CFTR therapy

CFTR modulators therapy

Code: 261 **Updated:** February 01, 2026

Background

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).**

The introduction of next generation CFTR protein modulators, for the first time, has offered 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 about 10% of CFTR patients (Desai M, 2022) still have ineligible mutations for the new therapy and need alternative approaches to restore CFTR function .

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.

Recent advances are focused on long term effectiveness and safety data, on the need of new biomarkers to monitor efficacy and tolerability of modulators and inequality access to CFTR modulators.

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

The corrector **VX-809** (**Lumacaftor**) in combination with **VX-770** (**ORKAMBI**™ by Vertex Pharmaceuticals) has been able 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) has been able 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) has been able to treat patients who have at least one copy of the F508del mutation.

In 2018 *(Ren CL, 2018)* the CF Foundation has published recommendations about CFTR modulators in CF patients. The standard of care for CFTR variant-specific therapy (including modulators) for people with cystic fibrosis (Southern KW, 2023) has been published in 2023.

In the Drug Development Pipeline 2025 of the CFFoundation , Kalydeco, **Orkambi**, **Symdeko**, **Trikafta and Aliftrek are** available for the patients and new compounds are in pre clinical and phase 1 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

Summary of studies on several molecules the resulted partially or totally ineffective in restoring CFTR function:

- **4-Na-phenylbutyrate** (Rubenstein RC, 1998)
- **4-phenylbutyrate** (Zeitlin PI, 2002)
- **Gentamicin (**(Wilschanski M, 2003),
- **Ataluren** (Sermet-Gaudelus I, 2010), (Kerem E, 2014), (Aslam AA, 2017) (Konstan MW, 2020)

In november 2017 a **Cochrane Review** 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.

- **Miglustat**: (Leonard A, 2012)
- **Riociguat:** (Derichs N, 2021)
- **QBW251:** (Kazani S, 2021)
- **MRT5005:** (Rowe SM, 2023)
- **LAU-7b:**

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.

CFTR modulators:

- **VX-770 Ivacaftor (Kalydeco)**: (Accurso FJ, 2010), (Ramsey BW, 2011), (Davies JC, 2013), (Davies J, 2013), (Barry PJ, 2014), , (Whiting P,2014), (Konstan MV, 2015), (Flume PA, 2012), (De Boeck K, 2014), (Moss RB, 2015), (Mc Garry ME, 2017), (Rosenfeld M, 2018), (Kerem E, 2020)

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.

- **VX-809 Lumacaftor + VX-770 Ivacaftor (Orkambi)**: (Boyle MP, 2014), (Wainright CE, 2015), (Elborn JS, 2016), (Konstan MW, 2017), (Ratjen F, 2017), (Jennings MT, 2017), (McColley SA, 2018), (McNamara JJ, 2019), (Wilson J, 2021), (Berkers G, 2021), (Rayment JH, 2022), (Stahl M, 2023)

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.

- **VX-661, Tezacaftor + VX-770, Ivacaftor (Symdeko or Symkevi):** (Taylor-Coursar JL, 2017), (Donaldson SH,2017), (McKone EF, 2020), (Munck A, 2020), (Flume PA, 2021), (Davies JC, 2021), (Hoppe JE, 2021), (Sawicki GS, 2022)

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.

A randomised crossover trial (Ng C, 2024) (2019-2020) at Nottingham University Hospitals investigated the effects of **tezacaftor-iva**

- **VX-445, Elexacaftor+ VX-661, Tezacaftor + VX-770, Ivacaftor(Trikafta or Kaftrio)** (Keating D, 2018), (Heijerman HGM, 2019), (Middleton PG, 2019), (Walker S, 2019), (Griese M, 2021), (Barry PJ, 2021), (Nichols DP, 2021), (Taylor-Cousar J, 2021), (Zemanick ET, 2021), (Berg P, 2022), (Sutharsan S, 2022), (McNally P, 2023), (Goralski JL, 2023), (Wainwright C, 2023)

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 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 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.

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 phase 3, open-label, single-arm extension study (Daines CL, 2025), investigated the long-term safety and efficacy of **ELX/TEZ/IVA** in Adults and Adolescents with Cystic Fibrosis and at Least One *F508del* Allele. Mean exposure to ELX/TEZ/IVA was 172.6 weeks. Most participants had adverse events classified as mild (12.8%) or moderate (60.7%) in severity. Eighteen participants (3.6%) had adverse events that led to treatment discontinuation. After starting ELX/TEZ/IVA, participants had consistent increases in percent predicted FEV_1 ($ppFEV_1$), Cystic Fibrosis Questionnaire-Revised respiratory domain score, and body mass index, with decreases in sweat chloride concentration and pulmonary exacerbations rates; these improvements were maintained through 192 weeks. The mean annualized rate of change in $ppFEV_1$ was 0.02 percentage points (95% CI, -0.14 to 0.19) after initiation of ELX/TEZ/IVA. During this 192-week open label extension study, the longest clinical study of a CFTR modulator to date, ELX/TEZ/IVA remained generally safe and well-tolerated. Participants had sustained improvements in lung function, respiratory symptoms, CFTR function, pulmonary exacerbation rates, and nutritional status.

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

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.

- **VX-121, Vanzacaftor + VX-770 Tezacaftor + D-IVA-Deutivacaftor (Aliftrek)**: (Uluer AZ, 2023)

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 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.

A retrospective 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.

Retrospective cohort study (Afonso PM, 2025) evaluated long-term effectiveness of cystic fibrosis modulator therapies after rapid adoption. Patients with CF in the U.S. Authors modeled data from 560 ivacaftor-treated individuals with the G551D variant. For between-subject comparisons, propensity scores to match the treated group with 2,800 untreated F508del homozygous individuals. Results showed an initial average improvement in ppFEV1 in ivacaftor-treated children and adults (ranging from 4.54 to 6.53% predicted based on within-subject comparison of before vs. after ivacaftor initiation). There was a slower decline in adults, compared to children. These ivacaftor-treated cohorts experienced less decline relative to their F508del homozygous counterparts (between-group differences in treated vs. control ranged from 0.36 to 0.64% predicted). Both the within- and between-subject comparisons demonstrated similar levels of ivacaftor effectiveness. However, small differences between the two approaches were observed in younger individuals. In conclusion, Ivacaftor was associated with improved ppFEV1 across all age groups, with the magnitude of improvement roughly 50% of that observed in clinical trials. The results support the need to account for modulator initiation bias and the use of within-subject analysis in future CFTR modulator effectiveness studies, but caution is advised in younger individuals due to developmental changes that may affect pre- and post-treatment comparability.

A systematic review and meta-analysis (Alruwaili TAM, 2025) of the treatment modalities available for children with CF revealed that the triple therapy indicated a significant reduction in CF-related complications, with an OR of 0.29 and an RR of 0.54, accompanied by low heterogeneity (I^2 = 0% for both). Physiotherapy and pulmonary exercises also yielded a beneficial effect, with an OR of 0.24 and an RR of 0.49, without heterogeneity. In contrast, nutritional interventions revealed non-significant outcomes (OR?=?6.91 and RR?=?2.63), suggesting the need to re-evaluate these strategies. Ivacaftor alone did not achieve statistical significance (OR?=?0.34 and RR?=?0.58), and the confidence intervals were broad, indicating uncertainty in the effect estimates. Azithromycin exhibited a positive effect on CF management, with an OR of 2.37 and an RR of 1.54. The overall pooled OR across all treatments was 0.71, with an RR not computed due to substantial heterogeneity (I^2=93%). The study underscores the effectiveness of certain treatments, such as triple therapy and physiotherapy exercises, for CF while highlighting the considerable variability in treatment outcomes. Notably, nutritional interventions need to be carefully reassessed. The findings emphasize integrating physiotherapy and targeted pharmacological interventions into standard CF management tailored to individual needs.

A Phase 3b, open-label study (Durieu I, 2025) evaluated the impact of Elexacaftor/Tezacaftor/Ivacaftor on glucose tolerance and abnormal glucose metabolism. Participants (CF patients ?12 years of age, heterozygous for F508del and a minimal function CFTR mutation, with either IGT or CFRD) had a mean change of -35.0 mg/dl (95% confidence interval [CI], -49.2 to -20.7 mg/dl; P?<?0.0001) (-1.9 mmol/L [95% CI, -2.7 to -1.2 mmol/L]). Among participants with abnormal glucose tolerance at baseline, 37.7% (95% CI, 24.8 to 52.1) had improvements in dysglycemia categorization at Week 48. Overall, 35.5% of participants had normal glucose tolerance at Week 48 compared with 13.0% at baseline. Safety was consistent with the established safety profile of ELX/TEZ/IVA. ELX/TEZ/IVA treatment led to clinically meaningful improvements in blood glucose regulation, with significant within-group decreases in blood glucose concentrations after oral glucose tolerance testing and improved dysglycemia categorization in people with CF with early IGT or CFRD.

A systematic review (Pietrzykowska A, 2025) studied cystic fibrosis-related diabetes in the era of modern treatment using CFTR modulators in pediatric patients. 5 studies met inclusion criteria - 1 clinical trial, 2 observational studies and 2 case reports. Evidence suggests CFTRm may improve glucose tolerance and insulin secretion in some pediatric patients, particularly in those with preserved ?-cell function or early-stage CFRD. However, results varied across studies with some showing no significant improvements in glycemic control. While early findings suggest CFTR modulators may offer metabolic benefits and potentially delay or reduce the need for insulin therapy in children CFRD, current evidence is limited. Larger, pediatric-focused clinical trials with standardized glycemic outcomes are essential to determine the long-term efficacy and safety of CFTRm in managing or preventing CFRD.

A systematic review with Network Meta-Analysis (Safeer VSM, 2025) studied comparative efficacy and safety of CFTR modulators for people with cystic fibrosis with phe508del mutation. 29 studies involving 6450 patients examining 34 treatment combinations were included. For adults treated over 4-8 weeks, vanzacaftor 10 mg-tezacaftor 100 mg-deutivacaftor 150 mg combination therapy had a

significant improvement over placebo in improving ppFEV(1) (MD: 15.9; 95% CrI: 7.2-24.2 [high certainty]) with a SUCRA of 92% suggesting the highest probability of effectiveness. Moreover, the vanzacaftor 20 mg-tezacaftor 100 mg-deutivacaftor 150 mg showed a significant reduction in sweat chloride levels (MD: -49.3 mmol/L; 95% CrI: -67.2 to -31.7 [high certainty]) and improved the CFQ-R scores (MD: 39; 95% CrI: 21.2-56.9; [high certainty]) when compared to placebo after 4-8 weeks of treatment. Our findings also highlighted that the triple combination therapies of vanzacaftor 20 mg-tezacaftor 100 mg-deutivacaftor 250 mg and elexacaftor 200 mg-tezacaftor 100 mg-ivacaftor 150 mg provided clinically meaningful improvements across all measured outcomes in adults treated for more than 8 weeks. Confidence in the estimates ranged from high to low, and safety analyses were limited by the low serious adverse event rates. These findings indicate that vanzacaftor-tezacaftor-deutivacaftor and elexacaftor-tezacaftor-deutivacaftor emerged as the most effective treatment options in adults. However, these results should be interpreted cautiously due to limited data and the low quality of existing evidence.

An RCT (Sermet-Gaudelus I, 2026) investigated the effect of elexacaftor-tezacaftor-ivacaftor on bronchial dilatations. Between March 22, 2021, and May 25, 2022, a total of 330 adolescents with cystic fibrosis were enrolled in the study, of whom 320 were treated with ETI for 12 months and included in analyses (mean age at ETI initiation 14·1 years [SD 1·5]; 162 [51%] female and 158 [49%] male participants). Of the 320 participants, 112 (35%) were switched from LI to ETI, and 208 (65%) were CFTR modulator-naive.

In 188 participants with available imaging analysis at both month 0 and month 12, the mean percentage of severely dilated bronchi (based on a bronchial outer diameter to adjacent artery diameter ratio [B(out/)A] of ?1·5) in bronchial generations G(1-6) decreased by 10·7%, from 40·3% (SD 18·9) at month 0 to 29·6% (16·8) at month 12 (p<0·0001). Based on median B(out)/A values of bronchus-artery pairs in the G(1-6) region, 32 (17%) of 188 participants improved from severe to moderate dilatation (B(out)/A ?1·1 and <1·5) and 19 (10%) from moderate to normal dilatation (B(out)/A <1·1) between month 0 and month 12. 14 (7%) participants progressed to a worse dilatation category. The changes in lung imaging metrics were correlated with the changes in sputum proinflammatory biomarkers.

Bronchial dilatations can reverse in adolescents with cystic fibrosis treated with ETI. The correlation with reduced airway inflammation provides insight into the effect of ETI on cystic fibrosis lung disease.

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;