# CFTR Modulators for the Treatment of Cystic Fibrosis

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## DISEASE OVERVIEW

Cystic fibrosis (CF) is an incurable, ultimately fatal inherited disorder that causes thick, sticky mucus to form in the lungs, pancreas, and other organs. In the lungs, thick mucus can damage tissue and block airways, making it difficult for patients to breathe and promoting lung infections.[1] Although lung disease is responsible for more than 80% of CF-related deaths, CF has many other manifestations, including pancreatic insufficiency, gastrointestinal problems, endocrine disorders, and male infertility.[1]

CF was first recognized as a disease in the late 1930s, and the term *cystic fibrosis* was used to describe the characteristic cyst formation and scarring (fibrosis) observed in the pancreas of these patients.[2] In 1949, Lowe and colleagues theorized that CF must be caused by a defect in a single gene, based on the disorder's autosomal recessive pattern of inheritance.[3] It wasn't until 1989 that investigators identified a member of the adenosine triphosphate (ATP)–binding cassette (or traffic ATPase) gene family as the one involved in CF.[4,5,6] Mutations in the *CFTR* gene result in defective cystic fibrosis transmembrane conductance regulator (CFTR) proteins, which in turn cause CF.[7,8,9] Normally, CFTR proteins located on the surface of the epithelial membrane act as chloride channels that in turn regulate the ENaC (epithelial sodium channel) and other anion channels at the cell surface. The complex interplay of these channels regulates the electrochemical gradient that allows appropriate airway surface liquid depth and mucus viscosity.[10,11] When these proteins are defective or missing, the body produces thick, viscous mucus.[12]

To date, more than 1,800 mutations of the *CFTR* gene have been identified.[13] *CFTR* mutations are divided into six classes, based on the mechanisms by which they cause disease (Table 1).[1,12,14] Class I mutations result in the presence of premature termination codons (PTCs). These "stop" codons do not allow the CFTR protein to be produced, leading to an absence of CFTR protein at the epithelial membrane. Class II mutations lead to the intracellular production of misfolded proteins. Class II includes the most common mutation, which involves a deletion that codes for phenylalanine at position 508 in the CFTR protein; hence, this defect is known as F508del.[12] In class III mutations (e.g., G551D), which affect about 4% of CF patients,[13,15] full-length CFTR proteins reach the cell surface but exhibit abnormal channel "gating," meaning they do not

open (gate) properly to allow a normal flow of chloride into and out of the cells.[15] Alternatively, in class IV mutations a normal amount of CFTR reaches the epithelial membrane but has reduced chloride conductance. Promoter or splicing errors, class V mutations, cause reduced CFTR at the epithelial membrane, but the CFTR that reaches the surface transports chloride appropriately. The final type of mutations, class VI, are c-terminus mutations that accelerate turnover of CFTR from the cell surface.[1,12,14]

More than 10 million Americans are asymptomatic carriers of a defective *CFTR* gene.[16] To develop CF, an individual must inherit two defective genes—one from each parent. Each time two carriers of a *CFTR* gene mutation conceive, they have a 25% chance of passing CF to their child, a 50% chance that the child will only be a carrier of the defective gene, and a 25% chance that the child will not have the defective gene at all.[16–19]

In the U.S., approximately 30,000 children and adults have CF.[13] The overall birth prevalence is one in 3,500, and an estimated 1,000 new cases are diagnosed each year.[13] Most

**Table 1 Classification of Gene Mutations That Cause Cystic Fibrosis[1,12,14]**

| Class | Exemplar Mutation | Description |
|---|---|---|
| I | G542X | Presence of premature termination codons (PTCs) causes CFTR protein synthesis to be defective or absent. |
| II | F508del | Impaired processing: misfolded CFTR proteins; defective protein maturation; premature protein degradation; CFTR proteins do not reach apical cell surface. |
| III | G551D | Disordered regulation: Full-length CFTR proteins reach apical cell surface but are not activated by ATP or cAMP; proteins exhibit abnormal chloride-channel "gating" (i.e., open time is reduced) |
| IV | R334W | Impaired function: Full-length CFTR proteins reach apical cell surface, but transport of chloride ions is reduced. |
| V | R117H | Synthesis and surface expression of normal CFTR proteins are reduced because of promoter or splicing abnormalities. |
| VI | 1811+1.6kbA>G | CFTR proteins reach apical cell surface, but C-terminus mutations result in accelerated turnover. |

ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate; CFTR= cystic fibrosis transmembrane conductance regulator

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# CFTR Modulators for the Treatment of Cystic Fibrosis

CF patients are diagnosed with the disease before they are 2 years old.[13] In the 1950s, few children with CF lived to attend elementary school.[20] In 2012, thanks to advances in medical treatment, the median predicted age of survival was 41.1 years.[13]

CF affects all racial and ethnic groups, but it is more common among Caucasians of Northern European descent.[13,21] Approximately one in 2,500 Caucasians is diagnosed with CF, compared with one in 15,100 African-Americans and one in 13,500 Hispanics.[16,22] About 72% of Caucasians have the F508del mutation, the most common gene mutation in CF.[13,19] In contrast, only about 44% of African Americans and 54% of Hispanics carry this mutation. Moreover, CF is the most lethal genetic disease among Caucasians.[17] Between 1999 and 2006, 3,708 people died of CF in the U.S.; 90% were white.[16] The age-adjusted death rate among Caucasians is 0.22 per 100,000, compared with 0.04 and 0.05 per 100,000 among African-Americans and Hispanics, respectively.[16]

Until recently, medical therapies were unable to target the underlying genetic cause of CF and could only address symptoms. For example, airway clearance therapies are used daily to dislodge airway mucus, pancreatic enzyme replacement is taken with each meal to help digest food, and antibiotics are used to treat lung infections.[1] Therefore, extensive research has focused on developing agents that can affect CF at the genetic level.[23] Because CF is caused by defects in a single gene, it is considered an ideal candidate for mutation-targeted therapy.[24]

The study of CFTR modifier medications represents a major revolution in CF treatment because these agents target the basic defect as opposed to targeting the effects of the disease. Although ivacaftor is the only FDA-approved CFTR modifier, other medications are in development.

Studies of CFTR modifier medications use a variety of different outcome measures, including sweat chloride, nasal potential difference (NPD), and the Cystic Fibrosis Questionnaire–Revised (CFQ-R).[15,25] The sweat chloride test measures the chloride content of the patient's sweat as an indicator of CFTR function. A sweat chloride value of more than 60 mmol/L is diagnostic for CF.[1] A decrease in sweat chloride to non-CF values may correlate with clinical changes, such as lung function. However, changes in which the sweat chloride value remains greater than 60 mmol/L have not been correlated with clinical outcomes. NPD testing is performed by running different solutions through the patient's nose; voltage measurements from these solutions are used to detect changes in CFTR function. Increases in CFTR function may result in clinical changes in CF patients, although a direct correlation has not been established.[25] CFQ-R is a measurement tool used to determine changes in health-related quality of life for CF patients. A clinically significant change in the CFQ-R score is defined as a change of 4 points.[15]

## IVACAFTOR

On January 31, 2012, the FDA approved ivacaftor (Kalydeco, Vertex Pharmaceuticals), a CFTR potentiator, for the treatment of CF patients 6 years of age and older with the G551D mutation, which represents about 4% of patients with CF.[13,26] As a CFTR potentiator, ivacaftor increases the time the CFTR channel is open, allowing chloride ions to flow through the CFTR proteins on the surface of epithelial cells.[27,28] Ivacaftor is the first FDA-approved treatment to target the basic defect in CF.

The approved dosage of ivacaftor is one 150-mg tablet taken orally every 12 hours (total daily dose, 300 mg) with fat-containing foods.[27]

### Clinical Efficacy Data

Ivacaftor (25, 75, 150, and 250 mg twice daily) was initially studied against placebo in 39 adult patients with CF who had at least one copy of G551D. The study consisted of two parts. In part 1, two 14-day courses of two different ivacaftor doses were given with a washout period in between.[15] Part 2 of the study examined the higher doses of ivacaftor (150 and 250 mg twice daily) against placebo for 28 days. The primary endpoint was safety and adverse event rates were similar between all groups.[15]

The sweat chloride test was used as an outcome. In the ivacaftor treatment group, sweat chloride decreased significantly from baseline ($P < 0.001$); however, this change was not statistically significant compared with placebo.[15] NPD testing was also used to evaluate CFTR function; changes from baseline were statistically significant in the 75-mg, 150-mg and 250-mg groups ($P = 0.03$, 0.01, and 0.05, respectively) but not statistically significant compared with placebo. Forced expiratory volume in one second ($FEV_1$) significantly increased from baseline at doses of at least 75 mg twice a day but did not change significantly compared with placebo.[15] Although small, the study showed promising outcomes with ivacaftor, and the decision was made to proceed to phase 3 trials with ivacaftor 150 mg twice a day.

FDA approval of ivacaftor was based on results from two pivotal phase 3 trials (ENVISION and STRIVE).[29,30] Eligible patients from these two studies were rolled over into an open-label extension study (PERSIST).[31]

In ENVISION, a randomized, double-blind, placebo-controlled trial of 52 patients ages 6 to 11 years, patients were treated with ivacaftor 150 mg every 12 hours for 48 weeks in addition to their prescribed CF therapies (Table 2). The use of inhaled hypertonic saline was not allowed during the study.[29]

The mean absolute change from baseline in percent predicted $FEV_1$ was 12.6% in the ivacaftor group versus 0.1% in the placebo group at 24 weeks ($P < 0.001$).[29] This effect persisted through 48 weeks of treatment.[29] Ivacaftor reduced sweat chloride to normal levels in some patients ($P < 0.001$) and showed a significant increase in body weight ($P < 0.001$) and a nonstatistically significant increase in CFQ-R scores of 6.1 points ($P = 0.109$).[29]

In the STRIVE trial, ivacaftor was evaluated in 161 CF patients ages 12 to 53 years.[30] Treatment with ivacaftor resulted in a significant improvement in $FEV_1$ compared with placebo (Table 2). Through week 24, there was a 10.4% increase from baseline in the percent predicted $FEV_1$ in the ivacaftor group compared with a 0.2% decrease in the placebo group, representing a treatment effect of 10.6% ($P < 0.001$). As in the ENVISION trial, this significant change persisted through 48 weeks.[30] The study also showed a significant decrease in sweat chloride of 48.1 mmol/L compared with placebo at 48 weeks, with some patients returning to normal levels.[30] Body weight and CFQ-R respiratory domain score increased significantly compared with placebo. At 48 weeks, 67% of patients in the ivacaftor group had not had a pulmonary exacerbation compared with 41% in the

**Table 2  Ivacaftor Clinical Trials**

| Reference<br>*Design* | *CFTR*<br>**Mutation** | **Population** | **Treatment**<br>*Duration* | **Results** |
|---|---|---|---|---|
| Ramsey (2011)[30]<br>*STRIVE:*<br>*Randomized,*<br>*double-blind,*<br>*placebo-*<br>*controlled* | G551D | Age 12–53 years<br>N = 161<br>$FEV_1$ 40–90% | IVA 150 mg b.i.d. or PBO b.i.d.<br>*48 wks* | • Percent change in $FEV_1$ from baseline to 24 wks ($P < 0.001$): IVA, 10.4%; PBO, −0.2%<br>• Percent change in $FEV_1$ from baseline to 48 wks compared with PBO ($P < 0.001$): IVA, 10.5%<br>• Percent of patients pulmonary exacerbation–free at 48 wks: IVA, 67%; PBO, 41%<br>• Change in body weight from baseline to 48 wks: IVA, 3.1 kg; PBO, 0.4 kg<br>• Sweat chloride change from baseline to 48 wks compared with PBO ($P < 0.001$): IVA, −48.1 mmol/L<br>• Change in CFQ-R respiratory domain from baseline to 48 wks ($P < 0.001$): IVA, 5.9 pts; PBO, −2.7 pts |
| Davies (2013)[29]<br>*ENVISION:*<br>*Randomized,*<br>*double-blind,*<br>*placebo-*<br>*controlled* | G551D | Age 6–11 years<br>N = 52<br>$FEV_1$ 40–105% | IVA 150 mg b.i.d. or PBO b.i.d.<br>*48 wks* | • Absolute change in $FEV_1$ percentage from baseline at 48 wks compared with PBO ($P < 0.001$): IVA, 10%<br>• Absolute change in $FEV_1$ percentage from baseline at 24 wks ($P < 0.001$): IVA, 12.6%; PBO, 0.1%<br>• Mean change in sweat chloride from baseline to 48 wks compared with PBO ($P < 0.001$): IVA, −54.3 mmol/L<br>• Body weight change from baseline to 48 wks compared with PBO ($P < 0.001$): IVA, 2.8 kg<br>• Absolute CFQ-R change from baseline to 24 wks compared with PBO ($P = 0.109$): IVA, 6.1 pts |
| McKone (2013)[31]<br>*PERSIST: Open-label extension* | G551D | Age ≥ 6 years<br>Patients had completed 48 wks of either ENVISION or STRIVE | IVA 150 mg b.i.d.<br>*96 wks (patients received 96 wks or 144 wks of IVA depending on ENVISION or STRIVE randomization)* | • Absolute change in percent predicted $FEV_1$:<br>  ◦ STRIVE (IVA ➜ IVA) Study start (48 wks of prior treatment): 9.4 ± 8.3<br>  ◦ STRIVE (IVA ➜ IVA) 144 wks: 9.4 ± 10.8<br>  ◦ STRIVE (PBO ➜ IVA) Study start: −1.2 ± 7.8<br>  ◦ STRIVE (PBO ➜ IVA) 96 wks: 9.5 ± 11.2<br>  ◦ ENVISION (IVA ➜ IVA) Study start (48 wks of prior treatment): 10.2 ± 15.7<br>  ◦ ENVISION (IVA ➜ IVA) 144 wks: 10.3 ± 12.4<br>  ◦ ENVISION (PBO ➜ IVA) Study start: −0.6 ± 10.1<br>  ◦ ENVISION (PBO ➜ IVA) 96 wks: 10.5 ± 11.5<br>• Absolute change in weight (kg):<br>  ◦ STRIVE (IVA ➜ IVA) Study start (48 wks of prior treatment): 3.4 ± 4.9<br>  ◦ STRIVE (IVA ➜ IVA) 144 wks: 4.1 ± 7.1<br>  ◦ STRIVE (PBO ➜ IVA) Study start: 0.3 ± 2.2<br>  ◦ STRIVE (PBO ➜ IVA) 96 wks: 3 ± 4.2<br>  ◦ ENVISION (IVA ➜ IVA) Study start (48 wks of prior treatment): 6.1 ± 2.9<br>  ◦ ENVISION (IVA ➜ IVA) 144 wks: 14.8 ± 5.7<br>  ◦ ENVISION (PBO ➜ IVA) Study start: 2.9 ± 1.8<br>  ◦ ENVISION (PBO ➜ IVA) 96 wks: 10.1 ± 4.1<br>• Absolute change in CFQ-R respiratory domain:<br>  ◦ STRIVE (IVA ➜ IVA) Study start (48 wks of prior treatment): 6.4 ± 16.8<br>  ◦ STRIVE (IVA ➜ IVA) 144 wks: 6.8 ± 19.6<br>  ◦ STRIVE (PBO ➜ IVA) Study start: −3.6 ± 14.1<br>  ◦ STRIVE (PBO ➜ IVA) 96 wks: 9.8 ± 16.2<br>  ◦ ENVISION (IVA ➜ IVA) Study start (48 wks of prior treatment): 7.4 ± 17.4<br>  ◦ ENVISION (IVA ➜ IVA) 144 wks: 10.6 ± 18.9<br>  ◦ ENVISION (PBO ➜ IVA) Study start: 0.8 ± 18.4<br>  ◦ ENVISION (PBO ➜ IVA) 96 wks: 10.8 ± 12.8 |

| Table 2  Ivacaftor Clinical Trials (continued) | | | | |
|---|---|---|---|---|
| **Reference** *Design* | *CFTR* **Mutation** | **Population** | **Treatment** *Duration* | **Results** |
| Davies (2013)[32] *Placebo-controlled, double-blind, crossover study* | G551D | Age > 6 years N = 17 FEV$_1$ > 90% LCI > 7.4 | Sequence 1: PBO ➜ WO ➜ IVA 150 mg b.i.d. Sequence 2: IVA 150 mg b.i.d. ➜ WO ➜ PBO *28-day treatment and WO periods* | • Average change in LCI from baseline compared with PBO ($P$ < 0.0001): IVA, −2.16 (95% CI, −2.88 to −1.44) • Average change in FEV$_1$ from baseline compared with PBO ($P$ = 0.0103): IVA, 8.67 (95% CI, 2.36 to 14.97) • Average change in FEF$_{25-75}$ from baseline compared with PBO ($P$ = 0.0237): IVA, 16.56 (95% CI, 2.30 to 27.71) |
| Barry (2013)[34] *Retrospective review* | G551D | Age 20–31 in IVA group N = 21 FEV$_1$ < 40% | IVA 150 mg b.i.d. (n = 21); matched controls (n = 35) *Median duration, 237 days* | • Absolute FEV$_1$ change from baseline ($P$ = 0.0075): IVA, 0.125 L; CON, 0.01 L • Percent predicted FEV$_1$ change from baseline ($P$ = 0.0092): IVA, 12.7%, CON, 2.2% • Median weight increase from baseline: IVA, 1.8 kg; CON, 0.1 kg • Median inpatient days per year decreased from 23 days to 0 days in the IVA group ($P$ = 0.001) • Median total intravenous antibiotic days per year decreased from 74 days to 38 days in the IVA group ($P$ = 0.002) |
| De Boeck (2013)[37] *KONNECTION: Randomized, double-blind, crossover, placebo-controlled* | Non-G551D gating mutations G178R, G551S, S549N, S549R, G970R, G1244E, S1251N, S1255P, G1349D | Age ≥ 6 years N = 39 FEV$_1$ ≥ 40% | Treatment sequence 1: IVA 150 mg b.i.d. ➜ WO ➜ PBO ➜ open-label Treatment sequence 2: PBO ➜ WO ➜ IVA 150 mg b.i.d. ➜ open-label *8 wks of IVA or PBO; 4–8 wks WO period; 16 wks open label* | • Absolute change from baseline percent predicted FEV$_1$ ($P$ < 0.0001): IVA, 7.49%; PBO, −3.19% • Absolute change from baseline BMI ($P$ < 0.0001): IVA, 0.68; PBO, 0.02 • Absolute change from baseline in CFQ-R respiratory domain ($P$ = 0.0004): IVA, 8.94 pts; PBO, −0.67 pts • Absolute change from baseline in sweat chloride (*mmol*/L): IVA, −52.28; PBO, −3.11 |
| Flume (2011)[35] *Randomized, double-blind, placebo-controlled, parallel group with open-label extension* | Homozygous F508del | Age ≥ 12 years Part 1: N = 140 Part 2: N = 33 42 patients were eligible for part 2 if change in FEV$_1$ ≥ 10% or sweat chloride decreased by at least 15 mmol/L at day 15 and week 8 | Part 1: IVA 150 mg b.i.d. or PBO *16 wks* Part 2: Open label IVA 150 mg b.i.d. *Up to 96 wks* | • Change in FEV$_1$ from baseline to week 16 compared with PBO ($P$ = 0.15): IVA, 1.7% (95% CI, −0.6 to 4.1) • Change in FEV$_1$ from week 16 to week 40: IVA, −3.5% ± 11.7% • Change in sweat chloride from baseline to week 16 compared with PBO ($P$ = 0.04): IVA, −2.9 mmol/L (95% CI, −5.6 to−0.2) • Change in sweat chloride from week 16 to week 40: IVA, 2.2 mmol/L ± 12.2 |

b.i.d. = twice daily; *CFTR* = cystic fibrosis transmembrane conductance regulator gene; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CON = control group; FEF$_{25-75}$ = average forced expiratory flow during the middle (25–75%) portion of the forced vital capacity; FEV$_1$ = forced expiratory volume in 1 second; IVA = ivacaftor; LCI = lung clearance index; PBO = placebo; pts = points; CI = confidence interval; wks = weeks; WO = washout

placebo group. This hazard ratio of 0.455 ($P$ = 0.001) highlights the potential for ivacaftor to keep patients exacerbation-free for longer periods.[30]

The PERSIST trial was a 96-week, open-label extension of both the ENVISION and STRIVE studies (Table 2). Of the 144 enrolled patients, 77 had received ivacaftor for 48 weeks and 67 had received placebo. All of the patients in PERSIST were treated with ivacaftor 150 mg every 12 hours.[31] The final results of PERSIST included patients treated with ivacaftor for totals of 96 weeks and 144 weeks. This data showed that patients who had been on placebo in ENVISION or STRIVE, and were then switched to ivacaftor, had an increase in absolute FEV$_1$ at both 48 weeks and 96 weeks of treatment, showed an increase in weight, and had improved CFQ-R respiratory domain scores.[31] Patients who were continuing ivacaftor treatment maintained the FEV$_1$ increase to 144 weeks. Patients originally in the STRIVE study who received ivacaftor treatment maintained their weight gain, and patients originally in the ENVISION study continued to gain weight. This difference is expected given the diverse age groups involved in the studies.[31] Overall, ivacaftor was well tolerated and its benefits persisted through 144 weeks of treatment.

# CFTR Modulators for the Treatment of Cystic Fibrosis

The patients enrolled in the STRIVE and ENVISION studies had a wide range of $FEV_1$, from 40% to 105%. In early lung-disease patients with a higher $FEV_1$, $FEV_1$ is an insensitive marker of disease and many not show a significant change despite a clinical effect.[32] Lung clearance index (LCI) measures ventilation inhomogeneity using a multiple breath washout technique. LCI can detect mild lung-function abnormalities.[32] A study evaluating LCI in patients being treated with ivacaftor showed significant improvements after 28 days of treatment ($P < 0.001$) (Table 2).[32] This technique was further utilized in a post-hoc analysis that was conducted on patients enrolled in STRIVE, ENVISION, and the previous study with $FEV_1$ at baseline greater than 90%.[33] The analysis showed that patients with high lung function but a borderline LCI had a decrease in LCI with ivacaftor treatment, indicating that ivacaftor provided benefit even in patients with high baseline lung functions.

The clinical trials of ivacaftor have excluded patients with $FEV_1$ of less than 40%. To assess the impact of ivacaftor treatment in these patients with severe lung disease, a retrospective review of patients was completed (Table 2). Patients completed a median of 237 days of therapy and were compared with matched controls.[34] Patients in the ivacaftor group had a significant improvement in absolute $FEV_1$ ($P = 0.0075$) compared with the control group. The patients in the ivacaftor group also had fewer inpatient days ($P = 0.001$) and intravenous antibiotic days ($P = 0.002$).[34] This retrospective review suggests the benefit of ivacaftor in patients with severe lung disease.

Ivacaftor was also studied in patients who are homozygous for F508del, but it did not prove effective (Table 2).[35] The study in CF patients more than 12 years old showed an $FEV_1$ change of only 1.7% when compared with placebo at 16 weeks ($P = 0.15$). From week 16 to week 40 of the study, the $FEV_1$ decreased 3.5%.[35] The study revealed that ivacaftor alone is not effective in homozygous F508del patients.

A phase 3 trial of ivacaftor monotherapy in CF patients with R117H showed a nonsignificant 2.1% increase in the mean absolute change from baseline in percent predicted $FEV_1$ ($P = 0.2$).[36] A subgroup analysis of patients at least 18 years old found a statistically significant 5% difference in the mean absolute change from baseline in percent predicted $FEV_1$ ($P = 0.01$). Although ivacaftor did not meet its primary endpoint in patients with R117H, Vertex planned to discuss the finding with the FDA to determine future direction.[36]

Ivacaftor has shown efficacy in patients with a G551D mutation, one of the class III "gating" mutations, and initially received FDA approval for patients with this mutation. Ivacaftor use in non-G551D gating mutations was studied in patients older than 6 years of age in a randomized, placebo-controlled crossover study (Table 2).[37] This study showed an absolute percent change in $FEV_1$ of 10.68% at eight weeks ($P < 0.0001$).[37] There was a significant increase in body mass index ($P < 0.0001$) and CFQ-R scores ($P = 0.0004$), with a decrease in sweat chloride similar to the trials in G551D patients ($P < 0.0001$). These promising results led to an FDA label expansion to include CF patients with the following eight mutations in addition to G551D: G178R, S549R, S549N, S549R, G551S, G1244E, S1251N, S1255P, and G1349D.[38]

## Clinical Considerations

Ivacaftor was well tolerated in clinical trials. The most common adverse events included headache (24%), oropharyngeal pain (22%), upper respiratory tract infection (22%), nasal congestion (20%), abdominal pain (16%), nasopharyngitis (15%), diarrhea (13%), rash (13%), nausea (12%), and dizziness (9%).[29,30] Serious adverse events included transaminase elevations (6%) above the upper limits of normal. Monitoring transaminases is recommended at baseline, every three months for the first year, and annually thereafter.[27] Therapy should be discontinued in patients who experience transaminase elevations greater than five times the upper limit of normal. One safety concern that arose in animal studies was the development of cataracts in juvenile rats that were given doses at 10 mg/kg per day and higher.[39] As a result, an ongoing study is assessing the ocular safety of ivacaftor in patients younger than 11 years old.[40] Regular eye exams should be recommended in patients taking ivacaftor until more is known about ocular risk.

Metabolism of ivacaftor is primarily hepatic, and dose adjustments are recommended in patients with hepatic impairment. A dose decrease to 150 mg daily is recommended in patients with Child-Pugh class B impairment, and caution should be used when administering ivacaftor to patients with severe hepatic impairment (Child-Pugh class C).[27] There is little renal elimination of ivacaftor, and dose adjustments in mild-to-moderate renal failure are not recommended; however, caution should be used in severe renal impairment.

Ivacaftor is a CYP3A substrate, but also has the potential to inhibit CYP3A and p-glycoprotein (P-gp). Ivacaftor is not recommended for administration with strong CYP3A inducers (i.e., rifampin, St. John's wort). Avoiding grapefruit juice and Seville oranges is also recommended during ivacaftor therapy.[27] If coadministered with strong CYP3A inhibitors (i.e., ketoconazole), the ivacaftor dose should be reduced to 150 mg twice a week. For moderate CYP3A inhibitors (i.e., fluconazole), ivacaftor should be reduced to 150 mg daily. Ivacaftor may increase the exposure to drugs that are CYP3A or P-gp substrates, including midazolam, digoxin, tacrolimus, and cyclosporine.

Note that ivacaftor was studied in combination with other CF therapies. It is important for patients to continue current treatment regimens until their reaction to ivacaftor can be assessed due to variability among patients. Because ivacaftor is an oral medication, adherence should be emphasized: Regular administration is required to see the benefits of the medication. In the phase 2 study, the benefit of ivacaftor therapy diminished shortly after therapy was withdrawn.[15] A recent paper suggests that missing even a single dose of ivacaftor can decrease the medication's effect on sweat chloride.[41]

Ivacaftor, the first drug in its class of CFTR potentiators, is an expensive medication with a yearly average wholesale price of $373,800.[42] Patient assistance is available for those who qualify.[43]

Ivacaftor represents an important breakthrough in CF management, and has provided benefit for patients with CF who have a G551D mutation. A postapproval longitudinal cohort study showed improvement in lung function, weight, sweat chloride, and exacerbation rate in a broad patient population.[44] Despite successful outcomes, several questions remain unanswered about ivacaftor. Foremost among these is whether

the drug is safe for eventual use in infants and in children younger than 6 years of age. Because CF lung disease begins in infancy,[45] it is important to start these therapies earlier than 6 years of age. Studies of ivacaftor in patients ages 2 to 5 with a G551D or a *CFTR* gating mutation are ongoing. These studies are evaluating dosing of 50 mg twice a day in patients who weigh less than 14 kg and 75 mg twice a day in patients who weigh 14 kg or more.[46]

Ivacaftor has successfully improved lung function and weight in patients with G551D and may soon benefit patients with other gating mutations and those younger than 6 years of age. The recent expansion of ivacaftor approval in February 2014 for other gating mutations will allow use of the drug in a larger patient population. Clinicians should continue to monitor ongoing research and literature to determine appropriate candidates for ivacaftor treatment.

## LUMACAFTOR (VX-809)

The F508del mutation, a class II mutation, results in misfolded CFTR proteins in the endoplasmic reticulum of epithelial cells, which prevents the proteins from reaching the cell surface. Initial *in vitro* data showed that lumacaftor could facilitate the "trafficking" of CFTR proteins,[47] thus allowing those proteins to reach the membrane and transport chloride.

In a subsequent phase 2a study, the safety and tolerability of lumacaftor were evaluated in 89 adult CF patients with homozygous F508del mutation (Table 3). The subjects were randomly assigned to receive once-daily lumacaftor (25, 50, 100, or 200 mg) or placebo for four weeks.[48] Lumacaftor demonstrated a dose response in the change in sweat chloride across the four active-treatment arms. Compared with placebo, the mean changes in sweat chloride were statistically significant with the 100-mg dose ($P = 0.0498$) and the 200-mg dose ($P = 0.0092$). Despite positive results with sweat chloride, there was no significant difference in pulmonary exacerbation rate, change in $FEV_1$, or change in CFQ-R score. Lumacaftor was well tolerated at all doses. A respiratory adverse event caused a patient to discontinue treatment in each of the active-treatment arms.

The study's pharmacokinetic findings supported a once-daily oral dosing regimen.[48] However, more recent data have shown that lumacaftor 400 mg twice a day had a larger area under the curve than 600 mg daily.[49] Due to the less-than-significant effects seen with lumacaftor or ivacaftor (Table 2)[35] alone in patients homozygous for F508del, the decision was made to study the combination of lumacaftor and ivacaftor for patients with the F508del mutation.

## LUMACAFTOR PLUS IVACAFTOR

The rationale behind the combination of lumacaftor and ivacaftor is that lumacaftor will help with the trafficking of the CFTR protein to the epithelial surface, where ivacaftor will help the CFTR protein open and transport chloride. A phase 2 trial was initiated to evaluate the safety and efficacy of combining lumacaftor and ivacaftor in CF patients with the F508del mutation.[50]

In the first part of the phase 2 study, 62 adult patients homozygous for F508del were treated with lumacaftor (200 mg) or placebo once daily for 14 days, followed by once-daily lumacaftor (200 mg) in combination with twice-daily ivacaftor (150 mg or 250 mg every 12 hours) or placebo for seven days (Table 3).[50] At baseline, the 62 patients had a mean age of 29.1 years, mean predicted $FEV_1$ of 66.9%, and mean sweat chloride of 101.9 mmol/L. A statistically significant reduction in sweat chloride of 9.10 mmol/L ($P < 0.001$) was observed after twice-daily ivacaftor 250 mg was added to once-daily lumacaftor from day 14 to day 21, but not after ivacaftor 150 mg was added. Compared with baseline, patients treated with lumacaftor and ivacaftor 250 mg demonstrated a 13.17 mmol/L reduction in sweat chloride. Eight (47%) of the 17 evaluable patients in this treatment arm had reductions in sweat chloride that exceeded 15.0 mmol/L, and four (24%) had reductions that exceeded 20.0 mmol/L. In all treatment arms, sweat chloride levels returned to baseline values after the completion of dosing with lumacaftor and ivacaftor.[50] On day 21, a within-group improvement in $FEV_1$ of 3.5% was observed in the ivacaftor 150-mg group, but not in the ivacaftor 250-mg group.[50]

No clinically important differences in the frequency or types of adverse events were observed among the treatment groups, and no serious adverse events occurred during the study. Overall, 83% of patients receiving active treatment and 86% receiving placebo experienced an adverse event; approximately half of these events were respiratory in nature.[50] The adverse-event profile observed during the seven days of treatment with lumacaftor and ivacaftor was similar to the profile observed during the prior 14 days of lumacaftor monotherapy. One patient receiving lumacaftor monotherapy discontinued therapy because of an increase in respiratory symptoms during the first seven days of the study.[50] This study led to the conclusion to continue with the dose of ivacaftor 250 mg every 12 hours; however, it was felt that the lumacaftor dose might not be optimized at 200 mg daily.

A second phase 2 trial was conducted on adult CF patients with homozygous and heterozygous F508del (Table 3).[51] Three groups of homozygous patients were randomly assigned to receive lumacaftor alone (200, 400, or 600 mg) for four weeks and then in combination with ivacaftor (250 mg twice daily) for an additional four weeks. One group of heterozygous patients received lumacaftor alone (600 mg) for four weeks and then in combination with ivacaftor (250 mg twice daily) for an additional four weeks.[51] The placebo group included both homozygous and heterozygous patients.

Homozygous F508del patients receiving ivacaftor and the highest dose of lumacaftor (600 mg) experienced a mean absolute improvement in lung function of 6.7% compared with placebo ($P = 0.002$) and a 3.4% improvement within the group ($P = 0.03$).[51] Patients treated with placebo experienced a mean absolute decline in lung function of 3.3% ($P = 0.03$) over the same period.

No decreases in sweat chloride were observed among patients receiving placebo on day 56. In homozygous patients treated with 600 mg of lumacaftor alone for four weeks, there was a statistically significant mean decrease in sweat chloride of 6.41 mmol/L compared with placebo ($P = 0.01$). An additional mean decrease in sweat chloride of 2.82 mmol/L was observed with combination treatment between days 28 and 56, but this difference was not statistically significant.[51]

The results in the heterozygous F508del group were not as significant as the homozygous groups. Heterozygous patients

| Table 3 Lumacaftor Clinical Trials | | | | |
|---|---|---|---|---|
| **Reference**<br>*Design* | *CFTR*<br>**Mutation** | **Population** | **Treatment**<br>*Duration* | **Results** |
| Clancy (2012)[48]<br>*Double-blind, placebo-controlled* | Homozygous F508del | Age 18–54 years<br>N = 89<br>$FEV_1 \geq 40\%$ | LUM 25 mg q.d.<br>LUM 50 mg q.d.<br>LUM 100 mg q.d.<br>LUM 200 mg q.d.<br>PBO<br>*28 days* | • Mean change in sweat chloride from baseline to day 28 compared with PBO:<br>  ◦ LUM 25 mg: 0.1 mmol/L<br>  ◦ LUM 50 mg: –4.61 mmol/L<br>  ◦ LUM 100 mg: –6.13 mmol/L (95% CI, –12.25 to –0.01; $P < 0.05$)<br>  ◦ LUM 200 mg: –8.21 mmol/L (95% CI, –14.33 to –2.1; $P < 0.01$)<br>• Number of pulmonary exacerbations ($P = 0.62$):<br>  ◦ LUM, 17%; PBO, 12%<br>• Mean change in $FEV_1$ from baseline to 28 days ($P = NS$):<br>  ◦ LUM 25 mg: –2.46%<br>  ◦ LUM 50 mg: –2.15%<br>  ◦ LUM 100 mg: 0.32%<br>  ◦ LUM 200 mg: 0.47%<br>  ◦ PBO: 0.07%<br>• CFQ-R change from baseline to 28 days:<br>  ◦ LUM 25 mg: –5.2 pts<br>  ◦ LUM 50 mg: –6.3 pts<br>  ◦ LUM 100 mg: –1.3 pts<br>  ◦ LUM 200 mg: 2.2 pts<br>  ◦ PBO: 4.5 pts |
| Boyle (2011)[50]<br>*Randomized, double-blind, placebo-controlled, multicenter, cohort* | Homozygous F508del | Age > 18 years<br>N = 62<br>$FEV_1 \geq 40\%$ | Part 1: LUM 200 mg q.d. or PBO<br>*14 days*<br>Part 2: LUM 200 mg q.d. + IVA 150 mg b.i.d., or LUM 200 mg q.d. + LUM 250 mg b.i.d., or PBO<br>*7 days of treatment* | • Change in $FEV_1$ percentage from day 1 to day 14:<br>  ◦ LUM 200 mg, –0.34%; PBO, 1.73%<br>• Change in $FEV_1$ percentage from day 14 to day 21:<br>  ◦ LUM + IVA 150 mg b.i.d.: 3.42% ($P < 0.05$ compared with baseline)<br>  ◦ LUM + IVA 250 mg b.i.d.: 0.57%<br>  ◦ PBO: –1.47%<br>• Mean change in sweat chloride from day 1 to day 14:<br>  ◦ LUM 200 mg, –4.21 mmol/L; PBO, –2.86 mmol/L<br>• Mean change in sweat chloride from day 14 to day 28:<br>  ◦ LUM + IVA 150 mg b.i.d.: –1.65 mmol/L<br>  ◦ LUM + IVA 250 mg b.i.d.: –8.96 mmol/L ($P < 0.05$ compared with PBO)<br>  ◦ PBO: 0.86 mmol/L |
| Boyle (2012)[51]<br>*Randomized, placebo-controlled* | Homozygous F508del | Age > 18 years<br>N = 82 | Period 1: LUM 200 mg, 400 mg, 600 mg q.d. or PBO<br>*28 days*<br>Period 2: period 1 treatment + IVA 250 mg b.i.d. or PBO<br>*28 days* | • Change in absolute $FEV_1$ percent predicted from baseline at 28 days of combination treatment (end of period 2):<br>  ◦ LUM 200 mg + IVA: 1.9%<br>  ◦ LUM 400 mg + IVA: 0.6%<br>  ◦ LUM 600 mg + IVA: 3.4%;<br>  ◦ PBO: –3.3%<br>• Sweat chloride change compared to PBO in LUM 600-mg group:<br>  ◦ End of period 1: –6.41 mmol/L<br>  ◦ Additional reduction at end of period 2: –2.82 mmol/L |
| | Heterozygous F508del | Age > 18 years<br>N = 27 | Period 1: LUM 600 mg q.d. or PBO<br>*28 days*<br>Period 2: period 1 treatment + IVA 250 mg b.i.d. or PBO<br>*28 days* | • Change in absolute $FEV_1$ percent predicted from baseline at 28 days of combination treatment (end of period 2):<br>  ◦ LUM 600 mg + IVA: –1.3%<br>  ◦ PBO: –3.7% |

b.i.d. = twice daily; *CFTR* = cystic fibrosis transmembrane conductance regulator gene; CFQ-R = Cystic Fibrosis Questionnaire-Revised; CI = confidence interval; $FEV_1$ = forced expiratory volume in 1 second; IVA = ivacaftor; LUM = lumacaftor; NS = nonsignificant; PBO = placebo; pts = points,

receiving lumacaftor (600 mg) and ivacaftor experienced a decline in absolute $FEV_1$ from baseline of 1.3%. Patients in the placebo group had an even further decline in absolute $FEV_1$ of 3.7%.[51] Given these results, the F508del heterozygous patients will need a different combination of CFTR modulator therapy.

Two 24-week phase 3 studies are investigating fixed-dose combinations of lumacaftor and ivacaftor in CF patients who are homozygous for the F508del mutation.[52,53,54] Both studies are being conducted in subjects ages 12 and older. These trials, TRAFFIC and TRANSPORT, are comparing lumacaftor (600 mg once daily or 400 mg every 12 hours) in combination with ivacaftor (250 mg every 12 hours) versus placebo over six months. An additional study is investigating the pharmacokinetics and safety of lumacaftor plus ivacaftor in children ages 6 to 11 with CF who are homozygous for the F508del mutation. The studies have been completed and patients are now in an open-label extension. Data from these studies are expected to support regulatory submissions in 2014.

## VX-661

VX-661 is another oral CFTR corrector similar to lumacaftor developed by Vertex Pharmaceuticals to treat CF. *In vitro*, a combination of VX-661 and ivacaftor resulted in greater CFTR activity compared with VX-661 alone.[55]

In February 2012, a phase 2, double-blind, placebo-controlled study of VX-661 was initiated in CF patients who were homozygous or heterozygous for the F508del mutation. The purpose of this trial is to evaluate the safety, efficacy, and pharmacokinetic and pharmacodynamic effects of VX-661 alone and when coadministered with ivacaftor.[56] Interim results were reported on the 128 adults with CF who were randomly assigned to four weeks of treatment with varying daily doses of VX-661 (10, 30, 100, or 150 mg) either as monotherapy, in combination with ivacaftor (150 mg taken every 12 hours), or placebo.[57] Interim results found decreases in sweat chloride with VX-661 alone and in combination with ivacaftor. A relative change in $FEV_1$ compared with placebo was significant at 28 days with VX-661 100 mg (9%) and 150 mg (7.5%) in combination with ivacaftor ($P = 0.01$ and $P = 0.02$ respectively).[57]

Adverse effects were similar in the treatment groups and placebo group, with the most common being pulmonary exacerbations, headache, and increased sputum. Overall, VX-661 was well tolerated; however, there were five reported adverse effects that caused drug discontinuation in the treatment group compared with none in the placebo group.[57] It is important to note that $FEV_1$ returned to baseline during the washout period following treatment. Preliminary results indicate that VX-661 is a promising corrector that could benefit patients with CF after further study.

## ATALUREN (PTC124)

Ataluren has been developed by PTC Therapeutics as a first-in-class PTC suppressor that addresses class I *CFTR* gene mutations.[58] Ataluren is structurally similar to the aminoglycoside antibiotic gentamicin in terms of its functional properties. The two compounds, however, are chemically distinct, and ataluren does not have the antibiotic characteristics or toxicity of an aminoglycoside.[59,60]

Ataluren targets nonsense mutations, which insert a termi-

nation codon in the middle of the *CFTR* gene. This premature "stop" signal (a class I mutation) prevents the cell from producing a full-length CFTR protein.[61,62] Ataluren has the ability to override this signal, thereby allowing the synthesis of a functioning protein.[63] Nonsense mutations in the *CFTR* gene are responsible for CF in approximately 10% of patients,[12,47] or about 3,000 individuals in the U.S.[13]

### Phase 2 Studies

In the first trial, the safety and activity of ataluren were evaluated in adults with CF with a class I *CFTR* mutation (Table 4). This study evaluated two different ataluren dosing regimens, a lower dose of ataluren three times daily (4, 4, and 8 mg/kg), and in the other cycle, a higher dose of the drug three times daily (10, 10, and 20 mg/kg).[25] Each cycle consisted of 14 days on and 14 days off ataluren. There was a significant change in NPD in both treatment groups, and approximately half of the patients had NPDs at normal values.[25]

Ataluren was then studied in 30 children and adolescents (6 to 18 years old) with nonsense-mutation CF (Table 4). The patients were assessed in two 28-day treatment cycles; each cycle consisted of 14 days on and 14 days off the drug.[64] Overall, 50% of the patients demonstrated a nasal chloride transport response (at least a –5 mV improvement), as assessed by the NPD. The total chloride response was higher with the larger dose (10, 10, and 20 mg/kg). The mean change in chloride transport for all evaluable patients was –4.2 mV ($P = 0.002$) after the two 28-day treatment cycles at both dose levels.[64]

In another phase 2 study, three months of treatment with ataluren significantly improved chloride channel activity and CF-related cough and showed positive trends in lung function in 19 adults (19 to 57 years old) with nonsense-mutation CF (Table 4)[65] in an extension of a previous short-term, open-label, phase 2a proof-of-concept trial.[25] The patients were treated with ataluren three times daily for 12 weeks at either a lower dose (4, 4, and 8 mg/kg) or a higher dose (10, 10, and 20 mg/kg). The patients were evaluated every four weeks, with an additional follow-up visit on day 112 (four months).

The two ataluren dosing regimens were similarly active and improved chloride transport in 67% of the patients. The aggregate mean change in total chloride transport for all patients was –5.4 mV ($P < 0.01$). At three months (day 84), $FEV_1$ and forced vital capacity (FVC) showed aggregate mean changes from baseline of 4.5% and 3.5%, respectively, for all patients. With the cessation of ataluren therapy, $FEV_1$ and FVC values reverted toward baseline. The study was not powered to detect statistical significance in these outcome measures.[65] As a secondary endpoint, CF-related cough was measured over a 24-hour period after each clinic visit. Ataluren was associated with a 23% aggregate mean reduction in the frequency of waking cough for all patients ($P = 0.006$).[65] From the results of these phase 2 trials, a phase 3 study was designed with the higher dosing regimen of ataluren.

### Phase 3 Study

A pivotal, long-term phase 3 trial was conducted to determine whether ataluren can improve physiological lung function, not just the nasal electrical gradient, in patients with nonsense-mutation CF. This study also evaluated the drug's long-term

**Table 4  Ataluren (PTC124) Clinical Trials**

| Reference Design | CFTR Mutation | Population | Treatment Duration | Results |
|---|---|---|---|---|
| Kerem (2008)[25] Randomized | Nonsense mutation (class I mutations) | Age 18–56 years Cycle 1: N = 23 Cycle 2: N = 21 $FEV_1 \geq 40\%$ | Cycle 1: ATA 4 mg/kg at breakfast, 4 mg/kg at lunch, 8 mg/kg with dinner Cycle 2: ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner *For each cycle: 14 days on treatment, then 14 days off treatment* | • Patients with NPD within normal range: ○ Cycle 1: 13 (57%) ($P = 0.0003$) ○ Cycle 2: 9 (43%) ($P = 0.02$) • Mean change in NPD chloride transport from baseline to day 14: ○ Cycle 1: –7.1 mV ± 7 ($P < 0.0001$) ○ Cycle 2: –3.7 mV ± 7.3 ($P = 0.032$) • Weight change from baseline: ○ Cycle 1: 0.6 kg ± 0.6 ($P < 0.001$) ○ Cycle 2: Maintained |
| Sermet-Gaudelus (2010)[64] Randomized, crossover | Class I mutations | Age 6–18 years N = 30 $FEV_1 \geq 40\%$ | ATA 4 mg/kg at breakfast, 4 mg/kg at lunch, 8 mg/kg with dinner ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner *14 days of treatment ➜ 14 day WO period ➜ 14 days of treatment (groups traded treatments after WO)* | • Mean change in chloride transport from baseline to end of cycle 2: ○ Low-to-high dosing: –4.6 mV ($P = 0.037$) ○ High-to-low dosing: –3.9 mV ($P = 0.046$) • Number of patients with NPD changes of at least –5 mV at the end of cycle 2: ○ Low-to-high dosing: 8 (53%) (95% CI, 30 to 76; $P < 0.0001$) ○ High-to-low dosing: 7 (47%) (95% CI, 24 to 70, $P = 0.0003$) |
| Wilschanski (2011)[65] Randomized | Class I mutations | Age 19–57 years N = 19 $FEV_1 \geq 40\%$ | ATA 4 mg/kg at breakfast, 4 mg/kg at lunch, 8 mg/kg with dinner ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner *12 wks* | • Mean change in chloride transport from baseline to 12 wks: ○ Low dose: –6.8 mV ($P = 0.004$) ○ High dose: –3.4 mV ($P = 0.025$) ○ Combined groups: –5.4 mV ($P < 0.001$) • Number of patients with NPD change of at least –5 mV at 12 wks: ○ Low dose: 7 (64%) (95% CI, 35 to 86; $P < 0.001$) ○ High dose: 4 (57%) (95% CI, 23 to 87; ($P < 0.001$) ○ Combined groups: 11 (61%) (95% CI, 39 to 80; ($P < 0.001$) |
| Rowe (2012)[66] Randomized, double-blind, placebo-controlled | Class I mutations | Age ≥ 6 years N = 238 $FEV_1$ 40–90% | ATA 10 mg/kg at breakfast, 10 mg/kg at lunch, 20 mg/kg with dinner PBO *48 wks* | • Relative mean $FEV_1$ percent predicted at 48 wks ($P = 0.124$): ATA, –2.5%; PBO, –5.5% • Pulmonary exacerbation rate ($P = 0.099$): ATA, 23% lower than PBO • Patient not treated with chronic inhaled antibiotics, relative change in percent $FEV_1$ predicted at 48 wks compared with PBO ($P = 0.015$): ATA, 6.7% |

ATA = ataluren; *CFTR* = cystic fibrosis transmembrane conductance regulator gene; $FEV_1$ = forced expiratory volume in 1 second; mV = millivolt; CI = confidence interval; NPD = nasal potential difference

safety as well as its effects on CF pulmonary exacerbations, health-related quality of life, antibiotic use for CF-related infections, and CF-related disruptions to daily living. A total of 238 patients 6 years of age and older were enrolled (Table 4). The participants were randomly assigned to receive either ataluren three times daily (10, 10, and 20 mg/kg) or placebo three times daily for 48 weeks.[66] Ataluren was supplied as a powder that could be mixed in water or milk. Upon completing this trial, participants were eligible to enter a 48-week, open-label extension study.[67]

At the end of the study period, patients in the ataluren group had a decrease in $FEV_1$ percent predicted of 2.5% compared with a decrease in the placebo group of 5.5%. The pulmonary exacerbation rate was lower in the ataluren group, but the difference was not statistically significant ($P = 0.099$).[66]

Patients were stratified in subgroups based on chronic inhaled tobramycin use. Inhaled tobramycin is a cornerstone of CF treatment, but it is structurally similar to ataluren. When patients on inhaled tobramycin were removed from the analysis, results improved, suggesting that inhaled tobramycin may interact with ataluren given their similar structure and competition for binding sites.[66] Based on this interaction, PTC Therapeutics is moving to study ataluren in patients not on chronic inhaled tobramycin therapy.

# CFTR Modulators for the Treatment of Cystic Fibrosis

## Clinical Considerations

Ataluren is not FDA approved but is currently produced for study in foil sachets that contain vanilla-flavored granules. These granules can be mixed with water, apple juice, or milk to form a suspension.[64] This dosage form may not be palatable to all patients, but it makes administration easier in patients who cannot swallow pills. Ataluren is dosed three times a day, which may influence adherence to the medication regimen.

Inhaled tobramycin may impact the efficacy of ataluren, and use of inhaled tobramycin is not being allowed during the current phase 3 study.[66] It may be difficult for some patients on chronic inhaled tobramycin to stop that therapy for treatment with ataluren. Ataluren will also have to be used with other chronic CF treatments. If approved, ataluren would be the first drug in its class; as with any new medication, it is important to watch for adverse effects. Ataluren reads through nonsense mutations; although it appears to be specific for premature stop codons, serious adverse effects could occur if ataluren reads through native stop codons. Patients on ataluren should be closely monitored for adverse effects if ataluren comes to market.

## OTHER POTENTIAL CFTR MODULATORS

In addition to the handful of agents that have reached clinical development, numerous compounds are being evaluated for their ability to interact with defects in the synthesis and function of CFTR proteins, with varying results. More than 30 compounds have undergone preclinical investigation to determine their suitability for CFTR modulation.[68] Three examples follow.

### 4PBA

*In vitro*, sodium 4-phenylbutarate (4PBA), a short-chain fatty acid, restored chloride transport in CF epithelial cells containing the F508del mutation, although the compound's mechanism of action was unclear.[69] In a subsequent clinical study of 18 CF patients with the F508del mutation, oral 4PBA only partially restored CFTR activity in the nasal epithelium and had no effect on sweat chloride concentrations.[70]

Another study showed, however, that treatment with 20 mg of oral 4PBA could induce significant chloride transport in nasal epithelia compared with placebo in 19 adult CF patients with the F508del mutation.[71] Additional evidence suggests that the combination of oral 4PBA with topical or aerosol flavonoids may restore CFTR function in CF airways.[72,73]

### VRT-532

The pyrazole VRT-532 was found to be a CFTR potentiator in proteins bearing the F508del mutation in human CF airway cultures.[74] Subsequent preclinical studies demonstrated that VRT-532 also functions as a CFTR corrector, rescuing the surface expression of proteins affected by F508del and G551D mutations.[75–78] VRT-532 has shown an approximately fivefold greater affinity for F508del than for G551D.[74]

### N6022

N6022 is a new injectable compound that has been shown to increase the amount of CFTR at the epithelial membrane and decrease the inflammation in the lungs.[79] N6022 works by increasing the level of S-nitrosoglutathione (GSNO) by inhibiting GSNOR, an enzyme that breaks down GSNO.[80] GSNO is a signaling molecule that decreases in people with CF. A phase 1b/2a clinical trial is studying the safety and pharmacokinetics of N6022 in adult CF patients with two copies of the F508del CFTR mutation.[81]

## CONCLUSION

CFTR modulators for the treatment of cystic fibrosis are a growing area that is quickly changing. Ivacaftor, the first CFTR potentiator to receive FDA approval, has overall been well tolerated and produced dramatic results in CF patients with a G551D mutation. The benefit of ivacaftor has been expanded to eight other gating mutations. For patients with two copies of F508del, the most common CF mutation, a combination of lumacaftor and ivacaftor has shown promising results, and phase 3 studies are under way.

Ataluren was a promising treatment for patients with CF and class I mutations; despite initial phase 3 results, it is possible that concomitant inhaled tobramycin may have reduced the true impact of the medication. The developer is planning further clinical trials excluding patients who use inhaled tobramycin.

VX-661 and other potential CFTR modulator compounds are under investigation. These medications may also prove useful in other CFTR-related diseases, such as pancreatitis in patients with mild CFTR variants. In the future it is hoped that all patients with CF will have a CFTR modulator medication or combination that corrects the underlying defect of their particular disease.

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