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Efficacy of lumacaftor-ivacaftor for the treatment of cystic fibrosis patients homozygous for the F508del-CFTR mutation

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Abstract

Cystic fibrosis (CF) results from mutations in the CF transmembrane conductance regulator (CFTR) gene, which codes for the CFTR channel protein. The most common mutation in CF is F508del, which produces a misfolded protein with diminished channel activity. The development of small-molecule CFTR-modulator compounds offers an exciting and novel approach for pharmacological treatment of CF. The corrector lumacaftor helps rescue F508del-CFTR to the cell surface, and potentiator ivacaftor increases F508del-CFTR channel activity. The combination of lumacaftor-ivacaftor (Vertex Pharmaceuticals Incorporated) represents the first FDA-approved therapy for CF patients with two copies of the F508del mutation. Although this combination therapy is the first treatment to directly target the F508del-CFTR mutation, patients taking this drug displayed only modest improvements in lung function. This article summarizes recent data from clinical trials and research discoveries relating to the lumacaftor-ivacaftor treatment, and considers options for identifying future therapies that will be most efficacious for all CF patients.

Keywords

CFTR; cystic fibrosis; lumacaftor; ivacaftor; F508del; modulator

1. Introduction

Cystic fibrosis (CF) is the most common life-limiting genetic disease in Caucasians. The underlying defect in CF is abnormal epithelial ion transport resulting from mutations in the

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Information resources

More information about CF including drugs currently in development and on-going clinical trials is available at the Cystic Fibrosis Foundation website (www.cff.org). Additional information on the lumacaftor-ivacaftor combination therapy and other Vertex drugs and Vertex press releases is available at their website (www.vrtx.com).

Declaration of interest

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CFTR protein, which mediates Cl^- and HCO_3^- transport of secretory and absorptive epithelial cells in multiple organs including lungs, pancreas, liver, intestine, and sweat glands. Although CF affects many organ systems, the primary cause of morbidity and mortality is airway disease related to disturbances of airway surface liquid (ASL) homeostasis. The absence of CFTR activity results in decreased Cl^- transport and enhanced Na^+ uptake via the epithelial sodium channel (ENaC) in airway epithelial cells, leading to excessive water absorption and the characteristic thick secretions [1–3]. Recent findings highlight the importance of CFTR-dependent HCO_3^- transport in mucus formation and clearance [4–6]. The thick and viscous mucus leads to mucus stasis, airway obstruction, persistent infection, inflammation, and a progressive decline in lung function [7–9]. Major clinical advances in treating the symptoms and delaying disease progression have significantly improved survival of CF patients [10]. Much of the progress in extending life expectancy has been due to comprehensive treatments including antibiotics to eradicate and/or manage bacterial lung infections as well as improved strategies to increase mucociliary clearance and nutritional status [11, 12].

Although substantial clinical gains have been made using therapies that targeted the consequences of CFTR dysfunction, the ultimate therapeutic goal is to restore normal (or near normal) CFTR function via drugs that modulate the activity of CFTR (CFTR modulators). However, this strategy is complicated by the fact that there are nearly 2000 different mutations that can cause CF and interfere with normal CFTR function in different ways. The most common CFTR mutation, F508del, produces a protein with a trafficking defect that prevents significant amounts of the protein from reaching the apical cell surface, and those proteins that do reach the surface are defective in channel gating [13]. This mutation is found in approximately 90% of CF patients in the US, with nearly 50% of patients homozygous for this mutation. Because the majority of CF patients carry the F508del mutation, the identification of therapeutics that correct this defect represents an attractive initial approach. Importantly, cross-sectional studies of patients with various residual levels of CFTR activity suggest that even 5% of normal CFTR activity could convey clinical benefit [14].

2. Overview of the market

According to the FDA website (www.fda.gov), an orphan disease is a disease that affects fewer than 200,000 people in the U.S. CF is therefore considered an orphan disease because it affects approximately 30,000 people in the U.S., as reported by the Cystic Fibrosis Foundation (www.cff.org). Of these individuals with CF, only 5% have a CFTR gating mutation such as G551D that may benefit from ivacaftor (Kalydeco; Vertex) treatment [15] but 50% are F508del-CFTR homozygotes that may benefit from the lumacaftor-ivacaftor combination treatment (Orkambi; Vertex) [16]. Nevertheless, costs of care for individual CF patients are high [17], and the CF drug market was predicted to reach $3.9 billion by 2019 based on annual revenues of individual therapeutic agents in the hundreds of millions of dollars [18]. However, this prediction was made prior to the introduction of CFTR modulators and may have underestimated the market, since these modulators have been priced aggressively with annual costs over $250,000–$300,000 [19, 20]. Ivacaftor has estimated annual revenues over $600 million, and the more recently released lumacaftor-

ivacaftor combination treatment has quarterly revenues that would support annual revenues of $1 billion dollars or more. These figures suggest that the market for CFTR modulators is potentially lucrative.

Both ivacaftor and the lumacaftor-ivacaftor combination drug have the market advantage of being the only drugs for their indication, as there are currently no other CFTR modulators approved by regulatory agencies. However, there are a large number of potential competitor compounds in various stages of clinical development, including some that are in late phase clinical trials. As described in more detail below, the clinical benefit seen in patients treated with the lumacaftor-ivacaftor combination therapy was modest, leaving opportunities for other drugs that have greater clinical impact [21]. Furthermore, the lumacaftor-ivacaftor drug was not effective in patients heterozygous for the F508del mutation, suggesting that a more potent modulator may be applicable to a larger group of patients.

There are several CFTR modulators currently in development (Table 1). Examples being tested in clinical trials include the following: N91115 (Nivalis), an S-nitrosoglutathione reductase (GSNOR) inhibitor predicted to function as a CFTR stabilizer, that is in phase 2 trials for F508del homozygous patients who are taking the lumacaftor-ivacaftor combination drug. QR-010 (ProQR Therapeutics), which repairs the genetic defect in RNA, is in phase 1b for F508del homozygous patients. QBW251 (Novartis), a CFTR modifier, is in phase 2 clinical trials for F508del homozygous and heterozygous patients. Riociguat (Bayer), stimulator of soluble guanylate cyclase, is in phase 2 for F508del homozygous patients, and is predicted to improve sweat chloride content and increase FEV_1. AbbVie/Galapagos has developed a triple-combination therapy with two corrector compounds (GLPG2222 and GLPG2665) and one potentiator (GLPG1837). VX-661 (Vertex) is a corrector compound expected to have a lower likelihood of drug interactions with ivacaftor, and is generally well tolerated by patients. VX-661 combined with ivacaftor is in phase 3 trials in patients homozygous for F508del allele, or heterozygous for F508del in which the copy of CFTR on their other chromosome is grouped according to the following responses to therapies: 1) is not predicted to respond to therapy, 2) has residual function, or 3) responds to ivacaftor. The results of a phase 2 study using VX-661 with and without ivacaftor in F508del homozygous patients showed reductions in sweat chloride with VX-661 alone and in the presence of ivacaftor, and showed significant but modest improvements in lung function (FEV_1) [22], similar to what was observed with the lumacaftor-ivacaftor combination therapy. If successful, these drugs being tested in the clinic may enter the market soon.

3. Introduction to the drug

CFTR modulators aimed at improving function of F508del mutation are generally divided into 2 main categories: correctors that rescue misfolded protein to the cell surface, and potentiators that improve channel activity [23]. Using high-throughput screening strategies, a series of small-molecule corrector compounds were identified that have corrector or potentiator activity that were then optimized through medicinal chemistry [24–28]. The initial corrector compound for clinical development was lumacaftor (structure shown in Figure 1, bottom), which has the chemical name 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2-yl]benzoic acid. The molecular formula

of lumacaftor is $C_{24}H_{18}F_2N_2O_5$ and the molecular weight is 452.41. In CF patients, the half-life of lumacaftor alone is approximately 26 hours [29]. Nearly all of lumacaftor (approximately 99%) is bound to plasma proteins, mainly albumin. In humans, the majority of lumacaftor is not extensively metabolized and is therefore excreted unchanged. However, in vitro and in vivo data have shown that the small amount of lumacaftor that is metabolized is done so via oxidation and glucuronidation [29]. Lumacaftor is thought to increase the conformational stability of CFTR by improving interactions of the intramolecular domains of CFTR protein during folding [30–33]. Data suggest that lumacaftor binds directly to CFTR [34] and restores F508del maturation and function up to 15% of WT CFTR in vitro [30–33, 35–37]. However, studies in cultured cells demonstrated that the channel activity of F508del-CFTR rescued to the cell surface remained low due to the residual gating defect [38]. This problem could be addressed through addition of the potentiator ivacaftor, which has the chemical name N-(2,4-di-tertbutyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. The molecular formula of ivacaftor is $C_{24}H_{28}N_2O_3$ and the molecular weight is 392.49. In healthy subjects, the half-life of ivacaftor when combined with lumacaftor is approximately 9 hours. Ivacaftor is a hydrophobic molecule and most of it (approximately 99%) is bound to plasma proteins, mainly alpha 1-acid glycoprotein and albumin [39]. In humans, ivacaftor undergoes extensive metabolism. In vitro and in vivo data indicate that metabolism of ivacaftor occurs primarily through CYP3A [40]. In cell cultures treated with lumacaftor and ivacaftor, it was found that ivacaftor accumulated in cells [41]. Ivacaftor was initially developed to improve activity of CFTR mutants with gating defects and was first approved to treat CF patients with the G551D mutation [42–45]. Ivacaftor appears to directly affect CFTR channel gating and was later approved for other gating mutations (G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D) as well as R117H. Ivacaftor also activates rescued F508del-CFTR that is present at the cell surface [45, 46], and the combination of lumacaftor with acute addition of ivacaftor yielded significantly improved F508del-CFTR channel activity in vitro [37]. Based on these studies and early phase clinical trials described below, the lumacaftor-ivacaftor combination therapy was predicted to result in an improvement in ASL hydration and produce more hydrated mucus that will enhance microbe clearance from the lungs, as reviewed in [16, 47, 48] and illustrated in Figure 2. The lumacaftor-ivacaftor drug is a tablet for oral administration containing 200 mg of lumacaftor and 125 mg of ivacaftor. For pharmacodynamics of ivacaftor-lumacaftor, changes in sweat chloride activity were measured in patients in the phase 2 clinical trial [49]. The difference between lumacaftor-ivacaftor treatment (lumacaftor 400 mg/ivacaftor 250 mg every 12 hours) and placebo was −11 mmol/L (95% CI −18, −4). However, this decrease in sweat chloride levels did not directly correlate with an improvement in lung function, as measured by FEV_1 [29].

4. Clinical efficacy

Although lumacaftor alone showed a strong increase in formation of mature F508del-CFTR in vitro [37], a phase 2a clinical study of CF patients homozygous for the misfolded F508del-CFTR mutation treated with lumacaftor did not show any significant changes in lung function at any of four dose levels tested (25, 50, 100, or 200 mg once daily) [50]. This was not entirely surprising, since CFTR rescued to the cell membrane by lumacaftor was

known to have reduced channel activity and rapid turnover from the cell surface [38, 51]. Therefore, a second Phase 2 clinical trial was conducted that combined lumacaftor at various doses with ivacaftor to address the gating defect [49], summarized in Table 2. In CF patients homozygous for the misfolded F508del-CFTR mutation, treatment with a combination of lumacaftor and ivacaftor resulted in modest but meaningful improvements in lung function, with the most significant effects at the higher lumacaftor doses (600 mg daily or 400 mg twice daily). However, in the same phase 2 trial, combination therapy using ivacaftor with lumacaftor in F508del heterozygous patients did not result in a significant change in FEV_1 [49].

Based on the phase 2 results, two phase 3 clinical trials, TRAFFIC and TRANSPORT, were conducted using a combination of lumacaftor (600 mg daily or 400 mg twice daily) and ivacaftor (250 mg twice daily) in patients 12 years and older homozygous for the F508del-CFTR mutation [52], summarized in Table 2. Both trials met their primary outcome measure of statistically significant improvement in FEV_1, although the increase of 2.6–4% [52] were modest and significantly below those observed with ivacaftor in CF patients with gating mutations (10.6–12.5%) [15, 54]. The TRAFFIC and TRANSPORT studies did show significant reduction in pulmonary exacerbations as an important secondary outcome measure, as well as other secondary measures including the Cystic Fibrosis Questionnaire-Revised (CFQ-R) quality of life respiratory scale and body mass index. Adverse events were generally similar between placebo and treatment groups, with the exception of increased chest tightness noted more frequently in the treatment groups.

The phase 3 TRAFFIC and TRANSPORT clinical studies lasted for 24 weeks, and the ongoing PROGRESS extension study is designed to address longer term effects. Preliminary results from PROGRESS suggest that improvements in lung function (FEV_1) and secondary outcomes in CF patients aged 12 and older with 2 copies of the F508del mutation taking lumacaftor-ivacaftor were maintained for an additional 24 weeks, though there were no further improvements [55].

5. Post-marketing surveillance

Since the lumacaftor-ivacaftor combination therapy was only recently approved in July of 2015, at this time there are no post-marketing surveillance data available beyond the PROGRESS extension study mentioned above. The results of safety and tolerability analyses in the PROGRESS extension study indicated that adverse events were similar to what was observed during the first 24 weeks of the study, with the most commonly observed events including shortness of breath, chest tightness, viral infection of the upper respiratory tract, and gastrointestinal symptoms, as listed in adverse events tables of the phase 2 and phase 3 trials [49, 52]. An observational study, PROSPECT, is ongoing and focuses on examining biomarkers of CFTR function and banking of specimens. This study will evaluate potential outcome markers including FEV_1 and sweat chloride in CF patients that have either partial or absent CFTR function (Part A) or are F508del patients receiving lumacaftor-ivacaftor combination treatment (Part B).

6. Regulatory affairs

The lumacaftor-ivacaftor combination therapy was approved for use in the US by the FDA, in Europe by the EU, and in Australia by the TGA in CF patients ages 12 and older who are homozygous for the F508del mutation [56–58]. There are approximately 8,500 CF patients in the US, 12,000 CF patients in Europe, and 1,000 CF patients in Australia who fit these criteria.

7. Conclusion

Up until recently, treatments for CF addressed only symptoms, but it is now clear that compounds that directly modulate the activity of CFTR represent a viable therapeutic strategy. In some ways, treatment with lumacaftor-ivacaftor represents a breakthrough therapy, since it is the first CFTR modulator that provides benefit for patients carrying the most common mutation in CF. However, despite very promising in vitro studies, the results from clinical studies showed only modest improvement. As discussed further below, additional laboratory studies have revealed that potentiator ivacaftor might destabilize F508del-CFTR rescued by lumacaftor. Such studies offer opportunities to develop more potent drugs and drug combinations for F508del and other CFTR mutations, with the ultimate goal of restoring CFTR activity in all patients with CF.

8. Expert commentary

The lumacaftor-ivacaftor drug received the designation of breakthrough therapy [59, 60]; however, the clinical impact on lung function and pulmonary exacerbations was less than that of ivacaftor in G551D patients and more similar to previous CF therapies targeted at downstream pathophysiology including dornase alfa (to cleave DNA, which breaks down thick secretions), hypertonic saline (to hydrate viscous mucus), or azithromycin (to fight bacteria) [20, 61–63]. In vitro studies on the action of lumacaftor and ivacaftor indicated that corrected F508del-CFTR is destabilized in the presence of these 2 compounds [41, 64], which may explain why the lumacaftor-ivacaftor combination treatment was less successful than anticipated and exemplifies the value of bench research to guide clinical drug development [65, 66]. There was hope that the newer corrector VX-661 might avoid the destabilizing effect of ivacaftor, but in vitro studies suggest that this may not be the case [41, 64] as ivacaftor interfered with restoring F508del-CFTR function whether lumacaftor or VX-661 was used as the corrector.

For future translation of promising in vitro data to clinical efficacy, the bioavailability of the agents’ exact drug concentrations in lung tissue should be considered. Matthes et al. [67] suggested that the inhibitory effects of the lumacaftor-ivacaftor combination therapy is due to high concentrations of free ivacaftor present in plasma, and that improving CFTR function would require lowering potentiator concentration and using more efficacious correctors. It was recently discovered that some other potentiators did not appear to markedly inhibit the correction of F508del [64, 68]. While it is important to identify potentiators that do not interfere with corrector action or CFTR stability, the goal should be

to develop drug combinations that exhibit additive or synergistic effects to obtain a marked improvement in CFTR function in vitro, and ultimately, patient lung function.

The clinical improvements seen in trials with lumacaftor-ivacaftor may be due to activity of this drug that is not directly related to the CFTR molecule. There is evidence that ivacaftor displays antimicrobial activity [69], which may enhance lung function by clearing infective microbes from the lung. An increase in CFTR activity is predicted to improve viscoelastic properties of mucus in CF patients, which in turn will lead to enhanced lung function [70]. However, whether the lumacaftor-ivacaftor drug might also directly affect mucus properties has not yet been investigated. It should also be considered that in vitro studies using ivacaftor have resulted in decreased activity of ENaC [41], which leads to an increase in airway surface hydration that may contribute to the observed improvement in lung function [71]. Although ENaC is regulated by CFTR, the drug activity of ivacaftor may be directly affecting ENaC. Indeed, modulation of ENaC activity is a strategy that is of interest to companies seeking to identify pharmaceuticals that repair the CF defect [72].

In October 2015, Vertex described next-generation correctors, VX-152 and VX-440, which are predicted to further improve rescue and activity of F508del-CFTR [73]. In HBE cells from patients homozygous for the F508del mutation, combining VX-152 or VX-440 together with VX-661 plus ivacaftor (triple combinations) resulted in chloride transport that was approximately three-fold greater than what was observed upon the lumacaftor-ivacaftor combination treatment of cells with the same genotype [73]. Importantly, similar findings were observed in HBE cells from patients heterozygous for F508del mutation in which the copy of CFTR on the other chromosome contains a mutation that results in minimal CFTR function. Treatment using these triple combinations also resulted in a significant increase in cilia beat frequency compared to treatment of cells with the same genotype with the lumacaftor-ivacaftor drug. These in vitro data using cell cultures suggest that a triple combination that includes a next-generation corrector with VX-661 plus ivacaftor may improve CFTR function in patients that are homozygous for the F508del mutation and in patients that are heterozygous for the F508del mutation when the other CFTR gene codes for a protein that displays minimal CFTR function. These correctors will be tested both alone and in combination with VX-661 plus ivacaftor in Phase 1 studies. Until more efficacious potentiators are identified, increasing corrector activity with multiple correctors [32] or addition of stabilizers may compensate for the detrimental effects of ivacaftor.

Considering the high cost of ivacaftor and the lumacaftor-ivacaftor combination therapy, an attractive goal is to identify drugs that target multiple CFTR defects to augment CFTR at the cell surface, channel function, and protein stability. Thus, discovery of new drug therapies should be aimed at identifying: 1) correctors that further improve processing of mutant CFTR to augment levels of CFTR at the cell surface, 2) correctors that also display substantial potentiator function, 3) correctors that also stabilize CFTR, 4) potentiators that do not destabilize CFTR, 5) stabilizers that can be used with correctors/potentiators. Because currently used potentiators are extremely expensive and their activity leads to destabilization of rescued F508del-CFTR at the plasma membrane, novel correctors that rescue the F508del-CFTR trafficking defect and also stabilize the protein at the cell surface may eliminate the need for potentiators.

9. Five-year view

The introduction of ivacaftor and the lumacaftor-ivacaftor combination therapy represent a turning point in treatment of CF, both because of their direct impact on CF care and what they represent for the future of CFTR modulators. The next five years will hopefully see approval of multiple other CFTR modulators that address different aspects of CFTR dysfunction. These will provide multiple options for individual CF patients, which we predict will be necessary to provide optimal care given the plethora of CFTR mutations that can cause disease.

The availability of new CFTR modulators will require us to rethink how we classify CFTR mutations. CFTR mutations have historically been grouped into different classes according to their defects. For example the misfolding mutation, F508del-CFTR, belongs to Class II while the gating mutation, G551D-CFTR, belongs to Class III. It could be anticipated that patients with other misfolding mutations may benefit from lumacaftor-ivacaftor combination treatment. However, while it would seem that different mutations that belong to the same class should respond similarly to drug treatments, recent observations indicate that the original mutation classifications do not accurately describe responses to CFTR modulators [74, 75]. Furthermore, patients with identical CFTR mutations may show diverse drug responses.

These observations suggest that a precision medicine approach will likely be needed to optimize patient therapies. One such approach involves the use of organoids readily prepared from rectal [35], bronchial, and nasal tissues derived from individual CF patients. These spheroid cultures display acute volume changes resulting from ion and fluid movement upon CFTR activation by drug treatments. Additionally, nasal and bronchial spheroid cultures can be used for examining mucus properties and ciliary function. This precision ex vivo approach would potentially allow testing of different combinations and doses of correctors and potentiators in individual patients, allowing development of optimal treatment strategies for each CF patient. Such studies are imperative for identifying and conducting preclinical testing of candidate compounds before they enter the clinical trials, maximizing the likelihood of achieving the dramatic enhancements in lung function and secondary outcomes necessary to make the therapy a worthwhile product for CF patients.

Approval of other CFTR modulators may also address concerns over cost. The lumacaftor-ivacaftor combination therapy is currently priced at $259,000 per year [19, 20], with ivacaftor at $311,000 per year [19], and the two drugs are predicted to represent well in excess of $1 billion dollars in revenue for Vertex Pharmaceuticals Inc. These revenues represent an enticing motivation for investment, which is enhanced by their orphan drug status that provides the manufacturer with certain benefits such as financial incentives and market exclusivity [20, 59]. However, this orphan drug designation also results in disproportionate overpricing, which may be unsustainable by patients and health insurance companies, particularly since these therapies would ideally be utilized throughout the life of a CF patient [76]. The relatively modest benefits of the lumacaftor-ivacaftor drug coupled with its high price have led many to question whether its clinical effect can justify its cost

[19]. Competition from other drugs that convey similar benefits could help reduce the cost to patients, as could more effective treatments that alter the cost-benefit ratio.

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Papers of particular interest are identified as:

* = of interest

** = of considerable interest

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Key issues

- Cystic fibrosis results from mutations in the CFTR gene, which codes for the CFTR channel protein. The most common mutation in CF patients is F508del, which produces a misfolded protein with diminished channel activity.
- Corrector and potentiator compounds directly affect CFTR function. Compounds predicted to enhance CFTR activity are currently in the clinical drug pipeline.
- The lumacaftor-ivacaftor drug is an FDA-approved combination therapy administered to CF patients homozygous for F508del-CFTR; however, this therapy resulted in modest improvements in lung function.
- Strategies to identify novel therapeutics must focus on drug combinations that improve CFTR maturation, function, and stability, thereby enhancing mucociliary clearance in the lungs. Preclinical laboratory testing of candidate compounds is important for understanding drug mechanisms.
- The goal of identifying effective therapies is to maximize benefit to patients without unreasonable costs.

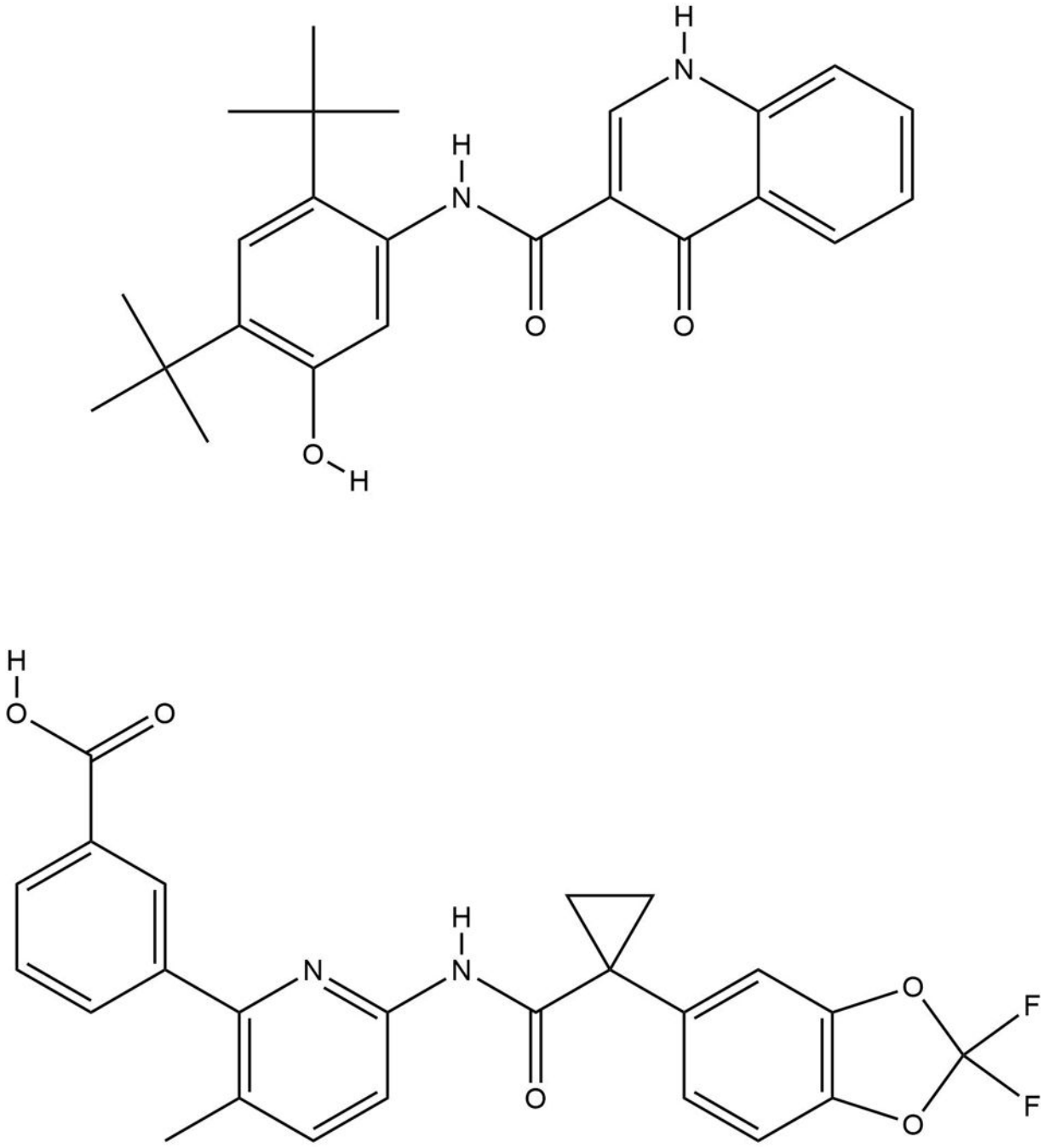

Figure 1. Drug Structures

Chemical structures of ivacaftor (top) and lumacaftor (bottom) are shown.

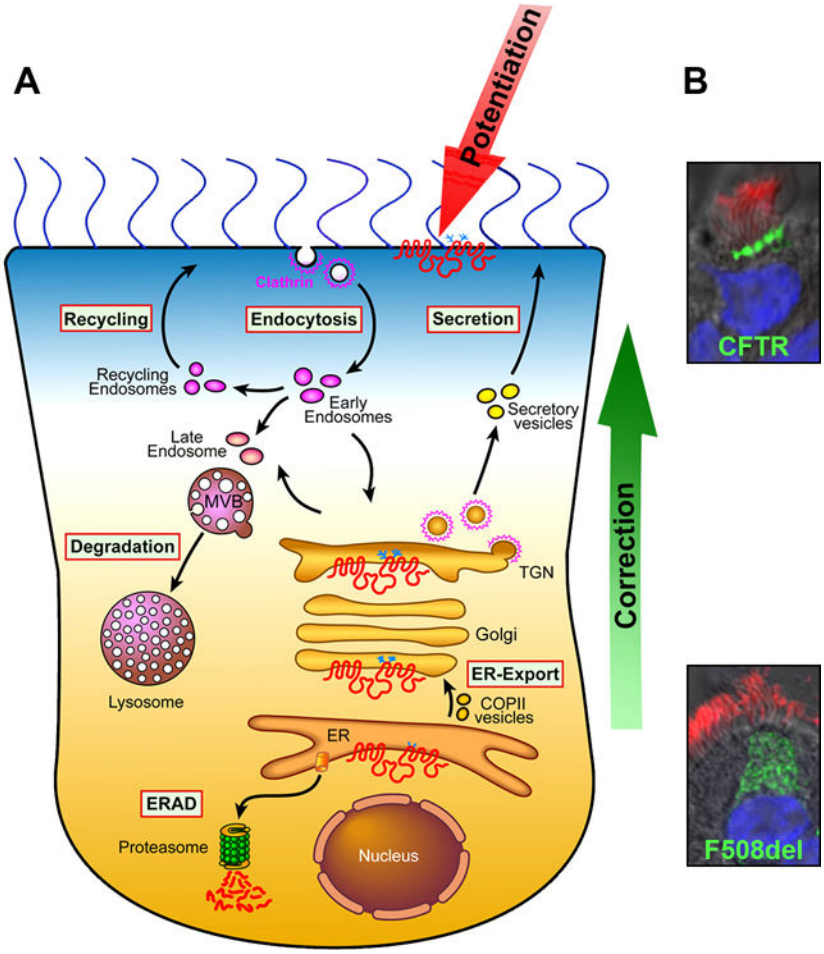

Figure 2. Correction and Potentiation of CFTR

A. Correctors promote transfer of mutant CFTR from the ER to the apical membrane, whereas potentiators enhance activity of apical CFTR. B. Trafficking defect of F508del-CFTR. Confocal immunofluorescence images show apical WT and intracellular-retained F508del-CFTR (green) expressed as Extope-variant in primary HBE cells. Cilia are stained in red and nuclei in blue.

Table 1

CFTR-targeting drugs currently in the drug pipeline or in clinical trials.

Company	Compound
AbbVie/Galapagos	Triple-combination therapy with two corrector compounds (GLPG2222 and GLPG2665) and one potentiator (GLPG1837)
Bayer	Riociguat to correct F508del function
Calista Therapeutics	CAL inhibitor CT-007 to stabilize CFTR at the cell membrane
Concert Pharmaceuticals	Potentiator compound CTP-656, a deuterium-modified version of ivacaftor
DiscoveryBioMed	Dual acting correcting and activating CFTR ligand
Flatley Discovery Lab	Corrector compounds FDL160, FDL169 FDL042(FDL282), FDL392, and FDL304
Genzyme/Sanofi	Non-viral gene transfer agent (PGM169/GL67A), corrector compounds for F508del-CFTR
Nivalis Therapeutics	N91115 to stabilize rescued F508del-CFTR
Novartis	Potentiator compound (QBW251) and other potentiator and corrector compounds (picolinamide)
Parion	Corrector compounds
PTC Therapeutics	Ataluren for treatment of CFTR nonsense mutations*
Pfizer	Corrector compounds (PYR-41 decreases the CFTR ubiquitination) and potentiator compounds (CP-628006)
ProQR Therapeutics	QR-010, a 33mer antisense oligonucleotide designed to repair F508del-CFTR encoded mRNA
Proteostasis Therapeutics	CFTR amplifier (PTI-428) that increases the levels of CFTR; combination of PTI-428 with corrector and potentiator compound (PTI-NC-733)
Reata Pharmaceuticals	Corrector compounds
Shire Rare Disease Unit	Technology to deliver normal CFTR to the lungs
Southern Research	Repurposing of known drugs for translational readthrough of rare CF nonsense mutations*
Traffick Therapeutics/AmorChem/NuChem Therapeutics	Correctors (NU001 and NU002) that are synergistic with VX-809 or VX-661 and VX-770
Vertex Pharmaceuticals	Next-generation correctors VX-152 or VX-440 that will be combined with corrector VX-661 and potentiator VX-770

*These compounds do not target F508del and therefore do not overlap with the therapeutic action of the lumacaftor-ivacaftor drug.

Table 2

Summary of phase 2 (Boyle et al [49]) and phase 3 (Wainwright et al [52]) studies with ivacaftor-lumacaftor combination treatment in CF patients ages 12 and older who are homozygous for F508del-CFTR.

Study	FEV_1*	BMI†	CFQ-R‡	Pulmonary exacerbations§	Number of participants
Phase 2 study, 8 weeks [37]					
Lumacaftor 200 mg/day	3.8 (−0.4 to 8.1)				23
Ivacaftor 250 mg twice/day	*P*= 0.077				
Lumacaftor 400 mg/day	2.7 (−1.7 to 7.0)				21
Ivacaftor 250 mg twice/day	*P*= 0.225				
Lumacaftor 600 mg/day	5.6 (1.2 to 10.0)				21
Ivacaftor 250 mg twice/day	*P*= 0.013				
Lumacaftor 400 mg twice/day	4.2 (−1.3 to 9.6)				11
Ivacaftor 250 mg twice/day	*P*= 0.132				
Phase 3 study, 24 weeks [38]					
TRAFFIC					
Lumacaftor 600 mg/day	4.0 (2.6 to 5.4)	0.16 (−0.04 to 0.35)	3.9 (0.7 to 7.1)	0.72 (0.52 to 1.00)	183
Ivacaftor 250 mg twice/day	*P*< 0.001	*P*= 0.11	*P*= 0.02	*P*= 0.05	
Lumacaftor 400 mg twice/day	2.6 (1.2 to 4.0)	0.13 (−0.07 to 0.32)	1.5 (−1.7 to 4.7)	0.66 (0.47 to 0.93)	182
Ivacaftor 250 mg twice/day	*P*< 0.001	*P*= 0.19	*P*= 0.36	*P*= 0.02	
TRANSPORT					
Lumacaftor 600 mg/day	2.6 (1.2 to 4.1)	0.41 (0.23 to 0.59)	2.2 (−0.9 to 5.3)	0.69 (0.52 to 0.92)	185
Ivacaftor 250 mg twice/day	*P*< 0.001	*P*< 0.001	*P*= 0.17	*P*= 0.01	
Lumacaftor 400 mg twice/day	3.0 (1.6 to 4.4)	0.36 (0.17 to 0.54)	2.9 (−0.3 to 6.0)	0.57 (0.42 to 0.76)	187
Ivacaftor 250 mg twice/day	*P*< 0.001	*P*< 0.001	*P*= 0.07	*P*< 0.001	
TRAFFIC + TRANSPORT Pooled					
Lumacaftor 600 mg/day	3.3 (2.3 to 4.3)	0.28 (0.15 to 0.41)	3.1 (0.8 to 5.3)	0.70 (0.56 to 0.87)	368
Ivacaftor 250 mg twice/day	*P*< 0.001	*P*< 0.001	*P*= 0.007	*P*= 0.001	
Lumacaftor 400 mg twice/day	2.8 (1.8 to 3.8)	0.24 (0.11 to 0.37)	2.2 (0.0 to 4.5)	0.61 (0.49 to 0.76)	369
Ivacaftor 250 mg twice/day	*P*< 0.001	*P*< 0.001	*P*= 0.05	*P*< 0.001	

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[*] Difference versus placebo for absolute change in percentage predicted FEV_1 (percentage points; 95% CI).

[†] Difference versus placebo in absolute change from baseline BMI; mean (95% CI).

[‡] Difference versus placebo in absolute change from baseline in CFQ-R respiratory domain; mean (95% CI). The minimal clinically important difference for stable patients on this scale is 4.0 points [53].

[§] Rate ratio (95% CI)

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