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New Therapeutic Approaches to Modulate and Correct CFTR

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Abstract

Personalized medicines are now available for over half the cystic fibrosis (CF) population with genotype-directed therapies that target the underlying defect of CF, abnormal cystic fibrosis transmembrane conductance regulator (CFTR) protein. This review summarizes current strategies that have been the foundation for development of CFTR modulators and focuses on recently approved therapies that improve the function and availability of CFTR protein. Lessons learned from dissemination of ivacaftor (Kalydeco) across the CF population responsive to this therapy as well as future approaches to predict and monitor treatment response of CFTR modulators are also discussed. The goal remains to expand patient-centered and personalized therapy to every person with CF, ultimately significantly improving life expectancy and quality of life for this disease.

Keywords

CFTR modulator; personalized medicine; therapeutics; potentiator; corrector

Introduction

The science of personalized medicine is taking shape in the cystic fibrosis (CF) community with genotype-directed therapies available for over half of the CF population. Personalized or precision medicines approach the treatment of disease by accounting for an individual's variability in genes, environment, and lifestyle. (1)

This momentum in precision medicine launched with the basic understanding of CF as a result of mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. (2–4) In the decades since CFTR gene identification, knowledge of CFTR mutations and their pathophysiologic consequences has rapidly expanded leading to the development of small-molecule therapies that target specific CFTR variants that have some level of CFTR protein produced. (5) These small molecule therapies are defined as CFTR modulators, a

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novel class of precision medicines directed to improve CFTR function and/or presence at the cell surface level.

In this review, we focus on therapeutic approaches, known as “potentiators” and “correctors” that explore our understanding of specific CFTR variants and aim to augment or repair function of the CFTR protein.

Approaching CFTR: Review of Structure and Function

CFTR, located in the apical membranes of epithelial cells in multiple exocrine organs, is a chloride and bicarbonate ion channel that regulates salt and fluid homeostasis. (6) The CFTR glycoprotein has multiple membrane-integrated subunits that form two membrane spanning domains (MSD), two intracellular nucleotide-binding domains (NBD) and a regulatory (R) domain, which acts as a phosphorylation site. (7, 8) MSD1 and MSD2 form the channel pore walls. Opening and closing of the pore is through ATP interactions with cytoplasmic NBD domains, leading to conformational changes of MSD1 and MSD2. (9) Gating and conductance is regulated through R domain phosphorylation with protein kinase A (PKA). (7)

The intricate regions of CFTR require processing and maturation to allow precise folding. CFTR structure must satisfy rigorous quality standards to be exported from the endoplasmic reticulum and subsequently transported to the cell surface. CFTR that fails to meet these standards is destined to endoplasmic reticulum-associated protein degradation (ERAD). (7) Such a complex quality control system operates at the detriment of efficiency, decreasing export production of even wild type CFTR to 33% of similar family cell transporters. (10)

Cystic fibrosis is a result of mutations that alter CFTR in these domains or the way these domains interact with each other. Ultimately, these defects affect the function or quantity of the channel at the cell surface. (5) With nearly 2000 disease-causing mutations identified in CFTR, variants have historically been categorized in five or six functional classifications (Figure 1). (8, 11) Class I mutations lead to a lack of protein synthesis, such as those with a premature termination codon present. Class II mutations are unable to mature, leading to early degradation through the mechanism of ERAD and resulting in CFTR rarely reaching the cell surface. Class III mutations are considered gating defects with abnormal regulation that make the pore non-functioning. Class IV defects have inefficient CFTR function with defective chloride conductance. Class V and VI mutations are those that lead to decreased quantity of CFTR at the cell surface as a result of promoter or splicing defects (V) or increased turnover from the cell surface (VI).

These categories of molecular mechanisms provide a useful framework to consider personalized therapeutic approaches (Table 1), but present an oversimplification in that a single variant can disrupt multiple functional classes. Phe508del, the most common CFTR allele, is a prime example of this complexity. Deletion of phenylalanine leads to instability and abnormal folding of the NBD1 region and increased ERAD, categorizing it classically as a class II mutation. (12, 13) A small portion of synthesized protein however is able to traffic to the cell membrane, but has increased degradation like a class VI mutation.

Additionally, Phe508del alters protein stability of NBD1 and MSD2, two important structural domains needed to open the channel, leading to defective gating as in a class III mutation. (5) Personalized therapeutic approaches need to consider the potential diversity of effects a single mutation may determine.

High Throughput Screening to Identify CFTR Modulators

Identifying modulators has been bolstered by the advent of high throughput screening (HTS). HTS uses robotic drug screening of over a million molecules in cell-based fluorescence assays of membrane potential or halide efflux to identify candidate compounds that restore CFTR activity in vitro. (14–16) HTS defined two approaches to identify modulators, termed potentiators and correctors. Potentiators are candidate agents that demonstrate improved CFTR chloride conductance in the absence of preincubation time for synthesis of new protein. It is presumed that potentiators augment ATP activation of the pore of nascent CFTR transcripts that have successfully trafficked to the cell surface. Candidate agents, termed correctors, focus on improved processing and chaperoning of CFTR. The corrector therapies rescue CFTR activity only after incubation time with the agent to promote stability and cell surface trafficking of CFTR protein.

HTS is an automated process that screens blindly to identify hundreds of chemical compounds with the outcome of CFTR-mediated chloride secretion (Figure 2). These compounds are deemed “hits” but require multiple cycles of medicinal chemistry including validation in a second assay, such as human bronchial epithelial cells. Among these “validated hits,” lead compounds are identified with a chemical scaffold that optimizes potency and selectivity. Ultimately, development candidates are refined in animal studies to develop drugs that are tested for safety and efficacy in clinical trials. (17)

Augmenting CFTR activity: the Potentiator approach

CFTR variants that benefit from the potentiator approach have absent or limited pore function, characteristic of functional class III or IV mutations. Potentiators can function through enhancing the open configuration or improving the gating of the CFTR channel. Gly551Asp-CFTR is the most prevalent gating mutation, present in 4–5% of individuals with CF. (18) This variant is thought to interfere with the NBD1 and its ability to interface with NBD2, a function crucial for pore opening. (19)

Production of ivacaftor (Kalydeco) is proof-of-concept of CFTR modulation. Hundreds of thousands of chemical compounds were screened through HTS to identify CFTR potentiator candidates and of these, ivacaftor (formerly known as VX-770) was selected for further development because of its favorable pharmacokinetic profile and its ability to augment various CFTR mutants. (17) Ivacaftor was rigorously tested in cell models and demonstrated an increase in chloride secretion for Gly551Asp/Phe508del-CFTR by approximately 10-fold, nearly 50% of activity seen with wild-type CFTR. This improvement was also reflected in improved mucociliary beating and increased apical fluid level. With these encouraging in vitro data, initial human trials with ivacaftor were started.

The safety profile of ivacaftor was evaluated in a phase 2 randomized placebo controlled trial of 39 adults with at least one copy of Gly551Asp-CFTR. (20) In addition to a reassuring safety profile with similar adverse events rates in placebo and treated groups, subjects demonstrated a significant improvement in lung function, the most responsive at a dose of 150mg/day. Additionally, markers of CFTR activity including nasal potential difference and sweat chloride concentration were shown to have significant improvements. With this evidence, ivacaftor was evaluated in a phase 3 trial, known as STRIVE, that enrolled 161 subjects, 12 years and older with at least one copy of the Gly551Asp mutation. (21) Individuals were randomized in a double-blind trial to receive 150 mg ivacaftor or placebo twice daily for 48 weeks. Within two weeks of therapy, the ivacaftor group demonstrated a 10.6% improvement in the primary end point, change from baseline of percent of predicted forced expiratory volume in 1 second (FEV₁). This effect was sustained through the 48 weeks of the study. Important secondary outcomes included a 55% reduction in pulmonary exacerbations through week 48, an increase in 2.7 kg of weight through week 48, and improved quality of life in respiratory domains, as determined by validated questionnaire. Biomarkers as in the phase 2 trial also demonstrated improvement in sweat chloride with ivacaftor, and the adverse event rates were similar in both groups. In fact, the serious adverse event rate was lower in the treated group compared to placebo (24% v. 42%) primarily driven by a decreased number of pulmonary exacerbations in the treated group. Similar magnitude of outcomes were confirmed and validated in a second phase 3 trial, known as ENVISION, which enrolled children ages 6 to 11 years with Gly551Asp-CFTR. (22)

The Food and Drug Administration (FDA) approved ivacaftor for 6 years and older with one copy of Gly551Asp-CFTR in 2012. Commonly reported side effects and monitoring recommendations on the prescribing label are summarized in Box 1. An open-label trial, known as PERSIST, monitored those on STRIVE and ENVISION, noting sustained benefits of 9.4% and 10.3% of absolute change in FEV₁ and weight gain at both 96 and 144 weeks. (23) Pulmonary exacerbation rate decreased in adolescents and adults, but not in the younger cohort, who had a much lower baseline frequency of pulmonary exacerbations.

In a phase 4 observational study, known as GOAL, Rowe and colleagues monitored 151 individuals with Gly551Asp-CFTR over a six-month period after they initiated ivacaftor. (24) Their report extended and confirmed phase 3 data with consistent and rapid improvement in FEV₁ % predicted and weight gain. Sweat chloride, as a marker of CFTR function, demonstrated reduction to near-normal values. Important subsets within the GOAL study provided preliminary information with mechanistic implications for these clinical outcomes, noting improvement in mucociliary clearance by gamma-scintigraphy and early neutralization of gastrointestinal pH. In addition, there were more initial indications that CFTR modulation may impact the microbiologic milieu in the CF airway. The number of patients with *P. aeruginosa* colonization decreased (25) and colonization with the anaerobe, *Prevotella*, increased. The relative abundance of *Prevotella* has been associated with higher lung function in CF patients. (26)

Beyond Gly551Asp-CFTR, ivacaftor has been studied in additional gating mutations. The KONNECTION trial enrolled 39 patients 6 years and older with at least one copy of a non-Gly551Asp gating mutation, including G178R, S549N, S549R, G551S, G970R, G1244E,

S1251N, S1255P, and G1349D. (27) In an adjusted model, the treatment group had a similar magnitude of clinical outcomes with absolute change in FEV₁ % predicted, body mass index, and validated respiratory domain score to the patients with Gly551Asp-CFTR in the STRIVE study. (21)

The potentiator approach would also augment function in typical class IV mutations with limited conductance, in which chloride and bicarbonate ion flow is only partially present. In a randomized, double-blind, placebo-controlled trial, the KONDUCT study enrolled 69 patients 6 years and older with one copy of Arg117His-CFTR, a known class IV mutation. (28) The primary end point was absolute change in FEV₁ % predicted. The KONDUCT trial demonstrated an approximately 2% absolute FEV₁ % predicted change for all patients that did not achieve statistical significance. The response to ivacaftor was age related. Patients 6 to 11 years of age in the treated group had a near normal baseline FEV₁ of 97.5% predicted and showed no treatment response with an absolute FEV₁ change of -2.8%. Patients 18 years and older with more established lung disease with mean FEV₁ ~ 60% had a 5% absolute improvement in lung function. Based on this evidence in the older patients, the FDA has approved ivacaftor for additional gating mutations, and Arg117His-CFTR for ages 6 years and older.

Ivacaftor pharmacokinetic and safety data was recently evaluated in children with specific gating mutations as young as 2 years which has ultimately led to FDA approval for children as young as 2 years of age with specific gating mutations G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H. (29, 30) With FDA approval of ivacaftor monotherapy for individuals 2 years of age and older with cystic fibrosis who carry at least one copy of a Class 3 mutation or Arg117His, this drug is available to treat almost 10% of the CF population in the US and many countries worldwide.

Yet, the most common mutation associated with CF is Phe508del with nearly half of patients in the US homozygous for this mutation. Although Phe508del is categorized as a Class 2 mutation, (see Approaching CFTR section above), a limited amount of Phe508del-CFTR does make it to the cell surface, making it a feasible target for the potentiator approach. (31) Thus, there was significant interest in testing ivacaftor monotherapy in the homozygous and heterozygous Phe508del population. In addition, ivacaftor improved channel open probability and chloride ion conductance in cultured human bronchial epithelial (HBE) cells from Phe508del homozygous patients which was an encouraging in vitro finding. (17) The DISCOVER study, a phase 2 trial, enrolled 140 patients with two copies Phe508del and randomized to placebo or ivacaftor at 150mg dose twice daily. (32) The study was not powered to measure efficacy, and demonstrated safety of ivacaftor in Phe508del homozygous patients with similar adverse events reported in placebo and ivacaftor groups (89.3% v. 87.5%). In the 16-week trial duration, followed by a 96-week open label extension, the ivacaftor-treated group had no significant improvement in lung function, rate of pulmonary exacerbation, or improvement in validated respiratory symptoms score. Thus, ivacaftor has not been approved as monotherapy for Phe508del homozygous patients.

Improved CFTR processing: the Corrector approach

CFTR modulators, termed “correctors” focus on improved cellular processing to increase its presence at the cell surface. (33) This approach can function through stabilizing CFTR and facilitating folding, minimizing ERAD, or encouraging stability at the cell membrane.

Given the prevalence of Phe508del-CFTR in the CF population, the corrector or rescue approach has targeted individuals with at least one copy of this mutation. Lumacaftor is a corrector compound, identified by HTS. The molecular mechanisms of lumacaftor monotherapy are not well understood, however studies suggest lumacaftor stabilizes domain interactions between NBD1 and MSD2 to improve Phe508del-CFTR cellular processing. (13, 33) *In vitro* models with cultured HBE cells demonstrated increased chloride secretion by 14% compared to non-CF HBE cells. (15, 34) Phase 2 testing of lumacaftor monotherapy in Phe508del homozygous patients was powered to detect differences in CFTR function by sweat chloride. (35) The study detected small, but significant improvement in sweat chloride in a dose-dependent effect, particularly with the maximum dose of 200 mg twice daily. This dose did not translate to significant changes in clinical outcomes including lung function, rates of pulmonary exacerbation, or validated patient-reported outcome scores. These data combined with *in vitro* work made clear that neither lumacaftor nor ivacaftor monotherapy is an effective treatment for the homozygous Phe508del-CFTR population in contrast to ivacaftor monotherapy on class III (Gly551Asp-CFTR) or class IV (Arg117His) mutations. (15, 21, 34, 35)

Combining Potentiator and Corrector Approaches

As described above, the Phe508del mutation spans multiple functional classes and thus a combined corrector and potentiator approach may be necessary to reach a threshold therapeutic effect. HBE cell work identified augmented effect of ivacaftor on CFTR function after lumacaftor exposure on homozygous Phe508del-CFTR HBE cells in support of this concept. (34) Lumacaftor, however, induces cytochrome P450 metabolism of ivacaftor, reducing its effects and requires higher dosing. (35) Higher dose ivacaftor (250mg twice daily) in combination with lumacaftor (600 mg daily or 400 mg twice daily) was studied in a dose escalation phase 2 trial in patients with one or two copies of Phe508del-CFTR. (36) Patients received an initial twenty-eight days of lumacaftor monotherapy prior to addition of the ivacaftor. The lumacaftor monotherapy period was associated with a decline in FEV₁ percent predicted and increased sensation of chest tightness and dyspnea in a subgroup of patients. In contrast, combined therapy (lumacaftor plus ivacaftor) over the subsequent 28 days, demonstrated a 6% increase in FEV₁ % predicted in Phe508del homozygous, resulting in a net increase of 3% in FEV₁ % predicted over the total 56 day treatment period. A cohort of Phe508del heterozygous patients was studied and did not demonstrate improvement in FEV₁ or other clinical markers of disease. Thus, the two phase 3 trials described below were limited to Phe508del homozygous patients only.

Combination lumacaftor-ivacaftor (Orkambi) underwent two phase 3 trials, known as TRAFFIC and TRANSPORT over a 24 week study period. (37) Each study was powered to detect an absolute change in FEV₁ in a randomized, double-blind, multi-center trial for

patients 12 years and older with 2 copies of Phe508del allele. Just over 1,100 people were enrolled in the two studies and were randomized to two dosing arms of lumacaftor (600mg once daily or 400mg twice daily) and the same dose of ivacaftor (250mg twice daily). Absolute change in FEV₁ significantly improved in each dosing arm with a range of 2.6–4% compared to placebo. Secondary outcome analysis pooled for patients treated in the lumacaftor 400mg twice daily dosing arm demonstrated a 39% lower rate of pulmonary exacerbations compared to placebo and a 0.24 increase in body mass index. Adverse events, pooled across the studies were 17.3–22.8% in the lumacaftor-ivacaftor treated groups and 28.6% in placebo, with the most common serious adverse event of pulmonary exacerbations. Common adverse events reported more frequently with treatment groups were primarily respiratory including dyspnea and chest tightness (Box 1). Elevation of liver function tests led to discontinuation or interruption of lumacaftor-ivacaftor treatment in 7 patients. Based on the overall efficacy and safety data, lumacaftor (400 mg twice daily)-ivacaftor (250 mg twice daily) was approved by the FDA for individuals 12 years and older with two Phe508del alleles, estimated to impact 8,500 individuals in the United States. (18, 38)

Additional Modulator Therapies

VX-661 is another first generation corrector targeted to Phe508del-CFTR. Early phase 2 results demonstrated safety with well-tolerated doses of 100 mg once daily and 50 mg twice daily of VX-661 in combination with 150mg twice daily of ivacaftor. (39) The study was performed in 39 people 18 years and old with 2 copies of Phe508del over a 12-week interval. In the small subset of patients with 100 mg dosing of VX-661 in combination with ivacaftor, FEV₁ percent predicted improved 4.4% at 4 weeks and 3% at 12 weeks compared to placebo. The study was of similar magnitude in FEV₁ percent predicted for individuals with Phe508del and Gly551Asp already on ivacaftor. VX-661 at 100mg and 150mg once daily in addition to ivacaftor 150mg twice daily had an approximately 4% improvement in FEV₁ percent predicted at 4 weeks. VX-661 in combination with ivacaftor is currently in a phase 3 study evaluating for absolute change in FEV₁ percent predicted. (40) The combination therapy is being tested in Phe508del homozygotes and heterozygotes. Patients will be classified into four cohorts based on genotype and presumed amount of CFTR function in the second mutation, 1) Phe508del/Phe508del homozygous, 2) Phe508del/gating defect allele (e.g. Class III), 3) Phe508del/residual function CFTR allele (e.g. Class IV), 4) Phe508del/minimal CFTR function allele (e.g. Class I, II).

Additional modulators are entering or are currently in phase 2 trials in the CF Foundation drug development pipeline. Riociguat (BAY 63-2521) is a soluble guanylate cyclase stimulator that increases nitric oxide, a pathway related to improved maturation and function of CFTR. (41) QBW251 is a potentiator currently being tested in people with one or two copies of Phe508del-CFTR as well as healthy patients. (42) Miglustat is an enzyme inhibitor presumed to improve impaired trafficking of Phe508del-CFTR protein and is being tested in homozygous Phe508del-CFTR patients. (43, 44) New molecules are being developed to target inhibition of S-nitrosoglutathione reductase (GSNOR) that also may improve cellular trafficking of Phe508del-CFTR. N91115 is an oral GSNOR inhibitor in phase 2 trials with Phe508del-CFTR homozygous adults on lumacaftor/ivacaftor therapy. (45)

Alternate therapeutic approaches: beyond correctors and potentiators

CFTR modulators require some production of the protein transcript in order to improve or repair its function. Important therapeutic approaches such as genetic modulation or gene-editing, target altered translation of the CFTR gene, but are not traditionally classified as CFTR modulators. Read-through agents or premature termination codon (PTC) suppressor therapies target approximately 10% of the CF population. (18) Ataluren, a PTC suppressor therapy reached a Phase 3 trial, but did not demonstrate a significant relative change in baseline FEV₁ percent predicted (−2.5% ataluren v. −5.5% placebo, $p=0.12$). (46) A 5.7 % relative change in FEV₁ percent predicted was seen in non-tobramycin users compared to 1.4% in those treated with inhaled tobramycin in *post hoc* subgroup analysis, suggesting that aminoglycoside therapy may interfere with ataluren effect. A second phase 3 trial in patients not receiving inhaled aminoglycosides is currently in progress. (47) New *in vitro* work with the most common PTC mutations, W1282X and G542X suggests constructs that respond to PTC suppression may have partial CFTR function that could be augmented with CFTR modulator use, lumacaftor and ivacaftor. (48)

Approaches to maximize the benefit of CFTR modulators

Tremendous progress has been made in the development of CFTR modulators. The goal remains to expand personalized therapy, targeted at the basic defect in CFTR to every person with CF. More CFTR modulators are in the pipeline and additional approaches continue to be developed and refined. As this novel class of medications expand, methods to predict and monitor treatment response become crucial. These methods must take into account the rarity of CFTR mutations and how to determine an individual's personalized response to therapy.

New systems such as organoids to use as personal human model systems are being assessed to predict response over a wide range of mutations. (49–51) Dekkers and colleagues have established primitive organoids from rectal punch biopsy cultures with intestinal stem cells. (49) These cultures contain an internal lumen and serve as a functional assay of CFTR by swelling in response to forskolin. This assay allows an *ex vivo* approach to detect organoid-based fluid transport and can serve as an efficient strategy to test variability in drug response in rare CFTR mutants. (50)

Individual phenotypic responses are also being considered through N-of-1 clinical trial design. Single subjects are monitored in a multi-crossover design of a randomized schedule to receive treatment or placebo with frequent outcome measurements to assess efficacy and profile adverse events. (52, 53) This study design may be a useful strategy to estimate individual treatment effects, but requires significant investment to design and monitor for outcomes. Additionally, outcome measures must be carefully chosen to distinguish baseline chronic disease variability over time from treatment effect. An N-of-1 study was recently completed for ivacaftor in patients with residual function CFTR mutations. (54)

Lessons from ivacaftor

Ivacaftor provides additional important lessons going forward, including the potential role of biomarkers more sensitive to early physiologic changes in young patients, such as lung

clearance index. (55) A phase 4 study of lumacaftor/ivacaftor known as the PROSPECT study is in progress to attempt to identify biomarkers of CFTR and CF disease progression in response to treatment. (56) Post approval studies can be augmented with data from the CF Foundation National Patient Registry (CFFNPR) for assessment of hospitalization risk and *Pseudomonas aeruginosa* infection as in the GOAL study or to estimate the long term impact of modulators with comparative rates of lung function decline. (24, 57) CFFNPR was also a useful adjunct to identify clinical and sociodemographic variables of baseline lung function, geography, and race as factors that may influence ivacaftor prescription. (58) Non-genetic determinants that play an important role in uptake and adherence of modulator therapy deserve ongoing attention to maximize clinical benefit of modulator therapies as they integrate into daily care.

Conclusions

CFTR modulators are proof-of-concept that personalized therapies can be integrated into clinical practice. These new therapies provide hope that the course of disease will be forever changed in people with CF. Evidence from the CFFNPR fuels this hope with a recent study demonstrating ivacaftor-treated Gly551Asp-CFTR patients have a nearly 50% reduction in the rate of decline of lung function compared to F508del control patients matched by propensity score. (57) Moving forward, future generations of modulators and adjunct systems to test and monitor these medications will continue to develop. The CF community remains steadfast to identify personalized therapies for all people with CF.

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Key Points

- CFTR mutations can be classified into defects that lead to reduced quantity or reduced function of CFTR protein, impairing critical salt and fluid homeostasis in multiple organs.
- Classification of mutations is a framework for therapeutic approaches to identify compounds that improve CFTR presence at the cell surface (corrector therapy) or augment channel function of the nascent protein (potentiator therapy).
- Ivacaftor (Kalydeco), the first approved CFTR potentiator for individuals with Class III (gating) mutations and Arg117His has demonstrated significant and sustained multisystem improvement.
- The combination of ivacaftor and lumacaftor (Orkambi) was approved in 2015 for individuals homozygous for the Phe508del mutation. Its long term clinical impact is not yet known.
- Novel systems and disease markers that address and monitor individualized response to therapies are being developed and will serve as important tools to explore current and future CFTR modulators.

Box 1: Warnings and precautions of approved CFTR modulator therapy and suggested monitoring

Ivacaftor	
Absorption	Take tablet with fat-containing food
Elevated liver transaminases	Monitor alanine and aspartate transaminases prior to initiation, every 3 months in the first year, and annually thereafter
Cataracts	Eye exam prior to initiation and follow-up for patients younger than 18 years of age
Drug interactions (St. John's wort, rifampin)	Decreases exposure to ivacaftor and co-administration is not recommended
Drug interactions (ketoconazole, fluconazole)	Increases exposure to ivacaftor. Dose adjustment of is needed.
Drug interactions (Seville oranges, grapefruit)	Increases exposure to ivacaftor. Avoid food containing grapefruit or Seville oranges.
Lumacaftor-Ivacaftor	
Absorption	Take tablet with fat-containing food
Elevated liver transaminases	Monitor alanine and aspartate transaminases prior to initiation, every 3 months in the first year, and annually thereafter
Liver disease	Childs-Pugh score classification and dose adjustment may be necessary. Caution in patients with advanced liver disease.
Cataracts	Eye exam prior to initiation and follow-up for patients younger than 18 years of age
Chest discomfort, dyspnea, breathing difficulties	Additional monitoring recommended for patients with FEV1% predicted <40 during therapy initiation
Drug interactions (hormonal contraceptives)	Decreased efficacy of hormonal contraception. Alternative methods of contraception and anticipation of menstrual-related adverse reactions.
Drug interactions (benzodiazepines, immunosuppressants, digoxin, corticosteroids, antidepressants, proton pump inhibitors)	Decreases efficacy of these medications. Dose adjustment, level monitoring if applicable, or alternative agent recommended. Co-administration not recommended.
Drug interactions (St. John's wort, rifampin, phenytoin)	Decreases exposure to lumacaftor-ivacaftor and co-administration is not recommended
Drug interactions (ketoconazole, itraconazole, voriconazole, clarithromycin)	Increases exposure to lumacaftor-ivacaftor. Dose adjustment may be needed when initiating therapy.

Figure 1.

Functional classes of CFTR mutations. Defects of CFTR are categorized into a lack of protein synthesis (Class I), incomplete maturation and early degradation (Class II), abnormal gating and regulation (Class III), inefficient chloride conductance (Class IV), decreased number of CFTR transcripts (Class V), and increased turnover of CFTR from the cell surface (Class VI). With permission from Banjar et al. International Journal of Pediatrics and Adolescent Medicine 2015;2:47–58.

Figure 2.
Summary of CFTR Modulator Drug Discovery through High Throughput Screening.

Table 1

CFTR mutation classes and summary of approved or potential therapies

Class	Impact on CFTR protein	Common Mutation (Legacy name)	Approved Therapy (dose)	Therapies in Development
I	Lack of protein synthesis (reduced quantity)	Trp1282X (W1282X)	–	Ataluren (Phase 3)
II	Abnormal processing with misfolding keeping it from reaching cell surface (reduced quantity)	Phe508del (deltaF508)	Lumacaftor/Ivacaftor (400mg Q12 hours/250mg Q12 hours)	VX-661/ Ivacaftor (Phase 3)
III	Reaches cell surface, but gating defect impairs function (reduced function)	Gly551Asp (G551D)	Ivacaftor (6 years+: 150mg Q12 hours; 2–5 years <14kg: 50mg Q12 hours; 2–5 years 14kg: 75mg Q12 hours)	VX-661/ Ivacaftor (Phase 3)
IV	Reaches cell surface, but conductance defect leads to faulty opening (reduced function)	Arg117His (R117H)	Ivacaftor (6 years+: 150mg Q12 hours; 2–5 years <14kg: 50mg Q12 hours; 2–5 years 14kg: 75mg Q12 hours)	VX-661/ Ivacaftor (Phase 3)
V	Created in insufficient quantities (reduced quantity)	3849+10 kb C→G	–	–
VI	Rapid turnover (reduced quantity)	Cys1400X (4326delITC)	–	–