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APPLICATION NUMBER:

206038Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 10, 2015
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 206038
Supplement#	
Applicant	Vertex Pharmaceuticals
Date of Submission	November 5, 2014
PDUFA Goal Date	July 5, 2015
Proprietary Name / Established (USAN) names	Orkambi/ lumacaftor/ivacaftor combination tablet
Dosage forms / Strength	Oral tablet/ lumacaftor 200 mg/ivacaftor 125 mg Dose is 2 tablets every 12 hours
Proposed Indication(s)	“... indicated for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who are homozygous for the <i>F508del</i> mutation in the <i>cystic fibrosis transmembrane conductance regulator (CFTR)</i> gene”
Recommended:	Approval

1. Introduction

The Applicant (Vertex Pharmaceuticals) submitted this 505(b)(1) NDA to support the safety and efficacy of lumacaftor 200 mg/ivacaftor 125 mg (LUM/IVA) fixed dose combination tablets (tradename Orkambi) at a dose of 2 tablets every 12 for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who are homozygous for the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene”. Ivacaftor is a small molecule drug that has been shown to increase chloride ion transport across the CFTR chloride channel (the ion channel which, if defective results CF) in epithelial cell membranes and, as such, is classified as a “CFTR potentiator”. Lumacaftor, another small molecule, is a new molecular entity that 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. The combination received Breakthrough Therapy designation on December 5, 2012, based on Phase 2 clinical data demonstrating an approximately 5% improvement over placebo in FEV1 in CF patients who received the LUM/IVA combination.

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This review will focus on the efficacy and safety findings from the Phase 3 program as well as the determination of the contribution of each of the lumacaftor and ivacaftor monotherapy components to the overall effect of the combination.

2. Background

Cystic Fibrosis (CF) Background

CF is a life-threatening autosomal recessive disease which affects about 70,000 individuals world-wide (30,000 in US). It is caused by mutations in the *CFTR* gene that results in lack of or inadequate function of the CFTR protein on the surface of epithelial cells. The CFTR protein is a chloride channel that helps regulate salt and water absorption and secretion across epithelial cells. There are about 2000 mutations that have been identified in the *CFTR*; as an autosomal recessive disease, patients need mutations in both *CFTR* alleles to develop CF. This application is focused on 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 in the *CFTR* gene with approximately 90% of CF patients having the *F508del* mutation on at least one allele and about 50% of CF patients being homozygous for it. 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 person with the *F508del* *CFTR* mutation will produce a truncated F508del-CFTR protein that lacks this phenylalanine residue. As a result, the truncated F508del-CFTR 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 F508del-CFTR that reaches the cell surface has reduced function, i.e., decreased open-ion channel probability. The result is a reduced amount of F508del-CFTR that reaches the epithelial cell membrane that also has reduced function. Ultimately, these deficiencies result in a relatively severe disease phenotype.

Clinical manifestations of CF are dependent on types of mutations, post-transcriptional modification of CFTR protein, and environmental factors. Typically, the lungs, GI system (intestines, pancreas, liver), and reproductive systems are the predominantly affected organs systems. Death is usually due to respiratory failure as a result of obstructive lung disease and chronic pulmonary infection. Ultimately, disease severity depends on the type of mutations present and well as other modifying factors, however, currently the median age for survival is the mid- to late 30's.

Rationale for Lumacaftor/Ivacaftor (LUM/IVA) Fixed Dose Combination

Ivacaftor

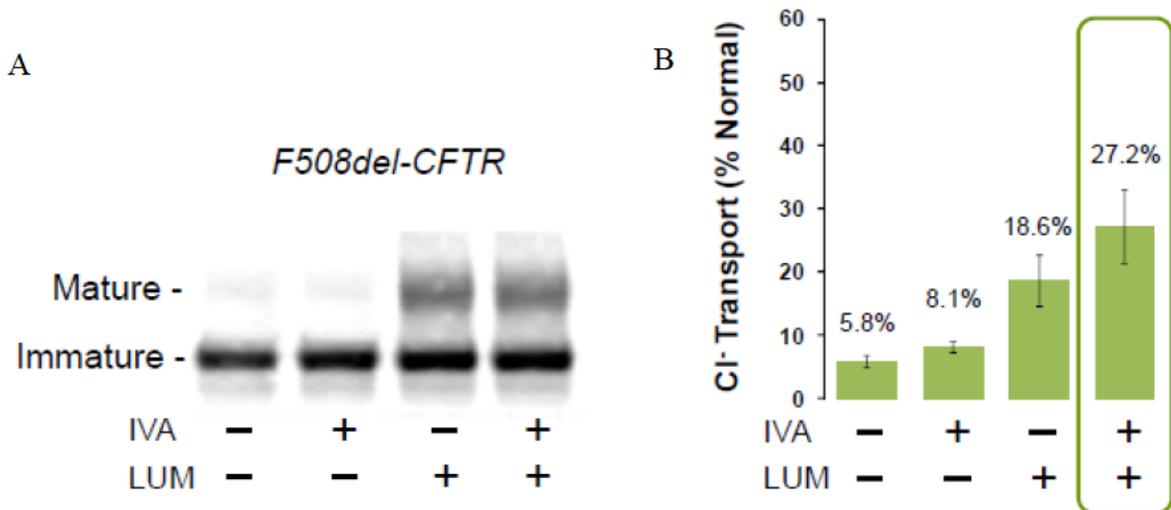
Ivacaftor is a small molecule drug that has been shown to increase chloride ion transport across the CFTR chloride channel in epithelial cell membranes. Its established drug class reflects this action as it is classified as a “CFTR potentiator”. It is currently approved in tablet and granule formulations in the US for the treatment of patients as young as 2 years of age with CF defined by having one of ten mutations in the *CFTR* gene (*G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H*). These mutations together encompass relatively few (about 2000) CF patients out of a total of approximately 30,000 patients with CF in the US and have in common the fact that the resultant translated CFTR ion channel, while demonstrating defective ion channel regulation, is present in the epithelial cell membrane and, therefore, amenable to potentiation by ivacaftor.

Lumacaftor

Lumacaftor, another small molecule, was developed by Vertex to work in conjunction with other CFTR-active drugs such as ivacaftor. While its mechanism of action is not completely understood, it appears to stabilize and promote 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. In vitro data suggest it does this by inducing a change in F508del CFTR protein conformation that is more like the normal “wild-type” CFTR resulting in increased F508del CFTR maturation. Experimental data generated by scientists at Vertex in cultured human bronchial epithelial cells suggest that an increase of F508del CFTR in the epithelial cell membrane restored overall F508del CFTR channel function to approximately 14% of normal levels.¹

Based on our current considerable knowledge of the defects in CFTR ion channel function as a result of mutations in the *F508del* gene, there is a scientific rationale that optimal therapy for CF patients homozygous for the *F508del* mutation in the *CFTR* will require a combination of CFTR modulating drugs that address the different CFTR functional defects associated with a given mutation. In that light, given the actions of the individual drug components, Vertex has hypothesized 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 (Figure 1).

Figure 1. In vitro data suggesting that lumacaftor facilitates processing of mutant CFTR to the cell surface (A) where chloride transport can be potentiated by ivacaftor (B)



Source: Slide CA-12 Vertex Pharmaceuticals May 12, 2015 PADAC presentation

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Regulatory Interactions

Early clinical studies conducted by Vertex suggested that neither lumacaftor nor ivacaftor alone appear to have a substantial beneficial effect in patients with CF homozygous for the *F508del* mutation. However, preliminary clinical evidence on the combination of lumacaftor and ivacaftor from study 809-102, discussed in more detail below, suggested that the combination of the 2 drugs had the potential for efficacy in patients with CF homozygous for the *F508del* mutation in the *CFTR*. As such, Vertex applied for and received FDA Breakthrough Therapy designation for the combination of lumacaftor and ivacaftor on December 7, 2012, to accelerate its development for the treatment of CF in patients who are homozygous for the *F508del* mutation in the *CFTR* gene. Ivacaftor monotherapy had previously received Breakthrough Therapy designation on November 13, 2012, for the treatment of CF in patients with *CFTR* gene mutations that result in CFTR ion channel “gating” defects and/or those with residual baseline CFTR channel function.

The clinical development programs for combination drug products are typically designed to assess the contribution of each drug monotherapy to the overall effect of the combination product. As such, phase 3 clinical studies for a 2 drug FDC product would usually consist of 4 treatment groups, the combination product proposed for marketing, each individual drug component at the same dose as is proposed for the FDC product, and a placebo in some situations. That being said, there are some circumstances under which an individual drug component(s) may not be included. The LUM/IVA phase 3 program lacked both monotherapy comparator groups for the following reasons:

Based on the results of study 770-104 of ivacaftor monotherapy in CF patients homozygous for the *F508del* mutation that was previously reviewed under the ivacaftor NDA, the Division had found ivacaftor alone to be not effective. This and the promising Phase 2 results for the LUM/IVA combination from study 809-102 resulted in a determination that an ivacaftor monotherapy arm would not be necessary in the Phase 3 studies (conveyed at the November 2, 2012, End-of-Phase 2 meeting).

Phase 2 data also from study 809-102 for the LUM/IVA program demonstrated that treatment of CF patients for 28 day with lumacaftor alone resulted in a dose-dependent decrease in FEV1. As a result, due to safety and ethical concerns, a lumacaftor only arm was not included in the phase 3 studies (conveyed at a February 12, 2013, meeting to discuss the negative findings).

Other significant regulatory interactions occurred at a January 8, 2014, meeting with the Division and at a Pre-NDA meeting on August 12, 2014. During the January meeting the Division recommended that the Applicant include sweat chloride assessments in the studies 809-103 and 809-104. The Division also noted that those trials were powered to detect even small effects on FEV1 and that the review would consider not only statistical evidence for presence of a treatment effect, but also the clinical importance of the treatment effect. At the Pre-NDA meeting the Division reiterated that the NDA submission should address the clinical relevance of the treatment effect observed in the phase 3 studies as well as the level of evidence that lumacaftor contributes to the efficacy of the product.

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The complete NDA 206038 package for the LUM/IVA combination oral tablet was submitted on November 5, 2014, for the proposed indication of treatment of CF in patients ages 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

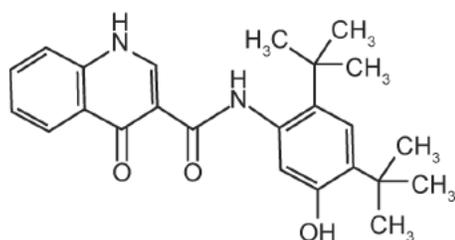
3. Chemistry, Manufacture, and Controls

From a CMC perspective, pending an overall acceptable recommendation from the facilities inspection, the Applicant has provided sufficient CMC information to assure the identity, strength, quality, and purity of the drug product to recommend approval.

The drug product is manufactured at 3 sites: [REDACTED] (b) (4) and the Vertex [REDACTED] (b) (4) facility in Boston. The manufacturing process for the LUM/IVA combination is novel in that it represents the first fully continuous drug product manufacturing process to be approved in the US [REDACTED] (b) (4) facility/Vertex-Boston).

The ivacaftor drug substance is a white to off white powder that is practically insoluble in water [REDACTED] (b) (4)

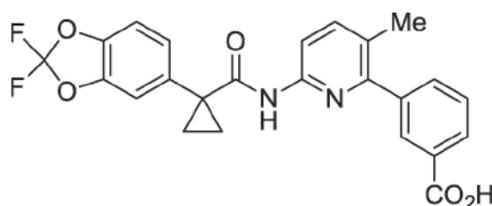
[REDACTED] Its molecular formula is $C_{24}H_{28}N_2O_3$ and molecular weight is 392.5.



ivacaftor

The lumacaftor drug substance is a white to off-white powder that is also practically insoluble in water. It is manufactured by [REDACTED] (b) (4)

[REDACTED] Its molecular formula is $C_{24}H_{18}F_2N_2O_5$ and molecular weight is 452.4.



lumacaftor

Drug Master Files were not referenced for this application as all pertinent information was adequately provided within the application.

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The LUM/IVA drug product (proposed tradename Orkambi) combines the active ingredients lumacaftor and ivacaftor as a fixed dose combination tablet. It is a pink, oval shaped, film coated tablet for oral administration plain on one side and “2V125” printed in black ink on the other side containing the active ingredients 200 mg of lumacaftor and 125 mg of ivacaftor (proposed dose 2 tablets twice daily) and compendial excipients. The packaging is an (b) (4) blister strip, 4 tablets per strip. The commercial configuration is a 112-count tablet box with 4 weekly-supply cartons, each carton containing 7 daily blister strips. Stability testing supports a 24 month shelf life.

4. Nonclinical Pharmacology and Toxicology

From the Nonclinical Pharmacology/Toxicology perspective, the recommendation is for approval. Completion of the ongoing 2-year carcinogenicity study of lumacaftor in rats will be a Post-Marketing Required (PMR) study.

The completed nonclinical development program for the LUM/IVA FDC consisted of studies with ivacaftor and lumacaftor, both alone and in combination.

Pharmacology and toxicology studies with the ivacaftor monoproduct are summarized in the Kalydeco (ivacaftor) product label. Key findings included bilateral cataracts in a juvenile rat study. As a result, Vertex is conducting a required post-marketing safety study to evaluate the risks of cataracts in pediatric patients who receive ivacaftor (<http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm>).

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 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.

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.

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 / female fertility, embryofetal survival, teratogenicity, and post-natal development and sexual maturation. Approximately one half of cystic fibrosis patients are homozygous for the *F508del CFTR* mutation and there is unmet medical need for this population. The lumacaftor-ivacaftor combination received Breakthrough Designation for this patient population on 12/5/2012.

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A carcinogenicity study is 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, the Applicant proposed, and the division agreed, that the two-year carcinogenicity study in rats could be completed post-approval as a PMR (see meeting minutes dated March 20, 2013, and communication dated August 5, 2013).

The nonclinical team is the lead discipline in the determination of the Established Pharmacological Class 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 the Applicant, 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”. For a thorough discussion on the rationale behind the designation, see the nonclinical review by Dr. Andrew Goodwin dated June 4, 2015.

5. Clinical Pharmacology/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

Steady state concentration of ivacaftor in healthy volunteers was achieved in 3-5 days. 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. For example, ketoconazole co-administration results in an 8.5-fold increase in exposure. In addition, strong inducers of CYP3A, such as rifampin, can significantly decrease ivacaftor exposure. The ivacaftor terminal half-life is approximately 12 hours which supports a twice daily dosing regimen.

Lumacaftor

Steady state concentration of lumacaftor in healthy volunteers was achieved in 5-14 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 glucouronidation. Lumacaftor is a strong inducer of CYP3A. The terminal half-life is approximately 26 hours which could support a once daily dosing regimen.

Lumacaftor/Ivacaftor

After twice daily dosing of LUM/IVA, steady state plasma concentrations of lumacaftor and ivacaftor were generally reached after approximately 7 days of treatment. The steady state

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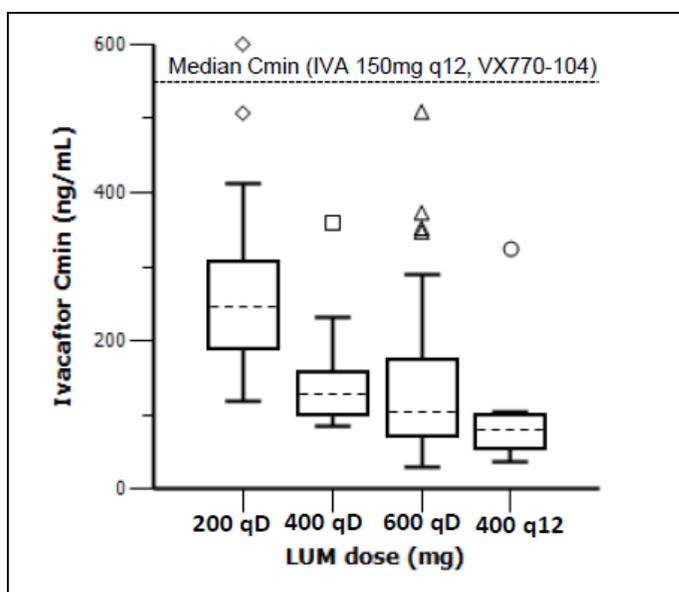
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exposure of ivacaftor is lower than that of Day 1 due to the CYP3A induction effect of lumacaftor.

There is a food affect for both lumacaftor and ivacaftor. When a single dose of LUM/IVA 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. Both lumacaftor and ivacaftor are 99% bound to plasma proteins.

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). This interaction affected dose selection of each component, which is discussed in the following section.

Figure 2. Ivacaftor (IVA) exposure in CF patients when IVA 250 mg q12 was co-administered with increasing doses of lumacaftor [(LUM) Study 809-102]



*Ivacaftor Cmin measured at 12 hour after morning dose after repeat dosing of LUM/IVA for 28 days

Source: FDA Clinical Pharmacology Reviewer

While co-administration of lumacaftor with ivacaftor substantially decreases ivacaftor exposure, lumacaftor exposure is not affected by ivacaftor.

There appears to be the potential for other lumacaftor drug drug interactions relevant to CF patients. In vitro studies suggest that lumacaftor has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19 as well as inhibit CYP2C8 and CYP2C9. Therefore, concomitant use of LUM/IVA may alter the exposure of many common concomitant medications used in CF patients, such as antibiotics, antifungals, proton pump inhibitors, ibuprofen, antidepressants, etc. As a result, concomitant use of LUM/IVA may require dose adjustment for some drugs. For additional information in regards to drug-drug interaction, refer to the clinical pharmacology review by Dr. Jianmeng Chen.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

The key clinical studies submitted to support safety and efficacy of the LUM/IVA FDC for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene are shown in Table 1 below. The design and conduct of these studies are briefly described below, followed by efficacy and safety findings and conclusions.

Table 1: Studies Relevant to the Lumacaftor/Ivacaftor Program

Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
809-101 US/Canada/EU March 2009- December 2009	PK, PD, and dose-ranging	93 CF patients ≥ 18 years	R, DB, PC, PG	LUM 25, 50, 100, 200 mg qd Placebo qd	28 days	Sweat Cl, NPD, FEV ₁ , CFQ-R resp domain
809-102* US October 2010- April 2014	PK, PD, and dose-ranging	97 CF patients ≥ 12 years homozygous or heterozygous for the <i>F508del</i> mutation (Cohorts 2, 3)	DB, PC	LUM 200 mg qd/LUM 200 mg qd+IVA 150 mg q12h 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	14-28 days (Cohorts 2, 3)	Change in sweat Cl FEV ₁ CFQ-R resp domain
809-103 US/EU/AUS 96 sites May 2013-April 2014	safety and efficacy	559 CF patients ≥ 12 years homozygous for the <i>F508del</i> mutation	R, DB, PC, PG	LUM 600 mg qd/IVA 250 mg q12h (185 patients) LUM 400 mg/IVA 250 mg q12h (187 patients) Placebo q12h (187 patients)	24 weeks	Absolute change in FEV ₁ Relative change in FEV ₁ Change in BMI Change in CFQ-R resp domain Response rate (≥5% increase in relative FEV ₁) CF Exacerbations
809-104 US/EU/AUS 91 sites April 2013-April 2014	safety and efficacy	563 CF patients ≥ 12 years homozygous for the <i>F508del</i> mutation	R, DB, PC, PG	LUM 600 mg qd/IVA 250 mg q12h (187 patients) LUM 400 mg/IVA 250 mg q12h (189 patients) Placebo q12h (187 patients)	24 weeks	Absolute change in FEV ₁ Relative change in FEV ₁ Change in BMI Change in CFQ-R resp domain Response rate (≥5% increase in relative FEV ₁) CF Exacerbations
809-105 US/EU/AUS 191 sites October 2013- ongoing	Safety extension of study 809- 103/104	1054 CF patients previously enrolled in studies 809- 103 and 809- 104	R, PG	LUM 600 mg qd/IVA 250 mg q12h LUM 400 mg/IVA 250 mg q12h	Up to 96 weeks	Safety
From ivacaftor monotherapy program in CF patients homozygous for the <i>F508del</i> mutation						
770-104 (part A) US 34 sites September 2009- July 2010	safety and efficacy	140 CF patients ≥ 12 years homozygous for the <i>F508del</i>	R, DB, PC, PG	150 mg ivacaftor tablets q12h Placebo q12h	16 weeks	Absolute change in FEV ₁ Change in sweat Cl Change in CFQ-R resp domain

		mutation				Change in weight/BMI CF Exacerbations
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*Study description is for Cohorts 2 and 3, those felt to be most relevant for dose determination
 PK=pharmacokinetics, PD=pharmacodynamics, R=randomized, DB = double-blind, PC = placebo-controlled, PG = parallel group, NPD=nasal potential difference, Cl=chloride, CFQ-R=cystic fibrosis respiratory questionnaire-revised
 [Source: NDA 206038, Module 2.7.6 Adapted from Synopses of Individual Studies

Lumacaftor and ivacaftor dose-ranging

Studies 809-101 and 809-102 formed the primary basis for dose selection for the lumacaftor/ivacaftor combination product program in CF patients homozygous for the *F508del* mutation. Dose selection was based on dose response for 2 principle endpoints, the pharmacodynamic endpoint, sweat chloride, and FEV1 as an assessment of lung function. The significant drug-drug interaction between lumacaftor, a CYP3A inducer and ivacaftor, a CYP3A substrate also needed to be taken into consideration.

Study 809-101

Study 809-101 was a double-blind, placebo-controlled, multiple-dose study investigating lumacaftor monotherapy in CF patients who were homozygous for the *F508del CFTR* mutation. Ninety-three CF patients were randomized to receive 25, 50, 100, or 200 mg of lumacaftor or placebo once daily for 28 days with 89 receiving study drug. While assessments of biomarkers (sweat chloride, nasal potential difference) suggested some possible small degree of drug activity at the highest (200 mg) dose, the results of this study did not support the clinical efficacy of lumacaftor monotherapy as there were no consistent positive changes in lung function (FEV1). As such, the study identified the need to study higher doses of lumacaftor which were assessed in study 809-102. Study 809-101 will not be discussed further.

Study 809-102

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. As such, it 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 LUM 400mg+IVA 250mg twice daily for a longer (56 day) treatment period. The results obtained from Cohorts 2 and 3 (see Figure 3 for Cohort designs) are the most relevant for the purpose of determining the

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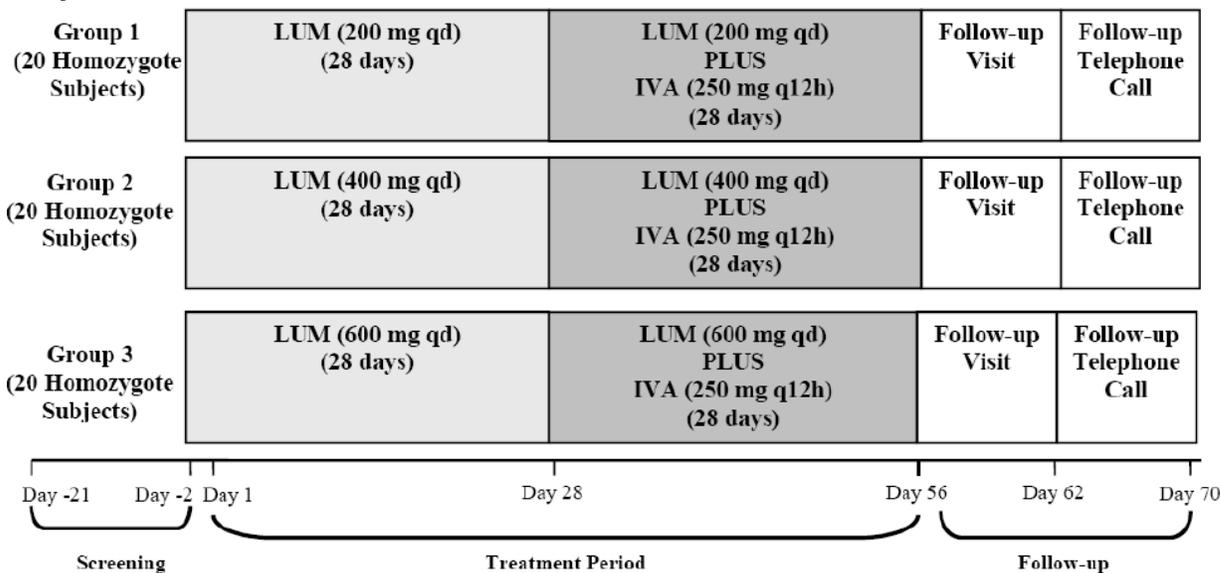
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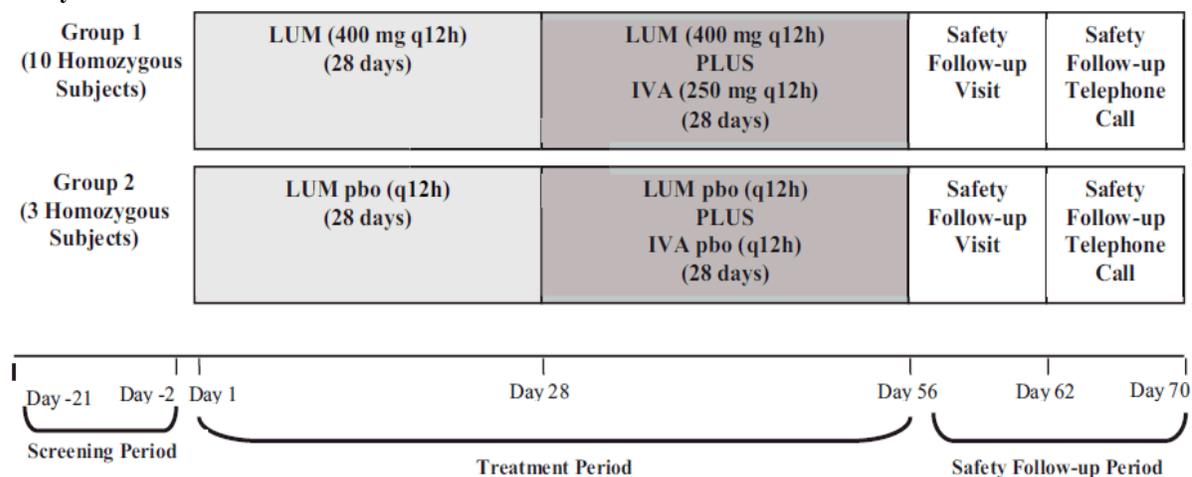
effect of lumacaftor monotherapy and the potential clinical activity for the lumacaftor/ivacaftor combination and will be the focus of the dose selection discussion.

Figure 3. Study 809-102 cohort 2 and 3 design

Study 809-102 Cohort 2



Study 809-102 Cohort 3



Results for sweat chloride demonstrated small reductions in sweat chloride for lumacaftor alone in the range of 5-8% from baseline with smaller reductions with the addition of ivacaftor (Table 2). Overall, the sweat chloride data appears to support lumacaftor doses of 400 mg once daily or greater.

Table 2. Study 809-102 Cohorts 2 and 3: change in sweat chloride compared to placebo

	Placebo (combined)	LUM 200mg qd	LUM 400mg qd	LUM 600mg qd	LUM 400mg q12h
Δ in sweat chloride (mmol/L) vs. placebo					
# of patients	26	21	19	20	10
Baseline to day 28 (lumacaftor alone) (95% CI)	--	-4.9 (-9.5, -0.28)	-8.3 (-13.0, -3.6)	-6.1 (-11.0, -1.4)	-8.2 (-14.1, -2.3)
Days 28-56 (+ 250 mg ivacaftor) (95% CI)	--	-1.0 (-7.2, 5.3)	-2.5 (-8.9, 4.0)	-4.3 (-10.7, 2.1)	-3.9 (-12.2, 4.4)
Baseline to day 56 (lumacaftor+ivacaftor) (95% CI)	--	-5.0 (-10.5, 0.48)	-9.8 (-15.3, -4.2)	-9.5 (-15.1, -3.9)	-11.0 (-18.3, -3.7)

Source: Module 2.7.2, Summary of Clinical Pharmacology; tables 15 and 16; p68

Lung function results demonstrated two points; that lumacaftor monotherapy resulted in dose-dependent decreases in lung function and that for the LUM/IVA combination, doses of lumacaftor 600 mg once daily and 400 mg twice daily appeared to have the greatest nominal treatment effect of 5.6% and 4.2% increases in absolute %predicted FEV₁, respectively (Table 3). Based on this data, Vertex selected both the lumacaftor 600 mg qd/ivacaftor 250 mg q12h and the lumacaftor 400 mg/ivacaftor 250 mg q12h doses to study further in the phase 3 program. Note that because of the significant drug-drug interaction between lumacaftor and ivacaftor, ivacaftor exposure in CF patients receiving the LUM/IVA FDC is markedly lower than that observed in CF patients receiving 150 mg ivacaftor alone, the approved dose for Kalydeco (Figure 2).

Table 3. Study 809-102 Cohorts 2 and 3: absolute change in %predicted FEV1 compared to placebo

	Placebo (combined)	LUM 200mg qd	LUM 400mg qd	LUM 600mg qd	LUM 400mg q12h
Δ in percent predicted FEV1 (PPFEV1) vs. placebo					
# of patients	27	21	20	20	11
Baseline to day 28 (lumacaftor alone) (95% CI)	--	0.24 (-3.7, 4.2)	-1.4 (-5.4, 2.6)	-2.7 (-6.7, 1.4)	-4.6 (-9.6, 0.4)
Days 28-56 (+ 250 mg ivacaftor) (95% CI)	--	3.52 (-0.5, 7.5)	3.6 (-0.4, 7.6)	7.8 (3.7, 11.9)	7.7 (2.6, 12.8)
Baseline to day 56 (lumacaftor+ivacaftor) (95% CI)	--	3.8 (-0.5, 8.1)	2.7 (-1.7, 7.0)	5.6 (1.2, 10.0)	4.2 (-1.3, 9.7)

Source: Module 2.7.2, Summary of Clinical Pharmacology, tables 15 and 16, pp70-71

Lumacaftor/ivacaftor combination phase 3 program

Studies 809-103 and 809-104

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. After a 28 day screening

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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.

Efficacy assessments, safety, and pharmacokinetic assessments were conducted on visits at study days 1 and 15 and weeks 4, 8, 16, and 24. At the Week 24 visit, subjects who completed the treatment period were allowed to enroll in the extension study 809-105.

A diagnosis of CF was confirmed/defined as a patient having a sweat chloride >60 mmol/L or 2 CF-causing mutations and chronic sinopulmonary or gastrointestinal/nutritional abnormalities. The genotypes of all patients were confirmed as homozygous for the *F508del* mutation in the *CFTR* gene. Other notable study inclusion criteria included a population ages 12 years and older, a FEV1 ≥ 40 to $< 90\%$ percent predicted, and stable CF disease as determined by the investigator. Patients who had abnormal renal or liver function as determined by laboratory studies (LFTs, GFR), a hemoglobin <10 g/L, chronic pulmonary infection with *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus*, history or evidence of cataracts or lens opacity at the screening exam were excluded. Patients with an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in CF therapy (including antibiotics) for pulmonary disease within 4 weeks before study day 1 were also excluded. Patients were allowed to use all regular concomitant CF therapies. Medications and foods noted to be moderate and strong CYP3A inducers or strong CYP3A inhibitors were not allowed within 14 days of first dose of study drug or throughout the 24-week treatment period.

Study enrollment was planned for approximately 167 CF 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. Note that this difference is in comparison to placebo, whereas combination products typically need to demonstrate a significant difference over each monocomponent.

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 included: 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, a CF-specific patient reported outcome that assesses respiratory symptoms, 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 the Applicant 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.

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The primary analysis was to be based on a mixed effects model for repeated measurements (MMRM) in the FAS population. A multiplicity adjustment approach using a simple Bonferroni correction and a hierarchical testing procedure was used to control the overall Type I error rate at 0.05 for the primary endpoint and the 5 key secondary endpoints across the 2 LUM/IVA combination dosing regimens. The testing hierarchy was as follows:

1. avg. absolute change from baseline in % predicted FEV1 at weeks 16 and 24 (the primary endpoint)
2. avg. relative change from baseline in % predicted FEV1 at weeks 16 and 24
3. absolute change from baseline in BMI at week 24
4. absolute change from baseline in the CFQ-R respiratory domain at week 24
5. FEV1 response defined as $\geq 5\%$ increase in avg. relative change from baseline in % predicted FEV1 at weeks 16 and 24
6. number of pulmonary exacerbations through week 24.

Efficacy Results

Disposition and Demographics

A total of 1122 subjects were enrolled in studies 809-103 and 809-104, of whom 1108 subjects (549 in study 809-103 and 559 in study 809-104) received at least 1 dose of study drug and, thus, comprised the full analysis set (FAS) population. Study patient retention was very good with 96-99% of CF patients completing the trials. In study 809-103, 25 (4.6%) patients stopped medication early and 12 (2.2%) of those also discontinued from the study. In study 809-104, 29 (5.2%) patients terminated study drug early and 14 (2.5%) prematurely discontinued from the study. The most common reason for discontinuation from study drug treatment was adverse events, occurring in 18 (3.3%) patients in study 809-103 and 19 (3.4%) patients in study 809-104, respectively.

Patient demographics were similar across the treatment groups for both studies. As would be expected, the large majority of patients were White (>98% overall). There were a slightly larger number of males enrolled in study 809-103 and slightly more females in study 809-104. The mean age for patients enrolled in the studies was approximately 25 years with a range of 12-64 years. The majority of patients were adult (71-77% across treatment groups) with the remainder between 12 and 17 years. Baseline FEV1 was very similar across treatment groups for both studies (approximately 60 per cent predicted) with a range from 31-94 % predicted in study 809-103 and 31-100 % predicted in study 809-104. Table 4 below contains the description of some of the more relevant patient demographics.

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Table 4. Study 809-103/104 Patient Demographics

Characteristic	Study 809-103			Study 809-104		
	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
Sex n, (%)						
Male	100 (54)	97 (53)	98 (54)	90 (48)	89 (48)	89 (48)
Female	84 (46)	86 (47)	84 (46)	97 (52)	96 (52)	98 (52)
Age (Years)						
n	184	183	182	187	185	187
Mean	25.0	24.7	25.5	25.7	24.3	25.0
SD	10.8	9.71	10.1	10.0	8.31	9.0
Range	12-64	12-54	12-57	12-55	12-48	12-54
Weight (kg)						
n	184	183	182	187	185	187
Mean	59.1	58.6	60.6	58.5	58.2	59.2
SD	11.7	11.7	12.2	13.1	12.9	12.1
Range	35.0-93.0	29.0-90.0	31.0-101.0	27.0-98.0	30.0-99.8	35.0-105.0
FEV₁ (% predicted)						
n	181	182	180	185	184	185
Mean	60.45	61.18	60.48	60.37	60.49	60.59
SD	13.22	13.31	14.29	14.32	13.83	14.01
Range	34.0-88.0	31.1-92.3	34.8-94.0	33.9-99.8	34.4-90.4	31.3-96.5
% predicted FEV₁ by severity n (%)						
<40	11 (6.0)	12 (6.6)	12 (6.6)	17 (9.1)	12 (6.5)	17 (9.1)
≥40 to <70	122 (66.3)	122 (66.7)	116 (63.7)	116 (62.0)	119 (64.3)	117 (62.6)
≥70 to ≤90	48 (26.1)	47 (25.7)	51 (28.0)	49 (26.2)	51 (27.6)	49 (26.2)
>90	0 (0.0)	1 (0.5)	1 (0.5)	3 (1.6)	2 (1.1)	2 (1.1)

Source: Module 2.7.3; Adapted from Summary of Clinical Efficacy; table 12 and 13; pp55-56 and 57-58

Primary Endpoint: FEV₁

The primary efficacy endpoint for both 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. In both studies, treatment with either dose of LUM/IVA resulted in statistically significant improvements in absolute change in % predicted FEV₁ compared to placebo, ranging from 2.7-3.0% for the proposed dose of LUM/IVA 400 mg/250mg q12h (Table 5).

Table 5. Studies 809-103/104. Absolute change from baseline in percent predicted FEV₁ at 24 weeks*

	Study 809-103			Study 809-104		
	Placebo n=184	LUM 600qd IVA 250 q12 n=183	LUM/IVA 400/250 q12 n=182	Placebo n=187	LUM 600qd IVA 250 q12 n=185	LUM/IVA 400/250 q12 n=187
Baseline PPF ₁	60.5	61.2	60.5	60.4	60.5	60.6
Average Δ from baseline at wk 16 and 24	-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)

* average of the treatment effects at Week 16 and at Week 24

Source: Module 5.3.5.1; Study 809-103 CSR; table 11-3; p144, Module 5.3.5.1; Study 809-104 CSR; table 11-4; p157

Secondary Endpoints

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Vertex designated 5 key secondary endpoints (outlined above) for both studies 809-103 and 809-104. As noted above, a hierarchical testing procedure was used to control the overall Type I error rate at 0.05 across the 2 LUM/IVA combination dosing regimens. Results are summarized below for the 5 key secondary endpoints noting when the hierarchical testing stopped as a result of failure to demonstrate statistical significance (Table 6). Similar to the presentation of the primary endpoint results, for consistency, the Applicant's analyses are presented. The results of the FDA's analyses, slightly different due to correction of minor stratification errors, can be found in the FDA statistical briefing. Sweat chloride data, a pharmacodynamic endpoint of interest, for the LUM 600 qd/IVA 250 q12 and LUM/IVA 400/250 q12 doses are also described from study 809-102 as they were not included in the LUM/IVA phase 3 program.

Table 6. Studies 809-103/104: Summary of key secondary endpoints

	Study 809-103			Study 809-104		
	Placebo	LUM 600qd IVA 250 q12	LUM/IVA 400/250 q12	Placebo	LUM 600qd IVA 250 q12	LUM/IVA 400/250 q12
Average relative change from baseline in PPFEV1 at weeks 16 and 24						
Relative 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/m²) at week 24						
Δ from baseline in BMI at week 24	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 in CFQR-RD at week 24	1.1	5.0	2.6	2.8	5.0	5.7
Difference from placebo (95% CI)	--	3.8 (0.7, 7.1)	1.5 (-1.7, 4.7)	--	2.2 (-0.9, 5.3)	2.9 (-0.3, 6.0)
FEV1 response ($\geq 5\%$ increase in avg. relative change in % predicted FEV1 at weeks 16 and 24)						
Yes, n (%)	41 (22.3)	85 (46.4)	67 (36.8)	42 (22.5)	85 (45.9)	77 (41.2)
Odds ratio vs 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, 1.0)	--	0.7 (0.5, 0.9)	0.6 (0.4, 0.8)

Source: Module 2.7.3; Summary of Clinical Efficacy; table 16, pp62-63

Relative change in % predicted FEV1

For both studies, treatment with LUM 400 mg/IVA 250 mg q12h resulted in statistically significant increases in relative change in % predicted FEV1 compared to placebo when expressed as the average of week 16 and 24 values at 4.3% and 5.3% for studies 809-103 and 809-104, respectively. In light of the statistically significant change in the primary endpoint, absolute change in % predicted FEV1, this is not unexpected since differences in FEV1 are generally greater when expressed as relative compared to absolute changes.

Absolute change in BMI at 24 weeks

Results for change in BMI were not consistent between studies. For study 809-103, the 0.1 kg/m² difference from placebo for the LUM 400 mg/IVA 250 mg dose was not significant while the difference of 0.4 kg/m² observed in study 809-104 reached statistical significance. Regarding further analyses, due to the failure of change in BMI to reach statistical significance in Study 809-103, the testing hierarchy for that study stopped at the BMI endpoint.

Change in CFQ-R respiratory domain at 24 weeks

The CFQ-R is a disease-specific, patient reported, health-related quality of life measure for cystic fibrosis that is a commonly used patient reported outcome measure (PRO) used in CF studies. The respiratory domain of the CFQ-R assesses respiratory symptoms that are clinically relevant to patients with CF such as cough, wheeze, congestion, sputum production, and difficulty breathing. The minimal clinically important difference (MCID) for the instrument has been reported as 4 points. For studies 809-103 and 809-104, differences from placebo in patients who received the LUM 400 mg/IVA 250 mg dose of 1.5 and 2.9 points were neither statistically significant nor reached the MCID of 4 points. This lack of benefit is notable given the statistically and clinically meaningful improvement in respiratory symptoms, as assessed by the CFQ-R respiratory domain, observed in all mutation subpopulations of CF patients for which ivacaftor monotherapy has been approved.

Response rate ($\geq 5\%$ increase in relative change in % predicted FEV1)

Responders, defined as patients who had a $\geq 5\%$ increase in relative % predicted FEV1 (avg. of weeks 16 and 24), consisted of 37% and 42% of CF patients who received LUM 400 mg/IVA 250 mg in studies 809-103 and 809-104 resulting in odds ratios of 2.0 and 2.4, respectively. Because the testing hierarchy stopped for both active treatment groups in both studies before these comparisons were made, the odds ratios were not considered statistically significant within the framework of the testing hierarchy.

Number of pulmonary exacerbations through week 24

Regarding pulmonary exacerbations, the number and annual rate of exacerbations for the LUM 400 mg/IVA 250 mg and placebo groups from study 809-103 was 73 (0.7) and 112 (1.1), respectively. For study 809-104, the values were 79 (0.7) for the LUM 400 mg/IVA 250 mg group and 139 (1.2) for the placebo group, respectively. This resulted in rate ratios of 0.7 and 0.6 for the LUM 400 mg/IVA 250 mg dose versus the placebo group in studies 809-103 and 809-104, respectively. The comparisons were not considered statistically significant since the testing hierarchy stopped before the comparisons were made.

Sweat Chloride

Sweat chloride level is felt to be diagnostic of CF when values are ≥ 60 mmol/L in the context of a patient with a constellation of symptoms consistent with CF. For the Vertex CF development programs it has been used as an in vivo pharmacodynamic assessment of CFTR ion channel activity in which a reduction would indicate increased channel activity and the potential for efficacy.

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As was seen in Table 2 above, administration of the 400 mg proposed dose of LUM alone q 12h to CF patients homozygous for the *F508del* mutation resulted in an 8 mmol/L decrease in sweat chloride from baseline. Addition of the proposed dose of 250 mg IVA q 12h resulted in a total decrease (LUM 400 mg + IVA 250 mg) from baseline in sweat chloride of 11 mmol/L. This difference represents an approximately 10% reduction in sweat chloride in patients receiving LUM 400 mg/IVA 250 mg.

It is not known, however, how and by what amount reductions in sweat chloride relate to clinical beneficial effects. However, as a generally accepted marker of the CFTR ion channel activity, a lack or low response in sweat chloride to an intervention would suggest a subsequent lack or decreased clinical benefit.

Contribution of lumacaftor to the LUM/IVA combination: Study 770-104

Because LUM/IVA is a combination product, the contribution of each component is important to understand. As noted previously, for combination programs, the phase 3 program usually compares the combination to one or both of the monotherapies, but placebo was the comparison in the LUM/IVA studies 809-103 and 809-104. As a true head to head comparison is lacking, the available data from the ivacaftor monotherapy program for CF patients homozygous for the *F508del* mutation (study 770-104) is relevant to help assess the contribution of lumacaftor to the LUM/IVA combination. To facilitate the comparison FDA statisticians used a non-inferiority approach which focused on the proposed LUM 400mg/IVA 250mg q12h dose and the FEV1 and exacerbation endpoint results. Although all studies evaluated changes in BMI and CFQ-R respiratory domain, these endpoints were not included in the non-inferiority analyses as they failed to show replicate evidence of a treatment effect in studies 809-103 and 809-104. For consistency, the results were calculated at the 16 week time point for both studies.

Study 770-104 was a randomized, double-blind, placebo-controlled, parallel-group study conducted to assess the safety and efficacy of ivacaftor monotherapy 150 mg q 12h in patients with CF homozygous for the *F508del* mutation in the *CFTR* gene. After 28 day screening and 14 day run-in periods, eligible patients were randomized 4:1 to receive ivacaftor 150 mg (n=112) q 12h or placebo (n=28) q12h for 16 weeks. This study was submitted to the Agency with the NDA 203188 to support the original approval of Kalydeco for CF patients with a *G551D* mutation in the *CFTR*, as discussed above. It was also submitted to this current NDA for the combination product.

Efficacy assessments, safety, and pharmacokinetic assessments were conducted on visits at study days 1 and 15 and weeks 8 and 16. Telephone contact was made at weeks 4 and 12 to assess for adverse events. At the Week 16 visit, subjects who completed the treatment period and had demonstrated a response to ivacaftor monotherapy (10% relative increase in FEV1 or a change in sweat Cl of 15 mmol/L or more were allowed to enroll in the open label extension (Part B).

The patient inclusion/exclusion criteria were quite similar to those of studies 809-103 and 809-104. A diagnosis of CF was confirmed/defined as a patient having defined as a sweat chloride >60mmol/L or 2 CF-causing mutations and chronic sinopulmonary or

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gastrointestinal/nutritional abnormalities. The genotypes of all patients were confirmed as homozygous for the *F508del* mutation in the *CFTR* gene. Other notable study inclusion criteria included a population ages 12 years and older, a FEV1 \geq 40 percent predicted, and stable CF disease as determined by the investigator. Patients who had abnormal renal or liver function as determined by laboratory studies (LFTs, GFR), a hemoglobin $<$ 10g/L, colonization with *Burkholderia cenocepacia*, *Burkholderia dolosa*, or *Mycobacterium abscessus* were excluded. Patients with an acute upper or lower respiratory infection, pulmonary exacerbation, or changes in CF therapy (including antibiotics) for pulmonary disease within 4 weeks before study day 1 were also excluded. Patients were allowed to use all regular concomitant CF therapies except inhaled hypertonic saline. Medications and foods noted to be moderate and strong CYP3A inducers or strong CYP3A inhibitors were not allowed within 14 days of first dose of study drug or throughout the 16-week treatment period.

Study enrollment was planned for approximately 120 patients; the study was not powered for efficacy.

The primary efficacy endpoint for the study was the absolute change in percent predicted FEV1 from baseline through week 16.

Secondary endpoints included: change from baseline in sweat chloride; change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain, a CF-specific patient reported outcome that assesses respiratory symptoms; rate of change of weight/BMI, pulmonary exacerbations, and relative change from baseline in % predicted FEV1

Efficacy Results

Disposition and Demographics

A total of 140 patients were enrolled in study 770-104, of whom 112 patients received ivacaftor monotherapy 150 mg q 12h and 28 received placebo. Study patient retention was very good with 93 % of patients completing the 16 week treatment period. The most common reason for discontinuation from study drug treatment was adverse events, occurring in 5 (3.6%) of patients.

Patient demographics were similar across the ivacaftor monotherapy and placebo treatment groups. As would be expected, almost all of the patients were White (99% overall). There were a slightly larger number of males enrolled than female (53% vs 47%). The mean age for patients enrolled in the study was approximately 23 years with a range of 12-52 years with the majority of patients being adults (64 %). There were fewer patients 12 to 17 years of age who received placebo 6 (21%) than who received ivacaftor monotherapy 44 (39%). Baseline FEV1 was similar across both treatment groups (approximately 79 % predicted) with a range from 40-129 % predicted. Table 7 below contains the description of patient demographics.

Table 7. Study 770-104 Patient Demographics

	Study 770-104		
	Placebo N=28	IVA 150mg q12 N=112	Overall N=140
Sex, n (%)			
Male	16 (57.1)	58 (51.8)	74 (52.9)
Female	12 (42.9)	54 (48.2)	66 (47.1)
Age (years)			
Mean	25.0	22.8	23.2
Range	12-39	12-52	12-52
Age groups, n (%)			
12 to <18 yrs	6 (21.4)	44 (39.3)	50 (35.7)
≥18 yrs	22 (78.6)	68 (60.7)	90 (64.3)
Weight (kg)			
Mean	63.2	58.2	59.2
Range	44.2-100.3	35.1-99.8	35.1-100.3
Baseline % predicted FEV1 n (%)			
<70	15 (53.6)	38 (33.9)	53 (37.9)
≥70 to ≤90	5 (17.9)	35 (31.3)	40 (28.6)
>90	8 (28.6)	39 (34.8)	47 (33.6)
Sweat Chloride (mmol/L)			
Mean	102	101*	102
Range	91-122	80-140	80-140

*n=111

Source: Module 5.3.5.1; Study 770-104 CSR; Adapted from table 11-1; pp117-118

Efficacy Endpoints

Study 770-104 was previously reviewed under NDA 203-188 and failed to show a significant treatment benefit for ivacaftor with respect to per cent predicted FEV1, CFQ-R respiratory domain, BMI, and rate of pulmonary exacerbations. Change in sweat chloride in response to ivacaftor monotherapy (-2.9 mmol/L) was small but statistically significant. The 95% CI for difference from placebo for the change from baseline through Week 16 is shown for each endpoint in Table 8.

Table 8. Study 770-104 efficacy endpoints

Endpoint	770-104
	Difference from placebo (95% CI)
Absolute change in ppFEV1	1.7 (-0.6, 4.1)
Change in sweat chloride (mmol/L)	-2.9 (-5.6, -0.2)
Change in CFQR-RD (score)	1.3 (-2.9, 5.6)
Change in BMI (kg/m ²)	-0.07 (-0.4, 0.2)
Pulmonary exacerbations (rate ratio)	0.68 (0.33, 1.4)

Source: FDA statistical reviewer

The similarity of the nominal treatment effects for important endpoints such as FEV1 and pulmonary exacerbations in study 770-104 for 150mg ivacaftor alone and studies 809-103 and 809-104 for the LUM 400mg/IVA 250mg dose raised the question of whether lumacaftor contributes any added benefit over that of ivacaftor alone. As mentioned above, in order to probe this issue, FDA statisticians used a non-inferiority approach focused on the proposed

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LUM 400mg/IVA 250mg q12h dose and the FEV1 and exacerbation endpoint results.

Evaluation of the small differences in patient demographics, baseline characteristics, FEV1 calculation equation (Knudson vs Hankinson), and use of hypertonic saline suggested that these differences were, indeed, minor and did not preclude use of the comparison to estimate the contribution of lumacaftor to the effect of the LUM/IVA combination. Slight differences in baseline FEV1 inclusion criteria between study 770-104 and studies 809-103 and 809-104 were also taken into consideration by removing patients with baseline FEV1 > 90% predicted from the analysis. Because of the differences in length of the treatment periods between the studies, 16 weeks for study 770-104 and 24 weeks for studies 809-103 and 809-104, the analyses were carried out at week 16.

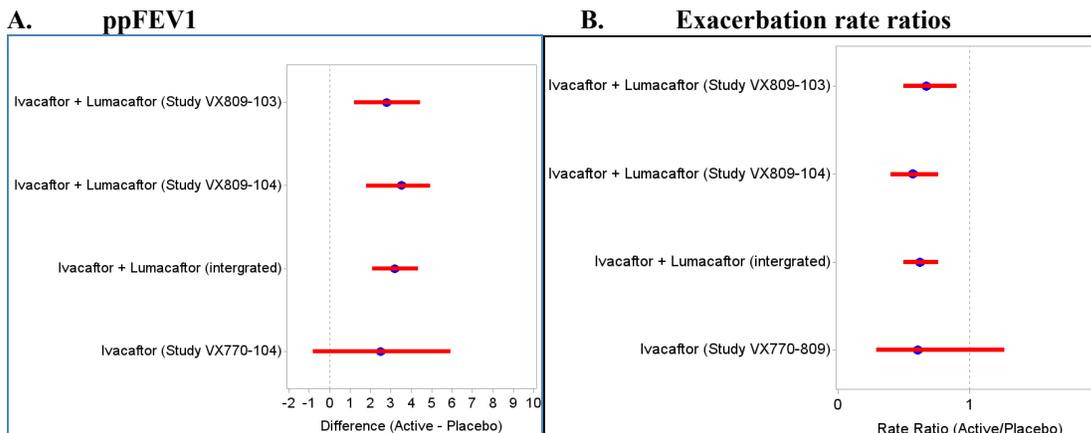
Results of the analyses show that at the 16 week timepoint, the point estimate for the treatment effect in absolute and relative change in per cent predicted FEV1 for ivacaftor alone was 2.2% and 3.2%. These values compare with 2.6 and 4.7% and 2.8% and 5.4% changes in absolute and relative percent predicted FEV1 for LUM/IVA studies 809-103 and 809-104, respectively. With regard to exacerbations, the exacerbation rate ratio versus placebo for study 770-104 was 0.61 compared to 0.62 for studies 809-103 and 809-104 combined (Table 9). These results are also summarized graphically in Figure 4 below. Both plots A and B demonstrate that since the 95% CIs for the difference from placebo for ivacaftor alone overlaps the 95% CIs for LUM/IVA for both the FEV1 and pulmonary exacerbation endpoints, one cannot exclude the possibility that treatment with ivacaftor alone or the LUM/IVA combination are no different from each other for these endpoints. For additional information and conclusions regarding the analyses refer to the FDA statistical review by David Petullo MS.

Table 9. FDA comparison of FEV1 and exacerbation rate ratios: LUM/IVA vs ivacaftor alone

	Study 770-104	Study 809-103	Study 809-104
Endpoint	Difference from placebo (SE)		
Absolute change in ppFEV1 (%)	2.2 (0.8)	2.6 (7.3)	2.8 (7.1)
Relative change in PPFEV1 (%)	3.2 (1.1)	4.7 (13.0)	5.4 (12.8)
Pulmonary exacerbations (rate ratio)	0.61 (0.37)	0.62 (0.1) Pooled data	

Source: FDA statistical reviewer

Figure 4. Graphic FDA comparisons of FEV1 and exacerbation rate ratios: LUM/IVA vs ivacaftor alone



Source: FDA statistical reviewer

Additional statistical analyses by Mr. Petullo directly comparing ivacaftor alone to LUM 400mg/IVA 250mg utilizing a synthesis statistical approach were also conducted for the FEV1 and pulmonary exacerbation endpoints. Results of these analyses demonstrated that superiority of the LUM 400mg/IVA 250mg to ivacaftor alone could not be established for any of the endpoints.

Summary of Efficacy

Overall, the results from LUM/IVA studies 809-103/104 demonstrate that, compared to placebo, LUM 400mg/IVA 250 mg q12h had a small but statistically significant effect in terms of the primary endpoint of absolute change from baseline in PPFEV1 at 24 weeks with a difference from placebo of 2.7-3.0% that translated into an exacerbation benefit at 24 weeks. Improvement in the secondary endpoint relative per cent predicted FEV1 was also statistically significant in both studies. The secondary endpoints change in BMI and CFQ-R respiratory domain failed to show substantial evidence of a treatment effect in that the BMI data were not replicated in the 2 trials and the CFQ-R respiratory domain effect was not to the level judged as clinically meaningful. LUM/IVA response rate and number of pulmonary exacerbations both demonstrated improvement but from a strict statistical perspective cannot be considered significant since the prospective statistical testing hierarchy stopped before the comparisons were made. Nevertheless, the exacerbation “nominal” benefit would be very important for CF patients.

Results from study 770-104, originally conducted for the original ivacaftor monotherapy program demonstrated a small statistically significant change in sweat chloride compared to placebo. While nominal treatment effects for lung function endpoints and pulmonary exacerbations were comparable to those for the LUM/IVA combination, the study was not powered for efficacy and statistical significance was not achieved.

The similarity of the nominal treatment effects in study 770-104 for 150mg ivacaftor alone and studies 809-103 and 809-104 for the LUM 400mg/IVA 250mg dose raised the question of whether lumacaftor contributes any added benefit over that of ivacaftor alone and begs the question if study 770-104 were powered similarly to studies 809-103 and 809-104, would the

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treatment effects for ivacaftor monotherapy also have been statistically significant, especially in relation to improvements in lung function and reductions in CF pulmonary exacerbations. In the absence of an ivacaftor alone arm in the LUM/IVA combination studies, FDA conducted statistical comparative analyses between ivacaftor monotherapy and the proposed LUM 400mg/IVA 250mg combination product dose in an attempt to determine whether the addition of lumacaftor to ivacaftor contributed to the overall treatment effect of the combination for lung function and pulmonary exacerbation endpoints. The results from these analyses could not exclude with that treatment effect for the LUM/IVA combination was different from ivacaftor alone, i.e., that lumacaftor contributed to the overall effect of the combination at least with respect to changes in ppFEV1 and pulmonary exacerbations.

Thus, while in vitro data suggest both the lumacaftor and ivacaftor components affect CFTR ion channel function and the scientific rationale is compelling that a combination product containing 2 drugs with different but complementary mechanisms of action would be necessary for optimal benefit, one cannot definitively conclude from the data available that lumacaftor makes a significant contribution to the clinical effect of the LUM/IVA combination product. That being said, the LUM/IVA combination provides a clinically meaningful benefit over placebo to CF patients homozygous for the *F508del* mutation and, given the lack of a CFTR-directed therapy for the large population of CF patients homozygous for the *F508del* mutation, requiring a head to head ivacaftor monotherapy vs LUM/IVA combination comparison to further define the contribution of the monocomponents prior to approval is, in my opinion, not justifiable. In hindsight, given the relatively small change in FEV1 observed in the LUM/IVA combination Phase 3 trials (less than that observed in Phase 2) that approximated the FEV1 response seen with ivacaftor alone, the lack of an ivacaftor monotherapy treatment group in the phase 3 trials was a flaw in the LUM/IVA development program. The Division is acutely aware of this deficiency and will need to ensure that future combination programs for CFTR modulators demonstrate that each component of the combination contributes to the overall effect of the combination.

8. Safety

Safety Database

The safety profile of LUM/IVA is based primarily on the pooled data from 1108 patients with CF 12 years and older who were homozygous for the *F508del* mutation in the *CFTR* gene and who received at least one dose of study drug in either of studies 809-103 or 809-104. In these studies, a total of 738 patients received the LUM/IVA combination; 369 CF patients received LUM 400 mg/IVA 250 mg q 12h, 369 patients received LUM 600 mg qd/IVA 250 mg q12h, and 370 patients received placebo. Of the 1108 patients, 49% were female and 99% were Caucasian (see table 5 for more detailed demographic information).

Deaths, Serious Adverse Events, and Discontinuations due to Adverse Events

There were no deaths reported during the 24-week placebo-controlled clinical studies, 809-103 and 809-104. One death, however, was reported to have occurred during the uncontrolled safety extension termed study 809-105. This patient was a 24 year old female with baseline FEV1 of approximately 50% predicted who was receiving LUM 400 mg/IVA 250 mg q 12h in study 809-103 when she developed a pulmonary exacerbation 175 days into the open-label extension. She was hospitalized for one week and discharged home to continue to receive IV

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antibiotic therapy. She worsened at home and was readmitted several days after discharge. She ultimately developed air leaks, was placed on mechanical ventilation, and transferred to another hospital where she was placed on extracorporeal membrane oxygenation therapy. She died of respiratory failure on day 197 of her participation in the extension study.

Consistent with the disease, most serious adverse events (SAEs) were related to pulmonary exacerbations of CF, which occurred in approximately 13% of patients who received LUM/IVA therapy and 24% of patients who received placebo. Other SAEs occurred relatively infrequently (< 2% in any group) and included hemoptysis and distal intestinal obstruction syndrome. An additional patient who received LUM 400 mg/IVA 250 mg was reported to have hepatic encephalopathy.

There were 37 CF patients (3.3%) who discontinued treatment due to an adverse event during the 24-week placebo-controlled studies. Adverse events leading to treatment discontinuation were more common in the LUM/IVA treatment groups compared to placebo groups (4.2% vs 1.6%). This difference was driven by small increases above placebo in the several AEs such as bronchospasm (0.3% vs 0%), dyspnea (0.3% vs 0%), and blood CPK increased (0.5% vs 0%).

Specific Safety Concerns

Liver-related safety concerns from the IVA monotherapy program and the finding of decreased pulmonary function (FEV1) in patients who received lumacaftor monotherapy lead specific analyses to assess for potential liver toxicity and respiratory-related AEs in the phase 3 program.

Liver-related safety concerns

While there were no differences between the LUM/IVA treatment groups compared to placebo in overall adverse events thought to be liver related (5.4-6.0% across treatment groups), more patients receiving LUM/IVA 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% LUM/IVA 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 LUM/IVA (0.4%) groups compared to none who received placebo. Overall, the hepatic safety analyses indicate that LUM/IVA exposure may be associated with liver-related adverse events as there were more SAEs, AEs leading to discontinuation, and transaminase elevations associated with bilirubin elevations in CF patients who received LUM/IVA than those who received placebo (see the clinical briefing by Dr. Robert Lim for a more detailed discussion).

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 LUM/IVA 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,

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respectively. Three of the events lead to treatment discontinuation compared to none in the placebo group and 2 events were reported as SAEs. These LUM/IVA-related respiratory AEs/SAEs tended to occur early after initiating LUM/IVA therapy (median time to onset was about 2 days). These data suggest that treatment with LUM/IVA can cause increased respiratory symptoms and AEs in some CF patients that can be severe enough to cause discontinuation from LUM/IVA treatment or thought to be life-threatening or require hospitalization (SAE).

Common Adverse Events

Common adverse events are listed in Table 10 below. Most AEs are reflective of what would be expected in patients with CF and show little difference between placebo and active treatment with LUM/IVA with the exception of dyspnea, abnormal respiration, flatulence, and rash favoring placebo and pulmonary exacerbation and pulmonary function test decreased favoring treatment with LUM/IVA.

Table 10. Adverse events that occurring in $\geq 5\%$ of patients in either LUM/IVA treatment group and greater than placebo

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM/IVA 400/250 q12 N=369	Total LUM/IVA N=738
Headache	58 (15.7)	58 (15.7)	58 (15.7)	116 (15.7)
Dyspnea	29 (7.8)	55 (14.9)	48 (13.0)	103 (14.0)
Hemoptysis	50 (13.5)	52 (14.1)	50 (13.6)	102 (13.8)
Diarrhea	31 (8.4)	36 (9.8)	45 (12.2)	81 (11.0)
Nausea	28 (7.6)	29 (7.9)	46 (12.5)	75 (10.2)
Respiration abnormal	22 (5.9)	40 (10.8)	32 (8.7)	72 (9.8)
Oropharyngeal pain	30 (8.1)	44 (11.9)	24 (6.5)	68 (9.2)
Pyrexia	34 (9.2)	35 (9.5)	33 (8.9)	68 (9.2)
Upper respiratory tract infection	20 (5.4)	24 (6.5)	37 (10.0)	61 (8.3)
Viral upper respiratory tract infection	25 (6.8)	28 (7.6)	23 (6.2)	51 (6.9)
Flatulence	11 (3.0)	20 (5.4)	24 (6.5)	44 (6.0)
Blood creatine phosphokinase increased	20 (5.4)	14 (3.8)	27 (7.3)	41 (5.6)
Rash	7 (1.9)	16 (4.3)	25 (6.8)	41 (5.6)
Sinusitis	19 (5.1)	24 (6.5)	16 (4.3)	40 (5.4)
Rhinorrhea	15 (4.1)	17 (4.6)	21 (5.7)	38 (5.1)
Vomiting	11 (3.0)	21 (5.7)	16 (4.3)	37 (5.0)
Influenza	8 (2.2)	16 (4.3)	19 (5.1)	35 (4.7)
Constipation	21 (5.7)	12 (3.3)	14 (3.8)	26 (3.5)

Source: Module 2.7.4; Adapted from Summary of Clinical Safety; table 17; pp55-56.

Summary of Safety

The safety database for the LUM/IVA program is based on safety data obtained in the ivacaftor monotherapy program, study 809-102 in which lumacaftor monotherapy resulted in dose dependent decreases in lung function (FEV1), and the placebo-controlled 24-week LUM/IVA FDC studies 809-103 and 809-104. For the most part, the nature of the adverse events identified for LUM/IVA are generally consistent with the types of events commonly observed in patients with CF and differed little from those observed in the placebo group with

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two exceptions; liver toxicity and increased respiratory symptoms such as dyspnea in patients shortly after initiating LUM/IVA therapy. While many patients with CF have disease-related liver disease, the safety data from both the ivacaftor monotherapy and the current combination product programs suggest that LUM/IVA exposure may be associated with more and/or more severe liver-related adverse events as there were more SAEs, AEs leading to discontinuation, and transaminase elevations associated with bilirubin elevations in CF patients who received LUM/IVA than those who received placebo. With regard to increased respiratory symptoms such as dyspnea, these types of adverse events were not observed in the ivacaftor monotherapy program but are more likely tied to lumacaftor or the specific LUM/IVA combination. While the mechanism by which these AEs occur is unknown, one can conjecture whether it is related to the finding that lumacaftor monotherapy results in further decreases in pulmonary function in patients with CF. However, despite the increased respiratory symptoms, the large majority of patients who received LUM/IVA were able to remain on therapy. In addition to the above, since the LUM/IVA FDC contains ivacaftor, the results of the ongoing required post-marketing study to assess for the risk of cataracts in pediatric patients who receive ivacaftor (tradename Kalydeco) will be relevant to the LUM/IVA FDC program.

9. Advisory Committee Meeting

A Pulmonary-Allergy Advisory Committee (PADAC) meeting was held on May 12, 2015, to discuss this application for LUM/IVA as a treatment of CF in patients 12 years of age and older who are homozygous for the *F508del* mutation in the *CFTR* gene. The questions to the committee, summary of discussion, and voting results are summarized below:

1. **DISCUSSION:** Discuss the available efficacy data for LUM 400 mg/IVA 250 mg fixed-dose combination (FDC) administered twice daily in patients with cystic fibrosis (CF) 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. Consider the following issues in the discussion: clinical significance of the observed treatment effect and contribution of lumacaftor in context to that for ivacaftor monotherapy.

Committee Discussion: The members of the committee commented that clinically relevant efficacy for lung function (FEV1) and exacerbations compared to placebo was clearly demonstrated. A panel member also noted that a 3% improvement in percent predicted FEV1 was small, but that improvements in other efficacy parameters alleviated this concern. Members commented that it was unclear from the existing data whether the combination is superior to IVA monotherapy.

2. **DISCUSSION:** Discuss the available efficacy data for ivacaftor monotherapy 150 mg twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene.

Committee Discussion: Committee members noted that, given the design of study 770-104, the current data for ivacaftor monotherapy 150 mg twice daily was insufficient to support efficacy in patients homozygous for the *F508del* mutation. Some members also commented that, as a result of the failure of the clinical program to provide a direct comparison of the LUM/IVA combination to ivacaftor alone, the currently available clinical data were insufficient to determine whether the combination was superior to monotherapy. It was

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specifically noted that such a deficiency put FDA and Committee members in a difficult or impossible position in trying to determine the contribution each individual drug component makes to the LUM/IVA combination and that such a deficiency should not be allowed to happen again in other CF drug combination programs.

3. VOTE: Do the available data demonstrate that lumacaftor contributes positively to the clinical efficacy seen for the lumacaftor plus ivacaftor FDC product in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene?

- A. Yes
- B. No
- C. Cannot determine

Please comment on the rationale for your vote and whether a clinical trial should be conducted to compare the LUM/IVA FDC to ivacaftor alone.

Yes=3

No=4

Cannot determine=6

Committee Discussion: The majority voted “no” or “cannot determine” that lumacaftor contributes to the clinical efficacy of the LUM/IVA combination. Some members who voted “yes” commented that ivacaftor alone did not have much of an effect, but the combination did which suggested to them that lumacaftor did contribute. Members who voted “no” commented that the range of the treatment effect observed for ivacaftor and the combination product was similar and, statistically, could not be distinguished from one another. Committee members voting “Cannot determine” commented that this question could not be answered based on the available data, and that the contribution of lumacaftor is difficult to determine. Some committee members commented they did not think that whether or not lumacaftor contributed to LUM/IVA was relevant in determining efficacy, only that a clinically meaningful benefit compared to placebo was demonstrated. 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 over placebo, did not feel an additional clinical trial should be conducted as it would hold prolong approval.

4. DISCUSSION: Discuss the safety data for LUM 400 mg/IVA 250 mg FDC twice daily in patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

Committee Discussion: Committee members commented that the hepatic and respiratory related safety concerns could be managed by monitoring transaminases and pulmonary function.

5. VOTE: Do the data support the safety of LUM 400 mg/IVA 250 mg FDC administered twice daily in patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene?

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If not, what further data should be obtained to more fully define the safety profile of LUM 400 mg/IVA 250 mg?

YES=13

NO=0

ABSTAIN=0

Committee Discussion: The committee members agreed the data support the safety of LUM 400 mg/IVA 250 mg administered twice daily in patients with CF 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. Members commented that the adverse effect profile is known and manageable.

6. VOTE: Do the available efficacy and safety data support approval of the LUM 400mg/IVA 250 mg FDC product administered twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene?

If not, what additional data should be obtained to further define the benefit risk profile of LUM 400 mg/IVA 250 mg twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene?

YES=12

NO=1

ABSTAIN=0

Committee Discussion: The large majority of committee members agreed that the efficacy and safety data support approval of the lumacaftor 400 mg/ivacaftor 250 mg FDC product administered twice daily in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene. The committee members voting “Yes” commented that the studies met their primary endpoints and there was a great unmet need. Some members expressed concern regarding the relatively small FEV1 effect size, the lack of an ivacaftor monotherapy arm in the phase 3 studies, and the potential precedent that could be set by approval when the clinical contribution of lumacaftor was uncertain. The committee member voting “No” commented that, the efficacy compared to ivacaftor alone cannot be determined.

Please see the transcript for the details of committee’s discussion.

10. Pediatrics

The efficacy and safety of the LUM/IVA combination in the CF pediatric population ages 12-17 has been addressed in studies 809-103 and 809-104. Cystic Fibrosis is an orphan disease and not subject to PREA. Based on the knowledge that CF is a genetic disease, which can manifest at birth, Vertex plans to conduct clinical studies in pediatric patients less than 12 years of age.

11. Other Relevant Regulatory Issues

- Financial Disclosure: The Applicant has submitted the FDA 3454 financial interest forms, in accordance with 21CFR part 54. There were 3 investigators with disclosable financial interests/arrangements, all received “significant payment of other sorts”, ^{(b) (6)}

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- DSI audits information: Audits were conducted at the Karen McCoy MD, Cori Daines MD, and Michael Konstan MD clinical study sites for this NDA submission as well as the Vertex establishment. No substantial issues that would negatively impact data integrity were identified.
- Other: There are no outstanding issues with consults received from the OPDP, DMEPA, or from other groups in CDER. The CDRH was consulted during previous ivacaftor reviews to help address the adequacy of available tests for identification of specific CF gene mutation identification. CDRH noted that there are several FDA-cleared diagnostic tests available that can detect the *F508del* mutation, the most common in the *CFTR* gene.

12. Labeling

The Applicant submitted proposed prescribing information, patient instruction sheet, and carton and container labeling for the LUM/IVA combination that included the tradename “Orkambi”. The label was reviewed by the appropriate disciplines within the Division who recommended various changes to correct formatting errors and to better describe the drug product and indicated population 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. At the time of this review, the final labeling language between Vertex and the Division is being finalized.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for approval of lumacaftor 200 mg/ivacaftor 125 mg FDC oral tablets (tradename Orkambi) two tablets every 12 hours for the treatment of cystic fibrosis in patients 12 years of age and older who are homozygous for the *F508del* mutation in the *CFTR* gene”.

- Risk Benefit Assessment

The overall risk-benefit assessment of Orkambi (lumacaftor 200 mg/ivacaftor 125 mg FDC tablets) at a dose of 2 tablets every 12 hours for treatment of patients with CF 12 years of age and older who are homozygous for the *F508del* mutation in the *CFTR* gene supports its approval. Treatment with Orkambi resulted in a small but statistically significant improvement in pulmonary function (FEV1) compared to placebo supported by a clinically relevant decrease in CF pulmonary exacerbations. Other endpoints such as change in body mass index also trended in a positive direction and supports efficacy compared to placebo. Whether the lumacaftor component of the combination product contributes to the overall clinical effect of Orkambi cannot be definitively demonstrated based on Phase 3 data, however, given the lack of other CF disease modifying therapies for the *F508del* mutation CF population, supportive in vitro data, and scientific rationale that a two-drug combination is necessary for optimal benefit in the *F508del* population, delaying approval pending further clinical investigation of the contributions is not in the best interest of the CF patient population. The safety profile of Orkambi suggests the potential for liver and respiratory adverse reactions that are balanced by the potential for benefit.

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- Recommendation for Post-marketing Risk Management Activities

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

- Recommendation for other Post-Marketing Study Commitments

Post-Marketing Required Study

- Two year carcinogenicity assessment in rats designed to assess the potential tumorigenicity of lumacaftor [REDACTED] (b) (4)

Final Protocol Submission:	Study is ongoing
Study/Trial Completion:	05/07/2015
Final Report Submission:	07/15/2015

- Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

References

1. Van Goor, R, Hadida S, Grootenhuis P, et al. Proc Natl Acad Sci USA 2011 Nov 15; 108(46):18843-18848.

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/s/

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06/10/2015