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APPLICATION NUMBER:

206038Orig1s000

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	206038
Priority or Standard	Priority
Submit Date(s)	November 5, 2014
Received Date(s)	November 5, 2014
PDUFA Goal Date	July 5, 2015
Division / Office	DPARP/ODE II
Reviewer Name(s)	Robert Lim
Review Completion Date	June 2, 2015
Established Name	Lumacaftor/Ivacaftor
(Proposed) Trade Name	Orkambi
Therapeutic Class	Unclassified/CFTR potentiator
Applicant	Vertex
Formulation(s)	Oral Tablet
Dosing Regimen	Lumacaftor 400mg/Ivacaftor 250mg q12
Indication(s)	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
Intended Population(s)	CF patients ≥12 years who homozygous for the *F508del* mutation in the CFTR gene

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The recommended regulatory action, from a clinical prospective, is Approval of the fixed dose combination (FDC) oral tablet of lumacaftor 400mg/ivacaftor 250mg q12 hours 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 demonstration of replicate evidence of efficacy along with an acceptable safety profile, warrants the recommendation of Approval.

1.2 Risk Benefit Assessment

To support the efficacy of the lumacaftor/ivacaftor (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 each LUM/IVA FDC study, both LUM/IVA doses demonstrated statistically significant increases in absolute percent predicted FEV1 ($ppFEV_1$) (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. LUM/IVA failed to demonstrate a statistically significant improvement in CFQ-R-respiratory domain scores in both studies. For BMI, a statistically significant improvement was observed in one study, but not the other. Positive treatment effects in both studies were observed for relative change in $ppFEV_1$ in both studies, which were statistically significant, and for response rate and number of exacerbations. Overall, these data demonstrate that LUM/IVA treatment results in a clinically meaningful benefit above placebo for *F508del* homozygous patients.

When comparing the nominal treatment effect of IVA alone from study 770-104 to LUM/IVA from studies 809-103 and 809-104, point estimates were numerically similar for the shared efficacy variables and given the wide 95% confidence intervals observed for IVA in study 770-104, it could not be determined if LUM/IVA offered an added clinical effect above IVA alone or if LUM contributed to the clinical effect of the combination.

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 system organ class (SOC) or preferred term (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 adverse events of interest; 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 in at least some patients. 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.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

None

2 Introduction and Regulatory Background

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 worldwide2. 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 to 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

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

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 probability4. Ultimately, these deficiencies result in a relatively severe disease phenotype.

2.1 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 FDC tablet for oral administration. The proposed product for marketing contains 200mg of LUM and 125mg of IVA with the proposed dose of 2 tablets given every 12 hours (LUM 400mg/IVA 250 mg).

2.2 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.

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

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]		

2.3 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.

2.4 Important Safety Issues With Consideration to Related Drugs

Ivacaftor:
Cataracts were seen in juvenile rats dosed with IVA 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 IVA. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating IVA treatment. Elevated transaminases have also been reported in patients with CF receiving IVA. Liver transaminases should be assessed in patients receiving IVA.

Lumacaftor:
During the dose-ranging program it was noted that LUM, when administered alone, caused a dose dependent decrease in $ppFEV_1$. One could hypothesize that this signal manifested as the nominal increase in respiratory AEs that were observed in Phase 3 studies and, as such, that some minority of patients may not tolerate the combination product. 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.

2.5 Summary of Presubmission 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 IVA 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 section 6 Review of Efficacy, the nominal treatment effect on $ppFEV_1$ compared to placebo was small (1.7%) and, in the context of IVA demonstrating a 10-12% increase in $ppFEV_1$ compared to placebo in patients with a *G551D* mutation, lead to the determination that IVA was not effective in patients homozygous for the *F508del* mutation.

The clinical program for LUM monotherapy was limited to early studies where it was demonstrated that LUM 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 IVA monotherapy control was not required for phase 3 studies based on data from Study 770-104 for the IVA monotherapy development program.

December 7, 2012:

- Breakthrough designation was granted for the LUM/IVA combination.

February 12, 2013 Type B meeting:

- Due to the safety concern over dose dependent decreases in $ppFEV_1$ following LUM monotherapy, a LUM monotherapy control was not required in the phase 3 studies [see section 4.4.2 Pharmacodynamics)
- To support an exacerbation claim the Division recommended replicate evidence in 48-week trials

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 LUM contributes to the efficacy of the product.
- Secondary endpoints would be an important part of the overall evaluation of efficacy.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This NDA was submitted on November 5, 2014. The submission was appropriately indexed and complete to allow for review. There were no issues with submission quality or data integrity. Three audits have been requested. The sites were reviewed for audit selection based on the following criteria: 1) Number of patients, 2) important protocol deviations, 3) discontinuations, 4) treatment effect size. As both discontinuations and important protocol violations were infrequent and generally evenly split across sites, and

because no single site appeared to drive efficacy results; the three sites were primarily selected based on the number of patients. Preliminary results from the clinical site audits did not demonstrate any findings which bring into question data integrity.

3.2 Compliance with Good Clinical Practices

A statement of compliance with Good Clinical Practices is located in the clinical study report, within the electronic submission.

3.3 Financial Disclosures

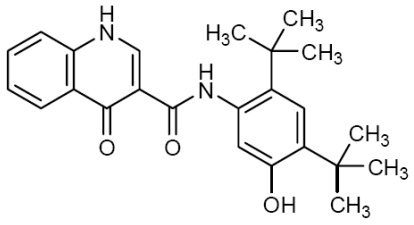
The Applicant has submitted a statement certifying that no debarred individuals were used in the conduct of the trials included in this NDA. See appendix 9.4 for financial disclosures.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

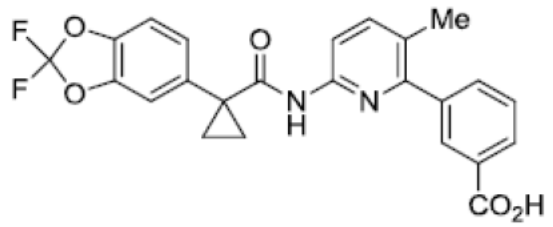
4.1 Chemistry Manufacturing and Controls

The proposed product combines lumacaftor and ivacaftor (LUM/IVA).

Ivacaftor:
The chemical name for ivacaftor (tradename Kalydeco) is N-(2, 4-Di-tert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxymide. The molecular formula of is $C_{24}H_{28}N_2O_3$ and its molecular weight is 392.49 grams per mole. Ivacaftor has the following structural formula:



Lumacaftor:
The chemical name for lumacaftor is 3-[6-({[1-(2,2-difluoro-1,3-benzodioxol-5-yl)cyclopropyl]carbonyl}amino)-3-methylpyridin-2- yl]benzoic acid. The molecular formula of is $C_{24}H_{18}F_2N_2O_5$ and its molecular weight is 452.41 grams per mole. Lumacaftor has the following structural formula:



The LUM/IVA drug product is an immediate release tablet for oral administration. For the proposed dose (LUM/IVA 400/250mg q12), the tablet contained 200mg of LUM and 125mg of IVA. The tablets were formulated as a (b) (4) pink film coated tablet. Each tablet contains the following excipients: microcrystalline cellulose, croscarmellose sodium, sodium laural sulfate, povidone (b) (4), hypromellose acetate succinate, and magnesium stearate. The tablet film coat contains polyvinyl alcohol, titanium dioxide, PEG (b) (4), talc, carmine, FD&C Blue #1 and #2, (b) (4)

The recommendation from the CMC Review is for Approval pending facility inspections. Please refer to the CMC Review for more detailed information.

4.2 Clinical Microbiology

The recommendation from the Clinical Microbiology Review is for Approval. Please refer to the primary Clinical Microbiology Review by Dr. Jessica Cole for more detailed information.

4.3 Preclinical Pharmacology/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 product label. Key findings included bilateral cataracts in a juvenile rat study.

The general toxicity of lumacaftor was evaluated in rat and dog studies of up to 6 and 12 months duration, respectively. Although CNS toxicity was evident in a 3-month study with dogs that a received a high dose of lumacaftor (approximately 3 times higher than the recommended clinical exposure), no target organs of toxicity were identified in either the chronic 6-month rat or 12-month 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.

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.

The Applicant also performed multiple *in vitro* pharmacology studies in human bronchoepithelial cells from *F508del* homozygous patients. These studies examined the effect of LUM, IVA, and LUM+IVA on *in vitro* chloride transport. The aggregate data from these *in vitro* studies suggest that the combination of LUM+IVA results in a greater effect on *F508del* CFTR chloride transport compared to the either LUM or IVA alone.

The recommendation from the Pharmacology Toxicology Review is for Approval. Please refer to Dr. Andrew Goodwin's primary Pharmacology/Toxicology Review for more detailed information

4.4 Clinical Pharmacology

4.4.1 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 may facilitate the cellular processing and trafficking of defective CFTR protein which may allow it to reach the cell surface.

4.4.2 Pharmacodynamics

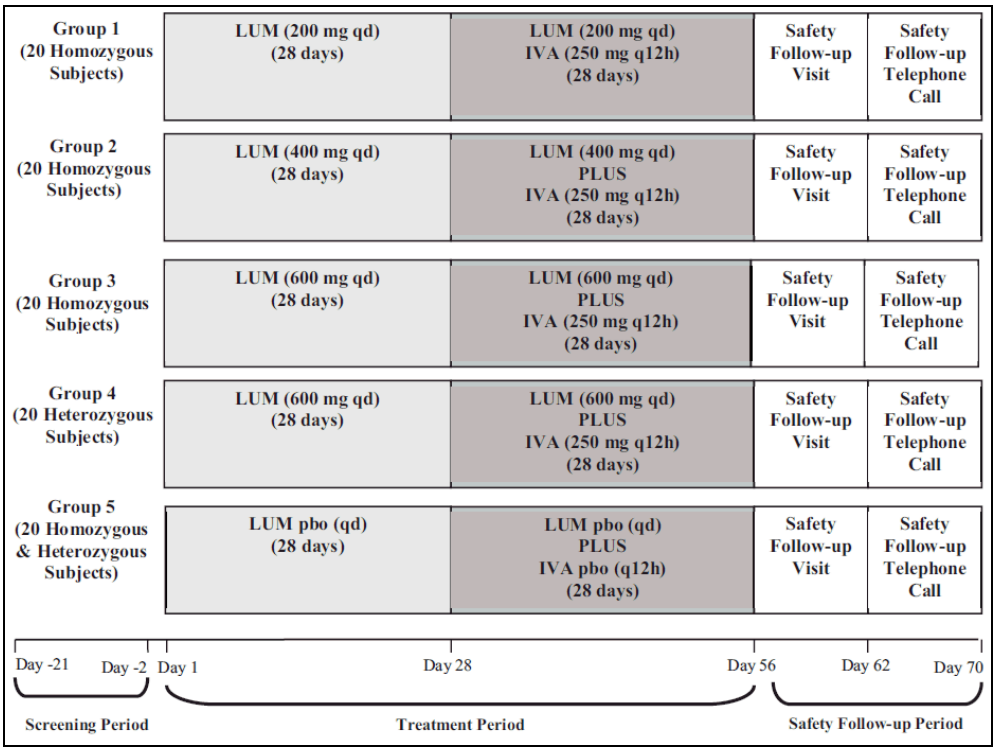
Dosing for the IVA component was initially based on the approved IVA monotherapy dose and subsequently the observed drug-drug interaction between LUM and IVA (see section 4.4.3 Pharmacokinetics). Because LUM is CYP3A inducer and IVA is a CYP3A substrate, co-administration of LUM with IVA results in substantially 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.

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 *F508del* 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 $ppFEV_1$.

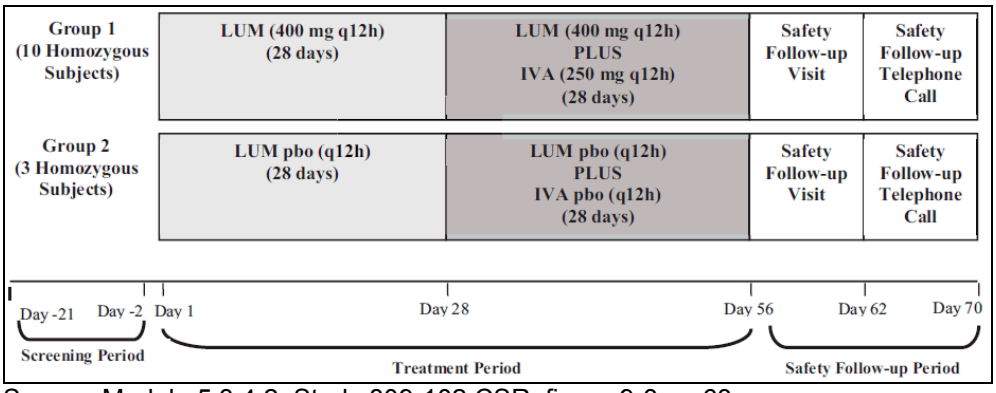
While this study included 4 cohorts (1-4), only cohorts 2 and 3 are relevant for LUM dose-ranging in *F508del* homozygous patients as these cohorts included both LUM alone and LUM/IVA treatment periods and *F508del* homozygous patients. Cohorts 2 and 3 consisted of an initial 28-day treatment period (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 1 and Figure 2.

Figure 1. Study 809-102. Cohort 2 Schematic



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

Figure 2. 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 2. 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 Statistical Review by David Petullo).

Table 2. Study 809-102 Cohorts 2 and 3. 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, pp68

After 28-days of treatment (day 0-28) sweat chloride values assessed at dosing decreased with all doses of LUM versus 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, additional decreases were not consistently observed across doses (see FDA Statistical Review by David Petullo). 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 or that the additive effect is not robust.

These sweat chloride results support the doses used in studies 809-103/104. However, it should be noted that the pharmacodynamic effect (10%) was modest, 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) were observed.

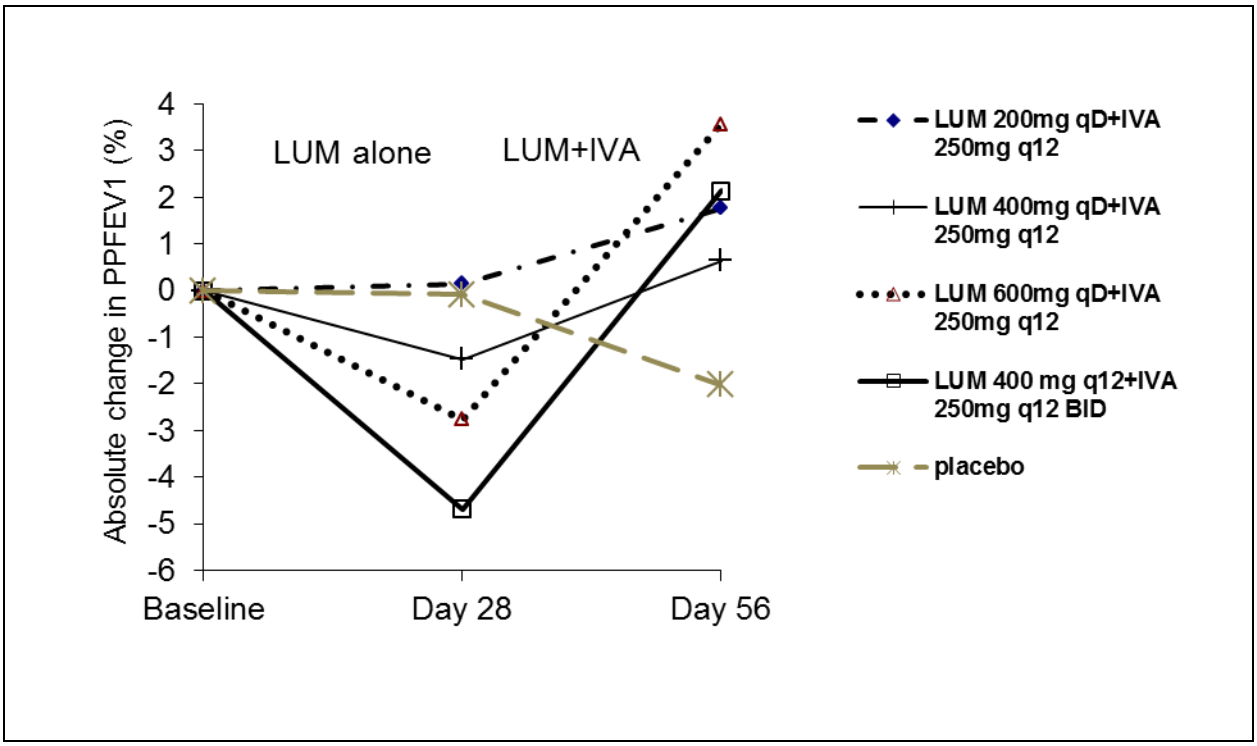
With regard to lung function, results showed that LUM monotherapy (baseline to day 28) resulted in a dose dependent decrease in $ppFEV_1$ in CF patients homozygous for the *F508del* mutation (Table 3). It was on this basis that LUM monotherapy was not required in the phase 3 LUM/IVA studies. In contrast, 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 3). Figure 3 summarizes the results for the within group comparisons in a graphical format.

Table 3. Study 809-102 Cohorts 2 and 3. 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 3. Study 809-102, Cohorts 2 and 3. Absolute change from baseline in percent predicted FEV_1 ($ppEFV_1$) at days 28 and 56 in *F508del* homozygous patients



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 on the safety signal inherent with lumacaftor monotherapy, exclusion a lumacaftor monotherapy treatment arm as well.

4.4.3 Pharmacokinetics

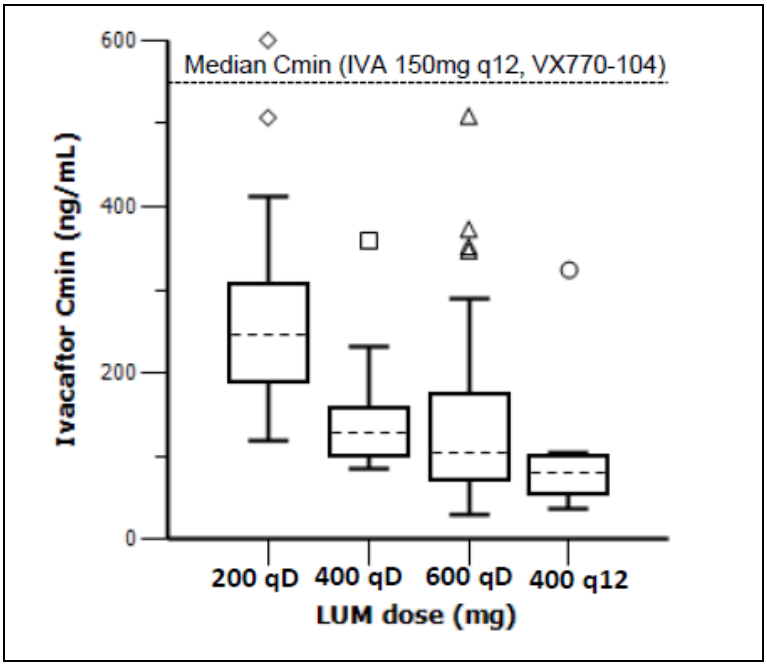
Ivacaftor:

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 4.

Figure 4. Ivacaftor exposure in CF patients when IVA 250mq12 was co-administered with varying doses of lumacaftor (study VX809-102)



Source: FDA Clinical Pharmacology Review

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.

The recommendation from the Clinical Pharmacology Review is for Approval. Please refer to the primary Clinical Pharmacology Review by Drs. Jianmeng Chen, Anshu Marathe for more detailed information

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The sources of clinical data used in this review are summarized in Table 4.

Table 4. Sources of clinical data

Study	Study Type/Design	Treatment Duration	Mutation	n	Treatment Arms	Endpoints	Regions/ Countries
809-102 Dates: 10/2010 -4/2014	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	Cohort 2-3: U.S. (75%) Europe (8%) Australia (17%) Cohort 4: U.S. (70%) Europe (18%) Australia (12%)
809-103 Dates: 5/2013-4/2014 **809-104** Dates: 4/2013-4/2014	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	809-103: U.S. (48%) Canada (5%) Europe (38%) Australia (9%) 809-104: U.S. (60%) Canada (2.5%) Europe (30%) Australia (8%)
809-105 Dates: 10/2013 - ongoing	Safety extension of 809-103/104	ongoing	*F508del* homozygous	1054	LUM 600mg qD/ IVA 250mg q12 LUM 400mg/IVA 250mg q12	Safety	
770-104 Dates: 9/2009-7/2011	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	U.S. (100%)

[a]this study contained 4 cohorts (1-4), however only data cohorts 2-4 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

5.2 Review Strategy

Support for efficacy of LUM/IVA in *F508del* homozygous CF patients 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 clinical 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 in which LUM monotherapy resulted in a dose-dependent decrease in $ppFEV_1$ in *F508del* homozygous patients (see Figure 3). 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 Study 770-104 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 IVA 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 and that approximated the $ppFEV_1$ point estimate for the previous IVA alone study 770-104, it is difficult to confirm whether the treatment effect for the LUM/IVA FDC is different than that observed for IVA monotherapy.

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 5.3 Discussion of Individual Studies/Clinical Trials. Efficacy data from studies 809-103, 809-104 and 770-104 are discussed in section 6 Review of Efficacy. Results from study 809-102 were previously discussed in section 4.4.2 Pharmacodynamics.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 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

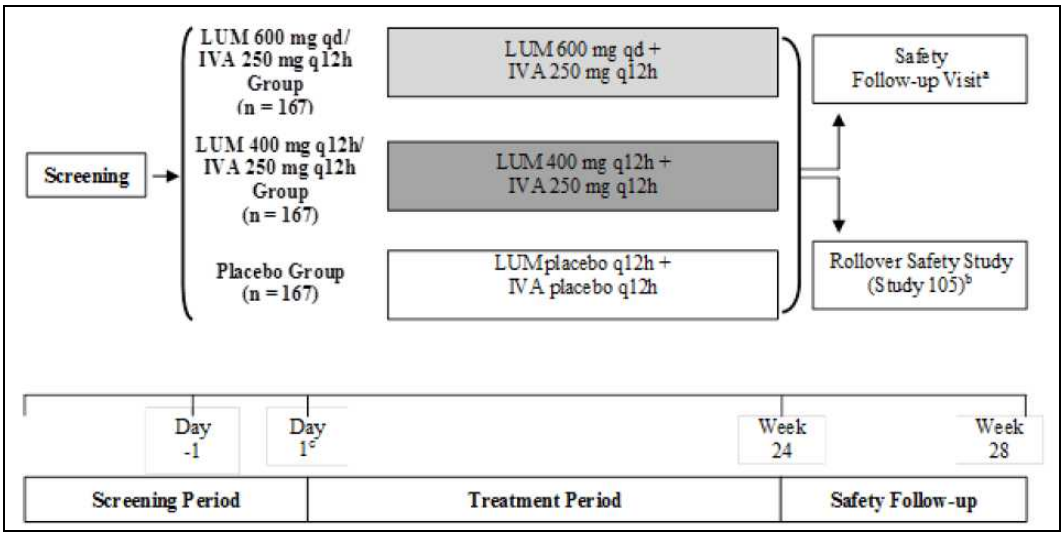
- To evaluate the safety of LUM/IVA through week 24 of treatment.
- To investigate the pharmacokinetics (PK) of lumacaftor and ivacaftor and their metabolites

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 ≥ 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 for respiratory symptoms relevant to patients with CF. The minimum clinically important difference is 4.

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.

5.3.2 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.

5.3.3 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.

5.3.4 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.

6 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. LUM/IVA failed to demonstrate a statistically significant improvement for CFQ-R respiratory domain in both studies. For BMI, a statistically significant improvement was observed in one study, but not the other. Positive treatment effects in both studies were observed for relative change in $ppFEV_1$, which were statistically significant, and for response rate and number of exacerbations. Overall, these data demonstrate that LUM/IVA treatment results in a clinically meaningful benefit above placebo for *F508del* homozygous patients.

With regard to IVA monotherapy (770-104), while there was a small numerical increase in $ppFEV_1$ when measured through the 16-week time point (the primary endpoint) compared to placebo with a point estimate of 1.7%, it was not statistically significant. For the efficacy endpoints of change in sweat chloride, weight, BMI, exacerbation, and CFQ-R-respiratory domain scores, the effect size was also small with p-values >0.05 except for sweat chloride. However, this study was not specifically powered to demonstrate efficacy.

When comparing the nominal treatment effect of IVA alone and LUM/IVA from study 770-104 to studies 809-103 and 809-104, the point estimates were numerical similar for the shared efficacy variables with 95% confidence intervals demonstrating considerable overlap (Table 8). 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, based on the data available, one cannot rule out that IVA alone may have a similar treatment effect, and whether LUM/IVA offers an additional clinical effect over IVA alone or if LUM contributes to the clinical effect of the combination 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 that the LUM/IVA treatment effect was not equivalent to IVA monotherapy or that LUM contributed to the clinical effect of LUM/IVA (see FDA Statistical Review by David Petullo).

Based on the available clinical data, it remains unproven whether LUM/IVA offers an added clinical effect above IVA alone and if LUM contributes to the LUM/IVA clinical effect in the *F508del* patient population. However, the scientific rationale for the combination suggests that each component contributes to the effect of the combination. The *in vitro* data also suggest an additive effect of LUM and IVA based on increases in chloride transport.

6.1 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.

6.1.1 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 effect of the LUM/IVA combination over ivacaftor monotherapy, relevant efficacy data from study 770-104 are also presented. Sections 6.1.2 and 6.1.3 will present the demographic and disposition results, respectively, for studies 809-103, 809-104, and 770-104. Efficacy data for studies 809-103 and 809-104 will be presented in sections 6.1.5 through 6.1.9. Efficacy data from study 770-104 will be presented in section 6.1.10.

6.1.2 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)	1 (0.7)
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

6.1.3 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 7Review of Safety).

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, few patients discontinued. Of the 1108 patients who receive study drug, 54 (4.9%) discontinued study treatment and 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

6.1.4 Analysis of Primary Endpoint(s)

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.

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)
p-value versus placebo		<0.0001	0.0003		0.0004	<0.0001

[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

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

6.1.5 Analysis of Secondary Endpoints(s)

Studies 809-103/104

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, the treatment effect all had nominal p-values >0.025 and were all below the MCID. 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)
p-value versus placebo		<0.0001	0.0006		0.0007	<0.0001
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)
p-value versus placebo		0.1122	0.1938		<0.0001	0.0001
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)	1.5 (-1.7, 4.7)	--	2.2 (-0.9, 5.3)	2.9 (-0.3, 6.0)
p-value versus placebo		0.0168[a]	0.3569[a]		0.1651	0.0736

[a]nominal p-value due to 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)	--	2.9 (1.9, 4.6)	2.1 (1.3, 3.3)	--	3.0 (1.9, 4.6)	2.4 (1.5, 3.7)
p-value versus placebo[a]		<0.0001	0.0023		<0.0001	<0.0001
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)	--	0.7 (0.5, 1.0)	0.7 (0.5, 1.0)	--	0.7 (0.5, 0.9)	0.6 (0.4, 0.8)
p-value versus placebo[a]		0.0491	0.0169		0.0116	0.0002

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

For the key secondary endpoints, in both studies, relative change from baseline in $ppFEV_1$ was supportive of the primary endpoint, as were the response rate and exacerbation endpoints, although not statistically significant due to earlier failures in the analysis hierarchy. In contrast, BMI was supportive of the primary endpoint in single study, and CFQ-R respiratory domain score was not supportive in either study.

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 a statistically significant improvement in CFQ-R-respiratory domain scores. For BMI, a statistically significant improvement was observed in one study, but not the other. Positive treatment effects in

both studies were observed for relative change in ppFEV1, which were statistically significant. Positive trends were also observed in both studies for response rate and number of exacerbations, however, these results were not statistically significant due to earlier failure in the analysis hierarchy. Overall these results indicate that LUM/IVA treatment resulted in clinically meaningful improvements compared to placebo.

6.1.6 Other Endpoints

Not applicable

6.1.7 Subpopulations

FDA statisticians performed subgroup analyses based on age, sex, $ppFEV_1$, and region (Table 16). 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 16. 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

6.1.8 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 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.

6.1.9 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.

6.1.10 Additional Efficacy Issues/Analyses

Contribution of the components to the combination
Studies 809-103 and 809-104 demonstrated that both LUM/IVA doses demonstrated statistically significant increases in absolute ppFEV1 compared to placebo ranging from 2.7-3.0% for the proposed dose of LUM 400mg/IVA 250mg q12. However, the effect size was numerically similar to that of ivacaftor 150mg q12 monotherapy in *F508del* homozygous CF patients observed in study 770-104. Given this numerical similarity, it is uncertain if LUM/IVA offered an added effect above IVA monotherapy or if the component contributed to the clinical effect of the combination. Results from study 770-104 are discussed below in the context of the LUM/IVA results from studies 809-103 and 809-104.

Study 770-104
The primary endpoint (absolute change from baseline) for study 770-104 was the same as for the LUM/IVA phase 3 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) in term of ppFEV1 through 16-weeks of treatment. 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, all p-values were >0.05. 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 17.

Table 17. 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)
p-value versus placebo		0.15
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)
p-value versus placebo		0.038
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)
p-value versus placebo		0.54
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)
p-value versus placebo		0.73
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)
p-value versus placebo		0.16
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)
p-value versus placebo		0.67
Number of pulmonary exacerbations		
Patients with events	8	20
Number of events Rate ratio vs placebo	10	25 0.68 (0.33, 1.4)
p-value versus placebo		0.28

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.

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 18). 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, based on the data available, one cannot rule out that IVA alone may have a similar treatment effect, and whether LUM/IVA offers an additional clinical effect over IVA alone or if LUM contributes to the clinical effect of the combination is uncertain.

Table 18. 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 that the LUM/IVA treatment effect was not equivalent to IVA monotherapy or that LUM contributed to the clinical effect of LUM/IVA (see FDA Statistical Review by David Petullo).

In summary, while *in vitro* data suggest lumacaftor may contribute to the effects of the LUM/IVA combination, based on the available clinical data, it cannot be definitively concluded that LUM/IVA offers an added clinical effect above IVA alone.

LUM/IVA in patients heterozygous for *F508del* mutation

One of the cohorts in study 809-104 (cohort 4) included CF patients who were heterozygous for the *F508del* mutation with a second allele predicted by the sponsor to be non-responsive to ivacaftor or to result in lack CFTR production. In this cohort 125 patients were randomized 1:1 to LUM 400mg/IVA 250mg q12 or placebo for a 56-day treatment period. The mean age of these patients was 30 years with baseline ppFEV1s of 61.5%. The primary efficacy endpoint for this cohort was change from baseline in ppFEV1 at day 56. Secondary endpoints included relative change in ppFEV1, BMI, CFQ-R respiratory domain, weight, and sweat chloride. Results for these endpoints are summarized in Table 19.

Table 19. Study 809-102 Cohort 4. Primary and Secondary endpoints

Endpoints	Change from Baseline		Treatment Effect (LUM/IVA minus Placebo)	
	Placebo N=63	LUM 400mg/IVA 250mg q12 N=62	Difference (95% CI)	p-value
Δ from baseline in ppFEV1	-1.23	-0.62	0.6 (-1.7, 2.9)	0.60
Relative Δ from baseline in ppFEV1	-2.2	-0.69	1.5 (-2.4, 5.4)	0.44
Δ from baseline in BMI	0.08	-0.04	-0.12 (-0.3, 0.1)	0.26
Δ from baseline in CFQ-R Respiratory Domain	-0.82	5.7	6.48 (1.4, 11.6)	0.01
Δ from baseline in weight (kg)	0.16	-0.11	-0.27 (-0.9, 0.3)	0.37
Δ from baseline in sweat chloride	-0.78	-11.9	-11.0 (-14.5, -7.6	<0.001

Source: Module 5.3.4.2; Study 809-102 CSR; table 14; pp9535-9536

These results appear to demonstrate that LUM/IVA has minimal non-statistically significant effects in *F508del* heterozygous patients in terms of ppFEV1, weight, and BMI. For CFQ-R respiratory domain and sweat chloride, the effect sizes are larger with nominal p-values <0.05. While these data are not supportive of efficacy, they are also not sufficient to definitively conclude that LUM/IVA has no effect in *F508del* heterozygotes, or any non-*F508del* homozygous CF patients.

7 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.

7.1 Methods

7.1.1 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).

7.1.2 Categorization of Adverse Events

The Applicant defined an adverse event (AE) as any untoward medical occurrence in a patient during the study, which does not require a causal relationship with study drug. Any abnormal laboratory assessment, ECG, vital sign or physical exam finding that was judged by the investigator as clinically significant worsening from baseline were to be reported as adverse events. Adverse events were classified using MedDRA Version 17.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Safety data was pooled across studies VX12-809-103 and 104.

7.2 Adequacy of Safety Assessments

7.2.1 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 20.

Table 20. 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 21. 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 21. 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.

7.2.2 Explorations for Dose Response

The phase 3 trials evaluated two doses of LUM/IVA to allow for an analysis of dose related safety. These analyses are embedded throughout this review of safety.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable

7.2.4 Routine Clinical Testing

Clinical laboratory testing in the phase 3 trials was performed as per tables in the individual trials reviewed 5.3 Discussion of Individual Studies/Clinical Trials

7.2.5 Metabolic, Clearance, and Interaction Workup

In this development program studies examining drug metabolism, clearance, and potential for interaction were performed by the Applicant (see section 4.4 Clinical Pharmacology).

7.2.6 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 phase 2 study, a dose dependent decrease in PPFEV1 was observed when lumacaftor was given as monotherapy. One could hypothesize that this signal manifested as the nominal increase in respiratory AEs that were observed in Phase 3 studies and, as such, that some minority of patients may not tolerate the combination product. 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.

7.3 Major Safety Results

7.3.1 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.

7.3.2 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 7.3.5 Submission Specific Primary Safety Concerns). Serious adverse event data are summarized in Table 22.

Table 22. 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

7.3.3 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 23.

Table 23. 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 was not observed in the placebo group. These data are summarized in Table 24.

Table 24. 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 25.

Table 25. 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.

7.3.4 Significant Adverse Events

See section 7.3.5.

7.3.5 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 26.

Table 26. 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 27.

Table 27. 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 28.

Table 28. 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)[a]	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) [a]	3 (0.4)

[a]Includes one patient with an elevation in bilirubin >2x ULN that was not included in the clinical data set
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 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 29.

Table 29. 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

Time to onset of respiratory related AESI are summarized in Table 30. The time to onset for the respiratory symptoms AESI was 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 30. 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 suggest that LUM/IVA exposure may result in increased respiratory symptoms and not be tolerated in a minority of patients .

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 31.

Table 31. 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

7.4 Supportive Safety Results

7.4.1 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 32. While there were some differences, they were generally small in magnitude.

Table 32. 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.

7.4.2 Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries including liver transaminases coagulation studies, and urinalyses. Findings regarding liver transaminases have already been discussed in section 7.3.5 Submission Specific Primary Safety Concerns and are not included in this discussion. For the remaining lab parameters, there were no clinically significant differences in either median or mean values when comparing placebo to LUM/IVA groups. These data were also analyzed in terms of potentially clinically significant (PCS) changes from baseline. The criteria used to define potentially clinically significant were reviewed and were reasonable. The analysis did not identify any clinically significant differences between groups.

7.4.3 Vital Signs

No clinically significant mean or median changes in systolic or diastolic blood pressure, heart rate, respiratory rate, body temperature, or oxygen saturation were observed in between placebo and LUM/IVA groups. These data were also analyzed in terms of potentially clinically significant (PCS) changes from baseline. The criteria used to define potentially clinically significant were reviewed and were reasonable. The analysis did not identify any clinically significant differences between groups.

7.4.4 Electrocardiograms (ECGs)

ECG data was analyzed in terms of potentially clinically significant (PCS) changes from baseline. The criteria used to define potentially clinically significant were reviewed and were reasonable. The number and percentage of patients with a PCS change from baseline were similar across treatment groups for PR interval and QRS duration. For both QTcF and QTcB, PCS changes were more common in the placebo group compared to either LUM/IVA dose group. Additionally, the percentage of patients with a normal baseline ECG who shifted to an abnormal ECG were similar when comparing placebo to either LUM/IVA group.

7.4.5 Special Safety Studies/Clinical Trials

Not performed

7.4.6 Immunogenicity

Not performed

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The 24-week placebo controlled studies included two LUM/IVA doses. Overall, no clear dose responses were demonstrated in terms of adverse events.

7.5.2 Time Dependency for Adverse Events

The safety profile from the placebo controlled safety set was similar to that observed in the ongoing extension study 809-105.

7.5.3 Drug-Demographic Interactions

Sub-group analysis was performed based on age, sex, and region. In general, when analyzing safety based on these sub-groups, results were consistent with the overall population and similar trends were observed when comparing placebo to LUM/IVA patients

7.5.4 Drug-Disease Interactions

Sub-group safety analysis was also performed based on baseline PPFEV1. In general, when analyzing safety in patients with baseline PPFEV1 ≥70% versus <70%, results were consistent with the overall population and similar trends were observed when comparing placebo to LUM/IVA patients.

7.5.5 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 co-administration of LUM/IVA with inhaled bronchodilator (ipratropium, albuterol, indacaterol, and tiotropium).

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

No human carcinogenicity studies have been performed for LUM/IVA

7.6.2 Human Reproduction and Pregnancy Data

The use of LUM/IVA in pregnant or lactating women has not been studied in adequate and well controlled trials. No pregnancies were reported in this trial.

7.6.3 Pediatrics and Assessment of Effects on Growth

Cystic Fibrosis is an orphan disease, and, as such, is not directly subject to pediatric study requirements as defined under the Pediatric Research Equity Act (PREA). However, trials VX12-809-103 and 104 included CF patients ≥12 to ≤17 years in age (n=290). Efficacy data in ≥12 to <18 year old age group were consistent with the ≥18 year age group (see 6 Review of Efficacy), as were the safety data.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable

7.7 Additional Submissions / Safety Issues

The Applicant submitted a 120-day safety report. No new safety issues were identified.

8 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 or that would affect the safety assessment of LUM/IVA.

9 Appendices

9.1 Literature Review/References

1. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry: 2013 Annual Data Report. Bethesda, Maryland;2014
2. Cystic Fibrosis Foundation. Cystic Fibrosis Foundation Patient Registry: 2013 Annual Data Report to the Center Directors. Bethesda, Maryland;2014
3. Farrell PM. The prevalence of cystic fibrosis in the European Union. J Cystic Fibrosis 2008;7(5):450-453.
4. 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
5. 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

9.2 Labeling Recommendations

At the time of this review, the label continues to be under review. Issues identified with the label include the following:

- Inclusion of efficacy and safety data from the ongoing safety extension study 809-105.
- (b) (4)
- Use of the term (b) (4) to describe LUM pharmacological class
- Lack of inclusion of data from dose-ranging study 809-102.
- Pooling of safety data from both LUM/IVA dose groups.
- Inclusion of (b) (4)

9.3 Advisory Committee Meeting

A Pulmonary-Allergy Advisory Committee was held on May 12, 2015 to discuss the safety and efficacy of LUM/IVA. The questions to the committee, summary of discussion, and voting results are as follows:

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

significance of the observed treatment effect and contribution of lumacaftor in context to that for ivacaftor monotherapy.

Committee Discussion: *The members of the committee commented that the trials clearly demonstrated statistically significant improvements compared to placebo in percent predicted FEV-1 with the LUM/IVA combination therapy. Multiple members also commented that, compared to placebo,there were also meaningful improvements in BMI and exacerbation reduction. Members commented that it was unclear from the existing data whether the combination is superior to IVA monotherapy. A panel member also noted that 3% improvement in percent predicted FEV1 was minimal, but that improvements in other efficacy parameters alleviated this concern.*

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

   Committee Discussion: *Committee members noted that, given the design of study 770-104,the current data for ivacaftor monotherapy 150 mg twice daily was insufficient to support efficacy in patients homozygous for the F508del mutation. Members also commented that the currently available clinical data was insufficient to determine whether the combination was superior to monotherapy. Some also commented that to make such a determination, a direct comparison would be necessary.*

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

   A. Yes
   B. No
   C. Cannot determine

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

   Yes=3 No=4 Cannot determine=6

   Committee Discussion: *A minority of the committee voted "yes" that lumacaftor contributes positively to the clinical efficacy seen for the lumacaftor plus ivacaftor combination product. The majority voted "no" or "cannot determine." Some who voted "yes" commented that ivacaftor alone did not have much of an effect, but the combination did which suggested to them that lumacaftor did contribute. Members who voted "no" commented that the range of the treatment effect*

observed for ivacaftor and the combination product was similar and could not be distinguished from one another. Committee members voting "Cannot determine" commented that this question could not be answered based on the available data, and that the contribution of LUM is difficult to determine despite the efficacy demonstrated by the combination product compared to placebo. Some committee members commented that they did not think that whether or not LUM contributed to LUM/IVA was relevant in determining efficacy.

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

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

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

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

   YES=13 NO=0 ABSTAIN=0

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

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

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

   YES=12 NO=1 ABSTAIN=0

   Committee Discussion: *The majority of the members agreed that the efficacy and safety data support approval of the lumacaftor 400 mg/ivacaftor 250 mg FDC product administered twice daily in patients with CF who are homozygous for the*

F508del mutation in the CFTR gene. The committee members voting "Yes", commented that the studies met the primary endpoints. However, some expressed concern regarding the effect size, the lack of monocomparator arm in the phase 3 studies, and the potential precedence that could be set by approval as the clinical contribution of lumacaftor was uncertain. The committee member voting "No", commented that, the efficacy compared to ivacaftor alone cannot be determined. Please see the transcript for details of the committee discussion.

9.5 Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206038

Submission Date(s): 11/05/2014

Applicant: Vertex

Product: Lumacaftor/ivacaftor

Reviewer: Robert Lim

Date of Review: 06/02/15

Covered Clinical Study (Name and/or Number): 809-103 and 809-104

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 1218 (primary and sub-investigators)		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3)		
Is an attachment provided with the reason:	Yes ☐	No ☒ (Request explanation from applicant)

From studies 809-103 and 809-104, there were 3 investigators with significant payments of other sorts: (b) (6)
These significant payments of other sorts were determined to not have significant impact upon the conduct of these clinical trials, given that the study was randomized, double-blinded, and placebo controlled with objective spirometric, nutritional and exacerbation related endpoints. Additionally, each investigator was responsible for enrolling a small number of patients to these multi-center trials.

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/s/

ROBERT H LIM
06/02/2015

ANTHONY G DURMOWICZ
06/02/2015

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Drug Products (HFD-570)

APPLICATION:	NDA206038	**CODE NAME:**	Orkambi
APPLICANT/SPONSOR:	Vertex	**USAN NAME:**	Lumacaftor/ivacaftor
MEDICAL OFFICER:	Robert Lim, MD		
TEAM LEADER:	Anthony Durmowicz, MD	**CATEGORY:**	CFTR (b) (4) /potentiator
DUE DATE:		**ROUTE:**	oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date	CDER Stamp Date	Submission	Comments
11/05/14	11/05/14	SD-3	NDA

RELATED APPLICATIONS

Document Date	Application Type	Comments

REVIEW SUMMARY:

Vertex has submitted a new NDA (206,038) for lumacaftor/ivacaftor (LUM/IVA) for the proposed indication of treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the *F508del* mutation in the CFTR gene. The proposed dose for LUM/IVA is 400/250mg q12. In the *F508del* mutation, due to abnormal processing, minimal CFTR reaches the apical membrane of epithelial cells and what little CFTR does reach the apical membrane has decreased chloride transport. The propose mechanism for LUM/IVA is that LUM allows for increased trafficking of CFTR to the apical membrane and IVA allows for increased Cl^- transport. Monotherapy IVA (NDA 203,188) is currently approved for the treatment of CF in patients with the following mutations: *G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N,* or *S549R.* However, under limitations of use, the IVA label states that it is not effective in CF patients homozygous for the *F508del* mutation. This was based on study in *F508del* homozygous CF patients where for percent predicted FEV1 (PPFEV1) the treatment relative to placebo was 1.7% (p=0.15). Because of this, inclusion of an IVA monotherapy arm in the phase 3 trials was not required. Additionally, due to a dose dependent decrease in FEV1 observed with LUM monotherapy in phase 2 trials, inclusion of a LUM monotherapy arm in phase 3 was also not required.

The phase 3 development program for LUM/IVA consists of two replicate studies (103 and 104). Studies 103/104 were 24-week, randomized, double-blind, placebo controlled studies which included three treatment arms (LUM 600mg qD+IVA250mg q12, LUM 400mg+IVA 250mg q12, and placebo). Following the 24-week treatment period, patients were eligible to continue in an open-label extension (study 105). The primary endpoint for studies 103/104 was absolute change from baseline in PPFEV1. Secondary endpoints included change from baseline in relative PPFEV1, BMI, CFQR-respiratory domain score, and pulmonary exacerbation. For the primary endpoint (per sponsor analysis), the results were statistically significant for both doses in individual studies (range: 2.6%-4%). In study 103, nominally statistically significant results were observed for all secondary endpoints except for BMI and CFQ-R respiratory domain score. In study 104, statistically significant (BMI) or nominally statistically significant results were observed for all secondary endpoints except CFQ- respiratory domain score. With regard to safety, there were no deaths and serious adverse events were more common in the placebo group compared to treatment groups.

It is worth noting that in terms of PPFEV1, for the proposed dose the mean treatment effect is modest at 2.8% and is similar in magnitude to that seen in *F508del* homozygous CF patients observed in the IVA monotherapy development program (1.7%). Given that a treatment of 1.7% was previously determined to not be clinically significant, whether or not the primary endpoint is supportive of efficacy will be a review issue.

This submission was adequately indexed, organized, and complete to allow for review. The filing checklist and slides from the filing meeting held on 12/3/14 are attached.

OUTSTANDING ISSUES:

1) Comments will be sent to the Applicant regarding the following:
   - The modest treatment effect in terms of PPFEV1.
   - The inclusion of (b) (4) in the label.
2) Determination of audit sites

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	___	**SAFE TO PROCEED**	___	**CLINICAL HOLD**	
NDA/SUPPLEMENTS:	X	**FILEABLE**	___	**NOT FILEABLE**	
	___	**APPROVAL**	___	**APPROVABLE**	___ **NOT APPROVABLE**
OTHER ACTION:					

1. Filing Checklist

NDA/BLA Number: 206,038 **Applicant: Vertex** **Stamp Date: 11/05/14**

Drug Name: **NDA/BLA Type: New**
Lumacaftor/ivacaftor

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	XX			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	XX			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	XX			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	XX			
5.	Are all documents submitted in English or are English translations provided when necessary?	XX			
6.	Is the clinical section legible so that substantive review can begin?	XX			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	XX			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	XX			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	XX			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	XX			
11.	Has the applicant submitted a benefit-risk analysis for the product?	XX			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505 (b)(1)

	Content Parameter	Yes	No	NA	Comment
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number:	XX			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	XX			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	XX			The pivotal trials include controls as previously agreed upon.
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	XX			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?				This is a subset of an orphan population. As such use of non-U.S. sites was required.
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	XX			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	XX			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	XX			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	XX			Given the fact that this is for an orphan indication, an adequate safety database is included
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			XX	Drug is chronically administered.

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

	Content Parameter	Yes	No	NA	Comment
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	XX			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	XX			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	XX			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			XX	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			XX	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			XX	This is an Orphan disease
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			XX	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	XX			Orphan disease
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	XX			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	XX			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	XX			
34.	Are all datasets to support the critical safety analyses available and complete?	XX			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	XX			

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	XX			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	XX			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	XX			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	XX			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ___yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

3) Comments will be sent to the Applicant regarding the following:
   - The modest treatment effect in terms of PPFEV1.
   - The inclusion of (b) (4) in the label.

Robert H Lim, MD

Reviewing Medical Officer Date

Anthony Durmowicz, MD

Clinical Team Leader Date

2. Filing-Planning Meeting slides

NDA 206038
Vertex
Lumacaftor/Ivacaftor
(LUM/IVA)

Filing Planning Meeting

Bob Lim

Lumacaftor/Ivacaftor

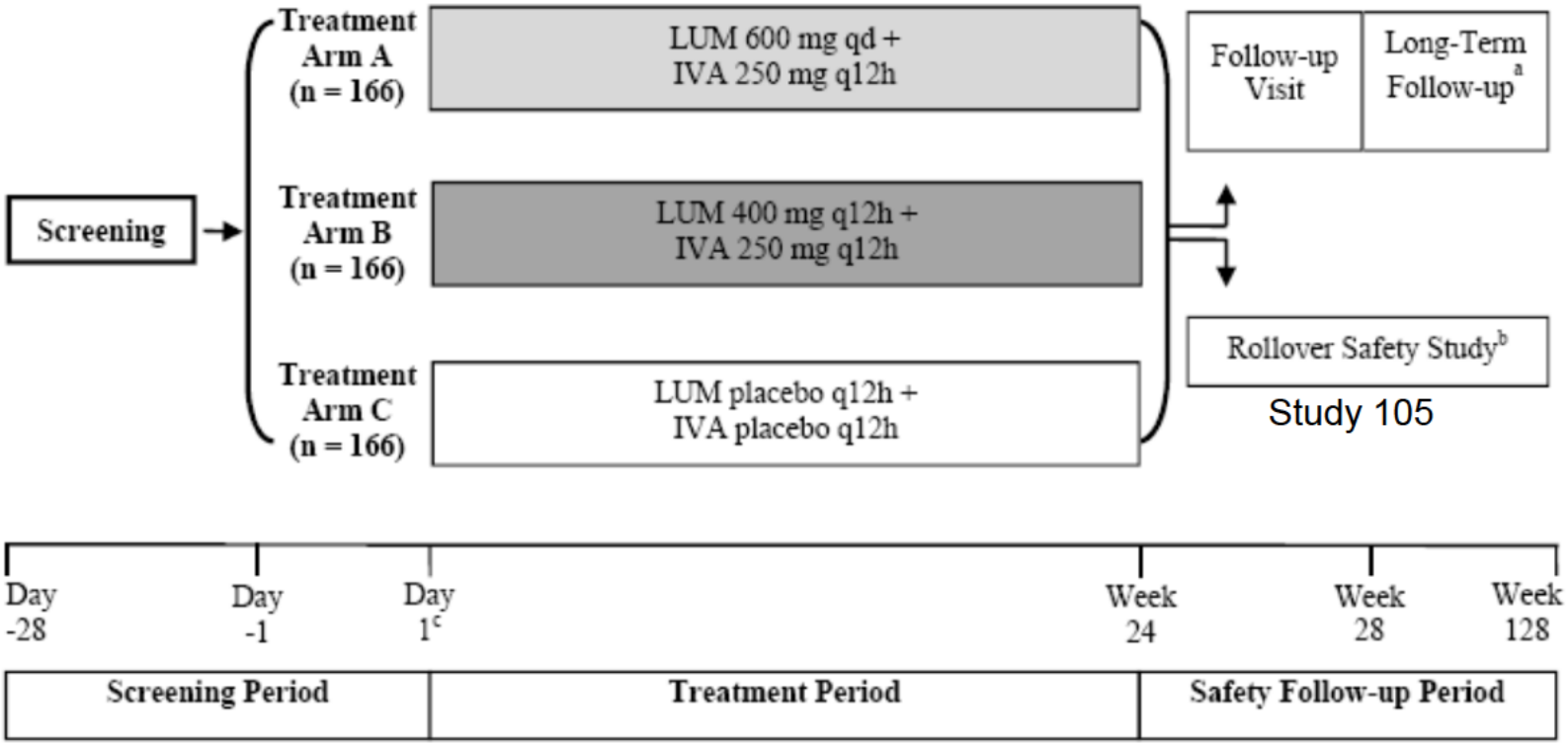
- Proposed Indication:
  - Treatment of CF in patients ≥12 years homozygous for F508del mutation
- Mechanism of action:
  - Lumacaftor: "(b) (4) that facilitates trafficking to cell surface
  - Ivacaftor: potentiator that increases open-channel probability once at cell surface
  - F508del – minimal CFTR get to cell surface and CFTR with decreased Cl- transport
- Proposed Dose: 400/250mg Q12
- Conclusion: Fileable

Regulatory Background

- EOP2 meeting (Nov. 2, 2012)
  - LUM monotherapy arm needed for both studies
  - IVA monotherapy arm not needed
    - Based on “negative” findings of Study 104 from original NDA submission
- Dec. 7, 2012:
  - Breakthrough Designation in combination with ivacaftor
- Dec. 21, 2012:
  - LUM monotherapy not required due to decreases in FEV1
- Feb 13, 2013
  - For reduction in exacerbations indication, the Division expects double-blinded data through 48 weeks in replicate trials

Study 103 and 104

Figure 9-1 Schematic of the Study Design



Efficacy

	Study 103			Study 104		
Endpoint Δ from baseline	PBO N=184	LUM 600mg qD IVA 250mg q12 N=183	LUM 400mg + IVA 250mg q12 N=182	PBO N=187	LUM 600mg qD IVA 250mg q12 N=185	LUM 400mg + IVA 250mg q12 N=187
PPFEV1 (wk16&24)	-0.44	3.6	2.2	-0.15	2.5	2.9
Δ from PBO		4.0*	2.6*		2.6*	3.0*
BMI (wk24)	0.19	0.35	0.32	0.07	0.48	0.43
Δ from PBO		0.16 (NS)	0.13 (NS)		0.41*	0.36*
CFQ-R (wk24)	1.1	5.0	2.6	2.8	5.0	5.7
Δ from PBO		3.88**	1.5 (NS)		2.2 (NS)	2.9 (NS)
≥5% FEV1 response	22%	46%	67%	23%	46%	41%
Odds ratio		2.9**	2.1**		3.0**	2.4**
#Exacerbations	112	79	73	139	94	79
Rate ratio		0.72**	0.66**		0.69**	0.57**

* Statistically significant within hierarchy
**nominal statistical significance because of location in hierarchy

IVA in DF508/DF508 – PPFEV1 =1.7%, RR exacerbation: 0.68
IVA in G551D hetero – PPFEV1= 10.6%, HR exacerbation: 0.40

Efficacy

	Pooled Studies		
Endpoint Δ from baseline	PBO N=371	LUM 600mg qD IVA 250mg q12 N=368	LUM 400mg + IVA 250mg q12 N=369
PPFEV1 (wk16&24)	-0.32	3.0	2.49
Δ from PBO		3.3	2.8
BMI (wk24)	0.13	0.41	0.37
Δ from PBO		0.28	0.24
CFQ-R (wk24)	1.88	4.94	4.1
Δ from PBO		3.1	2.2 (NS)
≥5% FEV1 response	83	170	144
Odds ratio		2.9	2.2
#Exacerbations	251	173	152
Rate ratio		0.70	0.61

No hierarchical testing strategy
P-value <0.05 except where indicated

IVA in DF508/DF508 – PPFEV1 =1.7%, RR exacerbation: 0.68
IVA in G551D hetero – PPFEV1= 10.6%, HR exacerbation: 0.40

Safety

Pooled 103 and 104	PBO N=370	LUM 600mg qD IVA 250mg q12 N=369	LUM 400mg + IVA 250mg q12 N=369
Completed Treatment	361 (97.6)	349 (94.6)	344 (93.2)
Discontinued due to AE	6 (1.6)	14 (3.8)	17 (4.6)
Deaths	0	0	0
SAEs	106 (28.6)	84 (22.8)	64 (17.3)
Any AEs	355 (96)	356 (97)	351 (95)
Elevated LFTs	17 (4.6)	18 (4.9)	20 (5.4)
Cataract	0	0	0
Respiratory symptoms AESI	51 (13.8)	88 (23.8)	81 (22.0)
Reactive airways AESI	20 (5.4)	24 (6.5)	24 (6.5)

DSI Audit

- Largest enrolling sites
- Largest treatment effect

Label

- Includes [redacted]
- Refers to lumacaftor as a [redacted]

Issues

- Lack of IVA monotherapy arm
- Advisory Committee?
- Label
- Audit sites

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT H LIM
12/17/2014

ANTHONY G DURMOWICZ
12/17/2014