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 postulated 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 patients (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 (De Boeck K, 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 2024 of the CFFoundation , besides **Kalydeco**, **Orkambi**, **Symdeko** and **Trikafta**, already available for the patients**, 6** compounds are taken into consideration regarding to restore CFTR function:

vanzacaftor/tezacaftor/deutivacaftoris in Phase III:

SION-638 (a corrector, a type of CFTR modulator designed to fix the defective CFTR protein so that it can move to the proper place on the cell surface. It aims to stabilize defective CFTR by targeting a specific location on the protein called nucleotide binding domain 1, or NBD1) is in Phase I

ELX-02 (designed to restore CFTR function in non sense mutations) is in Phase II

SION-109 (a corrector, a type of CFTR modulator designed to fix the defective CFTR protein so that it can move to the proper place on the cell surface. It aims to stabilize defective CFTR by targeting a specific location on the protein called intracellular loop 4, or ICL4) is in Phase I

Two compounds by **Sionna Therapeutics** and **Southern Research** are 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 PL, 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 **Ivacafto**r 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 function 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 chloride concentration in people 6-11 years of age, homozygous for the Phe508del CFTR mutation or heterozygous for the Phe508del mutation and a residual function 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 patients resulted in increased CFTR function in vitro and translated to improvements in enrolled patients. In both groups sweat chloride 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.

A phase 3 study (Walker S, 2019) evaluated the pharmacokinetics (PK), safety, tolerability, and efficacy of tezacaftor/ivacaftor in children aged 6 through 11 years with these mutations. After PK analysis in part A, 70 children received ?1 dose of tezacaftor/ivacaftor in part B; 67 children completed treatment. Exposures in children aged 6 through 11 years were within the target range for those observed in patients aged ?12 years. The safety profile of tezacaftor/ivacaftor was generally similar to prior studies in patients aged ?12 years. One child discontinued treatment for a serious adverse event of constipation. Tezacaftor/ivacaftor treatment improved sweat chloride levels and CFQ-R respiratory domain scores, mean ppFEV$_1$ remained stable in the normal range, and growth parameters remained stable over 24 weeks. Tezacaftor/ivacaftor was generally safe and well tolerated, and improved CFTR function in children aged 6 through 11 years with CF with F/F and F/RF genotypes, supporting tezacaftor/ivacaftor use in this age group.

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** demonstrated (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.

A Phase 2 study (Kazani S, 2021) assessed the Safety, Tolerability, Pharmacokinetics and preliminary pharmacodynamics of **QBW251** in healthy subjects and cystic fibrosis patients following single and multiple doses. Class IV mutations were present in 22 patients, Class III in 2 (both S549N), and 25 were homozygous for F508del. Icenticaftor was well-tolerated in healthy and CF subjects with no unexpected events or discontinuations in the CF groups. The most frequent study-drug related adverse events in CF patients were nausea (12.2%), headache (10.2%), and fatigue (6.1%). Icenticaftor 450 mg bid for 14 days showed significant improvements in all endpoints versus placebo in patients with Class III and IV mutations; mean %predicted FEV_1 increased by 6.46%, $LCI_{2.5}$ decreased by 1.13 points and sweat chloride decreased by 8.36 mmol/L. No significant efficacy was observed in patients homozygous for a single F508del. Icenticaftor was safe and well-tolerated in healthy volunteers and CF patients, and demonstrated clinically meaningful changes in lung function and sweat chloride level in CF patients with Class III and IV CFTR mutations.

A phase 3 oper label study (Zemanick ET, 2021) evaluated 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. The safety and pharmacokinetic profiles of ELX/TEZ/IVA were generally consistent with those observed in older patients. The most commonly reported adverse events included cough, headache, and pyrexia; in most of the children who had adverse events, these were mild or moderate in severity. Through Week 24, ELX/TEZ/IVA treatment improved the percentage of predicted FEV_1 (10.2 percentage points; 95% confidence interval [CI], 7.9 to 12.6), Cystic Fibrosis Questionnaire-Revised respiratory domain score (7.0 points; 95% CI, 4.7 to 9.2), lung clearance index $_{2.5}$ (-1.71 units; 95% CI, -2.11 to -1.30), and sweat chloride (-60.9 mmol/L; 95% CI, -63.7 to -58.2); body mass index-for-age *z*-score increased over the 24-week treatment period when compared with the pretreatment baseline. Our results show ELX/TEZ/IVA is safe and efficacious in children 6 through 11 years of age with at least one *F508del-CFTR* allele, supporting its use in this patient population.

A Phase 3, Open Label Study (Hoppe JE, 2021) evaluated 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. This extension study ran from May 12, 2017, to July 17, 2019. Of 60 participants enrolled and who received lumacaftor-ivacaftor in study 115, 57 (95%) were included in study 116 and continued to receive the study drug. A total of 47 (82%) of 57 participants completed 96 weeks of treatment. Most participants (56 [98%] of 57) had at least one adverse event during study 116, most of which were mild (19 [33%] participants) or moderate (29 [51%] participants) in severity. The most common adverse events were cough (47 [82%] participants), nasal congestion (25 [44%] participants), pyrexia (23 [40%] participants), rhinorrhoea (18 [32%] participants), and vomiting (17 [30%] participants). A total of 15 (26%) participants had at least one serious adverse event; most were consistent with underlying cystic fibrosis or common childhood illnesses. Respiratory adverse events occurred in five (9%) participants, none of which were serious or led to treatment discontinuation. Elevated aminotransferase concentrations, most of which were mild or moderate in severity, occurred in ten (18%) participants. Three (5%) participants discontinued treatment due to adverse events (two due to increased aminotransferase concentrations [one of whom had concurrent pancreatitis], considered as possibly related to study drug; and one due to gastritis and metabolic acidosis, considered unlikely to be related to study drug). No clinically significant abnormalities or changes were seen in electrocardiograms, vital signs, pulse oximetry, ophthalmological examinations, or spirometry assessments. Improvements in secondary endpoints observed in study 115 were generally maintained up to week 96 of study 116, including improvements in sweat chloride concentration (mean absolute change from study 115 baseline at week 96 of study 116 -29·6 mmol/L [95% CI -33·7 to -25·5]), an increase in growth parameters and pancreatic function, and stable lung function relative to baseline, as measured by the LCI. Lumacaftor-ivacaftor was generally safe and well tolerated, and treatment effects were generally maintained for the duration of the extension study. These findings support the use of lumacaftor-ivacaftor for up to 120 weeks in young children with cystic fibrosis aged 2 years and older homozygous for the F508del-CFTR mutation.

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 function, likely resulting in decreased risk for electrolyte disorders and metabolic alkalosis.

A RCT (Sutharsan S, 2022) assessed the magnitude and durability of the clinical effects of this triple combination regimen in people with cystic fibrosis homozygous for the F508del-CFTR mutation. Between Oct 3, 2019, and July 24, 2020, 176 participants were enrolled. Following the 4-week tezacaftor plus ivacaftor run-in period, 175 participants were randomly assigned (87 to the elexacaftor plus tezacaftor plus ivacaftor group and 88 to the tezacaftor plus ivacaftor group) and dosed in the treatment period. From baseline up to and including week 24, the mean CFQ-R respiratory domain score increased by 17·1 points (95% CI 14·1 to 20·1) in the elexacaftor plus tezacaftor plus ivacaftor group and by 1·2 points (-1·7 to 4·2) in the tezacaftor plus ivacaftor group (least squares mean treatment difference 15·9 points [95% CI 11·7 to 20·1], p<0·0001), the mean percent predicted FEV_1 increased by 11·2 percentage points (95% CI 9·8 to 12·6) in the elexacaftor plus tezacaftor plus ivacaftor group and by 1·0 percentage points (-0·4 to 2·4) in the tezacaftor plus ivacaftor group (least squares mean treatment difference 10·2 percentage points [8·2 to 12·1], p<0·0001), and the mean sweat chloride concentration decreased by 46·2 mmol/L (95% CI 43·7 to 48·7) in the elexacaftor plus tezacaftor plus ivacaftor group and by 3·4 mmol/L (1·0 to 5·8) in the tezacaftor plus ivacaftor group (least squares mean treatment difference -42·8 mmol/L [-46·2 to -39·3], nominal

p<0·0001). Most participants (70 [80%] in the elexacaftor plus tezacaftor plus ivacaftor group and 74 [84%] in the tezacaftor plus ivacaftor group) had adverse events that were mild or moderate in severity; serious adverse events occurred in five (6%) of 87 participants in the elexacaftor plus tezacaftor plus ivacaftor group and 14 (16%) of 88 participants in the tezacaftor plus ivacaftor group. One (1%) participant in the elexacaftor plus tezacaftor plus ivacaftor group discontinued treatment due to an adverse event of anxiety and depression. Two (2%) participants in the tezacaftor plus ivacaftor group discontinued treatment due to adverse events of psychotic disorder (n=1) and obsessive-compulsive disorder (n=1). The elexacaftor plus tezacaftor plus ivacaftor regimen was safe and well tolerated, and led to significant and clinically meaningful improvements in respiratory-related quality of life and lung function, as well as improved CFTR function, changes that were durable over 24 weeks and superior to those seen with tezacaftor plus ivacaftor in this patient population.

A phase 2 study (Stahl M, 2023) explored the impact of **VX-809/VX-770** on disease progression in subjects aged **2 through 5 years** , homozygous for F508del using chest magnetic resonance imaging (MRI). Fifty-one children were enrolled and received LUM/IVA (*n*?=?35) or placebo (*n*?=?16). For the change in chest MRI global score at Week 48, the Bayesian posterior probability of LUM/IVA being better than placebo (treatment difference, <0; higher score indicates greater abnormality) was 76%; the mean treatment difference was ?1.5 (95% credible interval, ?5.5 to 2.6). Treatment with LUM/IVA also led to within-group numerical improvements in $LCI_{2.5}$, growth parameters, and biomarkers of pancreatic function as well as greater decreases in sweat chloride concentration compared with placebo from baseline through Week 48. Safety data were consistent with the established safety profile of LUM/IVA. This placebo-controlled study suggests the potential for early disease modification with LUM/IVA treatment, including that assessed by chest MRI, in children as young as 2 years of age.

A RCT (Sawicki GS, 2022) assessed the safety and efficacy of tezacaftor/ivacaftor in an open-label, 96-week extension study. One-hundred thirty children enrolled and received ? 1 dose of tezacaftor/ivacaftor; 109 completed treatment. Most (n = 129) had ? 1 treatment-emergent adverse event (TEAE), the majority of which were mild or moderate in severity and generally consistent with common manifestations of CF. Exposure-adjusted TEAE rates were similar to or lower than those in the parent studies. Five (3.8%) had TEAEs leading to treatment discontinuation. Efficacy results from the parent studies were maintained, with improvements in lung function, SwCl concentration, CFQ?R respiratory domain score, and BMI observed from parent study baseline to Week 96. Tezacaftor/ivacaftor is generally safe and well tolerated, and treatment effects are maintained for up to 120 weeks. These results support long-term use of tezacaftor/ivacaftor in children ? 6 years of age with CF and F/F or F/RF genotypes.

A Phase 1/2 trial (Rowe SM, 2023) evaluated safety and tolerability in adults of **MRT5005** administered by nebulization measuring changes in CFTR protein levels and CFTR chloride channel activity. A total of 42 subjects were assigned to MRT5005 [31] or placebo [11]. A total of 14 febrile reactions were observed in 10 MRT5005-treated participants, which were mild [3] or moderate [11] in severity; two subjects discontinued related to these events. Additionally, two MRT5005-treated patients experienced hypersensitivity reactions, which were managed conservatively. The most common treatment emergent adverse events were cough and headache. No consistent effects on FEV1 were noted. MRT5005 was generally safe and well tolerated through 28 days of follow-up after the last dose, though febrile and hypersensitivity reactions were noted. The majority of these reactions resolved within 1-2 days with supportive care allowing continued treatment with MRT5005 and careful monitoring. In this small first-in-human study, FEV1 remained stable after treatment, but no beneficial effects on FEV1 were observed.

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.

Two phase 2 clinical trials (Uluer AZ, 2023) assessed the safety and efficacy of a once-daily combination of vanzacaftor-tezacaftor-deutivacaftor in participants with cystic fibrosis who were aged 18 years or older. In study VX18-561-101, participants treated with deutivacaftor 150 mg once daily (n=23) or deutivacaftor 250 mg once daily (n=24) had mean absolute changes in ppFEV$_1$ of 3·1 percentage points (95% CI -0·8 to 7·0) and 2·7 percentage points (-1·0 to 6·5) from baseline at week 12, respectively, versus -0·8 percentage points (-6·2 to 4·7) with ivacaftor 150 mg every 12 h (n=11); the deutivacaftor safety profile was consistent with the established safety profile of ivacaftor 150 mg every 12 h. In study VX18-121-101, participants with F/MF genotypes treated with vanzacaftor (5 mg)-tezacaftor-deutivacaftor (n=9), vanzacaftor (10 mg)-tezacaftor-deutivacaftor (n=19), vanzacaftor (20 mg)-tezacaftor-deutivacaftor (n=20), and placebo (n=10) had mean changes relative to baseline at day 29 in ppFEV$_1$ of 4·6 percentage points (-1·3 to 10·6), 14·2 percentage points (10·0 to 18·4), 9·8 percentage points (5·7 to 13·8), and 1·9 percentage points (-4·1 to 8·0), respectively, in sweat chloride concentration of -42·8 mmol/L (-51·7 to -34·0), -45·8 mmol/L (95% CI -51·9 to -39·7), -49·5 mmol/L (-55·9 to -43·1), and 2·3 mmol/L (-7·0 to 11·6), respectively, and in CFQ-R respiratory domain score of 17·6 points (3·5 to 31·6), 21·2 points (11·9 to 30·6), 29·8 points (21·0 to 38·7), and 3·3 points (-10·1 to 16·6), respectively. Participants with the F/F genotype treated with vanzacaftor (20 mg)-tezacaftor-deutivacaftor (n=18) and tezacaftor-ivacaftor (n=10) had mean changes relative to baseline (taking tezacaftor-ivacaftor) at day 29 in ppFEV$_1$ of 15·9 percentage points (11·3 to 20·6) and -0·1 percentage points (-6·4 to 6·1), respectively, in sweat chloride concentration of -45·5 mmol/L (-49·7 to -41·3) and -2·6 mmol/L (-8·2 to 3·1), respectively, and in CFQ-R respiratory domain score of 19·4 points (95% CI 10·5 to 28·3) and -5·0 points (-16·9 to 7·0), respectively. The most common adverse events overall were cough, increased sputum, and headache. One participant in the vanzacaftor-tezacaftor-deutivacaftor group had a serious adverse event of infective pulmonary exacerbation and another participant had a serious rash event that led to treatment discontinuation. For most participants, adverse events were mild or moderate in severity. Once-daily dosing with vanzacaftor-tezacaftor-deutivacaftor was safe and well tolerated and improved lung function, respiratory symptoms, and CFTR function. These results support the continued investigation of vanzacaftor-tezacaftor-deutivacaftor in phase 3 clinical trials compared with elexacaftor-tezacaftor-ivacaftor.

A double blind RCT, Phase 2 study Konstan MW, 2024) evaluated the efficacy and safety of LAU-7b that was administered to 166 adult CF subjects who received at least one dose of study drug (Intent-To-Treat population, ITT), of which 122 received ?5 treatment cycles (Per-Protocol population, PP). Both treatment arms showed a mean lung function loss at 24 weeks of 1.18 ppFEV(1) points with LAU-7b and 1.95 ppFEV(1) with placebo, a 0.77 ppFEV(1) (40 s) difference, p=0.345, and a 0.95 ppFEV(1) (49 %) difference in the same direction in PP population, p=0.263. Primary analysis of mean ppFEV(1) through 24 weeks showed differences of 1.01 and 1.23 ppFEV(1), in the ITT (65 % less loss, p=0.067) and PP populations (78 % less loss, reaching statistical significance p=0.049), respectively. LAU-7b had an acceptable safety profile. Although the study did not meet its primary efficacy endpoint in the ITT population, LAU-7b was generally well tolerated and showed evidence of preservation of lung function to support further development.

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.

The SIMPLIFY-MCC study (Donaldson SH, 2024) investigated the effect of discontinuing hypertonic saline (HS) or dornase alfa (DA) on mucociliary clearance (MCC) in elexacaftor/tezacaftor/ivacaftor (ETI) treated patients with CF (age ?12 years). While no significant differences in MCC endpoints were associated with HS discontinuation, significant improvement in whole and peripheral lung MCC was observed after discontinuing DA. These results suggest that pwCF on ETI with mild lung disease do not experience a subclinical deterioration in MCC that could later impact health outcomes after discontinuing HS, and in fact may benefit from improved MCC after stopping DA treatment.

A rerospective study (Cohen A, 2024) investigated the long-term therapy with CFTR modulators on glucose metabolism in adolescents and adults with cystic fibrosis (N=15; age range: 13-37 years). The 120-min OGTT value decreased from 159.7 mg/dL to 130.4 mg/dL post-CFTRm (p = 0.047). The average time elapsed between the two OGTTs was 49.87 months (ranging 9-157 months, median 38 months). Glycemic status improved in six pwCF (two CFRD to normal (NGT)/indeterminate (INDET) glucose tolerance; two impaired glucose tolerance (IGT) to INDET; two INDET to NGT) and worsened in one (IGT to CFRD). Six pwCF and NGT remained stable with no changes in glycemic status throughout the follow-up period. In conclusion, CFTRm therapy may decelerate the glycemic control deterioration in pwCF over an extended period. These findings indicate the need for periodic OGTTs following the initiation of CFTRm therapy to appropriately adjust insulin requirements and prevent hypoglycemia. Further larger cohorts are required to authenticate and substantiate these findings.

A single group prospective observational study (Stastna N, 2024) investigated the long-term effect of elexacaftor/tezacaftor/ivacaftor (ETI) on cardiorespiratory fitness in 10 adolescent patients with cystic fibrosis who completed two CPET measurements between January 2019 and February 2023. The authors observed significant improvement in peak workload, VO(2 peak), VO(2VT1), VO(2VT2), V(E)/VCO(2) slope, V(E), V(T), RQ, VO(2)/HR peak and RR peak. The mean change in VO(2)peak was 5.7 mL/kg/min, or 15.9% of the reference value (SD?±?16.6; p=?0.014). VO(2VT1) improved by 15% of the reference value (SD?±?0.1; p=?0.014), VO(2VT2)improved by 0.5 (SD?±?0.4; p=?0.01). There were no differences in other parameters. Exercise tolerance improved after elexacaftor/tezacaftor/ivacaftor treatment initiation. We suggest that the CFTR modulator alone is not enough for recovering physical decondition, but should be supplemented with physical activity and respiratory physiotherapy. Further studies are needed to examine the effect of CFTR modulators and physical therapy on cardiopulmonary exercise tolerance.

A randomised crossover trial (Ng C, 2024) (2019-2020) at Nottingham University Hospitals investigated the effects of tezacaftor-ivacaftor on gut dysfunction in 13 cystic fibrosis patients aged from 12 to 40 years using magnetic resonance imaging (MRI). Participants were randomly assigned to treatment sequences AB or BA (A:TEZ/IVA, B:placebo, each 28 days), with a 28-day washout period. 8 participants completed the full protocol and 1 dropped out. The remaining 4 participants followed the amended protocol. There were no significant differences between placebo and TEZ/IVA for OCTT (TEZ/IVA >360minutes [225,>360] vs. placebo 330minutes [285,>360], p=0.8) or secondary outcomes. There were no adverse events. No effect after TEZ/IVA was found on MRI metrics of gut function, GI symptoms or stool calprotectin. Effects might be detectable with larger studies, longer treatment or more effective CFTR modulators.

A Phase 2 trial (Stahl M, 2024) investigated the long-term impact of Lumacaftor/Ivacaftor treatment on Cystic Fibrosis Disease Progression in children 2 through 5 years of age homozygous for F508del. This trial had two parts: Part 1, a 48-week, randomized, double-blind, placebo-controlled study of LUM/IVA was followed by a 48-week open-label treatment period where all children received LUM/IVA. 49 children received ?1 dose of LUM/IVA in the open-label period (33 in the LUM/IVA to LUM/IVA group and 16 in the placebo to LUM/IVA group); mean exposure 47.1 (SD, 5.2) weeks. The mean absolute change in MRI global score (negative value = improvement) from baseline at Week 96 was -2.7 (SD 7.0; 95% CI, -5.2 to -0.1) in the LUM/IVA to LUM/IVA group and -5.6 (SD 6.9; 95% CI, -9.2 to -1.9) in the placebo to LUM/IVA group. Improvements in LCI(2.5), sweat chloride concentration, and markers of pancreatic function and intestinal inflammation were also observed in both groups. Growth parameters remained stable in both groups. The majority of children had adverse events (AEs) considered mild (38.8%) or moderate (40.8%). Two (4.1%) children discontinued LUM/IVA treatment due to AEs (distal intestinal obstruction syndrome [n=1] and alanine aminotransferase increase [n=1]). These findings confirm the potential for early LUM/IVA treatment to alter the trajectory of CF disease progression, including CF lung disease, in children as young as 2 years of age.

A retrospective observational study (Sütering T, 2024) investigated evaluated six pwCF (ages 6 to 66) with responsive CFTR mutations (M1101K, R347P, 2789+5G>A, G551D) undergoing off-label ETI therapy. Evaluations were conducted at 0, 3, 6, 9, and 12 months, assessing lung function (FEV_1), sweat chloride levels, body mass index (BMI), quality of life, medication satisfaction, ear, nose and throat (ENT) symptoms, and physical activity. A control group of four pwCF with classic symptoms and no ETI treatment was included. FEV_1 improved significantly after 3 and 6 months ($p < 0.05$) and stabilized by 12 months. Sweat chloride levels decreased significantly, with four pwCF achieving levels <60 mmol/L. Improvements in the upper and lower airway symptoms, medication satisfaction, and increased BMI were noted. In conclusion ETI demonstrates high efficacy in this small group of pwCF with rare CFTR mutations, offering a treatment option that warrants further monitoring and evaluation.

Two Phase 3 RCTs (Keating C, 2024) investigated safety and efficacy of vanzacaftor-tezacaftor-deutivacaftor versus elexacaftor-tezacaftor-ivacaftor in CF patients aged 12 years and older (SKYLINE Trials VX20-121-102 and VX20-121-103). In Trial VX20-121-102 between Sept 14, 2021, and Oct 18, 2022, 488 individuals were screened, of whom 435 entered the 4-week run-in period, and subsequently 398 were randomly assigned and received at least one dose of elexacaftor-tezacaftor-ivacaftor (n=202) or vanzacaftor-tezacaftor-deutivacaftor (n=196). Median age was 31·0 years (IQR 22·6-38·5), 163 (41%) of 398 participants were female, 235 (59%) were male, and 388 (97%) were White. In Trial VX20-121-103, between Oct 27, 2021, and Oct 26, 2022, 699 individuals were screened, of whom 597 entered the 4-week run-in period, and subsequently 573 participants were randomly assigned and received at least one dose of elexacaftor-tezacaftor-ivacaftor (n=289) or vanzacaftor-tezacaftor-deutivacaftor (n=284). Median age was 33·1 years (IQR 24·5-42·2), 280 (49%) of 573 participants were female, 293 (51%) were male, and 532 (93%) were White. The absolute change in least squares mean FEV(1) % predicted from baseline through week 24 for Trial VX20-121-102 was 0·5 (SE 0·3) percentage

points in the vanzacaftor-tezacaftor-deutivacaftor group versus 0·3 (0·3) percentage points in the elexacaftor-tezacaftor-ivacaftor group (least squares mean treatment difference of 0·2 percentage points [95% CI -0·7 to 1·1]; p<0·0001), and for Trial VX20-121-103, was 0·2 (SE 0·3) percentage points in the vanzacaftor-tezacaftor-deutivacaftor group versus 0·0 (0·2) percentage points in the elexacaftor-tezacaftor-ivacaftor group (least squares mean treatment difference 0·2 percentage points [95% CI -0·5 to 0·9]; p<0·0001). Most adverse events were mild or moderate, with the most common being infective pulmonary exacerbation (133 [28%] of 480 participants in the pooled vanzacaftor-tezacaftor-deutivacaftor group vs 158 [32%] of 491 in the pooled elexacaftor-tezacaftor-ivacaftor group), cough (108 [23%] vs 101 [21%]), COVID-19 (107 [22%] vs 127 [26%]), and nasopharyngitis (102 [21%] vs 95 [19%]). In conclusion Vanzacaftor-tezacaftor-deutivacaftor resulted non-inferior to elexacaftor-tezacaftor-ivacaftor in terms of FEV(1) % predicted, and was safe and well tolerated. Once daily dosing with vanzacaftor-tezacaftor-deutivacaftor reduces treatment burden, potentially improving adherence, compared with the twice daily regimen of the current standard of care. The restoration of CFTR function and the potential variants treated are also considerations that should be compared with currently available CFTR modulators.

A Phase 3b 96-week open-label extension study (Mall MA, 2025) investigated Elexacaftor/tezacaftor/ivacaftor in children aged ?6?years with cystic fibrosis heterozygous for F508del and a minimal function mutation. A total of 120 children were enrolled and dosed. One hundred and eighteen children (98.3%) had adverse events (AEs), which for most were mild (43.3%) or moderate (48.3%) in severity. The most common AEs (?20% of children) were COVID-19 (58.3%), cough (51.7%), nasopharyngitis (45.0%), pyrexia (40.0%), headache (37.5%), upper respiratory tract infection (30.8%), oropharyngeal pain (26.7%), rhinitis (24.2%), abdominal pain (22.5%), and vomiting (20.0%). Children who transitioned from the placebo and ELX/TEZ/IVA groups of the parent study had improvements from parent study baseline at Week 96 in mean sweat chloride concentration (-57.3 [95% CI: -61.6, -52.9] and -57.5 [95% CI: -62.0, -53.0] mmol·L(-1)), LCI(2..5) (-1.74 [95% CI: -2.09, -1.38] and -2.35 [95% CI: -2.72, -1.97] units), ppFEV(1) (6.1 [95% CI: 2.6, 9.7] and 6.9 [95% CI: 3.2, 10.5] percentage points), and CFQ-R respiratory domain score (6.6 [95% CI: 2.5, 10.8] and 2.6 [95% CI: -1.6, 6.8] points). In conclusion ELX/TEZ/IVA treatment was generally safe and well-tolerated, with a safety profile consistent with parent study and older age groups. After starting ELX/TEZ/IVA, children had robust improvements in sweat chloride concentration and lung function that were maintained through 96?weeks. These results demonstrate the safety and durable efficacy of ELX/TEZ/IVA in this pediatric population.

A systematic review and economic evaluation (Edwards SJ, 2025) evaluated the clinical effectiveness and cost-effectiveness of elexacaftor-tezacaftor-ivacaftor, tezacaftor-ivacaftor and lumacaftor-ivacaftor within their expected marketing authorisations for treating people with cystic fibrosis and at least one F508del mutation, compared with each other and with established clinical management before these treatments. Data from 19 primary studies and 7 open-label extension studies were prioritised in the systematic literature review. Elexacaftor/tezacaftor/ivacaftor was associated with a statistically significant increase in predicted forced expiratory volume in 1 second and weight-for-age z-score and a reduction in pulmonary exacerbations compared with established clinical management, lumacaftor/ivacaftor and tezacaftor/ivacaftor, and also led to a reduction in the rate of predicted forced expiratory volume in 1 second decline relative to established clinical management, although the magnitude of this decrease was uncertain. Lumacaftor/ivacaftor and tezacaftor/ivacaftor were also associated with a statistically significant increase in predicted forced expiratory volume in 1 second and reduction in pulmonary exacerbations relative to established clinical management, but with a smaller effect size than elexacaftor/tezacaftor/ivacaftor. There was some evidence that tezacaftor/ivacaftor reduced the rate of predicted forced expiratory volume in 1 second decline relative to established clinical management, but little evidence that lumacaftor/ivacaftor reduced the rate of predicted forced expiratory volume in 1 second decline relative to established clinical management. The incremental cost-effectiveness ratios from the economic analysis were confidential. However, for all genotypes studied the incremental cost-effectiveness ratios were above what would be considered cost-effective based on the National Institute for Health and Care Excellence threshold of £20,000-30,000 per quality-adjusted life-year gained. In conclusion, despite the improved clinical benefits observed, none of the cystic fibrosis transmembrane conductance regulator gene modulators assessed would be considered cost-effective based on the National Institute for Health and Care Excellence threshold of £20,000-30,000 per quality-adjusted life-year gained. This is largely driven by the high acquisition costs of cystic fibrosis transmembrane conductance regulator gene modulator treatments.

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.

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 was terminated (at Sponsor's discretion)

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 was completed

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 was completed

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 was completed

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 is ongoing

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 is ongoing

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 was completed

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)** is ongoing

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 was completed

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 was completed

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 was terminated

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

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 was completed

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 was completed

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 was completed

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 was completed

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 was terminated (strategic considerations)

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 was completed

A randomised, double-blind, placebo controlled, two-part study (**ISRCTN11798668**) is ongoing to evaluate the efficacy, safety, tolerability and pharmacokinetics of a repeat dose of inhaled **ETD001** in adult patients with cystic fibrosis. This copound is a novel inhaled, long-acting ENaC inhibitor is ongoing

A Phase 2a, Randomized, Placebo-Controlled, Double Blind Multiple Ascending Dose Study in Patients With Cystic Fibrosis Carrying the 3849 +10 Kb C->T Mutation (NCT06429176) is ongoing and will investigate Safety, Tolerability, Pharmacokinetics, and Preliminary Efficacy of SPL84, anti sense oligonucleotide (ASO), in Patients With Cystic Fibrosis is ongoing

A Clinical Trial (NCT06468527) aims to evaluate the efficacy and safety of Dirocaftor/Posenacaftor/Nesolicaftor in adults With CF (CHOICES).

A Phase 3 Open-label Study (EUCTR2021-005914-33) aims to evaluate the longterm safety and efficacy of Elexacaftor/Tezacaftor/Ivacaftor in cystic fibrosis subjects with non-F508del CFTR genotypes

A Phase 3 Study (NCT05422222) aims to evaluate the Pharmacokinetics, Safety, and Tolerability of VX 121/Tezacaftor/Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 Years of Age (VX21-121-105)

A Phase 3 Open-label Study (CTIS-2024-514173-22-00) will evaluate the Long-term Safety and Efficacy of VX-121/TEZ/D-IVA Combination Therapy in Subjects With Cystic Fibrosis

Proof-of-concept study (NCT07108153) will evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of SION-719 when added to Trikafta

Keywords

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