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APPLICATION NUMBER:

206038Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: June 25, 2015

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Director, Division of Pulmonary, Allergy, and Rheumatology,
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 206038

Applicant Name: Vertex Pharmaceuticals

Date of Submission: November 5, 2014

PDUFA Goal Date: July 5, 2015

Proprietary Name: Orkambi

Established Name: Lumacaftor/ivacaftor Tablets

Dosage form: Tablets for oral ingestion

Strength: Lumacaftor 200 mg and ivacaftor 125 mg

Proposed Indications: Treatment of cystic fibrosis (CF) in patients 12 years and older who are homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

Action: Approval

1. Introduction

Vertex submitted this 505(b)(1) NDA to support approval of the use of lumacaftor 200 mg and ivacaftor 125 mg fixed dose combination tablet at a dose of 2 tablets every 12 hours for the treatment of cystic fibrosis (CF) in patients 12 years and older who are homozygous for the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene. Ivacaftor was approved in January 2012 for the *G551D* mutation in the *CFTR* gene, and subsequently for other related mutations. Lumacaftor is a new molecular entity and not approved for any indication. The combination product received Breakthrough Therapy designation on December 7, 2012, based on phase 2 clinical data demonstrating approximately 5% improvement over placebo in FEV₁ in CF patients homozygous for the *F508del* mutation in the *CFTR* gene. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

Cystic fibrosis (CF) is an autosomal recessive, progressive, and usually fatal genetic disease most common in the Caucasian population. It occurs in approximately one out of every 3,500 children born in the United States and is an orphan drug population. Lack of properly functioning CFTR ion channel is responsible for the clinical sequelae of CF, including malabsorption of nutrients, and the inability to mobilize tenacious respiratory secretions, leading to recurrent pneumonia and lung damage. There are over 2000 mutations in the *CFTR* gene, some of which, when present in one or both *CFTR* alleles, results in the clinical constellation that is CF.

This application is for CF patients who are homozygous for the *F508del* mutation in the *CFTR* gene as the cause of their disease. This is the most common CF-causing mutation with approximately 90% of CF patients being heterozygous with one allele of the *CFTR* gene having the *F508del* mutation, and about 50% of CF patients being homozygous with both alleles of the *CFTR* gene having the *F508del* mutation. The mutation, generally classified as a “processing” mutation, is a deletion of the three nucleotides that comprise the codon for phenylalanine at position 508. Thus, a patient with the *F508del* *CFTR* mutation will produce a truncated F508del-CFTR protein that lacks this phenylalanine residue. As a result, the truncated protein does not fold correctly and the majority of it is degraded in the endoplasmic reticulum, not reaching the apical surface of the epithelial cell membrane where the CFTR is active. What small amount of the defective protein that reaches the cell surface has reduced function, i.e., decreased open-ion channel probability. The result is a CF with a relatively severe disease phenotype. Treatments for these patients are limited to alleviation of symptoms and treatment of complications. Therapies commonly used include mucolytics such as inhaled DNase, beta-agonist bronchodilators, inhaled antibiotics (tobramycin, aztreonam), and pancreatic enzyme supplements.

The rationale for combining ivacaftor and lumacaftor for treatment of *F508del* CF patients is based on sound in vitro scientific rationale. Ivacaftor is a small molecule drug that has been shown to increase chloride ion transport across the CFTR chloride channel in epithelial cell membranes. Lumacaftor, another small molecule, appears to work by stabilizing and promoting the proper folding of the defective *F508del*-CFTR protein during its processing in the endoplasmic reticulum, thereby allowing it to exit the endoplasmic reticulum and move to the apical surface of the epithelial cell membrane. The two drugs are proposed to be complementary such that the combined effect of lumacaftor and ivacaftor in CF patients homozygous for the *F508del* mutation would be to increase both the quantity (lumacaftor) and improve the function (ivacaftor) of the F508del-CFTR ion channel at the epithelial cell surface, resulting in improved overall chloride ion transport and clinical benefit. In vitro data generated in human bronchial epithelial (HBE) cells expressing F508del-CFTR protein supports this hypothesis and shows added benefit of the combination of lumacaftor and ivacaftor over either monocomponent product alone (Figure 1).

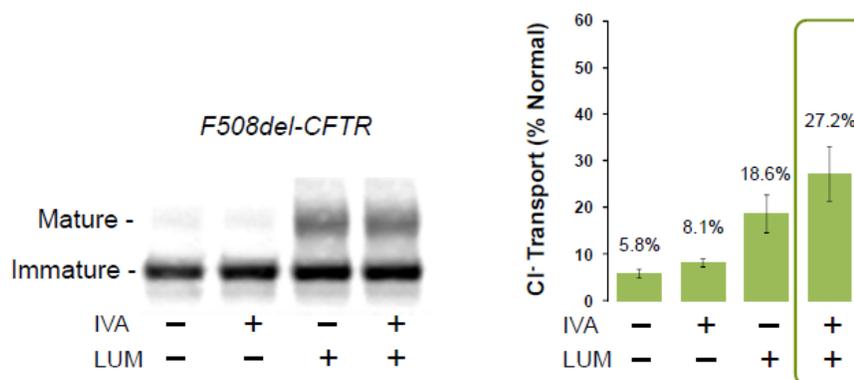


Figure 1. Protein expression (left panel) and chloride transport (right panel) in cell line

The Division and Vertex had typical milestone meetings, including an end-of phase 2 meeting on November 2, 2012, Type B meetings on February 12, 2013, and January 8, 2014, and a pre-NDA meeting on August 12, 2014. The major discussions at these meetings were the comparator arms for pivotal phase 3 studies, the effect size on the treatment effect of lumacaftor-ivacaftor combination product, and sweat chloride data available in the program.

Regarding the comparator arm for phase 3 studies, Agency and Vertex agreed that comparison of the lumacaftor-ivacaftor combination product to placebo would be adequate and that inclusion of single arm lumacaftor or ivacaftor would not be necessary. The reasoning for not including lumacaftor single arm in pivotal phase 3 studies was because in a phase 2 study (Study 809-102) lumacaftor alone treatment over 28 days resulted in dose-dependent decrease in FEV₁. The reasoning for not including an ivacaftor single arm in the pivotal phase 3 studies was because in a study with ivacaftor alone in CF patients homozygous for the *F508del* mutation (done previously for the ivacaftor program for the *G551D* mutation in the CFTR gene) improvement in FEV₁ was approximately 2%, a small effect size that was previously determined to provide no clinically meaningful benefit to CF patients with *F508del* mutation. Regarding the treatment effect size, the Division raised concern with Vertex that the phase 3 studies were powered to detect an FEV₁ treatment effect size that was lower than the FEV₁ effect size seen previously for ivacaftor alone. Regarding the sweat chloride, the Division expressed concern that sweat chloride was only assessed in a phase 2 study, and was not planned for assessment in phase 3 studies.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Orkambi tablets, contains 200 mg of lumacaftor and 125 mg of ivacaftor and standard compendial excipients. The drug product will be packaged as a 112-count tablet box containing a 4-week supply. The manufacturing process for the product employed Quality-by-Design (QBD) approach for the development of the product, manufacturing process, and control strategy. A fully continuous drug product manufacturing process was applied to the manufacturing of the product, which is unique and a new process. During clinical development program, a second dosage form containing 200 mg of lumacaftor and 83 mg of ivacaftor was produced and used in pivotal clinical studies. The second dosage form also had acceptable quality attributes supporting its use in clinical studies. The drug product is manufactured in three facilities – [REDACTED] (b) (4) and Vertex in Massachusetts. The Vertex facility in Massachusetts uses the fully continuous manufacturing process, while the other two facilities use the traditional manufacturing process. All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate or do not require review due to adequate information in the NDA. An expiry of 24 months is proposed and supported by submitted data.

4. Nonclinical Pharmacology and Toxicology

The non-clinical development program for the application consisted of studies with ivacaftor and lumacaftor, both alone and in combination. The pharmacology and toxicology of ivacaftor was reviewed previous for the single entity ivacaftor program. A key finding of note with ivacaftor was cataracts in a juvenile rat study. The general toxicity of lumacaftor was evaluated in rat and dog studies of up to 6 and 12 months duration, respectively. Although CNS toxicity was evident in a 3-month study with dogs that a received a high dose of lumacaftor (approximately 3 times higher than the recommended clinical exposure), no target organs of toxicity were identified in either the chronic rat or dog study. Regarding genetic toxicity, lumacaftor was negative in genetic toxicology tests including bacterial reverse mutation, in vitro mammalian chromosome aberration, and in vivo micronucleus assays. There was also no evidence of tumorigenicity in a 6-month carcinogenicity study in transgenic mice. Lumacaftor was also not associated with any adverse effects in developmental and reproductive toxicology studies, including male or female fertility, embryofetal survival, teratogenicity, or post-natal development and sexual maturation.

Toxicology studies evaluating the lumacaftor-ivacaftor combination were conducted in rats for up to 3 months and dogs for 1 month. Novel toxicities attributed to the combination included gastrointestinal findings in rats as well as cardiac and male reproductive effects in dogs. Bilateral, subcapsular cataracts were observed for one rat treated with the high dose of the combination. Lumacaftor in combination with ivacaftor lowered exposures to ivacaftor when compared to ivacaftor alone.

Carcinogenicity studies in both rats and mice are generally required to be included in the initial NDA submission. Given the unmet need for an efficacious therapy that addresses the defective CFTR ion channel, Vertex proposed, and the Division agreed, that the two-year carcinogenicity study in rats could be completed post-approval.

The nonclinical team is the lead discipline in the determination of the Established Pharmacologic Class (EPC) of a product. Ivacaftor has previously been designated as a “CFTR potentiator” based on its mechanism of action i.e., facilitates increased chloride transport by potentiating the channel-open probability of the CFTR protein at the cell surface. Lumacaftor, as a novel drug, did not belong to an EPC although in academic and drug development circles it and similar acting compounds have been referred to as CFTR “(b) (4)” the EPC the Applicant proposed. After a thorough review and discussion both internally and with Vertex, it was felt that designating lumacaftor as a CFTR “(b) (4)” was not fully justifiable based on what is known about its mechanism of action, to improve the conformational stability of mutant F508del CFTR ion channel, resulting in increased cellular processing and trafficking of it to the cell surface. As a result, the determination is to designate lumacaftor as a member of the EPC “CFTR conformational stabilizer.”

5. Clinical Pharmacology and Biopharmaceutics

Vertex submitted results from a comprehensive clinical pharmacology program that included studies to assess the pharmacokinetics and metabolism of the individual drug components lumacaftor and ivacaftor as well as the combination product. Ivacaftor is extensively metabolized in humans with the majority excreted in the feces. In vitro and clinical studies indicate that IVA is primarily metabolized by CYP3A. As such, co-administration with strong CYP3A inhibitors increases ivacaftor exposure. Steady state concentration of ivacaftor in healthy volunteers was achieved in 3-5 days. Lumacaftor is not extensively metabolized in human with most of the drug excreted unchanged in feces. In vitro and in vivo data indicate that lumacaftor is primarily metabolized via oxidation and glucuronidation. Lumacaftor is a strong inducer of CYP3A. The terminal half-life is approximately 26 hours that could support a once daily dosing regimen. Steady state concentration of lumacaftor in healthy volunteers was achieved in 5-14 days.

After twice daily dosing of lumacaftor-ivacaftor combination product, steady state plasma concentrations of lumacaftor and ivacaftor were generally reached after approximately 7 days of treatment. The steady state exposure of ivacaftor is lower than that of Day 1 due to the CYP3A induction effect of lumacaftor. There is a food affect for both lumacaftor and ivacaftor. When a single dose of lumacaftor-ivacaftor combination product was administered with fatty foods, lumacaftor exposure is approximately 2 times higher and ivacaftor exposure is 3 times higher than when taken in a fasting state. Since lumacaftor is a strong inducer of CYP3A and ivacaftor is a CYP3A substrate, when dosed together ivacaftor exposure is reduced in a lumacaftor dose-dependent manner. This drug-drug interaction is clinically relevant since, when dosed with lumacaftor 400 mg q12h, ivacaftor exposure is reduced by more than 80% (Figure 2). While co-administration of lumacaftor with ivacaftor substantially decreases ivacaftor exposure, lumacaftor exposure is not affected by ivacaftor.

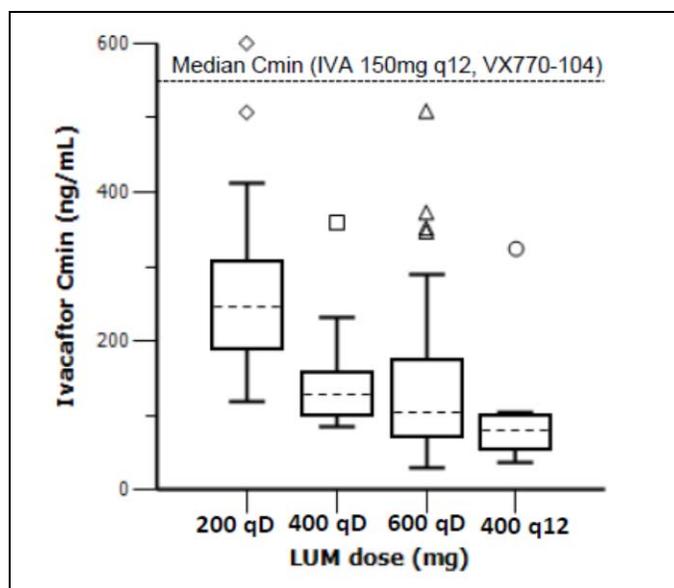


Figure 2. Ivacaftor exposure in CF patients when ivacaftor 250 mg q 12 hours was co-administered with increasing dose of lumacaftor (Study 809-102).

6. Clinical Microbiology

There are no outstanding clinical microbiology issues.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis for review and regulatory decision for this application are shown in Table 1.

Table 1. Relevant controlled clinical studies for the lumacaftor-ivacaftor combination product

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study design, objective - Study duration	Treatment groups ‡	N §	Efficacy Variables ¶	Regions and Countries
<i>Lumacaftor-ivacaftor combination product studies in F508del CF patients</i>					
809-102 [Cohort 2 & 3] [10/10 to 04/14]	- 12 yrs and older - homozygous or heterozygous for <i>F508del</i> - Phase 2, PK, PD, dose- ranging, cross-over, DB - 14 to 28 days	LUM 200 mg qd/LUM 200 mg qd+IVA 250 mg q12h LUM 400 mg qd/LUM 400 mg qd+IVA 250 mg q12h LUM 600 mg qd/LUM 600 mg qd+IVA 250 mg q12h LUM 400 q12h/LUM 400 mg q12h+IVA 250 q12h	97	Sweat chloride FEV ₁ CFRQ-R resp domain	US (75%), Europe, Australia
809-103 [05/13 to 04/14] Study 1	- 12 yrs and older - homozygous for <i>F508del</i> - Phase 3, safety and efficacy, parallel arm, DB - 24 weeks	LUM 600 mg qd/IVA 250 mg q12h LUM 400 mg/IVA 250 mg q12h Placebo q12h	185 187 187	1°: Δ FEV ₁ absolute change 2°: Δ FEV ₁ relative change, BMI, CFQ-R resp domain, response rate (≥5% increase in relative FEV ₁), CF Exacerbations	US (48%), Canada, Europe, Australia
809-104 [04/13 to 04/14] Study 2	- 12 yrs and older - homozygous for <i>F508del</i> - Phase 3, safety and efficacy, parallel arm, DB - 24 weeks	LUM 600 mg qd/IVA 250 mg q12h LUM 400 mg/IVA 250 mg q12h Placebo q12h	187 189 187	1°: Δ FEV ₁ absolute change 2°: Δ FEV ₁ relative change, BMI, CFQ-R resp domain, response rate (≥5% increase in relative FEV ₁), CF Exacerbations	US (60%), Canada, Europe, Australia
<i>Ivacaftor study in f508del CF (conducted for ivacaftor NDA for G551D CF patients)</i>					
770-104 (partA) [09/09 to 07/10]	- 12 yrs and older - homozygous for <i>F508del</i> - Phase 2, safety and efficacy, parallel arm, DB - 16 weeks	IVA 150 mg a12 h Placebo q12 hr	112 28	Δ FEV ₁ Absolute change	US (100%)
* Study ID shown (top to bottom) as Vertex's study number, and [month/year study started-completed], study as reported in the Orkambi product label † DB = double blind ‡ LUM = Lumacaftor, IVA= Ivacaftor § Intent to treat (ITT) ¶ FEV ₁ primary endpoint analysis was to test the difference between the active combination treatment group versus placebo using a mixed model with repeated measures.					

b. Design and conduct of studies

Study 809-102 was a randomized, double-blind placebo-controlled, multi-cohort study that evaluated multiple doses of lumacaftor alone once or twice daily and in combination with a 250 mg dose of ivacaftor administered twice daily. The objectives of the study were to assess the safety, efficacy, pharmacokinetics, and pharmacodynamics of lumacaftor alone and in combination with ivacaftor in CF patients who were homozygous for the *F508del* CFTR mutation. This study served as the principle dose selection study. The endpoints relevant to dose selection were the pharmacodynamic endpoint, sweat chloride, and FEV₁ as a measure of pulmonary function. The study consisted of 4 different cohorts; Cohort 1 assessed the effect of low dose lumacaftor alone and in combination with the marketed dose (150 mg twice daily) or a higher dose (250 mg twice daily) of ivacaftor, Cohort 2 assessed the effect of higher doses of lumacaftor (up to 600 mg once daily) alone and in combination with high dose ivacaftor (250 mg twice daily), Cohort 3 assessed the effect of a 400 mg twice daily dose of lumacaftor alone and in combination with ivacaftor (250 mg twice daily), and Cohort 4 assessed a dose of lumacaftor 400mg plus ivacaftor 250mg twice daily for a longer (56 day) treatment period. The results obtained from Cohorts 2 and 3 are the most relevant for the purpose of determining the effect of lumacaftor monotherapy and the potential clinical activity for the lumacaftor plus ivacaftor combination.

Studies 809-103 and 809-104 were identical randomized, double-blind, placebo-controlled, parallel group studies conducted to assess the efficacy and safety of 2 doses of LUM/IVA combination (LUM 600mg qd/IVA 250mg q12h and LUM/IVA 400/250mg q12h) in patients with CF homozygous for the *F508del* mutation in the *CFTR* gene (Figure 3). After a 28-day screening period, eligible patients were randomized 1:1:1 to receive LUM 600mg qd/IVA 250mg q12h, LUM/IVA 400/250mg q12h, or placebo twice daily for 24 weeks. The primary efficacy endpoint for the studies was the absolute change from baseline in percent-predicted FEV₁ at week 24 assessed as the average of the treatment effects at Week 16 and at Week 24. The 5 pre-specified secondary endpoints for testing in hierarchical order were: 1) average relative change from baseline in per cent predicted FEV₁ at weeks 16 and 24; 2) absolute change from baseline in body mass index (BMI) at week 24; 3) absolute change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score at week 24; 4) FEV₁ response defined as $\geq 5\%$ increase in average relative change from baseline in percent predicted FEV₁ at weeks 16 and 24; 5) number of pulmonary exacerbations through week 24. It is notable that sweat chloride, which Vertex has used in all previous CF phase 3 programs as a key pharmacodynamic and efficacy endpoint was not assessed in Studies 809-103 or 809-104.

For Studies 809-103 and 809-104, enrollment was planned for approximately 167 patients in each treatment group for each study. Based on the assumptions that the treatment difference for the primary endpoint (absolute change in % predicted FEV₁) would be 5%, a standard deviation of 8%, 10% of patients missing or dropping out, and a 2-sided test at 0.025 level, this sample size had about 99% power. However, given that there were about 187 patients enrolled per group, an observed mean difference as small as approximately 1.65% in FEV₁ could be statistically significant.

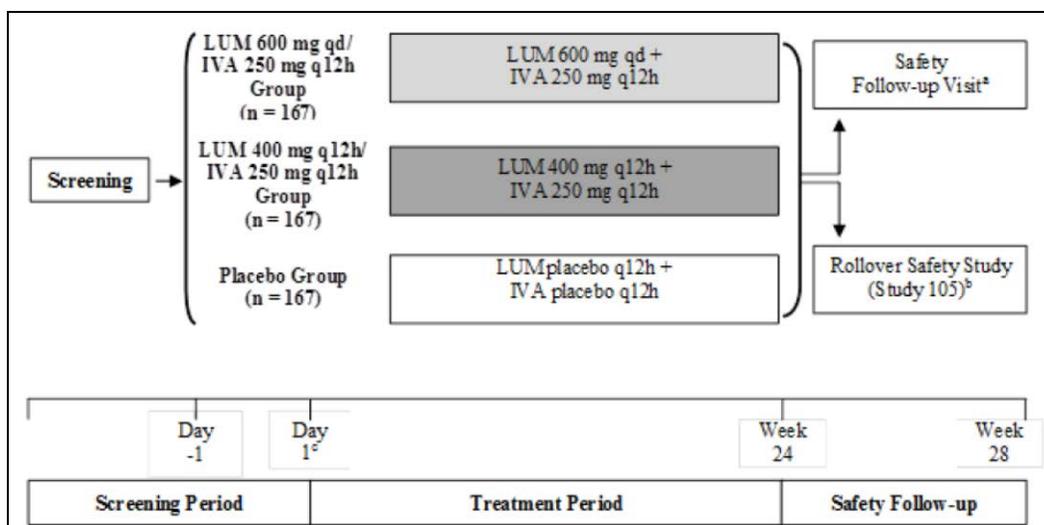


Figure 3. Study schematic, Study 809-103

c. Efficacy findings and conclusions

The clinical program supports the efficacy of lumacaftor plus ivacaftor combination product at a dose of lumacaftor 400 mg and ivacaftor 250 mg every 12 hours for the treatment of CF in patients 12 years and older who have the *F508del* mutation.

Sweat chloride data (available from Study 809-102 only) showed small reductions in sweat chloride for lumacaftor alone with further small additive reduction with addition of ivacaftor (Table 2).

Table 2. Change in sweat chloride and percent predicted FEV₁ compared to placebo for lumacaftor and for lumacaftor in combination with ivacaftor, Mean (95% CI), Study 809-102, Cohorts 2 and 3

	Lumacaftor 200 mg QD	Lumacaftor 400 mg QD	Lumacaftor 600 mg QD	Lumacaftor 400 mg Q 12 h
Δ in sweat chloride (mmol/L) vs. placebo				
Baseline to day 28 (lumacaftor alone)	-4.9 (-9.5, -0.28)	-8.3 (-13.0, -3.6)	-6.1 (-11.0, -1.4)	-8.2 (-14.1, -2.3)
Baseline to day 56 (lumacaftor +I vacaftor)	-5.0 (-10.5, 0.48)	-9.8 (-15.3, -4.2)	-9.5 (-15.1, -3.9)	-11.0 (-18.3, -3.7)
Δ in percent predicted FEV₁ vs. placebo				
Baseline to day 28 (lumacaftor alone)	0.24 (-3.7, 4.2)	-1.4 (-5.4, 2.6)	-2.7 (-6.7, 1.4)	-4.6 (-9.6, 0.4)
Baseline to day 56 (lumacaftor +I vacaftor)	3.8 (-0.5, 8.1)	2.7 (-1.7, 7.0)	5.6 (1.2, 10.0)	4.2 (-1.3, 9.7)

FEV₁ data from Study 809-102 showed a dose-dependent decrease with lumacaftor alone (Table 2, and Figure 5 baseline to day 28). Addition of ivacaftor to lumacaftor resulted in increase in FEV₁ that increased to levels higher than pre-treatment baseline (Table 2, and Figure 5 baseline to day 56). Based on this data, Vertex selected the two doses,

lumacaftor 600 mg qd plus ivacaftor 250 mg q12h and the lumacaftor 400 mg plus ivacaftor 250 mg q12h, to study further in the phase 3 program. This was reasonable.

Results of the sweat chloride data and FEV₁ data show small numerical benefit of addition of ivacaftor to lumacaftor, supporting the combination product.

The minimal change in sweat chloride with lumacaftor alone or in combination with ivacaftor, and dose-dependent decrease in FEV₁ with lumacaftor (Table 2, Figure 5) did not corroborate the expected findings from the in-vitro data (Figure 1). The in-vitro data did not appear to be a good predictor for clinical effect for lumacaftor.

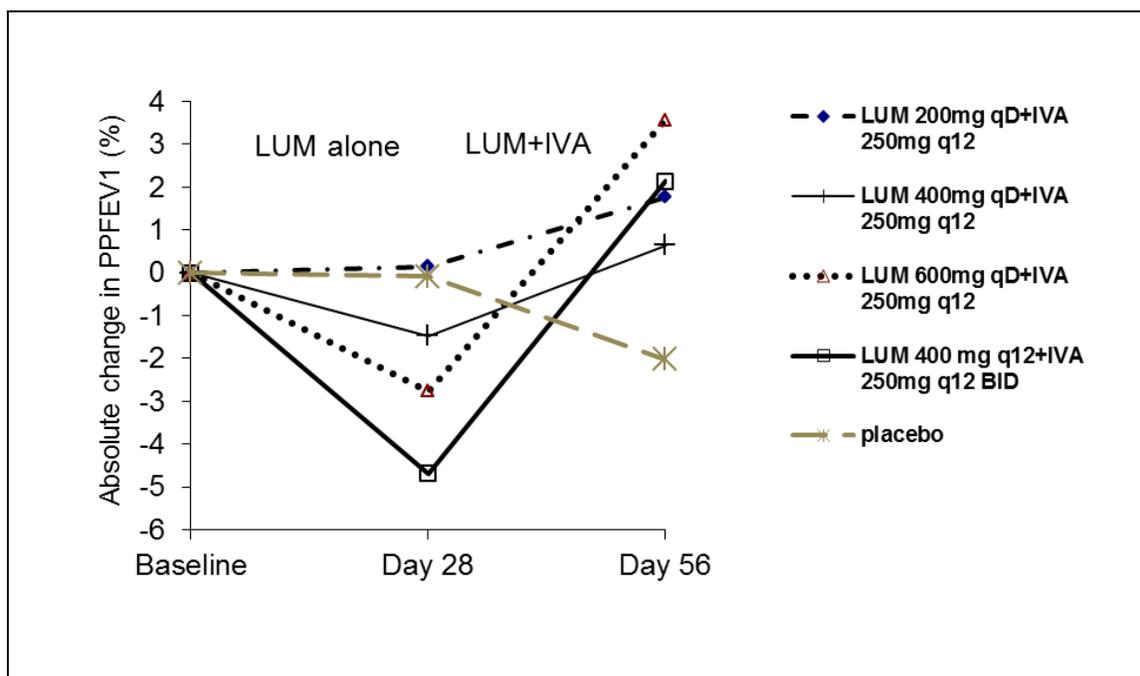


Figure 4. Absolute change from baseline in percent predicted FEV₁ at days 28 and 56 in *F508del* homozygous patients, Study 809-102, Cohorts 2 and 3.

The phase 3 studies compared two doses of the lumacaftor plus ivacaftor combination product to placebo. The reasoning for not including either of the active comparator arm in the program is stated in Section 2 above. Results of the primary and secondary efficacy variable for the two studies are shown in Table 4. Both studies showed a statistically significant improvement in FEV₁ with an effect size that was lower than the phase 2 study (Study 809-102). The secondary efficacy variables tended in the direction of improvement with the combination product over placebo, although most were not statistically significant because of the hierarchical analysis plan with loss of statistical significance at or below the secondary variable of BMI (Table 2). The numerical beneficial effect on pulmonary exacerbation is notable as it suggests that the numerically small but statistically significant improvement in FEV₁ is a meaningful clinical benefit.

The two doses of the combination product showed similar effect size across the efficacy measures and support Vertex’s decision to market the dose of lumacaftor 400 mg and ivacaftor 250 mg every 12 hours (LUM/IVA 400/250 q12 in Table 4).

Table 3. Summary of primary and secondary endpoints (listed in hierarchical order), Studies 809-103 and 809-104

	Study 809-103			Study 809-104		
	Placebo	LUM 600 qd IVA 250 q12	LUM/IVA 400/250 q12	Placebo	LUM 600qd IVA 250 q12	LUM/IVA 400/250 q12
Primary Endpoint: Absolute change from baseline in percent predicted FEV ₁ at weeks 16 and 24						
Δ from baseline	-0.4	3.6	2.2	-0.2	2.5	2.9
Difference from placebo (95% CI)	--	4.0 (2.6, 5.4)	2.6 (1.2, 4.0)	--	2.6 (1.2, 4.1)	3.0 (1.6, 4.4)
Relative change from baseline in percent predicted FEV ₁ at weeks 16 and 24						
Δ from baseline	-0.3	6.4	4.0	0.0	4.4	5.3
Difference from placebo (95% CI)	--	6.7 (4.3, 9.2)	4.3 (1.9, 6.8)	--	4.4 (1.9, 7.0)	5.3 (2.7, 7.8)
Absolute change from baseline in BMI (kg/m ²) at week 24						
Δ from baseline	0.2	0.4	0.3	0.1	0.5	0.4
Difference from placebo (95% CI)	--	0.2 (-0.0, 0.4)	0.1 (-0.1, 0.3)	--	0.4 (0.2, 0.6)	0.4 (0.2, 0.5)
Absolute change in CFQR respiratory domain (CFQR-RD) at week 24						
Δ from baseline	1.1	5.0	2.6	2.8	5.0	5.7
Difference from placebo (95% CI)	--	3.89 (0.7, 7.1)	1.5 (-1.7, 4.7)	--	2.2 (-0.9, 5.3)	2.9 (-0.3, 6.0)
FEV ₁ response(≥5% increase in average relative change in % predicted FEV ₁ at weeks 16 and 24)						
Δ from baseline	41 (22.3)	85 (46.4)	67 (36.8)	42 (22.5)	85 (45.9)	77 (41.2)
Difference from placebo (95% CI)	--	2.9 (1.9, 4.6)	2.0 (1.3, 3.3)	--	3.0 (1.9, 4.6)	2.4 (1.5, 3.7)
Number of pulmonary exacerbations						
Number of events	112	79	73	139	94	79
Event rate/year	1.1	0.8	0.7	1.2	0.8	0.7
Rate ratio vs placebo (95% CI)		0.7 (0.5, 1.0)	0.7 (0.5, 0.9)		0.7 (0.5, 0.9)	0.6 (0.4, 0.8)

The FDA statistical team compared the FEV₁ data and the exacerbation data (two efficacy variables of maximum interest) from the phase 3 studies submitted with this NDA to the ivacaftor alone study conducted in CF patients with the same *F508del* mutation (study characteristics shown in Table 1) with the intent of understanding the contribution of lumacaftor in clinical efficacy of the combination product. To make the comparisons as similar as possible, only patients with similar baseline FEV₁ range were included in the analysis (between 40% and 90% at baseline), and the FEV₁ analysis was done with the values obtained “at” the same time point of 16 weeks rather than “through” 16 weeks (“at” analysis includes data from one time point of 16 weeks, and “through” analysis includes data from 16 weeks and previous time points). Nevertheless, such comparison has limitations, as studies were done at different times, patients’ baseline demographics were not the same, background use of hypertonic saline were different, etc. Regardless of these limitations, these exploratory analyses were not able to demonstrate that the treatment effect of lumacaftor plus ivacaftor was any different from ivacaftor

alone for FEV₁ and pulmonary exacerbation with point estimates being similar and confidence intervals overlapping (Table 5).

Table 4. FEV₁ and pulmonary exacerbation data from Studies 809-103 and 809-103 (Current NDA) and Study 770-104 (Previous NDA for ivacaftor)

	Percent Predicted FEV₁ (95% CI)	Exacerbation Rate Ratio (95% CI)
	Δ from baseline LUM 400mg + IVA 250mg q12 hr vs placebo at week 16	
Study 809-103	2.8 (1.2, 4.4)	0.67 (0.50, 0.91)
Study 809-104	3.5 (2.1, 4.3)	0.57 (0.44, 0.76)
	Δ from baseline IVA 150 mg q12 hr vs placebo at week 16	
Study 770-104	2.6 (-1.1, 6.4)	0.61 (0.29, 1.26)

Efficacy conclusion:

The phase 3 clinical data showed that lumacaftor plus ivacaftor fixed dose combination product has statistically significant benefit over placebo in FEV₁ with a modest effect size of approximately 3% (Table 4 and Table 5). The numerical beneficial effect on pulmonary exacerbations places the improvement in FEV₁ in context, as it suggests that the numerically small but statistically significant improvement in FEV₁ is a meaningful clinical benefit. Other efficacy variables also favored the lumacaftor plus ivacaftor fixed dose combination product over placebo (Table 4). The contribution of the single ingredient lumacaftor and ivacaftor in the combination product can be gleaned from the in-vitro data suggesting additive benefit of the two (Figure 1), and early clinical data suggest some additive benefit on FEV₁ when ivacaftor is added to lumacaftor (Figure 5). The available clinical data are not adequate to determine whether lumacaftor provides additive clinical benefit over ivacaftor alone (Table 5). However, demonstration of additive clinical benefit of lumacaftor is not necessary in this specific situation. The lumacaftor plus ivacaftor combination product provides benefit over placebo (standard of care background treatment in this case), and for CF patients with *F508del* mutation the treatment options are limited. The natural course of CF patients with *F508del* mutation is devastating and lumacaftor plus ivacaftor combination product will provide benefit to these patients over the current standard of care treatment.

8. Safety

a. Safety database

The safety assessment of ivacaftor for CF patients who have the *F508del* mutation is primarily based on studies shown in Table 1.

b. Safety findings and conclusion

The submitted safety data support the safety of lumacaftor plus ivacaftor combination product for treatment of CF patients who have the *F508del* mutation in the CFTR gene. Vertex conducted a comprehensive safety analysis of the available data. Safety assessment in the clinical studies included evaluation of deaths, serious adverse events

(SAEs¹), common adverse events (AEs), vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Deaths, SAEs, dropouts and discontinuations:

There were no deaths in the placebo-controlled clinical studies. One death was reported in the open-label safety extension study. The death occurred in a 24 year old patient from complications related to pulmonary exacerbation. The death was not reported as related to the lumacaftor plus ivacaftor combination product.

Serious adverse events (SAEs) related to pulmonary exacerbation was reported in approximately 13% patients who received lumacaftor plus ivacaftor combination product and 24% patients who received placebo. Other SAEs were reported relatively infrequently (<2% in any group) and included hemoptysis and intestinal obstruction. One patient receiving lumacaftor plus ivacaftor combination product was reported to have hepatic encephalopathy (discussed further below in this section).

Dropouts and discontinuations were low in various treatment groups in the controlled clinical studies and occurred with comparable frequencies across treatment groups.

Common adverse events:

Common adverse events seen were typical of CF programs and showed little differences across treatment arms. Adverse events that were reported more frequency with lumacaftor plus ivacaftor treatment compared to placebo included dyspnea, abnormal respiration, flatulence, and rash.

Laboratory findings and ECGs:

No clinically meaningful effects on hematologic or chemistry parameters were noted in the clinical program. Assessments of ECGs did not reveal a safety signal.

Adverse events of interest:

Liver-related safety concerns from the ivacaftor monotherapy program and the finding of decreased pulmonary function (FEV₁) in patients who received lumacaftor monotherapy led to specific analyses to assess for potential liver toxicity and respiratory-related AEs. Menstrual abnormalities were also an event of interest due to observed increased metrorragia in lumacaftor plus ivacaftor combination product treatment compared to placebo from early phase studies.

¹ Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Liver related safety:

While there were no differences between the lumacaftor plus ivacaftor combination product treatment groups compared to placebo in overall adverse events thought to be liver related (5.4-6.0% across treatment groups), more patients receiving lumacaftor plus ivacaftor combination product had liver-related adverse events that were classified as SAEs (life-threatening or requiring hospitalization) or resulted in discontinuation from treatment (0.9% and 0.5% lumacaftor plus ivacaftor combination product patients vs 0 patients who received placebo). With regard to elevations in AST, ALT, and bilirubin, there were no discernable differences in AST or ALT elevations alone between treatment groups, however, when examining patients with ALT or AST elevations >3x ULN who also had total bilirubin elevations >2x ULN, there were three cases in patients who received lumacaftor plus ivacaftor combination product (0.4%) groups compared to none who received placebo. While the data do not show direct causal association between lumacaftor plus ivacaftor combination product and liver event, a contribution cannot be excluded. The product label will have appropriate warning language.

The patient reporting SAE of hepatic encephalopathy (mentioned above) was a 25-year-old male with a CF related liver cirrhosis, portal hypertension, splenomegaly, and thrombocytopenia. After 6 days of lumacaftor plus ivacaftor combination product treatment, the patient presented to ER with disorientation. Laboratory evaluation showed elevated transaminases and increased ammonia level, but bilirubin level was not reported. The patients improved over approximately a week on in hospital treatment. Based on the available information, causality to treatment cannot be assessed, but it is possible that the treatment could have contributed to hepatic decompensation.

Respiratory safety:

As a result of dose dependent decrease in pulmonary function observed in patients who received lumacaftor monotherapy, Vertex performed an analysis of safety analysis grouping together respiratory-related adverse events. CF patients who received lumacaftor plus ivacaftor combination product had an increased frequency of respiratory symptoms particularly dyspnea, and “respiration abnormal” at frequencies of 23% and 10% compared to 8% and 3% in patients who received placebo, respectively. Three of the events lead to treatment discontinuation compared to none in the placebo group and 2 events were reported as SAEs. These lumacaftor plus ivacaftor combination product related respiratory AEs/SAEs tended to occur early after initiating therapy (median time to onset was about 2 days). These data suggest that treatment with lumacaftor plus ivacaftor combination product can cause increased respiratory symptoms and AEs in some CF patients.

Menstrual abnormalities:

Female patients reported more menstrual abnormalities, mostly metrorrhagia, in the lumacaftor plus ivacaftor combination product treatment arms compared to placebo. This difference was more prominent in patients on hormonal contraception. This may be because lumacaftor is an inducer of CYP3A4.

Cataract:

Cataract is a finding of interest because of the observation of cataract with ivacaftor treatment in juvenile animal toxicology study. There were no cataracts seen in the lumacaftor plus ivacaftor development program.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on May 12, 2015, to discuss this application. Issues for discussion were the contribution of lumacaftor to the clinical efficacy of the lumacaftor plus ivacaftor combination product, overall efficacy, and overall safety. The voting questions included one specific question on the contribution of lumacaftor to the clinical efficacy of the combination product. In general the advisory committee members were of the opinion that the submitted data are adequate to support approval of the lumacaftor plus ivacaftor combination product (voting by committee members are shown in Table 10). The committee members opined that the current data for ivacaftor monotherapy are not sufficient to conclude efficacy for CF patients with the *F508del* mutation, and the data are not adequate to assess comparative clinical efficacy of the lumacaftor plus ivacaftor combination product to ivacaftor alone. Some committee members noted that they are placed in a difficult or impossible position in trying to determine clinical contribution of individual components and similar situations should be avoided in the future. Most committee members, given the unmet need for an efficacious therapy for this large population of patients with CF homozygous for the *F508del* mutation and the benefit demonstrated for lumacaftor plus ivacaftor combination product over placebo, did not feel that additional data are necessary to support approval or that could delay approval.

Table 5. AC voting on efficacy, safety, approvability, and large safety outcome trial

	Pediatric 12 to 17 years		
	Yes	No	Cannot determine
Contribution of lumacaftor to clinical efficacy of Orkambi	3	4	6
Safety of Orkambi	13	0	0
Approval of Orkambi	12	1	0

10. Pediatric

CF is an orphan disease and not subject to PREA. Based on the knowledge that CF is a genetic disease, which can manifest at birth, the applicant plans to conduct clinical studies in patients below 12 years of age.

11. Other Relevant Regulatory Issues

a. DSI Audits

DSI audited three clinic representative sites from the pivotal studies as well as the Vertex establishment. The clinical and statistical review teams recommended the clinic sites because these sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Four investigators had significant equity interest in Vertex. The number of subjects enrolled in the investigator sites was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Other

There are no outstanding issues with consults received from the OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

The proposed proprietary name Orkambi was previously reviewed by DMEPA and found to be acceptable.

b. Physician Labeling

Vertex submitted a label that conformed with the Physician Labeling Rule. The label was reviewed by various disciplines of this Division, and other Offices and Division of the Center. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to healthcare providers. Edits were also made to harmonize, where appropriate, the proposed Orkambi label to the label of the currently approved product, Kalydeco which is the ivacaftor component of the combination. The Division and Vertex are in discussion on the final labeling language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

There is a Patient Counseling Information (Instruction for Use and Patient Package Insert) that has been reviewed by the Division, DMPP, and other groups within the Center and found to be acceptable. There is no Medication Guide for this product.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Vertex has submitted adequate data to support approval of lumacaftor plus ivacaftor combination product at a dose of lumacaftor 400 mg and ivacaftor 250 mg every 12 hours for the treatment of CF in patients ^(b)₍₄₎ years and older who have the *F508del* mutation in the *CFTR* gene.

b. Risk Benefit Assessment

The overall risk-benefit assessment is favorable for the lumacaftor plus ivacaftor fixed dose combination product for the treatment of CF patients 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. The safety finding of note was potential for liver injury, which can be adequately informed in the product labeling. The demonstrated clinical benefit is a statistically significant improvement with lumacaftor plus ivacaftor fixed dose combination product over placebo in FEV₁ of a modest effect size of approximately 3%. There was a numerical beneficial effect on pulmonary exacerbation suggesting that the numerically small but statistical significantly improvement in FEV₁ is a meaningful clinical benefit. The available clinical data are not adequate to determine whether lumacaftor provides additive clinical benefit over ivacaftor alone. Demonstration of additive clinical benefit of lumacaftor is not necessary in this specific situation. The lumacaftor plus ivacaftor combination product provides benefit over placebo (standard of care background treatment in this case), and for CF patients with *F508del* mutation the treatment options are limited. The natural course of CF patients with *F508del* mutation is devastating and lumacaftor plus ivacaftor combination product will provide benefit to these patients over the current standard of care treatment.

c. Post-marketing Risk Management Activities

No post-marketing risk evaluation and management strategies are recommended.

d. Post-marketing Study Commitments

No PMR or PMC studies are recommended, other than the nonclinical carcinogenicity study noted in Section 4 above.

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/s/

BADRUL A CHOWDHURY
06/25/2015