CFTR therapy

CFTR modulators therapy

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Background

The current care guidelines for Cystic Fibrosis (CF) patients focus on the secondary pathophysiological effects of the CFTR dysfunctional protein; however, over the last 25 years, specific drugs aimed at the basic defect have been researched and discovered.

Up to now, in an interesting recent review (Lommatzsch ST, 2019), it has been affirmed 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.

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).

The major advantage of the above classification is the possibility of pursuing the same therapeutic strategy within each class.

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).

Recently, evolving knowledge on the molecular mechanisms responsible for defective CFTR “behaviour” has prompted new research focused on “repairing” each phase of the CFTR expression and function, thus creating a new combination of “CFTR modulators” referred to as “triplet CFTR compounds” (Chaudary N, 2018).

Moreover, 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).

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).

Corrective treatments that are mutations-independent and thus applicable to all patients, such as gene therapy, cell-based therapies and activation of alternative ion channels that bypass CFTR, are also being explored. Even if they are in early stages of development (De Boeck K, 2016), recently, the possibility to inhibit the epithelial sodium channel (ENaC) and potentially activate alternative chloride channels, has been studied (Martin SL, 2018) and CRISPR-Cas9, one of the most promising tool for gene editing, is being tentatively applied also to CF (Maranaj M, 2018).

In the international literature, the really significant results achieved by CFTR modulators in terms of clinical impact are summarized (Bell SC, 2015) (Amaral MD, 2015), (Clancy JP, 2018) (Lommatzsch ST, 2019) as well as all related issues (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 DP, 2017); the possibility that chronic treatments with CFTR modulators might have unexpected effects that cannot be predicted from short-term studies (Cholon DM, 2014); the clinical and ethical dilemmas about the high price of these drugs (Jones AM, 2015); the possible impact on fertility (Jones GD, 2015) and on pregnancy (Goss GH, 2016), (Heltshe SL, 2017).

The potentiator VX-770 (Ivacaftor: KalydecoÔ 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 and .

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+3A?G, A455E, D679G, E193K, K1060T, R117C, S945L, 2789+5G?A, A1067T, D1152H, E831X, L206W, R347H, etc.).

The corrector VX-445 (Eluxacaftor) in combination with VX-770 (TRIKAFTA™ by Vertex Pharmaceuticals) to treat patients ages 12 years and older who have at least one copy of the F508del mutation

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

Up to now:  
**KALIDEKO™** has been approved by FDA for patients from the age of ≥ 6 months with selected class III gating mutations, with R117H mutation and with 28 residual function mutations. The European Medicines Agency (EMA) and, specifically in Italy, the Italian Agency for drugs (AIFA), have approved KALIDEKO in patients aged ≥ 2 years who have class III gating mutations and for patients ≥18 years with R11H mutation.

**ORKAMBI™** has been approved for patients with two copies of the F508del mutation and ≥ 2 year old by FDA and EMA, and ≥ 12 yearold by 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 12 years of age or older, by FDA and EMA. Approval by AIFA is underway.

**TRIKAFTA™** has been approved by FDA in october 2019 for people with cystic fibrosis ages 12 and older who have at least one copy of the F508del mutation. Approvals by EMA and AIFA are underway.

**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 January 2020, an international RCT (Konstan MW, 2020) has been published about efficacy and safety of Ataluren in patients with
nonsense-mutation not receiving chronic inhaled aminoglycosides. In this study Ataluren did not demonstrated efficacy on respiratory function nor on pulmonary exacerbations rate.

In 2012 a RCT about 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 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 Technocity Assessment (Whiting P, 2014) even if the high cost and the lack of data about long-term effectiveness have been stressed.

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

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

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

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

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

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

A Cochrane review (Skilton M, 2019) evaluated existing RCTs on potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. The authors concluded that there is no evidence supporting the use of ivacaftor in people with the F508del mutation. Both G551D phase 3 trials demonstrated a clinically relevant impact of ivacaftor on outcomes at 24 and 48 weeks in adults and children (over six years of age) with CF. The R117H trial demonstrated an improvement in the respiratory QoL score, but no improvement in respiratory function. As new mutation-specific therapies emerge, it is important that trials examine outcomes relevant to people with CF.

In 2012 (Clancy JY, 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 (Warenecht 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 (Ratien 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 function 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 .

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 JL, 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 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 homozigous and in F508del/G551D patients resulted in sweat chloride decrease and lung function increase in both patient groups.

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 ™) 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 2018 (Davies JC,2018) a study that evaluated the effects of VX-659-tezacaftor-ivacaftor on Phe508del CFTR protein using human bronchial epithelial cells, showed that the combination therapy significantly improved the processing and trafficking of Phe508del CFTR protein as well as chloride transport in vitro. In patients, VX-659-tezacaftor-ivacaftor had an acceptable safety and resulted in lung function improvement in patients with Phe508del-Minimal Function CFTR mutation. In patients Homozygous for F508del already receiving SIMDEKO, adding VX-659 resulted in a further lung function improvement. The sweat chloride concentrations decreased in both patient populations.

In 2019 (van Koningsbruggen Rietschel S, 2019) a RCT phase 2 study (PELICAN study) showed that GLPG2737 in lumacaftor/ivacaftor-treated CF subjects homozygous for the F508del mutation was well tolerated and yielded significant decreases in sweat chloride concentration versus placebo.

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.

- In the Drug Development Pipeline 2019 of the CFFoundation, besides Kalydeco, Orkambi, Symdeko and Trikafta, already...
available in USA for the patients, 18 compounds are taken into consideration regarding to restore CFTR function:

**nine in phase 2:** VX-561 (formerly CTP-656; an altered form of potentiator Kalideko), *ABVV-2222* (formerly GLP2222) a CFTR corrector, *ABBV-3067* a CFTR potentiator, *ELX-02* (designed to restore CFTR function in non-sense mutations), *FDL169* (a new CFTR corrector), *PTI-428* (a CFTR amplifier), *PTI-801* (a new CFTR corrector), *PTI-808* (a new CFTR potentiator), *VX-121* (a new CFTR corrector).

**one in phase one:** *MRT5005* (designed to restore CFTR function by mRNA)

**eight in pre-clinical phase**

- **Ongoing trials:**

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

  A Phase 3b, in subjects aged 12 years and older who are homozygous for the F508del and who **discontinued treatment with Orkambi** due to respiratory symptoms considered related to treatment. This study is designed to evaluate the safety and efficacy of VX-661/VX-770 (NCT03150719) Vertex Pharmaceuticals Incorporated

  A rollover study to evaluate the safety and efficacy of long-term treatment with VX-809/VX-770 in subjects aged 6 years and older (NCT02544451) Vertex Pharmaceuticals Incorporated

  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) Vertex Pharmaceuticals Incorporated

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

  A Phase 3b, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-445/Tezacaftor/Ivacaftor in Cystic Fibrosis Subjects, Homozygous for F508del (NCT 04105972) Vertex Pharmaceuticals Incorporated

  A Phase 3, Open-label, Rollover Study to Evaluate the Safety and Efficacy of Long Term Treatment With VX-661/ VX-770 in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous or Heterozygous for the F508del-CFTR Mutation (NCT02565914) Vertex Pharmaceuticals Incorporated.

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

  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.

**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.

Safety and Pharmacokinetic Study of VX-809/VX-770 in Subjects from 1 to Less Than 2 Years of Age, Homozygous for F508del (NCT03601637) Vertex Pharmaceuticals Incorporated

A Phase 3 trial to evaluate the efficacy of VX-661/VX-770 in subjects aged 6 through 11 years, who are homozygous for the F508del or heterozygous for F508del with an eligible residual function mutation (NCT03559062) Vertex Pharmaceuticals Incorporated.

A Phase 3, Open Label Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of VX-661/VX-770 in Subjects 6 Through 11 Years of Age With Cystic Fibrosis, Homozygous or Heterozygous for the F508del CFTR Mutation (NCT02953314) Vertex Pharmaceuticals Incorporated.
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 (NCT03537651) Vertex Pharmaceuticals Incorporated

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

New targets for already studied compounds

A Phase 3 randomized, controlled, crossover study to evaluate the efficacy of VX-770 in CF patients who are 6 years of age and older and have either a 3849 + 10KB C>T or D1152H CFTR mutations (NCT03068312) Vertex Pharmaceuticals Incorporated

A Phase 4 study to evaluate efficacy of VX-661/VX-770 and VX-770 alone in Patients With W1282X Mutation (NCT03624101) University of Alabama at Birmingham

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 (NCT03911713) Vertex Pharmaceuticals Incorporated

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

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

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

A Phase 1/2 trial will evaluate safety and tolerability in adults of MR5005 administered by nebulization measuring changes in CFTR protein levels and CFTR chloride channel activity (NCT03375047) Translate Bio, Inc.

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

A clinical Phase 1, open-label, single-center study designed to evaluate the pharmacokinetics profile of a single oral dose of GLPG3067 in adult male subjects with cystic fibrosis (NCT03358931) Galapagos NV.

A Phase 1b, multi-center, open-label, nonrandomized multiple cohorts study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of a combination treatment of GLPG2451 and GLPG2222, with and without GLPG2737, in adult subjects Homozygous for the F508del CFTR mutation and Heterozygous for the F508del CFTR mutation with a potentiator non-responsive mutation on the second allele (NCT03540524) Galapagos NV.

A Phase 2 RCT to Evaluate Safety, Pharmacokinetics and Pharmacodynamics FDL169 in Subjects Homozygous for the F508del-CFTR Mutation (NCT03093714) Flatley Discovery Lab LLC.

A Phase 1 Study to Assess the Safety, Tolerability and Pharmacokinetics Profile of FDL176 in Healthy and CF subjects (NCT03173573) Flatley Discovery Lab LLC.

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 1/2 study assessing PTI-428 safety, tolerability, and pharmacokinetics in subjects including also those in treatment with VX-809/VX-777 and those in treatment with VX-770. (NCT02718495.) 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

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