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Safety and efficacy of treatment with lumacaftor in combination with ivacaftor in younger patients with cystic fibrosis

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Abstract

Introduction: Cystic fibrosis (CF) is the most common autosomal recessive disorder affecting approximately 70,000 people worldwide. The lack of functional cystic fibrosis transmembrane conductance regulator (CFTR) causes dysregulation of epithelial fluid transport in the lungs, gastrointestinal tract, and sweat glands.

Areas covered: The most common disease-causing CFTR mutation, F508del, is present in nearly 75% of those affected and results in a defective protein. Therapies to improve the function of this mutant protein have the promise to reduce morbidity and mortality in the majority of patients with CF. The combination of lumacaftor, which corrects the aberrant intracellular trafficking of F508del, and ivacaftor, which potentiates CFTR function, is known as Orkambi™, and is the first drug approved for the treatment of cystic fibrosis (CF) in patients who are homozygous for F508del. Orkambi™ is currently approved for use in children aged 2 and older based on recent data from open-label Phase 3 clinical safety studies. In older patients, treatment with lumacaftor/ivacaftor is associated with a modest, statistically significant improvement in lung function and reduced pulmonary exacerbations in placebo-controlled trials; these findings are also observed in Phase IV observational studies. While severe side effects are rare, chest tightness, elevation of transaminases, and cataracts have been reported and recommendations for monitoring have been established.

Expert opinion: Orkambi™ somewhat improves clinical outcomes for people with CF who are homozygous for the F508del mutation, and does so with a reasonable safety profile. This therapy represents a major advance in the therapy for CF, but further advances are needed, perhaps with addition of a third agent to this combination small molecule therapy, in order to expand both the targeted population and beneficial effects.

Keywords

Cystic Fibrosis; Lumacaftor; Ivacaftor; Orkambi™

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1. Introduction

Cystic fibrosis is disease of multiple organ systems that affects more than 70,000 children and adults worldwide. Pulmonary manifestations in the form of chronic respiratory infections and gradual respiratory decline, along with malnutrition that result from exocrine pancreatic insufficiency and digestive dysfunction are amongst the main complications leading to a shortened lifespan. CF is caused by mutations in the *CFTR* gene that result in absent or defective function of the cystic fibrosis transmembrane conductance regulator (CFTR) protein. CFTR is an anion channel located on the apical surface of epithelial cell membranes, and is intricate in regulating fluid transport in the production of mucus, sweat, saliva, tears, and digestive enzymes.

Over 2000 mutations or polymorphisms of CFTR are reported, and the varying mutations result in a wide disease severity depending on the amount of CFTR protein delivered to the membrane, the anion conductance of the mutant channel, and the duration of channel opening. Over the past decade, therapies directly targeting CFTR function, known collectively as CFTR modulators, have been developed for individuals with specific CFTR mutations.

The goal of this article is to review the available data on the efficacy and safety of the combination of two such CFTR modulators, lumacaftor and ivacaftor. A fixed combination when given together, known as OrkambiTM, targets the most common CF-causing mutation of CFTR, F508del. In addition to focusing on this agent in younger patients, which is now approve for ages two and older, we will discuss the future development of this class of agents.

2. Current needs, available therapies, and alternative compounds

The mainstay of CF care has traditionally focused on symptomatic treatment of CF disease manifestations. These treatments take the form of antibacterial agents for chronic infections, proper airway clearance to help in expelling retained mucus, orally administered pancreatic enzymes to replace absent endogenous production, and proper nutritional support. As CF is caused by defects in a single gene product, it was hypothesized that by understanding the functional molecular defects in the mutant proteins, specific small molecule therapies could be designed to overcome these molecular defects in these mutant CFTRs. The discovery and development of such CFTR modulator medications represents a major revolution in CF treatment because these agents target the underlying basic defect as opposed to the resulting symptoms of the disease. These modulators therefore hold the promise of fundamentally altering the course and progression of the manifestations of CF.

CF is caused by mutations in the *CFTR* genes, these mutations are grouped into classes based on the problems they cause in the production of the CFTR protein[1]. Class I consists of “protein production” mutations as a result of nonsense, splicing mutations, and deletions resulting in lack of functional CFTR protein[1]. Class II consists of “processing mutations” in which CFTR protein is created, however misfolded, which leads to impaired protein delivery to the apical epithelial membranes[1]. F508del mutation, the most common CFTR

mutation, belongs in Class II. Class III consists of “gating mutations” where the CFTR protein is created and moves to the cell surface, but the channel gate does not open properly[1]. Class IV consists of “conduction mutations” in which the function of the chloride channel is faulty, leading to decreased ion conductance[1]. Finally, Class V mutations are “insufficient protein mutations” which results in a reduced amount of normal CFTR protein at the epithelial membrane[1].

There are three main types of CFTR modulators: potentiators, correctors, and amplifiers[2]. Potentiators increase the opening of the CFTR channel, allowing increased flow of anions such as chloride through CFTR at the apical surface of epithelial cells[2]. Ivacaftor is a potentiator and is indicated for patients with G551D and other less common G511D-like mutations where sufficient numbers of CFTR channels with an isolated defect in gating, or appropriate opening upon stimulation, are present in the apical membrane; such mutant CFTRs are often grouped as class III mutations. Ivacaftor is also indicated for patients having mutations in CFTR that have residual function, perhaps due decreased ion conductance such as the Class IV mutation R117H, or due to decreased expression such as the Class V splicing efficiency mutation 3849+10kbC→T.

Correctors repair defective CFTR processing by facilitating proper folding and delivery of certain mutant CFTRs to the cell surface; as mentioned above, the most common CFTR mutation, F508del, has such a defect in intracellular processing and is the prototype of such a Class II mutation[2]. Lumacaftor and tezacaftor are examples of CFTR correctors that improve F508del processing. Single therapy with either the potentiator ivacaftor or the corrector lumacaftor have little respiratory benefit in patients with homozygous F508del mutation[3], likely because F508del also has defects in protein stability and channel opening. Therefore, combination therapy of lumacaftor/ivacaftor (Orkambi™) and tezacaftor/ivacaftor (Symdeko™) have since been developed for CF patients with homozygous *F508del* mutation; such therapies target both the processing defect (with lumacaftor or tezacaftor) and the channel opening defect (with ivacaftor). Both Orkambi and Symdeko result in similar improvements in clinical outcomes including improvement in quality of life, in respiratory function, and in lower pulmonary exacerbation rates[4]. Symdeko, however, appears to have a better safety profile, although data are not yet available for children younger than 12 years[4].

Amplifiers increase the amount of CFTR protein made by the cell; these may be useful adjuncts to F508del correctors[2]. As correction of F508del processing is an inefficient process within a cell, having more F508del within the cell may allow increased amounts of F508del to have corrected trafficking, and therefore lead to increased F508del function.

Lastly, Phase III clinical trials are now underway for “next-generation” correctors (VX-659 and VX-445) to be used as triple combination therapy. This use of a second corrector is an alternate strategy to overcome the inherent inefficiency of overcoming processing defects, and may benefit patients with single F508del mutation[2] for whom presently available therapies have not demonstrated efficacy. Amplifiers and “next-generation” modulators are currently in clinical development and are not yet available[2].

3. Lumacaftor/ivacaftor (Orkambi™)

Orkambi™ is a combination of lumacaftor and ivacaftor, a CFTR modulator indicated for the treatment of CF in patients age 2 years and older who are homozygous for the *F508del* mutation in the CFTR gene. In patients 12 years and older, it is taken as two tablets (each containing lumacaftor 100mg/ivacaftor 125mg) orally every 12 hours with fat-containing food. In children who weighed less than 14 kg, oral granules (lumacaftor 100mg/ivacaftor 125mg) every 12 hours are recommended. In children who weighed 14kg or more, oral granules (lumacaftor 150mg/ivacaftor 188mg) are taken. The oral granules are mixed with 1 teaspoon of soft food or liquid for administration. In two randomized, double-blind, placebo controlled phase III trials (TRAFFIC and TRANSPORT), lumacaftor/ivacaftor combination therapy was well tolerated by patients aged 12 years and older with CF who were homozygous for the *F508del*-CFTR mutation and led to improved lung function and body mass index (BMI) and reduced incidence of pulmonary exacerbations, with an acceptable safety profile[5]. The clinical benefits and safety of lumacaftor and ivacaftor for children aged 6–11 and 2–5 are discussed below.

3.1 Pharmacodynamics

The CFTR protein is an anion channel present at the surface of epithelial cells in multiple organs; depending on the tissue and location, CFTR may primarily transport chloride, bicarbonate, or both. The *F508del* mutation results in misfolding of the CFTR protein, causing a defect in cellular processing and trafficking that targets the protein for degradation; this severely reduces the quantity of CFTR[6]. The small amount of *F508del*-CFTR that reaches the cell surface is less stable and has low channel-open probability (defective gating) compared to the wild type CFTR protein. Lumacaftor improves the conformational stability of *F508del*-CFTR, resulting in increased, but still somewhat inefficient, processing and trafficking of mutant protein to the cell surface[5]. Ivacaftor is a CFTR potentiator that facilitates increased chloride transport by increasing the channel's open probability, referred to as gating, of the CFTR protein at the cell surface[5].

3.2 Pharmacokinetics and metabolism

The exposure (AUC, area under the curve) of lumacaftor is approximately 2-fold higher in healthy adult volunteers compared to that of patients with CF[7]. The exposure of ivacaftor is similar between healthy adult volunteers and patients with CF[7]. After twice-daily dosing, steady-state plasma concentrations of lumacaftor and ivacaftor in healthy subjects were generally reached after approximately 7 days of treatment, with an accumulation ratio of approximately 1.9 for lumacaftor[7]. The steady-state exposure of ivacaftor in combination with lumacaftor on Day 1 is lower than that of lumacaftor alone due to the CYP3A induction effect of lumacaftor[7]; this increases the metabolism of ivacaftor. Overall, the pharmacokinetics analyses are similar between pediatric patients age 2 through 5 years and 6 through 11 years compared to patients 12 years and older. There is higher exposure in individuals with impaired hepatic function compared to healthy subjects. It is recommended to reduce dose in patients with moderate or severe hepatic impairment[7]. The effect of renal impairment on dosing was not studied[7], but was not expected to be an issue since clearance is primarily through the feces.

Absorption: When a single dose of lumacaftor/ivacaftor was administered with fat-containing foods, lumacaftor exposure was approximately 2 times higher and ivacaftor exposure was approximately 3 times higher than when taken in a fasting state[7]. Therefore, patients should take the dose with fat-containing food; a typical CF Foundation recommended high fat diet satisfies this requirement.

Elimination: The half-life of lumacaftor is approximately 26 hours in patients with CF. The typical apparent clearance, CL/F(CV), of lumacaftor was estimated to be 2.38L/hr (29.4%) for patients with CF[7]. The half-life of ivacaftor given in combination with lumacaftor is approximately 9 hours in healthy subjects[7]. The typical CL/F(CV) of ivacaftor when given in combination with lumacaftor was estimated to be 25.1 L/hr (40.5%) for patients with CF[7].

Metabolism: Lumacaftor is not extensively metabolized in humans with the majority of lumacaftor excreted unchanged in the feces. In vitro and in vivo data indicate that lumacaftor is mainly metabolized via oxidation and glucuronidation[7]. Ivacaftor is extensively metabolized in humans. In vitro and in vivo data indicate that ivacaftor is primarily metabolized by CYP3A[7].

Drug Interactions: Lumacaftor is a strong inducer of CYP3A. Co-administration of lumacaftor with ivacaftor, a sensitive CYP3A substrate, decreased ivacaftor exposure by 80%. Ivacaftor is a weak inhibitor of CYP3A when given as a monotherapy. The net effect of lumacaftor/ivacaftor therapy is a strong CYP3A induction[7]. When initiating lumacaftor/ivacaftor in patients taking strong CYP3A inhibitors (e.g. itraconazole and voriconazole), it is recommended to reduce lumacaftor/ivacaftor dose for the first week of treatment. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended. These include benzodiazepines and immunosuppressants such as sirolimus and tacrolimus.

4. Clinical efficacy

4.1 Phase I and II study

In a Phase I study of healthy volunteers who received lumacaftor 200mg plus ivacaftor 250mg once weekly, the percent predicted forced expiratory volume in 1 s (ppFEV₁) declined by 4.1% within 4 hours of administering lumacaftor/ivacaftor, although this decline was reversed with the use of a short-acting bronchodilator. This decline was also attenuated when a long-acting bronchodilator was administered 12 hour prior to administering lumacaftor/ivacaftor[8].

In a Phase II study, mixed results were reported with varying outcomes in the effects of sweat chloride concentrations and ppFEV₁ in the lumacaftor/ivacaftor group compared to placebo [9].

4.2 Phase III study for patients age 6–11 years

In a phase 3 open-label safety trial (NCT01897233), 58 CF patients aged 6–11 years with stable CF disease and FEV₁ ≥ 40% received 200 mg lumacaftor/250 mg ivacaftor orally

every 12 hours for 24 weeks, followed by a 2-week washout period[10]. The study found no significant changes in ppFEV₁ during the treatment period (change from baseline at Week 24, + 2.5 percentage points; 95% confidence interval [CI], -0.2 to 5.2; p = 0.0671)[10]. However, there were significant improvements at Week 24 from baseline observed in sweat chloride (-24.8 mmol/L; 95% CI, -29.1 to -20.5; p < 0.0002), BMI z score (+0.15; 95% CI, 0.08 to 0.22; p < 0.0001), Cystic Fibrosis Questionnaire-Revised respiratory domain score (+5.4; 95% CI, 1.4 to 9.4; p = 0.0085), and lung clearance index based on lung volume turnover required to reach 2.5% of starting N₂ concentration (-0.88; 95% CI, -1.40 to -0.37; P = 0.0018)[10]. Adverse effects were mild and consistent with those of the TRAFFIC (NCT01807923) and TRANSPORT (NCT01807949) trials. These data supported a label expansion to the 6–11 years age group.

In a separate Phase 3, randomized, double-blind, placebo-controlled, multicenter study (NCT02514473), 206 patients were enrolled at 54 hospitals and medical centers in nine countries (the USA, Australia, Belgium, Canada, Denmark, France, Germany, Sweden, and the UK)[11]. Eligible patients had stable CF with FEV₁ ≥ 70%, and lung clearance index (LCI_{2.5}) ≥ 7.5. Patients were randomly assigned 1:1 to treatment of 200 mg lumacaftor/250 mg ivacaftor twice a day (n = 104) or placebo (n = 102) for 24 weeks. The primary endpoint of the study was the average change in lung function over the 24-week treatment period as measured by mean absolute change in lung clearance index (LCI)[11]. LCI was chosen as an endpoint as it reflects small airway disease and impaired ventilation in younger patients[12]. A higher LCI is suggestive of increased inhomogeneity of ventilation that can result from the inherently poor mucus clearance in CF[11, 12]. Thus, a decrease in LCI may reflect improved mucus clearance as a result of improved CFTR function.

By day 15 of active treatment, participants who received lumacaftor/ivacaftor saw significant decreases in LCI compared to those taking placebo (-1.09 units, 95% CI -1.43 to -0.75, p < 0.0001)[11]. This improvement was sustained throughout the 24-week period. The secondary endpoint included sweat chloride concentration, and again the lumacaftor/ivacaftor group saw a significant reduction in sweat chloride concentration compared to those in the placebo group (-20.8 mmol/L, 95% CI -23.4 to -18.2, p < 0.0001)[11]. Although ppFEV₁ did not change significantly from baseline in either lumacaftor/ivacaftor or placebo group, there was a significant treatment effect between two groups (+2.4 % predicted; 95% CI 0.4–4.4, p = 0.0182)[11]. There was also significant increase in BMI from baseline in both lumacaftor/ivacaftor and placebo groups, however treatment differences did not reach significance for either measure[11]. Similarly, CFQ-R domain scores were improved from baseline to week 24 in both groups, however difference observed between the groups was not significant[11].

4.3 Phase III study for patients age 2–5 years

In a multicenter, phase 3, open label study (NCT02797132), children aged 2–5 years were enrolled in a 15-day trial to assess pharmacokinetics and safety (n = 12) and a 24-week trial to assess safety, pharmacokinetics, pharmacodynamics, and efficacy (n = 60)[13]. The study was conducted from May 2016 to Sept 2017. Lumacaftor and ivacaftor therapy in this age group was associated with a significant decrease in mean sweat chloride concentration by

31.7 mmol/L at week 24 (95% CI –35.7 to –27.6, $p < 0.0001$)[13]. After a 2-week washout period (at week 26), sweat chloride concentration returned toward baseline. In addition, pancreatic function improved with increased fecal elastase-1 concentration by mean absolute change of 52.6 $\mu\text{g/g}$ (95% CI 22.5 to 82.7, $p < 0.0012$) and decreased serum immunoreactive trypsinogen (IRT) concentration by –130 ng/mL (95% CI –192.3 to –68.1, $p < 0.0001$)[13]. Growth parameters were also improved at day 24. Specifically, the mean absolute change in BMI Z score was 0.29 (0.14 to 0.45, $p < 0.0003$) the mean absolute change for weight-for-age Z score was 0.26 (0.15 to 0.38, $p < 0.0001$) and for stature-for-age Z score was 0.09 (0.02 to 0.15, $p < 0.0104$)[13].

Spirometry was performed, however ppFEV₁ showed substantial inpatient variability, which precluded drawing definitive conclusions[13]. This was likely due to difficulty performing spirometry consistently in this age group. LCI was assessed as an exploratory (optional) end-point. At baseline, the mean LCI_{2–5} was 9.01, which improved numerically, although not statistically significant, by a mean absolute change of –0.58 (95% CI –1.17 to 0.02, $p = 0.06$)[13].

Limitation of this study include the relatively small sample size. An ongoing extension study is underway to assess longer-term safety and durability of the beneficial effects of lumacaftor and ivacaftor in this age group[13].

5. Safety and Tolerability,

The safety profile in patients age 2 through 11 years of age during the open label trial was similar to that observed in those 12 years and older in Phase 3 trials. Respiratory events such as chest discomfort (often described as “tightness”) and dyspnea were observed more commonly in patients during initiation of lumacaftor/ivacaftor compared to those who received placebo (Tables 1, 2 & 3). Similar side effects were reported in retrospective cohort study of individuals followed at the Johns Hopkins CF Center [14]. Of the 116 patients studied, 46 (39.7%) reported adverse effects of the medication, with the vast majority (82.2%) being pulmonary in origin and included dyspnea, chest tightness, wheezing, and increased cough and congestion. 20 (17.2%) discontinued lumacaftor/ivacaftor as a result of these side effects. The incidence of drug discontinuation due to side effects was higher in females and in the group where individuals had an FEV₁% predicted of 40% or less prior to initiation of therapy. Lumacaftor/ivacaftor may also be associated with worsening mental health issues such as worsening anxiety and suicidal ideation in females [15], and acute drops in FEV₁ (mean absolute decrease of approximately 10% after the first dose) mainly through bronchoconstriction was also reported [16]. Clinical experience in patients with ppFEV₁ <40 is limited, and additional monitoring of these patients is recommended during initiation of therapy.

Elevated transaminases with concomitant elevations in total serum bilirubin have been reported in patients taking lumacaftor/ivacaftor (Table 4). It is therefore recommended that ALT, AST, and bilirubin be assessed prior to initiating Orkambi™, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of elevated transaminase and/or bilirubin levels, more frequent monitoring should occur. The medication

should be discontinued in patients with ALT or AST greater than $5 \times$ the upper limit of normal (ULN) when not associated with elevated bilirubin and in patients with ALT or AST elevations greater than $3 \times$ ULN when associated with bilirubin elevations greater than $2 \times$ ULN. Restarting the drug following resolution of these elevations should depend on the risk benefit ratio.

Non-congenital lens opacities have been reported in pediatric patients treated with lumacaftor/ivacaftor. Although other risk factors such as corticosteroid use and exposure to radiation were present in some cases, a possible risk attributable to lumacaftor/ivacaftor cannot be excluded. A baseline ophthalmological examination is recommended in pediatric patients initiating treatment with lumacaftor/ivacaftor.

6. Post-Marketing Surveillance

Because post-marketing reactions are reported voluntarily from a population of uncertain size, it is usually not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. In June 2017, the European Medicines Agency (EMA) launched a Cystic Fibrosis Registry Workshop due to the number of medications recently authorized to treat the disease. The goal of the registry is to use observational methods to collect uniform data on specified outcomes in a population defined by a particular disease, condition or exposure. Difficulties using this approach to collect data include: 1) Poor patient recruitment due to lack of physician engagement from administrative burdens, patient consent, low product usage, and competing registries 2) Suboptimal data quality 3) Lack of consistent data quality control and 4) Sustainability due to lack of funding.

Post-marketing cases of liver function decompensation including liver failure leading to death have been reported in CF patients with pre-existing cirrhosis with portal hypertension who were treated with lumacaftor/ivacaftor, but the relative contributions of these factors is not known.

Modest increases in baseline systolic and diastolic blood pressures were reported in the 24-week phase 3 TRAFFIC and TRANSPORT studies. PROGRESS, a 96 week extension study also noted this increase with one serious adverse event related to hypertension reported. No clinically significant changes or trends were observed to laboratory, vital signs measures, or electrocardiogram data with extended exposure to lumacaftor/ivacaftor[17].

Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Therefore, use of lumacaftor/ivacaftor with strong CYP3A inducers, such as rifampin, significantly reduces its effectiveness. Co-administration with other strong CYP3A inducers, such as rifabutin, phenobarbital, carbamazepine, phenytoin, and St. John's wort, is not recommended. Co-administration of lumacaftor/ivacaftor with CYP3A inhibitors, did not impact the exposure of lumacaftor, but increased ivacaftor exposure by 4.3-fold. No dose adjustment is necessary when CYP3A inhibitors are initiated in patients already taking lumacaftor/ivacaftor. However, when initiating ORKAMBI in patients taking CYP3A inhibitors (i.e. ketoconazole, itraconazole, posaconazole, and voriconazole, telithromycin, clarithromycin) the dose of lumacaftor/ivacaftor should be decreased to 1 tablet daily or 1 packet of oral

granules every other day (patients aged 2 through 5 years) for the first week of treatment to allow for the steady-state induction effect of lumacaftor. Following this period, the recommended daily dose can be initiated.

7. Regulatory Affairs

In January 2018, the European Commission approved the extension of the Marketing Authorization for lumacaftor/ivacaftor in children ages 6 through 11 with 2 copies of the F508del mutation. In Europe, there are approximately 3,400 children ages 6 through 11 who are homozygous for this mutation. In addition to the US, the medication is now available in Austria, Denmark, Germany, Ireland, Italy, Sweden, the Netherlands. Gaining market access in England, home to one of the highest numbers of CF patients anywhere in the world, has been challenging. Orkambi has been licensed for use in the UK for people with CF over the age of two who are homozygous for the F508del mutation. Despite this, the National Institute for Health and Care Excellence (NICE) has rejected its use. Vertex has been in disagreements with budget holder NHS England over pricing and reimbursement of lumacaftor/ivacaftor resulting in most patients in the country still being unable to access the drug. It is currently only prescribed to people in the UK on compassionate grounds meaning that Vertex Pharmaceuticals will provide the medication to people who meet certain criteria.

On August 20, 2018, Vertex Pharmaceuticals (Europe) announced that it has received the Pharmaceutical Benefits Advisory Committee's (PBAC) recommendation for lumacaftor/ivacaftor to be listed on the Pharmaceutical Benefits Scheme (PBS) in Australia for people ages six and over. Health Canada has approved the use of lumacaftor/ivacaftor in children ages 6 through 11, but to date, it has not yet been made available. An expert review plan from the Canadian Agency for Drugs and Technologies in Health (CADTH), said its review of the lumacaftor/ivacaftor clinical trials found the drug produced only slight improvements for about 25% of patients. It also reported that Vertex would have to reduce the price by more than 98% to satisfy the agency's value-for-money analysis. Vertex; however, will continue to provide the drug for free to Canadians who are on its compassionate-use plan.

In August, 2018, the US FDA approved the use of lumacaftor/ivacaftor in children ages 2 through 5 with two copies of the F508del mutation.

8. Conclusion

Cystic Fibrosis is a lethal autosomal recessive disorder affecting 70,000 individuals worldwide. The emergence of mutation-specific pharmacotherapies has sparked optimism regarding an elusive cure, or long-term treatment for the disease that addresses the disease's underlying cause, and therefore may modify disease progress. Ivacaftor, a CFTR potentiator, increases CFTR function by propagating channel while the CFTR correctors, lumacaftor, improves defective CFTR processing by increasing the conformational stability of mutant CFTR proteins such as F508del and increasing their proper maturation and delivery to the plasma membrane[18]. Results of clinical trials for lumacaftor/ivacaftor suggest a modest but statistically significant improvement in lung function, a slower ppFEV1 decline, and a reduction in the frequency of exacerbations when compared to controls. While the drug has

been generally well tolerated in the pediatric population serious adverse events related to elevated transaminases, dyspnea, hypertension, worsening mental health, and cataracts have been reported. A correlation may exist between advanced lung disease and the presence of more serious side effects although further studies in this population is needed. The drug is currently being prescribed in the USA, Australia, and several European countries. Although it has also been approved for use in Canada and the UK, disagreements regarding pricing and reimbursement has restricted access to the medication.

9. Expert Opinion

The limited efficacy of lumacaftor/ivacaftor in F508del-homozygotes (especially in comparison to ivacaftor in those with G551D and G551D-like Class III mutations) suggests that additional approaches will be necessary to achieve improved outcomes in F508del-homozygotes, as well as in patients with only 1 copy of F508del and a second CFTR allele with, for example, absent function (F508del het/min compound heterozygotes). Lumacaftor/ivacaftor was not beneficial in this latter population, and the recent and promising triple combination studies from Vertex have added a next-generation corrector to tezacaftor/ivacaftor rather than lumacaftor/ivacaftor. This is likely due to tezacaftor, which is highly related to lumacaftor, having decreased chest related symptoms, decreased drug-drug interactions and decreased liver function test alterations compared to lumacaftor.

Most recently, the US FDA has allowed the use of “theratyping” to advance personalized, mutation-directed therapies[19]. Theratyping aims to predicts how an individual will respond to specific modulators by studying biological changes of their own cells (primary nasal, airway or intestinal epithelial cells) *in vitro* when exposed to approved modulator agents[19]. This is a way to bring existing modulators with established efficacy and known safety profiles to people who have rare mutations where it is not practical or possible to conduct a robustly powered clinical trial for the specific rare mutation. This theratyping approach, as well as the development of next generation modulators, will likely lead to therapies to useful modulator therapies for the vast majority of individuals with CF.

Declaration of interest

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** of considerable interest

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Information resources:

**www.orkambihcp.com --provides summary of Orkambi clinical trials, dosing and administration, and safety profile for healthcare professionals

**www.vrtx.com-- vertex pharmaceutical summary for health professional, scientific information, and patient medication information

Article Highlights:

- Lumacaftor/ivacaftor is the first drug indicated for the treatment of CF in patients age 2 years and older who are homozygous for the F508del mutation.
 - Open label safety trials in children under the age of 2 may allow treatment even earlier in life and delay or mitigate of the development of CF clinical disease.
- Results from clinical trials reported a modest, but clinically significant improvement in lung function, a slower decline in ppFEV₁, and a reduction in pulmonary exacerbations when compared to placebo.
 - These improvements have been maintained in long term (96 week) open label follow up studies.
- The medication is usually well tolerated but there are increased incidences of chest symptoms (tightness) and elevated liver function tests, and severe adverse liver-related reactions have been reported in those with preexisting liver disease.
 - These side effects were not seen in the studies of tezacaftor/ivacaftor in patients 12 years and older.
 - Tezacaftor is highly related to lumacaftor and is believed to have the same mechanism of action, and therefore may be preferred for development of triple combinations including next generation correctors with complementary mechanisms of action.
- Ivacaftor is heavily metabolized by CYP3A4. Its metabolism is induced by lumacaftor, and co-administration of ivacaftor with CYP3A4 inhibitors such as clarithromycin and certain antifungals are contraindicated without significant dose adjustment.
- Other combinations of CFTR modulators, including amplifiers, correctors and potentiators, are in clinical development; some have reached Phase III trials. Within the next five years, it is expected that such “triple combinations” will both expand the population for which these therapies are useful by including F508del compound heterozygotes, and improve the efficacy of this small molecule approach.

Table 1:

Adverse Pulmonary Reactions

Reaction	TRIAL 1 (NCT01897233): 24 Weeks n/N (%) Reference [10]	TRIAL 2 (NCT02514473): 24 WEEKS n/N (%) Reference [11]	
		lumacaftor/ivacaftor	Placebo
Total Incidence	2/58 (3.0)	11/103 (11)	9/101 (9)
Dyspnea	1/58 (1.7)	5/103 (5)	5/101 (5)
Abnormal respirations	1/58 (1.7)	6/103 (6)	4/101 (4)
Chest discomfort	0/58 (0)	0/103 (0)	1/101 (1)

Table 2:

Frequently Observed Treatment-Emergent Adverse Events in 10% of Patients in Trial 1

	TRIAL 1 (NCT01897233): 24 Weeks Reference [10]
	ORKAMBI N=58
Any TEAEs, n (%)	55 (94.8)
Cough	29 (50.0)
Infective pulmonary exacerbation	12 (20.7)
Nasal congestion	12 (20.7)
Headache	12 (20.7)
Abdominal pain upper	8 (13.8)
Sputum increased	8 (13.8)

Table 3:

Any Treatment-Emergent Adverse Events in 5% of Patients and 3% Higher than Placebo in Trial 2

	TRIAL 2 (NCT02514473): 24 WEEKS Reference [11]	
	ORKAMBI N=103	Placebo N=101
Any TEAEs, n (%)	98 (95.1)	98 (97.0)
Productive cough	18 (17.5)	6 (5.9)
Nasal congestion	17 (16.5)	8 (7.9)
Oropharyngeal pain	15 (14.6)	10 (9.9)
Headache	13 (12.6)	9 (8.9)
Abdominal pain upper	13 (12.6)	7 (6.9)
Sputum increased	11 (10.7)	2 (2.0)
Rhinorrhea	10 (9.7)	5 (5.0)
Rash	6 (5.8)	1 (1.0)

Table 4:

Adverse Liver Reactions

Parameter	TRIAL 1 (NCT01897233): 24 Weeks n/N (%) Reference [10]	TRIAL 2 (NCT02514473): 24 WEEKS n/N (%) Reference [11]	
		lumacaftor/ivacaftor	Placebo
ALT or AST	lumacaftor/ivacaftor	lumacaftor/ivacaftor	Placebo
> 3 × ULN	11/57 (19.3)	13/103 (12.6)	8/101 (7.9)
> 5 × ULN	5/57 (8.8)	5/103 (4.9)	3/101 (3.0)
> 8 × ULN	3/57 (5.3)	1/103 (1.0)	2/101 (2.0)
Discontinuation due to adverse effects	1/57 (1.8)	2/103 (1.9)	2/101 (2.0)