**CFTR modulators therapy**

**Code:** 261  
**Updated:** December 15, 2022

### 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, and 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).


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

The potentiator VX-770 (Ivacaftor; Kalydeco™ 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+3AaG; A455E; S579G; E193K; K1060T, R117C, S945L, 2789-5G?A, A1067T, D1152H, E831X, L206W, R347H, S977F, 3272-26A?G, D110E, D1270N, F1052V, P67L, R352Q, 3849+10kbC?T, R352Q, E56K, F1074L, R74W, R1070W.**

**The corrector VX-445 (Elxacaftor) 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 months with selected class III gating mutations.
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 summarized in the Italian Cystic Fibrosis Foundation website (Stato regolatorio farmaci CFTR modulators).

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

- One in phase 3:
  - VX 121 (a new CFTR corrector)/TEZA/VXS61 (formerly CTP-656: an altered form of potentiator Kalideko),

- Three in phase 2:
  - ABVV-2222 (formerly GLPG2222, a CFTR corrector)/ABBV-3067 (a CFTR potentiator)/ABVV576 (a CFTR corrector)
  - ELX-02 (designed to restore CFTR function in non sense mutations),
  - VX-561 (deutivacafort, a new CFTR potentiator).

- Two in phase one:
  - AD710 (adenoassociated virus vector for gene delivery)
  - VX-522 (inhaled messenger RNA therapy)

- Twelve in pre-clinical phase

Issues

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

Identification of CFTR correctors or potentiators and related mutation targets

Features of CF candidates for therapy with CFTR modulators

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

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

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

What is known

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

One RCT, published in 2002, (Zeitlin 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:
Ataluren 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 Ataluren 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 (Ramsay 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 Tecnotoy Assessment (Whiting P, 2014) even if the high cost and the lack of data about long-term effectiveness have been stressed.

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

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

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

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

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

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

A Cochrane review (Skilton M, 2019) evaluated existing RCTs on potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. The authors concluded that there is no evidence supporting the use of Ivacaftor in people with the F508del mutation. Both G551D phase 2 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 76 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 (TRAIFIC 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 Clearance Index lung func 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 homozygous patients aged 12 years and old showed to be efficacious and safe.

In 2017 (Donaldson SH, 2017) SIMDEKO tested in F508del homozygous 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 pharmacokinetics 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. No safety concerns were found.

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.

A Cochrane Review (Southern SW, 2018) concluded that in CF patients Homozygous 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/ivacaftor 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 KALIDEXO™) 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.

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
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 also observed.

In 2021 (Taylor-Cousar J, 2021), a retrospective survey about pregnancy and infant outcomes in CF women who used TRIKAFTA during pregnancy and/or lactation, has been published. Data about 45 TRIKAFTA exposed pregnancies, showed complications in 2 mothers and 3 infants rated by clinicians as unknown relatedness to TRIKAFTA therapy.

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

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

**Unresolved questions**

**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.

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**Ongoing trials:**

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

A Phase 3, Open-label Study Evaluating the Long Term Safety and Efficacy of VX-659 with VX-661 and VX-770 in Subjects Who Are Homozygous or Heterozygous for the F508del Mutation ([NCT03447262](https://clinicaltrials.gov/ct2/show/NCT03447262?term=VX-659&cond=F508del&draw=2&rank=1)) Vertex Pharmaceuticals Incorporated

A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 with VX-661 and VX-770 in Subjects With Cystic Fibrosis Who Are Homozygous or Heterozygous for the F508del Mutation ([NCT03525574](https://clinicaltrials.gov/ct2/show/NCT03525574)) Vertex Pharmaceuticals Incorporated

A Phase 3b, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del ([NCT 04105972](https://clinicaltrials.gov/ct2/show/NCT04105972)) Vertex Pharmaceuticals Incorporated

A phase 3 RCT on VX-659/VX-661/ VX 770 in Subjects Heterozygous for the F508del Mutation and a Minimal Function Mutation. ([NCT03447249](https://clinicaltrials.gov/ct2/show/NCT03447249)) Vertex Pharmaceuticals

An Open Label Study to Evaluate the Efficacy of Long-term Treatment With PTC-124 in Combination with VX-770 in Subjects With Nonsense Mutation ([NCT03256868](https://clinicaltrials.gov/ct2/show/NCT03256868)) University of Alabama at Birmingham.

A phase 3 study to evaluate efficacy and safety of VX-659/VX-661/ VX 770 in Subjects without an F508del mutation ([NCT05274269](https://clinicaltrials.gov/ct2/show/NCT05274269)) Vertex Pharmaceuticals
A prospective, multicenter observational study to investigate VX-659/VX-661/ VX 770 efficacy in children (6-11 years with one or more copies of F508del mutation. The PROMISE (NCT04613128) Cystic Fibrosis Foundation

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

Age target extension

A phase 2 study to explore the impact of VX-809/VX-770 on disease progression in subjects aged 2 through 5 years, homozygous for F508del (NCT03625466) Vertex Pharmaceuticals Incorporated.


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

A Phase 3, Open Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661/VX-770 in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the F508del CFTR Mutation (NCT02955314) Vertex Pharmaceuticals Incorporated

A Phase 3 Roll-over study to evaluate the safety and efficacy of long-term treatment with VX-661/VX-770 in Subjects aged 6 years and older Homozygous or Heterozygous for the F508del-CFTR Mutation (NCT0357651) Vertex Pharmaceuticals Incorporated

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

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

New compounds

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

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

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

A Phase 2 study to evaluate the safety and efficacy of treatment with ENaC Inhibitor VX-371 in saline compared to saline alone in subjects who are >12 years of age, homozygous for the F508del CFTR mutation, and being treated with Orkambi. (NCT03709109) Vertex Pharmaceuticals Incorporated

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

A Phase 1/2 trial will evaluate safety and tolerability in adults of MRT5005 administered by nebulization measuring changes in CFTR protein levels and CFTR chloride channel activity (NCT03375407) Translate Bio, Inc.

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

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

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

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

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

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

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

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

Keywords

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