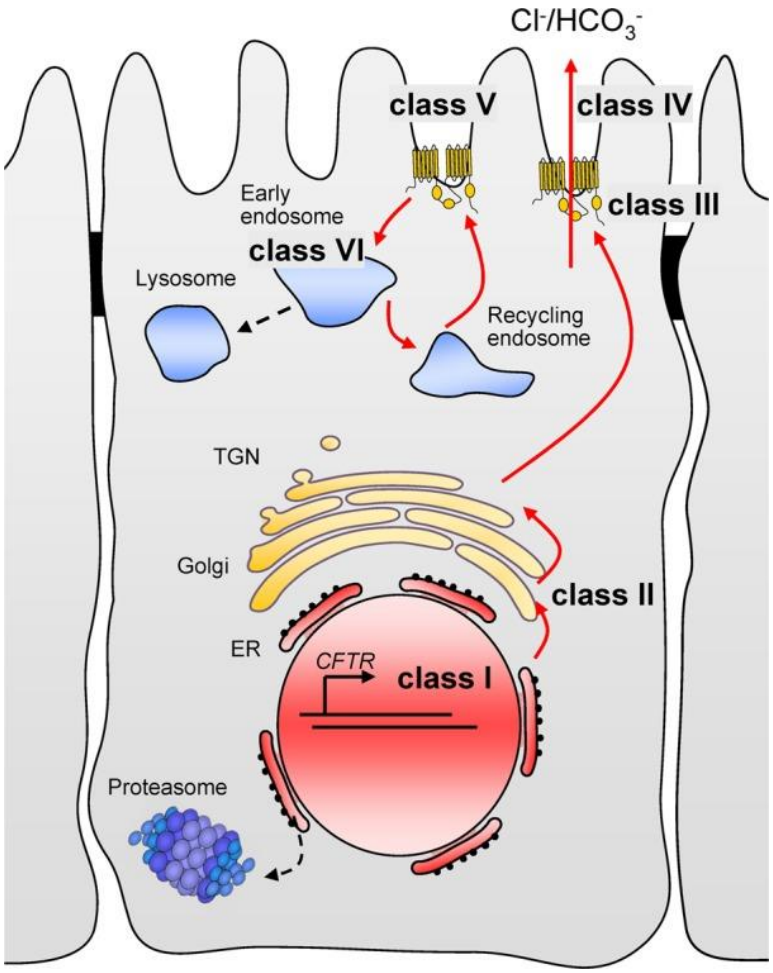

Figure 1: Diagram demonstrating the cellular phenotype of the classification of each CFTR variant.[15]

2.4. Treatment strategy

2.4.1. Relating treatment to pathophysiology

As mentioned previously, the CFTR channel is located on many epithelial surfaces throughout the body, making CF a multisystemic condition. Lung disease is closely linked to nutritional status.[17] Increased work of breathing, perhaps as a result of a respiratory infection, can lead to a reduced appetite and an increased need for calories as a result of inflammatory catabolism. It has been shown that having a body mass index (BMI) that is greater than or equal to 50% of a patient's age

correlates with a predicted percentage of forced expiratory volume in 1 second (FEV_1) greater than or equal to 90%.[18]

The name cystic fibrosis comes from the cysts and fibrosis that was noted in the pancreas of patients with the condition, and approximately 85% of the population with the disease are affected by pancreatic insufficiency by the age of 1 to 2 years. Pancreatic insufficiency leads to the malabsorption of protein, fat and fat-soluble vitamins and, in order to prevent growth failure, pancreatic enzyme replacement therapy (PERT) can be prescribed. The degree to which a patient with CF is pancreatic insufficient depends on the *CFTR* variant they have. If a patient with CF is pancreatic sufficient, they are at an increased risk of developing recurrent pancreatitis, which is a presentation for the diagnosis of the condition.[18]

Another extra-pulmonary complication of CF is cystic fibrosis related diabetes (CFRD), which significantly increases both morbidity and mortality in those living with the condition. Since the life expectancy of patients diagnosed with CF continues to increase, CFRD has become more prevalent,[19] with more than one-third of those aged 16 and over with CF being treated for CFRD, according to the UK CF Registry 2018. For those aged between 10-15, approximately 11% are on treatment.[20] The pathophysiology of CFRD is complex and multifactorial, although it is considered to be a unique form of diabetes. Unique to CFRD is the partial loss and dysfunction of pancreatic islets, leading to insulin deficiency. Additionally, there are fluctuating levels of insulin resistance due to chronic baseline inflammation, which periodically flares during times of infection. Finally, in order to maintain weight and prevent nutritional deficiencies, a very high caloric intake is required due to increased energy expenditure. CFRD also carries an increased risk of microvascular complications, much like both type 1 and type 2 diabetes.[19]

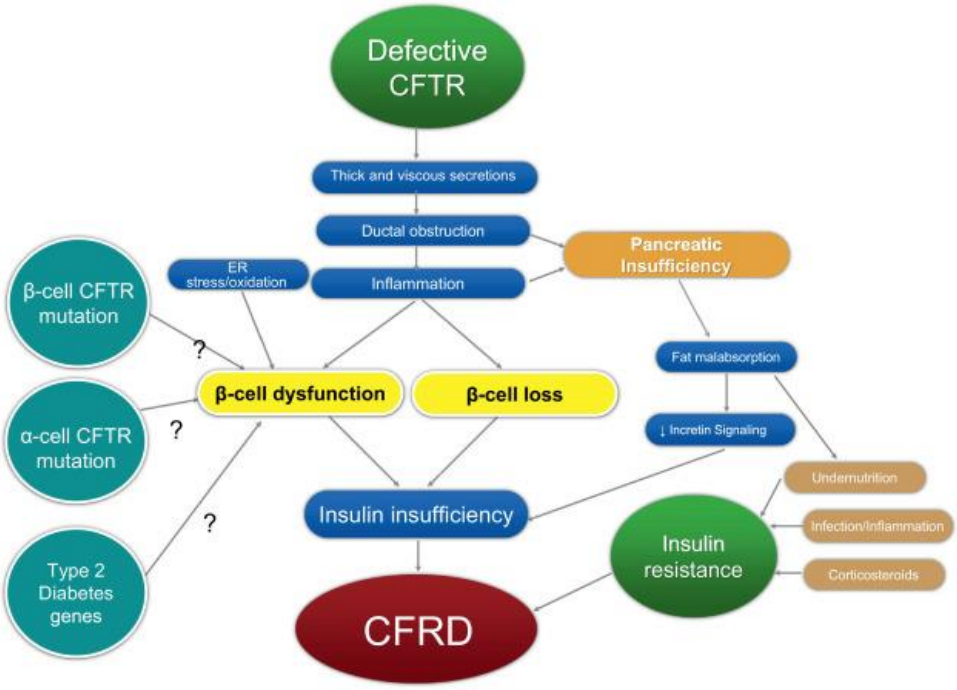

Figure 2: Diagram demonstrating the multifactorial and complex pathogenesis of CFRD.[19]

Low bone mineral density (BMD) is also a common finding in adults with CF. These patients have several risk factors for the development of low BMD, including malnutrition, diabetes, glucocorticoid therapy and chronic pulmonary infection. Consequently, compared with the general population, patients with CF have an increased fracture rate.[21]

CFTR proteins are found on the epithelial surfaces of the bile duct and gallbladder and, when dysfunctional, can lead to the secretion of viscous bile. The reduced movement of this thick bile carries the increased risk of infection, and the accumulation of toxic bile acids leads to the direct damage of hepatocytes. Cystic fibrosis associated liver disease (CFLD) is a common cause of death in CF patients, third only to lung disease and transplantation complications.[22]

In patients with CF, the intestinal mucus is extremely viscous and moves slowly. This increases the risk of meconium ileus during the neonatal period and, thereafter, distal intestinal obstruction

syndrome (DIOS). The symptoms of DIOS include distension, abdominal pain and vomiting and most episodes can be managed conservatively with intensive laxative treatment.[23]

2.4.2. Treating children with CF

Patients with CF are managed by a multidisciplinary team and there are three main principles that underpin treatment goals for all children with CF[24]:

- Excellent nutrition must be maintained
- Airways must be kept clear of infection
- Patients must stay active and exercise regularly

2.4.3. Excellent nutrition

Expert nutritional management is required for patients with CF as poor nutrition status is associated with decreased exercise tolerance and impaired pulmonary muscle function, leading to a decline in lung function. CF dietitians are therefore involved in providing management strategies to allow patients to maintain optimal nutritional status.[25]

The use of PERT with a high caloric diet and fat-soluble vitamin supplementation has been the standard nutritional care for pwCF, in order to achieve an adequate nutritional status. With an ageing CF population, due to increased survival rates, specialised CF dietitians must design nutritional management plans that focus on both micronutrient and macronutrient intake. These plans must be personalised to each patient of all ages and different disease stages, owing to the highly fluctuant patient care need throughout CF disease progression.[26]

In a systematic review examining anthropometric parameters in CF patients taking CFTR modulators, it was found that improved nutritional status was highly dependent on both the *CFTR* variant and therapy formulation used. Therefore, more research is needed into the effects of CFTR modulators on nutritional status, in order to determine the optimal nutritional management plans for those with CF in the future.[27]

2.4.3.1. Pancreatic enzyme replacement therapy & vitamin supplementation

Pancreatic insufficiency, the leading gastrointestinal clinical manifestation of CF, results in poor digestion and malabsorption of food due to a deficiency of pancreatic enzyme release.[28] PERT is used to counteract the malabsorption of nutrients and is given alongside fat-soluble vitamin supplements. In patients with CF, the secretion of pancreatic bicarbonate is impaired. A bicarbonate-rich environment provides the optimal conditions for pancreatic enzymes and so the use of acid suppression can supplement PERT. Acid suppression is also useful as a way to treat reflux symptoms, which must be carefully managed in lung transplant patients, and those with progressive pulmonary disease.[18]

2.4.3.2. Hepatic disease

Cystic fibrosis related liver disease is treated with ursodeoxycholic acid and, although it is unknown if this treatment affects histologic changes in the liver, liver transaminases can be normalised with its use.[18]

2.4.3.3. Intestinal disease

Meconium ileus is an early complication of CF, and occurs in around 10% of newborn infants with CF. It is caused by meconium obstructing the small intestine at the level of the terminal ileum, and patients present with intestinal obstruction. If patients experience abdominal distention, this may be severe enough to lead to respiratory distress. Patients that present with bilious emesis are required to be stabilised and are made nil by mouth. Intravenous access, in order to provide hydration, mechanical respiratory support, correction of coagulation disorders and empirical antibiotic coverage, is established. Additionally, the placement of a nasogastric tube decompresses the stomach and small intestine, and therefore reduces the risk of aspiration. Meconium ileus can be managed non-operatively through the use of therapeutic enemas.[29]

DIOS occurs when faecal matter combines with the sticky mucus in the CF intestine, usually in the terminal ileum and caecum, causing either partial or complete blockage. DIOS can be managed

medically, through the use of osmotic laxatives (for example lactulose and diatrizoate), stimulant laxatives (for example senna and sodium docusate) and mucolytics (for example oral N-acetylcysteine). Other agents may also be used, and surgery is regarded as the last resort treatment option, due to the high post-operative morbidity.[30]

2.4.3.4. CFRD

Insulin is currently the only treatment for CFRD; it improves calorie intake, reduces airway glucose levels and subsequently reduces the frequency of infections.[31]

2.4.3.5. CF related bone disease

Cystic fibrosis related bone disease can be prevented and managed by a multidisciplinary team. Initially, lifestyle measures are optimised to improve a patient's bone health and this can include improving vitamin D and calcium intake, as well as ensuring patients engage in weight bearing exercises and meet their individualised nutritional goals. Low BMD can also be caused by hypogonadism and delayed puberty, and the treatment of these causes should also be considered. Once osteoporosis has been diagnosed, bisphosphonates are prescribed.[32] CFTR modulators may also be beneficial in treating cystic fibrosis related bone disease, however more research is required to see if the use of these medications results in improved clinical outcomes.[33]

2.4.3.6. Salt regulation

Sodium chloride supplementation can be taken, especially in warmer months, due to patients with CF being at an increased risk of hyponatraemic dehydration.[18]

2.4.4. Keeping airways clean

More than 90% of deaths in CF patients are caused by lung disease[7] and the treatment of such involves the use of airway clearance techniques, antibiotics and mucolytic therapy.[34]

2.4.4.1. Airway clearance

The main aims of airway clearance techniques are to improve ventilation and reduce the risk of developing respiratory infections by removing secretions. A variety of techniques are used, which include postural drainage, active cycle of breathing techniques, autogenic drainage and high frequency chest wall oscillation. Exercise is also considered to play a vitally important role in CF physiotherapy.[35] One Cochrane review concluded that airway clearance techniques are able to increase mucus transport in the short term when compared with the use of no chest physiotherapy.[36]

In an overview of Cochrane systematic reviews evaluating airway clearance techniques for CF, there was little evidence found to justify the use of one technique over another. Instead, pwCF should choose a technique that they prefer, based on a number of factors including cost, practicality and comfort. The review also concluded that more research is needed in comparing airway clearance techniques.[37]

2.4.4.2. Antimicrobial prevention and therapy

Respiratory infections lead to inflammation and the development of bronchiectasis. Therefore, it is imperative that primary prevention strategies are implemented. Such strategies are included in infection control guidelines for CF. These recommendations include both individual and cohort segregation of CF patients, based on organism carrier statuses. Other measures include the use personal protective equipment by healthcare workers and patients, and regular handwashing.[38] Additionally, all patients with CF should follow national vaccination programmes. Pneumococcal vaccination is generally administered and all patients with CF should receive influenza vaccines annually from the age of 6 months. RSV infection may be associated with *Pseudomonas aeruginosa* (PA) colonisation, however an RSV vaccine is currently unavailable. Palivizumab is not recommended as immunoprophylaxis in CF.[39]

The commonest respiratory infections in preschool children are *Staphylococcus aureus (S. aureus)* and *Haemophilus influenzae*. In adolescents and adults, infection with PA becomes more prevalent.[38, 40]

PA infection in pwCF is associated with a more rapid pulmonary function decline and carries a greater risk of death. Consequently, early eradication of PA is essential to try to prevent chronic infection, which is impossible to eradicate.[38] It is therefore recommended that regular microbiological testing should take place to assess bacterial colonisation. For chronic infection, suppression therapy, such as colistin, tobramycin and aztreonam, is available.[3]

In order to reduce the incidence of methicillin-susceptible *S. aureus* (MSSA), UK guidelines recommend the use of anti-staphylococcal antibiotics up to the age of 3. NICE (National Institute for Health and Care Excellence) currently recommend offering flucloxacillin as prophylactic treatment against *S. aureus*, and recommend considering continuing this treatment up to age 6.[40, 41]

2.4.4.3. Mucolytic therapy

Patients with CF build-up viscous mucus in their lower airways, and hence mucolytic therapy aims to improve clearance of this material. Most of the mucus in CF is pus that contains adhesive material, such as polymerised DNA that has been derived from degraded neutrophils.[42] Dornase alfa is an enzyme used to breakdown the extracellular DNA causing the increased viscosity within the sputum of those with CF, consequently aiding airway clearance.[40] In a Cochrane systematic review evaluating the use of dornase alfa, it was found that its use may improve lung function and there was a decrease in pulmonary exacerbations in trials lasting longer than 6 months. Although there is not enough evidence to say that dornase alfa is better at improving lung function than other hyperosmolar agents,[43] it is currently the only mucolytic agent with efficacy that has been proven in CF.[42]

Mannitol is also used to increase the clearance of mucus. As a sugar, it creates an osmotic gradient that pulls water into the airway surface, leading to an increase in volume of the surface liquid.[40] A

Cochrane review evaluating the use of inhaled mannitol found that it could be considered as a CF treatment, though further research is required to evaluate the long term benefits of its use.[44]

Finally, hypertonic saline is a mucoactive agent that works via multiple mechanisms, including disrupting ionic bonds within the mucus, thereby reducing viscosity, and by increasing the depth of airway surface liquid by acting as an expectorant. Additionally, hypertonic saline triggers coughing, which in turn also increases the volume of mucus cleared.[45] A Cochrane review concluded that hypertonic saline is effective, alongside physiotherapy, during acute pulmonary exacerbations in adults, and the frequency of exacerbations is reduced with its use. However, there was insufficient evidence found in children aged 6 and under for the same outcome. Additionally, although its use results in an improvement in lung function after four weeks in those aged 12 years and over, this was not maintained at 48 weeks. The quality of the evidence used in the review ranged from very low to moderate.[46]

2.4.4.4. Airway inflammation

Airway inflammation in CF is caused by proinflammatory mediator secretions that promote neutrophil influx into the airways, leading to bronchiectasis. In patients with CF, the increased influx of neutrophils is thought to be due to an inflammatory response that is disproportionate to the initial stimulus.[47]

In a recent Cochrane systematic review, it was concluded that high-dose ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), has the potential to slow the development of pulmonary disease in children with CF. It is also a well-tolerated medication, though more research is required to determine the long-term effects of prolonged use of high doses of NSAIDs. Additionally, gastrointestinal protection is required whilst taking high doses of NSAIDs, as are regular safety profiles. Haematologic, hepatic and renal status monitoring are suggested to take place annually with the use of ibuprofen.[48]

Inhaled corticosteroids (ICS) are often used to reduce lung inflammation in pwCF. However, a recent Cochrane review concluded that there is insufficient evidence to show whether ICS may benefit pwCF. One study included in the review demonstrated that high doses of ICS adversely affected growth. Consequently, it is suggested that the prescribing of ICS for those with CF could be restricted to patients with recurrent, symptomatic wheezing that does not respond to bronchodilators, much like that for asthmatic patients.[49]

Other agents that are used against airway inflammation include leukotriene B4 receptor antagonists, azithromycin and antioxidants.[40]

2.4.5. Staying active and healthy

Staying active is a key component to achieving and maintaining respiratory excellence in CF.[24] Treadmill exercises allow for improved mucus clearance[50] and prescribed physical activity is recognised as a safe form of therapy.[51] Additionally, exercise has been associated with increased bone health; in a study looking at daily physical activity and bone disease in patients with CF, the participants with higher BMD scores were the most active.[52] Furthermore, there is evidence to suggest that poor glucose tolerance is linked with lower exercise capacity in CF patients.[53] Overall, exercise can be utilised as an airway clearance technique and is widely used to prevent metabolic syndrome, cardiovascular disease and obesity, amongst other conditions. In society, it is a socially acceptable therapy, helping to reduce the psychological burden placed on CF patients.[54]

2.4.6. CF and fertility

Around 98% of men who have CF are infertile due to the absence of seminal vesicles and associated congenital bilateral absence of the vas deferens. Infertility in women is generally due to disturbances in homeostasis as a result of, for example, nutritional failure, and direct changes in the reproductive tract. The cervical mucus can be thick and dehydrated, as CFTR proteins are found in great abundances in the cervix.[55]

Assisted reproductive technologies, such as sperm harvesting from the epididymis or testes, can mean that men with CF may be able to father their own biological children.[56] In vitro fertilisation (IVF) can be offered to couples and adoption is also an option for those wanting to start a family.[57]

2.5. Therapies which address the underlying defect

The *CFTR* gene was discovered in 1989 and, since then, our understanding of the genetic defects that cause CF has increased. This lead to the first variant-specific drug to be approved in 2012, ivacaftor.[3] The development of variant-specific medications has allowed recent treatment strategies for CF to not only manage the symptoms of the condition but also address the underlying causative defect. Despite this, however, it is unclear how the extrapulmonary complications of CF will be affected by modulator therapies, and so more research is needed in this field.[58]

2.5.1. Potentiators

The underlying mechanism of action of potentiators, which include ivacaftor, involves a wide range of processes. At the cell surface, they restore cAMP-dependent chloride channel activity to defective CFTR proteins, allowing for activated CFTR channels to remain open for longer.[59, 60]

Ivacaftor is an effective treatment in people with the c.1652G>A (G551D)[61] variant and has the potential to be useful in other class III defects. Ivacaftor has also shown some effectiveness in people with class IV variants c.350G>A (R117H).[61] It is also thought that CFTR potentiators may be effective in correcting the underlying gating defect in CFTR transported to the cell membrane in people with class II variants.[62]

2.5.2. Correctors

As a potentiator, ivacaftor can only be effective if CFTR is expressed on the cell surface, and this protein must be able to be activated via normal signalling mechanisms within the cell. This means that ivacaftor alone will not be effective with any variants that result in either improper trafficking or folding of the CFTR protein.[63]

Corrector medications specifically target c.1521_1523delCTT (F508del)[61] cellular misprocessing, and help to modulate the quality control mechanisms within the cell to alter recognition and processing of the CFTR protein. Therefore, it is said that corrector medications act as both "pharmacological chaperones" and "proteostasis regulators", though their exact mechanism of action is poorly understood.[59]

Examples of correctors include tezacaftor and lumacaftor. Despite the fact that correctors can allow the CFTR protein to reach the cell surface in people with the F508del variant, the protein itself might still not function properly. A Cochrane systematic review has examined the use of corrector monotherapy and correctors in combination with other agents, such as potentiators, to measure relevant clinical outcomes.[64]

In a recent study looking at triple therapy for people with the F508del-gating or F508del-residual function genotypes, it was concluded that elexacaftor-tezacaftor-ivacaftor was safe and efficacious, and the clinical benefit that was observed was found to exceed previous CFTR modulators.[65]

2.5.3. Readthrough compounds

As described previously, class I variants include premature termination codons that prevent CFTR protein synthesis. Nearly 5% of patients with CF have 1 copy of the c.1624G>T (G542X)[61] variant, which codes for a stop codon, leading to incomplete protein synthesis. Medications are only currently available for certain CF causing defects, including both class II and III variants.[66]

Currently, research into medications that will allow full-length proteins to be synthesised, by overriding premature stop codons, is being undertaken. These medications are known as readthrough compounds.[67]

Ataluren is a potential class I therapy for CF as it allows the cellular mechanisms to read through premature termination codon sequences. In a Cochrane systematic review looking at ataluren,

however, it was concluded that there is a lack of evidence to support its use as a therapy for pwCF. Ataluren was also associated with renal impairment.[68]

2.5.4. RNA therapies and gene editing techniques

Modulator therapies can be used in approximately 90% of the CF population; however, in the remaining patients, modulators are not appropriate treatments, due to either lack of tolerability or the presence of nonsense and splicing sequences. Consequently, gene therapy may be useful in this remaining cohort.[69]

Gene therapy encompasses both integrating and non-integrating therapies. Integrating gene therapy is permanent and here, a correct copy of the *CFTR* gene is incorporated into a patient's cells and becomes part of the genome. CAR-T therapy, an alternative form of integrating gene therapy, has been approved for the treatment of leukaemia and integrating gene therapy for CF is currently being tested in animals. In non-integrating gene therapy, however, the DNA with the correct copy of the *CFTR* gene remains separate from the genome. Therefore, although the cells can make functional CFTR proteins as a result of the therapy, it is not permanent.[70] In a clinical trial assessing non-integrating gene therapy for CF, it was found that lung function in the treatment group was stabilised, though full clinical evaluation (phase 2 and phase 3 trials) is needed before gene therapy can be used in clinical practice.[70, 71]

With RNA therapies, unlike in both integrating and non-integrating gene replacement therapies, the cell is given direct RNA copies. This is therefore a non-permanent treatment strategy and early-stage clinical trials are underway to evaluate the use of MRT5005, a potential RNA therapy, in adults with CF.[70, 72]

2.5.5. Amplifiers

An amplifier aims to increase CFTR protein synthesis within a cell.[73] A phase 2 study looking at PTI-428 in adults with CF showed that the medication was well tolerated and resulted in increased CFTR protein production,[74] which is promising for the future of this medication.

2.6. Efficacy and safety of variant specific therapies for pre-school children with CF

The symptoms of CF start from a very early age and, by diagnosing the condition early, appropriate clinical care, as well as enrolment in relevant clinical trials, can take place. Despite this, however, most therapeutic interventions have not had their efficacy assessed in children younger than 6 years of age. Instead, in this age group, the focus of drug development programmes has been on safety.[75]

In younger children, there are additional challenges to collecting data. KLIMB was an 84-week, open label extension of a previous study, KIWI, that evaluated the use of ivacaftor in children with CF aged 2 to 5 years old. The paper was the first of its kind to report efficacy and long-term safety of ivacaftor in the chosen age group; however, the study had several limitations. The age of the population studied led to the research being performed as an open-label trial, resulting in no placebo group. Also, spirometry data are challenging to obtain from younger children, meaning that very little suitable data was collected and analysed.[76]

The challenges of conducting clinical trials for younger children include, but are not limited to, ethical problems, recruitment obstacles and challenges in small populations. These barriers limit how well clinicians evaluate new medications in this age group.[77]

3. The Cochrane systematic review

3.1. The Cochrane Collaboration

The Cochrane Collaboration is an independent organisation that works internationally to produce trusted and accessible evidence. With over 7,500 Cochrane Systematic Reviews published in the Cochrane Library, the members and supporters of the Collaboration originate from over 190 countries and have been summarising best evidence for 28 years.[78]

The Cochrane Collaboration was named after Professor Archibald Cochrane, often referred to as 'the father of evidence-based medicine'. In 1972, Cochrane published arguably his most influential piece of work, entitled 'Effectiveness and Efficiency: Random Reflections on Health Services'. Through his work, Cochrane criticised the lack of scientific evidence steering medical practice and emphasised that all treatments should be based on randomised controlled trials (RCTs). Through continuously advocating the concepts of equality, efficiency and effectiveness, Cochrane outlined that collecting all RCTs would allow for accurate conclusions to be reached by clinicians. Professor Cochrane died in 1988 and the Cochrane Collaboration was formed following on from this, in 1993.[79]

The Cochrane Collaboration has published a handbook that outlines, in great detail, the preparation process of Cochrane systematic reviews, and also describes the process of maintaining these too. Within the handbook, it is explained that, although there are a number of organisations that publish systematic reviews, it is its rigorous methods that sets Cochrane apart. The Cochrane Methods Groups identify the key processes required for systematic reviews, including steps to allow for analysis and interpretation of results, and also for the minimisation of bias.[80] The work produced by the Cochrane Collaboration is therefore regarded as the benchmark for quality health care information.[78]

3.2. What is a systematic review?

Systematic reviews allow healthcare professionals to access up-to-date information as they summarise all of the evidence that answers a specific research question. The information provided by a systematic review is reliable due to the clear methods that are employed when conducting a review that aim to minimise bias.[81, 82]

Prior to starting a systematic review, a protocol is published. Where a protocol has been written by authors who have not yet read the available studies in the field, the impact of bias is reduced. This is because the definition of a systematic review question will not be influenced by any knowledge of the field. Consequently, as potentially knowledge of prior evidence may be inevitable, due to the retrospective nature of systematic reviews, the Cochrane Handbook for Systematic Reviews of Interventions suggests that non-content experts should be members of the review team. The protocol allows for the context of the review, the eligibility criteria of the participants and choice of outcomes to be outlined also.

Systematic reviews must be replicable and the highly structured methodology includes a number of sections. Firstly, the research question, decided 'a priori', is included, which precedes the scope of the review and information on which particular studies meet the eligibility criteria for inclusion. Any concerns of bias within the included studies in the review must be considered, and finally the included studies must be analysed, in order for balanced conclusions to be drawn.[81]

Alongside a systematic review, a meta-analysis may be performed, whereby data from various independent studies, aimed at addressing the same question, is combined in order to statistically analyse many results to integrate the findings, allowing for the calculation of an overall effect.[82, 83]

Following on from developing the research question and completing the systematic review, data extraction is completed. Whilst extracting data, whether they be numerical or categorical measures, it is imperative to consider measures of data variability and sample sizes. After data extraction has been completed, the differences between control and intervention groups, known as 'effect sizes',

are calculated. Due to variability between included studies, standardisation needs to take place also. Additionally, inverse variance, a type of weighting statistic, is often used to account for various factors that have an impact on the quality of data extracted, such as sample size and standard deviations. Finally, the differences between control and intervention groups across different studies are compared, often by using one of two models: 'random effects' and 'fixed effects' models.[83]

A forest plot is used to graphically report the results from a meta-analysis.[83, 84] Although a forest plot allows for heterogeneity to be demonstrated, as well as enabling the pooling of results, it cannot demonstrate publication bias (which is represented using a funnel plot). On a forest plot, the boxes represent the estimates of single studies, whilst the diamonds represent the pooled results. The horizontal lines that pass through the boxes, and the diamond shape width, both represent the length of the confidence interval. The vertical line is the line of no effect. This demonstrates where there is no difference between the control and intervention group. For adverse outcomes, any results that appear to the left of the vertical line favour the intervention over the control, and they will appear to the right of the vertical line if the outcome is desirable. The overall results are not considered to be statistically significant if the diamond touches the vertical line of no effect. Finally, a higher percentage weight means that the boxes are larger, and the overall influence of the study on the pooled results is greater. A higher percentage weight is often achieved when there is a narrower confidence interval and larger sample size.[84]

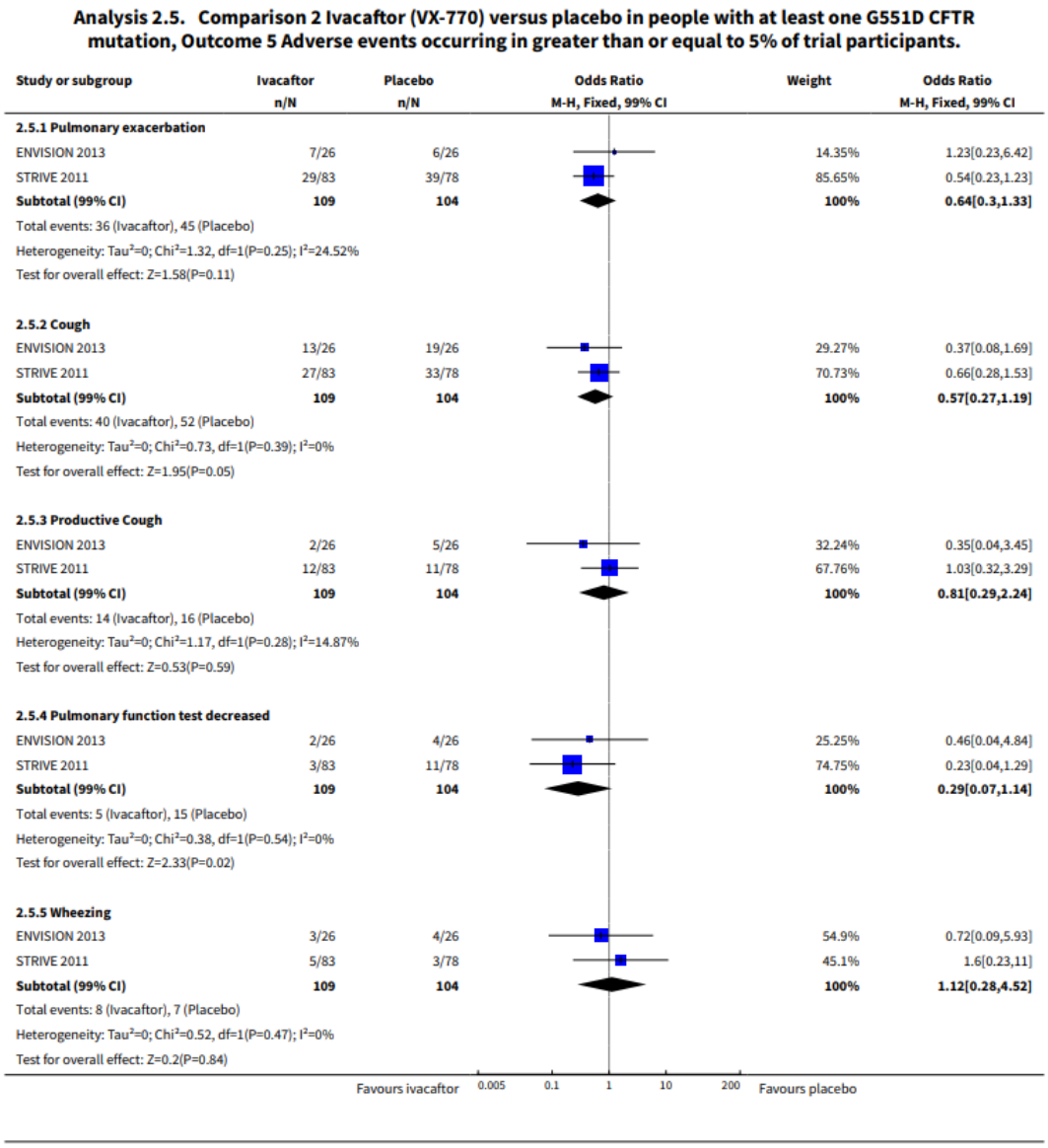

Figure 3: Example of a forest plot from a Cochrane systematic review on potentiators for CF. From Skilton M et al.[62]

If a p-value is less than 0.05, it can be concluded that there is a statistically significant difference between the results of two groups and, in this case, the diamond of a forest plot would not touch the line of no effect.

I^2 values represent heterogeneity and are given as percentages. If the I^2 values are less than or equal to 50%, a fixed effect model can be used. Conversely, where the I^2 values are greater than 50%, random effect models should be used as the heterogeneity is considered to be high.[84]

3.3. Why do a systematic review?

Systematic reviews are beneficial in many different ways. They offer a way to comprehensively summarise potentially vast amounts of available evidence on a specific topic, allowing for researchers to efficiently grasp an understanding of how to (or when not to) develop future work in a specialism.[85] By empowering healthcare professionals with all of the available evidence relating to a clinical question or treatment uncertainty, they will be informed to make better clinical decisions, thus benefitting their patient population.[86]

Alongside a systematic review, a meta-analysis may be performed. Combining data from various studies increases the overall sample size being investigated, allowing for the reduction in the size of the confidence interval for the point estimate of the effect. Consequently, a meta-analysis of similar RCTs is considered to be one of the highest levels of evidence.[86]

3.4. The challenge of systematic reviews

Despite the advantages that systematic reviews have, they naturally also present certain limitations. When screening for evidence, reviewers require access to a large number of journals and databases, meaning that the process is potentially expensive for non-academic researchers, and also time consuming. Additionally, with regards to searching for evidence, it is necessary to search institutional websites, as often research can be found outside of the formal peer-reviewed sources. However, this introduces bias to the process. Potentially useful websites may be excluded either due to lack of knowledge or resource constraints and this, combined with differences in website search functions, means that potentially useful studies can be overlooked.[87] Publication bias is also another important limitation to consider, especially for clinicians. Studies that do not outline statistically significant results may still be clinically important, even though they are less likely to be published.[88, 89] Where authors may have competing interests, this can lead to favouring a specific intervention too. Therefore, it is imperative that all authors declare any conflicts of interest in order for readers to appreciate the scope of potential bias in a review.[89]

3.5. Heterogeneity

The term heterogeneity describes the variability among studies in a review and can be categorised into methodological and clinical diversity, and statistical heterogeneity.[90]

Differences in the characteristics of participants can lead to clinical heterogeneity. Methodological heterogeneity arises when there are differences in the trial designs, and both of these factors contribute to statistical heterogeneity, whereby there are differences in the evaluated intervention effects.[90, 91]

When conducting meta-analyses, managing heterogeneity is difficult, and advice on how to manage such variation is limited. In a cross-sectional study looking at Cochrane reviews with substantial heterogeneity, one-third had major problems in managing this. The study suggests that strategies that could be used for addressing variation include checking that data extraction is correct, leaving out meta-analyses, conducting subgroup analyses, excluding studies and choosing random effects models.[92]

3.6. Background to Cochrane systematic review

My MPhil project this year has focused on completing a substantial update of a previous Cochrane systematic review, aimed at assessing the use of corrector medications in pwCF with class II *CFTR* variants.[2]

In the previous review, the authors concluded that there was a lack of evidence to show that there were clinically important effects on pwCF, homozygous for F508del, with the use of corrector monotherapy. There were 2 different dual therapy combinations examined (lumacaftor-ivacaftor and tezacaftor-ivacaftor), and both showed similar improvements in respiratory function and quality of life, although tezacaftor-ivacaftor was found to have a better safety profile. Finally, the review authors found that the evidence to show clinical efficacy for the use of triple combination therapy

(elexacaftor-tezacaftor-ivacaftor) was of a high quality, though they concluded that further studies were required for children aged under 12 years old.[2]

New trials have been completed since the last review, representing the fast-paced research output within the field of CF, and therefore an update was required. Both the rationale and eligibility criteria for the review remain unchanged.

3.6.1. Description of the intervention

Class II *CFTR* variants result in altered protein processing, leading to misfolding and the early break-down of the protein by the cell's control systems. This results in less CFTR protein reaching the cell surface membrane.[14, 15] An intervention to address this issue would therefore be required to overcome these cellular mechanisms, in order for the CFTR channels to reach the membrane.

3.6.2. How the intervention might work

Corrector medications can be used to target the F508del cellular misprocessing. Additionally, the medications have the ability to modulate the quality control mechanisms within the cell, in order to alter recognition and processing of the CFTR protein. Although the exact mechanisms of corrector medications are poorly understood, they can be referred to as both "pharmacological chaperones" and "proteostasis regulators".[59]

3.6.3. Why it is important to do this review

CFTR corrector medications are relatively new therapies and therefore it is imperative to review and critically appraise all RCTs within this field; this allows for up-to-date assessment of both the advantages and disadvantages of these therapies.[2] The commonest CF-causing variant is F508del, a class II *CFTR* variant, and so therapy to target this type of variant would benefit many pwCF. There is a significant cost associated with the treatment of pwCF using corrector therapies,[2] and therefore it is important to critically appraise all evidence, in order for healthcare providers to make informed decisions about the commissioning of such medications.

3.6.4. Objectives

To evaluate the use of CFTR corrector medications on clinically important pre-defined outcomes for pwCF with class II *CFTR* variants (most commonly F508del) of any age.

4. Methods for Cochrane systematic review

4.1. Identifying potentially eligible studies

The information specialist in the Cochrane Cystic Fibrosis & Genetic Disorders group team searched the Cystic Fibrosis Trials register, in order to identify studies for the review. The terms: 'drugs that correct defects in CFTR transcription, translation or processing' were used to search the database. This register is composed of electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (which is searched on a weekly basis) and results of a search of Embase to 1995. The register is also compiled of results from the handsearching of the *Journal of Cystic Fibrosis* and *Paediatric Pulmonology*.[2] The information specialist also aimed to identify unpublished work by searching the abstracts of the following three conferences: the European Cystic Fibrosis Conference, the North American Cystic Fibrosis Conference and the International Cystic Fibrosis Conference. The bibliographies of the included studies from the previous reviews were also screened, in order to highlight potentially eligible references for assessment.

In order to increase the breadth of the searches, the following trial registers were searched by myself (MH):

- World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch)
- European Medicines Agency (www.clinicaltrialsregister.eu/ctr-search/search)
- US National Institutes of Health Ongoing Trials Register Clinicaltrials.gov (www.clinicaltrials.gov)

For the first two registries listed above, the search terms used were: 'Cystic fibrosis AND (VX OR corrector)', and for the final registry, the search strategy involved the use of the advanced search form. The disease searched for was 'cystic fibrosis' and the 'other terms' used were 'VX OR corrector'. The study type searched for were 'Interventional Studies (Clinical Trials)'.

Where more information was required to assess the eligibility of the search results for inclusion within the review, the corresponding authors were contacted.

4.2. Assessing eligibility

As this was an update to the previous review carried out, the eligibility criteria for studies to be included for assessment remained the same. If a study result met all of the criteria below, it was eligible for inclusion[2]:

- Study type: All published or unpublished RCTs of parallel design were included, though quasi-RCTs were not. Cross-over studies did not meet the eligibility criteria for the review, as it was thought that the design of these studies was inappropriate; if the correctors were found to be effective, this would impact the course of the disease.
- Participant type: Participants of any age with CF have been included in the review, and the diagnosis of CF for these participants was confirmed by the presence of at least one class II *CFTR* variant, or by a mix of recognised clinical features of CF and a positive sweat test result. Participants with any level of disease severity have been included.
- Intervention type: The review focusses on CFTR correctors, of which the main variant targeted is F508del. Interventions that targeted DNA correction were not included, however RCTs in which the CFTR correctors were given alongside another drug class, for example potentiators, were included in the review.
- Outcome measure type: The review assessed a number of primary and secondary outcomes which are listed in section 4.3. of this thesis.

4.3. Outcomes recorded

Much like the eligibility criteria for the review, the outcomes that were assessed remained the same in this update.

4.3.1. Primary outcomes[2]:

1) Survival
2) Quality of life (this was measured using quantitative scores, for example the Cystic Fibrosis Questionnaire-Revised (CFQ-R))
    a) Quality of life total score
    b) Different reported sub-domains
3) Measures of lung function (litres or per cent predicted for age, sex and height)
    a) Relative change from baseline in forced expiratory flow rate at one second (FEV_1)
    b) Absolute values for FEV_1 (and absolute change from baseline in these values)
    c) Absolute values for forced vital capacity (FVC) (and absolute change from baseline in these values)
    d) Lung clearance index (LCI)
    e) Other relevant measures of lung function not listed above

4.3.2. Secondary outcomes[2]:

1) Adverse effects, which were previously classified into the following groups:
    a) Mild- determined by the fact that the therapy did not need discontinuation
    b) Moderate- determined by the fact that once the therapy is discontinued, the adverse effect also stops
    c) Severe- determined by the fact that the adverse effect is life-threatening or debilitating, or once the therapy is discontinued, the adverse effect does not stop
    d) Other adverse effects that do not fit into the above categories, which can be of any severity
2) Hospitalisation
    a) Number of days hospitalised
    b) Number of admissions
    c) Time from one admission to the next

3) Attendance at school or work (as determined, for example, by the number of days missed)
4) Additional courses of antibiotics (as determined by the total number of antibiotic courses, and the time from one antibiotic course to the next). This outcome also incorporated exacerbations in CF, as determined by increases in symptoms, increased antibiotic need or hospitalisation, or a combination of these.
    a) Oral
    b) Intravenous
    c) Inhaled
5) Change from baseline in sweat chloride levels
6) Radiological estimates of lung disease (this is assessed using any scoring system)
    a) Chest radiograph scores
    b) Computerised tomogram scores
7) Acquirement of respiratory pathogens
    a) *Pseudomonas aeruginosa*
    b) *Staphylococcus aureus*
    c) *Haemophilus influenzae*
    d) Other clinically relevant pathogen
8) Elimination of respiratory pathogens
    a) *Pseudomonas aeruginosa*
    b) *Staphylococcus aureus*
    c) *Haemophilus influenzae*
    d) Other clinically relevant pathogen
9) Relative change from baseline in nutrition and growth (including centiles or z scores)
    a) Weight
    b) Body mass index (BMI)
    c) Height

4.4. Data extraction

A data extraction form was used for all of the identified eligible studies, which helped to categorise information into continuous and dichotomous data. An example of the data extraction form used can be found in the appendix of this thesis.

During the data extraction process, in a similar way to the previous review, two of the review authors were required to independently assess the eligible studies (MH and JM), and where disagreements arose, a third author was consulted for advice (KWS).[2] At the end of the data extraction process, due to the large number of new trials that were eligible for inclusion since the last review, I prepared a presentation for all of the authors, which outlined the salient points from the new studies, and allowed for an opportunity to discuss how best to present the results in the review.

4.5. Risk of bias

Once data extraction was completed, the risk of bias of the included studies in the review was assessed independently by two different authors (MH and JM). Where disagreements arose between two authors regarding classifying the risk of bias, a third author was consulted for advice (KWS). Each study was assessed for bias using the guidance set out in Cochrane's tool for assessing risk of bias[93] and Cochrane's training handbook,[94] and allowed for the following types of bias to be assessed:

- Selection bias: This assesses the extent to which bias in each paper is due to the randomisation process, arising from either random sequence generation or allocation concealment. Assessing this type of bias also addresses whether the difference in baseline characteristics between intervention groups highlights an issue with the randomisation process.
- Performance bias: Evaluating the performance bias within studies allows for the detection of bias that is down to deviations from intended interventions. Authors are required to assess

the extent to which participants were aware of their intervention group during the trial, and also the extent to which the carers and professionals were aware of the participants' intervention during the study. Adequate blinding allows for reduction in this type of bias.

- Detection bias: This type of bias arises when outcome assessors are aware of the allocated interventions and is reduced when adequate blinding occurs. Detection bias arises due to the fact that assessment of outcomes can potentially be influenced by any prior knowledge of received interventions.
- Attrition bias: Where there is incomplete outcome data, attrition bias can arise. The amount of attrition bias will increase with more missing data; authors can only be sure that there is no bias when all participants are measured for each outcome, the percentage of data that are missing is low enough so that any bias is too small to be significant, or sensitivity analyses confirm that possible values for missing data would not make an important difference to the overall result.
- Reporting bias: This type of bias arises when there is selective reporting of outcome measures, and can arise from a desire for results to be significant enough to warrant publication.
- Other bias not covered by any of the above types.

For each of the types of bias above, the review authors determined whether each study had either a high, low or unclear risk, and provided a supporting statement for each judgement.

4.5.1. Publication bias and funnel plots

Publication bias arises when negative results are withheld from reporting, often due to the fact that positive results are more likely to be considered for publication. This can have serious negative consequences on health, as such bias can have a major impact on the available literature.[95]

In cases where protocols or trial records are unavailable, funnel plots may be used to help recognise cases of non-reporting bias. On the horizontal scale of a funnel plot, the effect estimate is plotted

and the measure of study size is plotted on the vertical axis. Therefore, at the bottom of the graph, effect estimates from small studies will be widely spread. With larger studies, the spread will narrow. A lack of bias will result in an inverted funnel that is symmetrical. Where publication bias occurs, the funnel plot will show an asymmetrical appearance, and have a gap at the bottom corner of the figure. A greater degree of asymmetry in a funnel plot indicates a larger amount of bias. However, using funnel plots to estimate bias has its limitations, as asymmetry can be due to a large number of reasons: chance, poor methodology, and true heterogeneity. Therefore, it is recommended that where asymmetry is noted, other possible explanations for this, aside from non-reporting bias, are considered. It is also recommended that using funnel plots to observe asymmetry should be used when at least 10 studies are included in the meta-analysis.[96]

4.6. Measures of treatment effect

In a similar fashion to the previous review, when dealing with binary outcomes, a pooled estimate of the treatment effect was calculated using either the pooled odds ratio and 95% confidence intervals or, when dealing with the analysis of separate adverse events, 99% confidence intervals. When working with continuous outcomes, the mean change from baseline and standard deviation was calculated for each group. Hazard ratios and 95% confidence intervals were reported when working with time-to-event data.[2]

Where the same outcomes have been reported in trials, these have been combined into a meta-analysis, and forest plots have been drawn.

4.7. Heterogeneity

As previously mentioned, the term heterogeneity describes the variability among studies in a review and can be categorised into methodological and clinical diversity, and statistical heterogeneity.[90]

When results for studies are depicted graphically, the lack of overlap of confidence intervals can indicate the presence of statistical heterogeneity.[97] The chi-squared test can be used to test for

heterogeneity, and a low P value from the test indicates that variation is present. However, the test is not useful when there are few included studies in the meta-analysis, as a non-significant result does not mean that heterogeneity is not present. It has been argued that heterogeneity will always be present; testing for its presence is not useful. Instead, assessing the impact of heterogeneity on meta-analyses provides a more useful way of quantifying its effect. An equation has been developed that links Cochran's heterogeneity statistic, or the chi-squared statistic (represented by the letter Q), and the degrees of freedom (represented by df). The equation used is[97, 98]:

$$I^2 = \left(\frac{Q - \mathrm{df}}{Q}\right) \times 100\%.$$

The I^2 statistic can be interpreted as[2, 97]:

- 0% - 40%: not likely to be important
- 30% - 60%: moderate heterogeneity may be present
- 50% - 90%: substantial heterogeneity may be present
- 75% - 100%: the heterogeneity present is considerable

As was the case in the previous update of the review, any heterogeneity identified was to be explored using subgroup analyses of potential confounding factors, provided that at least 10 studies were included in the meta-analysis. The confounders were classes of variants, sex and age.[2]

4.8. Sensitivity analysis

A sensitivity analysis is a way to assess the credibility of a trial by looking at the extent to which any of its results are changed by alterations in methodology, models, values of unmeasured variables or underlying assumptions in an investigation. After performing sensitivity analyses, if the results remain unchanged, the conclusions are said to be credible.[99]

5. Results of Cochrane systematic review

5.1. Context of this result section

The results of this Cochrane systematic review form part of a substantial update on this previously completed piece.[2] For this review, I identified 15 new search results and analysed the data from these, in accordance with the previously determined outcomes. The results of this review include a significant number of trials from the trials registry before they have been published in peer-reviewed papers and they will be presented below; I will highlight any major changes found for each outcome in the context of the previous reviews.

The new search results are comprised of nine studies assessing dual therapies (DAVIES 2021[100], MCKONE 2021[101], MUNCK 2020[102], NCT02070744[103], NCT02508207[104], NCT02730208[105], SCHWARZ 2021[106], STAHL 2021[107], WILSON 2021[108]) and six studies assessing triple therapies (BARRY 2021[65], NCT02951182[109], NCT02951195[110], NCT03447249[111], NCT03460990[112], SUTHARSAN 2021[113]).

5.2. Study selection

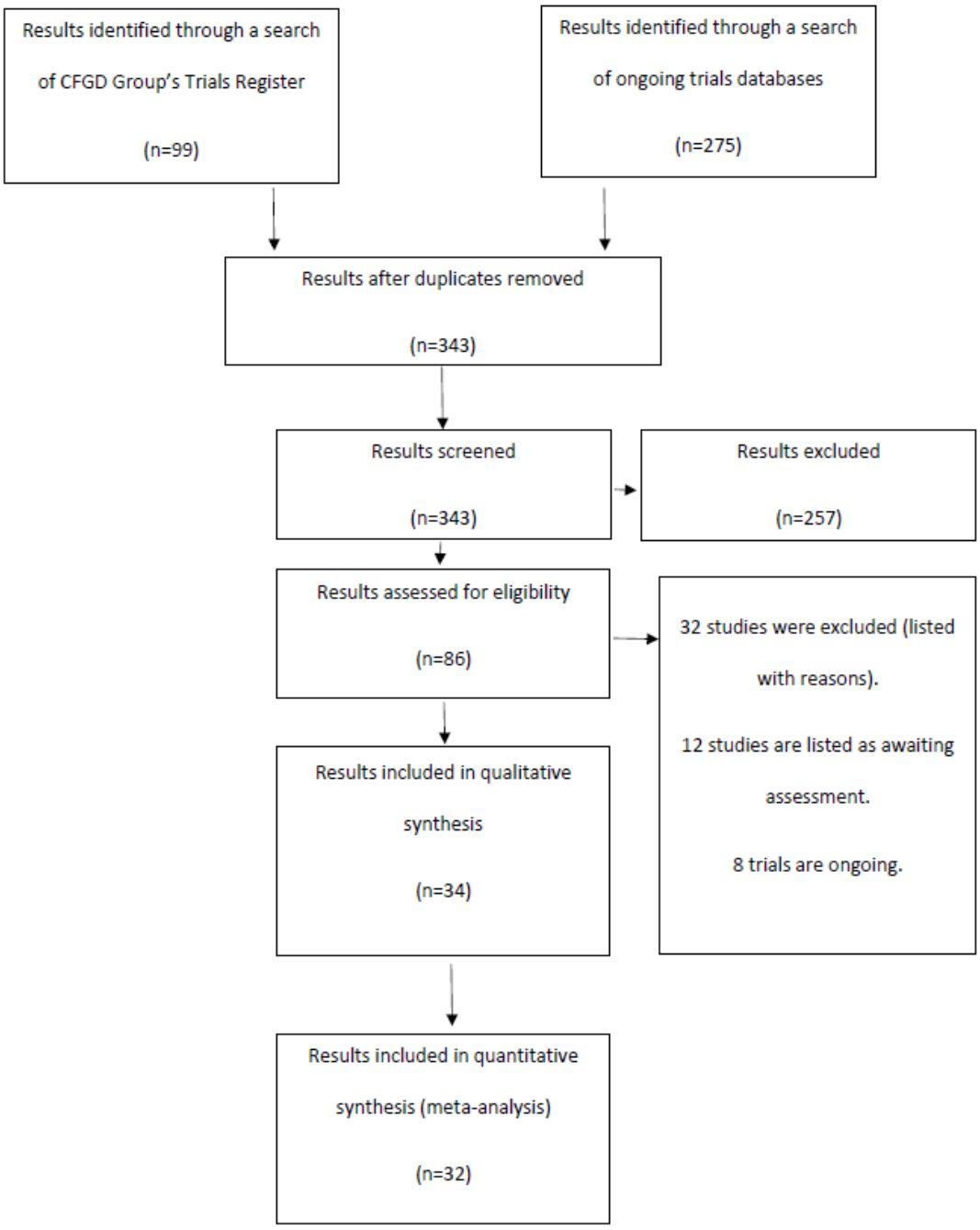

Figure 4: A PRISMA flow diagram detailing the search results and eligibility assessments.

5.2.1. Included studies

A summary of the newly included studies can be found in the appendix of this thesis.

Monotherapy

No new monotherapy studies were identified in this update of the review. The previous review included data on eight placebo-controlled monotherapy studies, with a total of 344 participants (BOYLE 2014[114], CLANCY 2012[115], DONALDSON 2014[116], DONALDSON 2017[117], HORSLEY 2017[118], MCCARTY 2002[119], RUBENSTEIN 1998[120], ZEITLIN 2002[121]).

Two studies examined lumacaftor monotherapy (BOYLE 2014[114], CLANCY 2012[115]), one evaluated N6022 (DONALDSON 2014[116]), one investigated cavosonstat (DONALDSON 2017[117]) and FDL169 was trialled in another study (HORSLEY 2017[118]). CPX was another drug evaluated in one trial (MCCARTY 2002[119]), and two studies looked at 4PBA (RUBENSTEIN 1998[120], ZEITLIN 2002[121]).

Dual combination therapy

Fifteen studies with a total of 2627 participants were included (DAVIES 2021[100], MCKONE 2021[101], MUNCK 2020[102], NCT02070744[103], NCT02508207[104], NCT02730208[105], SCHWARZ 2021[106], STAHL 2021[107], WILSON 2021[108], BOYLE 2014[114], DONALDSON 2018[122], RATJEN 2017[123], TAYLOR-COUSAR 2017[124], TRAFFIC 2015 and TRANSPORT 2015[125]) and one study contributed to the safety data (PROGRESS 2017[126]).

Nine studies compared tezacaftor-ivacaftor to either placebo or ivacaftor monotherapy in 1132 participants (Davies 2021[100], McKone 2021[101], Munck 2020[102], NCT02070744[103], NCT02508207[104], NCT02730208[105], Schwarz 2021[106], DONALDSON 2018[122], TAYLOR-COUSAR 2017[124]) and six studies compared lumacaftor-ivacaftor to placebo in 1495 participants (STAHL 2021[107], WILSON 2021[108], BOYLE 2014[114], RATJEN 2017[123], TRAFFIC 2015 and TRANSPORT 2015[125]).

Out of nine of the newly identified studies for this comparison, two compared lumacaftor-ivacaftor to placebo in participants homozygous for the F508del variant; one other study with 51 participants

aged two through five years of age compared either 100 mg twice daily lumacaftor-125 mg twice daily ivacaftor to placebo in subjects weighing less than 14kg at screening, or 150 mg twice daily lumacaftor-188 mg twice daily ivacaftor to placebo in those weighing at least 14kg at screening (STAHL 2021[107]) and one study with 70 participants compared 400 mg twice daily lumacaftor-250 mg twice daily ivacaftor to placebo (WILSON 2021[108]).

Five of the newly identified studies compared 100 mg once daily tezacaftor-150 mg twice daily ivacaftor to either a matched placebo or 150 mg twice daily ivacaftor in 497 participants. Two of the studies assessed this treatment regimen in participants who were either heterozygous for the F508del variant and a gating variant (MCKONE 2021[101]) or a minimal function variant (MUNCK 2020[102]). The other three studies included participants who were homozygous for the F508del variant (NCT02508207[104], NCT02730208[105], SCHWARZ 2021[106]). The duration of these studies ranged from 29 days (NCT02508207[104]) to 72 weeks (NCT02730208[105]).

One of the newly identified studies was eight weeks in length and included 67 participants. Participants were randomised 4:1 to tezacaftor-ivacaftor or a blinding group (placebo for homozygous F508del participants and ivacaftor for F508del/residual function participants). Those randomised to the tezacaftor-ivacaftor arm received either 50 mg once daily tezacaftor-75 mg twice daily ivacaftor (for those weighing less than 40kg on day 1) or 100 mg once daily tezacaftor-150 mg twice daily ivacaftor (for those weighing at least 40kg on day 1). For the participants who were homozygous for the F508del variant who were randomised to the blinding group, they received a matched placebo. Additionally, some participants who were heterozygous for the F508del variant and a residual function variant were either randomised to receive 50 mg once daily tezacaftor-75 mg twice daily ivacaftor (for those weighing less than 40kg on day 1), and an ivacaftor-matching placebo in the morning, or 100 mg once daily tezacaftor-150 mg twice daily ivacaftor and an ivacaftor matching placebo in the morning (for those weighing at least 40kg on day 1). For the participants who were heterozygous (F508del/residual function) who were randomised to the ivacaftor blinding

group, they either received a tezacaftor-ivacaftor matching placebo in the morning and 75mg twice daily ivacaftor (for those weighing less than 40kg on day 1), or they received a tezacaftor-ivacaftor matching placebo in the morning plus 150mg twice daily ivacaftor (for those weighing at least 40kg on day 1) (DAVIES 2021[100]).

One of the newly identified studies was 12 weeks in length and had 40 participants, each of whom were homozygous for the F508del variant. The study had two different arms; the first arm compared 50 mg twice daily tezacaftor-150 mg twice daily ivacaftor to a matched placebo, and the second arm compared two 50 mg once daily tablets of tezacaftor-150 mg twice daily ivacaftor to a matched placebo (NCT02070744[103]).

Triple combination therapy

Eleven studies with a total of 1804 participants were included for this treatment regimen (BARRY 2021[65], NCT02951182[109], NCT02951195[110], NCT03447249[111], NCT03460990[112], SUTHARSAN 2021[113], DAVIES 2018a and DAVIES 2018b[127], KEATING 2018[128], HEIJERMAN 2019[129], MIDDLETON 2019[130]). Four studies, with a total of 634 participants, compared VX-659-tezacaftor-ivacaftor to either tezacaftor-ivacaftor or to a triple placebo (NCT03447249[111], NCT03460990[112], DAVIES 2018a and DAVIES 2018b[127]). In a total of 1079 participants, five studies compared elexacaftor-tezacaftor-ivacaftor (ETI) to either tezacaftor-ivacaftor, triple placebo or ivacaftor (BARRY 2021[65], SUTHARSAN 2021[113], KEATING 2018[128], HEIJERMAN 2019[129], MIDDLETON 2019[130]). One study compared VX-440-tezacaftor-ivacaftor to triple placebo in 47 participants (NCT02951182[109]) and one study compared VX-152-tezacaftor-ivacaftor to triple placebo in 34 participants (NCT02951195[110]).

One of the six newly identified triple therapy studies compared 200 mg once daily elexacaftor-100 mg once daily tezacaftor-150 mg twice daily ivacaftor to either 150 mg twice daily ivacaftor monotherapy or 100 mg once daily tezacaftor-150 mg twice daily ivacaftor in 271 participants with the genotypes F508del/gating variant and F508del/residual function variant for eight weeks (BARRY 2021[65]). The other newly identified study looking at elexacaftor compared 200 mg once daily

elexacaftor-100 mg once daily tezacaftor-150 mg twice daily ivacaftor to 100 mg once daily tezacaftor-150 mg twice daily ivacaftor for 24 weeks. There were 176 participants in this study, and each were homozygous for the F508del variant (SUTHARSAN 2021[113]).

Two of the six newly identified triple therapy studies compared 240 mg once daily VX-659-100 mg once daily tezacaftor-150 mg twice daily ivacaftor to a matched placebo for 24 weeks and to 100 mg once daily tezacaftor-150 mg twice daily ivacaftor for 4 weeks respectively (NCT03447249[111], NCT03460990[112]). There were 385 participants in the 24 week study, and each were heterozygous for the F508del variant and had a minimal function variant (NCT03447249[111]). In the four week study, there were 116 participants, who were each homozygous for the F508del variant (NCT03460990[112]).

One of the newly identified studies had 47 participants who were either homozygous for the F508del variant, or heterozygous with a minimal function variant. This Phase 2 study was split into two parts; part 2 of this study has not been included in the Cochrane systematic review due to there being a washout period. Part 1 of the study was split into 3 parts, each lasting four weeks: participants in one cohort received 200 mg twice daily VX-440-100 mg once daily tezacaftor-150 mg twice daily ivacaftor; participants in the second cohort received 200 mg twice daily VX-440-50 mg twice daily tezacaftor-150 mg twice daily ivacaftor, and finally participants in the third cohort received 600 mg twice daily VX-440-50 mg twice daily tezacaftor-300 mg twice daily ivacaftor. Each cohort was compared against a placebo group (NCT02951182[109]).

The final newly identified study had 34 participants, who were either each heterozygous for the F508del variant and a minimal function variant, or homozygous for the F508del variant. This Phase 2 study was split into two parts; part 2 of this study has not been included due to an insufficient washout period. Part 1 of the study was split into 3 parts, each lasting two weeks: participants in one cohort received 100 mg twice daily VX-152-100 mg once daily tezacaftor-150 mg twice daily ivacaftor; participants in the second cohort each received 200 mg twice daily VX-152-100 mg once

daily tezacaftor-150 mg twice daily ivacaftor, and finally participants in the third cohort received 300 mg twice daily VX-152-100 mg once daily tezacaftor-150 mg twice daily ivacaftor. Each cohort was compared against a placebo group (NCT02951195[110]).

5.2.2. Excluded studies

In the latest update of this review, 7 studies were excluded, with a total of 13 related references. One previously excluded study was included in this update (SUTHARSAN 2021[113]).

One reference related to a study that looked at glycerol phenylbutyrate corrector therapy that had been terminated due to the funding ending.[131] One study, with six associated references, was looking at roscovitine, and was excluded due to the study having been terminated.[132] Two references related to one crossover study that looked at lumacaftor-ivacaftor.[133, 134] One study, with one associated reference, was excluded due to the fact that it was an open-label trial that did not assess any corrector as an intervention. Instead, the study looked at whether pwCF, who were established on Kaftrio, could safely stop taking their nebulised treatments.[135] One reference, relating to one study, was excluded after I contacted the author who explained that randomisation was not performed. The study aimed to compare lung ultrasound imaging and clinical characteristics before and after starting modulator therapy.[136] One study looking at FDL169 and FDL176, with one associated reference, was excluded due to the initial stages of the study not being randomised. The study was also conducted in healthy participants and, although Phase 4 of the study is due to be randomised in pwCF, the trial is currently suspended for business reasons.[137] The final study that was excluded had one associated reference and looked at VX-445-tezacaftor-ivacaftor. The study was excluded as it was not an RCT.[138]

After the last update of the review, there were 26 excluded studies, with 42 associated references.[2]

5.2.3. Ongoing studies

After completing the latest update of the review, 8 studies are classed as ongoing. Two studies are looking at GLPG2222,[139] two studies are looking at PTI-428,[140, 141] one study is looking at PTI-801 in combination with PTI-808, and in triple combination with PTI-428.[142]

One study is looking at cavosonstat (N91115) in participants who are already being treated with lumacaftor-ivacaftor.[143] Finally, two studies are looking at VX-121 combination therapy. The first study is looking at VX-121-tezacaftor-deutivacaftor in participants who are heterozygous for the F508del variant and a minimal function variant.[144] The other study is looking at VX-121-tezacaftor-deutivacaftor in participants who are homozygous for the F508del variant, heterozygous for the F508del variant and either a residual function or gating variant, or have no F508del variant and have at least one other triple combination responsive *CFTR* gene variant.[145]

5.2.4. Study quality

I have summarised the risk of bias assessments for each of the newly identified studies in the table below. Where there is a green box, this indicates a low risk of bias. An unclear risk of bias is indicated by a yellow box and a high risk of bias is indicated with a red box. The reasonings for each study's bias assessment scores can be found in the appendix of this thesis. In these boxes, I have justified the risk of bias assessment scores, where appropriate, using information retrieved from the published protocols, statistical analysis plan (of one study) and study details available on the clinicaltrials.gov website.

Table 1: Risk of bias assessments of the newly included studies for the latest update of the Cochrane systematic review

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Davies 2021							
McKone 2021							
Munck 2020							
NCT02070744							
NCT02508207							
NCT02730208							
Schwarz 2021							
Stahl 2021							
Wilson 2021							
Barry 2021							
NCT02951182							
NCT02951195							

NCT03447249							
NCT03460990							
Sutharsan 2021							

5.3. Effects of interventions

5.3.1. Monotherapy

No new monotherapy studies were identified in the update of the Cochrane systematic review. The summary of the monotherapy studies from the previous Cochrane review can be found in the appendix of this thesis.

5.3.2. Dual combination therapy

Primary outcomes

1) Survival

One participant in the tezacaftor-ivacaftor group of one study (n=98) died; this was not deemed to be related to the intervention (SCHWARZ 2021).[106]

2) QoL

a) Total QoL score

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

Lumacaftor-ivacaftor:

Two studies reported this outcome by measuring the Euro Quality of Life Scale (EuroQol) 5- Dimension-3 Level (EQ-5D-3L) Index Score at six months, and there were no

differences found between placebo groups and the intervention groups (TRAFFIC 2015, TRANSPORT 2015).[125]

b) QoL sub-domains

Lumacaftor-ivacaftor:

At 28 days, there was a statistically significant improvement in the CFQ-R respiratory domain score in both the 600 mg once daily lumacaftor-250 mg twice daily ivacaftor and 400 mg twice daily lumacaftor-250 mg twice daily ivacaftor groups, MD 3.32 (95% CI 1.13 to 5.51) and MD 4.13 (95% CI 1.94 to 6.31) respectively. This improvement was also seen when the two doses were pooled together, MD 3.70 (95% CI 1.81 to 5.58) (TRAFFIC 2015, TRANSPORT 2015).[125]

At six months, this statistically significant improvement was maintained in both the 600 mg lumacaftor and 400 mg lumacaftor groups, MD 3.04 (95% CI 0.76 to 5.32)[125] and MD 2.50 (95% CI 0.30 to 4.70)[108, 125] respectively. The difference was also maintained when both of these doses were pooled together, MD 2.83 (95% CI 0.91 to 4.74) (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125]

At six months, the EQ-5D-3L Visual Analog Scale (VAS) domain score was also reported in participants in the 600 mg and 400 mg lumacaftor groups; there was a statistically significant improvement seen in these individual groups and when pooled together (TRAFFIC 2015, TRANSPORT 2015).[125]

A paediatric study reported the absolute change from baseline of the CFQ-R respiratory domain score up to and including 24 weeks; although improvements were seen in the lumacaftor-ivacaftor group when compared to the placebo group, they were not statistically significant, MD 2.50 (95% CI -0.10 to 5.10) (RATJEN 2017).[123]

Tezacaftor-ivacaftor:

At one month, there was a statistically significant difference found, favouring the intervention group, in one study looking at CFQ-R respiratory domain scores, MD 5.10 (95% CI 2.99 to 7.21) (TAYLOR-COUSAR 2017).[124] In another study, the within-group change in treatment effect between tezacaftor-ivacaftor and placebo was 6.81 points (P=0.2451) (DONALDSON 2018).[122]

In the Davies study, through week eight, the mean within-group change from baseline in the CFQ-R respiratory domain score for the tezacaftor-ivacaftor group was 2.30 points (95% CI -0.10 to 4.60); P=0.0546), compared to a mean within-group change of 9.20 (SD 23.10) points in the placebo group, and 2.80 (SD 9.60) points in the ivacaftor group (DAVIES 2021).[100]

In another study, there was no difference found for the absolute change from baseline in the CFQ-R respiratory domain score at three months in the 50 mg twice daily tezacaftor-150 mg twice daily ivacaftor group compared to either placebo or 150 mg twice daily ivacaftor, MD 4.31 (95% CI -2.07 to 10.69) (NCT02070744).[103]

At six months, the statistically significant difference found, favouring the tezacaftor-ivacaftor group, was maintained in the pooled results of four studies (n=932) looking at 100 mg once daily tezacaftor-150 mg twice daily ivacaftor compared to either placebo or 150 mg twice daily ivacaftor, MD 2.89 (95% CI 2.48 to 3.29) (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124] The other domains of the CFQ-R questionnaire were examined at six months in one study; there was a greater improvement found in the tezacaftor-ivacaftor group compared to placebo for the physical functioning, treatment burden, health perceptions and vitality domains. In the remaining domains (social functioning, role functioning, eating problems, emotional

functioning, weight, digestive symptoms and body image), there were no statistically significant differences found (TAYLOR-COUSAR 2017).[124]

3) Physiological measures of lung function

a) FEV_1 (relative change from baseline)

Lumacaftor-ivacaftor:

At six months, participants in both the 600 mg[125] and 400 mg lumacaftor groups had higher relative changes from baseline in FEV_1 compared to the placebo groups, MD 5.63 (95% CI 3.80 to 7.47) and MD 4.69 (95% CI 2.91 to 6.46) respectively. This was also the case when the two doses were pooled, MD 5.12 (95% CI 3.57 to 6.67) (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125]

Tezacaftor-ivacaftor:

There was one study that found no significant difference between the intervention and control groups at one month (DONALDSON 2018).[122] At three months, there was no significant difference found in one study between the 50 mg twice daily tezacaftor-150 mg twice daily ivacaftor group compared to either the placebo or 150 mg twice daily ivacaftor groups, MD 1.73 (95% CI -3.91 to 7.36) (NCT02070744).[103] At six months, pooled data from four studies showed a greater relative change from baseline in FEV_1 (percent predicted) in the 100 mg once daily tezacaftor-150 mg twice daily ivacaftor groups compared to either placebo or 150 mg twice daily ivacaftor groups, MD 0.92 (95% CI 0.72 to 1.11) (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124]

b) FEV_1 absolute values

Lumacaftor-ivacaftor:

Participants in the 600 mg and 400 mg lumacaftor groups experienced significantly higher absolute changes from baseline in FEV_1 values at one month. This was also the case when the two doses were pooled (TRAFFIC 2015, TRANSPORT 2015).[125] At three weeks, non-significant improvements were seen in FEV_1 absolute values in another study (BOYLE 2014).[114]

At six months, the significant differences were maintained in the 600 mg lumacaftor[125] and 400 mg lumacaftor groups, MD 3.34 (95% CI 2.30 to 4.38), MD 2.83 (95% CI 1.81 to 3.84) respectively, and also when the two doses were pooled, MD 3.08 (95% CI 2.20 to 3.97) (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125]

Tezacaftor-ivacaftor:

There was a statistically significant improvement in FEV_1 values at one month in the pooled results of three studies, MD 3.54 (95% CI 2.39 to 4.69) (NCT02508207, DONALDSON 2018, TAYLOR-COUSAR 2017).[104, 122, 124]

In the Davies study, through week eight, the mean within-group change from baseline in FEV_1 (percent predicted) for the tezacaftor-ivacaftor group was 2.80 percentage points (95% CI 1.00 to 4.60); P=0.0024), compared to a mean within-group change of -3.70 (SD 6.10) percentage points in the placebo group, and -0.40 (SD 6.00) percentage points in the ivacaftor group (DAVIES 2021).[100]

At three months, there was no difference found in one study between the tezacaftor-ivacaftor and control groups, MD 1.06 (95% CI -1.62 to 3.74) (NCT02070744).[103]

At six months, the pooled results from four studies found that there was a greater change in the 100 mg once daily tezacaftor-150 mg twice daily ivacaftor group compared to either the placebo or 150 mg twice daily ivacaftor groups, MD 0.39 (95% CI 0.27 to 0.52) (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124]

c) FVC (absolute values and change from baseline)

This outcome was not recorded in any of the studies.

d) LCI

Lumacaftor-ivacaftor:

One study reported a statistically significant decrease (and therefore improvement) in $LCI_{2.5}$ in the lumacaftor-ivacaftor group compared to the placebo group at up to six months, MD -1.10 (95% CI -1.40 to -0.80) (RATJEN 2017).[123] Another study found a statistically significant decrease in $LCI_{2.5}$ in the lumacaftor-ivacaftor group compared to the placebo group at over six months, MD -0.69 (95% CI -1.35 to -0.03) (STAHL 2021).[107]

Tezacaftor-ivacaftor:

In the Davies study, through week eight, the mean within-group change from baseline in $LCI_{2.5}$ for the tezacaftor-ivacaftor group was -0.51 (95% CI -0.74 to -0.29); P<0.0001),

compared to a mean within-group change of 0.10 (SD 1.16) in the placebo group, and -0.61 (SD 0.88) in the ivacaftor group (DAVIES 2021).[100]

Furthermore, in the Davies study, through week eight, the mean within-group change from baseline in $LCI_{5.o}$ for the tezacaftor-ivacaftor group was -0.30 (95% CI -0.39 to -0.20); P<0.0001), compared to a mean within-group change of 0.08 (SD 0.36) in the placebo group, and -0.48 (SD 0.51) in the ivacaftor group (DAVIES 2021).[100]

e) Other measures of lung function

This outcome was not recorded in any of the studies.

Secondary outcomes

1) Adverse events

Lumacaftor-ivacaftor:

Shortness of breath was found to be statistically significantly more common in the 600 mg once daily lumacaftor-250 mg twice daily ivacaftor group when compared to placebo, OR 2.05 (99% CI 1.10 to 3.83),[125] and this was still the case when this data were combined with the 400 mg lumacaftor studies, OR 1.78 (99% CI 1.02 to 3.08).[108, 125] There were significantly fewer participants reporting 'cough' and infective pulmonary exacerbations as adverse events in the 400 mg twice daily lumacaftor-250 mg twice daily ivacaftor group compared to placebo, OR 0.59 (99% CI 0.40 to 0.87) and OR 0.60 (99% CI 0.42 to 0.87) respectively, and when the lumacaftor doses were combined, OR 0.65 (99% CI 0.46 to 0.91) and 0.64 (99% CI 0.46 to 0.88).[108, 125] Across

the combined lumacaftor doses, there were 163 out of 773 participants in the lumacaftor-ivacaftor groups, compared to 115 out of 405 participants in the placebo groups, that experienced at least one serious adverse event. This represents a non-significant difference for this outcome, OR 0.69 (99% CI 0.48 to 1.00) (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] There was a statistically significant mean increase in both systolic and diastolic blood pressure (5.1 (SE: 1.5) mm Hg and 4.1 (SE: 1.2) mm Hg) in participants over the study period of the TRAFFIC, TRANSPORT and PROGRESS studies (PROGRESS 2017).[126]

There were no other statistically significant differences in any adverse events found in any of the other studies reporting on this outcome.

Tezacaftor-ivacaftor:

In the four studies evaluating 100 mg once daily tezacaftor-150 mg twice daily ivacaftor, 10 out of 460 participants discontinued in the treatment groups, compared to 12 out of 465 participants in the control groups (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124] There were significantly fewer participants experiencing adverse events in one study in the control group, compared to the same treatment regimen, OR 20.00 (99% CI 1.38 to 288.99) (NCT02508207).[104] In two studies assessing this treatment regimen, there were two life-threatening adverse events reported in the tezacaftor-ivacaftor groups; one due to post influenza sepsis and multiple organ dysfunction syndrome and the other due to haemoptysis (SCHWARZ 2021, TAYLOR-COUSAR 2017).[106, 124]

In the Davies study, the most common adverse events in the tezacaftor-ivacaftor group were cough (14.8%), headache (14.8%) and productive cough (13.0%). Most of the adverse events in the intervention group were considered not related (38.9%) or unlikely related (18.5%) to the drug. There were no participants in the intervention group of this study who had adverse events

that led to either treatment interruption or discontinuation, and there were no life-threatening events recorded (DAVIES 2021).[100]

There were no statistically significant differences found in the occurrence of any of the adverse events reported on for this treatment regimen.

2) Hospitalisation

Lumacaftor-ivacaftor:

There was a 39% decrease in the rate of pulmonary exacerbation events leading to hospitalisation in the 600 mg once daily lumacaftor-250 mg twice daily ivacaftor group compared to placebo (P=0.003). Furthermore, there was a 61% decrease in the event rate in the 400 mg twice daily lumacaftor-250 mg twice daily ivacaftor group compared to placebo (P < 0.001) (TRAFFIC 2015, TRANSPORT 2015).[125]

Tezacaftor-ivacaftor:

In one study, the rate of pulmonary exacerbations that led to hospitalisation or treatment with intravenous antibiotics (or both) was lower in the tezacaftor-ivacaftor group, when compared to the placebo group, rate ratio 0.53 (95% CI 0.34 to 0.82) (TAYLOR-COUSAR 2017).[124]

3) School or work attendance

This outcome was not recorded in any of the studies.

4) Extra courses of antibiotics

Lumacaftor-ivacaftor:

The time-to-first pulmonary exacerbation was significantly longer, when compared to placebo, in both the 600 mg once daily and 400 mg twice daily lumacaftor groups in the TRAFFIC and TRANSPORT studies (hazard ratio: 0.70 (95% CI 0.57 to 0.87) and hazard ratio 0.61 (95% CI 0.49 to 0.76) respectively. There was also a significant reduction in the rate of exacerbations for both doses, when compared to placebo (rate ratio 0.70 (95% CI 0.57 to 0.87) and rate ratio 0.61 (95% CI 0.49 to 0.76) respectively). Similarly, there was also a significant reduction in the number of pulmonary exacerbations in both groups, OR 0.66 (99% CI 0.45 to 0.97) and OR 0.57 (99% CI 0.39 to 0.84) respectively (TRAFFIC 2015, TRANSPORT 2015).[125]

In another study, there were no significant differences found in the number of exacerbations reported at day 21 in the intervention and placebo groups (BOYLE 2014).[114] Similarly, there was no statistically significant difference found in the number of pulmonary exacerbations in the paediatric study (RATJEN 2017).[123]

Tezacaftor-ivacaftor:

One study found that the time-to-first pulmonary exacerbation in the tezacaftor-ivacaftor group, when compared to the placebo group, was significantly longer, hazard ratio: 0.64 (95% CI 0.46 to 0.89) (TAYLOR-COUSAR 2017).[124] In one study, the published paper showed a Kaplan-Meier plot of time-to-first pulmonary exacerbation, though, on the trials registry, due to less than 50% of events, the time-to-first event was not estimated. The number of participants with at least one pulmonary exacerbation was recorded, and there was no statistically significant difference between groups, OR 0.90 (99% CI 0.36 to 2.30). There was no difference between groups in the

study for the number of pulmonary exacerbation events, OR 0.97 (99% CI 0.40 to 2.39). There was also no difference between groups measuring the annualised rate of pulmonary exacerbation events ratio (MUNCK 2020).[102]

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

Lumacaftor-ivacaftor:

In one study, at 21 days, there was a statistically significant reduction in sweat chloride concentration in the 250 mg ivacaftor group, MD -10.90 mmol/L (95% CI -17.60 to -4.20). When both the 150 mg and 250 mg ivacaftor doses were combined, there was a significant reduction in sweat chloride concentration, MD -7.95 (95% CI -13.81 to -2.09) (BOYLE 2014).[114] At four weeks, in the paediatric study, there was a significant reduction in sweat chloride concentration in the lumacaftor-ivacaftor group when compared to the placebo group, MD -20.80 (95% CI -23.40 to -18.20) (RATJEN 2017).[123] At over six months, Stahl reported a greater reduction in sweat chloride in the lumacaftor-ivacaftor group compared to placebo, MD -26.40 (95% CI -34.57 to -18.23) (STAHL 2021).[107]

Tezacaftor-ivacaftor:

At one month, there was a reduction in sweat chloride concentration in the tezacaftor-ivacaftor groups, when compared to the placebo groups, in three studies, MD -9.14 mmol/L (95% CI -10.93 to -7.34) (NCT02508207, DONALDSON 2018, TAYLOR-COUSAR 2017).[104, 122, 124]
In the Davies study, through week eight, the mean within-group change from baseline in sweat chloride concentration for the tezacaftor-ivacaftor group was -12.30 mmol/L (95% CI -15.30 to -

9.30); P<0.0001), compared to a mean within-group change of -1.00 mmol/L (SD 12.30) in the placebo group, and -1.00 mmol/L (SD 9.00) in the ivacaftor group (DAVIES 2021).[100]

At three months, there was a significant reduction in the 50 mg twice daily tezacaftor-150 mg twice daily ivacaftor group when compared to either placebo or 150 mg twice daily ivacaftor, MD -8.70 (95% CI 12.47 to -4.93) (NCT02070744).[103]

At six months, there was also a significant reduction in the 100 mg once daily tezacaftor-150 mg twice daily ivacaftor groups in sweat chloride concentration, when compared to the control groups, MD -6.39 mmol/L (95% CI -6.90 to -5.87) (MCKONE 2021, MUNCK 2020, TAYLOR-COUSAR 2017).[101, 102, 124]

6) <u>Radiological measures of lung disease (assessed using any scoring system)</u>

Lumacaftor-ivacaftor:

In a sub-study of the Ratjen study (200 mg twice daily lumacaftor-250 mg twice daily ivacaftor), there were no differences found in the overall Brody score, or in the mean change in the bronchiectasis component of the Brody score, or in the mean change in the air trapping component of the Brody score (RATJEN 2017).[123] Stahl's study did not find a difference in the absolute change from baseline in MRI global chest score at over six months between the lumacaftor-ivacaftor and placebo groups, MD -1.40 (95% CI -5.24 to 2.44) (STAHL 2021).[107]

Tezacaftor-ivacaftor:

In one trial, there was no difference found between the tezacaftor-ivacaftor and placebo groups for the absolute change in total Brody/CF-CT score from baseline at 18 months, MD -1.48 (95% CI -7.25 to 4.29) (NCT02730208).[105]

7) Acquisition of respiratory pathogens

Lumacaftor-ivacaftor:

In the Stahl study, at over six months, there was no significant difference found between the lumacaftor-ivacaftor group and placebo group in the number of participants testing positive for *P.aeruginosa*, OR 0.21 (99% CI 0.01 to 5.36) (STAHL 2021).[107]

Tezacaftor-ivacaftor:

One trial found there to be no significant difference between the tezacaftor-ivacaftor group and the placebo group in the number of participants who had a pseudomonal lung infection, OR 5.81 (99% CI 0.10 to 341.36) (NCT02730208).[105]

8) Eradication of respiratory pathogens

This outcome was not recorded in any of the studies.

9) Nutrition and growth

Lumacaftor-ivacaftor:

At one month, there was no change found between participants in both the 600 mg once daily lumacaftor and 400 mg twice daily lumacaftor groups in the absolute change in BMI from baseline when compared to placebo. At six months, the participants experienced a greater

absolute change in BMI when compared to the placebo group, MD 0.29 (95% CI 0.16 to 0.43)[125] and MD 0.25 (95% CI 0.12 to 0.38) respectively (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] At six months, the paediatric study found there to be no significant difference in both the absolute change in BMI and absolute change in BMI-for-age Z-score between groups (RATJEN 2017).[123] Wilson's study reported no significant difference between study groups in the relative change from baseline in BMI, MD 1.00 (95% CI -1.14 to 3.14) (WILSON 2021).[108] At six months, the participants in the 600 mg lumacaftor and 400 mg lumacaftor groups also experienced a significantly higher weight gain when compared to placebo, MD 0.80 kg (95% CI 0.42 to 1.18) and MD 0.65 kg (95% CI 0.27 to 1.03) respectively; this was also the case when the two doses were pooled, MD 0.72 kg (95% CI 0.39 to 1.05) (TRAFFIC 2015, TRANSPORT 2015).[125] Stahl's study found no difference between study groups for the absolute change from baseline in weight-for-age Z-score at over six months, MD 0.20 (95% CI -0.01 to 0.41). The same study, at over six months, found a greater absolute change from baseline in BMI-for-age Z-score in the lumacaftor-ivacaftor group when compared to placebo, MD 0.44 (95% CI 0.09 to 0.79). No difference was found between groups for the absolute change from baseline in stature-for-age Z-score, MD -0.01 (95% CI -0.19 to 0.17) (STAHL 2021).[107]

Tezacaftor-ivacaftor:

In the Davies study, through week eight, the mean within-group changes from baseline in weight and weight Z-score for the tezacaftor-ivacaftor group were 0.30 kg (standard deviation (SD): 0.80) and -0.04 (SD:0.17), compared to mean within-group changes of 0.60 kg (SD 1.00) and -0.02 (SD: 0.15) in the placebo group, and 0.50 kg (SD 0.90) and 0.03 (SD: 0.23) in the ivacaftor group respectively (DAVIES 2021).[100] Neither the 50 mg twice daily or the 100 mg once daily tezacaftor-150 mg twice daily ivacaftor studies found a difference in the change from baseline in

body weight between intervention and control groups at three months, MD -0.10 (95% CI -0.66 to 0.46) and MD -0.11 (95% CI -1.01 to 0.79) respectively (MUNCK 2020, NCT02070744).[102, 103]

At one month in one study, no difference was found in the change from baseline in BMI between the tezacaftor-ivacaftor and placebo groups, MD -0.03 (95% CI -0.13 to 0.07) (TAYLOR-COUSAR 2017).[124]

In the Davies study, through week eight, the mean within-group changes from baseline in BMI and BMI Z-score for the tezacaftor-ivacaftor group were -0.04 kg/m^2 (SD: 0.43) and -0.08 (SD: 0.27), compared to mean within-group changes of 0.02 kg/m^2 (SD 0.41) and -0.05 (SD: 0.22) in the placebo group, and 0.11 kg/m^2 (SD 0.53) and 0.08 (SD: 0.37) in the ivacaftor group respectively (DAVIES 2021).[100] At over one month and up to six months, neither the 50 mg twice daily or the 100 mg once daily tezacaftor-150 mg twice daily ivacaftor studies found a difference in the change from baseline in BMI between intervention and control groups, MD -0.02 (95% CI -0.32 to 0.29) (NCT02070744)[103] and MD 0.01 (95% CI -0.10 to 0.13) respectively (MUNCK 2020, TAYLOR-COUSAR 2017).[102, 124] There was also no difference found for the absolute change from baseline in BMI Z-score between groups at three months in one study, MD -0.05 (95% CI -0.20 to 0.10) (MUNCK 2020).[102]

In the Davies study, through week eight, the mean within-group changes from baseline in height and height Z-score for the tezacaftor-ivacaftor group were 0.90 cm (SD: 0.70) and 0.01 (SD: 0.13), compared to mean within-group changes of 1.20 cm (SD 0.50) and 0.04 (SD: 0.08) in the placebo group, and 0.90 cm (SD 0.40) and -0.01 (SD: 0.07) in the ivacaftor group respectively (DAVIES 2021).[100]

5.3.3. Triple combination therapy

Primary outcomes

1) Survival

There were no deaths reported in any of the studies.

2) QoL

a) Total QoL score

This outcome was not recorded in any of the studies.

b) QoL sub-domains

VX-659-tezacaftor-ivacaftor

Participants with F508del/MF:

Two studies assessed the absolute change in CFQ-R respiratory domain score after one month of treatment. At both the 80 mg and 240 mg doses, results favoured the intervention, MD 10.00 (95% CI 0.29 to 19.71)[127] and MD 16.13 (95% CI 13.02 to 19.24)[111, 127] respectively. In the last review, there was no difference found for the 240 mg dose. No difference was found for the 400 mg group, MD 7.90 (95% CI -0.58 to 16.38) (DAVIES 2018b).[127]

At six months, the significant difference for the 240 mg group was maintained in one trial, MD 20.10 (95% CI 17.19 to 23.01) (NCT03447249).[111]

Participants with F508del/F508del

In addition to the study reporting for the 400 mg dose (DAVIES 2018b),[127] there were significant improvements in the CFQ-R respiratory domain score found for the 240 mg dose, when compared to tezacaftor-ivacaftor, MD 13.50 (95% CI 8.79 to 18.21) (NCT03460990).[112]

VX-152-tezacaftor-ivacaftor

Participants with F508del/MF

This regimen was tested in one newly identified study at doses of 100 mg twice daily VX-152, 200 mg twice daily VX-152 and 300 mg twice daily VX-152. Results favoured the intervention group at all dosage levels at day 15, MD 14.20 (95% CI 0.98 to 27.42), MD 29.40 (95% CI 16.97 to 41.83) and MD 26.20 (95% CI 13.71 to 38.69) respectively (NCT02951195).[110]

VX-440-tezacaftor-ivacaftor

Participants with F508del/MF and F508del/F508del

This regimen was tested in one study at doses of 200 mg twice daily VX-440-100 mg once daily tezacaftor-150 mg twice daily ivacaftor, 200 mg twice daily VX-440-50 mg twice daily tezacaftor-150 mg twice daily ivacaftor, and 600 mg twice daily VX-440-50 mg twice daily tezacaftor-300 mg twice daily ivacaftor. Results for the first two dosing schedules were pooled, and there was a difference found at one month, favouring the intervention group,

MD 16.1 (95% CI 5.40 to 26.80). For the final dosing schedule, there was a difference found, favouring the intervention group, MD 18.50 (95% CI 8.99 to 28.01) (NCT02951182).[109]

Elexacaftor-tezacaftor-ivacaftor

Participants with F508del/gating and F508del/residual function

One study reported the change in CFQ-R respiratory domain score through two months, with results showing an improvement with the 200 mg once daily elexacaftor-100 mg once daily tezacaftor-150 mg twice daily ivacaftor versus either 150 mg twice daily ivacaftor or 100 mg once daily tezacaftor-150 mg twice daily ivacaftor groups, MD 8.70 (95% CI 5.34 to 12.06) (BARRY 2021).[65]

Participants with F508del/F508del

At six months, one of the newly identified studies looking at 200 mg once daily elexacaftor-100 mg once daily tezacaftor-150 mg twice daily ivacaftor versus 100 mg once daily tezacaftor-150 mg twice daily ivacaftor, found that the CFQ-R respiratory domain score was improved in the treatment group, MD 15.90 (95% CI 11.74 to 20.06) (SUTHARSAN 2021).[113]

3) Physiological measures of lung function

a) FEV_1 (relative change from baseline)

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

VX-440-tezacaftor-ivacaftor

Participants with F508del/MF and F508del/F508del

In one trial, both the low dose pooled studies and the high dose study showed improvements through 1 month in the relative change from baseline in FEV_1% predicted, least squares MD 14.80 (95% CI 5.30 to 24.20) and MD 19.10 (95% CI 10.62 to 27.58) (NCT02951182).[109]

VX-152-tezacaftor-ivacaftor

Participants with F508del/MF

This regimen was tested in one study at doses of 100 mg twice daily VX-152, 200 mg twice daily VX-152 and 300 mg twice daily VX-152. Results favoured the intervention group at all dosage levels, MD 12.60 (95% CI 3.48 to 21.72), MD 21.30 (95% CI 12.73 to 29.87) and MD 17.10 (95% CI 8.05 to 26.15) respectively (NCT02951195).[110]

b) FEV_1 (absolute values and change from baseline)

VX-659-tezacaftor-ivacaftor

Participants with F508del/MF

In addition to the Davies 2018a study from the last review that demonstrated a statistically significant difference between treatment and control at up to one month, favouring the 120

mg twice daily VX-659 group, MD 10.00% (95% CI 3.04 to 16.96) (DAVIES 2018a),[127] there was a newly identified study found that examined this outcome. The trial, which looked at 240 mg once daily VX-659, also found an increase that was statistically significant in FEV_1 at one month, MD 14.00 (95% CI 12.34 to 15.66). In this trial, the absolute change in FEV_1 that was seen at one month was also seen through six months too, MD 14.20 (95% CI 12.54 to 15.86) (NCT03447249).[111]

Participants with F508del/F508del

In the last review, a dose of VX-659 400 mg was found to improve the FEV_1 at one month in the Davies 2018b study, MD 0.35 L (95% CI 0.19 to 0.51) (DAVIES 2018b).[127] In this review, at one month, the newly identified trial looking at 240 mg once daily VX-659 found an improvement in FEV_1 in the intervention group, MD 9.90 (95% CI 7.41 to 12.39) (NCT03460990).[112]

<u>VX-152-tezacaftor-ivacaftor</u>

Participants with F508del/MF

This regimen was tested in one study at doses of 100 mg twice daily VX-152, 200 mg twice daily VX-152 and 300 mg twice daily VX-152. Results favoured the intervention group at all dosage levels at day 15, MD 6.50 (95% CI 1.62 to 11.38), MD 10.50 (95% CI 5.92 to 15.08) and MD 8.80 (95% CI 3.98 to 13.62) respectively (NCT02951195).[110]

<u>VX-440-tezacaftor-ivacaftor</u>

Participants with F508del/MF and F508del/F508del

In one trial, both the low dose pooled arms and the high dose arm showed improvements through one month in the absolute change from baseline in FEV_1 % predicted, least squares MD 8.60 (95% CI 3.50 to 13.80) and MD 10.60 (95% CI 5.93 to 15.27) (NCT02951182).[109]

Elexacaftor-tezacaftor-ivacaftor

Participants with F508del/gating and F508del/residual function

One of the newly identified studies reported on this outcome through two months, looking at 200 mg once daily elexacaftor-100 mg once daily tezacaftor-150 mg twice daily ivacaftor versus either 150 mg twice daily ivacaftor or 100 mg once daily tezacaftor-150 mg twice daily ivacaftor. The study found a greater change from baseline in the treatment group compared to the control, MD 3.50 (95% CI 2.24 to 4.76) (BARRY 2021).[65]

Participants with F508del/F508del

One of the newly identified studies, looking at 200 mg once daily elexacaftor, reported on the absolute change in FEV_1 % predicted at six months and found there to be a greater change from baseline in the treatment group compared to the control, MD 10.20 (95% CI 8.26 to 12.14) (SUTHARSAN 2021).[113]

c) FVC (absolute values and change from baseline)

This outcome was not recorded in any of the studies.

d) LCI

This outcome was not recorded in any of the studies.

Secondary outcomes

1) Adverse events

VX-659-tezacaftor-ivacaftor versus control

Participants with F508del/MF

One newly identified study reported on this comparison with a dose level of VX-659 240 mg and found no difference between groups, OR 0.69 (99% CI 0.27 to 1.77) (NCT03447249).[111] In the last version of this review, there were also no differences found in the studies identified for this comparison (DAVIES 2018a and DAVIES 2018b).[127]

Participants with F508del/F508del

Two studies reported data for this outcome, and one of these, looking at 240 mg VX-659, was newly identified in the review. Both studies found no difference between intervention and control groups, OR 1.32 (99% CI 0.49 to 3.56) (NCT03460990)[112] and OR 1.11 (99% CI 0.08 to 14.81) (DAVIES 2018b) respectively.[127]

Elexacaftor-tezacaftor-ivacaftor versus control

Participants with F508del/F508del

Two studies from the previous review demonstrated no difference between groups at one month for the number of participants experiencing an adverse event, OR 0.94 (99% CI 0.46 to 1.96) (KEATING 2018, HEIJERMAN 2019).[128, 129] There was also no difference found in one of the newly identified studies at six months, OR 0.67 (99% CI 0.18 to 2.53) (SUTHARSAN 2021).[113]

Participants with F508del/gating and F508del/residual function

One study reported on this genotype for this combination and found no difference in the number of participants with treatment-emergent adverse events, up to 12 weeks, between intervention and control groups, OR 1.04 (99% CI 0.53 to 2.04) (BARRY 2021).[65]

VX-152-tezacaftor-ivacaftor versus placebo

Participants with F508del/MF

One study reported no difference in the number of adverse events between intervention and control groups for the 100 mg and 200 mg doses of VX-152, OR 0.06 (99% CI 0.00 to 4.02) and OR 0.13 (99% CI 0.00 to 7.63) respectively. At the 300 mg dose, every participant in both the intervention and placebo groups experienced treatment emergent adverse events and therefore an odds ratio was not estimatable (NCT02951195).[110]

VX-440-tezacaftor-ivacaftor versus placebo

Participants with F508del/MF and F508del/F508del

One newly identified study reported on this genotype for this combination. In both the treatment arms looking at 200 mg twice daily VX-440-100 mg once daily tezacaftor-150 mg twice daily ivacaftor and 200 mg twice daily VX-440-50 mg twice daily tezacaftor-150 mg twice daily ivacaftor, all nine participants experienced treatment emergent adverse events. This was compared to nine out of 11 participants in the placebo group. In the treatment arm looking at 600 mg twice daily VX-440-50 mg twice daily tezacaftor-300 mg twice daily ivacaftor, there was no difference found between the intervention and control groups for the number of participants with treatment emergent adverse events, OR 1.11 (99% CI 0.08 to 14.81) (NCT02951182).[109]

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

The adverse events that participants experience are recorded by maximum severity, making it impossible to accurately determine the number of mild adverse events in any of the included studies.

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

In the review, the number of moderate adverse events was determined by recording the number of adverse events that led to the discontinuation of therapy. In the studies where there is no published paper, it could not accurately be determined whether the therapy was discontinued or not (NCT02951182, NCT02951195, NCT03447249, NCT03460990).[109-112]

Elexacaftor-tezacaftor-ivacaftor

Participants with F508del/F508del

In the previous review, there was no difference found in the number of moderate adverse events at one month between the 200 mg elexacaftor and placebo groups in two studies, OR 0.94 (99% CI 0.39 to 2.26) (KEATING 2018, HEIJERMAN 2019).[128, 129]

One of the newly identified studies reported the number of participants experiencing moderate adverse events at six months, and found no difference between the 200 mg elexacaftor and tezacaftor-ivacaftor groups, OR 0.50 (99% CI 0.02 to 12.01) (SUTHARSAN 2021).[113]

Participants with F508del/gating and F508del/residual function

One newly identified study reported the number of participants experiencing moderate adverse events for this treatment regimen and genotype, and found there to be no difference between the intervention and control groups, OR 0.47 (99% CI 0.02 to 11.28) (BARRY 2021).[65]

c) Severe (life-threatening or debilitating, or which persists even after stopping treatment)

The review's definition of severe adverse events was equivalent to each of the included studies' definitions of serious adverse events. Therefore, the number of serious adverse events that were recorded are reported below.

VX-659-tezacaftor-ivacaftor

Participants with F508del/MF

The previous review reported that there were no differences found between intervention and placebo groups at any dose level, and there was no difference found at one month in the VX-659 240 mg group in the previous review in one study, OR 0.58 (99% CI 0.06 to 5.75) (DAVIES 2018b).[127] At six months, the newly identified study found that there were fewer participants with severe adverse events in the VX-659 240 mg treatment arm than the placebo group, OR 0.14 (99% CI 0.06 to 0.33) (NCT03447249).[111]

Participants with F508del/F508del

In the VX-659 240 mg group in the newly identified study, and in the VX-659 400 mg group from the previously identified study, there were no significant differences found between intervention and control groups in terms of the occurrence of severe adverse events, OR 5.48 (99% CI 0.10 to 305.22) (NCT03460990)[112] and OR 0.26 (99% CI 0.01 to 7.39) (DAVIES 2018b)[127] respectively.

Elexacaftor-tezacaftor-ivacaftor

Participants with F508del/F508del

In two of the previously identified studies looking at 200 mg elexacaftor, there was no difference found between intervention and control groups at one month in the number of severe adverse events, OR 0.19 (99% CI 0.02 to 1.92) (KEATING 2018, HEIJERMAN 2019).[128,

[129] At up to seven months in one of the newly identified studies looking at 200 mg elexacaftor, there was still no difference found between the intervention and control groups, OR 0.32 (99% CI 0.08 to 1.31) (SUTHARSAN 2021).[113]

Participants with F508del/gating and F508del/residual function

No difference was found between the intervention and control groups for this intervention and genotype in the number of severe adverse events, OR 0.41 (99% CI 0.10 to 1.72) (BARRY 2021).[65]

VX-152-tezacaftor-ivacaftor

Participants with F508del/MF

In one newly identified study looking at 100 mg twice daily, 200 mg twice daily and 300 mg twice daily VX-152, there was no difference found between the intervention and control groups for each dosing schedule, OR 0.20 (99% CI 0.00 to 13.86), OR 0.12 (99% CI 0.00 to 8.19) and OR 0.33 (99% CI 0.01 to 10.34) respectively (NCT02951195).[110]

VX-440-tezacaftor-ivacaftor

Participants with F508del/MF and F508del/F508del

One newly identified study looked at three different dosing schedules for this genotype. No participants in either of the following dosing schedules experienced severe adverse events: 200 mg twice daily VX-440-100 mg once daily tezacaftor-150 mg twice daily ivacaftor and

200 mg twice daily VX-440-50 mg twice daily tezacaftor-150 mg twice daily ivacaftor. No participants experienced severe adverse events in the matched placebo group. In the treatment arm receiving 600 mg twice daily VX-440-50 mg twice daily tezacaftor-300 mg twice daily ivacaftor, there was no difference found between the intervention and placebo groups in terms of the number of participants with severe adverse events, OR 3.48 (99% CI 0.06 to 212.67) (NCT02951182).[109]

2) Hospitalisation

This outcome was not recorded in any of the newly identified studies.

3) School or work attendance

This outcome was not recorded in any of the studies.

4) Extra courses of antibiotics

a) Time-to the next course of antibiotics

This outcome was not recorded in any of the studies.

b) Total number of courses of antibiotics

The occurrences of infective pulmonary exacerbations are reported under this outcome.

VX-152-tezacaftor-ivacaftor

Participants with F508del/MF

There were no differences between treatment and control groups at any of the 100 mg, 200 mg or 300 mg VX-152 dose levels for the number of participants experiencing exacerbations, OR 0.08 (99% CI 0.00 to 4.89), OR 0.11 (99% CI 0.00 to 2.92) and OR 0.11 (99% CI 0.00 to 2.92) (NCT02951195).[110]

VX-440-tezacaftor-ivacaftor

Participants with F508del/MF and F508del/F508del

There were 9 participants across each dosing schedule of VX-440-tezacaftor-ivacaftor out of 36 participants in total who experienced infective pulmonary exacerbations. This compares to 2 out of 11 participants in the placebo group. For the 600 mg twice daily VX-440-50 mg twice daily tezacaftor-300 mg twice daily ivacaftor dosing schedule, there was no difference found between the intervention and control groups for the number of participants experiencing pulmonary exacerbations, OR 0.90 (99% CI 0.07 to 12.00) (NCT02951182).[109]

VX-659-tezacaftor-ivacaftor

Participants with F508del/F508del

At the dose levels of 240 mg (from a newly identified study) and 400 mg (from a previously identified study) there was no difference found in the number of exacerbations between

intervention and control groups, OR 0.21 (99% CI 0.03 to 1.64) (NCT03460990)[112] and OR 1.03 (99% CI 0.11 to 9.34) (DAVIES 2018b).[127]

Participants with F508del/MF

One of the newly identified studies reported the number of pulmonary exacerbations, "defined as the treatment with new or changed antibiotic therapy (intravenous, inhaled, or oral) for greater than or equal to 4 sinopulmonary signs/symptoms". There were fewer participants in the intervention group experiencing pulmonary exacerbations at 6 months compared to the placebo group, OR 0.06 (95% CI 0.03 to 0.11) (NCT03447249).[111]

<u>Elexacaftor-tezacaftor-ivacaftor</u>

Participants with F508del/F508del

From the previous review, it was found that there were fewer participants in the intervention group that experienced exacerbations at one month, and this difference was statistically significant, OR 0.15 (99% CI 0.02 to 1.00) (KEATING 2018, HEIJERMAN 2019).[128, 129] In the update of the review, it was found that at up to seven months, there were fewer participants in the 200 mg elexacaftor group experiencing pulmonary exacerbations than in the control, OR 0.17 (99% CI 0.06 to 0.45) (SUTHARSAN 2021).[113]

Participants with F508del/gating and F508del/residual function

There were fewer participants experiencing pulmonary exacerbations in the 200 mg elexacaftor group than the control, OR 0.20 (99% CI 0.05 to 0.87) (BARRY 2021).[65]

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

VX-659-tezacaftor-ivacaftor

Participants with F508del/MF

In the previous review, it was found that the 120 mg twice daily dose of VX-659 reduced sweat chloride more than placebo at two weeks (DAVIES 2018a). At one month, there was also a reduction found at 80 mg, 240 mg and 400 mg (DAVIES 2018b).[127] In the newly identified study, there was also a reduction in sweat chloride at the 240 mg dose level and, when pooled with the data from the previously identified study, this demonstrated a statistically significant difference between groups, MD -43.50 (95% CI -46.19 to -40.81) (NCT03447249, DAVIES 2018b).[111, 127] At six months, at a dosage of 240 mg, the reduction in sweat chloride was maintained when compared to placebo, MD -44.50 (95% CI -47.14 to -41.86) (NCT03447249).[111]

Participants with F508del/F508del

At one month, one newly identified study, looking at a dose level of 240 mg, and one previously identified study, looking at a dose level of 400 mg, reported a greater reduction in sweat chloride compared to control, MD -48.70 (95% CI -53.83 to -43.57) (NCT03460990)[112] and MD -45.20 (95% CI -52.18 to -38.22) (DAVIES 2018b)[127] respectively.

VX-152-tezacaftor-ivacaftor

Participants with F508del/MF

For the 100 mg, 200 mg and 300 mg doses of VX-152, there was a reduction in sweat chloride when compared with the placebo groups, MD -19.40 (95% CI -29.45 to -9.35), MD -13.50 (95% CI -23.17 to -3.83) and MD -27.40 (95% CI -36.86 to -17.94) (NCT02951195).[110]

VX-440-tezacaftor-ivacaftor

Participants with F508del/MF and F508del/F508del

In one trial, both the participants in the low dose pooled arm and the high dose arm had greater reductions in sweat chloride levels when compared to the placebo group, least squares MD -22.3 (95% CI -32.1 to -12.4) and MD -34.70 (95% CI -43.54 to -25.86) respectively (NCT02951182).[109]

Elexacaftor-tezacaftor-ivacaftor

Participants with F508del/F508del

Through six months, there was a reduction in sweat chloride when compared with the control group at a dosage of 200 mg elexacaftor, MD -42.80 (95% CI -46.27 to -39.33) (SUTHARSAN 2021).[113]

Participants with F508del/gating and F508del/residual function

The sweat chloride levels were decreased in the intervention group for this treatment regimen and genotype when compared to the control group, MD -23.00 (95% CI -25.98 to -20.02) (BARRY 2021).[65]

6) Radiological measures of lung disease

This outcome was not recorded in any of the studies.

7) Acquisition of respiratory pathogens

This outcome was not recorded in any of the studies.

8) Eradication of respiratory pathogens

This outcome was not recorded in any of the studies.

9) Nutrition and growth

VX-659-tezacaftor-ivacaftor

Participants with F508del/MF

One of the newly identified studies reported results for the absolute change from baseline in BMI, BMI Z-score and body weight. Results favoured the intervention group at 6 months for each outcome, MD 1.11 (95% CI 0.92 to 1.30), MD 0.39 (95% CI 0.25 to 0.53) and MD 3.20 (95% CI 2.65 to 3.75) (NCT03447249).[111]

6. Discussion for Cochrane systematic review

In a study looking at the relative frequency of *CFTR* variant classes in European CF patients, 18 out of 23 European countries had at least 80% of patients that had one or more class II variant, of which F508del is the most common.[14] Therefore, the results of this review are significant because an intervention that specifically targets this variant has the potential to impact the lives of a large proportion of patients with CF.

There were 15 newly identified RCTs in the update of this review that studied corrector medications for patients with class II *CFTR* variants. Nine studies evaluated dual combination therapies; one phase three study evaluated tezacaftor-ivacaftor versus either placebo or ivacaftor (DAVIES 2021),[100] one phase three study evaluated tezacaftor-ivacaftor versus ivacaftor (MCKONE 2021),[101] two phase three studies evaluated tezacaftor-ivacaftor versus placebo (MUNCK 2020, SCHWARZ 2021),[102, 106] three phase two studies evaluated tezacaftor-ivacaftor versus placebo (NCT02070744, NCT02508207, NCT02730208)[103-105] one phase two study evaluated lumacaftor-ivacaftor versus placebo (STAHL 2021),[107] and finally one phase four study evaluated lumacaftor-ivacaftor versus placebo (WILSON 2021).[108]

Six studies evaluated triple combination therapies; one phase three study evaluated ETI versus either ivacaftor or tezacaftor-ivacaftor (BARRY 2021),[65] one phase two study evaluated VX-440-tezacaftor-ivacaftor versus placebo (NCT02951182),[109] one phase two study evaluated VX-152-tezacaftor-ivacaftor versus placebo (NCT02951195),[110] one phase three study evaluated VX-659-tezacaftor-ivacaftor versus placebo (NCT03447249),[111] one phase three study evaluated VX-659-tezacaftor-ivacaftor versus tezacaftor-ivacaftor (NCT03460990),[112] and finally one phase three study evaluated ETI versus tezacaftor-ivacaftor (SUTHARSAN 2021).[113]

The newly identified studies for this review were often difficult to extract and interpret data from due to the various genotype and drug dose combinations that were investigated. This reflects the variant specific nature of these therapies.

6.1. Monotherapy versus placebo or control

6.1.1. Summary of main monotherapy results

There were no clinically relevant improvements identified in the available quality of life data, nor were there any significant differences found in the clinical outcomes with either 4BPA, CPX or N6022. There was also no study that reported on survival, and there were no concerns identified in the safety of any dose of corrector when compared to placebo.

There was a significant improvement found in the absolute change in FEV_1 % predicted at the 400 mg dose of FDL169 when compared to placebo, MD 4.68 % predicted (95% CI 0.12 to 9.24); it is uncertain whether this is clinically significant (HORSLEY 2017).[118]

There was a non-significant reduction found in sweat chloride at the highest dose (200 mg) of cavosonstat, -4.10mmol/L (P=0.032). In the study looking at lumacaftor compared to placebo, there was a modest improvement at one month in sweat chloride, MD -8.21 mmol/L (95% CI -14.30 to -2.12) (CLANCY 2012),[115] and this improvement was deemed to not be sufficient enough to warrant any further investigation. It was found that there was a significant difference in the change in sweat chloride for the 600 mg dose of FDL169, showing an increase when compared to placebo, MD 8.84 mmol/L (95% CI 1.40 to 16.28).

6.1.2. Overall completeness & applicability of evidence

The enrolled participants in the monotherapy studies had two copies of the F508del variant. Although these single-agent studies have not been taken forward into Phase 3 studies, there are newer agents that are being assessed in early phase studies, such as cavosonstat (DONALDSON 2017).[117] The data for the Phase 1 study looking at FDL169 were provided in a poster and conference abstract (HORSLEY 2017).[118]

6.1.3. Quality of the evidence

There was limited relevant outcome data in the 4PBA, CPX, N6022 and FDL169 studies, and it was difficult to judge the risk of bias for various domains.

In the study of cavosonstat versus placebo, the quality of the evidence was deemed to be low to very low due to unclear study design, a lack of applicability of results to children and limited data, leading to wide confidence intervals.

6.2. Dual combination therapy versus placebo or control

6.2.1. Summary of main dual therapy results

There was one death in the tezacaftor-ivacaftor group of one study, and this was not deemed to be related to the drug being trialled (SCHWARZ 2021).[106] There were statistically significant increases in the CFQ-R respiratory domain scores when, at six months, data from the newly identified lumacaftor-ivacaftor trial were pooled with data from the previously identified trials, MD 2.83 (95% CI 0.91 to 4.74) (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] In the tezacaftor-ivacaftor studies looking at 100 mg once daily tezacaftor-150 mg twice daily ivacaftor compared to either placebo or ivacaftor, when the data were pooled at six months, there was a statistically significant increase in the CFQ-R respiratory domain score, MD 2.89 (95% CI 2.48 to 3.29) (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124] There were no significant differences between treatment groups found in both the paediatric Davies study and the 50 mg twice daily tezacaftor-150 mg twice daily ivacaftor versus either placebo or ivacaftor study (DAVIES 2021, NCT02070744).[100, 103]

At six months, when data from the newly identified lumacaftor-ivacaftor study were pooled with data from previous studies, there were statistically significant improvements found in both relative and absolute changes in FEV_1, MD 5.12 (95% CI 3.57 to 6.67) and 3.08 (95% CI 2.20 to 3.97) (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] There was an improvement in absolute change in FEV_1 values at one month in the pooled results of one newly identified study with two previously identified studies looking at 100 mg once daily tezacaftor-150 mg twice daily ivacaftor versus either placebo or ivacaftor, MD 3.54 (95% CI 2.39 to 4.69) (NCT02508207, DONALDSON 2018, TAYLOR-COUSAR 2017).[104, 122, 124] Data from the studies assessing this treatment regimen also showed a greater relative and absolute change from baseline in FEV_1 (percent predicted) at six months, MD 0.92 (95% CI 0.72 to 1.11) and MD 0.39 (95% CI 0.27 to 0.52) respectively (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124]

There were no significant differences found between treatment groups in the relative and absolute changes from baseline in FEV_1 at three months for the study looking at 50 mg twice daily tezacaftor-150 mg twice daily ivacaftor versus either placebo or ivacaftor, MD 1.73 (95% CI -3.91 to 7.36) and MD 1.06 (95% CI -1.62 to 3.74) (NCT02070744).[103] The paediatric Davies study found no significant differences in results between study groups (DAVIES 2021).[100]

There were statistically significant improvements in $LCI_{2.5}$ found in both the paediatric tezacaftor-ivacaftor study (-0.51 (95% CI -0.74 to -0.29); P<0.0001)) and paediatric lumacaftor-ivacaftor study, MD -0.69 (95% CI -1.35 to -0.03) (DAVIES 2021, STAHL 2021).[100, 107] In the paediatric Davies study, the mean change from baseline in $LCI_{5.0}$ was statistically significantly improved, -0.30 (95% CI -0.39 to -0.20); P<0.0001 (DAVIES 2021).[100]

Shortness of breath was found to be more common in the combined data from the 400 mg and 600 mg lumacaftor studies when compared to the control; there were fewer participants reporting cough and infective pulmonary exacerbations in these combined groups. Additionally, in these groups, there was a statistically significant difference in the number of people experiencing at least one serious adverse event, favouring the lumacaftor-ivacaftor groups, when compared to control (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] There were two life-threatening adverse events reported in the tezacaftor-ivacaftor groups (SCHWARZ 2021, TAYLOR-COUSAR 2017),[106, 124] and there were no statistically significant differences found in the occurrence of any of the adverse events reported on for this treatment regimen.

There was a statistically significant mean increase in both systolic and diastolic blood pressure in participants over the study period of the TRAFFIC, TRANSPORT and PROGRESS studies (PROGRESS 2017).[126]

There was no difference found between groups in the number of participants with at least one pulmonary exacerbation, the number of pulmonary exacerbation events and the annualised rate of pulmonary exacerbation events ratio in one study looking at tezacaftor-ivacaftor (MUNCK 2020).[102]

There was a reduction in sweat chloride in the lumacaftor-ivacaftor group compared to placebo (STAHL 2021),[107] and there were significant reductions in sweat chloride levels in all of the newly identified tezacaftor-ivacaftor studies reporting on this outcome (DAVIES 2021, MCKONE 2021, MUNCK 2020, NCT02070744, NCT02508207).[100-104]

There was no difference found in the radiological measures of lung disease and the acquisition of respiratory pathogens between treatment and control groups in either of the newly identified tezacaftor-ivacaftor or lumacaftor-ivacaftor studies (NCT02730208, STAHL 2021).[105, 107]

There was a greater absolute change in BMI in the 400 mg and 600 mg lumacaftor groups, when compared to placebo, at six months (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] There was also a greater absolute change from baseline in BMI-for-age Z-score in the lumacaftor group, when compared to placebo, in Stahl's paediatric study at over six months (STAHL 2021).[107] The previously identified paediatric study found no significant differences in both absolute change in BMI and BMI-for-age Z-score between treatment and control groups (RATJEN 2017).[123] The pooled results from participants in the TRAFFIC and TRANSPORT studies showed a significantly higher weight gain when compared to placebo, including when the results from the 400 mg and 600 mg doses were pooled (TRAFFIC 2015, TRANSPORT 2015).[125] No significant differences were found in any of the lumacaftor studies, between treatment and control groups, for the absolute change in BMI at one month (TRAFFIC 2015, TRANSPORT 2015),[125] the relative change from baseline in BMI (WILSON 2021),[108] the absolute change from baseline in weight-for-age Z-score and stature-for-age Z-score (STAHL 2021).[107]

There were no significant differences found in any of the nutrition and growth parameters in any of the tezacaftor-ivacaftor studies (DAVIES 2021, MUNCK 2020, NCT02070744, TAYLOR-COUSAR 2017).[100, 102, 103, 124]

6.2.2. Overall completeness & applicability of evidence

Two of the nine newly identified studies compared lumacaftor-ivacaftor to placebo in participants who were homozygous for the F508del variant. One of these, a Phase 4 study with a total of 70 participants, enrolled patients aged 12 years and over, who received the intervention for 24 weeks (WILSON 2021).[108] The other lumacaftor study was a Phase 2, two-part study, that enrolled 51 participants aged 2 to 5 years old. The received dose of medication was influenced by the weight of the participants, and the intervention was taken for 48 weeks (STAHL 2021).[107]

For the newly identified tezacaftor-ivacaftor studies, the durations ranged from 29 days (NCT02508207)[104] to 72 weeks (NCT02730208),[105] and included 604 participants with a range of the following genotypes: heterozygous for the F508del variant and a gating variant (MCKONE 2021),[101] or a minimal function variant (MUNCK 2020),[102] and homozygous for the F508del variant (NCT02070744, NCT02508207, NCT02730208, SCHWARZ 2021).[103-106] One paediatric study included participants who were homozygous for the F508del variant or heterozygous for the F508del variant and a residual function variant (DAVIES 2021).[100] The youngest age of an eligible participant in one of the included studies was 6 years old (DAVIES 2021).[100]

Most of the outcomes of the review were assessed by the studies, and there were a large number of participants included.

6.2.3. Quality of the evidence

Across the nine newly identified dual therapy studies, 725 participants were included, and the results from these studies were generally consistent. Within these, two studies focused on the paediatric population, with a total of 118 patients. Seven out of the nine studies had a high risk of attrition bias, and for some other domains, such as reporting bias, most studies had an unclear risk of bias. Eight out of the nine identified dual therapy studies had unclear risks of reporting bias (DAVIES 2021, MCKONE 2021, MUNCK 2020, NCT02070744, NCT02508207, NCT02730208, SCHWARZ 2021, WILSON 2021)[100-106, 108]; this was largely due to there being a lack of presented data

that were used to assess adverse events . There were some studies that had discrepancies in the presented data between the published papers and the information available on the trials registry website. In Munck's study, there was a discrepancy in the number of participants who completed the placebo treatment regimen. Additionally, Munck's study included a Kaplan-Meier plot of the time-to-first pulmonary exacerbation event, despite the trials registry stating that the data for time-to-first event were not estimated due to fewer than half of events.[102] In Schwarz's study, there was a discrepancy with the number of participants who completed the placebo treatment regimen,[106] and finally in Stahl's study, there were discrepancies in the number of participants analysed for outcomes.[107] I have therefore contacted all of the relevant study authors for further clarification on these matters. It was also unclear as to the precise extent to which the sponsors were involved in seven of the dual therapy studies (DAVIES 2021, MUNCK 2020, NCT02070744, NCT02508207, NCT02730208, SCHWARZ 2021, STAHL 2021).[100, 102-107]

6.3. Triple combination therapy versus placebo or control

6.3.1. Summary of main triple therapy results

There were statistically significant improvements found in all of the treatment regimens across the genotypes examined in the CFQ-R respiratory domain scores (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021, DAVIES 2018a, DAVIES 2018b),[65, 109-113, 127] with the only exception to this found in the 400 mg VX-659 trial, MD 7.90 (95% CI -0.58 to 16.38) (DAVIES 2018b).[127] For example, at six months, the 240 mg VX-659 group demonstrated a significant difference, favouring the intervention over the control, in participants with F508del/MF, MD 20.10 (95% CI 17.19 to 23.01) (NCT03447249).[111] There were also statistically significant improvements found in all of the studies assessing relative and absolute changes from baseline in FEV_1 (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109-113] For example, in one study looking at the relative change in FEV_1 in participants with F508del/MF taking 200 mg twice daily VX-152 versus control, results favoured the intervention, MD 21.30 (95% CI 12.73 to 29.87) (NCT02951195).[110] In another study evaluating the absolute change in FEV_1 for 200 mg once daily elexacaftor versus control in participants with F508del/F508del, results favoured the intervention, MD 10.20 (95% CI 8.26 to 12.14) (SUTHARSAN 2021).[113]

There were no significant differences found in the number of participants experiencing adverse events in the identified studies (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109-113] In one study, there were statistically significantly fewer participants with F508del/MF experiencing severe adverse events in the VX-659 240 mg treatment arm than the placebo group (NCT03447249),[111] and there were no other differences found in any of the treatment regimens for the number of participants experiencing moderate (where this could be determined) or severe adverse events (BARRY 2021, NCT02951182, NCT02951195, NCT03460990, SUTHARSAN 2021).[65, 109, 110, 112, 113] No study reported increases in blood pressure (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109-113].

There were fewer participants, with F508del/MF, in the 240 mg once daily VX-659 group experiencing pulmonary exacerbations at six months when compared to placebo (NCT03447249),[111] and there were also fewer participants with F508del/gating and F508del/residual function and F508del/F508del genotypes in the 200 mg elexacaftor group experiencing pulmonary exacerbations than in the control (BARRY 2021, SUTHARSAN 2021).[65, 113]

There were statistically significant decreases found in all of the treatment regimens across the genotypes examined in the sweat chloride levels of participants (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109-113] For the 240 mg once daily VX-659 study in participants with F508del/MF, there were statistically significant improvements in BMI, BMI Z-score and body weight found (NCT03447249).[111]

6.3.2. Overall completeness & applicability of evidence

The newly identified triple therapy studies had a total of 1029 participants and compared ETI to either ivacaftor or tezacaftor-ivacaftor (BARRY 2021, SUTHARSAN 2021),[65, 113] VX-440-tezacaftor-ivacaftor to triple placebo (NCT02951182),[109] VX-152-tezacaftor-ivacaftor to triple placebo (NCT02951195),[110] and VX-659-tezacaftor-ivacaftor to either triple placebo or to tezacaftor-ivacaftor (NCT03447249, NCT03460990).[111, 112] In the shortest study, the intervention was given for two weeks (NCT02951195),[110] and the intervention was given for 24 weeks in the two longest studies (NCT03447249, SUTHARSAN 2021).[111, 113] There was one study with a requirement for participants to be aged 18 years and over (NCT02951195),[110] and the other studies accepted participants aged 12 years and over (BARRY 2021, NCT02951182, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109, 111-113] One study included participants who had the genotypes F508del/gating or F508del/residual function (BARRY 2021),[65] one study looked at participants with the genotypes F508del/F508del and F508del/MF (NCT02951182),[109] two studies looked at participants with the genotype F508del/MF (NCT02951195, NCT03447249),[110, 111] and two studies looked at participants with the genotype F508del/F508del (NCT03460990, SUTHARSAN 2021).[112, 113]

Most of the outcomes of our review were reported by the included studies. We were unable to determine the number of mild adverse events, due to adverse events being recorded by maximum severity in the studies. Additionally, for the studies where no published paper was available, we could not accurately determine whether therapies had been discontinued, due to a lack of this published information. There were two studies in which the second parts of the trials were not eligible for this Cochrane systematic review, due to there being washout periods involved (NCT02951182, NCT02951195).[109, 110] Consequently, for these studies, this reduced the number of participants that we could analyse. As these studies were assessing new correctors (VX-440[109] and VX-152[110]), more work is needed to evaluate these drugs.

6.3.3. Quality of the evidence

Overall, there were six newly identified triple therapy studies with a total of 1029 participants; the results from these studies were generally consistent (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109-113] There was one triple therapy study that had conflicting information between the published paper and the trials registry website; the number of participants recorded as having infective pulmonary exacerbations was found to differ between the two (SUTHARSAN 2021).[113] I have contacted the author of the study to seek clarification on this. All of the identified studies were found to have low risks of selection, performance and detection bias, and two studies were found to have high risks of attrition bias (NCT03447249, NCT03460990).[111, 112] All studies were found to have an unclear risk of reporting bias, and this was due to a lack of ECG and vital signs data in the results, whether they were unremarkable or not, despite the protocol of the trials stating that these would be measured (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109-113] One study was found to have a high risk of 'other' bias due to some participants being included in the study, despite not meeting the eligibility criteria, and due to it being unclear as to the extent to which the sponsor was involved in the trial (NCT02951195).[110] It was unclear as to the precise extent to which the sponsors

were involved in all of the newly identified triple therapy studies (BARRY 2021, NCT02951182, NCT02951195, NCT03447249, NCT03460990, SUTHARSAN 2021).[65, 109-113]

6.4. Potential biases in the review process

Comprehensive searches of the Cystic Fibrosis and Genetic Disorders Review Group's CF Trials Register and online trials databases took place. In order to maximise the amount of evidence ascertained for this review, manual searching of journal conference abstracts was also conducted. Two review authors then individually screened and applied the inclusion and exclusion criteria to the obtained search results. Data from the included studies were then obtained by these authors using the data extraction form, and the risk of bias of each study was determined using the available information. If there were ever disagreements at any point in this review process, a third author was consulted. The extracted data were then analysed and checked by the statistician. Throughout the process, Cochrane methodology has been followed to reduce bias. Additionally, none of the authors of the review have funding from pharmaceutical bodies.

The comprehensive search strategy ensured that all available data has been accessed. Where more information has been needed, I have contacted the study authors and pharmaceutical company for further clarification. For example, in the study looking at VX-661 (NCT02070744),[103] I contacted Vertex Pharmaceuticals Incorporated to ask if there were any plans to publish the available data in a paper. After a series of email communications, I spoke to a representative on a telephone call; they were not able to comment on any future plans to publish data.

In terms of the limitations of the review, sometimes the definitions of various degrees of adverse events differed between our review and the included studies; the definitions of exacerbations also varied. It was therefore challenging to extract, interpret and present data for the adverse events of the studies. Also, two studies included washout periods which, following on from discussions with the other review authors, have been disregarded for the purposes of this review due to the nature of the corrector therapies causing fundamental changes to the respiratory system, meaning that any

data collected in a washout period were not appropriate to report (NCT02951182, NCT02951195).[109, 110]

Of fifteen new studies, seven were identified from a trials database (clinicaltrials.gov). Including data that have not yet been published in journals has allowed for the review to encompass a wide range of information. This is also a limitation of the review, as the data identified have not yet been peer-reviewed.

There were a number of discrepancies between data on the trials registry website and the published papers. Every effort has been made to contact the study authors to seek further clarification on these discrepancies, so that the most accurate data can be analysed for the purposes of this review.

6.5. Agreements and disagreements with other studies or reviews

During the process of completing the Cochrane systematic review, the authors became aware of another systematic review of triple therapies for patients with CF. We therefore appraised and compared this review to that of our own.

The systematic review was written by Wang et al. and was published in March 2022. The review looked at pwCF with at least one F508del variant. After searching for RCTs on PubMed, Web of Science and the Cochrane Library, the review included six RCTs, all of which were included in our Cochrane review (BARRY 2021, SUTHARSAN 2021, DAVIES 2018, KEATING 2018, HEIJERMAN 2019, MIDDLETON 2019).[65, 113, 127-130] Unlike our Cochrane review, Wang's review did not include data from any of the eligible trials on the trials registry, thus included a smaller range of data. The risk of bias was assessed in all of the eligible studies using Cochrane analysis. Wang assessed bias using five different aspects: selection, performance, detection, attrition and reporting bias. All of these aspects were used to assess bias in the Cochrane systematic review, however there was a further domain used in our review, entitled 'other bias', that was used to comment on any additional uncertainties with the included trials. Wang's assessments of bias differed from the Cochrane review; Wang determined that each study had a low risk of bias for each domain, and did not give reasons for each

justification. In the previously published Cochrane review, two studies were found to have unclear risks of both detection and reporting bias (DAVIES 2018, KEATING 2018).[2] Additionally, we determined both the newly identified studies from the update of our review to have unclear risks of reporting bias (BARRY 2021, SUTHARSAN 2021).[65, 113]

Wang's review assessed one of the groups of the Davies study (400 mg VX-659-tezacaftor-ivacaftor), therefore there were significant amounts of data that were missing from the analysis, including data involving VX-561,[127] when compared to the previous Cochrane review.[2] This was also the case for Keating's study, in which data were only included from the 200 mg elexacaftor-tezacaftor-ivacaftor group.

The conclusions of the Wang review were very similar to the conclusions of the updated Cochrane systematic review, and similar outcomes were measured. The review also commented on the fact that all patients included in the review were aged 12 and over, and therefore there is a need in the future to evaluate triple therapy combinations in younger CF patients. Wang did not identify any increases in blood pressure across the studies.[146]

7. Conclusions for Cochrane systematic review

7.1. Implications for practice

No new monotherapy studies were identified in this review and therefore, as per the previous review, there is still no evidence to support corrector monotherapy for patients with CF.[2] It is likely that future updates of this review will not include data from monotherapy studies.

There are large dual therapy studies included in the update of this review and in the previous review, showing small differences in outcomes.[2] Evidence for dual therapy combinations from this review demonstrates that although the therapy is more effective than monotherapy, and some of the differences identified were statistically significant, these differences were small when compared to the triple therapy data. Evidence from the 400 mg lumacaftor study (WILSON 2021)[108] allowed for the mean difference in CFQ-R respiratory domain score, when compared to the control, to move from a non-significant difference in the previous review[2] to a significant difference in this review when included in the meta-analysis. As a result of the Wilson study being added to the meta-analysis, there was no significant difference found between the intervention and control groups for the number of participants with at least one serious adverse event when the lumacaftor doses were combined (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] Any changes to the forest plots were small. I have included examples of forest plots from the Cochrane review in the appendix of this thesis. It is also noteworthy that dyspnoea was found to be more common in the combined data from the 400 mg and 600 mg lumacaftor groups, when compared to the control groups, in these studies (WILSON 2021, TRAFFIC 2015, TRANSPORT 2015).[108, 125] In terms of the 100 mg once daily tezacaftor-ivacaftor studies, the mean difference found at six months for the change in CFQ-R respiratory domains scores was reduced from 5.10 (95% CI 3.20 to 7.00) in the previous review[2] to 2.89 (95% CI 2.48 to 3.29) in the update, when data from the newly identified studies were combined in the meta-analysis (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124]

The mean differences in both the relative and absolute change from baseline in FEV_1 were reduced considerably when data from three of the newly identified tezacaftor-ivacaftor studies were combined in the meta-analysis at six months with data from a previously identified study. For the relative change at six months, this decreased from MD 6.80 (95% CI 5.30 to 8.30)[2] to MD 0.92 (95% CI 0.72 to 1.11) (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017),[101, 102, 106, 124] and for the absolute change at six months, this decreased from MD 4.00 (95% CI 3.10 to 4.90)[2] to MD 0.39 (95% CI 0.27 to 0.52) (MCKONE 2021, MUNCK 2020, SCHWARZ 2021, TAYLOR-COUSAR 2017).[101, 102, 106, 124] When data from two of the newly identified studies were included in the meta-analysis (MCKONE 2021, MUNCK 2020),[101, 102] the mean difference in sweat chloride was found to decrease by a smaller amount, when compared to the data in the previous review.[2]

New data have been made available in terms of dual therapy studies for paediatric patients; Stahl's study demonstrated a very small decrease in $LCI_{2.5}$, MD -0.69 (95% CI -1.35 to -0.03), and a small increase in BMI-for-age Z-score. There was also a reduction in the sweat chloride levels found that was statistically significant, and there were no other statistically significant differences found in any of the other measured outcomes (STAHL 2021).[107] Similarly, Davies' study evaluated tezacaftor-ivacaftor in 6 to 11 year olds, and found statistically significant improvements in $LCI_{2.5}$ (the within-group change was reduced by -0.51 (95% CI -0.74 to -0.29)) and sweat chloride concentrations, and improvements in CFQ-R respiratory domain scores, though these were non-significantly improved (the within-group change was 2.30 points (95% CI -0.10 to 4.60); P=0.0546) (DAVIES 2021).[100]

In terms of the newly identified triple therapy studies, there were new data for ETI that were consistent with previous studies in terms of the magnitude of the improvements in the efficacy outcomes measured. One of the newly identified studies examined patients with F508del/gating and F508del/residual function genotypes, allowing for the authors to conclude that just the presence of one F508del allele is sufficient for improvements to be seen with this triple therapy combination, even in patients already established on an effective modulator (ivacaftor) (BARRY 2021).[65] There

were also new correctors identified in this review: VX-440 and VX-152, with promising results identified, showing improvements across outcomes measured (NCT02951182, NCT02951195).[109, 110]

7.2. Implications for research

There are still a large number of variants that are non-responsive to the corrector medications identified in this review; 10% of patients with CF have variants that are not responsive to modulators or have unknown genotypes.[147] More research is therefore needed into medications or possible alternative therapies for these patients.

Throughout years of research, there have been significant steps forward for patients with eligible genotypes, and if new agents are discovered that may be efficacious, these will need to be looked at in detail. However, the way in which these new agents are trialled will need to be considered; drug companies must consider how they can evaluate any new benefits from these medications, given that the evidence behind triple therapy combination studies highlighted in this review is very strong. In addition to the respiratory system, other systems need to be evaluated in clinical trials, for example, the endocrine and gastrointestinal systems. Moving forward, outcomes that focus on the frequency of drug administration may be incorporated into clinical trials. In the future, there may be a time when other medications can be safely discontinued if the modulator therapies are proven to be beneficial. SIMPLIFY is a current trial that is aimed at evaluating whether patients taking ETI can safely stop hypertonic saline or dornase alfa treatments, thus aiming to evaluate how the treatment burdens can be reduced for CF patients.[148] Similarly, CF STORM, a longer trial, is also evaluating the impacts of stopping muco-active therapies in participants who are stable on triple therapy.[149] Additionally, long-term adherence to these medications must be evaluated, particularly if they are established at a young age. In the future, clinicians must consider how they can best support their patients as their quality of life changes too.

In future works, the cost-effectiveness and accessibility of these medications may be evaluated. Additionally, reported adverse events could be characterised as either events that occur due to the

consequences of the physiological impacts of the therapy (for example, this might include sinus pain, abdominal pain and testicular pain), or they could be characterised by any idiosyncratic changes (these might include mood changes and transaminitis). The quality of future safety reporting needs to improve with more comprehensive reporting of any adverse event.

Summary

From this update of the Cochrane systematic review, it is clear that there is currently no evidence to support the use of corrector monotherapy in pwCF and it is possible that with the advent of new, effective combination therapies, future clinical trials assessing corrector monotherapy will be unlikely. The additional data in this review reduces the evidence for efficacy for dual corrector therapy, and these agents can no longer be recommended as standard therapy. However, due to a lack of evidence in this area, this does not yet apply to younger pwCF. The identified triple therapy studies demonstrate significant and clinically relevant differences in reported outcomes, with improved safety profiles compared to lumacaftor-ivacaftor. It is likely that these therapies will prove to be transformational for pwCF with class II *CFTR* gene variants.

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Appendices

1. Data extraction form used for studies found to be eligible for inclusion in the Cochrane systematic review

Study Selection, Quality Assessment & Data Extraction Form

First author	Journal/Conference Proceedings etc	Year

Study eligibility

RCT/Quasi/CCT (delete as appropriate)	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No* / Unclear

*** Issue relates to selective reporting – when authors may have taken measurements for particular outcomes, but not reported these within the paper(s). Reviewers should contact trialists for information on possible non-reported outcomes & reasons for exclusion from publication. Study should be listed in 'Studies awaiting assessment' until clarified. If no clarification is received after three attempts, study should then be excluded.**

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.

References to trial

Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	Author(s)	Journal/Conference Proceedings etc	Year
A	*The paper listed above*		
B	*Further papers*		

Participants and trial characteristics

Participant characteristics	
	Further details
Age (mean, median, range, etc)	
Sex of participants (numbers / %, etc)	
Disease status / type, etc (if applicable)	
Other	

Trial characteristics
see Appendix 1, usually just completed by one reviewer

Risk of bias

We recommend you refer to and use the method described in the Cochrane Reviewers' Handbook, Version 5.1*

Allocation of intervention	
State here method used to generate allocation and reasons for grading →	Risk of bias (circle)
	Low (Random)
	High (e.g. alternate)
	Unclear

Concealment of allocation **Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding**	
State here method used to conceal allocation and reasons for grading →	Risk of bias (circle)
	Low
	High
	Unclear

Blinding	
Person responsible for participants care	Yes / No
Participant	Yes / No
Outcome assessor	Yes / No
Other (please specify)	Yes / No

Intention-to-treat An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not.	
All participants entering trial	
15% or fewer excluded	
More than 15% excluded	
Not analysed as 'intention-to-treat'	
Unclear	

Were withdrawals described? Yes ☐ No ☐ not clear ☐
Discuss if appropriate.....
.....

Selective outcome reporting	
Have you been able to access the trial protocol?	
Are all outcomes listed in protocol reported in the full trial paper?	

Data extraction

Outcomes relevant to your review Copy and paste from 'Types of outcome measures'	
	Reported in paper (circle)
Survival	Yes / No
QoL (total and subdomains)	Yes / No
FEV1 relative change from baseline - % pred or L	Yes / No
FEV1 absolute values or change from baseline - % pred or L	Yes / No
FVC absolute values and change from baseline - % pred or L	Yes / No
LCI	Yes / No
Other relevant physiological measures of lung function	Yes / No
Adverse effects	Yes / No
Hospitalisation (number of days, number of episodes, time to next hospitalisation)	

School or work attendance (i.e. number of days missed)	Yes / No
Extra courses of antibiotics (oral, inhaled, IV) time to next course and number of courses	Yes / No
Sweat chloride (change from baseline)	Yes / No
Chest radiograph scores or CT score	Yes / No
Acquisition of respiratory pathogens (Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenza, other)	Yes / No
Eradication of respiratory pathogens (Pseudomonas aeruginosa, Staphylococcus aureus, Haemophilus influenza, other)	Yes / No
Relative change from baseline in weight or BMI or height	Yes / No

For Continuous data							
Code of paper	Outcomes (rename)	Unit of measurement	Intervention group		Control group		Details if outcome only described in text or other data presented, e.g. P value
			n	Mean (SD)	n	Mean (SD)	
A etc	Outcome A						
	Outcome B						
	Outcome C						
	Outcome D						
	Outcome E						
	Outcome F						

For Dichotomous data			
Code of paper	Outcomes (rename)	Intervention group (n) n = number of participants, not number of events	Control group (n) n = number of participants, not number of events
A	Outcome G		
	Outcome H		
	Outcome I		
	Outcome J		
	Outcome K		
	Outcome L		

Other information which you feel is relevant to the results
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review.

References to other trials

Did this report include any references to **published reports** of potentially eligible trials not already identified for this review?		
First author	Journal / Conference	Year of publication
Did this report include any references to **unpublished data** from potentially eligible trials not already identified for this review? If yes, give list contact name and details		

Appendix 1

Trial characteristics	
	Further details
Single centre / multicentre	
Country / Countries	
How was participant eligibility defined?	
How many people were randomised?	
Number of participants in each intervention group	
Number of participants who received intended treatment	
Number of participants who were analysed	
Drug treatment(s) used	
Dose / frequency of administration	
Duration of treatment (State weeks / months, etc, If cross-over trial give length of time in each arm)	
Median (range) length of follow-up reported in this paper (state weeks, months or years or If not stated)	
Time-points when measurements were taken during the study	
Time-points reported in the study	
Time-points you are using in Meta-View	
Trial design (e.g. parallel / cross-over*)	
Other	

* If cross-over design, please refer to the Cochrane Editorial Office for further advice on how to analyse these data

References

Cochrane Reviewers' Handbook, Version 5.1
Higgins JPT, Green S (editors). *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

2. Summary of characteristics and results for each of the newly included studies in the Cochrane systematic review

Table 2: Summary of characteristics and results for Davies 2021[100]:

Population	67 participants aged 6 to 11 years old who were homozygous for the F508del variant or heterozygous for the F508del variant and a residual function variant.
Intervention	Participants with genotype F508del/F508del received tezacaftor-ivacaftor in the morning and ivacaftor in the evening for 8 weeks. Participants with genotype F508del/residual function received tezacaftor-ivacaftor and placebo matched to ivacaftor in the morning and ivacaftor in the evening for 8 weeks. The dosage of the study drug was dependent on the weight of the participant.
Comparison	Placebo: Participants with genotype F508del/F508del received placebo matched to tezacaftor-ivacaftor in the morning and placebo matched to ivacaftor in the evening for 8 weeks. Ivacaftor: Participants with genotype F508del/residual function received placebo

	matched to tezacaftor-ivacaftor in the morning and ivacaftor in the morning and evening for 8 weeks. The dosage of the study drug was dependent on the weight of the participant.
Outcomes	Primary outcome measure: Absolute change in $LCI_{2.5}$ from baseline through week 8. Secondary outcome measures: Absolute change in sweat chloride from baseline at week 8. Absolute change in CFQ-R respiratory domain score from baseline through week 8. Safety and tolerability as measured by adverse events and serious adverse events from first dose of study drug up to safety follow-up visit (up to week 12).
Key results	The $LCI_{2.5}$ and sweat chloride concentrations were improved, and the CFQ-R respiratory domain score increased, though this was not significant.

Table 3: Summary of characteristics and results for McKone 2021[101]:

Population	156 participants aged 12 years and over who were heterozygous for the F508del variant and a gating variant.
Intervention	100 mg tezacaftor – 150 mg ivacaftor once daily in the morning and 150 mg ivacaftor once daily in the evening for 8 weeks.
Comparison	150 mg ivacaftor every 12 hours as monotherapy for 8 weeks.
Outcomes	Primary outcome: Absolute change in % predicted FEV_1 (from baseline through week 8). Secondary outcomes: Relative change in **%** predicted FEV_1 (from baseline through week 8). Absolute change in sweat chloride (from baseline through week 8). Absolute change in CFQ-R respiratory domain score (from baseline through week 8). Number of participants with adverse events and serious adverse events [Time Frame: Baseline up to Week 16] PK parameters of VX-661, M1-661, ivacaftor, and M1-ivacaftor [time frame: pre-dose on

	week -2 for run-in period; pre-dose on week 2 for active comparator period].
Key results	No significant differences were found in the percent predicted FEV_1 or any key secondary endpoint between the intervention and control groups. The concentrations of sweat chloride decreased more in the intervention group when compared to the control group during the active comparator treatment period.

Table 4: Summary of characteristics and results for Munck 2020[102]:

Population	168 participants aged 12 years and over who were heterozygous for the F508del variant and a minimal function variant.
Intervention	100 mg tezacaftor- 150 mg ivacaftor in the morning and 150 mg ivacaftor in the evening up to week 12.
Comparison	Placebo matched to tezacaftor-ivacaftor in the morning and placebo matched to ivacaftor in the evening up to week 12.
Outcomes	Primary outcome measure: Absolute change from baseline in FEV_1 % predicted. Secondary outcome measures: Change from baseline in CFQ-R respiratory domain, number of pulmonary exacerbations, absolute change in BMI, relative change from baseline in % predicted FEV_1 through week 12, absolute change from baseline in sweat chloride through week 12, number of participants with at least one pulmonary exacerbation through week 12, absolute change from baseline in BMI z-score at week 12 (in participants less than [<] 20 years old at the time of screening), absolute change from

	baseline in body weight at week 12, number of participants with treatment-emergent adverse events and serious adverse events [time frame: baseline up to week 16], trough plasma concentrations (Ctrough) of VX-661, VX-661 metabolite (M1 VX-661), ivacaftor (IVA) and IVA metabolite (M1-IVA) [time frame: pre-morning dose on week 2, week 4, week 8 and week 12].
Key results	There were no significant improvements in the percent predicted FEV_1 or any key secondary endpoint between the intervention and control groups. Tezacaftor-ivacaftor was generally safe.

Table 5: Summary of characteristics and results for NCT02070744[103]:

Population	40 participants aged 18 years and over who were homozygous for the F508del variant.
Intervention	50 mg twice daily tezacaftor – 150 mg twice daily ivacaftor for 12 weeks. Two tezacaftor 50 mg tablets once daily – 150 mg twice daily ivacaftor for 12 weeks.
Comparison	Matched placebo.
Outcomes	Primary outcome measure: Number of participants with treatment-emergent adverse events and serious adverse events [time frame: baseline (PC phase) up to 112 days]. Secondary outcome measures: Absolute change from baseline in % predicted forced expiratory volume in 1 second (FEV_1) through week 12 [time frame: baseline (PC phase), through week 12]. Relative change from baseline in percent predicted FEV_1 through week 12 [time frame: baseline (PC phase), through week 12]. Absolute change from baseline in sweat chloride through week 12 [time frame: baseline (PC phase), through week 12].

	Absolute change from baseline in body weight at week 12 [time frame: baseline (PC phase), week 12]. Absolute change from baseline body mass index at week 12 [time frame: baseline (PC phase), week 12]. Absolute change from baseline in Cystic Fibrosis Questionnaire-Revised respiratory domain score through week 12 [time frame: baseline (PC phase), through week 12]. Maximum plasma concentration (Cmax) of VX-661 and ivacaftor [time frame: pre-dose, 2, 3, 4, 6, 9 and 12 hours post-dose on day 85]. Area under the concentration versus time curve from time 0 to 24 hours of VX-661 [time frame: pre-dose, 2, 3, 4, 6, 9 and 12 hours post-dose on day 85]. Area under the concentration versus time curve from time 0 to 12 hours of ivacaftor [time frame: pre-dose, 2, 3, 4, 6, 9 and 12 hours post-dose on day 85]. Time to reach Cmax (Tmax) of VX-661 and ivacaftor [time frame: pre-dose, 2, 3, 4, 6, 9 and 12 hours post-dose on day 85].

Key results	The sweat chloride concentrations were statistically significantly reduced, however there were no other statistically significant differences found between the intervention and control groups in the other relevant outcomes of this study.

Table 6: Summary of characteristics and results for NCT02508207[104]:

Population	34 participants aged 18 years and over who were homozygous for the F508del variant.
Intervention	Participants received 100 mg tezacaftor – 150 mg ivacaftor once daily in the morning followed by 150mg ivacaftor once daily in the evening for 29 days.
Comparison	Matched placebo.
Outcomes	Primary outcome measure: Absolute change from baseline in mucociliary clearance at day 28. Secondary outcome measures: Absolute change from baseline in % predicted forced expiratory volume in 1 second at day 28. Absolute change from baseline in small-bowel area under the curve over 1-minute mean pH increments at day 29. Absolute change from baseline in sweat chloride at day 29. Number of participants with adverse events and serious adverse events.
Key results	The sweat chloride concentrations were statistically significantly reduced, and there was a statistically significant improvement seen in

	the placebo group for the number of participants experiencing treatment-emergent adverse events. There were no other statistically significant differences found between the intervention and control groups in the other relevant outcomes of this study.

Table 7: Summary of characteristics and results for NCT02730208[105]:

Population	41 participants aged 12 years and over who were homozygous for the F508del variant.
Intervention	Participants received 100 mg tezacaftor – 150 mg ivacaftor once daily in the morning and 150 mg ivacaftor once daily in the evening for 72 weeks.
Comparison	Matched placebo.
Outcomes	Primary outcome measure: Absolute change in total brody/CF-CT score [time frame: from baseline at week 72]. Secondary outcome measures: Number of participants with treatment-emergent adverse events and serious adverse events [time frame: day 1 up to week 76].
Key results	There were no statistically significant differences found between the intervention and control groups in the relevant outcomes of this study.

Table 8: Summary of characteristics and results for Schwarz 2021[106]:

Population	98 participants aged 12 years and over who were homozygous for the F508del variant.
Intervention	Participants received 100 mg tezacaftor – 150 mg ivacaftor once daily in the morning and 150 mg ivacaftor once daily in the evening for 56 days.
Comparison	Matched placebo.
Outcomes	Primary outcome measure: Incidence of respiratory adverse events of special interest (RAESIs) [time frame: day 1 up to day 84]. Secondary outcome measures: Absolute change in % predicted FEV_1 (from baseline to the average of the day 28 and day 56 measurements). Relative change in % predicted FEV_1 (from baseline to the average of the day 28 and day 56 measurements) Absolute change in CFQ-R respiratory domain score % predicted FEV_1 (from baseline to the average of the day 28 and day 56 measurements).

	Tolerability (defined as the number and proportion of study participants who discontinue treatment) (up to day 56) Adverse events and serious adverse events (adverse events, abnormal laboratory values, vital signs or pulse oximetry) (safety follow-up (up to 28 days after last dose of study drug)).
Key results	There were statistically significant improvements found in the intervention group for the absolute and relative change from baseline in % predicted FEV_1. There were no other statistically significant differences found between the intervention and control groups in the other relevant outcomes of this study.

Table 9: Summary of characteristics and results for Stahl 2021[107]:

Population	51 participants aged 2 to 5 years old who were homozygous for the F508del variant.
Intervention	Participants received lumacaftor-ivacaftor for 48 weeks. The dosage of the study drug was dependent on the weight of the participant.
Comparison	Matched placebo.
Outcomes	Primary outcome measure: Absolute change from baseline in MRI global chest score at week 48 [time frame: from baseline at week 48]. Secondary outcome measures: Absolute change in lung clearance index 2.5 through week 48 [time frame: from baseline through week 48]. Absolute change in weight-for-age Z-score at week 48 [time frame: from baseline at week 48]. Absolute change in stature-for-age Z-score at week 48 [time frame: from baseline at week 48]. Absolute change in body mass index-for-age Z-score at week 48 [time frame: from baseline at week 48].

Key results	There was a statistically significant decrease in $LCI_{2.5}$ in the lumacaftor-ivacaftor group when compared to the placebo group, and a statistically significant increase in BMI-for-age Z-score in the lumacaftor-ivacaftor group when compared to the placebo group. There was also a statistically significant improvement found in the sweat chloride concentrations of the intervention group. There were no other statistically significant differences found between the intervention and control groups in the other relevant outcomes of this study.

Table 10: Summary of characteristics and results for Wilson 2021[108]:

Population	70 participants aged 12 years and over who were homozygous for the F508del variant.
Intervention	Participants received 400 mg lumacaftor – 250 mg ivacaftor every 12 hours for 24 weeks.
Comparison	Matched placebo.
Outcomes	Primary outcome measure: Relative percentage change from baseline in VO2max during cardiopulmonary exercise testing at week 24. Secondary outcome measures: Relative percentage change from baseline in exercise duration during cardiopulmonary exercise testing at week 24. Absolute change from baseline in exercise duration during cardiopulmonary exercise testing at week 24. Absolute change from baseline in VO2max during cardiopulmonary exercise testing at week 24. Absolute change from baseline in oxygen consumption (VO2) at anaerobic threshold at week 24. Relative percentage change from baseline in VO2 at anaerobic threshold at week 24.

	Absolute change from baseline in functional VO2 gain at week 24. Relative percentage change from baseline in functional VO2 gain at week 24. Absolute change from baseline in pulmonary ventilation (VE) versus carbon dioxide production (VCO2) slope at week 24. Relative percentage change from baseline in pulmonary ventilation versus carbon dioxide production slope at week 24. Absolute change from baseline in percent predicted forced expiratory volume in 1 second at week 24. Relative percentage change from baseline in percent predicted forced expiratory volume in 1 second at week 24. Absolute change from baseline in BMI at week 24. Relative percentage change from baseline in BMI at week 24. Absolute change from baseline in cystic fibrosis questionnaire-revised respiratory domain score at week 24.

	Number of participants in each severity category of patient health questionnaire (PHQ-8). Number of participants in each severity category of generalized anxiety disorder (GAD-7) scores. Absolute change from baseline in daily physical activity counts as determined by actigraphy at week 24. Relative (percent) change from baseline in physical activity as determined by actigraphy at week 24. Absolute change from baseline in duration of sleep time at week 24. Relative (percent) change from baseline in duration of sleep time at week 24. Absolute change from baseline in time above sedentary duration at week 24. Relative (percent) change from baseline in time above sedentary duration at week 24. Number of participants with adverse events and serious adverse events.
Key results	There were no statistically significant differences found between the intervention

	and control groups in the relevant outcomes of this study.

Table 11: Summary of characteristics and results for Barry 2021[65]:

Population	271 participants aged 12 years and over who were heterozygous for the F508del variant and either a gating or residual function variant.
Intervention	Participants received 200 mg once daily elexacaftor – 100 mg once daily tezacaftor – 150 mg twice daily ivacaftor in the treatment period for 8 weeks.
Comparison	Participants who were heterozygous for the F508del variant and a gating variant received 150 mg twice daily ivacaftor. Participants who were heterozygous for the F508del variant and a residual function variant received 100 mg once daily tezacaftor – 150 mg twice daily ivacaftor.
Outcomes	Primary outcome measure: Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) for elexacaftor-tezacaftor-ivacaftor group [time frame: from baseline through week 8]. Secondary outcome measures: Absolute change in sweat chloride for elexacaftor-tezacaftor-ivacaftor group [time frame: from baseline through week 8].

	Absolute change in ppFEV$_1$ for the elexacaftor-tezacaftor-ivacaftor group compared to the control group [time frame: from baseline through week 8]. Absolute change in sweat chloride for the elexacaftor-tezacaftor-ivacaftor group compared to the control group [time frame: from baseline through week 8]. Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score for the elexacaftor-tezacaftor-ivacaftor group [time frame: from baseline through week 8]. Absolute change in CFQ-R respiratory domain score for the elexacaftor-tezacaftor-ivacaftor group compared to the control group [time frame: from baseline through week 8]. Safety and tolerability as assessed by number of participants with treatment-emergent adverse events and serious adverse events [time frame: day 1 up to week 12].
Key results	There were statistically significant improvements seen across outcomes and, in terms of safety, there were statistically

	significantly fewer participants experiencing cough and infective pulmonary exacerbations of cystic fibrosis in the intervention group, when compared to the control.

Table 12: Summary of characteristics and results for NCT02951182[109]:

Population	47 participants aged 12 years and over who were either homozygous for the F508del variant or heterozygous for the F508del variant and a minimal function variant.
Intervention	Cohort 1A: Participants received 200 mg VX-440 every 12 hours - 100 mg once daily tezacaftor - 150 mg twice daily ivacaftor as triple combination for 4 weeks. Cohort 1B: TC Low Dose: Participants received 200 mg VX-440 every 12 hours - 50 mg tezacaftor every 12 hours - 150 mg ivacaftor every 12 hours as triple combination for 4 weeks. Part 1 Cohort 1B: TC High Dose: Participants received 600 mg VX-440 every 12 hours – 50 mg tezacaftor every 12 hours – 300 mg ivacaftor every 12 hours as triple combination for 4 weeks.
Comparison	Matched placebo.
Outcomes	Primary outcome measures: Safety and tolerability as assessed by number of participants with treatment emergent adverse events and serious adverse events [time frame: from first dose of study drug in the

	treatment period through safety follow-up visit (up to day 57 for part 1 and day 85 for part 2)]. Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) [time frame: from baseline through day 29]. Secondary outcome measures: Absolute change in sweat chloride concentrations [time frame: from baseline through day 29]. Relative change in $ppFEV_1$ [time frame: from baseline through day 29]. Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score [time frame: from baseline at day 29]. Pre-dose plasma concentration (Ctrough) of VX-440, tezacaftor, M1-TEZ, ivacaftor and M1-IVA [time frame: pre-dose at day 8, day 15 and day 29].
Key results	There were significant improvements across relevant outcomes in the intervention groups.

Table 13: Summary of characteristics and results for NCT02951195[110]:

Population	34 participants aged 18 years and over who were heterozygous for the F508del variant and a minimal function variant.
Intervention	Part 1 Cohort 1A: Participants received VX-152 100 mg every 12 hours - tezacaftor 100 mg once daily - ivacaftor 150 mg every 12 hours for 2 weeks. Part 1 Cohort 1B: Participants received VX-152 200 mg every 12 hours - tezacaftor 100 mg once daily - ivacaftor 150 mg every 12 hours for 2 weeks. Part 1 Cohort 1C: Participants received VX-152 300 mg every 12 hours - tezacaftor 100 mg once daily - ivacaftor 150 mg every 12 hours for 2 weeks.
Comparison	Matched placebo.
Outcomes	Primary outcome measures: Safety and tolerability as assessed by number of participants with treatment emergent adverse events and serious adverse events [time frame: day 1 through safety follow-up visit (up to day 43 for part 1 and Day 71 for part 2)].

	Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) at day 15 for part 1 and part 2 cohort 2A [time frame: from baseline at day 15]. Secondary outcome measures: Absolute change in sweat chloride concentrations at day 15 for part 1 and part 2 cohort 2A [time frame: from baseline at day 15]. Relative change in $ppFEV_1$ at day 15 for part 1 and part 2 cohort 2A [time frame: from baseline at day 15]. Absolute change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score at day 15 for part 1 and part 2 cohort 2A [time frame: from baseline at day 15]. Pre-dose plasma concentration (Ctrough) of VX-152, tezacaftor, M1-TEZ, ivacaftor, and M1-IVA [time frame: pre-dose at day 8, day 15 and day 29].
Key results	There were significant improvements across relevant outcomes in the intervention groups.

Table 14: Summary of characteristics and results for NCT03447249[111]:

Population	385 participants aged 12 years and over who were heterozygous for the F508del variant and a minimal function variant.
Intervention	Participants received VX-659 240 mg - tezacaftor 100 mg - ivacaftor 150 mg as fixed-dose combination tablets in the morning and ivacaftor 150 mg in the evening.
Comparison	Matched placebo.
Outcomes	Primary outcome: Absolute change in FEV_1 % predicted [time frame: from baseline at week 4]. Secondary outcomes: Absolute change in $ppFEV_1$ [time frame: from baseline through week 24]. Number of pulmonary exacerbations. Time-to-first pulmonary exacerbation. Absolute change in sweat chloride. Absolute change in CFQ-R respiratory domain score. Absolute change in BMI. Absolute change in BMI Z-score for participants <=20 years of age at baseline (from baseline at week 24). Absolute change in body weight.

	Safety and tolerability as assessed by the number of participants with treatment-emergent adverse events and serious adverse events. Observed pre-dose concentration of VX-659, tezacaftor, M1-TEZ, and ivacaftor.
Key results	There were significant improvements across all relevant outcomes for this study. In terms of safety, there were statistically fewer participants in the intervention group experiencing serious adverse events, infective pulmonary exacerbations of cystic fibrosis, nausea, cough and haemoptysis. There were statistically fewer participants in the control group experiencing upper respiratory tract infections.

Table 15: Summary of characteristics and results for NCT03460990[112]:

Population	116 participants aged 12 years and over who were homozygous for the F508del variant.
Intervention	Participants received VX-659 240 mg - tezacaftor 100 mg - ivacaftor 150 mg as fixed-dose combination tablets in the morning and ivacaftor 150 mg in the evening.
Comparison	Placebo - tezacaftor 100 mg - ivacaftor 150 mg as fixed-dose combination tablets in the morning and ivacaftor 150 mg in the evening.
Outcomes	Primary outcome: Absolute change in FEV_1 % predicted. Secondary outcomes: Absolute change in sweat chloride. Absolute change in CFQ-R respiratory domain score. Safety and tolerability as assessed by the number of participants with treatment-emergent adverse events and serious adverse events. Observed pre-dose concentration of VX-659, tezacaftor, M1-TEZ, and ivacaftor.
Key results	There were significant improvements across all relevant outcomes for this study.

Table 16: Summary of characteristics and results for Sutharsan 2021[113]:

Population	176 participants aged 12 years and over who were homozygous for the F508del variant.
Intervention	Participants received elexacaftor 200 mg once daily - tezacaftor 100 mg once daily - ivacaftor 150 mg every 12 hours in the treatment period for 24 weeks.
Comparison	Participants received tezacaftor 100 mg once daily - ivacaftor 150 mg every 12 hours in the treatment period for 24 weeks.
Outcomes	Primary outcome measure: Absolute change in CF Questionnaire-Revised (CFQ-R) respiratory domain score from baseline through week 24. Secondary outcome measures: Absolute change in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) from baseline through week 24. Absolute change in sweat chloride from baseline through week 24. Safety and tolerability as assessed by number of participants with treatment-emergent adverse events and serious adverse events [time frame: from day 1 in the treatment period up to 28 days after last dose of study

	drug or to the completion of study participation date, whichever occurs first (up to week 28)].
Key results	There were significant improvements across all relevant outcomes for this study. In terms of safety, there were statistically fewer participants in the intervention group experiencing infective pulmonary exacerbations of cystic fibrosis.

3. Risk of bias assessments for each of the newly included studies in the Cochrane systematic review

Table 17: Risk of bias assessments for Davies 2021[100]:

This study was an RCT examining tezacaftor-ivacaftor versus either placebo or ivacaftor in 67 participants aged 6 to 11 years of age who were either homozygous for the F508del variant or heterozygous for the F508del variant and a residual function variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	Interactive web or voice response system used to assign subjects to treatment. The randomisation code was produced by Vertex Biostatistics or a qualified randomisation vendor. The Vertex study biostatistician planned to review and approve the production of the final randomisation list, which was then to be reviewed and approved by a designated unblinded biostatistician who was not a member of the study execution team (SET).

Allocation concealment (selection bias)	Low risk of bias	An interactive web or voice response system was used to assign subjects to treatment.
Blinding of participants and personnel (performance bias)	Low risk of bias	All study personnel blinded and there is a clear statement of the exceptions to this in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	Clinicaltrials.gov states that masking was quadruple (participant, care provider, investigator, outcomes assessor). All study personnel blinded and there is a clear statement of the exceptions to this in the protocol.
Incomplete outcome data (attrition bias)	High risk of bias	All randomised participants analysed against outcomes, however according to the published paper, the mean and standard deviation values, and P values were based off fewer participants than within the group (for example, the P value

		for the change in sweat chloride was based on 48 participants), with no explanations offered as to why these numbers were lower than the 54 participants in the intervention group.
Selective reporting (reporting bias)	Unclear risk of bias	Unable to find exact values for 'standard 12-lead ECGs' and other parameters used to assess adverse events. Though these may have been measured, they are not stated in results or supplement regardless of if they were unremarkable or not.
Other bias	Unclear risk of bias	Baseline characteristics generally balanced. It is unclear as to the extent to which the funders were involved in designing, writing up and publishing the report.

Table 18: Risk of bias assessments for McKone 2021[101]:

This study was an RCT examining tezacaftor-ivacaftor versus ivacaftor in 156 participants aged 12 years and over who were heterozygous for the F508del variant and a gating variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	The randomisation codes were produced by the designated vendor. No Vertex biostatistician was unblinded to the actual randomisation list before database lock.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used to assign subjects to study treatment using a list of randomisation codes generated by a designated vendor.
Blinding of participants and personnel (performance bias)	Low risk of bias	All subjects, site personnel, including the investigator, the site monitor, and the study team, were blinded. Protocol sets out conditions when blinding could/should be broken.

Blinding of outcome assessment (detection bias)	Low risk of bias	All subjects, site personnel, including the investigator, the site monitor, and the study team, were blinded. Protocol sets out conditions when blinding could/should be broken.
Incomplete outcome data (attrition bias)	High risk of bias	Out of 76 in the intervention group, only 74 were analysed for change in sweat chloride. Full set analysis was completed for 74 participants in IVA monotherapy group (75 started this regimen), and only 72 were analysed for absolute and relative change in $ppFEV_1$, 73 were analysed for change in CFQ-R and 70 for change in sweat chloride. Within the IVA monotherapy group, 6 participants ended treatment early, and reasons were given for each, however no further detail was given for 2 participants than 'other'.

Selective reporting (reporting bias)	Unclear risk of bias	States in methods that it would measure 12-lead ECG and vital signs, though these may have been measured, they are not stated in results or supplement regardless of if they were unremarkable or not.
Other bias	Low risk of bias	Different groups of participants are balanced in baseline characteristics. Paper states how Vertex Pharmaceuticals Incorporated participated in study and publication.

Table 19: Risk of bias assessments for Munck 2020[102]:

This study was an RCT examining tezacaftor-ivacaftor versus placebo in 168 participants aged 12 years and over who were heterozygous for the F508del variant and minimal function variants.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	Does not state method by which participants are randomised.
Allocation concealment (selection bias)	Unclear risk of bias	Does not state method by which allocations are concealed.
Blinding of participants and personnel (performance bias)	Unclear risk of bias	There was insufficient information on how blinding was maintained.
Blinding of outcome assessment (detection bias)	Unclear risk of bias	There was insufficient information on how outcome assessor blinding was maintained.
Incomplete outcome data (attrition bias)	High risk of bias	Out of 83 in intervention group, only 82 were analysed for absolute and relative change in ppFEV$_1$, change in BMI and absolute change in

		body weight. 79 analysed for change in sweat chloride. Out of 85 in placebo group, only 84 were analysed for change in sweat chloride. No further explanations given for missing participants. Conflicting information between the clinicaltrials.gov website and the supplementary figures available in Munck's published paper. According to clinicaltrials.gov, 85 participants completed the placebo group treatment however according to the supplementary figures, only 84 participants completed the placebo treatment regimen.
Selective reporting (reporting bias)	Unclear risk of bias	Unable to access trial protocol.

		Munck's paper states that it would measure ECGs and vital signs, though these may have been measured, they are not stated in results or supplement regardless of if they were unremarkable or not. Also, clinicaltrials.gov states that "Time-to-first pulmonary exacerbation was planned to be estimated using Kaplan-Meier (KM) estimates. However, due to less than 50% of events, time-to-first event data was not estimated. Instead, number of participants with at least one pulmonary exacerbation event were collected and are reported", however there is a Kaplan-Meier Plot of Time to First Pulmonary Exacerbation Event in the supplementary figures of Munck's paper.

Other bias	Unclear risk of bias	Well-matched baseline characteristics. However, as it is stated that Vertex funded the study, it is unclear as to the extent to which they were involved in designing, writing up and publishing the report.

Table 20: Risk of bias assessments for NCT02070744[103]:

This study was an RCT examining tezacaftor-ivacaftor versus placebo in 40 participants aged 18 years and over who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Unclear risk of bias	Does not state method by which participants are randomised. Unable to access trial protocol.
Allocation concealment (selection bias)	Unclear risk of bias	Does not state method by which allocations are concealed.
Blinding of participants and personnel (performance bias)	Unclear risk of bias	States on clinicaltrials.gov that masking is triple (participant, care provider, investigator), although unable to access trial protocol to find exact method of blinding.
Blinding of outcome assessment (detection bias)	Unclear risk of bias	States on clinicaltrials.gov that masking is triple (participant, care provider, investigator), although unable to access trial protocol to find exact method of blinding.

Incomplete outcome data (attrition bias)	High risk of bias	One participant didn't complete an intervention group, and the reason given for this was 'randomized, but not treated', with no other information given. There were only 36 participants analysed out of 39 participants for absolute change in sweat chloride. No reasons given for missing participants.
Selective reporting (reporting bias)	Unclear risk of bias	Unable to access trial protocol to find initial outcomes set.
Other bias	Unclear risk of bias	Characteristics of participants generally well balanced (however, there were 14 females and 25 males- unable to determine if this gender imbalance impacted results). Unable to determine the extent to which the sponsor

		was involved in designing and conducting the trial.

Table 21: Risk of bias assessments for NCT02508207[104]:

This study was an RCT examining tezacaftor-ivacaftor versus placebo in 34 participants aged 18 years and over who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system (IWRS) was used to assign subjects to treatment using a list of randomization codes generated by a designated vendor. The only Vertex personnel involved in developing the randomization specifications and reviewing the dummy randomization code list was the Study Biostatistician (SB), who was blinded to the final randomization code list and the actual treatment assignments.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system (IWRS) was used to assign subjects to treatment using a list of randomization

		codes generated by a designated vendor.
Blinding of participants and personnel (performance bias)	Low risk of bias	Matched placebo - double-blind RCT. Blinding of treatment codes and applicable study data was maintained until the database was locked for the final analysis. The subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded with the exceptions to this clearly stated in trial protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	The subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded with the exceptions to this clearly stated in trial protocol.
Incomplete outcome data (attrition bias)	High risk of bias	Out of 27 participants in intervention group, only 23 were analysed for absolute

		change from baseline in sweat chloride at day 29. Due to lack of published paper, it was unclear as to why there were fewer participants analysed for this outcome.
Selective reporting (reporting bias)	Unclear risk of bias	Methods stated that 12-lead ECGs and vital signs would be measured, however exact values for the parameters used to assess safety and tolerability were not available in results, whether unremarkable or not.
Other bias	Unclear risk of bias	Characteristics of participants generally well balanced. Unable to determine the extent to which the sponsor was involved in designing and conducting the trial.

Table 22: Risk of bias assessments for NCT02730208[105]:

This study was an RCT examining tezacaftor-ivacaftor versus placebo in 41 participants aged 12 years and over who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system was used to assign subjects to treatment, with the randomisation code produced by Vertex Biostatistics or a qualified randomisation vendor. The Vertex study biostatistician was said to review and approve the production of the final randomisation list, which would then be reviewed and approved by an unblinded biostatistician, who was not a member of the study execution team.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used.

Blinding of participants and personnel (performance bias)	Low risk of bias	Matched placebo - double-blind RCT. The subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded with the exceptions to this clearly stated in trial protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	The subjects and all site personnel, including the investigator, the site monitor, and the study team, were blinded with the exceptions to this clearly stated in trial protocol.
Incomplete outcome data (attrition bias)	Low risk of bias	All randomised participants were analysed.
Selective reporting (reporting bias)	Unclear risk of bias	Methods states that ECGs and vital signs will be measured, however exact values for the parameters used to assess

		safety and tolerability were not available in results, whether unremarkable or not.
Other bias	Unclear risk of bias	Characteristics of participants generally well balanced. Unable to determine the extent to which the sponsor was involved in designing and conducting the trial.

Table 23: Risk of bias assessments for Schwarz 2021[106]:

This study was an RCT examining tezacaftor-ivacaftor versus placebo in 98 participants aged 12 years and over who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	Participants were stratified by age, sex and percent predicted FEV_1 and then randomised 1:1 to either TEZ/IVA or placebo. An interactive web response system was used for randomisation following a list of randomisation codes generated by a designated vendor.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used.
Blinding of participants and personnel (performance bias)	Low risk of bias	The subjects and site personnel, including the investigator, the site monitor, and the study team were blinded and exceptions are listed in the statistical analysis plan.

Blinding of outcome assessment (detection bias)	Low risk of bias	This was a double-blind RCT, with the use of a matched placebo. All study personnel were blinded to subject treatment, with the exceptions clearly stated in the trial protocol.
Incomplete outcome data (attrition bias)	Low risk of bias	All randomised participants were included in the analysis. There is discrepancy between clinicaltrials.gov and the published paper- according to clinicaltrials.gov, 1 person in the placebo group didn't complete the treatment regimen, however in the published paper, it states that 2 didn't. This, however, was not enough for the authors to raise the risk of bias.
Selective reporting (reporting bias)	Unclear risk of bias	States that study would measure vital signs, though these may have been

		measured, they are not stated in results or supplement regardless of if they were unremarkable or not.
Other bias	Unclear risk of bias	Baseline characteristics generally balanced (however, there were 61 females compared to 36 males- unclear as to how this gender imbalance may have affected results). Study states how Vertex Pharmaceuticals Incorporated participated in study, however the extent to which support was provided by the other funders is unclear.

Table 24: Risk of bias assessments for Stahl 2021[107]:

This study was an RCT examining lumacaftor-ivacaftor versus placebo in 51 participants aged 2 to 5 years old who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web or voice response system was used to assign subjects to treatment, with the randomisation code produced by Vertex Biostatistics or a qualified randomisation vendor. The Vertex study biostatistician was said to review and approve the production of the final randomisation list, which would then be reviewed and approved by an unblinded biostatistician, who was not a member of the study execution team.
Allocation concealment (selection bias)	Low risk of bias	An interactive web or voice response system was used.

Blinding of participants and personnel (performance bias)	Low risk of bias	This was a double-blind RCT with the use of a matched placebo. The subjects/caregivers and all site personnel, including the investigator and the study monitor, and the Vertex study team remained blinded to treatment assignments until database lock for Part 1 (i.e., database lock for data up to and including the Week 48 Visit) with the exceptions to this clearly stated in trial protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	The subjects/caregivers and all site personnel, including the investigator and the study monitor, and the Vertex study team remained blinded to treatment assignments until database lock for Part 1 (i.e., database lock for data up to and including the Week 48 Visit) with the exceptions to

		this clearly stated in trial protocol.
Incomplete outcome data (attrition bias)	High risk of bias	There were only 32 participants analysed out of 35 in the intervention group, and 15 out of 16 analysed in the placebo group for the absolute change from baseline in MRI global chest score at week 48 (no detail given as to why there were missing participants). There was also conflicting information regarding the number of participants analysed for outcomes between clinicaltrials.gov and the published paper.
Selective reporting (reporting bias)	Low risk of bias	All outcomes listed in protocol are reported in the full trial paper.
Other bias	Unclear risk of bias	Characteristics of participants generally well balanced (however, there were 18 females and 33 males- unable

		to determine if this gender imbalance impacted results). Unable to determine the extent to which the sponsor was involved in designing and conducting the trial.

Table 25: Risk of bias assessments for Wilson 2021[108]:

This study was an RCT examining lumacaftor-ivacaftor versus placebo in 70 participants aged 12 years and over who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web or voice response system was used to assign subjects to treatment, with the randomisation code produced by Vertex Biostatistics or a qualified randomisation vendor. The Vertex study biostatistician was said to review and approve the production of the final randomisation list, which would then be reviewed and approved by an unblinded biostatistician, who was not a member of the study team.
Allocation concealment (selection bias)	Low risk of bias	An interactive web or voice response system was used to assign subjects to treatment.

Blinding of participants and personnel (performance bias)	Low risk of bias	The subjects and all site personnel, including the investigator, the site monitor, and the study team were blinded. There is a clear statement of the exceptions to this in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	This was a double-blind randomised controlled trial, with the use of a matched placebo. The subjects and all site personnel, including the investigator, the site monitor, and the study team were blinded. There is a clear statement of the exceptions to this in the protocol.
Incomplete outcome data (attrition bias)	High risk of bias	A number of outcomes (including outcomes relevant to our review) reported data for fewer participants than the number assigned to that group. For example, only 30 out of 34 participants in the intervention group were

		analysed for both absolute and relative change from baseline in percent predicted forced expiratory volume in 1 second at week 24. No explanation was given for missing participants.
Selective reporting (reporting bias)	Unclear risk of bias	States in protocol that safety and tolerability assessments would be based on a number of parameters e.g. vital signs, though there are no exact values presented in results.
Other bias	Low risk of bias	Baseline characteristics generally well balanced (though there were 13 females compared to 21 males in the intervention group). Paper outlined the extent to which Vertex Pharmaceuticals Incorporated were involved (sponsor was involved in the study design and analysis and interpretation of the data, with collaboration from the

		authors. The sponsor helped develop the report with input, review, and approval from the authors).

Table 26: Risk of bias assessments for Barry 2021[65]:

This study was an RCT examining ETI versus either ivacaftor or tezacaftor-ivacaftor in 271 participants aged 12 years and over who were heterozygous for the F508del variant and either a gating or residual function variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system (IWRS) was used to assign subjects to treatment. The randomization code list will be produced by Vertex Biometrics or a qualified randomization vendor.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system (IWRS) was used to assign subjects to treatment.
Blinding of participants and personnel (performance bias)	Low risk of bias	All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the treatment codes. Individuals

		who may have been unblinded are outlined in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the treatment codes. Individuals who may have been unblinded are outlined in the protocol.
Incomplete outcome data (attrition bias)	Low risk of bias	All randomised participants were analysed and reasons were given in the supplementary materials as to why some participants discontinued in the trial at certain points. There appears to be missing data for exploratory endpoints e.g. absolute change in BMI, though the authors of the review decided that this does not raise the risk of bias.

Selective reporting (reporting bias)	Unclear risk of bias	Methods state that ECGs and vital signs will be measured, however these have not been stated in results, whether unremarkable or not.
Other bias	Unclear risk of bias	Characteristics of participants were generally well balanced; however, it is unclear as to the extent to which the sponsors were involved in designing, writing up and publishing the report.

Table 27: Risk of bias assessments for NCT02951182[109]:

This study was an RCT examining VX-440-tezacaftor-ivacaftor versus placebo in 47 participants aged 12 years and over who were either homozygous for the F508del variant or heterozygous for the F508del variant and a minimal function variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system (IWRS) was to be used to assign subjects to treatment. The randomization code list was to be produced by Vertex Biometrics or a qualified randomization vendor.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used to assign subjects to treatment.
Blinding of participants and personnel (performance bias)	Low risk of bias	This was a double-blind, placebo-matched randomised controlled trial. All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team were blinded to the treatment

		codes with the exceptions to this outlined in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team were blinded to the treatment codes with the exceptions to this outlined in the protocol.
Incomplete outcome data (attrition bias)	Low risk of bias	Not all of the participants who were randomised were analysed for Ctrough data, and there wasn't an explanation as to why these participants weren't included in the analysis. However, this wasn't an outcome for this review, so risk of bias is not increased.
Selective reporting (reporting bias)	Unclear risk of bias	Methods stated that ECGs and vital signs would be measured to assess safety and tolerability, however exact values for these measurements could not be

		found in results, whether unremarkable or not.
Other bias	Unclear risk of bias	There were 11 females and 62 males, and it was unclear as to whether this gender imbalance affected the results. Also, it was unclear as to the extent to which the sponsor was involved in designing and reporting the results from the trial.

Table 28: Risk of bias assessments for NCT02951195[110]:

This study was an RCT examining VX-152-tezacaftor-ivacaftor versus placebo in 34 participants aged 18 years and over who were heterozygous for the F508del variant and a minimal function variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system (IWRS) was to be used to assign subjects to treatment. The randomization code list was to be produced by Vertex Biometrics or a qualified randomization vendor.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used to assign subjects to treatment.
Blinding of participants and personnel (performance bias)	Low risk of bias	This was a double-blind randomised controlled trial. All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team were blinded to the treatment codes with the

		exceptions outlined in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	All subjects, site personnel (including the investigator, the site monitor, and the study team), and the Vertex study team were blinded to the treatment codes with the exceptions outlined in the protocol.
Incomplete outcome data (attrition bias)	Low risk of bias	There appears to be missing data for Ctrough values, with no explanation offered as to why certain participants have been missed. However, this is not an outcome for this review, and so this does not increase the risk of bias. Out of 46 participants enrolled in Part 2, 4 participants discontinued during the run-in period and were not randomised in the treatment period, without any further explanation given. However,

		part 2 of this study is not being included in this review, due to there being a washout period, and so this does not increase the risk of bias.
Selective reporting (reporting bias)	Unclear risk of bias	Protocol stated that safety and tolerability measurements would be based on ECGs and vital signs, and there aren't exact values for these in the results, whether they were unremarkable or not.
Other bias	High risk of bias	There are 4 participants with FEV_1 values that are less than 40 percent that appear to have been analysed, despite the inclusion criteria of the study stating that subjects must have an FEV_1 ≥40% and ≤90% of predicted normal for age, sex, and height at screening. Also, the extent to which the sponsor was involved in this

		trial is unclear due to the lack of a published paper.

Table 29: Risk of bias assessments for NCT03447249[111]:

This study was an RCT examining VX-659-tezacaftor-ivacaftor versus placebo in 385 participants aged 12 years and over who were heterozygous for the F508del variant and a minimal function variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system (IWRS) was to be used to assign subjects to treatment. The randomization code list was to be produced by Vertex Biometrics or a qualified randomization vendor.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used to assign subjects to treatment.
Blinding of participants and personnel (performance bias)	Low risk of bias	This was a double-blind, placebo matched, randomised controlled trial. All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the

		treatment codes. Individuals who may have been unblinded are listed in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were blinded to the treatment codes. Individuals who may have been unblinded are listed in the protocol.
Incomplete outcome data (attrition bias)	High risk of bias	Three participants who were enrolled in the study were not dosed in TC treatment period (and it was unclear as to why this was the case). Five participants in the placebo group did not complete the regimen, and the reason for three of these participants is listed as 'other', with no further detail given. It is unclear as to why the 'safety set' for both the placebo and

		treatment groups was 189 and 193 participants respectively, though 190 and 192 started each regimen. It is unclear as to the number of participants who would be evaluable for the absolute change in BMI Z-score for participants <=20 years of age at baseline (from baseline at week 24). Also, the number of participants who were analysed for the PK outcome for each measurement was smaller than the overall number of participants in the treatment group, with no explanation as to why this was the case. However, this alone did not raise the risk of bias, as the measurement of PK values is not an outcome for this review.
Selective reporting (reporting bias)	Unclear risk of bias	It is stated in the study that ECGs and vital signs would be measured. Although these may have been measured, they are

		not stated in the results, regardless of if they were unremarkable or not.
Other bias	Unclear risk of bias	The characteristics of the participants are generally well balanced, though it is unclear as to the extent to which the sponsor was involved in designing and reporting the trial results.

Table 30: Risk of bias assessments for NCT03460990[112]:

This study was an RCT examining VX-659-tezacaftor-ivacaftor versus tezacaftor-ivacaftor in 116 participants aged 12 years and over who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system (IWRS) was to be used to assign subjects to treatment. The randomization code list was to be produced by Vertex Biometrics or a qualified randomization vendor.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used to assign subjects to treatment.
Blinding of participants and personnel (performance bias)	Low risk of bias	This was a double-blind study. All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were to be blinded to the treatment codes. Individuals

		who may have been unblinded are listed in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were to be blinded to the treatment codes. Individuals who may have been unblinded are listed in the protocol.
Incomplete outcome data (attrition bias)	High risk of bias	For certain Ctrough measurements, there appears to be fewer participants analysed at specified time points than the overall number of participants who were randomised, without any further explanation as to why this was the case. Though this alone did not increase the risk of bias for this review, there were also five participants who were included in the run-in period but not dosed in the TC

		treatment period, without any further explanation as to why this was the case.
Selective reporting (reporting bias)	Unclear risk of bias	The trial protocol states that safety and tolerability assessments would be based on ECGs and vital signs. There aren't exact values recorded of these in the results, whether they were unremarkable or not.
Other bias	Unclear risk of bias	The characteristics of participants are generally well-balanced, though it is unclear (due to the lack of a published paper) as to the extent to which the sponsor was involved in designing and reporting the trial.

Table 31: Risk of bias assessments for Sutharsan 2021[113]:

This study was an RCT examining ETI versus tezacaftor-ivacaftor in 176 participants aged 12 years and over who were homozygous for the F508del variant.

Type of bias	Risk of bias	Support for judgement
Random sequence generation (selection bias)	Low risk of bias	An interactive web response system (IWRS) was to be used to assign subjects to treatment. The randomization code list was to be produced by Vertex Biometrics or a qualified randomization vendor.
Allocation concealment (selection bias)	Low risk of bias	An interactive web response system was used to assign subjects to treatment.
Blinding of participants and personnel (performance bias)	Low risk of bias	This was a double-blind study. All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were to be blinded to the treatment codes. Individuals

		who may have been unblinded are listed in the protocol.
Blinding of outcome assessment (detection bias)	Low risk of bias	All subjects (and their parents/caregivers/companions), site personnel (including the investigator, the site monitor, and the study team), and members of the Vertex study team were to be blinded to the treatment codes. Individuals who may have been unblinded are listed in the published protocol (clinicaltrials.gov).
Incomplete outcome data (attrition bias)	Low risk of bias	All randomised participants were analysed.
Selective reporting (reporting bias)	Unclear risk of bias	The methods of the study state that ECGs and vital signs would be measured, however the exact values of the parameters used to measure safety and tolerability are not provided, whether unremarkable or not.
Other bias	Unclear risk of bias	The characteristics of participants are generally well

		matched. However, it is unclear as to the extent to which the sponsor was involved in designing the trial and publishing the report.

4. Summary of monotherapy results

No new monotherapy studies were identified in the update of the Cochrane systematic review. I will therefore summarise the main findings of the last version of the review below[2]:

Primary outcomes

1) Survival

There were no recorded deaths in any of the studies.

2) Quality of life

a) Total QoL score

This data was not recorded by any of the included studies.

b) Different sub-domains

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

Across all doses of lumacaftor (25 mg, 50 mg and 200 mg), participants had significantly lower CFQ-R scores in all domains when compared with participants in the placebo groups (CLANCY 2012).[115] There was no difference found between participants taking cavosonstat and participants in the placebo group for both CFQ-R respiratory and eating domain scores (DONALDSON 2017).[117]

When looking at FDL169 when compared to placebo, participants taking both 400 mg (n=6) and 800 mg (n=8) had CFQ-R respiratory domain scores that favoured the intervention

groups, MD 5.09 (95% CI -2.72 to 12.90) and MD 8.84 (95% CI 1.40 to 16.28) respectively. No difference was found between the 600 mg and placebo groups, MD -4.33 (95% CI -12.01 to 3.35) (HORSLEY 2017).[118]

3) Physiological measures of lung function

a) FEV_1 (relative change from baseline)

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

Lumacaftor, N6022 and cavosonstat were all trialled for this outcome, and there was no difference found between any of the intervention groups, at any drug dose, and the placebo groups (CLANCY 2012, DONALDSON 2014, DONALDSON 2017).[115-117]

b) FEV_1 (absolute values)

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

For both of the studies looking at lumacaftor and cavosonstat respectively, there were no differences found between treatment and placebo groups for this outcome (BOYLE 2014, DONALDSON 2017).[114, 117]

When comparing FDL169 to placebo, in the 400 mg group (n=6), there was a larger increase than in the placebo group (n=7), MD 4.68 (95% CI 0.12 to 9.24). In both the 600 mg (n=6) and 800 mg (n=8) groups, there were no differences between the intervention and placebo groups, MD 2.80 (95% CI -1.82 to 7.42) and MD 0.68 (95% CI -3.80 to 5.16) respectively (HORSLEY 2017).[118]

c) FVC

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

There were no differences found between the cavosonstat group and the placebo group in the study (n=51) reporting on this outcome (DONALDSON 2017).[117]

d) LCI

This outcome was not reported by any of the studies.

e) Other relevant physiological measures of lung function

No study reported on any other measures of lung function.

Secondary outcomes

1) Adverse effects

Lumacaftor- there were no significant differences found between the number of participants experiencing adverse events in the lumacaftor and placebo groups (BOYLE 2014, CLANCY 2012).[114, 115]

N6022- there were no significant differences found between the number of participants experiencing adverse events in the N6022 and placebo groups (DONALDSON 2014).[116]

Cavosonstat- there were no significant differences found between the number of participants experiencing adverse events in the cavosonstat and placebo groups. All of the adverse events that occurred in the study of this drug were deemed to be mild or moderate in severity (DONALDSON 2017).[117]

FDL169- there were no significant differences found between the number of participants experiencing adverse events in the FDL169 and placebo groups (HORSLEY 2017).[118]

CPX- there were no significant differences found between the number of participants experiencing adverse events in the CPX and placebo groups (MCCARTY 2002).[119]

4BPA- there were no significant differences found between the number of participants experiencing adverse events in the 4BPA and placebo groups (RUBENSTEIN 1998, ZEITLIN 2002).[120, 121]

2) Hospitalisation

This outcome was not reported by any of the studies.

3) School of work attendance

This outcome was not reported by any of the studies.

4) Extra courses of antibiotics

b) Time-to the next course of antibiotics

This outcome was not reported by any of the studies.

b) Total number of courses of antibiotics

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

Lumacaftor- there were no significant differences found between the number of participants experiencing pulmonary exacerbations in the lumacaftor and placebo groups (BOYLE 2014, CLANCY 2012).[114, 115]

FDL169- In this Phase 1 study, three participants had an infective respiratory exacerbation, though it was unclear as to whether this was physician- or protocol-defined. There were no participants in the 400 mg group (n=6) who experienced an exacerbation, one participant had an exacerbation in the 600 mg group (n=6), as did one participant in the 800 mg group (n=8). Finally, one participant in the placebo group (n=7) experienced an exacerbation (HORSLEY 2017).[118]

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

Lumacaftor- in one study (n=89), there were reductions found in the sweat chloride concentrations for the participants taking 25 mg, 50 mg, 100 mg and 200 mg lumacaftor at day seven when compared with placebo. There were no significant differences found at 28 days in the participants taking 25 mg and 50 mg lumacaftor respectively when compared to placebo. At one month, there were significant differences found, when compared to placebo, in participants taking 100 mg lumacaftor, MD -6.13 (95% CI -12.25 to -0.01) and 200 mg lumacaftor, MD -8.21 (95% CI -14.30 to -2.12) (CLANCY 2012).[115] In the second study, at day 14, there was no

significant difference found in results between participants taking 200 mg lumacaftor and participants in the placebo group, MD -2.75 (95% CI -7.65 to 2.15) (BOYLE 2014).[114]

Cavosonstat- in the study (n=51) looking at this outcome, there was no significant difference found between the sweat chloride concentrations of the participants in the cavosonstat and placebo groups, MD -3.30 (95% CI -9.13 to 2.53) (DONALDSON 2017).[117]

FDL169- there were no differences found between the sweat chloride concentrations of the participants taking 400 mg (n=6) and placebo (n=7), MD 2.47 (95% CI -4.47 to 9.41) and 800 mg (n=8) and placebo, MD 3.48 (95% CI -3.35 to 10.31). There was a larger reduction in sweat chloride found in the placebo group than in the 600 mg group (n=6), MD 8.07 (95% CI 0.98 to 15.16) (HORSLEY 2017).[118]

CPX- there were no significant differences found between participants in the CPX and placebo groups for the reduction in sweat chloride concentrations (MCCARTY 2002).[119]

4BPA- there were no significant differences found between participants in the 4PBA groups and placebo groups for the reduction in sweat chloride concentrations (RUBENSTEIN 1998, ZEITLIN 2002).[120, 121]

6) Radiological measures of lung disease

This outcome was not reported by any of the studies.

7) Acquisition of respiratory pathogens

b) *P aeruginosa*

This was an outcome in the 4PBA study, but results were not reported (ZEITLIN 2002).[121]

8) Eradication of respiratory pathogens

This outcome was not reported by any of the studies.

9) Nutrition and growth

This outcome was not reported by any of the studies, either in terms of weight, BMI or height.

Figure 5: FEV_1 % predicted (relative change from baseline) for tezacaftor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone.[101, 102, 106, 122, 124]

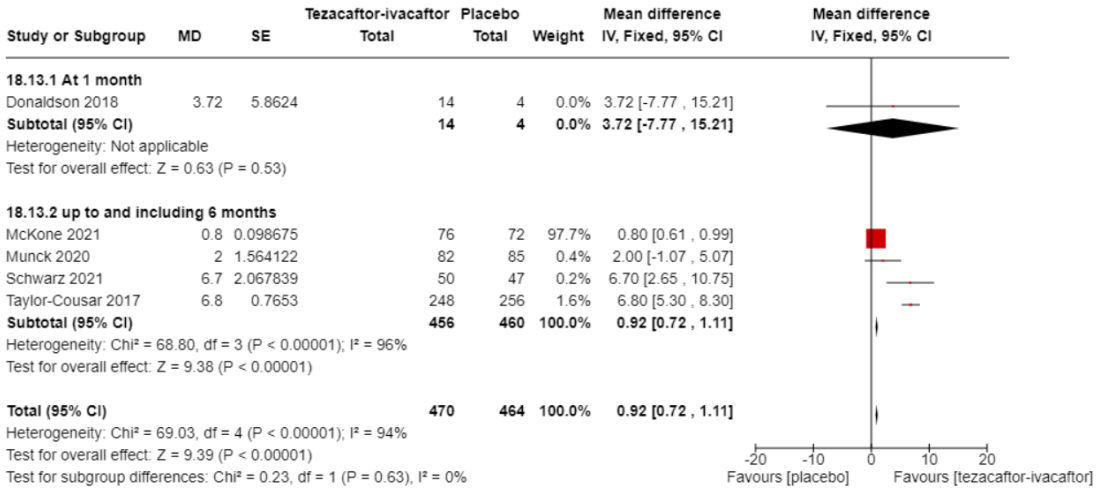

Figure 6: FEV_1 % predicted (absolute change from baseline) for tezacafor (100 mg once daily) plus ivacaftor (150 mg twice daily) versus either placebo or ivacaftor (150 mg twice daily) alone.[101, 102, 104, 106, 122, 124]

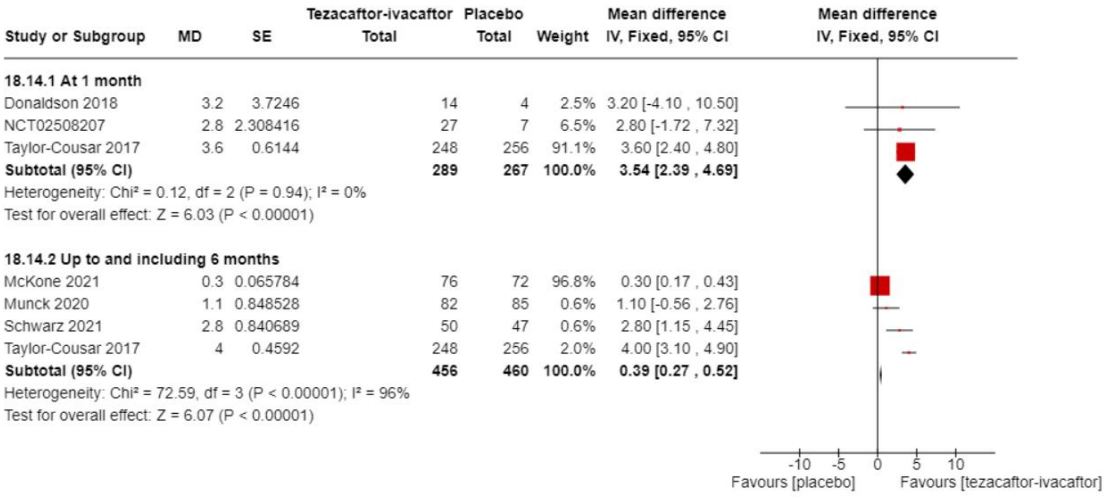

Figure 7: Quality of life – CFQ-R respiratory domain (absolute change from baseline) for lumacaftor (400 mg twice daily) plus ivacaftor (250 mg twice daily) versus placebo.[108, 125]

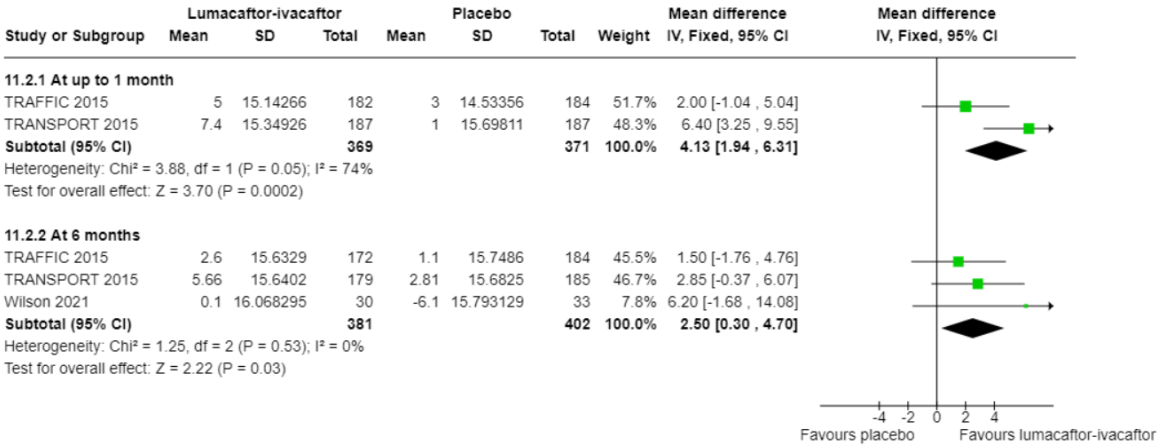

Figure 8: Sweat chloride (absolute change from baseline) for VX-440 (600 mg twice daily) plus tezacaftor (50 mg twice daily) plus ivacaftor (300 mg twice daily) versus placebo.[109]