PULMONARY-ALLERGY DRUGS ADVISORY COMMITTEE MEETING

FDA Briefing Document

May 12, 2015

NDA# 206038: for lumacaftor/ivacaftor combination oral tablets for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene.

1

Disclaimer Statement

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the new drug application (NDA) 206038, for lumacaftor/ivacaftor combination oral tablets for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508*del mutation in the *cystic fibrosis transmembrane conductance regulator (CFTR)* gene, to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

2

FDA Briefing Package

DIVISION MEMORANDUM

Date: April 15, 2015

From: Anthony G. Durmowicz, MD
Clinical Team Leader
Division of Pulmonary, Allergy, and Rheumatology Products,
Center for Drug Evaluation and Research, FDA

To: Members, Pulmonary-Allergy Drugs Advisory Committee

Subject: Overview of the FDA background materials for New Drug Application (NDA # 206038), for lumacaftor and ivacaftor fixed dose combination oral tablets (proposed trade name Orkambi) for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene.

I. Introduction

Thank you for your participation in the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting to be held on May 12, 2015. As members of the PADAC you provide important expert scientific advice and recommendation to the US Food and Drug Administration (the Agency) on various regulatory decisions. The upcoming meeting is to discuss the NDA from Vertex Pharmaceuticals for lumacaftor and ivacaftor fixed dose combination oral tablets (proposed trade name Orkambi) for the treatment of CF in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. This memorandum summarizes the contents of the Agency background material and the key issues and topics for discussion at the meeting. While the discussion will include safety, the main topic at the May 12, 2015, PADAC meeting will be efficacy and whether the submitted data support the efficacy of lumacaftor and ivacaftor fixed dose combination (FDC) tablets for the proposed indication (CF patients 12 years of age and older who are homozygous for the *F508del* mutation in the *CFTR* gene). The briefing package includes both clinical and statistical briefing documents. The materials prepared by the Agency contain findings and opinions based on reviews of information submitted by Vertex. These background materials represent preliminary findings, and do not represent the final position of the Agency. An important piece in our decision on this application will be the opinions and input that we receive from you at this meeting.

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 Cystic Fibrosis Transmembrane Conductance Regulator (*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. As such, they represent the types of mutations most likely to benefit from ivacaftor monotherapy.

Lumacaftor

Lumacaftor, another small molecule, has been developed by Vertex to promote CFTR intracellular processing and trafficking. While its mechanism of action is not completely understood, it appears to 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] However, it is not known to what extent positive in vitro findings in cell systems will translate to a clinical benefit. Additionally, it should be noted that while overall channel chloride transport appears to increase in vitro, the F508del CFTR defect (deletion of the amino acid phenylalanine at position 508) is not corrected.

Given the actions of the individual drug components, Vertex proposes 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.

II. Regulatory Background

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.

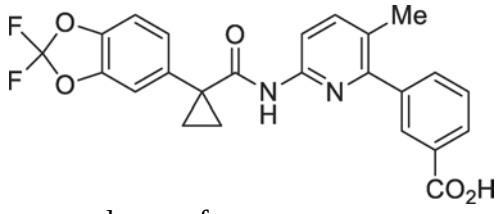
The clinical development programs for combination drug products are typically designed to assess the contribution of each drug monotherapy to the overall effect of the combination product. As such, phase 3 clinical studies for a 2 drug FDC product would usually consist of 4 treatment groups, the combination 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. Whether or not to include one or both monocomponents of the LUM/IVA combination product was a significant issue discussed during regulatory interactions with the company. Pertinent to the discussion was that, 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 and had placed the statement "Not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene" in the Limitations of Use section of the Kalydeco label. A more detailed discussion both on whether or not to include the individual components of the LUM/IVA combination product in the phase 3 clinical studies and of the efficacy data for study 770-104 (ivacaftor monotherapy in *F508del* CF patients) can be found in Section VI (Clinical/Statistical-Efficacy) below.

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.

Vertex has now submitted this current lumacaftor/ivacaftor sNDA for the treatment of CF in patients ages 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene, the proposed indication we will be discussing at the May 12, 2015 PADAC meeting.

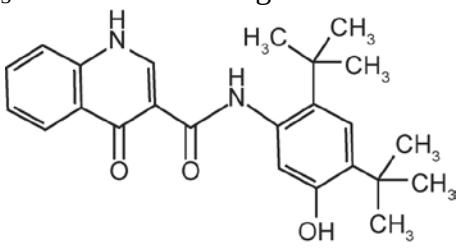
III. Product Information

The proposed product combines the active ingredients lumacaftor and ivacaftor as a fixed dose combination tablet. Lumacaftor is a white to off white powder that is practically insoluble in water. Its molecular formula is $C_{24}H_{18}F_2N_2O_5$ and molecular weight is 452.4.



lumacaftor

Ivacaftor is also a white to off white powder that is practically insoluble in water. Its molecular formula is $C_{24}H_{28}N_2O_3$ and molecular weight is 392.5.



ivacaftor

The LUM/IVA drug product (proposed tradename Orkambi) is a pink, oval shaped, film coated tablet for oral administration containing the active ingredients 200 mg of lumacaftor and 125 mg of ivacaftor (proposed dose 2 tablets twice daily) and compendial excipients.

IV. Nonclinical Pharmacology and Toxicology

The 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 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.

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 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.

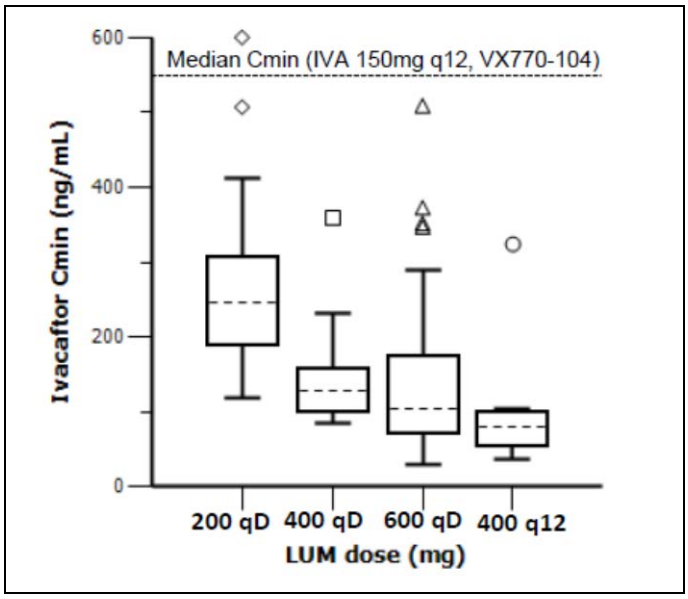
V. Clinical Pharmacology

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. After twice daily dosing of LUM/IVA, steady state plasma concentrations of lumacaftor and ivacaftor were generally reached after approximately 7 days of treatment, with an accumulation ratio of approximately 1.9 for lumacaftor. The steady state exposure of ivacaftor is lower than that of Day 1 due to the CYP3A induction effect of lumacaftor. 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. Lumacaftor is not extensively metabolized in human with most of the drug excreted unchanged in feces. It is, however, a strong inducer of CYP3A enzymes. The terminal half-life of lumacaftor is approximately 26 hours. Ivacaftor is primarily metabolized by CYP3A enzymes and excreted in the feces. The terminal half-life of ivacaftor is approximately 12 hours.

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

Figure 1. 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.

VI. 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, FEV1, 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 *F508del* 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 FEV1 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 *F508del* 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 *F508del* 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 *F508del* mutation						
770-104 (part A) US 34 sites September 2009-July 2010	safety and efficacy	140 CF patients ≥ 12 years homozygous for the *F508del* mutation	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 Change in weight/BMI CF Exacerbations

*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

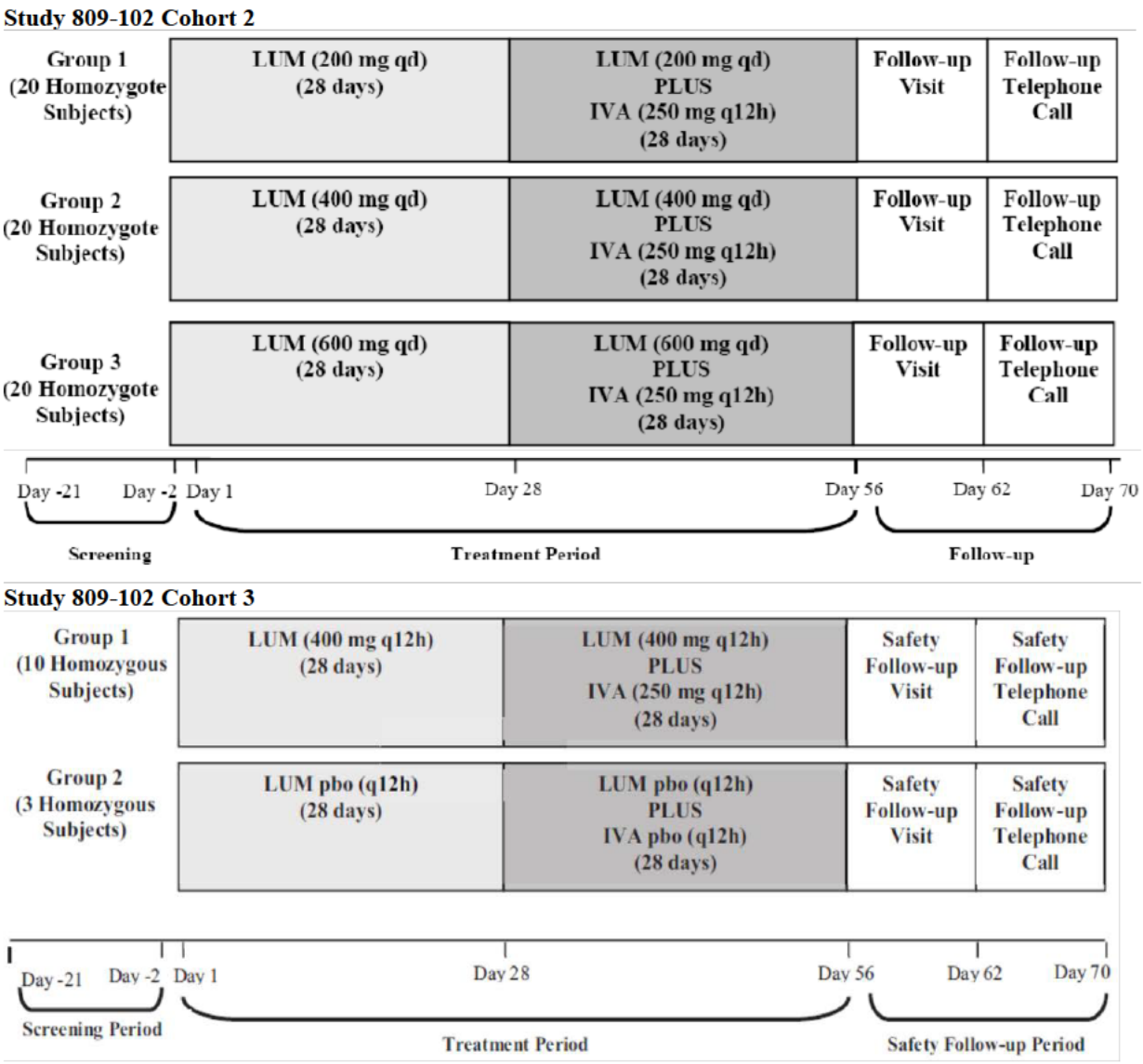
Lumacaftor and ivacaftor dose-ranging
Studies 809-101 and 809-102 formed the primary basis for dose selection for the lumacaftor/ivacaftor combination product program in CF patients homozygous for the *F508del* mutation. Dose selection was based on dose response for 2 principle endpoints, the pharmacodynamic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

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 2 for Cohort designs) are the most relevant for the purpose of determining the 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 2. Study 809-102 cohort 2 and 3 design



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 1).

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

As mentioned above, the decision whether or not to include ivacaftor and/or lumacaftor alone treatment arms in the LUM/IVA combination product phase 3 program was a significant issue that was discussed with the company. Below is the rationale at the time for not including either lumacaftor or ivacaftor alone treatment groups in studies 809-103 and 809-104.

Lack of requirement for a lumacaftor treatment group
As noted above, clinical development programs for combination drug products are typically designed to assess the contribution of each drug monotherapy to that of the combination product. Initial phase 3 study designs for the LUM/IVA FDC included a lumacaftor monotherapy arm based on in vitro data and early clinical studies. However, over the course of study 809-102 cohorts 2 and 3 in which CF patients homozygous for the *F508del* mutation received treatment with lumacaftor alone for 28 days at doses ranging from 200 mg once daily to 400 mg twice daily, treatment of CF patients with lumacaftor monotherapy resulted in a dose-dependent decrease in FEV1 (Table 3). As a result, due to the potential negative effect (risk to patients) of lumacaftor monotherapy on pulmonary function, at an end-of-phase 2 meeting on February 12, 3013, the Division agreed that a lumacaftor monotherapy arm was not warranted for the LUM/IVA phase 3 studies and that the results of study 809-102 would be included in the prescribing information if the LUM/IVA combination therapy was to be approved.

Lack of requirement for an ivacaftor treatment group
Ivacaftor was initially approved on January 31, 2012, for treatment of CF in patients 6 years of age and older who have a *G551D* mutation in the *CFTR* gene, the subpopulation of CF patients defined by a mutation that results in faulty ion channel regulation felt most likely to be responsive to CFTR potentiation by ivacaftor. Approval was based on the robust results obtained from two phase 3 studies of ivacaftor in CF patients, one in patients 12 years of age and older (study 770-102) and another in patients 6 to 11 years of age (study 770-103), where treatment with ivacaftor 150 mg orally twice daily resulted in improvements in absolute % predicted FEV1 (the primary endpoint) of 10.6% and 12.5% respectively. Other clinically meaningful endpoints (weight gain, respiratory symptoms, and pulmonary exacerbations) were also supportive. Additionally, the pharmacodynamic endpoint sweat chloride, an assessment of CFTR activity, decreased markedly (approximately 50%).

In addition to CF patients with a *G551D* mutation in the *CFTR* gene, CF patients who were homozygous for the *F508del* mutation (the patient population addressed in this NDA submission) were also studied in the original ivacaftor program (study 770-104). While considered a "processing" mutation of the CFTR gene and, therefore presumed not likely to be responsive to ivacaftor monotherapy, patients with the *F508del* mutation were included for two reasons. First, while not predicted to have a meaningful clinical response to ivacaftor based on the type of mutation, in vitro studies performed on cells expressing the *F508del* mutation in the *CFTR* gene demonstrated significant increases in chloride transport in response to ivacaftor suggesting the possibility of a positive biologic effect in humans.[2,3] Given that the *F508del* is the most common mutation and represents the majority of CF patients, it was important to define the effect of ivacaftor in this population. Second, the *G551D* mutation program was small due to the low number of CF patients who have the *G551D* mutation (approximately 4%). As such, the ivacaftor study in CF patients homozygous for the *F508del* mutation considerably increased the ivacaftor safety database thereby enabling a better assessment of the risk associated with chronic ivacaftor treatment which, at the time, was a new molecular entity.

The results of study 770-102 of ivacaftor monotherapy in patients with a *G551D* mutation when compared to the results of study 770-104 in CF patients homozygous for the *F508del* mutation yielded dramatically different conclusions. While results for the *G551D* mutation CF population demonstrated statistically significant and clinically meaningful improvement across all major endpoints suggesting this could be a highly efficacious therapy for those CF patients, the results in the *F508del* homozygous CF population, while trending in a positive direction for most endpoints, did not reach statistical significance (except for change in sweat chloride) (Table 4). It is in this context that the Division concluded that ivacaftor monotherapy was not effective in patients with CF who are homozygous for the *F508del* mutation in the *CFTR* gene as is described in the Kalydeco label. Another part of the reasoning for inclusion of the data in the Kalydeco label with negative language, i.e., "not effective in patients with CF who are homozygous for the *F508del* mutation…', was to set the expectations appropriately for CF patients homozygous for the *F508del* mutation who may consider using Kalydeco and thereby deter off label use. That language, in the context of this meeting, should not be taken to mean that ivacaftor has no potential benefit in patients homozygous for the *F508del* mutation especially when taking into consideration both that study 770-104 was not powered to assess efficacy and the relatively low treatment effect the LUM/IVA FDC demonstrated in studies 809-103 and 809-104.

In interpreting the results of study 770-104 (ivacaftor alone in *F508del* homozygous CF patients), it is important to note that no formal sample size or power analysis was performed for the study. Rather, the sample size of approximately 120 patients (randomized 4:1 ivacaftor to placebo) was selected more as a reasonable size to provide additional ivacaftor safety data. However, its design and the number of patients enrolled suggest that the study was underpowered compared to the ivacaftor study 770-102 and the LUM/IVA FDC studies,809-103 and 809-104. This point is important when one looks at the results of study 770-104 in the context of the results of studies 809-103 and 809-104 and notes that while the nominal treatment effect for most endpoints is similar, the results for some endpoints in studies 809-103 and 809-104 reached statistical significance (Table 4). This could be due to the fact that for these studies which enrolled about 187 subjects in each group, an observed mean difference in the primary endpoint, absolute change in % predicted FEV1, as small as around 1.65% could be statistically significant. When looked at in this light, i.e., that the highly powered 809-103 and 809-104 studies demonstrated positive results compared to placebo, one has to reconsider that if it was powered similarly, whether the 1.7% nominal ivacaftor monotherapy treatment effect observed in study 770-104 would have also been statistically significant.

Table 4. Treatment effects for CF related endpoints across IVA monotherapy and LUM/IVA programs

	# of patients		Efficacy Endpoints (95% CI)			
Study Number ***CFTR mutation***	**Placebo n**	**IVA n**	**PPFEV1 (%)**	**CFQR-RD (score)**	**BMI (kg/m^2)**	**Exacerbation (rate ratio)**
Study 770-102* *G551D*	78	83	10.6 (8.6, 12.6)	8.1 (4.7, 11.4)	--	0.43[a] (0.27, 0.68)
Study 770-104* *F508del/F508del*	28	112	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-0.07 (-0.4, 0.2)	0.68 (0.3, 1.4)
	Placebo	**LUM/IVA**	Δ from baseline **LUM/IVA 400/250mg q12** at week 24 (95% CI)			
Study 809-103** *F508del/F508del*	184	182	2.6% (1.2, 4.0)	1.5 (-1.7, 4.7)	0.1 (-0.1, 0.3)	0.7 (0.5, 1.0)
Study 809-104** *F508del/F508del*	187	187	3.0% (1.6, 4.4)	2.9 (-0.3, 6.0)	0.4 (0.2, 0.5)	0.6 (0.4, 0.8)

*endpoint assessed through 24 and 16 weeks for studies 770-102 and 770-103, respectively
**endpoint assessed at 24 weeks
[a] evaluated at 48 weeks
Source: statistical review of NDA 203188, table 4 and 10; pp13 and 30; and clinical review section 6.1.5, Module 5.3.5.1; Study 770-104 CSR; tables 11-11, 11-14, 11-16, 11-18; pp.131, 138,140, 143, Module 2.7.3; Summary of Clinical Efficacy; table 16; pp.62-63

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 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 >60mmol/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 <10g/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 ≥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.

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 ≥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 5 below contains the description of some of the more relevant patient demographics.

Table 5. 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
FEV_1 (% 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 FEV_1 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 6).

Table 6. 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 PPFEV1	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

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 7). 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 7. 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/m^2) 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(≥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/m^2 difference from placebo for the LUM 400 mg/IVA 250 mg dose was not significant while the difference of 0.4 kg/m^2 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 (≥5% increase in relative change in % predicted FEV1)
Responders, defined as patients who had a ≥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.

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 compared to the approximately 40-50% reduction in CF patients with *CFTR* mutations for which ivacaftor monotherapy is currently approved.

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.

Study 770-104 (ivacaftor monotherapy)

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. Therefore, 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 substantial evidence of a treatment effect in in studies 809-103 and 809-104. For consistency, the results were calculated at the 16 week timepoint 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. Note that 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 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 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 8 below contains the description of patient demographics.

Table 8. 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 9.

Table 9. Study 770-104 efficacy endpoints

	770-104
Endpoint	**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

Effect of LUM/IVA Combination vs Ivacaftor Alone

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 raises the question of whether lumacaftor contributes any added benefit over that of ivacaftor alone and begs the question if an ivacaftor

alone arm were included in the LUM/IVA combination studies, would the treatment effects for ivacaftor alone also have been significant, especially in relation to improvements in lung function and reductions in CF pulmonary exacerbations. As mentioned above, in order to probe this issue, FDA statisticians used a non-inferiority approach focused on the proposed LUM 400mg/IVA 250mg q12h dose and the FEV1 and exacerbation endpoint results. Careful evaluation of the patient demographics and baseline characteristics were felt to be highly similar between studies thus, allowing for such a comparison. Slight differences in baseline FEV1 inclusion criteria between study 770-104 and studies 809-103 and 809-104 were 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 10). These results are also summarized graphically in Figure 3 below. Both plots A and B demonstrate that since the 95% CI for the difference from placebo in FEV1 and pulmonary exacerbations for ivacaftor alone overlaps the 95% CIs for LUM/IVA combination one cannot, assuming any reasonable non-inferiority margin, 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 Part B the FDA statistical analysis briefing document by David Petullo MS.

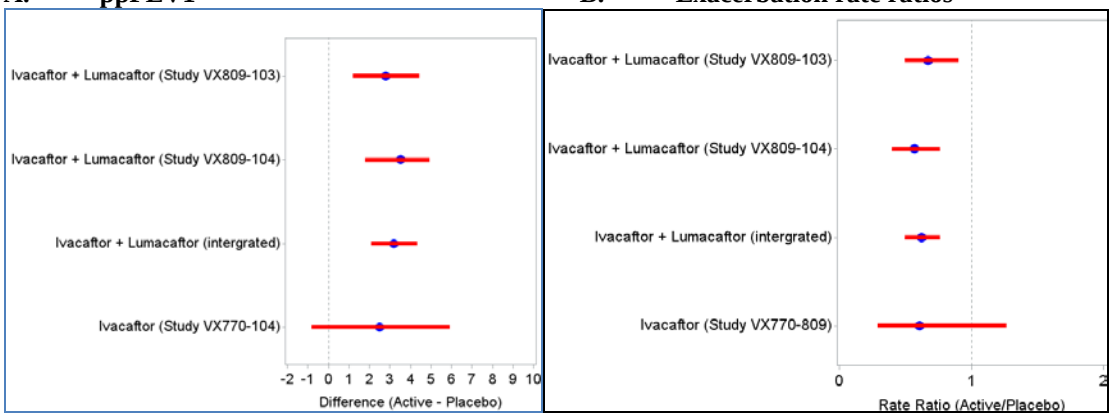
Table 10. FDA comparison of FEV1 and exacerbation rate ratios: LUM/IVA vs ivacaftor alone

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

A. ppFEV1 **B. Exacerbation rate ratios**



Source: FDA statistical reviewer

Additional analyses 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 (see Part B of FDA statistical brief).

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%. 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. LUM/IVA response rate and number of pulmonary exacerbations demonstrated nominal improvements but are not considered statistically significant since the prospective statistical testing hierarchy stopped before the comparisons were made.

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 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 any level of confidence that LUM/IVA was different from ivacaftor, i.e., the possibility that LUM/IVA not was equivalent to ivacaftor with respect to changes in ppFEV1 and pulmonary exacerbations.

VII. Clinical/Statistical- 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 XX 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 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, 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 of require hospitalization (SAE).

Common Adverse Events
Common adverse events are listed in Table 11 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 11. Adverse events that occurring in ≥5% of patients 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 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.

VIII. Summary

The purpose of the PADAC meeting is to discuss the adequacy of the efficacy and safety data submitted by Vertex Pharmaceuticals for the LUM 400 mg /IVA 250 mg FDC oral tablet formulation taken twice daily for the treatment of cystic fibrosis in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. Because the comparator in the phase 3 clinical trials for the LUM/IVA combination was placebo and lacked individual drug component treatment arms that combination product development programs typically require in order to show that the combination product provides benefit over that of the individual components, a discussion of the results and interpretation of study 770-104 of ivacaftor alone in CF patients homozygous for the *F508del* mutation in the *CFTR* gene previously conducted for the ivacaftor monotherapy program is also important. This is especially so since the current ivacaftor (Kalydeco) label states that ivacaftor is not effective in CF patients homozygous for the *F508del* mutation.

However, when the results of study 770-104 are now evaluated in the context of the relatively small treatment effects observed in CF patients who received LUM 400mg/IVA 250mg in studies 809-103 and 809-104, the question arises both whether lumacaftor contributes any added benefit over that of ivacaftor alone and whether ivacaftor monotherapy itself has a positive treatment effect that would have been able to demonstrated if study 770-104 were powered for efficacy similar to studies 809-103 and 809-104.

As such, an important discussion for the PADAC to have on May 12th is not only whether treatment with LUM 400mg/IVA 250mg demonstrates statistically and clinically significant improvements in CF-related endpoints compared to placebo but also whether treatment with LUM 400 mg/IVA 250 mg FDC q 12h offers additional benefit over ivacaftor alone.

This is an important discussion in light of the large population of CF patients affected and lack of alternative treatment options for cystic fibrosis patients homozygous for the *F508del* mutation in the *CFTR* gene. At the PADAC meeting, Vertex will present an overview of the clinical program, which will be followed by the Agency's presentation of the efficacy and safety data. Please keep in mind the following draft topics that will be discussed and deliberated upon following the presentations.

References

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

2. Van Goor F, Hadida S, Grootenhuis P, et al. Proc Natl Acad Sci U S A. 2009 Nov 3; 106(44):18825-30.

3. Van Goor F, Haihui Y, Burton B, Hoffman B, Journal of Cystic Fibrosis 2014; 13:29–36.

Draft Topics for Discussion

1. Discuss the efficacy data for LUM 400 mg/IVA 250 mg FDC twice daily in CF patients 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. Consider the following issues in the discussion: size of the treatment effect and contribution of lumacaftor in context to that for ivacaftor monotherapy.

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

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

Should a clinical study be conducted to compare the LUM/IVA combination to ivacaftor alone?

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

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

If not, what further data should be obtained?

6. Do the efficacy and safety data support approval of the LUM 400 mg/IVA 250 mg fixed dose combination product twice daily in CF patients who are homozygous for the *F508del* mutation in the *CFTR* gene?

If not, what further data should be obtained?

Clinical Briefing Document for the Pulmonary Allergy Drugs Advisory Committee Meeting

May 12, 2015

Lumacaftor/Ivacaftor Oral Tablets (Orkambi) NDA 206038

Proposed Dose: Lumacaftor 400mg/Ivacaftor 250mg q12 hours

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

Reviewer: Robert Lim, MD

Department of Health & Human Services

Food & Drug Administration
Center for Drug Evaluation & Research
Division of Pulmonary, Allergy and Rheumatology Products
Silver Spring, MD 20993

Table of Contents

Table of Tables

Table of Figures

1 Introduction and Regulatory Background

1.1 Brief Clinical Background

Cystic fibrosis (CF) is an autosomal recessive genetic disease that affects approximately 30,000 children and adults in the United States[1], and approximately 70,000 children and adults worldwide[2]. CF affects all ethnic and racial groups, but is most common in Caucasians. There is no cure for cystic fibrosis, and despite progress in the treatment of the disease, the predicted median age of survival for a person with CF is the mid-to late-30's[1,3.]

CF results from mutations the cystic fibrosis transmembrane conductance regulator (CFTR) gene which leads to decreased amount or abnormal function of CFTR protein. The CFTR protein is an epithelial chloride ion channel present on the apical surface of epithelial cell membranes. CFTR aids in the regulation of salt and water absorption and secretion throughout the body. Lack of properly functioning CFTR is responsible for the clinical sequelae of CF, including malabsorption of nutrients and the inability to mobilize tenacious respiratory secretions, leading to recurrent infections and lung damage. Over time, the CF lung is exposed to a cycle of infection, inflammation, and damage, which causes progressive and irreversible airways obstruction, bronchiectasis, and ultimately respiratory failure. Because it is a recessive genetic disease, in order to present with clinical CF disease, one must have two mutations in the *CFTR* gene. To date, almost 2,000 mutations in CFTR have been identified.

The most common *CFTR* mutation is *F508del*. In the United States, approximately 90% of patients carry at least one *F508del* allele[1], with approximately 50% of patients being homozygous for the *F508del* mutation. The *F508del* mutation results in the loss of phenylalanine at the 508 position of the CFTR protein. As a result, the CFTR protein is not able to fold properly, which leads to its retention in endoplasmic reticulum where the majority of it is degraded. Therefore, the amount of *F508del* CFTR protein that is ultimately inserted into the epithelial cell apical surface is greatly reduced. In addition to defective trafficking, ion transport in the *F508del* CFTR protein appears to be abnormal. In experimental models*F508del* CFTR protein expressed on the epithelial cell apical surface has a decreased half-life and reduced open-channel probability[4]. Ultimately, these deficiencies result in a relatively severe disease phenotype.

[1] Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry: 2013 annual data report. Bethesda, Maryland;2014
[2] Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cystic Fibrosis 2008;7(5):450-453.
[3] MacKenzie T, et al. Longevity of Patients with Cystic Fibrosis in 2000 to 2010 and Beyond: Survival Analysis of Cystic Fibrosis Foundation Patient Registry. *Ann Int Med* 2014; 161:233-241
[4] Dalemans W, Barbry P, Champigny G, Jallat S, Dott K, Dreyer D, *et al*. Altered chloride ion channel kinetics associated with the ΔF508 cystic fibrosis mutation. *Nature* 1991; **354**: 526–8

1.2 Product Information

The proposed product combines lumacaftor and ivacaftor (LUM/IVA). The chemical name for ivacaftor (IVA) is N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxymide. It is an orally-bioavailable small molecule that is a potentiator of the CFTR chloride channel present in the epithelial cell membrane. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR.

The chemical name for lumacaftor (LUM) is 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2- yl]benzoic acid. Lumacaftor is an orally bioavailable small molecule that may facilitate the cellular processing and trafficking of defective CFTR protein which allows it to reach the epithelial cell apical surface.

The LUM/IVA drug product is an immediate release fixed drug combination (FDC) tablet for oral administration. The proposed product for marketing is a FDC tablet containing 200mg of LUM and 125mg of IVA with the proposed dose of 2 tablets given every 12 hours (LUM 400mg/IVA 250 mg). The Applicant's rationale for the LUM/IVA combination is that LUM will allow for increased trafficking of the F508del CFTR chloride channel to the epithelial cell surface where IVA will work to potentiate chloride transport.

1.3 Tables of Currently Available Treatments for Proposed Indications

Except for IVA in a limited number of CFTR mutation subpopulations, which does not include CF patients homozygous for the *F508del* mutation, there are no FDA-approved products available that are directed at the cause of cystic fibrosis (i.e., the absent or defective CFTR ion channel). However, a number of drugs are used to treat the symptoms and sequelae of the disease. Medications used to treat CF patients are summarized in Table 1. Note that not all are FDA approved for use in CF.

Table 1. Treatments for CF

Active Ingredient	Trade Name	FDA-approved for CF Indication?
CFTR potentiator		
Ivacaftor	Kalydeco	Yes; *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, and R117H* mutations
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		
Tobramycin (nebulized)	TOBI	Yes
Tobramycin (dry powder)	TIP	Yes
Aztreonam (nebulized)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
Inhaled Treatments used as Mucolytics		
Dornase alpha (DNase)	Pulmozyme	Yes
Hypertonic Saline (7%)	----	No
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase™	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol, etc.	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Anti-Inflammatory Agents		
Oral azithromycin	Zithromax	No
Oral high-dose Ibuprofen	Motrin, Advil, etc.	No
[Source: Approved labeling data from Drugs@FDA,.gov]		

1.4 Availability of Proposed Active Ingredient in the United States

Ivacaftor (tradename Kalydeco) is currently FDA-approved for the treatment of CF patients ≥2 years of age with the *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, or R117H* mutation in the *CFTR* gene. Lumacaftor is not approved as a monotherapy or combination product anywhere in the world.

1.5 Important Safety Issues With Consideration to Related Drugs

Ivacaftor:
Cataracts were seen in juvenile rats dosed with ivacaftor at dose levels of 10 mg/kg/day and higher. Cases of non-congenital lens opacities/cataracts have also been reported in pediatric patients treated with ivacaftor. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating ivacaftor treatment.

Elevated transaminases have also been reported in patients with CF receiving ivacaftor. Liver transaminases should be assessed in patients receiving ivacaftor.

Lumacaftor:
During the dose-ranging program it was noted that lumacaftor, when administered alone, caused a dose dependent decrease in percent predicted forced expiratory capacity in one second ($ppFEV_1$). Increases in metrorrhagia in LUM/IVA treated patients were also observed in early phase trials. Worsening of liver function and elevation in liver transaminases has been observed in CF patients receiving LUM/IVA in clinical trials.

1.6 Summary of Regulatory Activity Related to Submission

Ivacaftor tablets (NDA 203,188) were approved on January 31, 2012, for the treatment of CF in patients ≥ 6 years of age who have a *G551D* mutation in the *CFTR* gene at a dose of 150mg every 12 hours with a fat-containing food. On February 21, 2014, December 30, 2015, and March 17, 2015 the indication was expanded to ultimately include the following additional mutations: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R*, or *R117H* in CF patients ≥2 years of age.

The initial clinical development program for ivacaftor for CF patients who have a *G551D* mutation in the *CFTR* gene included a clinical trial of ivacaftor in CF patients homozygous for the *F508del* mutation in the *CFTR* gene (Study 770-104). In this study, which will be discussed in more detail in sections 3.3 Discussion of Individual Studies/Clinical Trials and 4 Review of Efficacy, the nominal treatment effect on $ppFEV_1$ compared to placebo was small (1.7%) and, in the context of ivacaftor demonstrating a 10.6% increase in $ppFEV_1$ compared to placebo in patients with a *G551D* mutation, lead to the determination that ivacaftor was not effective in patients homozygous for the *F508del* mutation.

The clinical program for lumacaftor monotherapy was limited to early studies where it was demonstrated that lumacaftor monotherapy demonstrated a dose-dependent reduction in ppFEV1 in CF patients homozygous for the *F508del* mutation and thus, a safety concern that precluded its use as a monotherapy.

The LUM/IVA combination product was developed under IND 79,521.Major regulatory interactions relevant to this submission are summarized below:

November 2, 2012 End-of-Phase 2 (EOP2) meeting:

- An ivacaftor monotherapy control was not required for phase 3 studies based on data from the ivacaftor monotherapy development program.

February 12, 2013 Type B meeting:

- Due to the safety concern over dose dependent decreases in FEV_1 following lumacaftor monotherapy, a lumacaftor monotherapy control was not required in

the phase 3 studies [see section 3.2 Dose Selection/Rationale (Study 809-102)].
- To support an exacerbation claim the Division recommended replicate evidence in 48-week trials

December 7, 2012:
- Breakthrough designation was granted for the lumacaftor/ivacaftor combination.

January 8, 2014 Type B meeting:
- The Division recommended that the Applicant include sweat chloride data in the phase 3 trials.
- The Division commented that the pivotal trials were powered to detect even small effects on $ppFEV_1$ and that review of effectiveness would consider not only statistical evidence for presence of a treatment effect, but also the clinical importance of the treatment effect.

August 12, 2014 Pre-NDA meeting:
- The Division recommended that the submission should address the clinical relevance of the treatment effect observed in the pivotal studies and the level of evidence that lumacaftor contributes to the efficacy of the product.
- Secondary endpoints would be an important part of the overall evaluation of efficacy.

2 Clinical Pharmacology

2.1 Mechanism of Action

Ivacaftor is classified as a potentiator of the CFTR protein. The CFTR protein is a chloride channel present at the surface of epithelial cells in multiple organs. Ivacaftor appears to increase the probability of CFTR channel opening to enhance chloride transport.

Lumacaftor's mechanism of action is not completely understood. It appears to facilitate the cellular processing and trafficking of defective CFTR protein which may allow it to reach the cell surface.

2.2 Pharmacokinetics

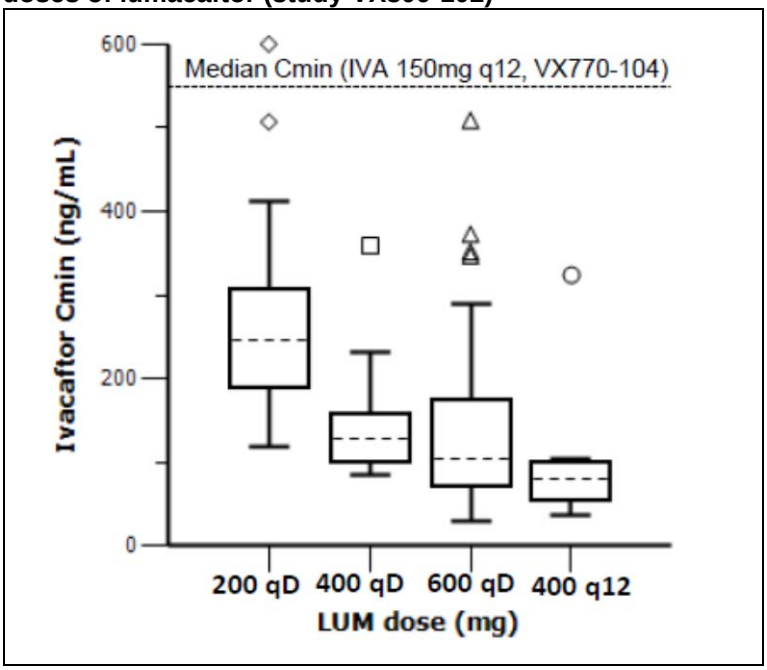
Ivacaftor:
Steady state concentration of IVA in healthy volunteers was achieved in 3-5 days with an accumulation ratio ranging from 2.2 to 2.9. When given alone with food containing fat, exposure to IVA is 2 to 4 fold higher. IVA is almost totally bound to plasma proteins (99%). It is extensively metabolized 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, such as ketoconazole, can significantly increase IVA exposure. Ketoconazole co-administration results in an 8.5-fold increase in IVA exposure Strong inducers of CYP3A, such as rifampin, can significantly decrease IVA exposure. Rifampin co-administration results in a 9-fold decrease in IVA exposure. The terminal half-life is approximately 12 hours which supports a twice daily dosing regimen.

Lumacaftor:
The exposure of LUM is approximately 2-fold higher in heathy volunteers compared to CF patients. Steady state concentration of LUM in healthy volunteers was achieved in 5-14 days with an accumulation ratio ranging from 1.9 to 2.2. LUM peak plasma concentration occurred 4-hours after dosing in the fasted state versus 6-hours in the fed state. LUM is also almost totally bound to plasma proteins (99%). LUM is not extensively metabolized in humans with the majority excreted in the feces. *In vitro* and *in vivo* data indicate that LUM is primarily metabolized via oxidation and glucouronidation. LUM is a strong inducer of CYP3A. The terminal half-life is approximately 26 hours which could support a once daily dosing regimen.

Lumacaftor/Ivacaftor:
As LUM is a strong inducer of CYP3A and IVA is a CYP3A substrate, there is the possibility of a drug drug interaction between LUM and IVA. In fact, IVA, when dosed with LUM, results in significantly lower IVA exposure than when IVA is dosed alone for the same nominal IVA dose. In a PK study in healthy volunteers, LUM exposure reduced IVA exposure by approximately 80%. Similar results were observed when IVA 250mg q12 was co-administered with LUM in CF patients during the LUM/IVA dose-ranging study 809-102. IVA exposure data when given with varying doses of LUM are summarized in Figure 1.

Figure 1. Ivacaftor exposure in CF patients when IVA 250mq12 was co-administered with varying doses of lumacaftor (study VX809-102)



Source: FDA Clinical Pharmacology Reviewer

While co-administration of LUM with IVA substantially decreases IVA exposure, LUM exposure is not affected by IVA.

As LUM is a strong CYP3A inducer and because *in vitro* studies suggest that LUM has the potential to induce CYP2B6, CYP2C8, CYP2C9, and CYP2C19; and inhibit CYP2C8 and CYP2C9; 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

3 Sources of Clinical Data, Review Strategy, and Trial Design

3.1 Tables of Studies/Clinical Trials

The sources of clinical data used in this review are summarized in Table 2.

Table 2. Sources of clinical data

Study	Study Type/Design	Treatment Duration	CF Population	n	Treatment Arms	Endpoints
809-102	Dose-ranging Multi-cohort[a], R, DB, PC, MC, PG	Up to 56-days total	*F508del* homo- and heterozygous	312	LUM 200mg qD (14day) followed by addition of IVA 150mg or 250mg q12 (7day) LUM 200, 400, 600mg qD, or 400mg q12 (28day) followed by addition of IVA 250mg q12 (28day)[b] LUM 400mg q12 (28day) followed by addition of IVA 250mg q12 (28day)[b] LUM 400mg+IVA 250mg q12 (56day) Placebo	$ppFEV_1$ Sweat Chloride
809-103/ 104	Safety/Efficacy R, DB, PC, MC, PG	24-weeks	*F508del* homozygous	1108	LUM 600mg qD/ IVA 250mg q12 LUM 400mg/IVA 250mg q12 Placebo	1^{o-} $ppFEV_1$ Others: CFQR-Resp, BMI Exacerbation
809-105	Safety extension	ongoing	*F508del* homozygous	1054	LUM 600mg qD/ IVA 250mg q12 LUM 400mg/IVA 250mg q12	Safety
770-104	Safety/Efficacy R, DB, PC, MC, PG	16-weeks	*F508del* homozygous	140	IVA 150mg q12 Placebo	1^{o-} $ppFEV_1$ Others: CFQR-Resp, Weight, BMI Sweat chloride Exacerbation

[a]this study contained 4 cohorts (1-4), however only data cohorts 2 and 3 are included in this review.
[b]these doses were explored in cohorts 2 and 3.
LUM=lumacaftor, IVA=ivacaftor, R=randomized, DB=double-blind, PC=placebo controlled, MC=multicenter, PG=parallel group, qD=once daily, q12=every 12 hours, $ppFEV_1$=percent predicted force expiratory volume in 1 second, BMI=body mass index, CFQR-Resp=Cystic Fibrosis Questionnaire Revised-Respiratory Domain

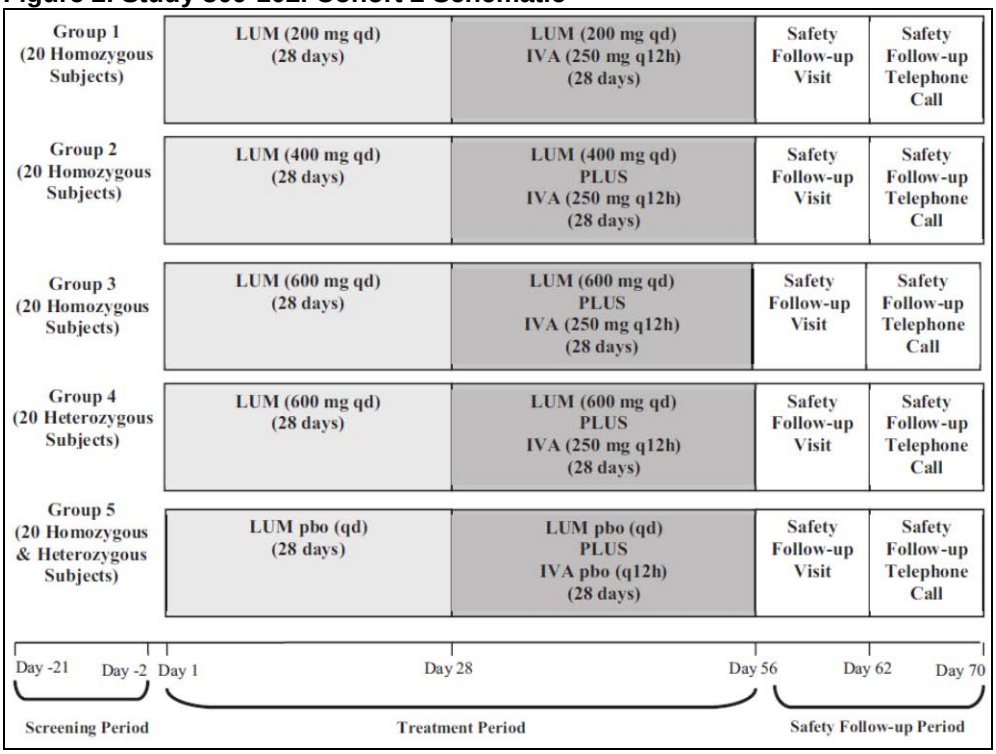
3.2 Dose Selection/Rationale (Study 809-102)

Dosing for the IVA component was initially based on the approved IVA monotherapy dose and subsequently the observed drug-drug interaction between LUM and IVA (see section 2 Clinical Pharmacology). Because LUM is CYP3A inducer and IVA is a CYP3A substrate, co-administration of LUM with IVA results in substantially lower IVA exposures. As such, for LUM/IVA, compared to the approved IVA monotherapy dose of 150mg q12, the Applicant used a higher IVA dose of 250mg q12 in the LUM/IVA dose-ranging trial and pivotal trials. Despite the nominally higher IVA dose in the LUM/IVA combination, IVA exposure was still lower substantially lower compared to IVA 150mg q12 monotherapy (Figure 1).

Dosing for the LUM component of LUM/IVA was based primarily on data from dose-ranging study 809-102. This was a randomized, double-blind placebo controlled, multi-cohort study evaluating multiple doses of LUM alone and LUM/IVA in terms of safety, efficacy, pharmacokinetics, and pharmacodynamics. To be included, patients had to be heterozygous or homozygous for the *F508del* mutation, ≥18 years of age, and have a baseline ppFEV1 ≥40%. For *F508de*l heterozygous patients, the second allele had to encode for a mutation predicted by the Applicant to either result in lack of CFTR production or to be non-responsive to IVA alone. Patients remained on their stable CF medications during the study. Relevant endpoints included sweat chloride and $ppFEV_1$.

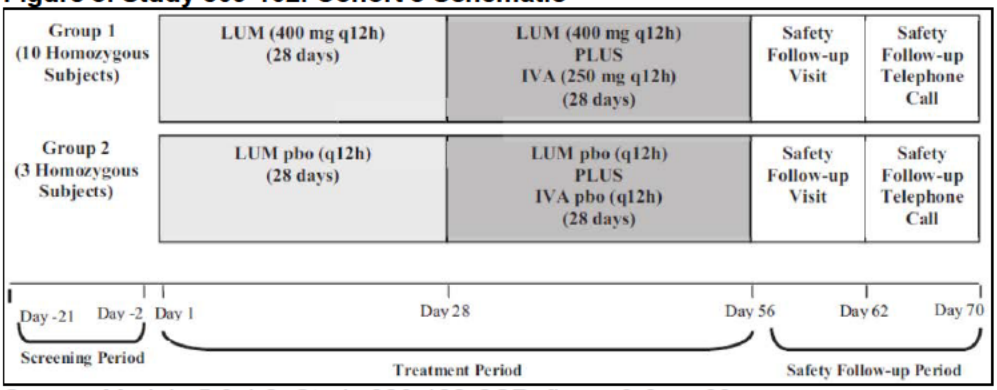
While this study included 4 cohorts (1-4), only cohorts 2 and 3 are relevant for LUM dose-ranging in *F508del* homozygous patients as these cohorts included both LUM alone and LUM/IVA treatment periods and *F508del* homozygous patients. Cohorts 2 and 3 consisted of an initial 28-day treatment period (baseline to day 28) where patients were treated with LUM alone at 200mg, 400mg, or 600mg once daily (qD) or 400mg every 12 hours (q12). Immediately following the initial treatment period IVA 250 mg every 12 hours was added for a second 28-day treatment period (day 29-56). During the second treatment period patients received both drugs. Given the half-life of LUM, both qD and q12 dosing was explored for the LUM component. The schematics for cohorts 2 and 3 are shown in Figure 2 and Figure 3.

Figure 2. Study 809-102. Cohort 2 Schematic



Source: Module 5.3.4.2, Study 809-102 CSR, figure 9-2, pg62

Figure 3. Study 809-102. Cohort 3 Schematic



Source: Module 5.3.4.2, Study 809-102 CSR, figure 9-3, pg63

Sweat chloride was assessed at baseline and on days 28 and 56. On days 28 and 56, sweat chloride was measured at dosing and 4-hours post-dosing. Sweat chloride results in *F508del* homozygous patients demonstrated that both LUM and LUM/IVA treatment results in small decreases in sweat chloride values compared to placebo (assessed at dosing). These results are summarized in table Table 3. Note that the combined placebo group for cohorts 2 and 3 includes six patients who were *F508del* heterozygous, however, FDA statisticians performed an analysis removing the heterozygous placebo patients and the results similar and the interpretation unchanged (see FDA Statistics Review).

Table 3. Study 809-102. Change in sweat chloride versus placebo between treatment periods in *F508del* homozygous patients (cohort 2 and 3) when assessed at dosing

	Placebo (combined) [a]	LUM 200mg qD	LUM 400mg qD	LUM 600mg qD	LUM 400mg q12
Δ in sweat chloride (mmol/L) vs. placebo assessed at dosing					
# of patients	26	21	19	20	10
Baseline to day 28 [b] (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)
Day 28-56[c] (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 [c] (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)

[a]Includes *F508del* heterozygous patients
[b]LUM alone was given from baseline to day 28 in all groups
[c]All LUM therapy doses were given in combination with IVA 250mg q12 from day 29-56
Source: Module 2.7.2, Summary of Clinical Pharmacology, tables 15 and 16, p68

After 28-days of treatment (day 0-28) sweat chloride values assessed at dosing decreased with all doses of LUM versus to placebo (range: -4.9 to – 8.3mmol/L). When IVA 250mg q12 was added to the LUM dose for an additional 28-days (day 28-56), there were small additional decreases in sweat chloride values. When analyzing the entire 56-day treatment period, the differences from placebo for the three highest doses, LUM 400mg qD/IVA 250mg q12, LUM 600mg qD/IVA 250mg q12, and LUM 400mg/IVA 250mg q12, results were similar at -9.8mmol/L, -9.5mmol/L and -11.0mmol/L,

respectively. As baseline sweat chloride values were approximately 100mmol/L, this represented an approximately 10% decrease in sweat chloride values from day 0-56. These sweat chloride data were supportive of taking any of the 3 doses forward (LUM 400mgqD/IVA250mg q12h, LUM 600mg qD/IVA 250mg q12h, and LUM 400mg/IVA 250mg q12h).

In addition to measuring sweat chloride at dosing, it was also measured four hours post-dosing. For change from baseline at days 28 and 56, the results were consistent with the at-dosing data, with decreases in sweat chloride at both time-points. However, when examining change in sweat chloride when IVA 250mg q12 was added to LUM for an additional 28-days (day 28-56), in contrast to the at-dosing data, no additional decreases were observed (see FDA Statistics Review). This may imply the small additional decreases in sweat chloride values at dosing observed when IVA was added to LUM therapy were related to chance.

While these sweat chloride results support the doses used in studies 809-103/104, the clinical relevance of such a modest effect (10%) is uncertain especially when compared to IVA monotherapy's effect in *G551D* and *R117H* patients, where sweat chloride decreases of approximately 50mmol/L (~50% from baseline) and 24mmol/L (~34% from baseline), respectively, seemed to be associated with potential clinical benefit, at least at the population level.

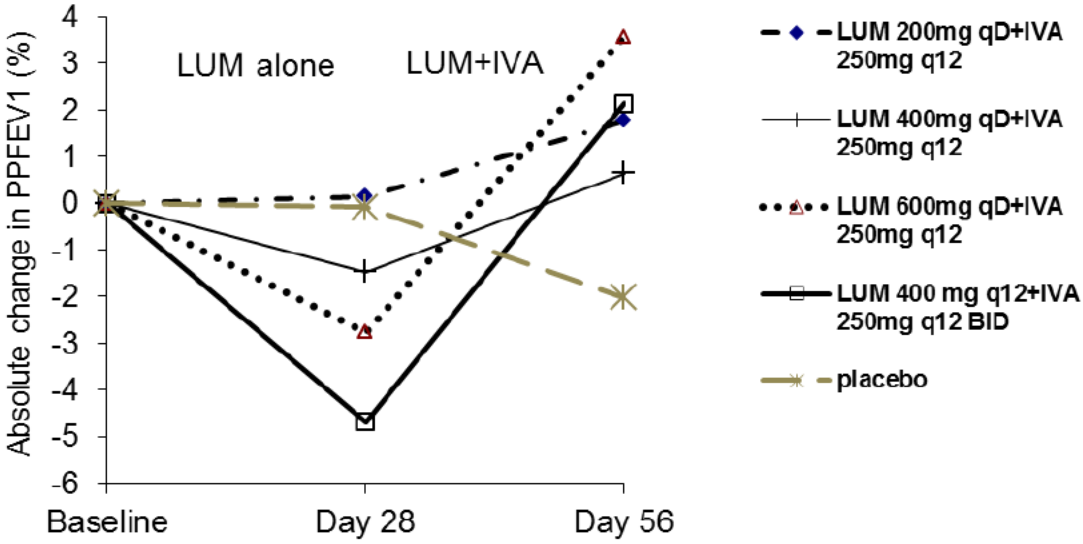
With regard to lung function, results showed that LUM monotherapy (baseline to day 28) resulted in a dose dependent decrease in $ppFEV_1$ in CF patients homozygous for the *F508del* mutation (Table 4). It was on this basis that LUM monotherapy was not required in the phase 3 LUM/IVA studies. In contrast, during the 28-day treatment period with LUM (200mg qD, 400mg qD, 600 qD, and 400mg q12) in combination with IVA 250mg q12 (baseline to day 56), an increase of 5.6% and 4.2% compared to placebo in ppFEV1 was observed in the LUM 600mg qD/IVA 250mg q12 and LUM 400mg/IVA 250mg q12 groups, respectively. Smaller improvements were seen in the lower LUM dose groups (Table 4). Figure 4 summarizes the results for the within group comparisons in a graphical format.

Table 4. Study 809-102. Absolute change percent predicted FEV_1 versus placebo between treatment periods in *F508del* homozygous patients (cohorts 2 and 3)

	Placebo (combined)[a]	LUM 200mg qD	LUM 400mg qD	LUM 600mg qD	LUM 400mg q12
Δ in percent predicted FEV1 vs. placebo					
# of patients	27	21	20	20	11
Baseline to day 28[b] (95% CI)	--	0.24 (-3.7, 4.2)	-1.4 (-5.4, 2.6)	-2.7 (-6.7, 1.4)	-4.6 (-9.6, 0.36)
Day 28-56[c] (95% CI)	--	3.52 (-0.45, 7.5)	3.6 (-0.43, 7.6)	7.8 (3.7, 11.9)	7.7 (2.6, 12.8)
Baseline to day 56[c] (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)

[a]Includes *F508del* heterozygous patients
[b]LUM alone was given from baseline to day 28 in all groups
[c]All LUM therapy doses were given in combination with IVA 250mg q12 from day 29-56
Source: Module 2.7.2, Summary of Clinical Pharmacology, tables 15 and 16, pp70-71

Figure 4. Study 809-102. Absolute change from baseline in percent predicted FEV_1 ($ppFEFV_1$) at days 28 and 56 in *F508del* homozygous patients (cohorts 2 and 3)



Source: FDA generated from data from module 2.7.2, Summary of Clinical Pharmacology, table 16,pg 70

It is worth noting that while LUM monotherapy treatment decreased sweat chloride values, for the clinical endpoint $ppFEV_1$, the effect was the opposite with a clear dose-dependent worsening which was statistically significant when change in $ppFEV_1$ is presented as the relative change from baseline. This contrast highlights the fact that improvements (decreases) in sweat chloride as a result of lumacaftor were not associated with clinical benefit (increase in $ppFEV_1$) . Additionally, while the cause of

the LUM mediated dose-dependent in $ppFEV_1$ is not known, these data would imply that LUM may have off-target effects not necessarily related to CFTR function.

In summary, these ppFEV1results supported the further exploration of the LUM 600mg qD/IVA 250mg q12 and LUM 400mg/IVA 250mg q12 doses in the phase 3 studies and warranted, based of the safety signal inherent with lumacaftor monotherapy exclusion of inclusion of a lumacaftor monotherapy treatment arm as well.

3.3 Review Strategy

The clinical program in *F508del* homozygous CF patients for LUM/IVA is primarily based on two replicate 24-week clinical studies (studies 809-103/104), in which 2 LUM/IVA combination doses were compared to placebo; and study 770-104, the only clinical study to assess the effect of IVA alone in *F508del* homozygous CF patients. Studies 809-103/104 included three treatment arms, which were as follows: 1) placebo, 2) LUM 600mg qD/IVA 250mg q12, and 3) LUM 400mg/IVA 250mg q12. No monotherapy comparator arms were included. Study 770-104 included IVA 150mg q12 and placebo treatment arms.

For combination products such as LUM/IVA, selection of the appropriate control group(s) for comparison is important to allow for determination efficacy. Typically, for this type of product, phase 3 studies include a monotherapy comparator(s) to allow for demonstration of an added benefit of the combination product over each monotherapy. In the case of this product, neither LUM nor IVA monotherapy comparators were required. With regard to LUM, this was due to findings from dose-ranging study 809-102. This study demonstrated that LUM monotherapy resulted in a dose-dependent decrease in $ppFEV_1$ in *F508del* homozygous patients (see Figure 4). Therefore, for safety and ethical reasons a LUM monotherapy comparator was not required for the phase 3 studies.

An IVA monotherapy comparator arm was also not required based on findings from the IVA monotherapy program (NDA 203,188). In that program, IVA demonstrated a statistically and clinically significant treatment effect in CF patients who carried at least one *G551D* mutation in the *CFTR* gene. In that development program, Vertex also studied IVA in CF patients who were *F508del* homozygous (study 770-104). In contrast to the *G551D* trials, in *F508del* homozygous patients, while point estimates for some efficacy parameters were positive (e.g., $ppFEV_1$ and exacerbation), the IVA effect size was small in magnitude and not statistically significant. However, it is worth noting that no formal sample size or power analysis was performed for this study and the sample size was chosen primarily to provide additional safety information for IVA. Key results from these studies summarized in Table 5.

Table 5. Treatment effect of ivacaftor monotherapy in patients with the *G551D* mutation and homozygous for the *F508del* mutation

	Δ from baseline **IVA** alone (n=83) versus placebo (n=78) through week 24 (95% CI)				
G551D **≥12 years old**	ppFEV$_1$ (%)	CFQ-R Respiratory Domain (score)	Sweat (mmol/L)	Weight (kg)	Exacerbation (rate ratio)
IVA 150mg q12	10.6% (8.6, 12.6)	8.1 (4.7, 11.4)	-47.9 (-51.3, -44.5)	2.8 (1.8, 3.7)	0.43[a] (0.27, 0.68)
F508del **homozygous ≥12 years old Study 770-104**	Δ from baseline **IVA** alone (n=112) versus placebo (n=28) through week 16 (95% CI)				
IVA 150mg q12	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-2.9 (-5.6, -0.15)	-0.16 (-1.1, -0.7)	0.68 (0.3, 1.4)

[a]exacerbation rate ratio through week 48
Source: NDA 203188 statistical review, table 4 and 10, pp13 and 30; & clinical review section 6.1.5, pg.63

When examined in the context of the robust efficacy results for the *G551D* population, the Division concluded that ivacaftor was not effective in CF patients homozygous for the *F508del* mutation. Based on this, an IVA comparator arm was not required for the LUM/IVA phase 3 studies. However, given the results of the highly powered LUM/IVA studies 809-103 and 809-104, in which statistically significant but small improvements for the primary endpoint, ppFEV$_1$, were noted that approximated those for the previous IVA alone study 770-104, the question now arises whether the treatment effect for the LUM/IVA FDC is different than that observed for IVA monotherapy. As such, efficacy data from the IVA monotherapy study (770-104) will be presented in addition to that from the LUM/IVA studies 809-103 and 809-104.

Assessment of safety is based primarily on the pooled safety data from the 24-week placebo controlled phase 3 trials (studies 809-103 and 809-104). Supportive evidence of safety is derived from safety data from the ongoing extension study (809-105) of studies 809-103 and 809-104.

Protocol reviews for these trials are included in section 3.3 Discussion of Individual Studies/Clinical Trials. Efficacy data from studies 809-103, 809-104 and 770-104 are discussed in section 4 Review of Efficacy. Results from study 809-102 were previously discussed in section 3.2 Dose Selection/Rationale (Study 809-102).

3.3 Discussion of Individual Studies/Clinical Trials

3.3.1 Efficacy and Safety Study 809-103

This multi-national study intended to provide primary evidence of efficacy and safety for LUM/IVA compared to placebo. This study was performed from 5/28/2013-4/29/2014

Study title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

Objectives

Primary

- To evaluate the efficacy of LUM/IVA through week 24 in CF patients homozygous for the *F508del* mutation.

Secondary

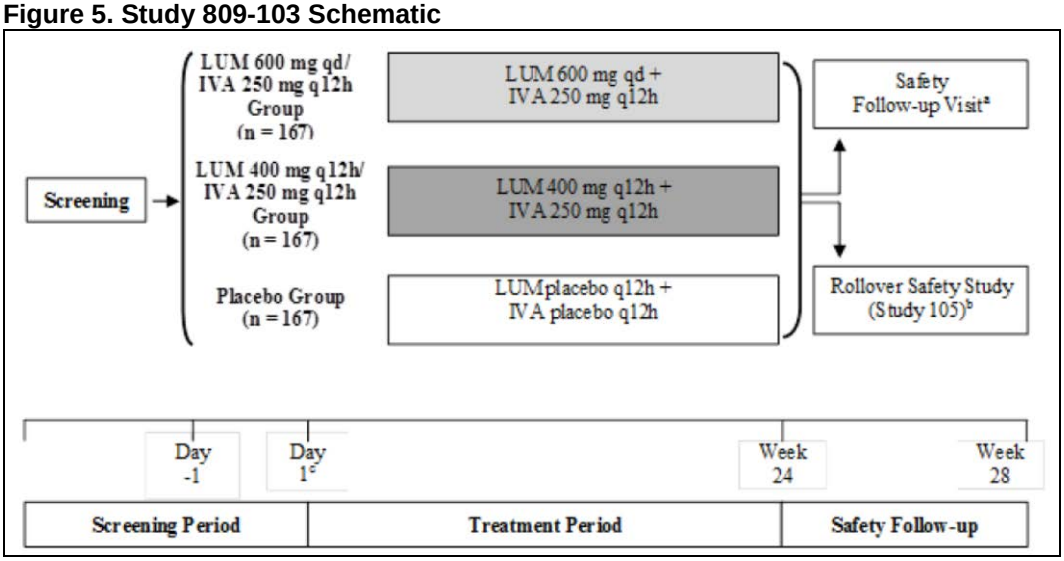
- To evaluate the safety of LUM/IVA through week 24 of treatment.
- To investigate the pharmacokinetics (PK) of lumacaftor and ivacaftor and their metabolites

Study Design and Conduct

Overview

This is a Phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study in patients with CF who are homozygous for the *F508del* mutation. This study was designed to evaluate the efficacy and safety of 2 doses of LUM/IVA (LUM 600mg qD/IVA 250mg q12 and LUM 400mg/IVA 250mg q12) compared to placebo. This study included a 28-day screening period, a 24-week treatment period, and a safety follow-up visit. After the screening period, eligible patients were randomized (1:1:1) to 1 of 3 treatment arms. During the treatment period, clinic assessments occurred at days 1and 15 and weeks 4, 8, 16, and 24. In addition, telephone contact occurred at day 3, week 12, and week 20. At the Week 24 visit, subjects who completed the treatment period were allowed to enroll in the extension study VX12-809-105. If patients decline participation in the extension study, a safety follow-up visit occurred 4 weeks after the week 24 visit. The study is summarized schematically in Figure 5. Assessments are summarized in Table 6.

Figure 5. Study 809-103 Schematic



Source: Module 5.3.5.1, Study 809-103 CSR, figure 9-1, pg 41

Table 6. Study 809-103. Assessment Schedule

Event/Assessment	Day 1	Day 3	Day 15	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Safety Follow-up Visit Wk 28
Clinic visit	X		X	X	X		X		X	X
Telephone contact		X				X		X		
Inclusion/exclusion	X									
CFQ-R	X		X	X	X		X		X	X
EQ-5D-3L	X		X	X	X		X		X	X
TSQM	X		X	X	X		X		X	X
Weight and height	X		X	X	X		X		X	X
Complete PE	X								X	
Pregnancy test	X			X	X	X	X	X	X	X
Standard digital ECG	X		X	X	X		X		X	X
Ambulatory ECG	X		X							
Vital signs	X		X	X	X		X		X	X
Pulse oximetry	X		X	X	X		X		X	X
Spirometry	X		X	X	X		X		X	X
Serum chemistry	X		X	X	X	X	X	X	X	X
Hematology	X		X	X	X		X		X	X
Coagulation	X								X	X
Urinalysis	X								X	X
Single PK sampling							X			
Serial PK sampling	X		X	X	X					
DNA sample A and B (optional)			X							
Blood biomarker analysis (optional)	X								X	
Sputum samples (optional)	X								X	
Other events related to outcome	X	X	X	X	X	X	X	X	X	
Randomization	X									
Study drug count			X	X	X		X		X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Concomitant treatments and procedures	X	X	X	X	X	X	X	X	X	X

Source: Module 5.3.5.1, Study 809-103 CSR; table 9-5; pg 60-62

Trial population

This trial randomized 549 CF patients ≥12 years of age who were homozygous for the *F508del* mutation. Patients were stratified by age (<18 versus ≥18 years of age), sex (male versus female), and FEV_1 severity determined at the Screening Visit (<70% versus ≥70% predicted).

Key Inclusion Criteria

1. Male or female patient age ≥ 12 years, with confirmed diagnosis of cystic fibrosis defined as:

- A sweat chloride $\geq$ 60mmol/L by quantitative pilocarpine iontophoresis OR 2 identified CF-causing genetic mutations
- AND chronic sinopulmonary or gastrointestinal/nutritional abnormalities

2. Homozygous for *F508del* mutation with genotype confirmed at screening
3. FEV_1 ≥40% and <90% predicted of normal for age/gender/height at screening
4. Stable CF as judged by the investigator

Key Exclusion Criteria

1. History of any illness or condition that, in the opinion of the investigator, might have confounded the results of the study or posed an additional risk in administering study drug to patient
2. Any clinically significant lab abnormalities at screening that would interfere with study assessments or pose an undue risk for the patient
3. An acute upper or lower respiratory infection, pulmonary exacerbation, or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before Day 1 (first dose of study drug)
4. Pregnant, planning a pregnancy, breastfeeding, or not willing to follow contraception requirements
5. Hemoglobin <10 g/dL at screening
6. Abnormal liver function, at screening, defined as any 3 or more of the following: ≥3x upper limit of normal (ULN) serum aspartate transaminase (AST), ≥3x ULN serum alanine transaminase (ALT), ≥3x ULN gamma-glutamyl transpeptidase (GGT), ≥3x ULN serum alkaline phosphatase, or ≥2x ULN total bilirubin
7. Abnormal renal function at screening, defined as glomerular filtration rate (GFR) ≤50 mL/min/1.73 m^2 for subjects >18 years of age; ≤45 mL/min/1.73 m^2 for subjects age 12 to 17 years (inclusive)
8. History of solid organ or hematological transplantation
9. History of alcohol, medication or illicit drug abuse within 1 year before Day 1 (first dose of study drug)
10. Colonization with organisms associated with more rapid decline in pulmonary status (e.g. *Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus*)
11. History or evidence of cataract or lens opacity at screening

Patient removal criteria

Patients were discontinued from study drug treatment if any of the following criteria were met:

1. Pregnancy
2. A subject had 1 of the following and no alternative etiology (e.g., viral hepatitis or alcohol ingestion) for the elevated transaminase is identified, regardless of whether ALT or AST levels had improved:
   - An elevated ALT or AST of >8 × ULN
   - ALT or AST >5 × ULN for more than 2 weeks
   - An elevation of ALT or AST >3 × ULN in association with total bilirubin >2x ULN and/or clinical jaundice

3. Participation in another trial

Patients may have been discontinued from study drug treatment after discussion with the Vertex medical monitor if any of the following criteria were met:

1. A subject developed a medical condition that required prolonged concomitant therapy with a prohibited medication or prolonged interruption of the study drug.
2. A subject developed a life-threatening adverse event, or a serious adverse event (SAE) that placed them at immediate risk.
3. A subject was noncompliant with study requirements.
4. A subject had 1 of the following and no alternative etiology (e.g., viral hepatitis or alcohol ingestion) for the elevated transaminase is identified, regardless of whether ALT or AST levels had improved:
   - An elevated ALT or AST of >8 × ULN
   - ALT or AST >5 × ULN for more than 2 weeks
   - An elevation of ALT or AST >3 × ULN in association with total bilirubin >2x ULN and/or clinical jaundice
5. Development of a cataract of lens opacity

Aside from specifying that patients must be F508del homozygous, these eligibility criteria are similar to that used in the IVA monotherapy phase 3 development program.

Treatments

Treatment groups

LUM 600mg qD/IVA 250mg q12

Patients in this group received 3 tablets of LUM/IVA 200/83mg in the morning and 2 tablets of IVA 125mg in the evening. These patients also received 2 tablets of IVA/LUM 200/125 matching placebo to maintain treatment blinding in the morning and evening.

LUM 400mg/IVA 250mg q12

Patients in this group received 2 tablets of LUM/IVA 200/125 mg in the morning and evening. These patients also received 3 tablets of IVA/LUM 200/83mg matching placebo in the morning to maintain treatment blinding.

Placebo

These patients received 5 placebo tablets in the morning (3 tablets of LUM/IVA 200/83 matching placebo and 2 tablets of LUM/IVA 200/125 mg matching placebo) and 4 in the evening (2 tablets LUM/IVA 200/125 matching placebo and 2 tablets IVA 125mg matching placebo).

Concomitant/Restricted Medications:

All medications taken by the patients were recorded and all subjects were questioned about concomitant medications at all visits. Patients were kept on their stable CF medications. Restricted medications are summarized in Table 7.

Table 7. Study 809-103. Restricted Medications

	Study Period	
Restricted Medication/Food	**Screening Period**	**Treatment Period**
Certain fruits and fruit juices	None allowed within 14 days before the first dose of the study drug	None allowed
Moderate and strong CYP3A inducers	None allowed within 14 days before the first dose of the study drug	None allowed
Strong CYP3A inhibitors	None allowed within 14 days before the first dose of the study drug	None allowed

CYP: cytochrome P450
Note: The use of restricted medication in subjects with a medical need will be addressed on a case-by-case basis with the medical monitor.

Source: Module 5.3.5.1, 809-103 protocol version 5, table 10-1, pg 32

Efficacy Parameters

Primary endpoint

The primary endpoint was absolute change in ppFEV1 from baseline at week 24 (assessed as the average treatment effects at week 16 and 24). Baseline was defined as the most recent non-missing measurement collected prior to initial administration of study drug. The primary endpoint was analyzed in the full analysis set (FAS) which consisted of all patients who received at least one dose of study drug.

Key Secondary endpoints

Trial secondary endpoints included the following key secondary endpoints:

- Average relative change from baseline in ppFEV$_1$ at Week 16 and at Week 24
- Absolute change from baseline in body mass index (BMI) at Week 24
- Absolute change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score at Week 24
- Response defined as ≥5% increase in average relative change from baseline in percent predicted FEV$_1$ at Week 16 and at Week 24.
- Number of pulmonary exacerbations through Week 24

The CFQ-R is a disease-specific health-related quality of life measure for cystic fibrosis. It consists of generic and CF-specific scales (grouped into 3 modules and 9 domains) that measure quality of life, health perception, and symptoms over a 2-week recall period. It is available in age-appropriate formats, including a child age 6-11 interview format, a self-reported child age 12-13, an adolescent/adult form for ages >14 years, and a parent proxy format. The respiratory domain of CFQ-R has also been utilized independently to evaluate symptoms and perceptions of respiratory health and quality of life.

Pulmonary exacerbations were defined as a new or change in antibiotics therapy (IV, oral, or inhaled) for any 4 or more of the following symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough

- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature >38^{o}C
- Anorexia/weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10%
- Radiographic changes indicative of a pulmonary exacerbation

The exacerbation definition is consistent with that used in the pivotal trials in the IVA monotherapy development programs.

Other secondary endpoints
This trial also pre-specified other secondary endpoints which were as follows:

- Absolute change from baseline in BMI z-score at Week 24 for subjects <20 years old
- Absolute change from baseline in body weight at Week 24
- Time-to-first pulmonary exacerbation through Week 24
- Event of having at least 1 pulmonary exacerbation through Week 24
- Absolute change from baseline in EuroQol 3-Level (EQ-5D-3L) score at Week 24
- Absolute change from baseline in Treatment Satisfaction Questionnaire for Medication (TSQM) domains at Week 24

Sweat chloride was not assessed in this study.

Safety assessments
Monitored safety parameters included the following and were assessed as per Table 6.

- Spontaneous and elicited adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs
- Physical examinations
- Clinical laboratory evaluations
- Vital signs
- ECG
- Pregnancy testing
- Ophthalmologic exams were performed at screening

Ethics:
This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

Statistical Analysis

Analysis populations
The sponsor pre-specified 3 analysis populations. The full analysis set (FAS) consisted of all randomized patients who received study drug. These were categorized by planned treatment. This population was used for the primary analysis. The per protocol set (PPS) consisted of the FAS minus patients with major protocol deviations. Major protocol violations were defined as those that may have a substantial effect on the efficacy assessment. The PPS was used in sensitivity analyses. The safety set (SS) consisted of all patients who received study drug. This population was categorized by actual treatment.

Efficacy Analysis
The primary endpoint was analyzed using mixed model repeated measures (MMRM) in the FAS. Analysis of key secondary endpoints was similar to the primary endpoint. To control for type I error, Vertex used a hierarchal testing procedure. The testing hierarchy is as follows:

1) Average absolute change from baseline in $ppFEV_1$ at Week 16 and at Week 24,
2) Average relative change from baseline in $ppFEV_1$ at Week 16 and at Week 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) Response defined as ≥5% increase in average relative change from baseline in $ppFEV_1$ at Week 16 and at Week 24
6) Number of pulmonary exacerbations through Week 24.

For the other secondary endpoints, there were no corrections for multiplicity.

Protocol Amendments
There were three protocol amendments. The first amendment was submitted on July 25, 2013. The amendment was made in response to input from regulatory agencies. Relevant changes in Version 2.0 include modifying the primary endpoint from relative change from baseline in $ppFEV_1$ "through week 24" to "at week 24." Similar changes were also made to some secondary endpoints. The secondary endpoint of change from baseline in BMI z-score was also added to account for normal growth in children. In the second amendment submitted February 5, 2014, the most relevant change was swapping the key secondary endpoint of absolute change from baseline in $ppFEV_1$ at week 24 with the primary endpoint of relative change from baseline in $ppFEV_1$ at week 24. In addition, more frequent liver function testing was added. In the final amendment submitted February 24, 2014, the protocol was amended to clarify which patients were required to complete the safety follow-up visit. Overall, these amendments did not adversely impact interpretation of study data.

3.3.2 Efficacy and Safety Study 809-104

This multinational study was intended to provide replicate evidence of efficacy and safety for LUM/IVA compared to placebo. This study was performed from 4/11/2013-4/25/2014

Study title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination With Ivacaftor in Subjects Aged 12 Years and Older With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

This protocol was identical to VX12-809-103. This trial randomized 559 CF patients ≥12 years of age homozygous for the *F508del* mutation.

3.3.4 Safety Extension Study 809-105

This is the ongoing the safety extension of studies 809-102, 103 and 104. This study included 2 parts (A and B), however, only part A will be discussed as part A is most relevant for the proposed indication. This study was initiated on 10/24/2013.

Study title: A Phase 3, Rollover Study to Evaluate the Safety and Efficacy of Long-term Treatment with Lumacaftor in Combination with Ivacaftor in Subjects Ages 12 Years and Older with Cystic Fibrosis, Homozygous (part A) or Heterozygous (part B) for the *F508del* Mutation

Objectives
The primary objective of this extensions study was to evaluate the long-term safety and tolerability of LUM/IVA in CF patients homozygous (part A) or heterozygous (part B) for the *F508del* mutation.

Study Design and Conduct
Overview
This was a parallel-group, multicenter, uncontrolled extension study in CF patients homozygous or heterozygous for the *F508del* mutation and who participated in studies 809-102, 809-103, and 809-104. This study consisted of two parts, A and B. Part A included patients from study 809-103 and 809-104. Part A included a treatment cohort and an observational cohort. In the treatment cohort, patients who had completed study 809-103 and 809-104 were eligible to enroll. Patients who received LUM/IVA in the previous studies continued on the same treatment. Patients who had received placebo in the previous studies were randomized to receive LUM 600mg qD/IVA 250mg q12 or LUM 400mg/IVA 250mg q12 for 96-weeks.

Efficacy assessments
Primary endpoint

There were no primary efficacy endpoints as this was primarily a safety study.

Secondary endpoints
This study included multiple efficacy related secondary endpoints. These included endpoints related to ppFEV$_1$, BMI, weight, exacerbation, and CFQ-R-respiratory domain scores. There were no sweat chloride related endpoints.

Safety assessments
Monitored safety parameters were similar to previous studies

Ethics:
This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

Protocol Amendments
The study protocol was amended twice. In the first amendment, submitted on February 5, 2014, additional liver function test monitoring was added. The second amendment, submitted on September 22, 2014. This amendment updated the protocol to reflect the Applicant's evaluation of the efficacy data in *F508de*l heterozygous patients. Based on the Applicant's analysis, there appeared to be no overall evidence of benefit in these patients. As such, the protocol stated that all part B patients must be notified and recommended that these patients discontinue.

3.3.3 Safety and Efficacy Study 770-104 (ivacaftor monotherapy)

This study evaluated the safety and efficacy of IVA monotherapy in *F508del* homozygous patients. As the primary efficacy/safety studies (809-103 and 809-104) included LUM/IVA and placebo control arms, but did not include IVA monotherapy controls, results from this study were submitted to provide context for the magnitude of the LUM/IVA treatment effect. This study included 2 parts (A and B). Part A was double-blind, randomized, placebo controlled and part B was a 96-week open-label extension that patients who demonstrated a clinical response to IVA monotherapy were eligible to enroll in. A total of 33 (29%) of the CF patients who received IVA and 5 (18%) who received placebo were eligible to roll over into Part B. However, the open-label extension was discontinued following an interim analysis at week 40 from which the Applicant concluded that efficacy was not sustained. This review will focus on the placebo-controlled Part A. This study was performed from 9/29/09-7/20/11.

Study title: A Phase 2, Randomized, Double-blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Safety and Efficacy of VX-770 in Patients Aged 12 Years and Older with Cystic Fibrosis Who Are Homozygous for the *F508del-CFTR* Mutation

Objectives

Primary

- To evaluate the safety and efficacy of 16 weeks of treatment with IVA in CF patients who are *F508del* homozygous.

Secondary

- To investigate the pharmacokinetics (PK) of ivacaftor and its metabolites

Study Design and Conduct

Overview

This was a randomized, double-blind, placebo-controlled, parallel-group multi-center study (Part A) with an open-label extension (Part B) of IVA 150mg q12 hours, in patients with CF who were *F508del* homozygous. Part A included a screening period (28-days), run-in period (14-days), and 16-week treatment period. During the treatment period patients were seen in clinic on day 1, day 15, week 4, 8, and 12. In part A, the Applicant planned to enroll approximately 120 patients who would be randomized 4:1 (IVA:placebo).

Trial population

Part A of this trial enrolled 140 CF patients ≥12 years of age who were homozygous for the *F508del* mutation (28 placebo, 112 IVA). The inclusion and exclusion criteria were largely similar to trials 809-103/104, except that the $ppFEV_1$ based inclusion criteria did not specify an upper limit. This study allowed for baseline $ppFEV_1$ of ≥40%, whereas studies 809-103 and 809-104, allowed for a baseline $ppFEV_1$ of ≥40% and <90%. Additionally, use of hypertonic saline within 4-weeks of prior to study drug dosing was also an exclusion criterion in this study.

Treatments

Treatment groups included IVA 150mg q12 hours and placebo for 16-weeks.

Concomitant/Restricted Medications:

All medications taken by the patients were recorded and all subjects were questioned about concomitant medications at all visits. Patients were able to be maintained kept on all their stable CF medications with the exception of inhaled hypertonic saline which was prohibited during the treatment period in part A, but allowed in part B.

Efficacy Parameters

Primary endpoint

Part A

The primary endpoint was absolute change in $ppFEV_1$ from baseline through week 16. The primary endpoint was analyzed in the full analysis set (FAS) which consisted of all patients who received at least one dose of study drug.

Key Secondary endpoints

Secondary endpoints included the following:

- Change from baseline in sweat chloride through 16

- Change from baseline in Cystic Fibrosis Questionnaire–Revised (CFQ-R) respiratory domain score through Week 16
- Rate of change in weight through week 16

This study also included a tertiary endpoint of pulmonary exacerbations through week 16, where exacerbations were defined as in studies 809-103 and 809-104

Safety assessments
Monitored safety parameters were similar to previous studies.

Ethics:
This trial was conducted according to the principles of Good Clinical Practice, the World Medical Association Declaration of Helsinki (1989), and ICH guidelines. An institutional review board reviewed and approved this protocol. No changes were made without the IRB's approval.

Statistical Analysis
The sponsor pre-specified 3 analysis populations. The full analysis set (FAS), per protocol set (PPS), and safety set (SS) were defined as in studies 809-103 and 809-104. The primary endpoint was analyzed using mixed model repeated measures (MMRM) in the FAS.

Note that no formal sample size or power analysis was performed for this study. The 120 sample was based on clinical considerations and was chosen primarily to provide additional safety information for IVA.

Protocol Amendments
The study protocol was amended 8 times. These amendments were primarily clarifying or administrative in nature, or increased the safety monitoring of the program. Overall, these amendments did not adversely impact interpretation of study data.

4 Review of Efficacy

Efficacy Summary

To support the efficacy of the LUM/IVA FDC in *F508del* homozygous patients, the Applicant submitted replicate 24-week clinical studies (809-103 and 809-104), in which 2 LUM/IVA combination doses were compared to placebo; and study 770-104, the only clinical study to assess the effect of IVA alone in *F508del* homozygous CF patients. Study 770-104 was included to allow for comparisons of the IVA monotherapy treatment effect to the LUM/IVA treatment effect observed in studies 809-103 and 809-104, as those studies did not include an IVA monotherapy arm.

Across both LUM/IVA FDC studies, both LUM/IVA doses demonstrated similar statistically significant increases in absolute ppFEV$_1$ (the primary endpoint) compared to

placebo, ranging from 2.7-3.0% for the proposed dose of LUM 400mg/IVA 250mg q12. These studies also included five key secondary endpoints, which were analyzed in a hierarchical manner as follows: 1) relative change in $ppFEV_1$, 2) absolute change in BMI, 3) change in CFQ-R-respiratory domain score, 4) response rate (% of patients with a ≥5% relative change in $ppFEV_1$), and 5) number of exacerbations. For these endpoints, LUM/IVA failed to demonstrate a significant improvement in BMI or CFQ-R-respiratory domain. Positive treatment effects were observed for relative change in $ppFEV_1$, which were statistically significant, and for response rate and number of exacerbations.

With regard to IVA monotherapy (770-104), while there was a small numerical increase in $ppFEV_1$ (the primary endpoint) compared to placebo with a point estimate of 1.7%, it was not statistically significant. For the secondary endpoints of change in sweat chloride, weight, and CFQ-R-respiratory domain scores, the effect size was also small and only sweat chloride had a p-value of <0.05. Results for exacerbation rate and BMI were consistent with primary and secondary analyses.

When comparing the nominal treatment effect of IVA alone and LUM/IVA from study 770-104 to studies 809-103 and 809-104, point estimates were numerical similar for the shared efficacy variables with 95% confidence intervals demonstrating considerable overlap (Table 17). This would suggest that the both products have a similar treatment effect in the *F508del* population. While study 770-104 did not demonstrate statistically significant results, this may have been more related to study design rather than lack of effect, as 770-104 was not powered to demonstrate efficacy and was much smaller than studies 809-103 and 809-104. As such, had study 770-104 been powered and sized as the much larger LUM/IVA studies were, it is possible that statistical significance would have been achieved with a similar effect size. While LUM/IVA offers a treatment benefit above placebo, IVA alone may also have a similar benefit, and whether LUM/IVA offers an additional benefit over IVA alone is uncertain.

Table 8. Treatment effect for LUM 400mg/IVA 250mg q12 and IVA 150mg q12 versus placebo in *F508del* homozygous CF patients

	# of patients [a]		Δ from baseline **IVA 150 mg q12** v. placebo through week 16 (95% CI)			
Study Number	**Placebo**	**IVA**	**ppFEV$_1$ (%)**	**CFQR-RD (score)**	**BMI (kg/m^2)**	**Exacerbation (rate ratio)**
Study 770-104	28	112	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-0.07 (-0.4, 0.2)	0.68 (0.3, 1.4)
	Placebo	**LUM/IVA**	Δ from baseline **LUM 400mg/IVA 250mg q12** v. placebo at week 24 (95% CI)			
Study 809-103	184	182	2.6% (1.2, 4.0)[b]	1.5 (-1.7, 4.7)	0.1 (-0.1, 0.2)	0.7 (0.5, 0.9)
Study 809-104	187	187	3.0% (1.6, 4.4)[b]	2.9 (-0.3, 6.0)	0.4 (0.2, 0.5)	0.6 (0.4, 0.8)

[a]Full Analysis Set
[b]assessed as the average of the treatment effect at week 16 and 24
Source: Module 5.3.5.1; Study 770-104 CSR; tables 11-11, 11-14, 11-16, 11-18; pp.131, 138,140, 143
Module 2.7.3; Summary of Clinical Efficacy; table 16; pp.62-63

In order to further explore this uncertainty, the FDA performed comparative statistical analyses between IVA monotherapy and LUM 400mg/IVA 250 mg q12, the proposed dose. Based on these analyses, it could not be concluded with any level of confidence that the LUM/IVA treatment effect was not equivalent to IVA monotherapy (see Part B of the FDA Statistical Review document by David Petullo, MS)

4.1 Indication

The proposed indication for this fixed dose combination is for the treatment of cystic fibrosis (CF) in patients age 12 years and older who homozygous for the *F508del* mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The proposed dose for LUM/IVA is 400/250mg q12 hours.

4.1.1 Methods

Support for efficacy in *F508del* homozygous CF patients is primarily derived from two replicate 24-week studies (809-103 and 809-104) where 2 doses of LUM/IVA were compared to placebo; and from study 770-104 from the ivacaftor monotherapy program which assessed the effect of IVA alone in *F508del* homozygous CF patients. As study 770-104 is used to help determine the benefit of the LUM/IVA combination over ivacaftor monotherapy, relevant efficacy data from study 770-104 will also be presented.

4.1.2 Demographics

Studies 809-103 and 809-104
Patient demographic data and baseline characteristics for studies 809-103 and 809-104 are summarized in Table 9. The patients in both studies were predominantly white, aged ≥18 years, and approximately equally split between males and females. Baseline weights ranged between 58-60kg with BMI's of approximately 21kg/m^2. Baseline

$ppFEV_1$ ranged between 60-61% with the majority of patients with a $ppFEV_1$ between 40% and 70%. Across treatment groups and across studies, these parameters were fairly similar.

Table 9. Studies 809-103 and 809-104. Patient Demographics

	Study 809-103			Study 809-104		
	Placebo N=184	LUM 600qd IVA 250 q12 N=183	LUM 400/ IVA 250 q12 N=182	Placebo N=187	LUM 600qd IVA 250 q12 N=185	LUM 400/ IVA 250 q12 N=187
Sex, n (%)						
Male	100 (54.3)	97 (53.0)	98 (53.8)	90 (48.1)	89 (48.1)	89 (47.6)
Female	84 (45.7)	86 (47.0)	84 (46.2)	97 (51.9)	96 (51.9)	98 (52.4)
Age (years)						
Mean	25.0	24.7	25.5	25.7	24.3	25.0
Median	22	23	23.5	24	23	24
Age groups						
12 to <18	53 (28.8)	53 (29.0)	52 (28.6)	43 (23.0)	43 (23.2)	46 (24.6)
≥18	131 (71.2)	130 (71.0)	130 (71.4)	144 (77.0)	142 (76.8)	141 (75.4)
Race, n(%)						
White	183 (99.5)	180 (98.4)	176 (96.7)	186 (99.5)	183 (98.9)	185 (98.9)
Black	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	1 (0.5)	0 (0.0)
Asian	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)
Not Collected per local regulations	1 (0.5)	1 (0.5)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.5)	2 (1.1)	0 (0.0)	1 (0.5)	2 (1.1)
Weight (kg)						
Mean	59.1	58.6	60.6	58.5	58.2	59.2
Median	57	58	60	57	58	58
BMI (kg/m2)						
Mean	21.0	21.1	21.7	21.0	21.0	21.3
Median	20.8	21.0	21.2	20.9	20.7	21.1
Percent predicted FEV_1						
Mean	60.5	61.2	60.5	60.4	60.5	60.6
Median	60.4	61.8	58.7	60.5	60.6	61.5
Percent predicted FEV_1 at baseline, 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)	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	1 (0.5)	1 (0.5)	3 (1.6)	2 (1.1)	2 (1.1)

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

Study 770-104

Patient demographic data and baseline characteristics for study 770-104 are summarized in Table 10. Patients were predominantly white, aged ≥18 years, and

approximately equally split between males and females. Baseline mean weights were higher in the placebo group compared to the IVA 150mg q12 group, however, BMI's were similar across groups. Mean baseline $ppFEV_1$ values were similar between treatment groups and approximately a third of patients had mean $ppFEV_1$ values greater than 90%.

Table 10. 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
Median	24	19.5	21
Age groups			
12 to <18	6 (21.4)	44 (39.3)	50 (35.7)
≥18	22 (78.6)	68 (60.7)	90 (64.3)
Race, n(%)			
White	28 (100.0)	111 (99.1)	139 (97.9)
Black	0	1 (0.9)	
Asian			
Weight (kg)			
Mean	63.2	58.2	59.2
Median	64.9	55.9	56.4
BMI (kg/m2)			
Mean	22.2	21.2	21.4
Median	21.5	20.35	20.6
Percent predicted FEV_1			
Mean	74.8	79.7	78.7
Median	67	79	79
Percent predicted FEV_1 at baseline, 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)

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

4.1.3 Subject Disposition

Studies 809-103 and 809-104

Patient disposition data is summarized in Table 11. In both studies, more patients in the LUM/IVA treatment arms discontinued treatment and from the study compared to placebo. This was primarily driven by adverse events (see section 5.3.3 Dropouts and/or Discontinuations).

Table 11. Studies 809-103/104. Patient Disposition

	Study 809-103			Study 809-104		
	Placebo N=184	LUM 600qd IVA 250 q12 N=183	LUM 400/ IVA 250 q12 N=182	Placebo N=187	LUM 600qd IVA 250 q12 N=185	LUM 400/ IVA 250 q12 N=187
Completed Treatment	180 (97.8)	172 (94.0)	172 (94.5)	182 (97.3)	176 (95.1)	172 (92.0)
Discontinued Treatment	4 (2.2)	11 (6.0)	10 (5.5)	5 (2.7)	9 (4.9)	15 (8.0)
Adverse event	4 (2.2)	8 (4.4)	6 (3.3)	2 (1.1)	6 (3.2)	11 (5.9)
Subject refusal	0	2 (1.1)	1 (0.5)	2 (1.1)	1 (0.5)	1 (0.5)
Not meet eligibility criteria	0	0	2 (1.1)	0	0	0
Non-compliance	0	0	0	0	0	2 (1.1)
Physician Decision	0	0	1 (0.5)	0	0	0
Pregnancy	0	1 (0.5)	0	0	0	0
Completed Study	182 (98.9)	179 (97.8)	176 (96.7)	185 (98.9)	180 (97.3)	180 (96.3)
Discontinued Study	2 (1.1)	4 (2.2)	6 (3.3)	2 (1.1)	5 (2.7)	7 (3.7)
Adverse event	2 (1.1)	1 (0.5)	2 (1.1)	1 (0.5)	2 (1.1)	2 (1.1)
Withdrawal of consent	0	3 (1.6)	2 (1.1)	1 (0.5)	2 (1.1)	2 (1.1)
Non-compliance	0	0	0	0	0	1 (0.5)
Physician decision	0	0	1 (0.5)	0	0	0
Other	0	0	1 (0.5)	0	1 (0.5)	2 (1.1)

Source: Module 2.7.3; Summary of Clinical Efficacy; table 11; pg 54

While there were differences in treatment and study discontinuations between LUM/IVA and placebo groups, overall, very few patients discontinued. Of the 1108 patients who receive study drug, only 54 (4.9%) discontinued study treatment and only 26 (2.3%) discontinued from the study.

Study 770-104

Patient disposition data for the placebo controlled portion (part A) of study 770-104 is summarized in Table 12. Disposition data for the open-label extension (part B) is not provided as it was prematurely discontinued. Overall treatment discontinuations were low and similar percentages of patients across treatment groups completed the 16-week treatment period. The most common reason for treatment discontinuation was adverse events. Compared to studies 809-103 and 809-104, a similar percentage of patients completed treatment.

Table 12. Study 770-104. Patient disposition (part A)

	Study 770-104		
	Placebo N=28	IVA 150mg q12 N=112	Overall N=140
Completed 16-weeks of treatment	26 (92.9)	104 (92.9)	130 (92.9)
Discontinued Treatment	2 (7.1)	8 (7.1)	10 (7.1)
Adverse event	2 (7.1)	3 (2.7)	5 (3.6)
Lost to follow-up	0	1 (0.9)	1 (0.7)
Non-compliance	0	2 (1.8)	2 (1.4)
Prohibited medication	0	1 (0.9)	1 (0.7)
Other	0	1 (0.9)	1 (0.7)

Source: Module 5.3.5.1; Study 770-104 CSR; table 10-1; pg111

4.1.4 Analysis of Efficacy

Studies 809-103/104

Primary Endpoint

The primary endpoint in both studies 809-103 and 809-104 was absolute change from baseline in ppFEV$_1$ at week 24. This was assessed as the average of the treatment effects at weeks 16 and 24. Percent predicted FEV$_1$ is an appropriate endpoint for a disease where the major cause of death is respiratory failure. Similar endpoints were also used in the ivacaftor monotherapy development programs.

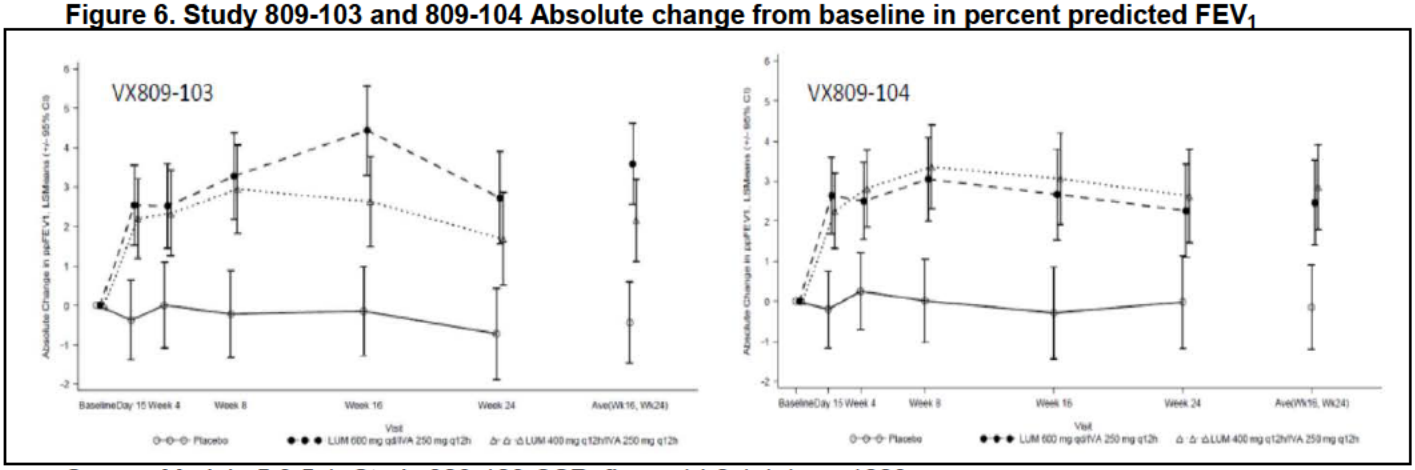
In both trials, both LUM/IVA doses demonstrated a statistically significant improvement in ppFEV$_1$ when compared to placebo for the primary endpoint. The treatment effect was similar between doses, and was also similar when compared to the separate week 16 and at week 24 results. Results for the primary endpoint are summarized in Table 13 and in Figure 6.

Table 13. Study 809-103 and 809-104. Primary Endpoint. Absolute change from baseline in percent predicted FEV_1 at week 24[a]

	Study 809-103			Study 809-104		
	Placebo N=184	LUM 600qd IVA 250 q12 N=183	LUM 400/ IVA 250 q12 N=182	Placebo N=187	LUM 600qd IVA 250 q12 N=185	LUM 400/ IVA 250 q12 N=187
Absolute change from baseline in ppFEV1						
Baseline						
N	181	182	180	185	184	185
Mean	60.5	61.2	60.5	60.4	60.5	60.6
Absolute Δ from baseline	-0.4	3.6	2.2	-0.2	2.5	2.9
Difference from placebo	--	4.0 (2.6, 5.4)	2.6 (1.2, 4.0)	--	2.6 (1.2, 4.1)	3.0 (1.6, 4.4)

[a]assessed as the averaged of the treatment effects at week 16 and 24
Source: Module 5.3.5.1; Study 809-103 CSR; table 11-3; pg144
Module 5.3.5.1; Study 809-104 CSR; table 11-4; pg157

Figure 6. Study 809-103 and 809-104 Absolute change from baseline in percent predicted FEV_1



Source: Module 5.3.5.1; Study 809-103 CSR; figure 14.2.1.1.1; pg 1003
Module 5.3.5.1; Study 809-104 CSR; figure 14.2.1.1.1; pg 1002

While there was a statistically significant improvement for the primary endpoint, it was modest, with a range of 2.6-3.0% for the proposed dose (LUM 400mg/IVA 250mg q12). Given the modest effect size in terms of $ppFEV_1$ demonstrated for LUM/IVA, while these results are statistically significant, it is uncertain if it represents a clinically meaningful benefit above placebo. As such, determination of efficacy may rely in large part on support from other clinically relevant endpoints, such BMI/weight and exacerbation

Secondary Endpoints
The key secondary endpoints for these studies were as follows:

1. Average relative change from baseline in $ppFEV_1$ at Week 16 and at Week 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. Percent of patients with a ≥5% increase in average relative change from baseline in percent predicted FEV_1 at Week 16 and at Week 24 (response rate).
5. Number of pulmonary exacerbations through Week 24

To control for type I error, the key secondary endpoints were tested hierarchically in the order listed above.

Results for the first key secondary endpoint of average relative change in ppFEV$_1$ at week 16 and 24 were consistent with the primary endpoint. Statistically significant improvements were observed in both LUM/IVA doses when compared to placebo.

For BMI, the results were not consistent between studies. In study 809-104, the change from baseline in BMI at week 24 compared to placebo for both dose groups was approximately 0.4 kg/m^2 and was statistically significant. This corresponded with a weight gain versus placebo of approximately 1-1.1kg. In contrast, in study 809-103, change from baseline versus placebo in BMI ranged from 0.13-0.16 kg/m^2 across LUM/IVA groups and was not statistically significant. This corresponded to a weight gain versus placebo of approximately 0.3 to 0.4kg. Based on these BMI data, LUM/IVA did not demonstrate a consistent clinical benefit in terms of BMI at either dose.

For the key secondary endpoint of change from baseline in CFQ-R respiratory domain score at week 24, the LUM 600mg qD/IVA 250mg q12 dose in study 809-103 demonstrated a treatment effect of 3.9 with a p-value was <0.025. However, this was considered nominal due to earlier failure in the analysis hierarchy. This is also less than the MCID of 4. For the remaining doses across both studies, all values were below the MCID. As with BMI, for CFQR-respiratory domain score, neither LUM/IVA dose demonstrated a consistent clinical benefit above placebo.

Results for BMI and CFQ-R-respiratory domain are summarized in Table 14.

Table 14. Studies 809-103 and 809-104. Key secondary endpoints. Relative change in $ppFEV_1$, absolute change in BMI, and absolute change in CFQR-respiratory domain.

	Study 809-103			Study 809-104		
	Placebo N=184	LUM 600qd IVA 250 q12 N=183	LUM 400/ IVA 250 q12 N=182	Placebo N=187	LUM 600qd IVA 250 q12 N=185	LUM 400/ IVA 250 q12 N=187
Average Relative Change from baseline in $ppFEV_1$ at week 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 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)	--	0.16 (-0.0, 0.4)	0.13 (-0.01, 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)	--	3.9 (0.7, 7.1)[a]	1.5 (-1.7, 4.7)[a]	--	2.2 (-0.9, 5.3)	2.9 (-0.3, 6.0)

[a]not significant based on earlier failure in analysis hierarchy
Source: Module 2.7.3; Summary of Clinical Efficacy; table 16, pp62-63

With regard to the remaining key secondary endpoints, in both studies, patients in both LUM/IVA dose groups in both studies had a higher response rate compared to placebo as demonstrated by percent of patients who had ≥5% relative change in $ppFEV_1$ ('responders'); and pulmonary exacerbations occurred at a lower rate in LUM/IVA groups compared to placebo. While there was a positive treatment effect in term of responders and exacerbations, due to earlier failure in the analysis hierarchy, these results were not considered statistically significant. However, these data are still suggestive of efficacy relative to placebo, particularly the exacerbation endpoint. These data are summarized in Table 15.

Table 15. Studies 809-103 and 809-104. Key Secondary Endpoints. Patients with ≥5% improvement in $ppFEV_1$ and Pulmonary Exacerbation

	Study 809-103			Study 809-104		
	Placebo N=184	LUM 600qd IVA 250 q12 N=183	LUM 400/ IVA 250 q12 N=182	Placebo N=187	LUM 600qd IVA 250 q12 N=185	LUM 400/ IVA 250 q12 N=187
Average relative change ≥5% increase on $ppFEV_1$ averaged at week 16 and 24 (response rate)						
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)[a]	--	2.9 (1.9, 4.6)	2.1 (1.3, 3.3)	--	3.0 (1.9, 4.6)	2.4 (1.5, 3.7)
Number of pulmonary exacerbations						
Patients with events	73	55	55	88	68	54
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)[a]	--	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	--	0.7 (0.5, 0.9)	0.6 (0.4, 0.8)

[a]nominal p-value due to earlier failure in analysis hierarchy
Source: Module 2.7.3; Summary of Clinical Efficacy; table 16, pp62-63

Overall, the data from the key secondary endpoints were inconsistent. While the relative change from baseline in $ppFEV_1$ was consistent with the primary endpoint, the key secondary endpoints of BMI and CFQ-R respiratory score were not. And while both the responder and exacerbation endpoints numerically favored both doses of LUM/IVA compared to placebo in both studies, neither were statistically significant due to earlier failures in the analysis hierarchy.

Other secondary endpoints included change from baseline in BMI for age z-scores (patients <20years), change from baseline in bodyweight, and time to first exacerbation. The results were consistent with those for the related key secondary endpoints.

Across both LUM/IVA FDC studies, both doses demonstrated similar statistically significant increases in absolute ppFEV1 (the primary endpoint) compared to placebo, ranging from 2.7-3.0% for the proposed dose of LUM 400mg/IVA 250mg q12. For the key secondary endpoints, LUM/IVA failed to demonstrate consistent significant improvement in BMI or CFQ-R-respiratory domain. Positive treatment effects were observed for relative change in ppFEV1, which were statistically significant. Positive trends were also observed for number of exacerbations, however, these results were not statistically significant due to earlier failure in the analysis hierarchy.

Study 770-104

The primary endpoint (absolute change from baseline) was the same as for the LUM/IVA studies albeit assessed through week 16 rather than as the average of the week 16 and 24 week values. When IVA 150mg q12 was compared to placebo, the difference was relatively small and not statistically significant with a point estimate of 1.7% and a 95% confidence interval of (-0.6, 4.1). The secondary endpoints in 770-104 were change from baseline in sweat chloride, CFQ-R respiratory domain scores, and

change in weight through week 16. Additionally, relative change from baseline $ppFEV_1$, change from baseline in BMI, and exacerbation rate were also assessed through week 16. Except for the pharmacodynamic endpoint of sweat chloride, differences from placebo were not significant. The magnitude of the treatment effect across these assessments was relatively small, though the majority trended in the positive direction. These data are summarized in Table 16.

Table 16. Study 770-104. Primary, Secondary, and Other Efficacy Variables.

	Study 770-104	
	Placebo N=28	**IVA 150mg q12 N=112**
Primary Endpoint		
Absolute change from baseline in $ppFEV_1$ through week 16		
Δ from baseline through	-0.2	1.5
Difference from placebo	--	1.7 (-0.6, 4.1)
Secondary Endpoints		
Change from baseline in sweat chloride through week 16 (mmol/L)		
Δ from baseline through	0.1	-2.7
Difference from placebo	--	-2.9 (-5.6, -0.2)
Change from baseline in CFQR-respiratory domain through week 16 (score)		
Δ from baseline through week 16	-1.44	-0.12
Difference from placebo	--	1.3 (-2.9, 5.6)
Change from baseline in weight through week 16 (kg)		
Δ from baseline through week 16	0.9	0.78
Difference from placebo	--	-0.2 (-1.1, 0.7)
Other Efficacy Variables		
Relative change from baseline $ppFEV_1$ through week 16		
Relative Δ from baseline at week 16	0.13	2.6
Difference from placebo	--	2.4 (-0.9, 5.8)
Change from baseline BMI through week 16 (kg/m^2)		
Δ from baseline at week 16	0.26	0.19
Difference from placebo	--	-0.07 (-0.4, 0.2)
Number of pulmonary exacerbations		
Patients with events	8	20
Number of events	10	25
Rate ratio vs placebo		0.68 (0.33, 1.4)

Source: NDA 203188 clinical review; table 16; pg 72
Module 5.3.5.1; Study 770-104 CSR; tables 11-16, 11-18, 11-21; pp140, 143, and 148

When these endpoints were assessed at the individual time-points during the study, the results were consistent with the through week 16 data.

Overall, the results from LUM/IVA studies 809-103 and 809-104 demonstrate that, compared to placebo, LUM 400mg/IVA 250mg q12 had a small, but statistically significant effect in terms of the primary endpoint of absolute change from baseline in $ppFEV_1$. For the secondary endpoints, statistically significant increases in relative change in ppFEV1 were observed with nominal improvements in exacerbation, though not statistically significant due the hierarchical testing strategy used by the Applicant.

There was no consistent significant benefit in CFQR-respiratory domain scores or BMI. In contrast to studies 809-103 and 809-104, while the results for IVA alone study 770-104 demonstrated small positive effects for the majority of efficacy variables reviewed, none were statistically significant. Although it should be noted that 770-104 was not powered to for efficacy.

When comparing the nominal treatment effect of IVA alone and LUM/IVA from study 770-104 to studies 809-103 and 809-104, point estimates were numerical similar for the shared efficacy variables with 95% confidence intervals demonstrating considerable overlap (Table 17). This would suggest that the both products have a similar treatment effect in the *F508del* population. While study 770-104 did not demonstrate statistically significant results, this may have been more related to study design rather than lack of effect, as study 770-104 was not powered to demonstrate efficacy and was much smaller than studies 809-103 and 809-104. As such, had study 770-104 been powered and sized as the much larger studies 809-103 and 809-104 were, it is possible that statistical significance would have been achieved with a similar effect size. While LUM/IVA offers a treatment benefit above placebo, IVA alone may also have a similar benefit, and whether LUM/IVA offers an additional benefit over IVA alone is uncertain.

Table 17. Treatment effect for LUM 400mg/IVA 250mg q12 and IVA 150mg q12 versus placebo in *F508del* homozygous CF patients

	# of patients [a]		Δ from baseline **IVA 150 mg q12** v. placebo through week 16 (95% CI)			
Study Number	**Placebo**	**IVA**	**ppFEV$_1$ (%)**	**CFQR-RD (score)**	**BMI (kg/m^2)**	**Exacerbation (rate ratio)**
Study 770-104	28	112	1.7% (-0.6, 4.1)	1.3 (-2.9, 5.6)	-0.07 (-0.4, 0.2)	0.68 (0.3, 1.4)
	Placebo	**LUM/IVA**	Δ from baseline **LUM 400mg/IVA 250mg q12** v. placebo at week 24 (95% CI)			
Study 809-103	184	182	2.6% (1.2, 4.0)[b]	1.5 (-1.7, 4.7)	0.1 (-0.1, 0.3)	0.7 (0.5, 0.9)
Study 809-104	187	187	3.0% (1.6, 4.4)[b]	2.9 (-0.3, 6.0)	0.4 (0.2, 0.5)	0.6 (0.4, 0.8)

[a]Full Analysis Set
[b]assessed as the average of the treatment effect at week 16 and 24
Source: Module 5.3.5.1; Study 770-104 CSR; tables 11-11, 11-14, 11-16, 11-18; pp.131, 138,140, 143
Module 2.7.3; Summary of Clinical Efficacy; table 16; pp.62-63

In order to further explore this uncertainty, FDA statisticians performed comparative statistical analyses between IVA monotherapy and LUM 400mg/IVA 250 mg q12, the proposed dose. As the studies included different length treatment periods, analyses were perform at the week 16 landmark, as that time-point was common to all studies. The analyses also took into account small differences in baseline ppFEV$_1$ inclusion criteria between the IVA alone and LUM/IVA studies by removing from the analyses patients with a baseline ppFEV$_1$ of >90%. Analyses were also performed including all patients regardless of baseline ppFEV1 with similar results. Based on these analyses, it could not be concluded with any level of confidence that the LUM/IVA treatment effect

was not equivalent to IVA monotherapy (see Part B of the FDA Statistical Review document by David Petullo, MS).

4.1.5 Subpopulations

FDA statisticians performed subgroup analyses based on age, sex, ppFEV$_1$, and region (Table 18). For the primary endpoint, for each subgroup, the results favored both dose of LUM/IVA over placebo. These analyses did not suggest any meaningful differences between any of the subgroups.

Table 18. Study 809-103 and 809-104. Subgroup Analyses

Statistics	Study 809-103			Study 809-104		
	Placebo N=184	LUM 600qD IVA 250 q12 N=183	LUM 400/ IVA 250 q12 N=182	Placebo N=187	LUM 600 qD IVA 250 q12 N=185	LUM 400/ IVA 250mg q12 N=187
Absolute change from baseline in ppFEV1 at 24[a]						
Sex (Male)						
N	96	93	94	87	87	84
LS mean (SE)	-0.5 (0.7)	3.1 (0.7)	2.1 (0.7)	-0.5 (0.8)	2.6 (0.8)	3.2 (0.8)
LS mean difference (95% CI)	--	3.7 (1.7, 5.6)	2.6 (0.7, 4.6)	--	3.1 (0.9, 5.1)	3.8 (1.5, 6.0)
Sex (Female)						
N	84	83	78	96	94	96
LS mean (SE)	-0.3 (0.8)	4.2 (0.8)	2.3 (0.8)	0.1 (0.7)	2.3 (0.7)	2.5 (0.7)
LS mean difference (95% CI)	--	4.5 (2.4, 6.5)	2.6 (0.6, 4.7)	--	2.2 (0.3, 4.1)	2.32 (0.4, 4.2)
Age (≥12 to <18 years)						
N	49	51	49	42	42	44
LS mean (SE)	0.5 (1.2)	4.8 (1.2)	3.7 (1.2)	0.8 (1.3)	2.7 (1.3)	2.4 (1.3)
LS mean difference (95% CI)	--	5.2 (1.9, 8.6)	4.1 (0.8, 7.5)	--	2.0 (-1.7, 5.6)	1.7 (-2.0, 5.3)
Age (≥18 years)						
N	131	125	123	141	139	136
LS mean (SE)	-0.6 (0.5)	3.0 (0.6)	1.4 (0.6)	-0.7 (0.6)	2.1 (0.6)	2.8 (0.6)
LS mean difference (95% CI)	--	3.6 (2.1, 5.1)	2.0 (0.6, 3.5)	--	2.8 (1.3, 4.4)	3.5 (1.9, 5.0)
$ppFEV_1$ at Screening (<70%)						
N	123	115	117	121	118	122
LS mean (SE)	-0.1 (0.6)	3.4 (0.6)	2.9 (0.6)	-0.9 (0.7)	2.1 (0.7)	2.7 (007)
LS mean difference (95% CI)	--	3.4 (1.8, 5.1)	3.0 (1.3, 4.6)	--	3.1 (1.4, 4.8)	3.6 (1.9, 5.2)
$ppFEV_1$ at Screening (≥70%)						
N	49	59	52	57	59	56
LS mean (SE)	-1.0 (1.1)	4.5 (1.0)	1.2 (1.1)	1.1 (1.0)	2.4 (1.0)	2.7 (1.0)
LS mean difference (95% CI)	--	5.5 (2.6, 8.4)	2.2 (-0.8, 5.2)	--	1.4 (-1.5, 4.2)	1.6 (-1.3, 4.5)
Region (North America)						
N	99	95	87	120	116	108
LS mean (SE)	0.00 (0.7)	3.4 (0.7)	1.8 (0.8)	-0.7 (0.7)	2.4 (0.7)	2.9 (0.7)
LS mean difference (95% CI)	--	3.4 (1.5, 5.4)	1.8 (-0.2, 3.7)	--	3.11 (1.3, 5.0)	3.6 (1.8, 5.5)
Region (Europe)						
N	68	62	69	47	56	55
LS mean (SE)	-1.4 (0.9)	3.7 (0.9)	3.0 (0.9)	0.5 (1.0)	1.6 (0.9)	2.5 (1.0)
LS mean difference (95% CI)	--	5.1 (2.6, 7.5)	4.3 (20., 6.7)	--	1.1 (-1.6, 3.8)	2.1 (-0.6, 4.7)
Region (Australia)						
N	13	19	16	16	9	17
LS mean (SE)	0.4 (1.8)	4.3 (1.3)	0.7 (1.5)	1.3 (1.7)	7.9 (2.3)	3.7 (1.7)
LS mean difference (95% CI)	--	3.8 (-0.5, 8.1)	0.3 (-4.1, 4.7)	--	6.6 (1.0, 12.3)	2.4 (-2.5, 7.2)

[a]assessed as the average of the treatment effects at weeks 16 and 24
Source: FDA analysis

4.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

Studies 809-103 and 809-104 included two doses of LUM/IVA (LUM 600mg qD/IVA 250mg q12 and LUM 400mg/IVA 250mg q12). The Applicant has proposed the LUM 400mg/IVA 250mg q12 hour dose. Between the two studies doses, there were no large differences between in terms of efficacy or safety which would make one dose superior to the other. However, because of the different presentation (lack of need for separate ivacaftor only tablets), the LUM 400mg/IVA 250mg q12 hour dose may have a lower potential for medication error.

4.1.7 Discussion of Persistence of Efficacy and/or Tolerance Effects

When examining absolute change from baseline in ppFEV1 over the 24-week treatment period, improvements in $ppFEV_1$ were observed after approximately 2-weeks of treatment and appeared to be sustained over the 24-week treatment period. As such in terms of ppFEV1, efficacy appears to persist over the entire 24-week treatment period.

5 Review of Safety

Safety Summary

The safety information for LUM/IVA is derived primarily from the 24-week placebo controlled phase 3 studies (809-103 and 809-104). These studies constituted the placebo controlled safety set and included a total of 1108 patients: 369 patients on LUM 600mg qD/IVA 250mg q12, 369 patients on LUM 400mg/IVA 250mg q12, and 370 patients on placebo. Additional support for safety is derived from study 809-105, the ongoing uncontrolled extension of studies 809-103 and 809-104.

There were no deaths in the placebo controlled safety set and a single death in the extension study. Serious adverse events (SAE) occurred more commonly in placebo patients compared to LUM/IVA patients. Adverse events leading to treatment discontinuation were more common in LUM/IVA groups compared to placebo. This difference did not appear to driven single SOC or PT. Safety data from the extension study with regard to SAEs and AEs leading to discontinuation were consistent with the placebo controlled safety set.

Additional safety analyses were also performed in the placebo controlled safety set to assess for potential liver and respiratory related effects, as well as effects on menstruation. Liver-related SAEs and AEs leading to discontinuation, while not common, occurred in LUM/IVA groups, but not in placebo. The occurrence of transaminase elevations were similar across treatment groups, however, transaminase elevations of >3x the upper limit of normal (ULN) associated with bilirubin elevations >2x ULN, while rare, occurred in LUM/IVA groups, but not in placebo. These types of cases were not observed in the IVA monotherapy program. These safety data suggest

that LUM/IVA exposure may be associated with liver toxicity. Respiratory symptom related AEs occurred sooner after dosing and more commonly in LUM/IVA patients compared to placebo. Additionally, respiratory symptom related SAEs and AEs leading to discontinuation, while rare, occurred in LUM/IVA patients, but not in placebo patients. These data suggest that LUM/IVA exposure is associated with the occurrence of respiratory symptom related AEs. With regard to effects on menstruation, adverse events related to menstrual abnormalities were more common in women in the LUM/IVA groups compared to placebo, especially in patients on hormonal contraception.

Given the potential cataract risk associated with ivacaftor, it is also worth noting that no cataracts were observed in the LUM/IVA safety database and that the cataract risk in ivacaftor is currently being evaluated in a postmarketing study.

The safety data submitted with the NDA was sufficient to assess the safety of LUM/IVA. While the general analysis of deaths and adverse events did not reveal specific safety concerns, the additional safety analyses suggest that LUM/IVA exposure may be associated with liver, respiratory, and menstrual related adverse events.

5.1 Methods

5.1.1 Studies/Clinical Trials Used to Evaluate Safety

To support safety, Vertex submitted pooled safety data from the 24-week phase 3 studies (809-103 and 809-104) and the extension of these studies (809-105).

5.2 Adequacy of Safety Assessments

5.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The safety assessment for LUM/IVA was based primarily on the pooled data from the 24-week placebo controlled studies (809-103 and 809-104). This will be referred to as the placebo controlled safety set. Mean and median exposures were similar between treatment groups and almost all patients were exposed for >16 to ≤24 weeks. The exposure data are summarized in Table 19.

Table 19. Exposure in Placebo Controlled Safety Set

	Placebo N=370	LUM 600qd/ IVA 250 q12 N=369	LUM 400/ IVA250 q12 N=369	Total LUM/IVA N=738
Total Exposure (days)				
Mean	165.4	161.2	161.7	161.5
Median	168	168	168	168
Exposure Duration				
>0 to ≤ 8-weeks	4 (1.1)	15 (4.1)	12 (3.3)	27 (3.7)
>8 to ≤16 weeks	2 (0.5)	2 (0.5)	4 (1.1)	6 (0.8)
>16 to ≤24 weeks	290 (78.4)	268 (72.6)	291 (78.9)	559 (75.7)
>24 weeks	74 (20.0)	84 (22.8)	62 (16.8)	146 (19.8)

Source: Module 2.7.4; Summary of Clinical Safety; table 7; pg 39

To support long-term safety, the sponsor submitted safety data from the ongoing study 809-105, which is the extension of studies 809-103 and 809-104. The exposure data as of a cut-off date of July 21, 2014 are summarized in Table 20. Of the patients in the extension study, 116 completed 24-weeks of treatment with LUM/IVA in studies 809-103/104 and an additional 24-weeks of treatment in the extension, for a total of 48-weeks of exposure.

Table 20. Exposure in study 809-105

	Exposure in Study 809-105			
	LUM/IVA→LUM/IVA[a]		PBO→LUM/IVA[b]	
	LUM 600qd IVA 250 q12 N=334	LUM 400/ IVA 250 q12 N=340	LUM 600qd IVA 250 q12 N=177	LUM 400/ IVA 250 q12 N=176
Total Exposure (days)				
Mean	135	131.7	132.7	133.7
Median	119	120	119	120.5
Exposure Duration				
≥1 dose	334 (100.0)	340 (100.0)	177 (100.0)	176 (100.0)
≥8 weeks	326 (97.6)	331 (97.4)	171 (96.6)	170 (96.6)
≥16 weeks	269 (80.5)	263 (77.4)	138 (78.0)	147 (83.5)
≥24 weeks	86 (25.7)	74 (21.8)	43 (24.3)	37 (21.0)
≥32 weeks	5 (1.5)	6 (1.8)	3 (1.7)	4 (2.3)

[a]patients on LUM/IVA in studies 809-103 and 809-104
[b]patients on placebo in studies 809-103 and 809-104
Source: Module 2.7.4; Summary of Clinical Safety; table 8; pg 40

Overall, the safety database is sufficient in size to get a sense of the safety of LUM/IVA when taken chronically. The review of safety will focus on the placebo controlled safety set as it represents a relatively long exposure and includes a placebo for comparison. Additionally, analysis of the uncontrolled safety data from the extension study revealed no new safety concerns not already identified from the placebo controlled safety set.

5.2. Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Ivacaftor (CFTR potentiator):
Cataracts were seen in juvenile rats dosed with ivacaftor at dose levels of 10 mg/kg/day and higher. Cases of non-congenital lens opacities/cataracts have also been reported in pediatric patients treated with ivacaftor. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating ivacaftor treatment. Elevated transaminases have also been reported in patients with CF receiving ivacaftor.

Lumacaftor:
There are no other drugs in this class. However, in a dose-ranging study, a dose dependent decrease in ppFEV1 was observed when lumacaftor was given as monotherapy. Increases in metrorrhagia in LUM/IVA treated patients compared to placebo were also observed in early phase trials. Worsening of liver function and elevation in liver transaminases has been observed in CF patients receiving LUM/IVA in clinical trials.

Studies included in this submission regularly monitored transaminases and performed screening ophthalmologic evaluation. Patients with cataracts were excluded from the study. Additionally, specific safety analyses were performed to assess for liver toxicity, respiratory related adverse events, and menstrual abnormalities.

5.3 Major Safety Results

5.3.1 Deaths

There were no deaths reported in the 24-week phase 3 studies (placebo controlled safety set). As of the safety cut-off date, there has been a single death in extension study 809-105. This death occurred in a 24-year old female (03-089-06) on LUM 400mg/IVA 250mg q12. This patient had previously completed 24-weeks of treatment with LUM/IVA in study 809-103. Baseline ppFEV1 in study 809-103 was 50% and at week 24 was 55%. On day 175 of the extension study, she experienced a pulmonary exacerbation of CF. She was admitted to the hospital for IV antibiotics and was discharged after approximately 1-week with an additional 3-weeks of home IV antibiotics. Her ppFEV1 at discharge was 41%. Several days after discharge, she was readmitted for worsening symptoms. During her hospitalization, she developed pneumomediastinum and subcutaneous emphysema. Her respiratory status continued to deteriorate. She was intubated and underwent bronchoscopy. Due to worsening respiratory status, she was transferred to an outside hospital for lung transplant evaluation/listing. On arrival, she was placed on extracorporeal membrane oxygenation. Later that day, patient had fixed and dilated pupils. The following day (day 197), the patient died due to respiratory failure. Based on the available clinical information, causality cannot be assessed.

5.3.2 Nonfatal Serious Adverse Events

In general, serious adverse events (SAE) were what would be expected in a CF population. Overall SAEs occurred more commonly in placebo patients compared to LUM/IVA patients. The most common SAEs by system organ class (SOC) were infection and infestations (18.3%) and respiratory thoracic and mediastinal disorders (2.0%). Events in the infections and infestations SOC occurred more commonly in placebo patients compared to LUM/IVA patients. This was driven by the PT infective pulmonary exacerbation of CF. Consistent with the exacerbation related efficacy data, based on percentages, almost twice as many placebo patients experienced an exacerbation compared to LUM/IVA patients at either dose. For the respiratory thoracic, and mediastinal SOC, events were more common LUM/IVA patients compared to placebo, however this did not appear to be driven by a single PT. For a discussion of liver-related SAEs, see Submission Specific Primary Safety Concerns). Serious adverse event data are summarized in Table 21.

Table 21. Placebo Controlled Safety Set. Serious Adverse Events that occurred in ≥2 patients in any treatment group

	Placebo N=370	LUM 600 qD IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
Subjects with Any SAEs	106 (28.6)	84 (22.8)	64 (17.3)	148 (20.1)
Infections and infestations	94 (25.4)	64 (17.3)	45 (12.2)	109 (14.8)
Infective pulmonary exacerbation of cystic fibrosis	89 (24.1)	55 (14.9)	41 (11.1)	96 (13.0)
Pneumonia	0	2 (0.5)	1 (0.3)	3 (0.4)
Bronchopulmonary aspergillosis allergic	0	2 (0.5)	0	2 (0.3)
Influenza	2 (0.5)	2 (0.5)	0	2 (0.3)
Bronchitis	2 (0.5)	1 (0.3)	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	3 (0.8)	11 (3.0)	8 (2.2)	19 (2.6)
Hemoptysis	3 (0.8)	4 (1.1)	5 (1.4)	9 (1.2)
Cough	0	2 (0.5)	1 (0.3)	3 (0.4)
Bronchospasm	0	2 (0.5)	0	2 (0.3)
Dyspnea	0	2 (0.5)	0	2 (0.3)
Gastrointestinal disorders	8 (2.2)	8 (2.2)	5 (1.4)	13 (1.8)
Distal intestinal obstruction syndrome	5 (1.4)	2 (0.5)	2 (0.5)	4 (0.5)
Constipation	2 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Investigations	1 (0.3)	3 (0.8)	6 (1.6)	9 (1.2)
Blood creatine phosphokinase increased	0	0	2 (0.5)	2 (0.3)
General disorders and administration site conditions	0	5 (1.4)	0	5 (0.7)
Implant site thrombosis	0	2 (0.5)	0	2 (0.3)
Medical device complication	0	2 (0.5)	0	2 (0.3)
Renal and urinary disorders	3 (0.8)	1 (0.3)	1 (0.3)	2 (0.3)
Nephrolithiasis	2 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Vascular disorders	3 (0.8)	1 (0.3)	0	1 (0.1)
Deep vein thrombosis	2 (0.5)	0	0	0

Source: Module 2.7.4; Summary of Clinical Safety; table 22; pg 62-63

5.3.3 Dropouts and/or Discontinuations

Of the 1108 patients in the placebo controlled safety set, 54 patients (4.9%) discontinued treatment. Discontinuations of treatment were more common in the LUM/IVA groups (average 6%) compared to placebo (2.4%). This was driven primarily by adverse events (4.2% versus 1.6%). Discontinuations from the studies were also more common in the LUM/IVA groups (3%) compared to placebo (1.1%). However, this difference was not driven by adverse events, but rather by withdrawal of consent and "other". Upon further investigation, the most common explanation for "other" was not meeting inclusion criteria, specifically genotype. These data are summarized in Table 22.

Table 22. Pooled placebo controlled trials. Reasons for Discontinuation of Treatment and Study.

	Placebo N=370	LUM 600qD IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738	Overall total N=1108
Completed Treatment	361 (97.6)	349 (94.6)	344 (93.2)	693 (93.9)	1054 (95.1)
Discontinued Treatment	9 (2.4)	20 (5.4)	25 (6.8)	45 (6.1)	54 (4.9)
Adverse event	6 (1.6)	14 (3.8)	17 (4.6)	31 (4.2)	37 (3.3)
Refused further dosing (not due to AE)	2 (0.5)	3 (0.8)	2 (0.5)	5 (0.7)	7 (0.6)
Did not meet eligibility criteria	0	0	2 (0.5)	2 (0.3)	2 (0.2)
Noncompliance with study drug	0	0	2 (0.5)	2 (0.3)	2 (0.2)
Other, noncompliance	0	0	0	0	0
Physician decision	0	0	1 (0.3)	1 (0.1)	1 (0.1)
Requires prohibited medication	1 (0.3)	1 (0.3)	0	1 (0.1)	2 (0.2)
Pregnancy	0	1 (0.3)	0	1 (0.1)	1 (0.1)
Other	0	1 (0.3)	1 (0.3)	2 (0.3)	2 (0.2)
Completed Study	366 (98.9)	360 (97.6)	356 (96.5)	716 (97.0)	1082 (97.7)
Discontinued Study	4 (1.1)	9 (2.4)	13 (3.5)	22 (3.0)	26 (2.3)
Adverse event	3 (0.8)	3 (0.8)	4 (1.1)	7 (0.9)	10 (0.9)
Withdrawal of consent (not due to AE)	1 (0.3)	5 (1.4)	4 (1.1)	9 (1.2)	10 (0.9)
Lost to follow-up	0	0	0	0	0
Other, noncompliance	0	0	1 (0.3)	1 (0.1)	1 (0.1)
Physician decision	0	0	1 (0.3)	1 (0.1)	1 (0.1)
Other	0	1 (0.3)	3 (0.8)	4 (0.5)	4 (0.4)

Source: Module 2.7.4; Summary of Clinical Safety; table 11; pp 46-47

Adverse events leading to treatment discontinuation were more common in the both LUM/IVA dose groups compared to placebo groups. This difference did not appear to driven single SOC or PT, but rather appeared to be driven by small numerical differences in multiple PTs. Elevation in blood creatine phosphokinase was the most common PT in the LUM/IVA groups that lead to discontinuation and also occurred only in LUM/IVA group. These data are summarized in Table 23.

Table 23. Placebo Controlled Safety Set. Adverse events leading to treatment discontinuation.

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
Patients who discontinued treatment	**9 (2.4%)**	**20 (5.4%)**	**25 (6.8)**	**45 (6.1%)**
Patients with Any AEs Leading to Treatment Discontinuation	6 (1.6)	14 (3.8)	17 (4.6)	31 (4.2)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	5 (1.4)	3 (0.8)	8 (1.1)
Hemoptysis	2 (0.5)	0	3 (0.8)	3 (0.4)
Bronchospasm	0	2 (0.5)	0	2 (0.3)
Dyspnea	0	2 (0.5)	0	2 (0.3)
Respiration abnormal	0	1 (0.3)	0	1 (0.1)
Investigations	1 (0.3)	1 (0.3)	6 (1.6)	7 (0.9)
Blood creatine phosphokinase increased	0	0	4 (1.1)	4 (0.5)
Forced expiratory volume decreased	0	0	1 (0.3)	1 (0.1)
Liver function test abnormal	0	1 (0.3)	0	1 (0.1)
Pulmonary function test decreased	0	0	1 (0.3)	1 (0.1)
Blood alkaline phosphatase increased	1 (0.3)	0	0	0
Gastrointestinal disorders	0	3 (0.8)	1 (0.3)	4 (0.5)
Diarrhea	0	1 (0.3)	0	1 (0.1)
Frequent bowel movements	0	1 (0.3)	0	1 (0.1)
Nausea	0	0	1 (0.3)	1 (0.1)
Vomiting	0	1 (0.3)	0	1 (0.1)
Infections and infestations	0	1 (0.3)	2 (0.5)	3 (0.4)
Infective pulmonary exacerbation of cystic fibrosis	0	0	2 (0.5)	2 (0.3)
Pneumonia	0	1 (0.3)	0	1 (0.1)
Nervous system disorders	0	1 (0.3)	1 (0.3)	2 (0.3)
Dizziness	0	1 (0.3)	0	1 (0.1)
Hepatic encephalopathy	0	0	1 (0.3)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.3)
Rash	0	1 (0.3)	1 (0.3)	2 (0.3)
Acne	1 (0.3)	0	0	0
Blood and lymphatic system disorders	0	0	1 (0.3)	1 (0.1)
Thrombocytosis	0	0	1 (0.3)	1 (0.1)
Cardiac disorders	0	1 (0.3)	0	1 (0.1)
Tachycardia	0	1 (0.3)	0	1 (0.1)
Hepatobiliary disorders	0	1 (0.3)[a]	0	1 (0.1)
Hepatitis cholestatic	0	1 (0.3)	0	1 (0.1)
Immune system disorders	0	0	1 (0.3)	1 (0.1)
Drug hypersensitivity	0	0	1 (0.3)	1 (0.1)
Musculoskeletal and connective tissue disorders	0	0	1 (0.3)	1 (0.1)
Myalgia	0	0	1 (0.3)	1 (0.1)

Neoplasms benign, malignant and unspecified	1 (0.3)	0	0	0
Renal cancer	1 (0.3)	0	0	0
Psychiatric disorder	1 (0.3)	0	0	0
Bradyphrenia	1 (0.3)	0	0	0

[a]an additional patient (04-114-01) had the SAE of cholestasis and hepatitis at week 24. Study drug was withdrawn, but is not counted in this table because they had completed the treatment period.
Source: Module 5.3.5.3; Integrate Summary of Safety Phase 3; table 2.2.5; pp1602-1604

When examining adverse events leading to treatment interruption, these events occurred in similar or lower percentages of patients in LUM/IVA groups compared to placebo. These data are summarized in Table 24.

Table 24. Adverse events that occurred in ≥2 patient/group and lead to interruption of treatment

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
Patients with Any AEs Leading to Treatment Interruption	**25 (6.8)**	**20 (5.4)**	**22 (6.0)**	**42 (5.7)**
Infections and infestations	10 (2.7)	9 (2.4)	5 (1.4)	14 (1.9)
Infective pulmonary exacerbation of cystic fibrosis	8 (2.2)	5 (1.4)	3 (0.8)	8 (1.1)
Gastrointestinal disorders	7 (1.9)	4 (1.1)	7 (1.9)	11 (1.5)
Vomiting	2 (0.5)	2 (0.5)	2 (0.5)	4 (0.5)
Distal intestinal obstruction syndrome	2 (0.5)	0	2 (0.5)	2 (0.3)
Nausea	2 (0.5)	2 (0.5)	0	2 (0.3)
Constipation	3 (0.8)	0	0	0
Investigations	5 (1.4)	4 (1.1)	5 (1.4)	9 (1.2)
Alanine aminotransferase increased	2 (0.5)	1 (0.3)	2 (0.5)	3 (0.4)
Aspartate aminotransferase increased	2 (0.5)	1 (0.3)	2 (0.5)	3 (0.4)
Blood creatine phosphokinase increased	2 (0.5)	1 (0.3)	2 (0.5)	3 (0.4)
Respiratory, thoracic and mediastinal disorders	2 (0.5)	2 (0.5)	2 (0.5)	4 (0.5)
Hemoptysis	2 (0.5)	1 (0.3)	1 (0.3)	2 (0.3)
Skin and subcutaneous tissue disorders	1 (0.3)	2 (0.5)	1 (0.3)	3 (0.4)
Rash	0	2 (0.5)	1 (0.3)	3 (0.4)
Nervous system disorders	2 (0.5)	0	2 (0.5)	2 (0.3)
Headache	2 (0.5)	0	1 (0.3)	1 (0.1)

Source: Module 2.7.4; Summary of Clinical Safety; table 24; pg66

It is worth noting that elevations in creatine phosphokinase leading to treatment interruption occurred with similar frequency across treatment groups.

5.3.4 Submission Specific Primary Safety Concerns

Due to liver-related safety concerns from the IVA monotherapy program, in the LUM/IVA program, specific analyses were performed to assess for potential liver toxicity based on both clinical lab data and adverse event reporting. In addition, due to the dose dependent decreases in ppFEV1 when LUM was given alone, safety analyses were also performed assessing for respiratory related adverse events. Specific analysis of menstrual abnormalities was also performed by the Applicant, due observations in the phase 2 studies. No cataracts were reported during studies 809-103/104 or extensions study 809-105.

Hepatic Safety
For the analysis of hepatic safety, the Applicant grouped together PTs meant to represent elevated transaminases. This was designated an adverse event of special (AESI). The PTs that constituted the AESI of elevated transaminases were reviewed and were reasonable. The chosen terms were similar to a previous analysis the Applicant had performed in the IVA monotherapy program. Vertex also provided an analysis based on events in the SOC hepatobiliary disorder. For both categorizations, events were similar between LUM/IVA groups and placebo in terms of all adverse events and adverse events leading to treatment interruption. However, for AEs leading to treatment discontinuation and SAEs, there were no Applicant defined liver related events in the placebo group compared to 1-4 in the LUM/IVA groups. These data are summarized in Table 25.

Table 25. Placebo Controlled Safety Set. Applicant defined liver-related events

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
Patients with any liver-related AEs	20 (5.4)	20 (5.4)	22 (6.0)	42 (5.7)
AESI of elevated transaminases	17 (4.6)	18 (4.9)	20 (5.4)	38 (5.1)
Hepatobiliary disorder AE (SOC)	3 (0.8)	2 (0.5)	3 (0.8)	5 (0.7)
AEs related to the liver leading to treatment interruption	4 (1.1)	3 (0.8)	4 (1.1)	7 (0.9)
AEs related to the liver leading to treatment discontinuation	0	3 (0.8)	1 (0.3)	4 (0.5)
Serious AEs related to the liver	0	4 (1.1)	3 (0.8)	7 (0.9)

Source: Module 2.7.4; Summary of Clinical Safety; table 25; pg71

All liver-related SAEs resulted in either treatment discontinuation or treatment interruption. These events are summarized in Table 26.

Table 26. Placebo Controlled Safety Set. LUM/IVA patients with liver-related SAEs or treatment discontinuations

Patient#	Adverse event	SAE (y/n)	Start (days from day 1)	Action
LUM 600mg qD/IVA 250mg q12				
03-031-03 35/Female	Hepatitis cholestatic	Y	13	Treatment discontinuation
04-011-03 32/Female	LFT abnormal	Y	15	Treatment discontinuation
04-114-01 33/M	Cholestasis, hepatitis	Y	169	Treatment discontinuation
04-322-03 15/Male	Elevated liver enzymes	Y	57	Treatment interrupted
LUM 400mg/IVA 250mg q12				
03-813-01 23/Female	Elevated AST, ALT, GGT	Y	109 and 121	Treatment interrupted[a]
04-065-06 26/Male	Hepatic encephalopathy	Y	6	Treatment discontinuation
04-097-07 19/Female	LFT abnormal	Y	1	Treatment discontinuation

[a]Patient 03-813-01 had ongoing study drug interruption at the Week 24 Visit in Study 103 but did not enroll in Study 105.

Source: Module 2.7.4; Summary of Clinical Safety; table 26; pg72

Of the 7-patients with SAEs, for three, the events were not considered resolved at the end of the study reporting period. However, for two of the cases (03-813-01 and 04-097-07) both with LFT elevations/abnormalities, while LFTs did not return to baseline/normal, at last follow-up they had decreased to <3x the upper limit of normal (ULN). For the third patient (04-114-01) who had SAEs of cholestasis and hepatitis, while the SAEs were ongoing at the end of the study reporting period, additional safety follow-up after the reporting period ended indicated that the SAE had resolved. While the numbers are small, the SAE and discontinuation data suggest that LUM/IVA use may be associated with liver toxicity.

In addition to the Applicant's analysis of liver-related AESI, the reviewer also analyzed adverse events using standardized MedDRA Queries (SMQs) representing liver-related events. The SMQ analysis was largely consistent with the Applicant's AESI analysis, in that for liver-related adverse events, numbers were similar between treatment groups, and for liver-related SAEs, events were numerically more common in LUM/IVA groups compared to placebo. This is not surprising as Applicant's grouped terms largely overlapped with the terms included in the liver-related SMQ's.

The Applicant also assessed for potential liver toxicity by monitoring clinical labs during the placebo controlled studies. Liver function testing was performed at day 1, 15, and weeks 4, 8, 12, 16, 20, and 24. Based on change from baseline in mean values at week 24, there were no large differences between placebo and LUM/IVA groups for ALT, AST, and total bilirubin. An analysis was also performed based on maximum on-treatment values. This is summarized in Table 27.

Table 27. Placebo Controlled Safety Set. Maximum on-treatment liver function test values

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
ALT				
>3 × ULN to ≤5 × ULN	15 (4.1)	13 (3.6)	8 (2.2)	21 (2.9)
>5 × ULN to ≤8 × ULN	1 (0.3)	4 (1.1)	1 (0.3)	5 (0.7)
>8 × ULN	0	3 (0.8)	1 (0.3)	4 (0.5)
AST				
>3 × ULN to ≤5 × ULN	4 (1.1)	8 (2.2)	7 (1.9)	15 (2.0)
>5 × ULN to ≤8 × ULN	5 (1.4)	4 (1.1)	2 (0.5)	6 (0.8)
>8 × ULN	2 (0.5)	3 (0.8)	2 (0.5)	5 (0.7)
ALT or AST				
>3 × ULN to ≤5 × ULN	12 (3.3)	12 (3.3)	11 (3.0)	23 (3.1)
>5 × ULN to ≤8 × ULN	5 (1.4)	7 (1.9)	2 (0.5)	9 (1.2)
>8 × ULN	2 (0.5)	3 (0.8)	3 (0.8)	6 (0.8)
Total bilirubin				
>2x ULN	1 (0.3)	2 (0.5)	1 (0.3)	3 (0.4)
ALT or AST and Total Bilirubin				
ALT or AST >3x ULN and total bilirubin >2x ULN	0	2 (0.5)	1 (0.3)	3 (0.4)

Source: Module 2.7.4; Summary of Clinical Safety; table 29; pg78.

For AST, ALT, and total bilirubin, while elevations were seen in some patients, the numbers were similar between treatment groups. However, when examining patients with ALT or AST elevations >3x ULN and with total bilirubin elevations >2x ULN, there were three cases in the LUM/IVA groups and none in the placebo group. Transaminase elevations coupled with bilirubin elevations is of some concern as this may imply that LUM/IVA exposure can result in liver toxicity. Brief clinical summaries for the patients with LFT >3x ULN and total bilirubin >2 x ULN are provided below.

Patient 04-065-06:
This was a 25 year old white male with a history of CF related liver disease, hepatic cirrhosis, portal hypertension, splenomegaly, and thrombocytopenia. After six days of LUM 400mg/IVA 250mg q12, the patient presented to the emergency room with disorientation. Lab evaluations demonstrated elevated transaminases and ammonia levels. Bilirubin was not reported. The SAE of hepatic encephalopathy was reported. Study drug was discontinued and patient was admitted to the hospital where he was treated with lactulose and intravenous antibiotics. Repeat labs demonstrated elevated transaminase, bilirubin, and ammonia levels. Hepatitis work-up was negative. Over the eight day hospitalization, the patient continued to improve and was eventually discharged. The event was considered resolved. Based on the available information, causality cannot be assessed, however, it is possible that LUM/IVA exposure may have contributed to hepatic decompensation in a patient with pre-existing CF related liver disease.

Patient 04-114-01:
This was a 33 year old white male with a history of a fatty liver. After 24 weeks of treatment with LUM 600mg qD/ IVA 250mg q12, the patient presented with jaundice, nausea, tea-colored urine and elevated transaminases and bilirubin. CT and abdominal ultrasound revealed gall-bladder thickening, no stones, and no common bile duct dilatation. The SAE of hepatitis and cholestasis was reported. Hepatitis A, B, and C serologies were negative. Due to suspected acalculous cholecystitis, the patient underwent cholecystectomy. Liver biopsy performed at the time suggested a drug-related etiology. A second biopsy was performed approximately 3-months later with findings that appeared to be multifactorial, with the most prominent feature being portal fibrosis with bile ductular proliferation attributed to CF. Hepatitis E serologies were also sent at that time. Hepatitis E IgG was positive indicating previous hepatitis E infection, but IgM was negative indicating no acute infection. Retrospective analysis of baseline and week 16 serum hepatitis E IgG and IgM were negative. As hepatitis E IgM can decline rapidly after acute infection, these results may imply that an acute hepatitis E infection occurred between week 16 of treatment and the latest hepatitis E assessment. It is possible that the initial transaminase and bilirubin elevations were related to acute hepatitis E. While the transaminase/bilirubin elevations and the SAEs of cholestasis and hepatitis were ongoing at the end of the study reporting period, later safety follow-up demonstrated that the events had resolved. This patient's presentation may be consistent with acute hepatitis, however, a contributing role for LUM/IVA cannot be ruled out.

Patient 03-031-03:
This was a 35 year old white female with history of mild transaminase elevations. After 13 days of treatment with LUM 600mg qD/IVA 250mg q12, she developed sudden onset epigastric pain and pruritis. Labs tests drawn two days later revealed elevated transaminases and bilirubin. On day 18, the patient was hospitalized with a diagnosis of cholestatic hepatitis. Study drug was withdrawn. Ultrasound revealed bile duct dilatation, mild gallbladder thickening, with some sludging, but no stones. The treating physician suspected a passed gall stone. Hepatitis serologies were negative (A, B, C). Ursodiol was initiated. The patient was discharged after several days when labs and clinical picture were improved. On day 73, the cholestatic hepatitis was considered resolved and by day 91 transaminases and bilirubin returned to normal.

While these cases are concerning as elevations in transaminases coupled with elevated bilirubin imply significant liver damage, causality cannot be definitively assessed, given other potential contributing/confounding factors. However, a contribution of LUM/IVA cannot be ruled out. It is also worth noting that in the extension study, no cases of transaminase elevations of >3x ULN associated with bilirubin >2x ULN have been reported. Overall, based on liver-related AESIs and maximum on treatment lab values, LUM/IVA use may be associated with increased risk of liver toxicity.

Sub-group analyses were also performed in patients with a history of liver function test (LFT) elevations versus those without. Not surprisingly, a higher percentage of patients

with a history of elevated LFTs, developed elevated transaminases compared to those without a history of elevated LFTs. This was true across all treatment groups.

Overall, the hepatic safety analyses indicate that LUM/IVA exposure may be associated with liver-related events, specifically SAEs, AEs leading to discontinuation, and transaminase elevations associated with bilirubin elevations. However, it should be noted that this is based on a relatively small number of events in a patient population prone to liver disease.

Respiratory Safety
In the phase 2 study 809-102, a dose dependent decrease in ppFEV1 was observed with increasing LUM doses (see section 3.2). Due to this observation and the target patient population, the Applicant performed a safety analysis grouping together PTs meant to represent respiratory symptoms and reactive airways [adverse events of special interest (AESI)]. For the respiratory symptoms AESI, defined as the preferred terms chest discomfort, dypnea, or respiratory abnormal, events were more common in the LUM/IVA groups compared to placebo. In contrast, for the reactive airways AESI, defined as the preferred terms asthma, bronchial hyperreactivity, bronchospasm, or wheezing, the percentages of patients with events were similar between LUM/IVA and placebo groups. For both respiratory AESI, serious AEs or AEs leading to treatment discontinuation while not common, were observed only in the LUM 600mg qD/IVA 250mg q12 group and not in placebo. For these three cases, the AEs leading to discontinuation were respiration abnormal, dyspnea, and dyspnea, and all occurred within 2-days of the initial LUM/IVA dose. These results are summarized in Table 28.

Table 28. Respiratory Adverse Events of Special Interest (AESI)

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
Patients with any respiratory symptoms or reactive airways AESI	63 (17.0)	99 (26.8)	95 (25.7)	194 (26.3)
Respiratory symptoms AESI	51 (13.8)	88 (23.8)	81 (22.0)	169 (22.9)
Chest discomfort	5 (1.4)	7 (1.9)	7 (1.9)	14 (1.9)
Dyspnea	29 (7.8)	55 (14.9)	48 (13.0)	103 (14.0)
Respiration abnormal	22 (2.9)	40 (10.8)	32 (8.7)	72 (9.8)
Respiratory symptoms AESI leading to treatment interruption	1 (0.3)	1 (0.3)	0	1 (0.1)
Respiratory symptoms AESI leading to treatment discontinuation	0	3 (0.8)	0	3 (0.4)
Serious respiratory symptoms AESI	0	2 (0.5)	0	2 (0.3)
Reactive airways AESI	20 (5.4)	24 (6.5)	24 (6.5)	48 (6.5)
Asthma	5 (1.4)	4 (1.1)	8 (2.2)	12 (1.6)
Bronchial hyperreactivity	0	1 (0.3)	2 (0.5)	3 (0.4)
Bronchospasm	1 (0.3)	7 (1.9)	5 (1.4)	12 (1.6)
Wheezing	15 (4.1)	12 (3.3)	11 (3.0)	23 (3.1)
Reactive airways AESI leading to treatment interruption	0	0	0	0
Reactive airways AESI leading to treatment discontinuation	0	2 (0.5)	0	2 (0.3)
Serious reactive airways AESI	0	2 (0.5)	0	2 (0.3)

Source: Module 2.7.4; Summary of Clinical Safety; table 36; pg98

These results indicate that patients treated with LUM/IVA are more likely to have adverse events related to respiratory symptoms than placebo patients.

Time to onset of respiratory related AESI are summarized in Table 29. The time to onset for the respiratory symptoms AESI was much shorter for both LUM/IVA groups compare to placebo. Additionally, in the LUM/IVA groups the majority of events (75-80%) occurred within one week of dosing. In contrast, for the placebo group, events were spread throughout the treatment 24-week treatment period. For the reactive airways AESI, the same pattern was not observed.

Table 29. Time to onset of respiratory related adverse events of special interest

Time to onset (days)	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
Respiratory Symptom AESI				
N	51	88	81	169
Mean	51.7	22.8	18.9	20.9
Median	43	1.5	2.0	2.0
Reactive Airways AESI				
N	20	24	24	48
Mean	34.4	20.7	48.3	34.5
Median	22	5	50	14

Source: Module 2.7.4; Summary of Clinical Safety; table 39; pg101

The Applicant also analyzed respiratory related AESI based on prior bronchodilator use. Not surprisingly, for both placebo and LUM/IVA groups, almost all respiratory related AESI occurred in patients with previous bronchodilator use (93-98%). When analyzed based on baseline ppFEV1 (≥40% vs <40%) and age (≥18years and ≥12 years to <18 years) the results were generally consistent with the overall population with events in the respiratory symptom AESI occurring more commonly in LUM/IVA patients compared to placebo.

These safety data strongly suggest that LUM/IVA exposure may result in increased respiratory symptoms.

Menstrual Abnormalities
Due to an observed increase in metrorrhagia in LUM/IVA treated patients compared to placebo from early phase trials, the Applicant grouped together PTs representative of menstrual abnormalities in a custom MedDRA Query (CMQ). The terms included in this grouping were reviewed and were reasonable. Female patients who reported events in the menstrual abnormality CMQ were more common in both LUM/IVA dose groups compared to placebo. This difference was much more prominent when comparing female patients on hormonal contraception. This may be because LUM is an inducer of CYP3A. While there were differences in the menstrual abnormality CMQ, it did not appear to be driven by any single PT in the grouping. These data are summarized in Table 30.

Table 30. Placebo Controlled Database. Menstrual Abnormality CMQ

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
Total Female patients	181	182	182	364
Menstrual Abnormality CMQ	3 (1.7)	17 (9.3)	19 (10.4)	36 (9.9)
On hormonal contraception	1 (0.6)	12 (6.6)	15 (8.2)	27 (7.4)
No hormonal contraception	2 (0.6)	5 (2.7)	4 (2.2)	9 (2.5)

Source: Module 2.7.4; Summary of Clinical Safety; table 45; pg 111

5.4 Supportive Safety Results

5.4.1 Common Adverse Events

Overall, the observed AEs were typical for this study population. The most common AEs by preferred term were infective exacerbation of CF, cough, and headache. Common adverse events that occurred more frequently in LUM/IVA groups compared to placebo are summarized in Table 31. While there were some differences, they were generally small in magnitude.

Table 31. Placebo Controlled Safety Database. Adverse events that occurred in ≥5% in any treatment group and were more common in any LUM/IVA group compared to placebo.

	Placebo N=370	LUM 600qd IVA 250 q12 N=369	LUM 400/ IVA 250 q12 N=369	Total LUM/IVA N=738
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)
Nasopharyngitis	40 (10.8)	23 (6.2)	48 (13.0)	71 (9.6)
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)
Fatigue	29 (7.8)	30 (8.1)	34 (9.2)	64 (8.7)
Upper respiratory tract infection	20 (5.4)	24 (6.5)	37 (10.0)	61 (8.3)
Abdominal pain	32 (8.6)	26 (7.0)	33 (8.9)	59 (8.0)
Viral upper respiratory tract infection	25 (6.8)	28 (7.6)	23 (6.2)	51 (6.9)
Rhinitis	18 (4.9)	30 (8.1)	16 (4.3)	46 (6.2)
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)
Abdominal pain upper	18 (4.9)	22 (6.0)	12 (3.3)	34 (4.6)

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

5.4.2 Laboratory Findings, Vital Signs, and ECGs

There were no clinically important trends identified in clinical laboratory results (serum chemistry, hematology, coagulation studies, urinalysis), vital signs (heart rate, blood pressure, temperature, respiratory rate), or ECGs that were attributable to LUM/IVA use.

5.4.3 Other Safety Explorations

Other safety explorations such as time dependency for AEs, dose dependency for AEs, drug-demographic, and drug-disease interactions were performed. Overall, these explorations did not reveal safety concerns that have not already been discussed.

5.4.4 Drug-Drug Interactions

Clinical pharmacology study VX12-809-009 assessed for interactions between LUM/IVA and ciprofloxacin, itraconazole, rifampin, and various inhaled bronchodilators. This

study demonstrated that ciprofloxacin and rifampin had minimal effect on LUM pharmacokinetics (PK), but both did decrease IVA exposure. Itraconazole did not affect LUM PK, but did increase IVA exposure. The PK of LUM and IVA were comparable on coadministration of LUM/IVA with inhaled bronchodilator (ipratropium, albuterol, indacaterol, and tiotropium).

6 Postmarket Experience

There is no postmarketing experience with LUM/IVA. However, IVA monotherapy was approved on 1/31/12. Since that time no new issues have been identified that would alter the risk-benefit profile of IVA monotherapy in its approved indication nor that would affect the safety assessment of LUM/IVA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

PART A: REVIEW OF PHASE 3 STUDIES

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE

FOR LUMACAFTOR AND IVACAFTOR ORAL TABLETS (ORKAMBI)

NDA 206-038

Statistical briefing material for the Pulmonary-Allergy Drugs Advisory Committee
May 12, 2015

Lan Zeng
Division of Biometrics II

1 INTRODUCTION

Cystic fibrosis (CF) is a chronically debilitating, autosomal recessive disease associated with serious morbidity and a high rate of premature mortality. The proposed medicinal product, Orkambi, is a fixed dose combination of lumacaftor (LUM) and ivacaftor (IVA) proposed for the treatment of CF patients aged 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. This mutation covers approximately 50% of patients diagnosed with CF in the United States.

The applicant's phase 3 program consisted of two replicate trials, studies VX12-809-103 (809-103) and VX12-809-104 (809-104). These were randomized, double-blind, placebo-controlled, parallel-group trials that evaluated the efficacy and safety of lumacaftor in combination with ivacaftor (LUM/IVA). The two trials had nearly identical designs each with 3 arms: lumacaftor 600 mg once daily and ivacaftor 250 mg twice daily (LUM 600 mg qd/IVA 250 mg q12h), lumacaftor 400 mg and ivacaftor 250 mg twice daily (LUM 400mg/IVA 250mg q12h), and placebo twice daily (placebo). Per conversations with the Agency, there were no lumacaftor or ivacaftor monotherapy arms included the phase 3 trials. As such it is difficult if not impossible to evaluate the effect of each individual component to the combination therapy.

The applicant also submitted results from study VX08-770-104 (770-104) that evaluated ivacaftor as monotherapy. The focus of this review will be the phase 3 studies that evaluate the efficacy of LUM/IVA. An evaluation of study 770-104 and comparison between its results and the results of studies 809-103 and 809-104 can be found in Part B of the statistical briefing document.

2 STUDIES 809-103 AND 809-104

2.1 STUDY DESIGN

Each trial was a 24-week, multicenter, randomized, double-blind study with 3 parallel groups. Enrollment was limited to subjects who were 12 years of age and older, had 40% to 90% ppFEV$_1$ at screening, and were clinically stable at the start of the study. Subjects were stratified by age (<18 versus ≥18 years old), sex (male versus female), and ppFEV$_1$ severity at screening (<70% or ≥70%); and then randomized equally to one of three treatment arms: LUM 600 mg qd/IVA 250 mg q12h, LUM 400mg/IVA 250mg q12h, and placebo. Readers are referred to the clinical section of the PADAC briefing document for a detailed description of the study design.

2.2 ENDPOINTS

In both studies, the primary endpoint was the absolute change from baseline in $ppFEV_1$ at Week 24, assessed as the average of the treatment effects at Week 16 and at Week 24. The baseline value was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the initial administration of study drug. Absolute change from baseline was calculated as post-baseline value minus baseline value.

There were five key secondary efficacy endpoints.

1. Average relative change from baseline in $ppFEV_1$ at Week 16 and at Week 24
2. Absolute change from baseline in body mass index (BMI) at Week 24
3. Absolute change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain at Week 24.
4. Response defined as ≥5% increase in average relative change from baseline in $ppFEV_1$ at Week 16 and at Week 24
5. Number of pulmonary exacerbations through Week 24.

Relative change from baseline was calculated in as $100 \times \frac{post\text{-}baseline\ value - baseline\ value}{baseline\ value}$.

2.3 STATISTICAL METHADOLOGIES

The analysis population was defined as the full analysis dataset (FAS), which included all randomized subjects who received any amount of study drug. The treatment assignments for the FAS were as randomized.

The primary analysis was to test the difference between each dose of LUM/IVA versus placebo using a mixed effects model with repeated measures (MMRM). Both on-treatment measurements and measurements after treatment discontinuation (for subjects who discontinued dosing early) were included in primary analyses. The MMRM model included subject as a random effect, treatment, visit, and treatment-by-visit interaction as fixed effects, with adjustments for sex, age group at baseline, and $ppFEV_1$ severity at screening. The model assumed an unstructured covariance and the Kenward-Roger approximation was used for the denominator degrees of freedom. The primary result obtained from the model was the average of the treatment effects for Weeks 16 and 24.

The analyses for the five key secondary efficacy endpoints were as follows. Average relative change in $ppFEV_1$, change in BMI, and change in CFQ-R were compared using an MMRM model similar to the primary analysis. Response, defined as ≥5% increase in average relative change from baseline in $ppFEV_1$ at Week 16 and at Week 24, was analyzed using a 2-sided Cochran-Mantel-Haenszel (CMH) test stratified by sex, baseline age group, and ppFEV1 severity at screening. A subject with a missing average absolute change from baseline in ppFEV1 at Week 16 and at Week 24 will be considered a non-responder. Number of pulmonary exacerbations through Week 24 was based on

regression analysis for a negative binomial distribution with sex, baseline age group, and ppFEV1 severity at screening as covariates.

To account for the comparison of two doses of LUM/IVA to placebo, a Bonferroni correction was applied to control the overall Type I error rate at 0.05. A sequential testing strategy was utilized to account for multiple key secondary endpoints. For each individual trial, a hierarchical testing procedure was used for the primary and key secondary endpoints at $\alpha = 0.025$ for each active treatment arm separately. The order of testing for the key secondary endpoints was as listed above. At each step, the comparison was considered statistically significant if the p-value < 0.025 and all previous tests also met this level of significance. If a test failed, all results from subsequent tests were considered descriptive (nominal p-values).

2.4 RESULTS OF PRIMARY ANALYSIS

During the review cycle some discrepancies were noted between the coding of the stratification variables (age, gender, and baseline $ppFEV_1$) and the actual values in subject-level datasets. When the discrepancies were accounted for by using the actual values, the conclusion of the primary analysis did not change. However, there are slight differences in the numbers from this analysis as compared to those reported by the applicant.

Results from the comparison of the primary efficacy endpoint, absolute change from baseline in $ppFEV_1$, are shown in Table 1. As pre-specified, each dose of LUM/IVA was compared to placebo using $\alpha = 0.025$. In both studies, regardless of dose, treatment with LUM/IVA demonstrated a statistically significant improvement in $ppFEV_1$. These results were consistent when the actual values for baseline age, sex, and $ppFEV_1$ at screening from the clinical database were included in the MMRM (Reviewer's analysis).

Table 1. Absolute change from baseline in ppFEV1 at Week 24*, FAS

Statistics	Study 809-103			Study 809-104		
	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
Baseline						
N	181	182	180	185	184	185
Mean (SD)	60.5 (13.2)	61.2 (13.3)	60.5 (14.3)	60.4 (14.3)	60.5 (13.8)	60.6 (14.0)
Absolute Δ from baseline at Week 24*						
N	180	176	172	183	181	180
Mean (SD)	-0.6 (6.5)	3.5 (7.0)	2.1 (7.1)	-0.5 (6.6)	2.2 (7.5)	2.6 (6.7)
Applicant						
LS mean within-group change (SE)	-0.4 (0.5)	3.6 (0.5)	2.2 (0.5)	-0.2 (0.5)	2.5 (0.5)	2.9 (0.5)
LS mean difference vs placebo (95% CI)	NA	4.0 (2.6, 5.4)	2.6 (1.2, 4.0)	NA	2.6 (1.2, 4.1)	3.0 (1.6, 4.4)
Reviewer						
LS mean within-group change (SE)	-0.5 (0.5)	3.6 (0.5)	2.1 (0.5)	-0.2 (0.5)	2.3 (0.6)	2.8 (0.5)
LS mean difference vs placebo (95% CI)	NA	4.1 (2.7, 5.5)	2.7 (1.2, 4.1)	NA	2.5 (1.0, 4.0)	3.0 (1.5, 4.4)

*Assessed as the average of the treatment effects at Week 16 and at Week 24
Source: Reviewer

The results from the analyses of absolute change from baseline in ppFEV1 at Week 24 are presented in Table 2. These results are consistent with the average of the parameter at Week 16 and at Week 24 as presented in Table 1.

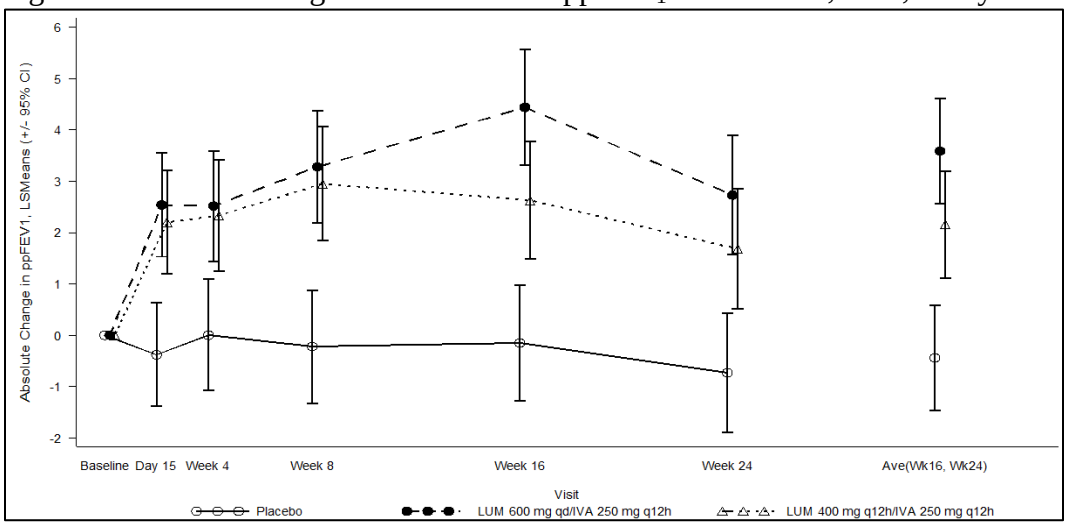
Table 2. Absolute change from baseline in ppFEV1 at Week 24, FAS

Statistics	Study 809-103			Study 809-104		
	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
Baseline						
N	181	182	180	185	184	185
Mean (SD)	60.5 (13.2)	61.2 (13.3)	60.5 (14.3)	60.4 (14.3)	60.5 (13.8)	60.6 (14.0)
Absolute Δ from baseline at Week 24						
N	173	170	166	177	176	173
Mean (SD)	-0.7 (7.0)	2.7 (8.0)	1.6 (7.6)	-0.3 (7.1)	2.1 (8.2)	2.5 (7.5)
Applicant						
LS mean within-group change (SE)	-0.7 (0.6)	2.7 (0.6)	1.7 (0.6)	-0.02 (0.6)	2.3 (0.6)	2.6 (0.6)
LS mean difference vs placebo (95% CI)	NA	3.5 (1.9, 5.1)	2.4 (0.8, 4.0)	NA	2.3 (0.7, 3.9)	2.7 (1.1, 4.2)
Reviewer						
LS mean within-group change (SE)	-0.7 (0.6)	2.7 (0.6)	1.6 (0.6)	-0.06 (0.6)	2.2 (0.6)	2.5 (0.6)
LS mean difference vs placebo (95% CI)	NA	3.5 (1.8, 5.1)	2.4 (0.7, 4.0)	NA	2.2 (0.6, 3.8)	2.6 (0.9, 4.2)

Source: Reviewer

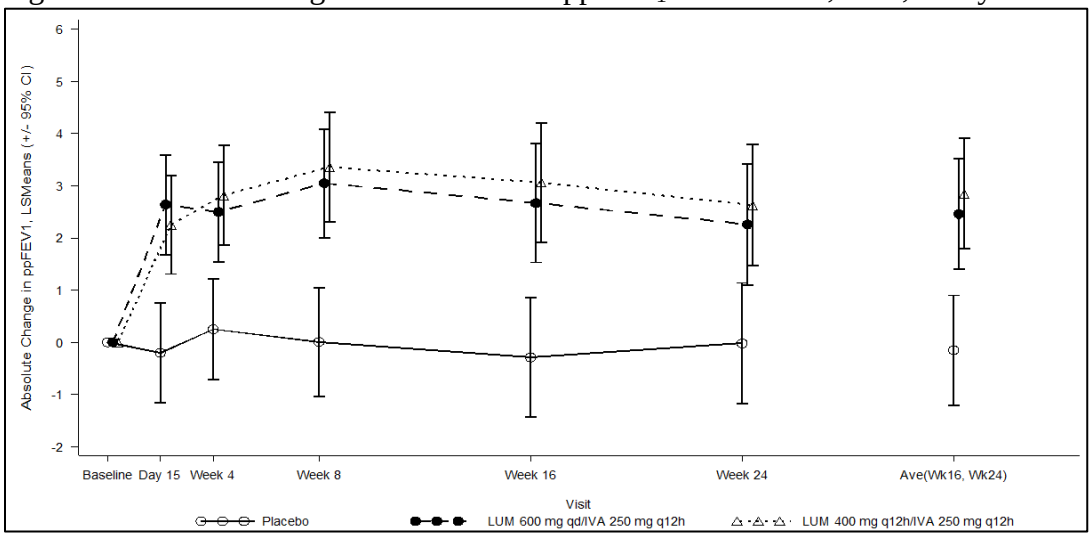
Figures 1 and 2 illustrate the absolute change from baseline in $ppFEV_1$ at each visit. For both active treatment groups in both studies, statistically significant mean absolute improvements in $ppFEV_1$ were observed at each visit when compared to the placebo group (p-values ≤ 0.05). There were no adjustments for multiplicity in these analyses. This is considered supportive of the primary analyses.

Figure 1. Absolute change from baseline in $ppFEV_1$ at each visit, FAS, Study 809-103



Source: Clinical Study Report, Figure 11-11

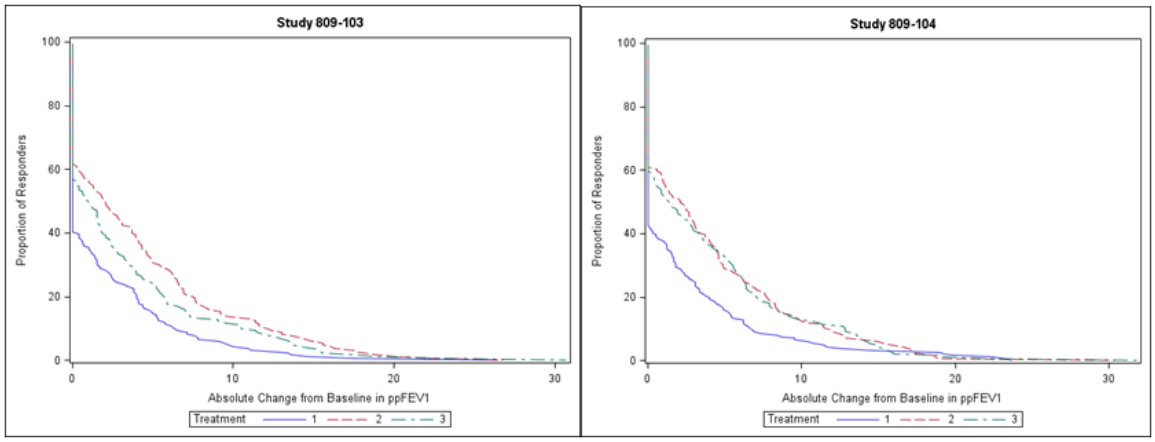
Figure 2. Absolute change from baseline in $ppFEV_1$ at each visit, FAS, Study 809-104



Source: Clinical Study Report, Figure 11-16

The overall discontinuation rates in studies 809-103 and 809-104 were 3.3% and 3.7 %, respectively. To assess the robustness of the primary endpoint analyses with respect to missing data, the applicant performed sensitivity analyses using the MMRM approach with on-treatment measurements only and an ANCOVA model with multiple imputations for missing data. Both analysis generated results that were consistent with the primary analysis. Additional supportive analyses based on the Per Protocol population and a rank-based ANCOVA model also demonstrated results that were consistent with the primary analysis. Figure 3 presents results from a continuous responder analysis conducted by the reviewer where patients who discontinued from the study regardless of reason were considered non-responders. The x-axis shows absolute change from baseline in $ppFEV_1$ at Week 24 and the y-axis shows the corresponding percentage of patients achieving that level of response. The figures demonstrate that a higher proportion of patients treated with LUM/IVA responded better compared to placebo patients.

Figure 3. Absolute change from baseline in ppFEV1 at Week 24, FAS



1: Placebo; 2: LUM 600 mg qd/IVA 250 mg q12h; 3: LUM 400mg/IVA 250 mg q12h
Source: Reviewer

2.5 KEY SECONDARY MEASURES

The key secondary endpoints were tested sequentially for each dose if the primary endpoint was significant at α=0.025. Since the primary endpoint was significant in each study, the key secondary endpoints were tested (Table 3). The analyses using the actual values for baseline age, sex, and $ppFEV_1$ at screening from the clinical database were consistent the applicant's results (Table 4).

For the 1st key secondary efficacy endpoint, relative change from baseline in $ppFEV_1$ assessed as the average of the treatment effects at Week 16 and Week 24, there was a significant treatment effect in favor of LUM/IVA regardless of dose in both studies. Based on the hierarchical testing procedure, the 2nd endpoint, absolute change from baseline in BMI at Week 24 was tested for a treatment effect in both studies. Significance was only noted in study 809-104. As shown by bold text in Tables 3 and 4, the testing hierarchy was broken at BMI in study 809-103 and CFQ-R respiratory domain in study 809-104.

In study 809-103 treatment with LUM/IVA resulted in an increase in both active treatment groups in terms of absolute change from baseline in BMI at Week 24, the 2nd key secondary efficacy endpoint. However, the improvement did not reach statistical significance for either dose. Therefore, the testing hierarchy stopped at this endpoint for both active treatment groups. The results for the 3rd key secondary endpoint (CFQ-R) and 4th key secondary endpoint (Response of $\geq$5% in relative change in $ppFEV_1$) were not considered significant and are not discussed further although results are presented in the Tables 3 and 4. Pulmonary exacerbations, the 5th key secondary endpoint, was also not considered statistically significant (even though the p-value < 0.05) as the testing hierarchy had stopped before the comparison was made.

In study 809-104 treatment with LUM/IVA resulted in significant increase in both active treatment groups for the 2nd key secondary efficacy endpoint of absolute change from baseline in BMI at Week 24. The testing continued for the 3rd key secondary efficacy endpoint, absolute change from baseline in the CFQ-R respiratory domain score at Week 24. There were improvements due to treatment with LUM/IVA but the results were not statistically significant. Based on the hierarchical testing procedure, the testing hierarchy stopped at this endpoint for both active treatment groups. The results for 4th key secondary endpoint (Response of $\geq$5% in relative change in $ppFEV_1$) and 5th key secondary endpoint (pulmonary exacerbations) were not considered significant and are not discussed further although results are presented in the Tables 3 and 4.

Table 3. Summary of key secondary endpoints (Applicant's analysis), FAS

Analysis	Statistics	Study 809-103			Study 809-104		
		Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
1) Relative Δ from baseline in $ppFEV_1$ at Week24* (%)	Mean	-0.3	6.4	4.0	0.0	4.4	5.3
	Difference	NA	6.7	4.3	NA	4.4	5.3
	(95% CI)		**(4.3, 9.2)**	**(1.9, 6.8)**		**(1.9, 7.0)**	**(2.7, 7.8)**
2) Absolute Δ from baseline in BMI at Week 24 (kg/m^2)	Mean	0.2	0.4	0.3	0.1	0.5	0.4
	Difference	NA	0.2	0.1	NA	0.4	0.4
	(95% CI)		(-0.0, 0.4)	(-0.1, 0.3)		**(0.2, 0.6)**	**(0.2, 0.5)**
3) Absolute Δ from baseline in CFQ-R respiratory domain score at Week 24 (points)	Mean	1.1	5.0	2.6	2.8	5.0	5.7
	Difference	NA	3.9	1.5	NA	2.2	2.9
	(95% CI)		(0.7, 7.1)	(-1.7, 4.7)		(-0.9, 5.3)	(-0.3, 6.0)
4) Response of ≥5% in relative Δ from baseline in $ppFEV_1$ at Week 24*	Yes, n(%)	41 (22.3)	85 (46.4)	67 (36.8)	42 (22.5)	85 (45.9)	77 (41.2)
	Odds ratio	NA	2.9	2.1	NA	3.0	2.4
	(95% CI)		(1.9, 4.6)	(1.3, 3.3)		(1.9, 4.6)	(1.5, 3.7)
5) Number of pulmonary exacerbations from baseline through Week 24	No. events	112	79	73	139	94	79
	Event rate/year	1.1	0.8	0.7	1.2	0.8	0.7
	Rate ratio	NA	0.7	0.7	NA	0.7	0.6
	(95% CI)		(0.5, 1.0)	(0.5, 1.0)		(0.5, 0.9)	(0.4, 0.8)

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

Source: Reviewer

Table 4. Summary of key secondary endpoints (Reviewer's analysis), FAS

Analysis	Statistics	Trial 809-103			Trial 809-104		
		Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
1) Relative Δ from baseline in $ppFEV_1$ at Week 24* (%)	Mean	-0.5	6.3	3.9	-0.1	4.1	5.1
	Difference	NA	6.8	4.4	NA	4.2	5.2
	(95% CI)		**(4.3, 9.3)**	**(1.9, 7.0)**		**(1.6, 6.8)**	**(2.6, 7.8)**
2) Absolute Δ from baseline in BMI at Week 24 (kg/m^2)	Mean	0.2	0.4	0.3	0.1	0.5	0.4
	Difference	NA	0.1	0.1	NA	0.4	0.4
	(95% CI)		(-0.1, 0.3)	(-0.1, 0.3)		**(0.2, 0.6)**	**(0.2, 0.6)**
3) Absolute Δ from baseline in CFQ-R respiratory domain score at Week 24 (points)	Mean	1.2	5.5	2.9	3.1	5.5	6.2
	Difference	NA	4.3	1.6	NA	2.4	3.1
	(95% CI)		(1.0,7.5)	(-1.6, 4.9)		(-0.7, 5.6)	(-0.1, 6.2)
4) Response of ≥5% in relative Δ from baseline in $ppFEV_1$ at Week 24*	Yes, n(%)	41 (22.3)	85 (46.4)	67 (36.8)	42 (22.5)	85 (45.9)	77 (41.2)
	Odds ratio	NA	2.9	2.1		2.8	2.3
	(95% CI)		(1.9,4.6)	(1.3, 3.4)	NA	(1.8, 4.4)	(1.5, 3.6)
5) Number of pulmonary exacerbations from baseline through Week 24	No. events	112	79	73	139	94	79
	Event rate/year	1.1	0.8	0.7	1.2	0.8	0.7
	Rate ratio	NA	0.7	0.7	NA	0.7	0.6
	(95% CI)		(0.5, 1.0)	(0.5, 0.9)		(0.5, 0.9)	(0.4, 0.8)

*Assessed as the average of the treatment effects at Week 16 and at Week 24
Source: Reviewer

2.6 SUBGROUP ANALYSES

Subgroup analyses were performed to assess the consistency of treatment effects across demographic and clinical subgroups including gender, age, region, and $ppFEV_1$ severity at screening. These analyses were conducted for study 809-103 and study 809-104 separately. The treatment effects were evaluated in each subgroup using the same MMRM model as used for the primary analysis. Results from each individual study are presented in Table 5.

The conclusions from subgroup analyses were consistent with those from the study population as a whole. For each subgroup, analysis of absolute change from baseline in $ppFEV_1$ favored both doses of LUM/IVA. There were no robust trends suggestive of meaningful differences between any of the subgroups. For some subgroups, interpretation of outcomes should be treated with caution due to the small number of subjects.

Table 5. Absolute change from baseline in ppFEV1 at Week 24* by subgroup, FAS

	Statistics	Trial 809-103			Trial 809-104		
		Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250	Placebo	LUM 600 /IVA 250	LUM 400 /IVA 250
Gender	**Male,** n	96	93	94	87	87	84
	Average Δ from baseline (SE)	-0.5 (0.7)	3.1 (0.7)	2.1 (0.7)	-0.5 (0.8)	2.6 (0.8)	3.2 (0.8)
	Difference from placebo	NA	3.7	2.6	NA	3.1	3.8
	(95% CI)		(1.7, 5.6)	(0.7, 4.6)		(0.9, 5.3)	(1.5, 6.0)
	Female, n	84	83	78	96	94	96
	Average Δ from baseline (SE)	-0.3 (0.8)	4.2 (0.8)	2.3 (0.8)	0.1 (0.7)	2.3 (0.7)	2.5 (0.7)
	Difference from placebo	NA	4.5	2.6	NA	2.2	2.3
	(95% CI)		(2.4, 6.5)	(0.6, 4.7)		(0.3, 4.1)	(0.4, 4.2)
Age	**≥12 to<18 years,** n	49	51	49	42	42	44
	Average Δ from baseline (SE)	0.5 (1.2)	4.8 (1.2)	3.7 (1.2)	0.8 (1.3)	2.7 (1.3)	2.4 (1.3)
	Difference from placebo	NA	5.2	4.1	NA	2.0	1.7
	(95% CI)		(1.9, 8.6)	(0.8, 7.5)		(-1.7, 5.6)	(-2.0, 5.3)
	≥18 years, n	131	125	123	141	139	136
	Average Δ from baseline (SE)	-0.6 (0.5)	3.0 (0.6)	1.4 (0.6)	-0.7 (0.6)	2.1 (0.6)	2.8 (0.6)
	Difference from placebo	NA	3.6	2.0	NA	2.8	3.5
	(95% CI)		(2.1, 5.1)	(0.6, 3.5)		(1.3, 4.4)	(1.9, 5.0)
Region	**North America,** n	99	95	87	120	116	108
	Average Δ from baseline (SE)	0.0 (0.7)	3.4 (0.7)	1.8 (0.8)	-0.7 (0.7)	2.4 (0.7)	2.9 (0.7)
	Difference from placebo	NA	3.4	1.8	NA	3.1	3.6
	(95% CI)		(1.5, 5.4)	(-0.2, 3.7)		(1.3, 5.0)	(1.8, 5.5)
	Europe, n	68	62	69	47	56	55
	Average Δ from baseline (SE)	-1.4 (0.9)	3.7 (0.9)	3.0 (0.9)	0.5 (1.0)	1.6 (0.9)	2.5 (1.0)
	Difference from placebo	NA	5.1	4.3	NA	1.1	2.1
	(95% CI)		(2.6, 7.5)	(2.0, 6.70)		(-1.6, 3.8)	(-0.6, 4.7)
	Australia, n	13	19	16	16	9	17
	Average Δ from baseline (SE)	0.4 (1.8)	4.3 (1.3)	0.7 (1.5)	1.3 (1.7)	7.9 (2.3)	3.7 (1.7)
	Difference from placebo	NA	3.8	0.3	NA	6.6	2.4
	(95% CI)		(-0.5, 8.1)	(-4.1, 4.7)		(1.0, 12.3)	(-2.5, 7.2)
$ppFEV_1$ at Screening	**<70%,** n	123	115	117	121	118	122
	Average Δ from baseline (SE)	-0.1 (0.6)	3.4 (0.6)	2.9 (0.6)	-0.9 (0.7)	2.1 (0.7)	2.7 (0.7)
	Difference from placebo	NA	3.4	3.0	NA	3.1	3.6
	(95% CI)		(1.8, 5.1)	(1.3, 4.6)		(1.4, 4.8)	(1.9, 5.2)
	≥70%, n	49	59	52	57	59	56
	Average Δ from baseline (SE)	-1.0 (1.1)	4.5 (1.0)	1.2 (1.1)	1.1 (1.0)	2.4 (1.0)	2.7 (1.0)
	Difference from placebo	NA	5.5	2.2	NA	1.4	1.6
	(95% CI)		(2.5, 8.4)	(-0.8, 5.2)		(-1.5, 4.2)	(-1.3, 4.5)

*Assessed as the average of the treatment effects at Week 16 and at Week 24
Source: Clinical Study Report

3 CONCLUSION

Results from the two phase 3 studies were similar; both dosing regimens of LUM/IVA were superior to placebo in terms of spirometry function. In study 809-103, treatment with LUM 600 mg qd/IVA 250 mg q12h and LUM 400mg/IVA 250mg q12h resulted in statistically significant average improvements in $ppFEV_1$ of 3.6% and 2.2%, respectively. The placebo response in this study was -0.4%. In study 809-104, the estimated mean improvement in $ppFEV_1$ was 2.5% for the LUM 600 mg qd/IVA 250 mg q12h group and 2.9% for the LUM 400mg/IVA 250mg q12h group. The placebo response in this study was -0.2%. The results were similar for absolute change from baseline in $ppFEV_1$ regardless of how change was determined, change at Week 24 or the average of Week 16 and Week 24. These results were also consistent regardless of age, sex, geographic region, disease severity at screening. Missing data was minimal and was not a concern.

Consistent improvements from baseline were also observed for the five key secondary endpoints; however; due to the sequential testing strategy employed to control the overall type I error, only the first key secondary endpoint (relative change in $ppFEV_1$) provided replicated evidence of a treatment effect. The analyses of BMI, CFQ-R, response rate based on improvement in $ppFEV_1$, and pulmonary exacerbations were not considered statistically significant.

Overall, the assessment of efficacy in the phase 3 clinical trials demonstrated that LUM/IVA regardless of dose provided consistent statistically significant benefit over placebo in terms of $ppFEV_1$. However, the clinical meaningfulness of the magnitude of the improvement remains to be determined by the clinical review team. Specifically for the proposed dose of LUM 400mg/IVA 250mg q12h, the average benefit was 2.6% over placebo in study 809-103 and 3.0% in study 809-104. These effect sizes are similar to that of ivacaftor alone. The reader is referred to Part B of the statistical briefing document for additional discussion on this issue.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

Statistical Review and Evaluation

PART B: CONTRIBUTION OF LUMACAFTOR AND EFFECT OF LUMACAFTOR/IVACAFTOR ON SWEAT CHLORIDE

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE
FOR ORKAMBI (IVACAFTOR/LUMACAFTOR)
NDA 206-038

Statistical briefing material for the Pulmonary-Allergy Drugs Advisory Committee
May 12, 2015

David Petullo
Division of Biometrics II

1 INTRODUCTION

The applicant submitted the results from two efficacy studies, VX12-809-103 (809-103) and VX12-809-104 (809-104) that evaluated placebo and two doses of lumacaftor/ivacaftor (LUM/IVA). These studies demonstrated a statistically significant treatment benefit in improving lung function (FEV_1). However, these studies did not evaluate either lumacaftor or ivacaftor as monotherapies. The Applicant's rationale for not including each component as monotherapy was that treatment with lumacaftor demonstrated a dose dependent decrease in percent predicted FEV_1 ($ppFEV_1$) in study VX12-809-102 (809-102), and ivacaftor was shown to be ineffective in study VX08-770-104 (770-104). Based on the results of study 770-104, the current label indicates in the *Limitations of Use* section that ivacaftor is "not effective in patients with CF who are homozygous for the F508del mutation in the CFTR gene."

The Division agreed that evaluation of lumacaftor as a monotherapy would not be required as it is unlikely to be developed for use as a single ingredient therapy and demonstrated a dose-dependent decrease in $ppFEV_1$. However, ivacaftor did not demonstrate such a decrease in $ppFEV_1$ and is an approved drug. In an attempt to evaluate the contribution of lumacaftor, the results from study 770-104 are discussed with respect to the results from studies 809-103 and 809-104 using a non-inferiority (NI) approach. In studies 809-103 and 809-104, this approach considers the dose indicated on the proposed label, LUM 400mg/IVA 250mg q12h, and changes in $ppFEV_1$ and exacerbation rates. Although all studies evaluated changes in BMI and CFQ-R, these endpoints were not included as they failed to show substantial evidence of a treatment effect in in studies 809-103 and 809-104. Changes in $ppFEV_1$ and exacerbation rates were significantly better than placebo in these studies. Note, adjustments for multiplicity were not considered, a p-value < 0.05 was considered significant. The reader is referred to the clinical and Part A of statistical sections of the PADAC briefing document for consideration of multiplicity and significance.

Studies 809-103 and 809-104 did not evaluate changes in sweat chloride, considered a diagnostic marker of CF and indicator of CFTR ion channel function. The results from study 809-102 were evaluated to explore changes in sweat chloride following 4 weeks of treatment with lumacaftor monotherapy followed by four weeks of treatment with LUM/IVA.

2 CONTRIBUTION OF LUMACAFTOR

The applicant's rationale for not evaluating ivacaftor or lumacaftor as monotherapies is given below.

> A lumacaftor monotherapy arm was not included in Studies 103 and 104 because results from Study 102 showed a dose-dependent decline in percent predicted FEV1 during treatment with lumacaftor monotherapy. This decline was statistically significant at the highest lumacaftor dose tested (400 mg q12h, within-group analysis). Given the lack of efficacy of lumacaftor monotherapy in clinical studies, coupled with a low response in vitro to lumacaftor alone in airway epithelial cells from patients homozygous for the F508del-CFTR mutation, further clinical evaluation of lumacaftor monotherapy was considered unlikely to reveal significant benefit.
>
> An ivacaftor monotherapy arm was not included in Studies 103 and 104 because evaluating the overall results from Study 770-104 had previously demonstrated that there was no clinically meaningful benefit after 16 weeks of treatment with ivacaftor monotherapy (150 mg q12h) in subjects homozygous for the F508del-CFTR mutation.

The Agency agreed with the rationale provided for not evaluating the contribution of ivacaftor to the combination product. However, the contribution of lumacaftor does need to be evaluated, i.e. does the combination product provides a treatment benefit over ivacaftor monotherapy. The Applicant's argument in our view is essentially identical to a non-inferiority (NI) argument but is missing an essential piece. The Applicant concluded that LUM/IVA is superior to ivacaftor by making the following assumptions.

1. Placebo was shown to be similar or non-inferior to ivacaftor (Study 770-104)
2. LUM/IVA was superior to placebo (Studies 809-103 and 809-104)
3. LUM/IVA is better than ivacaftor since LUM/IVA beat placebo and placebo was shown to be non-inferior to ivacaftor.

The absence of a statistically significant difference between ivacaftor alone and placebo does not in itself establish that ivacaftor is similar enough to placebo to sustain this argument. Study 770-104 does, however, provide an upper confidence bound on the difference between ivacaftor and placebo, so that it permits the inferiority of placebo to ivacaftor to be assessed. As I will show, this bound is not tight enough for the purpose. That is, the combined results of Study 770-104 with 809-103 and 809-104 do not show that the effect LUM/IVA is more than that of ivacaftor alone.

To evaluate the contribution of lumacaftor to LUM/IVA, I continued with the NI approach to test if LUM/IVA was superior to ivacaftor with respect to ppFEV1 and pulmonary exacerbations utilizing the synthesis method. This approach required an assessment of the constancy assumption, i.e., were the studies similar in design, patient population, standard of care, and so forth. This approach considers that LUM/IVA was superior to placebo but does not depend on the conclusion that ivacaftor was similar to placebo. The synthesis method which does not require a NI margin, allowed a comparison of LUM/IVA to ivacaftor by combining the variance across studies. A 95%

confidence (CI) for the difference between ivacaftor and LUM/IVA was derived. If this CI excluded 0 (1 for exacerbations), one could conclude with 95% confidence that LUM/IVA was superior to placebo if one is willing to accept that the effect of ivacaftor in study 770-104 was similar across studies.

Below I discuss the study design, endpoints, statistical analysis, and results from study 770-104. For a detailed discussion of studies 809-103 and 809-104, the reader is referred to the clinical and Part A of the statistical sections of the PADAC briefing document.

2.1 STUDY DESIGN

Study 770-104 was a randomized, double-blind, placebo controlled trial that evaluated the safety and efficacy of ivacaftor in subjects 12 years of age and older with CF homozygous for the *F508del CFTR* mutation. This study was conducted in two parts, A and B. Part A was a 16-week, double-blind, placebo-controlled study where eligible subjects were randomized in 4:1 ratio to ivacaftor 150 mg or placebo administered every 12 hours (q12h). No formal sample size power calculations were performed for this study with respect to efficacy. A sample size of 120 subjects was deemed adequate to evaluate the safety of the ivacaftor in patients homozygous for the *F508del* mutation. Subjects who completed 16 weeks of study drug treatment in Part A, and met a pre-defined responder criterion could elect to participate in Part B. The protocol-defined responder criteria were established based on changes in FEV_1 and sweat chloride, given the desired clinical benefit of ivacaftor (improvement in lung function) and its mechanism of action. This review focuses on Part A of study 770-104.

2.2 ENDPOINTS

Lung function (FEV_1) was measured at baseline, day 15, Week 8, and Week 16. Pulmonary exacerbations were defined as new, or changed, antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the following signs or symptoms: change in sputum, new or increased hemoptysis, increased cough, increased dyspnea, malaise, fatigue, or lethargy, temperature above 38°C (equivalent to approximately 100.4°F), anorexia or weight loss, sinus pain or tenderness, change in sinus discharge, change in physical examination of the chest, decrease in pulmonary function by 10%, radiographic changes indicative of pulmonary infection. This definition of an exacerbation was the same in studies 809-103 and 809-104.

2.3 STATISTICAL METHODOLOGIES

Changes from baseline at Week 16 in $ppFEV_1$ (absolute and relative), were compared between ivacaftor and placebo using an ANCOVA model with treatment and baseline value. A crude rate of pulmonary exacerbation (number of events/days on study) was determined for each treatment arm and the rate ratio between placebo and ivacaftor was obtained.

To evaluate the contribution of lumacaftor, a NI approach was explored after it was determined that the studies were similar enough in design that the constancy assumption was not violated. To obtain an estimate of the treatment effect with respect to $ppFEV_1$ and rate of pulmonary exacerbations, the results from studies 809-103 and 809-104 were integrated. Next, 95% CIs for the difference from placebo were calculated for ivacaftor (study 770-104) and LUM/IVA. The synthesis method was utilized to combine the variance from study 770-104 with the integrated results from studies 809-103 and 809-104. If the 95% CI for the difference between LUM/IVA and ivacaftor does not contain zero, superiority was established.

2.4 RESULTS

Study 770-104 was previously reviewed under NDA 203-188 and failed to show a significant treatment benefit for ivacaftor with respect to $ppFEV_1$, CFQ-R, BMI, and rate of pulmonary exacerbations. Changes in sweat chloride were significantly different from placebo but did not consider any adjustments for multiplicity. The 95% CI for difference from placebo for the change from baseline through Week 16 is shown for each endpoint in Table 1. Exacerbation is presented as a rate ratio of ivacaftor and placebo.

Table 1. Efficacy results from study 770-104

Endpoint	difference from placebo	95% CI
ΔppFEV1	1.7[a]	[-0.6, 4.1]
Δ sweat chloride	-2.9[a]	[-5.6, -0.2]
Δ CFQ-R	1.3[a]	[-2.9, 5.6]
Δ BMI	-0.07[b]	[-0.4, 0.2]
Exacerbation (rate ratio)	0.68[c]	[0.33, 1.4]

Source: Reviewer
a: MMRM with baseline, age, visit, treatment, and visit*treatment
b: LME with treatment, visit, age, baseline $ppFEV_1$
#: Poisson regression with age, baseline $ppFEV_1$, visit, treatment, and visit*treatment

Considering the constancy assumption, the similarity of the trials was examined. The main differences between study 770-104 and studies 809-103 and 809-104 were duration of treatment and inclusion criteria. Study 770-104 consisted of 16 weeks of double-blind treatment whereas studies 809-103 and 809-104 were 24 weeks. To adjust for the differences in treatment duration, for changes in $ppFEV_1$, the change from baseline at Week 16 was examined rather than through 16 weeks, i.e., a repeated measures analysis. For exacerbation, annualized crude rates were considered without an adjustment for treatment duration. With respect to baseline lung function, subjects with a baseline $ppFEV_1$ greater than 90% were excluded. There were 8 placebo subjects and 38 ivacaftor subjects whose baseline $ppFEV_1$ was greater than 90%. Additionally there was 1 subject in study 809-103 and 5 subjects in study 809-104 whose baseline $ppFEV_1$ was greater than 90%. The results using all patients regardless of baseline lung function is also reported as it would represent all randomized and treated subjects.

The demographics and baseline characteristics with the exception of baseline $ppFEV_1$ across the three studies were deemed to be similar enough to proceed with the NI approach. The reader is referred to the clinical sections of the PADAC briefing document for the demographics and baseline characteristics from studies 770-104, 809-103 and 809-104.

$ppFEV_1$: The results for lung function are presented in terms of $ppFEV_1$ at baseline and change from baseline at Week 16 (absolute and relative) for each study in Table 2. From studies 809-103 and 809-104, only the results from the dose that is indicated on the proposed label, LUM 400mg/IVA 250mg q12h were presented.

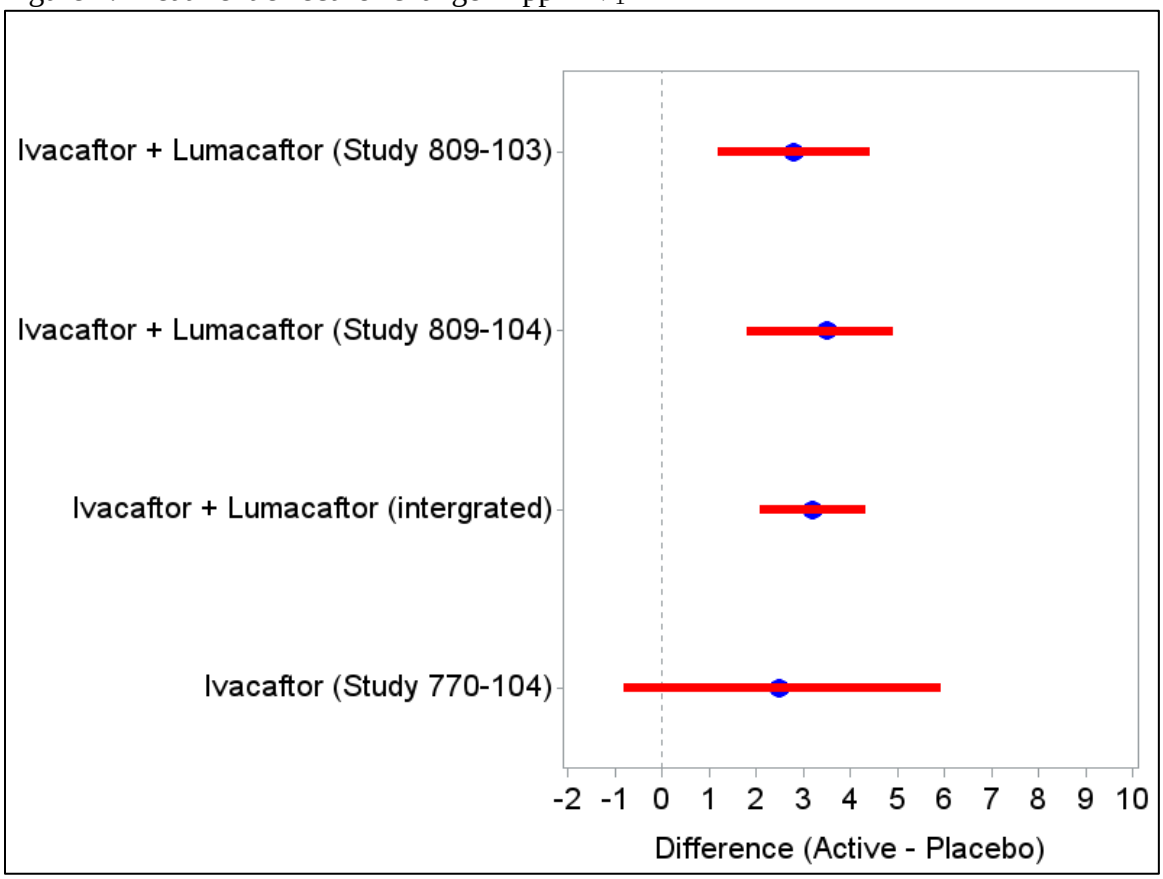
Table 2. Summary of $ppFEV_1$ at week 16 for all randomized subjects

Study	Time Point	$ppFEV_1$, LSMEAN* (SE)		
		placebo	Ivacaftor (150 mg q12h)	LUM 400mg / IVA 250mg q12h
770-104	Baseline	73.2 (4.5)	76.9 (2.2)	-
	Absolute Change*	-0.3 (1.5)	2.2 (0.8)	-
	Relative change#*	-0.4 (2.1)	3.2 (1.1)	-
809-103	Baseline	60.3 (13.1)	-	60.5 (14.3)
	Absolute Change	-0.2 (7.2)	-	2.6 (7.3)
	Relative change#	0.3 (12.6)	-	4.7 (13.0)
809-104	Baseline	60.2 (14.4)	-	60.3 (14.0)
	Absolute Change	-0.7 (7.2)	-	2.8 (7.1)
	Relative change#	-0.7 (13.4)	-	5.4 (12.8)

Source: Reviewer
*ANCOVA with baseline $ppFEV_1$, # Relative change is define as % change from baseline

The difference from placebo for change in $ppFEV_1$ for ivacaftor and LUM/IVA for all randomized subjects regardless of baseline lung function is presented in Figure 1 along with the associated 95% CI. The treatment effect for the pooled studies is also presented.

Figure 1. Treatment effect for change in $ppFEV_1$



Source: Reviewer

The data from study 770-104 was combined or synthesized with the results from the integration of studies 809-103 and 809-104. The 95% CI for the difference between LUM/IVA and ivacaftor is shown in Table 3. Results are presented with respect to baseline $ppFEV_1$, $\geq$ 40% or between 40-90%.

Table 3. Comparison of $ppFEV_1$ for LUM/IVA and ivacaftor by baseline $ppFEV_1$

Baseline $ppFEV_1$	Study	LSMEAN* [95% CI]	SE
40-90%	LUM/IVA (integrated)	3.2 [2.1, 4.3]	0.6
	770-104	2.6 [-1.1, 6.4]	1.9
	Combo-Mono (synthesized)	0.6 [-3.3, 4.5]	2.0
≥40%	LUM/IVA (integrated)	3.2 [2.1, 4.3]	0.6
	770-104	2.5 [-0.8, 5.9]	1.7
	Combo-Mono (synthesized)	0.7 [-2.8, 4.1]	1.8

Source: Reviewer
*ANCOVA with treatment and baseline $ppFEV_1$

Superiority was not established. Inclusion or exclusion of subjects based on baseline lung function was irrelevant.

Pulmonary Exacerbations: Crude exacerbation rates for the integrated LUM/IVA studies and study 770-104 are presented in Table 4. The definition of an exacerbation was identical in all studies. As results were similar for with respect to baseline lung function, results are presented for all randomized subjects.

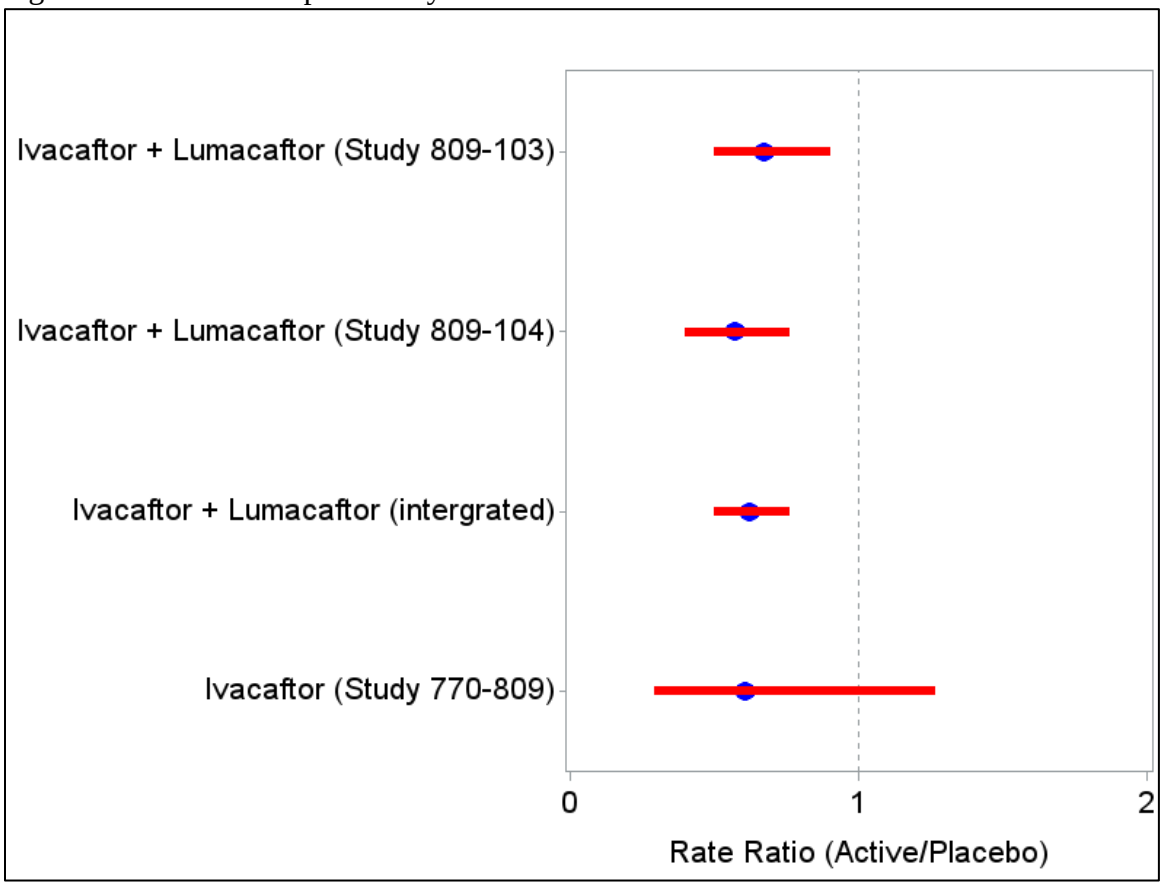
Table 4. Summary of pulmonary exacerbations

Study	Statistics	Exacerbations		
		placebo	Ivacaftor (150 mg q12h)	LUM 400mg / IVA 250mg q12h
770-104	n	28	112	-
	days on study	3038	12504	-
	Annual rate	1.2	0.73	-
	Rate ratio	-	0.61	-
	SE		0.37	-
Integrated*	n	371	-	369
	days on study	62427	-	61,057
	Annual rate	1.5	-	0.91
	Rate ratio	-	-	0.62
	SE	-	-	0.1

Source: Reviewer
*Studies 809-103 and 809-104

The rate ratios and associated 95% CIs are shown Figure 2. A ratio of one would indicate no difference in exacerbation rates.

Figure 2. Rate ratio for pulmonary exacerbations



Source: Reviewer

A direct comparison of LUM/IVA to ivacaftor is presented via the synthesis method in Table 5. Results are summarized based on baseline ppFEV$_1$, 40% or greater and between 40% and 90%. When I considered baseline ppFEV$_1$ between 40% and 90%, 10 subjects with 10 events were excluded from study 770-104. There were no events excluded from the LUM/IVA studies. However, days on study for those subjects that had baseline ppFEV$_1$ greater than 90% were not counted when determining exacerbation rates.

Table 5. Rate ratio of pulmonary exacerbations

Baseline $ppFEV_1$	Study	Exacerbations Rate Ratio [95% CI]	SE
40-90%	LUM/IVA (integrated)	0.62 [0.51, 0.76]	0.10
	770-104	0.56 [0.27, 1.17]	0.37
	Combo/Mono (synthesized)	1.10 [0.52, 2.37]	0.44
≥40%	LUM/IVA (integrated)	0.62 [0.50, 0.76]	0.06
	770-104	0.68 [0.33, 1.37]	0.18
	Combo/Mono (synthesized)	1.02 [0.48, 2.18]	0.39

Source: Reviewer

Again, as observed with change in $ppFEV_1$, superiority was not established and baseline lung function was irrelevant.

2.5 DISCUSSION

The Applicant's claims that ivacaftor was similar to placebo, LUM/IVA was better than ivacaftor, and hence LUM/IVA was better than ivacaftor is misleading. The use of the words "similar" and "better" refer to results that are in fact indistinguishable. In my opinion, it would be a bad idea to conclude that ivacaftor was similar to placebo and even worse to conclude that LUM/IVA was better than placebo. To correct this, I utilized an approach that assumed that LUM/IVA was better than placebo and the effect of ivacaftor in study 770-104 would be similar in studies 809-103 and 809-104. The results from these analyses could not conclude with any level of confidence that LUM/IVA was significantly different from ivacaftor with respect to changes in $ppFEV_1$ and pulmonary exacerbations. Exclusion of subjects with greater than 90% $ppFEV_1$ at baseline did not impact the conclusions.

On February 23 an information request was sent to the sponsor requesting an evaluation of the contribution of lumacaftor to LUM/IVA. Below is an excerpt from the response that was received.

1. The nature of the molecular defect caused by the *F508del-CFTR* mutation is well established and LUM is essential to address the underlying cause of disease in patients homozygous for the *F508del-CFTR* mutation.

2. Nonclinical data quantitate the contribution of each drug to the improvement in F508del-CFTR function, and show that there is minimal effect of IVA alone while superior improvement in F508del-CFTR function is provided by the combination of LUM and IVA compared to either agent alone.

3. The improvements in F508del-CFTR function in vitro translate to the sweat chloride response in subjects homozygous for the *F508del-CFTR* mutation, and confirm that superior improvement is provided by the combination of LUM and IVA compared to either agent alone.

4. Clinical evidence demonstrates that LUM/IVA combination therapy is highly efficacious and clinically superior to IVA monotherapy in homozygous *F508del-CFTR* subjects, confirming that LUM is an essential component of the combination product.

A robust Phase 3 clinical program demonstrated rapid, consistent, and sustained improvements in respiratory and systemic parameters with LUM/IVA combination therapy, notably including marked reductions in severe pulmonary exacerbations. LUM/IVA was well-tolerated, with a favorable safety profile in more than 1000 subjects. This positive clinical benefit/risk profile supports approval of the LUM/IVA combination therapy in patients age 12 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene. In contrast, as indicated in the Kalydeco label, IVA monotherapy evaluated in this population did not show a consistent and meaningful clinical benefit.

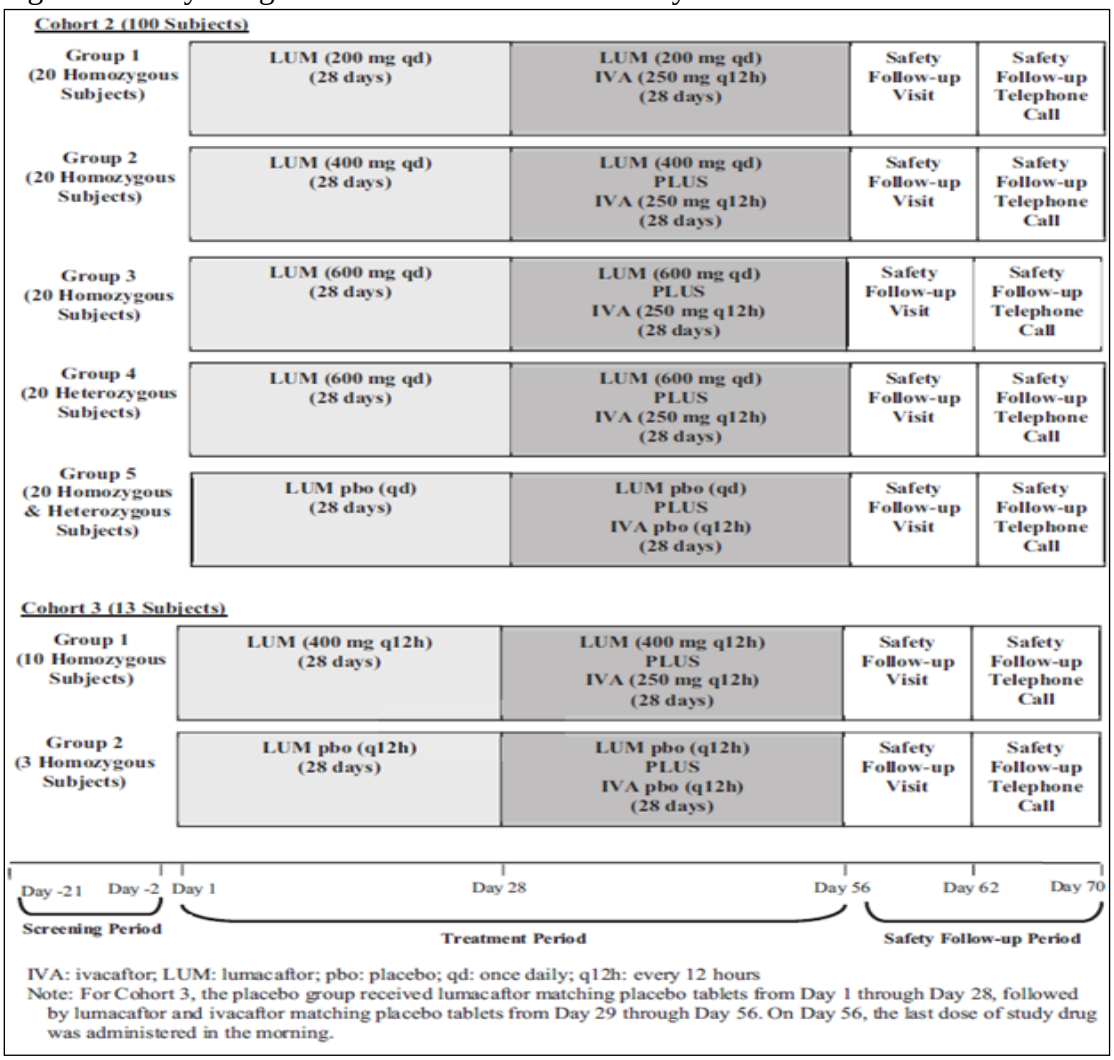
The applicant also provided the results from an integrated analysis of studies 770-104, 103, and 102 noting the limitations of such an analysis (results not shown). This analysis did not demonstrate a significant difference between LUM/IVA and ivacaftor.

3 SWEAT CHLORIDE

3.1 STUDY DESIGN

Study 809-102 was a randomized, double-blind, placebo-controlled, dose-ranging study that evaluated lumacaftor monotherapy and LUM/IVA in subjects that had the *F508del* mutation in the *CFTR* gene. This study was conducted in four different cohorts; however, this review focuses on the homozygous subjects from cohorts 2 and 3 where subjects received lumacaftor for 28 days followed by LUM/IVA for an additional 28 days. A schematic of the study design for cohorts 2 and 3 is shown in Figure 3. The reader is referred to the clinical section of the PADAC briefing document for a detailed discussion of the study design.

Figure 3. Study design for Cohorts 1and 2 from study 809-102



Source: modified from figures 9-2 and 9-3 of applicant's CSR

3.2 ENDPOINTS

Sweat chloride was measured before study drug administration at baseline and on days 28 and 56. An additional measurement was taken 4 hours after study drug administration on days 28 and 56.

3.3 STATISTICAL METHODOLOGIES

Sweat chloride (mmol/L) is presented as the mean and standard deviation at baseline, Day 28, change from baseline at Day 28, Day 56, and the change from baseline at Day

56. The change from baseline at days 28 and 56 used sweat chloride values measured at treatment administration and 4 hours after treatment administration. The change in sweat chloride is compared to placebo for each dosing regimen of active drug using an ANCOVA model with treatment and baseline sweat chloride. In this analysis, the placebo groups for cohorts 2 and 3 were pooled as the changes in sweat chloride appeared similar. Missing data was minimal therefore only available data were analyzed.

3.4 RESULTS

A summary of sweat chloride results is presented in Table 6. Results are summarized according to when sweat chloride was measured.

Table 6. Summary of sweat chloride data for homozygous subjects in Cohorts 2 and 3

SWCl measured	Time	Sweat Chloride (mmol/L), mean (stdev)				
		Pooled Placebo	lumacaftor/ivacaftor (mg)[c]			
			200[a]/250[b]	400[a]/250[b]	600[a]/250[b]	400[b]/250[b]
At dosing	Baseline	97.5 (8.8)	97.1 (9.8)	98.2 (7.1)	98.8 (11.9)	102.4 (8.9)
	Δ Day 28	0.6 (7.7)	-4.4 (6.8)	-8.1 (7.6)	-6.0 (11.0)	-9.3 (9.2)
	Δ Day 56	0.2 (9.3)	-3.9 (9.6)	-8.9 (11.4)	-8.9 (10.2)	-12.2 (6.6)
4-hours post-dose	Baseline	97.5 (8.8)	97.1 (9.8)	98.2 (7.1)	98.8 (11.9)	102.4 (8.9)
	Δ Day 28	3.7 (7.7)	-3.3 (9.4)	-7.1 (14.3)	-8.4 (10.8)	-2.6 (14.3)
	Δ Day 56	3.2 (10.9)	0.2 (9.0)	-6.1 (12.5)	-6.4 (11.5)	-3.4 (7.8)

Source: Reviewer
a: once daily dosing, b: twice daily dosing, c: during weeks 1-4, subjects received lumacaftor, during weeks 5-8, subjects received lumacaftor/ivacaftor

Regardless of when sweat chloride was measured, either at time of study drug administration or 4 hours after administration, there was a decrease in sweat chloride irrespective of dose. Difference from placebo is shown in Table 7.

Table 7. Difference from placebo for change in sweat chloride

measured	Day	Difference from placebo for change in SWCL (mmol/L) , LSMEAN* [95% CI] lumacaftor/ivacaftor (mg)[c]			
		200[a]/250[b]	400[a]/250[b]	600[a]/250[b]	400[b]/250[b]
At dosing	28	-5.5 [-10.5,-0.5]	-8.8 [-13.9, -3.7]	-6.7 [-11.8. -1.7]	-8.9 [-15.2, -2.6]
	56	-4.7 [-10.7, 1.3]	-9.5 [-15.5, -3.5]	-9.2 [-15.3, -3.1]	-10.7 [-18.5, -2.9]
4-hours Post-dose	28	-7.0 [-13.8, -0.2]	-6.3 [-15.7, 3.1]	-12.1 [-19.1, -5.1]	-4.2 [-13.5, 5.0]
	56	-3.5 [-10.1, 3.0]	-9.5 [-16.1, -2.9]	-9.6 [-16.2, -2.9]	-5.0 [-13.2,3.2]

Source: Reviewer
a: once daily dosing, b: twice daily dosing, c: during weeks 1-4, subjects received lumacaftor, in weeks 5-8, subjects received lumacaftor/ivacaftor

3.5 DISCUSSION

There was a decrease in sweat chloride following four weeks of treatment with lumacaftor regardless of dose. However, the effect observed after an additional four weeks of treatment with LUM/IVA depends on when sweat chloride was measured. If measured at the time of treatment administration, there was some added benefit, i.e., there was a numerical decrease in sweat chloride following an additional four weeks of treatment with LUM/IVA. However, if sweat chloride was measured four hours after study drug administration, there was no additional benefit, in fact in most cases the sweat chloride increased although it did not return to baseline levels. However, these decreases observed for sweat chloride, approximately10 mmol/L, were small especially in the context of the sweat chloride response observed for ivacaftor in the *G551D* and *R117H* mutations, approximately 50 and 24 mmol/L, respectively.

4 CONCLUSION

The contribution of lumacaftor to the efficacy of the proposed combination product has not been shown. In addition, the Applicant reported that the results from study 770-104 demonstrated that ivacaftor provides no clinically meaningful benefit. However, the estimated effect of LUM/IVA on $ppFEV_1$ was 2-3% which is similar to the plausible effects noted for ivacaftor (estimate: 1.7%; 95% CI: -0.6%, 4.1%), questioning the clinical relevance of the LUM/IVA effect.

Treatment with lumacaftor for four weeks produced a small numerical decrease in sweat chloride that was maintained after an additional four weeks of treatment with LUM/IVA. There was some variability in the results depending on when sweat chloride was measured, either at dosing or 4 hours after doing. Regardless, the mean decreased observed at Week 16 was still numerically lower than mean response at baseline. However, the decreases observed for sweat chloride were small when compared to the sweat chloride response noted for ivacaftor in the *G551D* and *R117H* mutations.