CFTR therapy

CFTR modulators therapy

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Background

Care guidelines for Cystic Fibrosis (CF) patients have focused, in the past, only on the secondary pathophysiological effects of the CFTR dysfunctional protein; however, over the last 30 years, specific drugs aimed at the basic defect have been researched and discovered

Cystic Fibrosis is caused by genetic mutations in the CF Transmembrane Conductance Regulator (CFTR), a channel-protein responsible for the exchange of chloride and bicarbonate across the apical membrane of the epithelial cells.

More than 2000 mutations in the CFTR gene are known, which cause the channel to work improperly, either affecting the amount of protein that reaches the cell surface or the function of the protein itself at the cell surface. CFTR mutations have been divided into six different classes: impaired biosynthesis (class I); defective protein maturation and accelerated degradation (class II); defective regulation of CFTR at the plasma membrane (class III); defective chloride conductance (class IV); diminished CFTR transcription (class V) and accelerated turnover at the cell surface (class VI).

A drug discovery program has been developed to investigate the molecular and cellular basis of CFTR mutations and to design effective treatments to enhance CFTR intracellular trafficking (**correctors**), CFTR ion channel function (**potentiators**) and to increase the amount of CFTR protein at the cell surface, making more CFTR available for other CFTR modulators to work on **(amplifiers).** Regarding **correctors**, new research (Veit G, 2018) focused on "repairing" each phase of the CFTR expression and function, has postuleted that compounds targeting distinct structural defects of CFTR can synergistically rescue it. High-throughput cell-based screens and mechanistic analysis identified three small-molecule series that target CFTR defects: C1 -type correctors, C2-type correctors and C3-type correctors. The approach currently tailored to a specific functional class of mutations, could be, in the future, further refined at individual levels by exploiting recent advances in ex vivo drug testing methods (Ikpa PT, 2014), (Martiniano SL, 2016), (Beekman JM, 2016), (Pranke IM, 2017).

It has been affirmed (Amaral MD, 2015), (Clancy JP, 2018) (Lommatzsch ST, 2019), (De Boeck K, 2020) (Goetz DM, 2021) (Fajac I, 2022) that in the near future, early introduction of next generation CFTR protein modulators may, for the first time, offer the CF community a future in which CF is no longer the most common lethal autosomal recessive disease in Caucasian individuals, but a chronic disease with a normal life expectancy.

Up to now, however, it is important to note that more than 10% of CFTR patiens (Desai M, 2022) have ineligible mutations for the new therapy and need alternative approaches to restoring CFTR function (Fajac I, 2021) (Despotes K, 2022), (Deletang K, 2022) (Lee RE, 2022) In 2018, an International Project by the Clinical Trial Network of European CF Society started to classify CF patients on the basis of the intestinal organoids' response to different CFTR-modulators. In the same year, the Cystic Fibrosis Foundation (CFF) organized a workshop of international experts to discuss the use of preclinical model systems (CFTR modulators theratyping) to examine the nature of CF-causing variants in CFTR and the role of in vitro CFTR modulator testing and to obtain information for the in vivo modulator use. (Clancy JP, 2019).

Recently data about effectiveness and safety in children (Li Q, 2022), in extrapulmonary clinical problems (Hasan S, 2022), (McKay I, 2022) and on pregnancy (Goss CH,2016), (Heltshe SL, 2017), (Jain R,2022) are investigated.

Moreover issues associated with the new therapy are discussed (Mayer-Hamblett N, 2016): the need of new biomarkers to valuate efficacy and tolerability of modulators (K De Boeck, 2014); difficulties to organize placebo-controlled trials (VanDevanter DR, 2017); the possibility that chronic treatments with CFTR modulators might have unexpected effects that cannot be predicted from short-term studies (Cholon DM, 2014) (Dagenais RVF, 2020); the clinical and ethical dilemmas about the high price of these drugs (Jones AM, 2015), and the possible disparities in access to high-quality specialized care (Burgel PR, 2022);

The potentiator **VX-770** (Ivacaftor: **Kalydeco**Ô by Vertex Pharmaceuticals) has been the first CFTR modulator able to demonstrate to be effective in CF.

Other compounds are available for CF patients:

The corrector **VX-809** (**Lumacaftor**) in combination with **VX-770** (**ORKAMBI**™ by Vertex Pharmaceuticals) to treat patients with two copies of the F508del mutation.

The corrector **VX-661 (Tezacaftor)** in combination with **VX-770** (**SYMDEKO**™ or **SYMKEVI** ™by Vertex Pharmaceuticals) to treat patients who have two copies of the F508del mutation, or who have at least one mutation that is responsive to treatment with SYMDEKO: 711+3AàG; A455E; D579G; E193K; K1060T, R117C, S945L, 2789+5G?A, A1067T, D1152H, E831X, L206W, R347H, S977F, 3272-26A?G, D110E, D1270N, F1052V, P67L, R352Q, 3849+10kbC?T, D110H, E56K, F1074L, R74W, R1070W.

The corrector **VX-445 (Elaxacaftor)** in combination with **VX-770** e **VX-661(TRIKAFTA**™ by Vertex Pharmaceuticals) to treat patients who have at least one copy of the F508del mutation.

In 2018 (Ren CL, 2018) the Cystic Fibrosis Foundation has published recommendations about CFTR modulators in CF patients

Up to now:

In United States **KALIDEKO™** has been approved by **FDA** for patients from the age of ³ 4 months with selected class III gating

mutations, with R117H mutation and with 28 residual function mutations. The European Medicines Agency **(EMA)** has approved KALIDEKO in patients aged ³ 4 months who have class III gating mutations and for patients with R117H mutation. In Italy, the Italian Agency for drugs **(AIFA)** has approved KALIDEKO in patients aged ³ 12 months who have class III gating mutations and for patients aged ³ 18 years with R117H mutation.

ORKAMBI™ has been approved for people ³ 2 years old with two copies of the F508del mutation by FDA, EMA and AIFA

SYMDEKO™ or **SYMKEVI™** has been approved to treat patients with either two copies of the F508del mutation or at least one mutation that is responsive to this combination for patients 6 years of age or older by FDA and EMA. AIFA has approved **SYMKEVI™** for patients 12 years of age or older with either two copies of the F508del mutation or one F508del mutation and one Residual Function mutation.

TRIKAFTA™ (KAFTRIO™) has been approved by FDA and EMA and AIFA for people ages 6 years and older, who have at least one copy of the F508del mutation.

These data are summerized in the Italian Cystic Fibrosis Foundation website (Stato regolatorio farmaci CFTR modulators)

In the Drug Development Pipeline 2022 of the CFFoundation , besides **Kalydeco**, **Orkambi**, **Symdeko** and **Trikafta**, already available for the patients**, 16** compounds are taken into consideration regarding to restore CFTR function:

One in phase 3:

VX 121(a new CFTR corrector)/**TEZA**/**VX561**(formerly CTP-656:an altered form of potentiator Kalideko),

Three in phase 2:

ABVV-2222 (formerly GLPG2222, a CFTR corrector /**ABBV-3067** (a CFTR potentiator)/ **ABVV576** (a CFTR corrector)

ELX-02 (designed to restore CFTR function in non sense mutations),

VX-561 (deutivacaftor, a new CFTR potentiator).

Two in phase one:

AD710 (adenoassociated virus vector for gene delivery)

VX- 522 (inhaled messanger RNA therapy)

Twelve in pre-clinical phase

Issues

Safety and efficacy of corrective treatments applicable to all patients irrespective of mutations

Identification of CFTR correctors or potentiators and related mutation targets

Features of CF candidates for therapy with CFTR modulators

Impact of CFTR modulators on clinical outcomes (respiratory condition, quality of life, survival, nutritional parameters, sputum, radiological features)

Sensitive and specific surrogate biomarkers to investigate the efficacy of CFTR modulators

Safety of CFTR modulators, especially on a long term basis.

What is known

In 1998 (Rubenstein RC,1998) a RCT showed that **4-Na-phenylbutyrate** had induced partial restoration of CFTR function in the nasal epithelia of deltaF508-homozygous CF patients.

One RCT, published in 2002, (Zeitlin PI,2002) studied the safety and efficacy of three doses **of 4-phenylbutyrate** in 19 **F508del homozygous** patients; the minimum tested dose (20 mg) showed good tolerability and a significant induction of chloride transport.

One RCT, published in 2003 (Wilschanski M, 2003), showed that **gentamicin** treatment had caused a significant reduction in basal potential difference in the 19 patients carrying stop mutations both in patients who were homozygous for stop mutations and in those who were heterozygous, but not in patients who were homozygous for DeltaF508.

One RCT, published in 2010, (Sermet-Gaudelus I, 2010) studied the safety and efficacy of **Ataluren (PTC124)** in 30 CF patients with a nonsense mutation (class I mutations) in at least one allele: a significant induction of chloride transport was demonstrated on NPD and the drug was well tolerated

In May 2014 (Kerem E,2014) a study about **Ataluren** for the treatment of patients with nonsense-mutation has been published:

Atalauren did not improve lung function in the studied patients, but it has been speculated that the drug might be beneficial for patients not taking chronic inhaled tobramycin.

In november 2017 a Cochrane Review (Aslam AA,2017) about this topic has included two parallel randomised controlled trials in which **Ataluren** was compared to placebo for a duration of 48 weeks in 238 participants (age range 6 to 53 years). It has been concluded that there is, currently, insufficient evidence to determine the effect of Ataluren as a therapy for people with class I mutations.

In march 2020 a RCT (Konstan MW, 2020) showed that neither ppFEV1 change nor pulmonary exacerbation rate over 48 weeks were statistically different between **Atalauren** treatment group and placebo groups and stated that development of a nonsense-mutation CF therapy remains elusive.

In 2012 a RCT about of the impact of **miglustat** (Leonard A,2012) did not show any significant changes in the total chloride secretion assessed by nasal potential difference, in sweat chloride or in lung function values.

In 2021 (Derichs N, 2021) a multicenter phase 2 study about **Riociguat** therapy in **F508del homozygous** patients was terminated due to lack of efficacy and the changing landscape of CF therapeutic development.

In 2010 an observational study (Accurso FJ,2010) showed that **VX-770 (Ivacaftor)** was associated with within-subject improvements in CFTR and lung function in patients with at least one **G551D**-CFTR mutation.

In 2011 a multicenter RCT (Ramsey BW,2011) demonstrated that **Ivacaftor** in patients with **G551D** mutation improved lung function at 2 weeks and sustained through 48 weeks. Substantial improvements were also observed in the risk of pulmonary exacerbations, patient-reported respiratory symptoms, weight, and concentration of sweat chloride.

In 2013 a RCT (Davies JC, 2013) in patients with CF **aged 6-11 years** with a **G551D**-CFTR mutation on at least one allele, **Ivacaftor** demonstrated to be safe and able to improve pulmonary function, weight, and CFTR activity also in patients who are younger and healthier than those in previously studied populations.

In the same year a RCT (Davies J,2013) showed that in patients aged 6 years or older who have at least one **G551D**-CFTR allele, **Ivacaftor** led to improvements in **Lung Clearence Index**, that can be a more sensitive alternative to FEV1 in detecting response to intervention in these patients with mild lung disease.

In March 2014 (Barry PJ,2014) **Ivacaftor** has demonstrated clinical improvements in CF patients with **G551D** mutation and **FEV1 lower than 40% and/or lung transplant listing.**

Ivacaftor clinical efficacy in patients with **G551D** mutation was stated, in 2014, by a **Health Tecnology Assessment**,(Whiting P,2014) even if the high cost and the lack of data about long-term effectiveness have been stressed.

In 2015 (Konstan MV, 2015) a **post-hoc analysis** suggested that the majority of patients with **G551D**-CFTR and clinical characteristics similar to those present in patients enrolled in the previous phase 3 RCT could benefit from **Ivacaftor** therapy.

In 2012, a phase 2 RCT study Flume PA, 2012 showed that **Ivacaftor** alone is not an effective therapeutic approach for patients who are **homozygous for F508del-CFTR**.

In 2014 (De Boeck K,2014) RCT showed that eight weeks of **Ivacaftor**, in patients with **selected non-G551D gating mutations**, resulted in significant improvements in lung function, nutritional status, sweat chloride, and CFQ-R scores.

In July 2015**, Ivacaftor** has shown (**Moss RB,2015**) a significant improvement in sweat chloride values and CFQ-R respiratory domain scores in adult patients with R117H (Arg117His) mutation.

In 2017**(Mc Garry ME, 2017)** A RCT showed that **Ivacaftor** is able to decrease sweat chloride concentration in patients with residual CFTR function mutation.

In 2018 (Rosenfeld M,2018) a phase 3 single-arm study (ARRIVAL study) **Ivacaftor** was generally safe and well tolerated in children aged **12 to <24 months** for up to 24 weeks and was associated with rapid and sustained reductions in sweat chloride concentrations. Improvements in biomarkers of pancreatic function suggest that ivacaftor preserves exocrine pancreatic function if started early. The study is continuing in infants younger than 12 months.

A **Cochrane review** (Skilton M, 2019) evaluated existing RCTs on potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. The authors concluded that there is no evidence supporting the use of **Ivacaftor** in people with the F508del mutation. Both G551D phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes at 24 and 48 weeks in adults and children (over six years of age) with CF. The R117H trial demonstrated an improvement in the respiratory QoL score, but no improvement in respiratory function. As new mutation?specific therapies emerge, it is important that trials examine outcomes relevant to people with CF and their families and that adverse events are reported robustly and consistently. Post?market surveillance is essential and ongoing health economic evaluations are required.

In 2020 a RCT (Kerem E, 2020), showed that in CF people **aged ?6 years** with a **3849+10kb C ?T or D1152H mutation**, **Ivacaftor** treatment improved clinical endpoints vs placebo and that the organoid assay may assist in identification of ivacaftor-responsive mutations but did not predict magnitude of clinical benefit.

In 2012 (Clancy JB,2012) **VX-809 (Lumacaftor)** a CFTR corrector showed in a phase II study to have a similar adverse event profile to placebo for 28 days in **F508del-CFTR homozygous** patients, and demonstrated biological activity with positive impact on CFTR function in the sweat gland.

In 2014, (Boyle MP, 2014) in a phase II RCT**, a combination therapy (ORKAMBI)** of **Lumacaftor**) combined **with Ivacaftor**, was studied in subjects **Homozygous and Heterozygous for F508del**. The results supported a further exploration of the combination therapy as a treatment in this setting.

In 2015, two (TRAFIC and TRANSPORT) phase 3 RCT (Wainright CE,2015) have shown that **ORKAMBI**, in patients 12 years of age or

older **homozygous for F508del**, provided a benefit in terms of lung function and rate of pulmonary exacerbations.

In 2016, a pooled analysis (Elborn JS,2016) of the two trials, in which efficacy and safety data have been considered in subgroups based on baseline ppFEV1, confirmed that **ORKAMBI** benefits patients with cystic fibrosis **homozygous for Phe508del** CFTR who have varying degrees of lung function impairment.

In 2017 a phase III extension study (Konstan MW,2017) demonstrated that the long-term safety profile of **ORKAMBI** in **homozygous for Phe508del** was consistent with previous RCTs. Benefits continued to be observed with longer-term treatment: ORKAMBI was associated with a 42% slower rate of ppFEV1 decline than in matched registry controls.

An RCT published in 2017 (Ratjen F, 2017) regarding treatment with **ORKAMBI** revealed that this combination was associated with statistically significant improvements in lung function, as measured by Lung Clearence Index lung funcion in patients aged **6–11 years homozygous for *F508del-CFTR***.

In 2017 **ORKAMBI** therapy has been proved (Rowe SM, 2017) to improve sweat chloride and respiratory symptom scores in patients **Heterozygous for F508del**, even if no meaningful benefit was seen in ppFEV1 or body mass index .

About ORKAMBI some concerns have been emerged, in observational studies, about relatively high rate of drug intolerance, above all in patients with more advanced lung disease (Jennings MT, 2017).

In 2018 a post hoc analyses of pooled phase III data (McColley SA, 2018) showed that **ORKAMBI** significantly reduced pulmonary exacerbations even in patients **homozygous for Phe508del** without early lung function improvement.

An open-label Phase 3 study (McNamara JJ, 2019) showed that **ORKAMBI** was safe and well tolerated in children aged **2-5 years homozygous for *F508del-CFTR*** for 24 weeks. Efficacy findings also suggested that early intervention with **ORKAMBI** has the potential to modify the course of disease.

In 2021 a phase 4 trial (Wilson J, 2021), has studied the impact of **ORKAMBI** on exercise tolerance in CF patients **? 12 years** of age and **homozygous for F508del- CFTR**. It has been not able to show a significant impact of **ORKAMBI** therapy if compared with placebo.

In 2021, an exploratory study (Berkers G, 2021) based on organoid response in A455E-CFTR patients, did not show a statistically difference between **ORKAMBI** and placebo.

In 2017 an RCT (Taylor-Coursar JL, 2017) showed that **VX-661(Tezacaftor)/Ivacaftor combination therapy (SIMDEKO)** in **F508del homozigous patients** aged 12 years and old showed to be efficacious and safe.

In 2017 (Donaldson SH,2017) SIMDEKO tested in F508del homozigous patients and in F508del/G551D patients resulted in sweat chloride decrease and lung function increase in both patient groups.

In 2020 (McKone EF, 2020) a phase 3, randomized, double-blind, parallel-group study to evaluate SIMDEKO in people with cystic fibrosis heterozygous for F508del-CFTR and a gating mutation, demonstrated clinical efficacy, even if not significantly greater than IVA alone in participants ?12 years of age.

In 2020 (Munck A, 2020) a phase 3 RCT evaluated efficacy, safety, tolerability and phamacokinetics of SIMDEKO in patients ? 12 years of age and of age heterozygous for the F508del-CFTR mutation and a minimal function mutation (F/MF) and did not show a clinically meaningful benefit in participants.

In 2021 (Flume PA, 2021) an open-label extension study (EXTEND) showed SIMDEKO clinical benefit of long-term treatment for people aged 12 years or older homozygous for the Phe508del CFTR mutation or heterozygous for the Phe508del mutation and a residual fuction mutation.

In 2021 (Davies JC, 2021) a phase 3, double bind, parallel-group study, showed that **SIMDEKO** improved lung function (assessed by LCI) and sweat cloride concentration in people 6-11 years of age, homozygous for the Phe508del CFTR mutation or heterozygous for the Phe508del mutation and a residual fuction mutation. No safety concerns were found.

A Cochrane Review (Southern SW, 2018) concluded that in CF patients **Homozigous for F508del** there is insufficient evidence that **monotherapy** with CFTR modulators mutation has clinically important effects. Otherwise combination therapies (**ORKAMBI and SIMDEKO**) have similar small improvements in clinical outcomes: quality of life has moderate-quality evidence; respiratory function has high-quality evidence; lower pulmonary exacerbation rates have moderate-quality evidence. ORKAMBI is associated with an increase in early transient shortness of breath and longer-term increases in blood pressure; these effects were not observed for SIMDEKO, but safety data for children under 12 years of age are not available. In this age group, lumacaftor /vacaftor had an important impact on respiratory function with no apparent immediate safety concerns, but this should be balanced against the increase in blood pressure and shortness of breath seen in longer-term data in adults when considering this combination for use in young people with CF.

In 2018 (Keating D, 2018) a phase 2 RCT with a **triple combination of VX445 (Elaxacaftor)/Teza/Iva** (**TRIKAFTA**™ or **KALIDEKO** ™) in **F508del/F508del and F508del/Minimal Function (MF)** CFTR mutation patiens resulted in increased CFTR function in vitro and translated to improvements in enrolled patients. In both groups sweat chlroide resulted decreased and the respiratory domain score of the CFQ-R questionnaire improved.

In 2019 (Heijerman HGM, 2019) a Phase 3 RCT has showed that **TRIKAFTA** is able to provide clinically robust benefit compared with tezacaftor plus ivacaftor alone, with a favourable safety profile in people with cystic fibrosis who are homozygous for the F508del mutation.

In 2019 (Middleton PG, 2019) another Phase 3 study, has showed that **TRIKAFTA** was efficacious also in patients with Phe508del and minimal function genotypes, in whom previous CFTR modulator regimens were ineffective.

In 2021 interim results from an Open-Label Phase 3 Clinical Trial (Griese M, 2021) validated the durability of **TRIKAFTA** efficacy responses, with no emerging safety concerns, in the CF patients previously enrolled in the phase 3 RCTs and evaluated in a

longer follow-up period.

In 2021 **TRIKAFTA** demonstated (Barry PJ, 2021) to be efficacious and safe in patients with *Phe508del*-gating or *Phe508del*-residual function genotypes and to confer additional benefit relative to previous CFTR modulators

In 2021 (Nichols DP, 2021) **TRIKAFTA** in the post-approval study PROMISE, about the broad effects of the clinical use through 30 months , confirmed improvements in lung function respiratory symptoms and BMI. A significant reduction in sweat chloride concentration has been been also observed.

In 2021 (Taylor-Cousar J, 2021) a retrospective survey about pregnancy and infant outcomes in CF women who used **TRIKAFTA** during pregnancy and/or lactation, has been published.

Data about 45 **TRIKAFTA** exposed pregnancies, showed complications in 2 mothers and 3 infants rated by clinicians as unknown relatedness to **TRIKAFTA** therapy.

In 2022 (Mall MA,2022) a RCT demonstrated that **TRIKAFTA,** in children **6 Through 11 Years** of Age with **F508del/Minimal Function** CFTR mutation, shows significant improvements in lung condition and was safe and well tolerated.

In 2022 (Berg P, 2022) a single center study observed that TRIKAFTA is effective in restoring renal CFTR funtion, likely resulting in decreased risk for elocrolyte disorders and metabolic alkalosis

The RECOVER study (McNally P, 2023) investigated the improvement in lung clearance index and chest CT scores with Elexacaftor/Tezacaftor/Ivacaftor treatment in people with cystic fibrosis aged 12 years and older. 117 people with CF aged 12 and above were recruited to the study. The study was conducted in seven sites in Ireland and the UK. 12 years and older homozygous for the F508del mutation (F508del/F508del)) or heterozygous for F508del and a minimum function mutation (F508del/MF) were recruited prior to starting ETI and followed up over 12 months. Significant improvements were seen in LCI (-2.5, 95%CI -3.0, -2.0) and ppFEV1 (8.9, 95%CI 7.0 - 10.9), ppFVC (6.6, 95%CI 4.9 - 8.3) and ppFEF25-75% (12.4, 95%CI 7.8 - 17.0). Overall PRAGMA-CF scores reflecting airways disease (-3.46 , 95%CI -5.23 , -1.69). Scores for trapped air, mucus plugging and bronchial wall thickening improved significantly, but bronchiectasis scores did not. Sweat chloride levels decreased in both F508del/F508del (-43.1, 95%CI -47.4, -38.9) and F508del/MF (-42.8, 95%CI -48.5, -37.2) groups. CFQ-R Respiratory Domain (RD) scores improved by 14.2 points (95%CI 11.3, 17.2). At one year, sweat chloride levels were significantly lower in the F508del/F508del group compared to the F508del/MF group (33.93 v. 53.36, p<0.001). In conclusion ETI is associated with substantial improvements in LCI2.5, spirometry and PRAGMA-CF CT scores in people with CF aged 12 years and older. ETI led to improved nutrition and quality of life. People in the F508del/F508del group have significantly lower sweat chloride on ETI treatment compared to the F508del/MF group.

One CDSR (Southern KW, 2023) investigated corrector therapies (with or without potentiators) for people with cystic fibrosis (children and adults) with class II CFTR gene variants (most commonly F508del). 34 RCTs of parallel design lasting between 1 day and 48 weeks were included: eight monotherapy RCTs (344 participants) (4PBA, CPX, lumacaftor, cavosonstat and FDL169), 16 dual?therapy RCTs (2627 participants) (lumacaftor?ivacaftor or tezacaftor?ivacaftor) and 11 triple?therapy RCTs (1804 participants) (elexacaftor?tezacaftor?ivacaftor/deutivacaftor; VX?659?tezacaftor?ivacaftor/deutivacaftor; VX?440?tezacaftor?ivacaftor; VX?152?tezacaftor?ivacaftor). Participants in 21 RCTs had the genotype F508del/F508del, in seven RCTs they had F508del/minimal function (MF), in one RCT F508del/gating genotypes, in one RCT either F508del/F508del genotypes or F508del/residual function genotypes, in one RCT either F508del/gating or F508del/residual function genotypes, and in three RCTs either F508del/F508del genotypes or F508del/MF genotypes. Results from 16 RCTs may not be applicable to all pwCF due to age limits (e.g. adults only) or non?standard designs (converting from monotherapy to combination therapy). Monotherapy - Investigators reported no deaths or clinically relevant improvements in quality of life (QoL). There was insufficient evidence to determine effects on lung function. No placebo?controlled monotherapy RCT demonstrated differences in mild, moderate or severe adverse effects (AEs); the clinical relevance of these events is difficult to assess due to their variety and few participants (all F508del/F508del). Dual therapy - In a tezacaftor?ivacaftor group there was one death (deemed unrelated to the study drug). QoL scores (respiratory domain) favoured both lumacaftor?ivacaftor and tezacaftor?ivacaftor therapy compared to placebo at all time points (moderate?certainty evidence). At six months, relative change in forced expiratory volume in one second (FEV1) % predicted improved with all dual combination therapies compared to placebo (high? to moderate?certainty evidence). More pwCF reported early transient breathlessness with lumacaftor?ivacaftor (odds ratio (OR) 2.05, 99% confidence interval (CI) 1.10 to 3.83; I2 = 0%; 2 studies, 739 participants; high?certainty evidence). Over 120 weeks (initial study period and follow?up), systolic blood pressure rose by 5.1 mmHg and diastolic blood pressure by 4.1 mmHg with twice?daily 400 mg lumacaftor?ivacaftor (80 participants). The tezacaftor?ivacaftor RCTs did not report these adverse effects. Pulmonary exacerbation rates decreased in pwCF receiving additional therapies to ivacaftor compared to placebo (all moderate?certainty evidence): lumacaftor 600 mg (hazard ratio (HR) 0.70, 95% CI 0.57 to 0.87; I2 = 0%; 2 studies, 739 participants); lumacaftor 400 mg (HR 0.61, 95% CI 0.49 to 0.76; I2 = 0%; 2 studies, 740 participants); and tezacaftor (HR 0.64, 95% CI 0.46 to 0.89; 1 study, 506 participants). Triple therapy - No study reported any deaths (high?certainty evidence). All other evidence was low? to moderate?certainty. QoL respiratory domain scores probably improved with triple therapy compared to control at six months (six studies). There was probably a greater relative and absolute change in FEV1 % predicted with triple therapy (four studies each across all combinations). The absolute change in FEV1 % predicted was probably greater for F508del/MF participants taking elexacaftor?tezacaftor?ivacaftor compared to placebo (mean difference 14.30, 95% CI 12.76 to 15.84; 1 study, 403 participants; moderate?certainty evidence), with similar results for other drug combinations and genotypes. There was little or no difference in adverse events between triple therapy and control (10 studies). No study reported time to next pulmonary exacerbation, but fewer F508del/F508del participants experienced a pulmonary exacerbation with elexacaftor?tezacaftor?ivacaftor at four weeks (OR 0.17, 99% CI 0.06 to 0.45; 1 study, 175 participants) and 24 weeks (OR 0.29, 95% CI 0.14 to 0.60; 1 study, 405 participants); similar results were seen across other triple therapy and genotype combinations. Authors concluded that there is insufficient evidence of clinically important effects from corrector monotherapy in pwCF with F508del/F508del. Additional data in this review reduced the evidence for efficacy of dual therapy; these agents can no longer be considered as standard therapy. Their use may be appropriate in exceptional circumstances (e.g. if triple therapy is not tolerated or due to age). Both dual therapies (lumacaftor?ivacaftor, tezacaftor?ivacaftor) result in similar small improvements in QoL and respiratory function with lower pulmonary exacerbation rates. While the effect sizes for QoL and FEV1 still favour treatment, they have reduced compared to our previous findings. Lumacaftor?ivacaftor was associated with an increase in early transient shortness of breath and longer?term increases in blood pressure (not observed for tezacaftor?ivacaftor).

Tezacaftor?ivacaftor has a better safety profile, although data are lacking in children under 12 years. In this population, lumacaftor?ivacaftor had an important impact on respiratory function with no apparent immediate safety concerns, but this should be balanced against the blood pressure increase and shortness of breath seen in longer?term adult data when considering lumacaftor?ivacaftor. Data from triple therapy trials demonstrate improvements in several key outcomes, including FEV1 and QoL. There is probably little or no difference in adverse events for triple therapy (elexacaftor?tezacaftor?ivacaftor/deutivacaftor; VX?659?tezacaftor?ivacaftor/deutivacaftor; VX?440?tezacaftor?ivacaftor; VX?152?tezacaftor?ivacaftor) in pwCF with one or two F508del variants aged 12 years or older (moderate?certainty evidence). Further RCTs are required in children under 12 years and those with more severe lung disease.

The SIMPLIFY study (Gold LS, 2024) compared the costs of outpatient medications between people taking ETI who continued or discontinued (1) dornase alfa or (2) hypertonic saline from 2 clinical trials and project cost differences in the US CF population if these 2 medications were used only intermittently for symptom relief instead of chronically. A total of 392 participants from the dornase alfa trial and 273 from the hypertonic saline trial were included in analyses. The adjusted difference in median medication costs was not significant for the hypertonic saline trial, but a significantly decreased 6-week cost of medications in the dornase alfa trial (adjusted median difference in costs between discontinue and continue of $5,860 (95% CI = $4,870-$6,850); P < 0.0001) was observed. About two-thirds of people with CF was estimated to use ETI and dornase alfa in the United States; if they discontinued dornase alfa except for intermittent use, the resulting annual savings would be $1.21 billion. Although the costs of dornase alfa and hypertonic saline are smaller compared with ETI, reduction in use would lead to substantial prescription drug cost savings and reduce the treatment burden. However, individual benefits of these therapies should be considered, and decisions regarding changes in therapy remain an important discussion between people with CF and their providers.

One retrospective, single center study (Guenther EL, 2024) investigated the impact of chronic medication de-escalation in patients with cystic fibrosis taking elexacaftor, tezacaftor, ivacaftor. The study included 174 CF patients on elexacaftor/tezacaftor/ivacaftor (ETI), six years and older with at least one copy of F508del. The mean ppFEV(1) at baseline, month 1, and month 12 was 67%, 78%, and 87% respectively. The mean difference in absolute change in ppFEV(1) from baseline to month 1 compared to baseline to month 12 after the initiation of ETI was 1.53% (95% CI: -0.49 to 3.55). De-escalating supportive therapies for those on ETI was non-inferior to remaining on all supportive therapies. This suggests that medications may be able to be discontinued under the context of a de-escalation algorithm, which may decrease medication burden and cost and increase quality of life.

Unresolved questions

Safety and efficacy of corrective treatments applicable to all patients irrespective of mutation class.

Identification of CFTR correctors or potentiators and related mutation targets.

Features of CF candidates for therapy with CFTR modulators.

Impact of CFTR modulators on clinical outcomes (respiratory condition, quality of life, survival, nutritional parameters, sputum, radiological features).

Sensitive and specific surrogate biomarkers to investigate the efficacy of CFTR modulators

Safety of CFTR modulators, also for long time treatments.

Ongoing trials:

Phase III, long-term, roll-over studies about already studied compounds:

A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of **Lumacaftor/Ivacaftor** Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for F508del and 12 to <24 Months of Age at Treatment Initiation (**NCT04235140**). Vertex Pharmaceuticals Incorporated

A Phase 3, Open-label Study Evaluating the Long Term Safety and Efficacy of **VX-659 with VX-661 and VX-77**0 in Subjects Who Are Homozygous or Heterozygous for the F508del Mutation **(NCT03447262)** Vertex Pharmaceuticals Incorporated

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of **VX-445 with VX-661 and VX-770** in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation **(NCT03525574)** Vertex Pharmaceuticals Incorporated

A Phase 3b, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of **VX-445/Tezacaftor/Ivacaftor** in Cystic Fibrosis Subjects, Homozygous for F508del

(NCT 04105972) Vertex Pharmaceuticals Incorporated

A phase 3 RCT on **VX-659/VX-661/ VX 770** in Subjects Heterozygous for the F508del Mutation and a Minimal Function Mutation. (**NCT03447249)** Vertex Pharmaceuticals

An Open Label Study to Evaluate the Efficacy of Long-Term Treatment With **PTC-124** in Combination with **VX-770** in Subjects With Nonsense Mutation **(NCT03256968)** University of Alabama at Birmingham.

A phase 3 study to evaluate efficacy and safety of **VX-659/VX-661/ VX 770** in Subjects **without an F508del mutation (NCT05274269)** Vertex Pharmaceuticals

A prospective, multicenter observational study to investigate **VX-659/VX-661/ VX 770** efficacy in children (6-11 years with one or more

copies of **F508del mutation**. The PROMISE (NCT04613128) Cystic Fibrosis Foundation

An observational study to determine if **VX-659 /VX-661/ VX 770** improves signs and symptoms of CF related sinus disease (NCT04056702) Cystic Fibrosis Foundation

Age target extension

A phase 2 study to explore the impact of **VX-809/VX-770** on disease progression in subjects aged **2 through 5 years**, homozygous for f508del (NCT03625466). Vertex Pharmaceuticals Incorporated.

A Rollover Safety Study of **VX-809/VX-770** in Subjects Aged **2 Years and Older**, Homozygous for the F508del-CFTR Mutation (NCT03125395) Vertex Pharmaceuticals Incorporated.

A Phase 3, open-label study about safety and efficacy of long-term **VX-770** treatment in subjects who are **<24 months** of age at treatment initiation and have a CFTR gating mutation (NCT03277196) Vertex Pharmaceuticals Incorporated.

A Phase 3, Open Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of **VX-661/VX-770** in Subjects **6 Through 11 Years** of Age With Cystic Fibrosis, Homozygous or Heterozygous for the F508del CFTR Mutation (NCT02953314) Vertex Pharmaceuticals Incorporated

A Phase 3roll-over study to evaluate the safety and efficacy of long-term treatment with **VX-661/VX-770** in Subjects aged **6 years and older** Homozygous or Heterozygous for the F508del-CFTR Mutation) (NCT03537651) Vertex Pharmaceuticals Incorporated

A Phase 3 open label study to evaluate pharmacokinetics (PK), safety, tolerability, efficacy, and pharmacodynamic effect **VX- 445/VX-661/VX-770** in Subjects **6 Through 11 Years** of Age with F/F or F/MF genotypes (NCT03691779) Vertex Pharmaceuticals Incorporated

A prospective study to evaluate changes in lung function in CF **women** during **pregnancy** and for 2 years after pregnancy based on exposure to **highly effective CFTR modulators**(NCT04828382)

New compounds

A Phase 1/2 to study **VX-121** in combination with **VX-809/VX-770** in **healthy subjects** and in subjects with cystic fibrosis (NCT03768089) Vertex Pharmaceuticals Incorporated

A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of **VX-561** in Subjects Aged 18 Years and Older (NCT 03911713) Vertex Pharmaceuticals Incorporated

A Phase 2, RCT to Evaluate the Safety and Efficacy of **VX-121 /VX-661/VX-561** patients with F508del and a Minimal Function mutation and in patients Homozygous for F508del (NCT03912233) Vertex Pharmaceuticals Incorporated

A Phase 2 study to evaluate the safety and efficacy of treatment with ENaC Inhibitor **VX-371** in saline compared to saline alone in subjects who are >12 years of age, homozygous for the F508del CFTR mutation, and being treated with Orkambi. (NCT02709109) Vertex Pharmaceuticals Incorporated.

A Phase 2 study to assess the Safety, Tolerability, Pharmacokinetics and preliminary pharmacodynamics of **QBW251** in healthy subjects and cystic fibrosis patients following single and multiple doses. (NCT02190604) Novartis Pharmaceuticals.

A Phase 1/ 2 trial will evaluate safety and tolerability in adults of **MRT5005** administered by nebulization measuring changes in CFTR protein levels and CFTR chloride channel activity NCT03375047) Translate Bio, Inc.

A Phase 1/2 Double Blind, Placebo Controlled, Dose Escalation Trial to study **Glycerol Phenylbutyrate** Corrector (Ravicti) Therapy for patients homozigous for f508del (NCT02323100) National Jewish Health.

A Phase 1 Study Assessing **PTI-428** Safety, Tolerability, and Pharmacokinetics in Subjects **on VX-770** as background therapy (NCT03258424) Proteostasis Therapeutics, Inc.

A Phase 2, RCT to Assess the Safety, Tolerability, Pharmacokinetics, and Effect of **PTI-428** in Subjects, in treatment with VX-661/VX-770. (NCT03591094) Proteostasis Therapeutics, Inc.

A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of **PTI 808** in Healthy Adult Subjects and in Adults With Cystic Fibrosis (NCT03251092) Proteostasis Therapeutics, Inc

A Phase 1/2 study to evaluate Safety, Tolerability, and Pharmacokinetics of **PTI-808, PTI-801, and PTI-428 Combination** Therapy in Subjects With Cystic Fibrosis who are either homozygous for the F508del mutation or heterozygous with at least one F508del mutation. (NCT03500263) Proteostasis Therapeutics, Inc.

A Phase 2 study to evaluate the safety, tolerability, and efficacy of **ABBV-3067** given alone and in combination with various doses of **ABBV-2222** in adults with Cystic Fibrosis who are homozygous for the F508del mutation. (NCT03969888) AbbVie

An interventional RCT to assess safety and efficacy of the combination therapy galicaftor/navocaftor (**ABBV-119**) in adult patients who are either homozygous for F508del mutation or heterozygous for F508del and a Minimal Function mutations . (NCT04853368) AbbVie

A Phase 2 Open Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Multiple Dose Levels of Subcutaneously Administered **ELX-02** in Patients With at Least One G542X Allele (NCT04135495) Eloxx Pharmaceuticals, Inc.

Keywords

G551D-CFTR; Cystic Fibrosis Transmembrane Conductance Regulator; Ivacaftor; Lumacaftor; Tezacaftor; VX-661; VX-770; VX-809;