CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211358Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	211358
Priority or Standard	Priority
Submit Date(s)	February 7, 2018
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PDUFA Goal Date	August 7, 2018
Division/Office	DPARP/ODEII
Review Completion Date	August 7, 2018
Established Name	lumacaftor/ivacaftor
(Proposed) Trade Name	Orkambi oral granules
Pharmacologic Class	Unclassified / cystic fibrosis transmembrane conductance regulator (CFTR) potentiator
Code name	
Applicant	Vertex Pharmaceuticals Incorporated
Formulation(s)	Oral granules
Dosing Regimen	Every 12 hours
Applicant Proposed Indication(s)/Population(s)	Treatment of cystic fibrosis (CF) in patients 2 years and older, homozygous for the *F508del*-CFTR mutation in the CFTR gene
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Patient with fibrosis (CF) in patients age 2 years and older, homozygous for the *F508del*-CFTR mutation in the CFTR gene

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DMPP=Division of Medical Policy Programs
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonization
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science

OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

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1. Executive Summary

1.1. Product Introduction

The proposed product, Orkambi granules, is a fixed dose combination of lumacaftor and ivacaftor (LUM/IVA). 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 cystic fibrosis transmembrane conductance regulator (CFTR) protein which allows it to reach the epithelial cell apical surface.

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 on the epithelial cell membrane. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability of the CFTR.

LUM/IVA tablets (NDA 206038) were approved on July 2, 2015, for the treatment of CF in patients ≥ 12 years of age who are homozygous for the *F508del* mutation in the CFTR gene at a dose of LUM400/IVA250 mg every 12 hours with a fat-containing food. On August 31, 2016, the indication was expanded to include the CF patients 6 to less than 12 years of age at a dose of LUM200/IVA250 mg every 12 hours. This NDA is for a new LUM/IVA formulation (granules) and proposes to expand the indication to include the 2 to less than 6 year old age group at a dose of LUM150/IVA188 mg for patients ≥14kg and LUM100/IVA125 mg for patients <14kg every 12 hours. As this age group generally has difficulties swallowing tablets, the granule formulation is more pediatric friendly, as the granules may be mixed with soft food or liquid for administration.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommend regulatory action is Approval for LUM/IVA granules at a dose of LUM150/IVA188 mg for patients ≥14kg and LUM100/IVA125 mg for patients <14kg every 12 hours for the treatment of cystic fibrosis in patients 2 to less than 6 years of age who are homozygous for the *F508del* mutation.

LUM/IVA tablets (NDA 206038) are approved for the treatment of CF patients aged 6 years and older who are homozygous for the *F508del* mutation in the CFTR gene. In this NDA, the Applicant has submitted data from a pharmacokinetic (PK)/safety study (study 115) to support the use of LUM/IVA granules in patients 2 to less than 6 years of age who are homozygous for the *F508del* mutation in the CFTR gene.

Study 115 was a two-part, non-randomized, uncontrolled, open-label PK (part A, 15-day duration, n=12) and safety (part B, 24-week duration, n=60) study in patients 2 to less than 6

years of age. Results demonstrated that when LUM150/IVA188 mg was administered to patients ≥14kg and LUM100/IVA125 mg was administered to patients <14kg every 12 hours, systemic exposures were comparable to that observed in the adolescent/adult population at the approved dose. Because of the comparable systemic exposures and because the disease process in the adolescent/adult population is the same as that in the 2 to less than 6 year old population, efficacy in the proposed age group can be extrapolated from the adolescent/adult population where efficacy has been demonstrated in placebo-controlled clinical trials. Additionally, Week 24 data from Part B demonstrated decreases in the pharmacodynamic endpoint of sweat chloride in both LUM/IVA granule treatment groups (LUM100/IVA125 mg = -33.5 mmol/L; LUM150/IVA188 mg = -30.7 mmol/L), suggesting a pharmacodynamic response to the LUM/IVA granule treatment. Study 115 did not reveal any new safety signals.

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1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lumacaftor/ivacaftor (LUM/IVA) tablets (NDA 206038), tradename Orkambi, are approved for the treatment of CF in patients ≥ 6 years of age who are homozygous for the *F508del* mutation in the CFTR gene. In this NDA, the Applicant has submitted data from a pharmacokinetic/safety study (study 115) to support the use of a new granule formulation of LUM/IVA in patients 2 to less than 6 years of age at a dose of LUM150/IVA188 mg for patients ≥14kg and LUM100/IVA125 mg for patients <14kg every 12 hours. The recommended regulatory action is Approval of LUM/IVA granules for the treatment of cystic fibrosis patients aged 2 to less than 6 years who are homozygous for the *F508del* mutation in the CFTR gene.

CF results from mutations to the CFTR gene which leads to decreased amount or abnormal function of CFTR protein. The most common *CFTR* mutation is *F508del*. In the United States, approximately 90% of patients carry at least one *F508del* allele, with approximately 50% of patients being homozygous for the *F508del* mutation[1]. Currently, in addition to the treatments of the symptoms and sequelae of the disease, Orkambi (lumacaftor/ivacaftor) and Symdeko (tezacaftor/ivacaftor) tablets are the only drugs that are FDA approved for targeting the underlying cause of CF in patients who are homozygous for the *F508del* mutation in the CFTR gene. The granule formulation for Orkambi (proposed in this NDA) is more age appropriate than tablets, as patients aged 2 to less than 6 years often cannot swallow tablets and this formulation can be administered mixed with food or liquid.

Study 115 was an open-label, uncontrolled, two-part pharmacokinetic (part A, 15-day duration, n=12) and safety (part B, 24-week duration n=60) study in patients 2 to less than 6 years of age who were homozygous for the *F508del* mutation in the CFTR gene. PK results demonstrated that when LUM150/IVA188 mg was administered to patients ≥14kg and LUM100/IVA125 mg administered to patients <14kg every 12 hours, systemic exposures were comparable to that observed in the adolescent/adult population. Because of the comparable systemic exposures and because the disease process in the adolescent adult population is the same as that in the 2 to less than 6 year old population, efficacy in the proposed age group can extrapolated from the adolescent/adult population where efficacy had been demonstrated in placebo-controlled clinical trials. In Part B, the changes from baseline in sweat chloride, a pharmacodynamic endpoint, were seen in both LUM/IVA granule treatment groups, which is consistent with that observed in the previous LUM/IVA tablet clinical trials, suggesting a pharmacodynamic response to the LUM/ IVA granule treatment.

With regard to safety, in Part B of study 115, no deaths were reported and 4 patients experienced SAEs. One patient each had SAEs of

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gastroenteritis viral and constipation, and two patients had pulmonary exacerbations of CF. The three most common AEs were cough, vomiting, and pyrexia. Overall, the AEs were generally consistent with common manifestations of CF disease or common illnesses in patients 2 to less than 6 years of age. In the LUM/IVA tablet product label, the listed Warnings and Precautions include liver-related events, respiratory events, increased blood pressure and cataracts, which were specifically evaluated in the safety analysis in study 115. Nine patients had a maximum on-treatment liver transaminase elevations of >3x ULN. Of these patients, five had values which were >8x ULN. None had elevations of total bilirubin. Six patients had respiratory events/symptoms. No patients developed cataracts and no clinically meaningful changes in blood pressure from baseline were observed in the study. Overall, the safety profile in the 2 to less than 6 year old age group was consistent with the older age group and no new safety signals were identified in study 115.

In summary, efficacy in the proposed age group was extrapolated from the previous LUM/IVA tablet trials in the older population. The decreases of sweat chloride from baseline were seen in both LUM/IVA granule treatment groups, suggesting a pharmacodynamic response to the LUM/IVA granule treatment. With regard to safety, no new safety signals were identified in study 115. The demonstration of an acceptable safety profile along with the extrapolated efficacy and the change of sweat chloride as a pharmacodynamic response to the treatment, warrants the recommendation of Approval.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cystic fibrosis is a rare, progressive, and usually fatal autosomal recessive genetic disease. In the United States, approximately 90% of patients carry at least one *F508del* allele in the CFTR gene, with approximately 50% of patients being homozygous for the *F508del* mutation.	The CFTR mutation included in the proposed indication represent most patients with CF in the US.
Current Treatment Options	• In addition to the treatments of the symptoms and sequelae of the disease, Orkambi (lumacaftor/ivacaftor) and Symdeko (tezacaftor/ivacaftor) tablets are the only drugs that are FDA approved for the treatment of CF patients who are homozygous for the *F508del* mutation in the CFTR and target the underlying cause of CF. However, neither of two approved products are indicated for CF patients aged 2 to less than 6 years.	There are no approved therapies for *F508del* homozygous patients 2 to less than 6 years of age, which target the cause of CF. As such, treatment options for this age group are needed. The granule formulation for lumacaftor/ivacaftor proposed in this NDA is more age appropriate than tablets, as the patients aged 2 to less than 6 years often cannot swallow tablets and this formulation can be administered mixed with food or liquid.
Benefit	• Based on results from study 115, the Applicant has demonstrated that when lumacaftor/ivacaftor granules were administered to CF patients homozygous for the *F508del* mutation who were aged 2 to less than 6 years, systemic exposures were comparable to that observed in the adolescent/adult population. Decreases in the pharmacodynamic endpoint of sweat chloride was also observed in study patients.	Lumacaftor/ivacaftor granules provide a clinically relevant treatment benefit for *F508del* homozygous CF patients 2 to less than 6 years of age based on extrapolation of efficacy from the adolescent/adult population. Efficacy can be extrapolated as the disease process in this age group is similar to the older age group, efficacy has previously been demonstrated in the older age group, and systemic exposures are comparable between these age groups. Additionally, a decreased sweat chloride level from baseline after LUM/IVA granule treatment suggested a pharmacodynamic response.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• The adverse events observed in this study were consistent with common manifestations of CF disease or common illnesses in patients 2 to less than 6 years of age. Four out of a total of 60 patients experienced SAEs. No deaths were reported. Specific safety analyses were performed for the Warnings and Precautions listed in the approved LUM/IVA tablet label. Five patients had a maximum on-treatment transaminase elevations of >8x ULN, but without bilirubin elevations; six patients had respiratory events/symptoms. No patients developed cataracts nor were clinically meaningful changes in blood pressures observed. • No REMS (Risk Evaluation and Mitigation Strategy) is proposed.	No new safety signals were identified in study 115. The potential risks of liver transaminase elevations, respiratory events, cataracts, and increased blood pressure can be managed through labeling and routine pharmacovigilance.

1.4. Patient Experience Data

No patient experience data relevant to LUM/IVA granule efficacy or safety were provided in this submission. However, in the initial approval of Orkambi tablets (NDA 206038), patient symptoms were reported using the Cystic Fibrosis Questionnaire – Revised (CFQ-R) respiratory domain. The CFQ-R is a disease-specific health-related quality of life measurement tool that assesses several domains. The respiratory domain includes patient-reported symptoms such as difficulty breathing. The clinical trials used to support the initial approval of Orkambi tablets report data from CFQ-R respiratory domain in patients aged 12 years and older (see approved Orkambi tablet label). These data were considered in this application.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application, include:	Section where discussed, if applicable
	☐ Clinical outcome assessment (COA) data, such as	
	☐ Patient reported outcome (PRO)	
	☐ Observer reported outcome (ObsRO)	
	☐ Clinician reported outcome (ClinRO)	
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
x	Patient experience data that was not submitted in the application, but was considered in this review.	

CDTL Benefit-Risk Summary:

The Applicant has submitted adequate data to support approval of LUM/IVA granules at a dose of LUM150/IVA188 mg for patients ≥14kg and LUM100/IVA125 mg for patients <14kg every 12 hours for the treatment of cystic fibrosis in patients 2 to less than 6 years of age who are homozygous for the *F508del* mutation.

The overall benefit-risk assessment supports approval of LUM/IVA granules at the proposed dose in the proposed group. Because of the comparable systemic exposures and because the disease process in the adolescent/adult population is the same as that in the 2 to less than 6 year old population; efficacy in the proposed age group can be extrapolated from the adolescent/adult population

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where efficacy had been demonstrated in placebo controlled clinical trials. No new safety findings were identified for this age group. Overall, the benefit-risk of this product is favorable.

The various reviews of CMC, Clinical Pharmacology, and Nonclinical teams support approval.

The CDTL recommends Approval of this application.

X Robert H. Lim -S

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Date: 2018.08.07 07:56:45 -04'00'

Robert Lim, MD
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

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

CF results from mutations 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, with approximately 50% of patients being homozygous for the *F508del* mutation[1]. 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 the endoplasmic reticulum where the majority of it is degraded. Therefore, the amount of F508del CFTR protein that is ultimately inserted into the epithelial cell apical surface is greatly reduced. In addition to defective trafficking, ion transport in the F508del CFTR protein appears to be abnormal. In experimental models, F508del CFTR protein expressed on the epithelial cell apical surface has a decreased half-life and reduced open-channel probability[4]. Ultimately, these deficiencies result in a relatively severe disease phenotype.

2.2. Analysis of Current Treatment Options

Except for IVA, LUM/IVA tablets and tezacaftor (TEZ)/IVA in a limited number of CFTR mutation subpopulations, there are no FDA-approved products available that are directed at the cause of cystic fibrosis (i.e., the absent or defective CFTR ion channel). However, a number of drugs are used to treat the symptoms and sequelae of the disease. Medications

used to treat CF patients are summarized in Table 1. Note that not all are FDA approved for use in CF.

Table 1. Treatments for CF

Active Ingredient	Trade Name	FDA-approved for CF Indication?
CFTR potentiator or "corrector"		
Ivacaftor	Kalydeco	Yes; one mutation in the CFTR gene that is responsive to Ivacaftor*
Lumacaftor/ivacaftor	Orkambi tablets	Yes; homozygous *F508del* mutation
Tezacaftor/ivacaftor	Symdeko	Yes; homozygous *F508del* mutation or at least one mutation in the CFTR gene that is responsive to tezacaftor/ivacaftor#
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		
Tobramycin (nebulized)	TOBI	Yes
Tobramycin (dry powder)	(b) (4)	Yes
Aztreonam (nebulized)	Cayston	Yes
(b) (4)		
Inhaled Treatments used as Mucolytics		
Dornase alpha (DNase)	Pulmozyme	Yes
(b) (4)		
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		
(b) (4)		
(b) (4)		

Source: Approved labeling data from Drugs@FDA.gov accessed on 05/22/2018

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

This product is a new LUM/IVA formulation (granules) that proposes to expand the indication to include the 2 to less than 6 year old age group. LUM/IVA tablets were approved on July 2, 2015, for the treatment of CF in patients ≥ 12 years of age who are homozygous for the *F508del* mutation in the CFTR gene. On August 31, 2016, the indication of the tablets was expanded to include the CF patients 6 to less than 12 years of age. In the LUM/IVA tablet label, the listed Warnings and Precautions include liver-related events, respiratory events, increased blood pressure, and cataracts.

3.2. Summary of Presubmission/Submission Regulatory Activity

Prior to submission of this NDA, LUM/IVA has been the subject of multiple regulatory proceedings. LUM/IVA tablets were granted Fast Track Designation on January 17, 2008 (IND 79521), Breakthrough Therapy Designation on December 07, 2012, and Orphan Drug Designation (Designation No.14-4348) on June 30, 2014. LUM/IVA tablets (NDA 206038) were approved on July 2, 2015, for the treatment of CF in patients ≥ 12 years of age who are homozygous for the *F508del* mutation in the CFTR gene at a dose of LUM400/IVA250 mg every 12 hours. This approval was based on the demonstration of efficacy in replicate phase 3 efficacy/safety trials. On August 31, 2016, the indication was expanded to include the CF patients 6 to less than 12 years of age at a dose of LUM200/IVA250 mg every 12 hours. This approval was based on results from a pharmacokinetic/safety trial and extrapolation of efficacy.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

OSI inspection was requested for Study 115 (analytical lab, validation report and analytical study report), and the Office of Study Integrity and Surveillance (OSIS) recommended accepting the Applicant's data without a site inspection as the site was recently inspected and inspectional outcome was adequate.

4.2. Product Quality

The application is recommended for Approval from the CMC/quality perspective.

This NDA involves two drug substances, lumacaftor (LUM) and ivacaftor (IVA). The Applicant has

provided no detailed information on either lumacaftor or ivacaftor in this NDA, but has cross-referenced their NDAs 206038 and 203188, which use these same drug substances for other solid oral dosage forms for CF. Therefore, no detailed CMC review was necessary in support of this application, as we can rely on the established and approved CMC information supporting the earlier applications utilizing these drug substances.

The drug product, Orkambi, is a fixed-dose combination (lumacaftor/ivacaftor) oral granules dosage form with two strengths (100mg/125mg and 150mg/188mg, respectively) and is intended for weight-based dosing to pediatric patients by oral administration with small volumes (~5 mL) of soft food or liquid. The FDC granules use the (b) (4) that is identical to those of the 100 mg lumacaftor/125 mg lower strength ivacaftor tablet formulation approved under NDA 206038. The specifications proposed for the two dosage strengths are identical and adequate for their intended purposes from a quality perspective. All analytical test methods used for testing of finished drug product and corresponding method validation information were included in the submission. Based on the assessment provided in the submission, in response to the requests for information, there is a low risk for the introduction of Class 1, Class 2A, or any other elemental impurities in to the drug product.

The proposed shelf-life of 24 months is supported by stability data up to 12 months at long-term (25°C/60 % RH) and 6 months at accelerated (40°C /75 % RH) conditions. Short-term in-use stability/compatibility studies demonstrated acceptable chemical stability up to 1 hour after mixing the FDC granules with water, apple juice, applesauce, carrot puree, fat free yogurt, infant formula and chocolate pudding, supporting their use as media for drug administration.

The current lumacaftor/ivacaftor drug product consists of granules in a (b) (4) for oral administration. The same fixed-ratio granule formulation is used for both granule strengths of 100 mg lumacaftor/125 mg ivacaftor and 150 mg lumacaftor /188 mg ivacaftor. (b) (4)

In terms of facilities, there are seven that are utilized for the production of the drug product. Based on file review, all seven facilities are acceptable to support the approval of the application.

The Biopharmaceutics review focused on the dissolution method development, dissolution data, dissolution specification, and *in vitro* soft-food interaction study. The Applicant has adopted the dissolution methods developed for Orkambi, 200 mg/125 mg tablets for the proposed products, which is acceptable. The dissolution methods demonstrate discriminatory power (b) (4) for both lumacaftor and ivacaftor, an (b) (4). The Agency agrees with the following dissolution acceptance criteria: 1) lumacaftor: NLT (b) (4)% (Q) in 20 minutes; 2) ivacaftor NLT (b) (4)% (Q) in 15 minutes. From a biopharmaceutics perspective, the drug products were found to be compatible with those soft-foods studied, assuming the oral granules are intended to be mixed with food and administered within a short time-frame, as indicated in the patient instructions.

Some minor modifications to the labels and labeling are warranted and will be addressed during labeling negotiations and in conjunction with DMEPA recommendations.

The application is recommended for Approval from the CMC/quality perspective.

4.3. Devices and Companion Diagnostic Issues

Not applicable

5 Nonclinical Pharmacology/Toxicology

Refer to NDA 206038 for an extensive discussion of pharmacology and toxicology of the lumacaftor-ivacaftor combination product. The discussion below is limited to new information provided in NDA 211358.

The lumacaftor/ivacaftor drug product intended for the 2-5 year old population under the current NDA consists of granules in a (b) (4) for oral administration. As shown in the following table [excerpted from the Applicant's submission], the level of each of the excipients of this fixed-dose combination (FDC) is well below the previously approved levels based on a database search. Therefore, there is no safety concern for this new formulation from the nonclinical perspective.

Table 2. Composition of Lumacaftor/Ivacaftor FDC Granules

Component	Quality Standard	Component Function	Amount per Sachet (mg)		(b) (4)
			100/125 mg	150/188 mg	
Lumacaftor drug substance	(b) (4)	Active Ingredient	100.0	150.0	
Ivacaftor (b) (4) (b) (4)	(b) (4)		(b) (4)		
Croscarmellose sodium	(b) (4)				
Microcrystalline cellulose					
Povidone (b) (4)					
Sodium lauryl sulfate					
(b) (4)					
Total	---	---	**331.1**	**497.4**	
(b) (4)					

The only nonclinical study reports included in this NDA submission were dose-ranging and definitive juvenile rat studies. The juvenile animal studies (JAS) support the application of Orkambi in younger population, but are not required for the approval of the proposed patient

population (2-5 y.o.) in the current application. The studies were originally reviewed by Dr. Andrew Goodwin in a memo dated September 14, 2016 and the findings are summarized briefly as follows.

In the definitive JAS. rats were dosed with lumacaftor from Postnatal Day (PND) 7-90 at 0 (vehicle), 125, 250, or 500 mg/kg/day by oral gavage. One test article-related death in the high dose (HD) male group was noted on PND 10. The pup was noted with a thin, pale, yellow body and 25% weight loss. The clinical signs noted were consistent with the deaths at 1000 mg/kg/day in the dose-ranging study. At the HD of 500 mg/kg/day, 17-18% decreases in body weight gain vs. controls were noted early in the dosing period from PND 7-17. However, there were no cumulative body weight effects over the entire dosing from PND 7-90. Further, there were no test article-related developmental effects. The glandular stomach (erosion, hemorrhage) was identified as a target organ in HD females. Based on test article-related mortality and stomach findings at the HD, the mid-dose (MD) of 250 mg/kg/day was considered as the No-Observed Adverse Effect Level (NOAEL). Lumacaftor exposure increased in a less than dose-proportional manner. No sex-related differences in exposure were observed. No evidence of accumulation after repeated dosing from PND 7 to PND 90 was observed. At the NOAEL of 250 mg/kg/day, the $AUC_{0\text{-}24hr}$ of lumacaftor was 1300 ug*hr/mL (average of males and females).

A JAS with ivacaftor was conducted and reviewed by Dr. Marcie Wood (memo dated June 28, 2012) and Dr. Andrew Goodwin (memo dated March 9, 2017) under IND 074633. No NOAEL was identified in that study based on findings of cataracts. This adverse finding in the ivacaftor JAS has been captured in Section 8.4 of the product label for Kalydeco, Orkambi, and Symdeko (refer to memo by Dr. Marcie Wood dated August 27, 2012 under NDA 203188). The table below provides lumacaftor and ivacaftor exposures in the JAS compared to exposures expected in subjects 2-5 years old receiving Orkambi.

Table 3. Lumacaftor-Ivacaftor Exposure Comparison

Juvenile Rat Toxicity	Species	Doses (mg/kg)	$AUC_{0\text{-}24h}$ µg.hr/ml (M/F)	Safety Margin Based on AUC*
LUM	SD rats	125	964	1.6
		250 (NOAEL)	1300	2.2
		500	1700	2.8
IVA	SD rats	10	26	2
		50	156	13

*$AUC_{0\text{-}24h}$ LUM in human: 600 µg.hr/ml at 150/188 mg/day of fixed dose LUM/IVA.
$AUC_{0\text{-}24h}$ IVA in human: 12 µg.hr/ml at 150/188 mg/day of fixed dose LUM/IVA.

There are no outstanding pharmacology-toxicology issues.

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Dong Zhao, PhD, DABT
Primary Reviewer

Andrew Goodwin, PhD
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

This NDA for Orkambi granules proposes to expand the already approved indication for Orkambi tablets [lumacaftor/ivacaftor tablets (LUM/IVA), NDA 206038, initially approved on Jul 2, 2015] to include pediatric patients 2 to 5 years of age. Orkambi tablets are approved for "the treatment of cystic fibrosis (CF) in patients age 6 years and older who are homozygous for the F508del mutation in the CFTR gene". The approved dose is 400/250 mg q12h in patients 12 years and older, and 200/250 mg q12h in patients 6-11 years of age, administered with fat-containing food. As CF is a genetic disorder, the pathophysiology of CF remains the same with the same CFTR gene mutations. It is therefore reasonable to assume that patients 2-5 years of age would have similar response to Orkambi as patients 12 years and older. Thus, the efficacy of Orkambi in children 2-5 years of age could be extrapolated from efficacy in patients 12 years of age and older based on comparable lumacaftor/ivacaftor exposure.

The proposed dose for patients 2-5 years old is LUM/IVA 100/125 mg taken orally every 12 hours for patients weighing <14 kg, and LUM/IVA 150/188 mg taken orally every 12 hours for patients weighing ≥ 14 kg. The clinical pharmacology information for LUM/IVA tablets was reviewed previously with the original application (NDA 206038 by Dr. Jianmeng Chen, DARRTS date5/28/2015). The major Clinical Pharmacology findings for this review are as follows:

- With the proposed dosing regimen, the lumacaftor/ivacaftor exposure in children 2-5 years of age is generally comparable to the LUM/IVA exposure in adults and adolescents (≥12yrs) with the approved dosing regimen based on the population pharmacokinetic analyses.

- The ratio of the proposed dose of lumacaftor and ivacaftor in the 2-5 years old patients is the same as the approved dose ratio in patients 6 through 11-years old (200/250 mg BID). However, the ratio differs from that approved in ≥12-year-old population (400/250 mg BID). The key factor that impacts the LUM: IVA dose ratio in different age groups is the drug clearance/exposure changes as a function of weight (see section 6.3.2 and Appendix 15.4 for details).

- The pediatric to-be-marketed granule formulation of lumacaftor/ivacaftor (100/125 mg packet) has exposures comparable to the FDC tablets (LUM/IVA 100/125 mg tablets), when given with fat-containing food.

- OSI inspection was requested for Study 115 (analytical lab, validation report and analytical study report), and the Office of Study Integrity and Surveillance (OSIS) recommended accepting the Applicant's data without a site inspection as the site was recently inspected and inspectional outcome was adequate.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Following oral administration of Orkambi oral granules, lumacaftor 100 mg/ivacaftor 125 mg every 12 hours, the mean lumacaftor (±SD) AUCss was 180 (45.5) µg/mL*h and the mean ivacaftor (±SD) AUCss was 5.92 (4.61) µg/mL*h, comparable to the mean AUCss of lumacaftor and ivacaftor in patients 12 years and older administered Orkambi tablets. Following oral administration of Orkambi oral granules, lumacaftor 150 mg/ivacaftor 188 mg every 12 hours, the mean lumacaftor (±SD) AUCss was 217 (48.6) µg/mL*h and the mean ivacaftor (±SD) AUCss was 5.90 (1.93) µg/mL*h, comparable to the mean AUCss of lumacaftor and ivacaftor in patients 12 years and older administered ORKAMBI tablets (Table 5).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose of LUM/IVA for patients 2 to 5 years of age is

- Pediatric patients age 2 through 5 years and weighing less than 14 kg: one packet of granules (each containing lumacaftor 100 mg/ivacaftor 125 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food.
- Pediatric patients age 2 through 5 years and weighing 14 kg or greater: one packet of granules (each containing lumacaftor 150 mg/ivacaftor 188 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat-containing food.

CF patients 2-5 years of age are predicted to have generally comparable exposure (AUC) of lumacaftor and ivacaftor as patients 12 years and older following the proposed dosing regimens. See section 6.3.2 for details.

Therapeutic Individualization

Dose adjustment was proposed by Applicant in pediatric patients aged 2 to 5 years with moderate hepatic impairment based on the simulation using a population PK model (Table 4). The dose was proposed to be 1 packet of oral granules [redacted] (b) (4) for the patients aged 2 to 5 years with normal hepatic function. The dose approved in patients aged 6 years and above with moderate hepatic impairment was two tablets in the morning and 1 tablet in the evening, which is ¾ of the daily dose for the patients aged 6 years and above with normal hepatic function. It appears that the proposed dose reduction in patients aged 2 to 5 years with moderate hepatic impairment may result in lower exposure and is not consistent with what is approved in patients aged 6 years and above with moderate hepatic impairment.

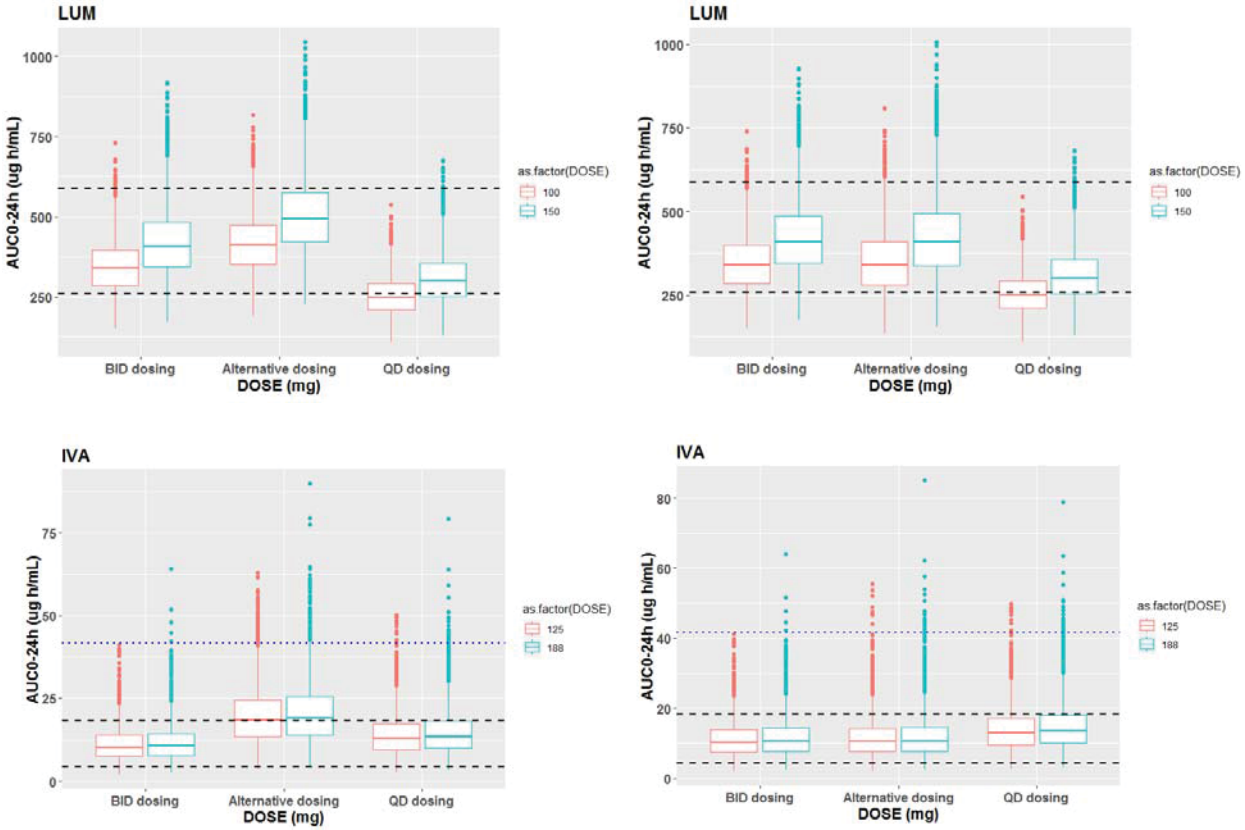
Table 4. Dose in patients with normal hepatic function and dose adjustment in patients with moderate hepatic impairment

<table>
<tr><th>Age</th><th>Weight</th><th>Normal hepatic function</th><th colspan="2">Moderate hepatic impairment</th></tr>
<tr><td>12 years and above</td><td>-</td><td>Two tablets (each containing L200/I125 mg) BID</td><td colspan="2" rowspan="2">Two tablets in the morning and 1 tablet in the evening</td></tr>
<tr><td>6 to 11 years</td><td>-</td><td>Two tablets (each containing L100/I125 mg) BID</td></tr>
<tr><td rowspan="2">2 to 5 years</td><td>≥14 kg</td><td>One packet of granules (each containing L150/I188 mg) BID</td><td rowspan="2">[redacted] (b) (4)</td><td>FDA’s recommendations</td></tr>
<tr><td><14 kg</td><td>One packet of granules (each containing L100/I125 mg) BID</td><td>One packet of granule twice daily on day 1 and one packet of granules once daily on day 2</td></tr>
</table>

Therefore, the Reviewer simulated the exposure of LUM and IVA in patients aged 2 to 5 years under the following scenarios:

- normal hepatic function patients receiving one packet of granules every 12 hours (BID dosing),
- moderate hepatic impairment patients receiving one packet of granules every 12 hours on day 1 and one packet of granules once daily on day 2, followed by this alternating scheme (Alternative dosing)
- moderate hepatic impairment receiving one packet of granules every 24 hours (QD dosing).

Figure 1. Steady State $AUC_{0\text{-}24h}$ comparison in patients aged 2 to 5 years with normal hepatic function or moderate hepatic impairment on 1st day (left) and 2nd day (right) of dosing



BID dosing represents BID dosing in patients aged 2 to 5 years with normal hepatic function; Alternative dosing represents BID dosing on day 1 and QD dosing on day 2 in patients aged 2 to 5 years with moderate hepatic impairment; QD dosing represent the QD dosing in patients aged 2 to 5 years with moderate hepatic impairment; black dashed lines represent the 90% confidence interval for $AUC_{0\text{-}24h}$ of subjects aged 12 years and above receiving L400 q12h, L600 q24h, or I250 q12h; blue dashed lines represent the maximum steady state $AUC_{0\text{-}24h}$ in patients aged 2 to 5 years with normal hepatic function who received IVA monotherapy in the Phase 3 study; blue boxes represent the patients with body weight ≥14 kg and red boxes represent the patients with body weight <14 kg
Source: Reviewer's independent analysis

The results show that the Reviewer's proposed alternate dosing regimen (two doses on day 1 followed by one dose on the next day) is likely to result in comparable steady state LUM exposure in patients aged 2 to 5 years with moderate hepatic impairment compared to that in patients aged 2 to 5 years with normal hepatic function. (b) (4)

On the other hand, the Reviewer's proposed

alternate dosing scheme result in higher exposure of IVA on the 1st dosing day in patients aged 2 to 5 years with moderate hepatic impairment compared to that in patients aged 2 to 5 years with normal hepatic function. However, the exposure is still lower than the maximum steady state exposure in patients aged 2 to 5 years with normal hepatic function who received IVA monotherapy in the Phase 3 study and is unlikely to raise safety concerns. Therefore, the Reviewer proposed dosing regimen (**one packet of granules every 12 hours on day 1 and one packet of granules in 24 hours on day 2, followed by this alternating scheme**) is more reasonable than QD dosing in this population from both efficacy and safety perspective. It should be noted that few pediatric patients aged 2 to 5 years are expected to have impaired hepatic function.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General pharmacology and PK of LUM/IVA has been reviewed with the original application (NDA 206038, Dr. Jianmeng Chen, DARRTS date 5/28/2015).

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Cystic fibrosis is a genetic disorder, and it is reasonable to assume that patients 2-5 years of age would have similar disease and similar response to ORKAMBI as patients 12 years and older. Therefore, the Division agreed in previous interactions, that the efficacy of ORKAMBI in the 2-5 year old age group could be extrapolated from the data in patients 12 years and older based on comparable PK. This NDA contains two clinical studies:

- Study VX15-809-014 investigated the relative BA of L100/I125 as a granule formulation versus the tablet formulation, the effect of food on the BA of L100/I125 as a granule formulation, and the dose proportionality of the granule formulation.
- Study VX15-809-115 (Study 115) was a two-part, open-label study to evaluate the safety and pharmacokinetics of LUM/IVA combination therapy in subjects aged 2 through 5 years with CF, homozygous for the F508del CFTR mutation. PK was the primary objective of Part A,and safety and tolerability were the primary objectives of Part B.
- Population PK models (ReportN329) for LUM and IVA were utilized for evaluation of PK results obtained in Study 115.

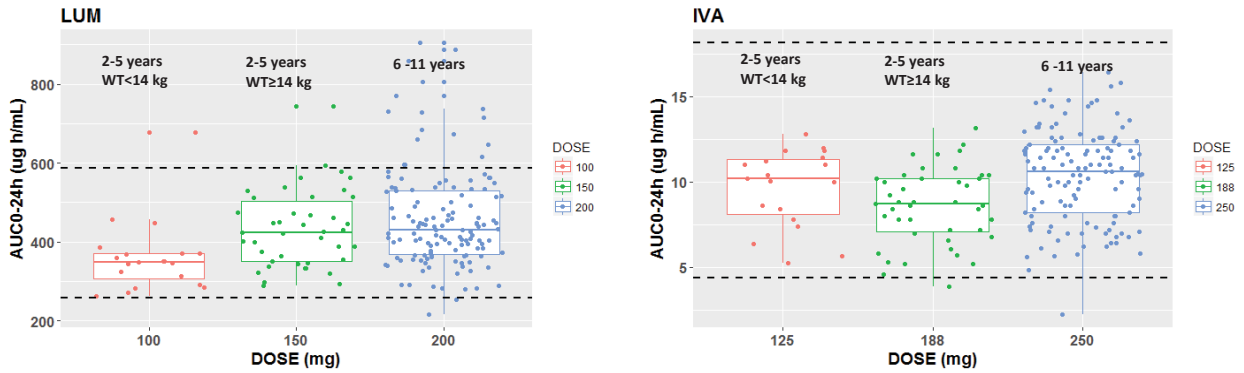
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes, the proposed dose is reasonable from a clinical pharmacology perspective as the LUM and IVA exposures achieved in pediatrics of ages 2-5 years of age, below and above 14 kg, are generally comparable to patients 12 years and older. The comparable PK of LUM and IVA supports the efficacy extrapolation in patients 2-5 years old.

The dosing regimen for LUM/IVA in pediatric patients aged 2 to 5 years is proposed to be L150/I188 q12h for patients weighing ≥14 kg and L100/I125 q12h for patients weighing <14 kg. The proposed dosing regimen was used in a Phase 3 study (Study 115) in cystic fibrosis (CF) patients aged 2 to 5 years and sparse PK samples were collected.

A population PK analysis was conducted by Applicant based on pooled PK data from Study 115 and two Phase 3 studies (Studies 109 and 011) in CF patients aged 6 to 11 years. The $AUC_{0\text{-}24h}$ were generated using the population PK model and compared with those in patients aged 6 to 11 years and 12 years and above. The results are listed in Figure 2. The exposure in patients aged 2 to 5 years was comparable with that in patients aged 6 to 11 years for both LUM and IVA. The exposure in patients aged 2 to 5 years was also well within the exposure range in patients aged 12 years and above. There findings suggest that the studied dose is reasonable.

Figure 2. Comparison of $AUC_{0\text{-}24h}$ at steady-state for patients aged 2 to 5 years and patients aged 6 to 11 years for LUM (left) and IVA (right)



Black dashed lines on the left represent the 90% confidence interval for $AUC_{0\text{-}24h}$ of subjects aged 12 years and above receiving L400 q12h, L600 q24h, or I250 q12h
Source: Reviewer's independent analysis

The following table provided by Applicant shows numerical comparisons of AUC values for LUM and IVA across age groups (2 years of age and older) collected in multiple studies. In CF subjects 2 through 5 years of age, the range of LUM and IVA exposures was comparable to those in subjects 12 years of age and older. Although the projected mean IVA AUC in CF subjects 2 through 5 years of age is higher than the exposures in CF subjects 12 years of age and older

receiving LUM/IVA, the mean exposure values (5.92 and 5.90 µg·hr/mL) are well below those seen in CF subjects 12 years of age and older (9.24 to 10.7 µg·hr/mL), 6 through 11 years of age (20.0 µg·hr/mL), and 2 through 5 years of age (10.5 µg·hr/mL) receiving IVA monotherapy.

Table 5. LUM and IVA Exposure (AUC_{0-12h}) in CF subjects by Age Group

Age Group	N[a]	LUM AUC_{0-12h} (µg·hr/mL)		N[b]	IVA AUC_{0-12h} (µg·hr/mL)	
		Median (range)	Mean (SD)		Median (range)	Mean (SD)
2 through 5 years (body weight <14 kg)	20	175 (131, 339)	180 (45.5)	19	4.64 (2.41, 22.8)	5.92 (4.61)
2 through 5 years (body weight ≥14 kg)	42	212 (145, 372)	217 (48.6)	42	5.99 (3.09, 12.5)	5.90 (1.93)
6 through 11 years	165	215 (108, 452)	224 (59.1)	161	5.69 (2.16, 20.0)	6.17 (2.68)
12 through 17 years	98	241 (130, 496)	241 (61.4)	98	3.58 (1.78, 10.3)	3.89 (1.56)
18 years and older	264	209 (122, 418)	217 (47.9)	264	3.41 (1.35, 17.3)	3.80 (1.94)

Source: Applicant's summary of clinical pharmacology, Page 13, Table 3

Is the bioavailability of this pediatric formulation comparable to the original formulation (in adults)?

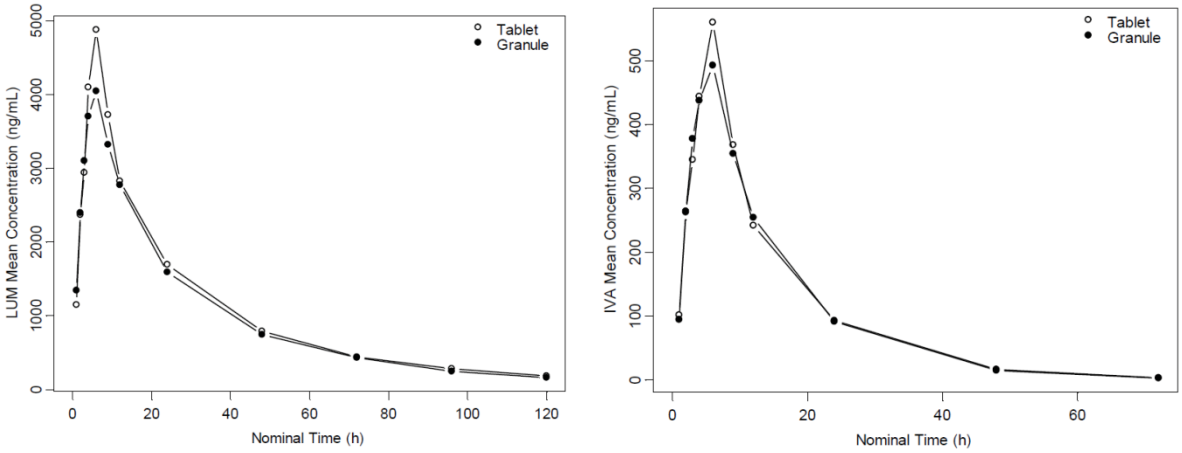
Yes. Overall, the LUM and IVA exposures of the pediatric FDC granules formulation (100/125 mg packet) were comparable with LUM/ IVA FDC tablets [L100/I125 mg tablet (approved formulation for patients 6-11 years old)] when given with fat-containing food in healthy adult subjects. In a comparative bioavailability study (Study 014), the bioavailability of LUM and IVA as a granule formulation was comparable to that of the reference tablet formulation at the same dose of LUM 100 mg/IVA 125 mg (Table 6, Figure 3).

Table 6. Analysis of Relative Bioavailability of the Granule Formulation Versus the Tablet Formulation as a Single LUM 100-mg/IVA 125-mg Dose in the Fed Condition

Comparison	Analyte	Parameter	N		GLSM Ratio (%)	90% CI
			Reference (Tablet)	Test (Granule)		
LUM 100 mg/ IVA 125 mg Granule Versus Tablet	LUM	C_{max} (ng/mL)	16	16	80.8	(75.4, 86.5)
		$AUC_{0-\infty}$ (h·ng/mL)	16	14[a]	92.5	(87.1, 98.3)
	IVA	C_{max} (ng/mL)	16	16	84.6	(74.2, 96.5)
		$AUC_{0-\infty}$ (h·ng/mL)	16	16	98.8	(93.5, 104)

Source: Table 2-2, Synopsis Study VX15-809-014

Figure 3. Lumacaftor and Ivacaftor Plasma Concentration Versus Time Profiles of the LUM 100-mg/IVA 125-mg Dose by Formulation



Source: Figure 11-1, Figure 11-2, CSR VX15-809-014

PK was dose proportional between LUM 100-mg/IVA 125-mg and LUM 150-mg/ IVA 188-mg doses of the granule formulation. The slope estimate, β1 were approximately 1 (Table 7).

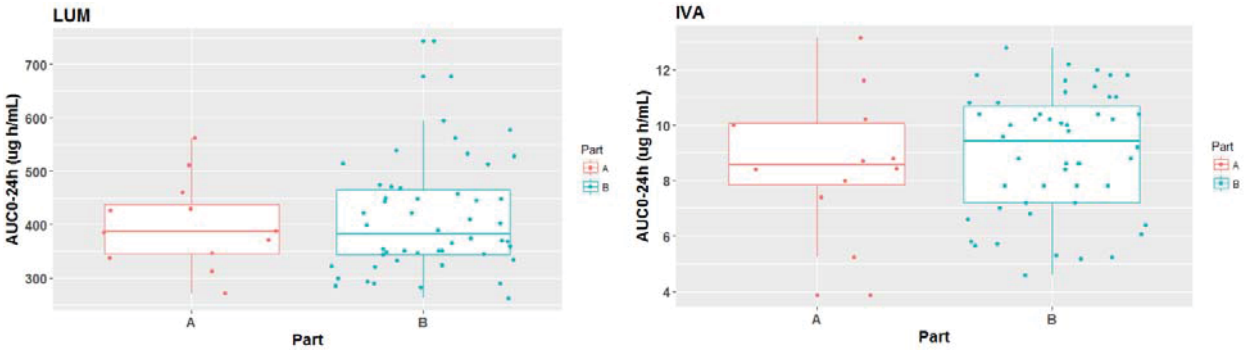
Table 7. Dose Proportionality Power Model Results

Comparison	Analyte	Parameter	Point Estimate of β_1	90% CI
LUM 100 mg/ IVA 125 mg Versus LUM 150 mg/ IVA 188 mg	LUM	C_{max} (ng/mL)	1.09	(0.87, 1.30)
		$AUC_{0-\infty}$ (h·ng/mL)	1.07	(0.88, 1.27)
	IVA	C_{max} (ng/mL)	1.09	(0.92, 1.25)
		$AUC_{0-\infty}$ (h·ng/mL)	0.98	(0.88, 1.09)

Source: Table 11-5, CSR VX15-809-014

Also, based on population pharmacokinetics analysis, the relative bioavailability for FDC granules compared to tablet is 87% and 79%, respectively for LUM and IVA in pediatric CF subjects (Study 115, See Appendix 15.4, Table 2 and 4). On Jun 8, 2018, Vertex sent a response to a FDA CMC IR and stated that the granule sizes were different in Part A and Part B of Study 115. The d50 granule particle size of Part A (lot B16029) is (b) (4), and the d50 granule size of Part B (Lot 6064308) is (b) (4). The impact of granule sizes on exposure was not identified by the population PK model. The exposure (AUC_{0-24h}) of subjects from Part A and Part B of Study 115 derived from population PK model were compared as shown below. The exposures were comparable in subjects from Part A and Part B of Study 115.

Figure 4. Comparison of AUC_{0-24h} at steady-state for patients from Part A and Part B of Study 115 for LUM (left) and IVA (right)



Source: Reviewer's independent analysis

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic or extrinsic factors?

There are no DDI studies or renal and hepatic impairment studies conducted in pediatric patients. Dose adjustment in pediatric patients is based on information known from adult data. See section 6.2.2.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

There are no DDI studies conducted in pediatric patients. Dose adjustment in pediatric patients is based on information known from adult data.

Food effect was assessed for FDC granules (LUM100/IVA125 mg packet) in healthy adult subjects (Study 014). Following oral administration, Tmax was delayed from approximately 2 hours in the fasted state to 6 hours in the fed state for both LUM and IVA. The extent of absorption for both LUM and IVA was greater in the fed state (Table 8).

Table 8. Food Effect on the Granule Formulation as a Single LUM 100-mg/IVA 125-mg Dose

Comparison	Analyte	Parameter	N Reference (Fasted)	N Test (Fed)	GLSM Ratio (%)	90% CI
LUM 100 mg/ IVA 125 mg Granules, Fed Versus Fasted	LUM	C_{max} (ng/mL)	15	16	153	(133, 175)
		$AUC_{0-\infty}$ (h·ng/mL)	13[a]	14[a]	117	(108, 126)
	IVA	C_{max} (ng/mL)	15	16	188	(152, 233)
		$AUC_{0-\infty}$ (h·ng/mL)	15	16	180	(159, 204)

Source: Table 2-3, Synopsis Study VX15-809-014

Based on the results of Study 014, ORKAMBI granules were administered with fat-containing food in CF patients 2-5 years old in Study 115. Therefore, ORKAMBI granules should be administered with fat-containing food.

Question on clinically relevant specifications (TBD)?

Not applicable.

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Ping Ji, PhD for Anshu Marathe, PhD
Team Leader

Jingyu Jerry Yu, PhD
Team Leader

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

To support the proposed expansion of the indication to include the 2 to less than 6 year old population, the Applicant submitted clinical data from study 115 (Table 9).

Table 9. Summary of clinical studies included in this submission

Study Number	Study Type/ Design	CF Mutation	Population	n	Treatment Arms	Countries
115	Open-label Safety and PK	Homozygous *F508del* mutation	2 to less than 6 years	Part A: 12 Part B: 60	LUM100/IVA125 mg q12h (<14kg) LUM150/IVA188 mg q12h (≥14kg)	USA, Canada

7.2. Review Strategy

The Applicant submitted clinical data from study 115 to support expansion of the indication to include patients 2 to less than 6 years of age. Study 115 was an open-label pharmacokinetic (PK) and safety study in patients 2 to less than 6 years of age. This study included two parts (A and B). Part A included a 15-day treatment period where the PK of LUM/IVA granules was assessed and dosing was determined. Part B included an open-label 24-week treatment period where safety was assessed. As Part A only included a 15-day treatment period compared to the 24-week treatment period in Part B, this review will focus on Part B only. While this study was a safety/PK study, the Applicant also included pharmacodynamics (PD) and efficacy-related endpoints. Note that efficacy in the 2 to less than 6 year old population was extrapolated from the older population.

The protocol for study 115 and the efficacy data are discussed in section 8.1; the safety data are reviewed in section 8.2.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Study 115:

Title: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 To Less Than 6 Years With Cystic Fibrosis, Homozygous for the *F508del-CFTR* Mutation

- Study start date: May 13, 2016
- Study completion: September 8, 2017
- Study report date: January 5, 2018
- Study sites: U.S.A. and Canada

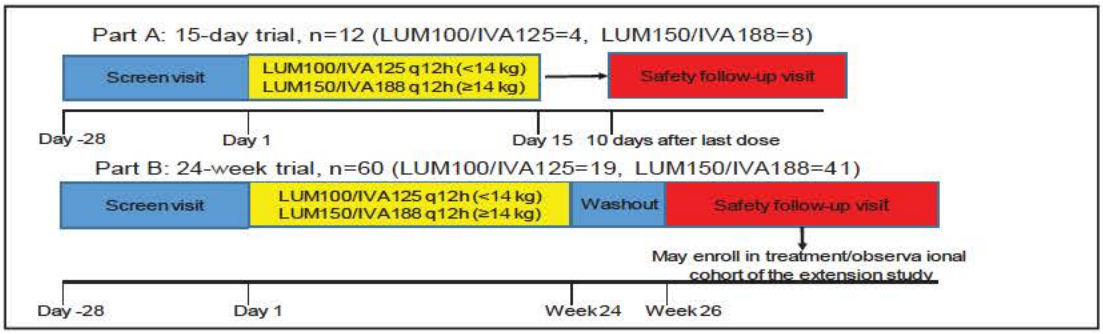
Trial Design

This was a 2-part (A and B) non-randomized, open-label study of LUM/IVA granules in CF patients ages 2 to less than 6 years of age who were homozygous for the *F508del* mutation. In Part A, there was a 28-day screening period followed by a 15-day treatment period, where eligible patients received either LUM100/IVA125 mg (<14kg) or LUM150/IVA188 mg (≥14kg) q12 hours. During the 15-day treatment period, PK samples were collected at 3-4 hours after the morning doses on Day 1, within 1 hour before the morning dose on Day 8, and within 1 hour before the morning dose, at 2 hours and at 3-4 hours after the morning dose on Day 15. Patients received an ophthalmologic exam before the first dose.

In Part B, there was also a 28-day screening period. This was followed by a 24-week open-label treatment period. Study visits occurred on Day 1 and at Weeks 2, 4, 8, 16, and 24 andwere followed by a safety follow-up visit at Week 26. Patients' PK samples were collected within 1 hour before the morning dose and at 2-6 hours after the morning dose on Day 15, at Week 4 and 24. Patients received an ophthalmologic exam before the first dose and at Week 24 or 26. Following the treatment period, all patients were allowed to continue in the open-label extension study (116). The trial schematic for Parts A and B are summarized in Figure 5**.** See Table 20 in appendix 15 for assessment schedule.

Reference ID: 4303047

Figure 5. Study 115 Schematic



Objectives/Rationale

Part A:

- Primary Objective
  - To evaluate the pharmacokinetics (PK) of lumacaftor (LUM) and ivacaftor (IVA) and their respective metabolites in patients aged 2 to less than 6 years with cystic fibrosis (CF), homozygous for *F508del* mutation
- Secondary Objective
  - To evaluate the safety of LUM/IVA combination therapy in patients aged 2 to less than 6 years with CF, homozygous for *F508del* mutation

Part B:

- Primary Objective
  - To evaluate the safety of LUM/IVA combination therapy in patients aged 2 to less than 6 years with CF, homozygous for *F508del* mutation
- Secondary Objective
  - To evaluate the pharmacodynamics (PD) of LUM/IVA combination therapy in patients aged 2 to less than 6 years with CF, homozygous for *F508del* mutation
  - To evaluate the off-drug PD response after the Washout Period
  - To evaluate the PK of LUM and IVA and their respective metabolites in patients aged 2 to less than 6 years with CF, homozygous for *F508del* mutation

Trial population

This trial included 12 (Part A) and 60 (Part B) CF patients 2 to less than 6 years of age who were homozygous for the *F508del* mutation

Key Inclusion Criteria

1. Male or female age 2 to less than 6 years with a confirmed diagnosis of CF at the screen visit. CF was defined as follows:
   - Two CF-causing mutations AND
   - Chronic sinopulmonary disease OR gastrointestinal/nutritional abnormalities; OR

- Part B only: a sweat chloride value ≥60 mmol/L as documented in the patient's medical record OR from the sweat chloride test result obtained at the screening visit

2. Patients who are homozygous for the *F508del* mutation
3. Weight ≥8kg at screening

Key Exclusion Criteria

1. History of any comorbidity reviewed at the screening visit that, in the opinion of the investigator, could confound the results of the study or pose an additional risk in administering LUM/IVA to the patients
2. An acute upper or lower respiratory infection, pulmonary exacerbation (PEx), or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1 (first dose of LUM/IVA)
3. Any of the following abnormal laboratory values at the Screening Visit:
   - Hemoglobin <10 g/dL
   - Alanine transaminase (ALT), aspartate transaminase (AST), or total bilirubin >2 × upper limit of normal (ULN)
   - Glomerular filtration rate ≤45 mL/min/1.73 m^2
4. Ongoing or prior participation in an investigational drug study (including studies investigating LUM and/or IVA) within 30 days of the screening visit
5. History of cataract/lens opacity or evidence of cataract/lens opacity determined to be clinically significant by a licensed ophthalmologist at the screening visit

Key Patient Removal Criteria

LUM/IVA administration was interrupted if any of the following criteria were met:

- ALT or AST ≥8 × ULN
- ALT or AST ≥5 × ULN for more than 2 weeks
- ALT or AST ≥3 × ULN in association with total bilirubin ≥2 × ULN and/or clinical jaundice

If no alternative etiology (e.g., viral hepatitis) for the elevated transaminases was identified, LUM/IVA was discontinued in consultation with the Applicant medical monitor or authorized designee.

The patients included in this study were representative of CF patients. The key inclusion, exclusion and removal criteria in this study were similar to those in the previous LUM/IVA tablet clinical trials in the older population. It is reasonable to extrapolate efficacy in the proposed age group from the older population.

Treatments

The LUM/IVA granule dose in study 115 was LUM100/IVA125 mg for patients <14kg and LUM150/IVA188 mg for those ≥14kg q12 hours.

Prohibited Medications

Restricted medications included any CYP3A inhibitors and inducers, grapefruit/grapefruit juice, pomelos, star fruit and Seville oranges at least within 14 days before day 1 of Part A or B and throughout the treatment period.

Study Endpoints

The endpoints of the study are summarized in Table 10.

Table 10. Study 115. Assessed endpoints

Endpoints	Study 115 Part A	Study 115 Part B
Primary	PK parameters of LUM and IVA	Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, ophthalmological examinations, and spirometry
Secondary	• PK parameters of the metabolites of LUM and IVA • Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry, hematology, coagulation studies, and urinalysis), standard 12-lead ECGs, vital signs, pulse oximetry, and spirometry	• Absolute change from baseline in sweat chloride at Week 24 • Absolute change in sweat chloride from Week 24 at Week 26 • Absolute change from baseline in BMI and BMI-for-age z-score at Week 24 • Absolute change from baseline in weight and weight-for-age z-score at Week 24 • Absolute change from baseline in stature and stature-for-age z-score at Week 24 • Absolute change from baseline in LCI2.5 at Week 24 • Absolute change from baseline in LCI5.0 at Week 24 • Time-to-first pulmonary exacerbation through Week 24 • Number of pulmonary exacerbations through Week 24 • Number of CF-related hospitalizations through Week 24 • Absolute change in FE-1 levels from baseline at Week 24 • Absolute change in serum levels of IRT from baseline through Week 24 • Change in microbiology cultures from baseline at Week 24 • Absolute change from baseline in ppFEV1 at Week 24
Others		• Acceptability/palatability of LUM/IVA granules at Day 1 • PK parameters of LUM, IVA, and their respective metabolites

AEs: adverse events; BMI: body mass index; CF: cystic fibrosis; FE-1: fecal elastase 1; IRT: immunoreactive trypsinogen; IVA: ivacaftor; LCI: lung clearance index; LUM: lumacaftor; PD: pharmacodynamics; PK: pharmacokinetic; ppFEV1: percent predicted forced expiratory volume in 1 second
Source: study 115 clinical overview document in the NDA submission; table 11; pp10

Safety was the primary endpoint in this study similar to the PK/safety studies used to support previous ivacaftor granule approvals, and the secondary endpoints in these studies were also generally similar. Additionally, sweat chloride was a common pharmacodynamic secondary endpoint across these studies.

Pulmonary exacerbation (PEx) was defined as follows in study 115:
New or changed treatment with oral, inhaled, or IV antibiotics AND fulfillment of 1 criterion from List A or 2 criteria from List B, within the period 3 days before antibiotic start date through antibiotic stop date.

List A:

- Decrease in ppFEV1 ≥10 change from highest value in the past 6 months before the first dose, unresponsive to albuterol (if applicable)
- Oxygen saturation <90% on room air or ≥5% decrease from baseline
- New lobar infiltrate(s) or atelectasis on chest x-ray
- Hemoptysis (more than streaks on more than 1 occasion in past week)

List B:

- Increased work of breathing or respiratory rate (duration ≥3 days)
- New or increased adventitial sounds on lung examination (duration ≥3 days)
- Weight loss ≥5% decrease from highest value or decrease across 1 major percentile for age in past 6 months
- Increased cough (duration ≥3 days)
- Worked harder to breathe during physical activity (duration ≥3 days)
- Increased chest congestion or change in sputum (duration ≥3 days)

The definition for exacerbation in this study differs from that used in studies used to support previous LUM/IVA tablet approval. The previous studies included similar types of symptoms, however included additional symptoms such as sinus tenderness, change in sinus discharge, and malaise/fatigue/lethargy. These were likely not included in this study's criteria given the age group studied. This age group lacks fully formed sinuses and malaise/lethargy/fatigue would likely be difficult to characterize. Additionally, to be defined as an exacerbation in the previous LUM/IVA tablet studies, a patient was required to have at least 4 symptoms which trigger antibiotic treatment as compared to just 1 criterion from List A or 2 criteria from List B.

Statistical Analysis Plan

Analysis of safety was descriptive with no formal statistical testing.

Protocol Amendments

This protocol was amended 2 times. Pertinent changes are summarized. The first amendment was dated August 1, 2016. The major changes in this amendment included the addition of a washout period to evaluate the off-drug PD response in Part B and the removal of the inclusion criterion of ppFEV1 ≥40 from Parts A and B. Additionally, important changes in Part B included making the LCI assessment optional and adding serial postdose vital sign assessments on day 1. The second amendment was submitted on April 17, 2017. Major changes included the supply of a short-acting bronchodilator (SAB) for patients in Part B (if not already prescribed).

8.1.2. Study Results

Compliance with Good Clinical Practices

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

Financial Disclosure

- See section 15.2.

Patient Disposition

Patient disposition is summarized in Table 11. Fifty-six (93.3%) patients completed LUM/IVA treatment, and 57 (95.0%) patients completed the study. One patient in the LUM100/IVA125 mg group prematurely discontinued LUM/IVA treatment 1 month early due to a miscommunication; this patient completed the study. Three patients in the LUM150/IVA188 mg group prematurely discontinued from both LUM/IVA treatment and the study because of AEs of AST or ALT elevations. Note that the data presented in all the tables in Section 8 of this document were confirmed by the primary clinical reviewer and consistent with the Applicant's analyses.

Table 11. Study 115. Patient disposition

Disposition	LUM100/IVA125 mg N=19, n(%)	LUM150/IVA188 mg N=41, n(%)	Total N=60, n(%)
Completed LUM/IVA treatment	18 (94.7)	38 (92.7)	56 (93.3)
Prematurely discontinued treatment	1 (5.3)	3 (7.3)	4 (6.7)
Reason for discontinuation			
Adverse event	0	3 (7.3)	3 (5.0)
Miscommunication	1 (5.3)	0	1 (1.7)
Last completed on-treatment scheduled visit			
Day 1	0	0	0
Day 3	0	0	0
Day 15	0	1 (2.4)	1 (1.7)
Week 4	0	2 (4.9)	2 (3.3)
Week 8	0	0	0
Week 12	0	0	0
Week 16	1 (5.3)	0	1 (1.7)
Week 20	0	0	0
Week 24	0	0	0
Completed study	19 (100.0)	38 (92.7)	57 (95.0)

Source: Study 115 CSR; table 10-2; pp71

Protocol Violations/Deviations

Important protocol deviation (IPD), defined as a protocol deviation that had the potential to affect the interpretation of study results, occurred in 7 patients with one IPD each. Four patients did not have an ophthalmologic examination (OE) at either Week 24 or the safety follow-up visit (OE was completed outside of visit window); two had compliance of <80%, and one received the lower dose for 4 weeks (Week 4 up to Week 8).

Table of Demographic Characteristics

Patient demographic and baseline data for Part B of study 115 are presented in Table 12.

Table 12. Study 115. Baseline characteristics

	LUM100/IVA125mg N=19	LUM150/IVA188mg N=41	Total N=60
Sex, n(%)			
Male	10 (52.6)	21 (51.2)	31 (51.7)
Female	9 (47.4)	20 (48.8)	29 (48.3)
Race, n(%)			
White	18 (94.7)	41 (100.0)	59 (98.3)
Other	1 (5.3)	0	1 (1.7)
Age (months)			
Mean	31.6	49.9	44.1
Median	30.0	49.0	43.5
Age category, n(%)			
<3 years	14 (73.7)	5 (12.2)	19 (31.7)
≥3 years	5 (26.3)	36 (87.8)	41 (68.3)
Mean Percent Predicted FEV1	95.6	83.1	83.8
Mean Sweat Chloride (mmol/L)	105.5	106.0	105.8
Mean BMI (kg/m^2)	15.99	15.98	15.98

Source: study 115 CSR; table 10-5 and 10-6; pp74-76

In summary, 98.3% of patients enrolled in the study were white, which is consistent with the U.S. CF population, and reflects the fact that CF is most common in Caucasians. Thirty-one (51.7%) were male and forty-one (68.3%) were ≥3 years of age. The mean BMI was 15.98 kg/m^2, the mean percent predicted FEV1 was within normal limits, and the mean sweat chloride level (105.8 mmol/L) was significantly higher than normal. The BMI, mean percent predicted FEV1 and sweat chloride values are consistent with those seen in the CF patients 2 to less than 6 years of age who are homozygous for the *F508del* mutation in the CFTR gene.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Consistent with the diagnosis of CF, all patients had baseline fecal elastase-1 (FE-1) levels <200 µg/g, which suggests pancreatic insufficiency in these patients. The most common medical history conditions (≥30% by preferred term) of these patients were pancreatic failure (83.3%), gastroesophageal reflux disease (43.3%), and CF lung (38.3%); these are common manifestations in CF patients.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

In general, the treatment compliance was high. The mean LUM/IVA compliance was 99.2%, and 58 (96.7%) patients were ≥80% compliant with LUM/IVA. Mean LUM/IVA compliance values were similar in the LUM100/IVA125 mg q12h and LUM150/IVA188 mg q12h groups.

All patients used concomitant medication. The three most common concomitant medications included salbutamol, dornase alfa and multivitamins (Aquadek) which are commonly used in CF patients.

Efficacy Results – Primary Endpoint

The primary endpoint of this trial was safety and will be discussed in section 8.2.

Data Quality and Integrity

This NDA was submitted on 02/07/18. The submission was appropriately indexed and complete to allow for review. There were no issues with submission quality or data integrity.

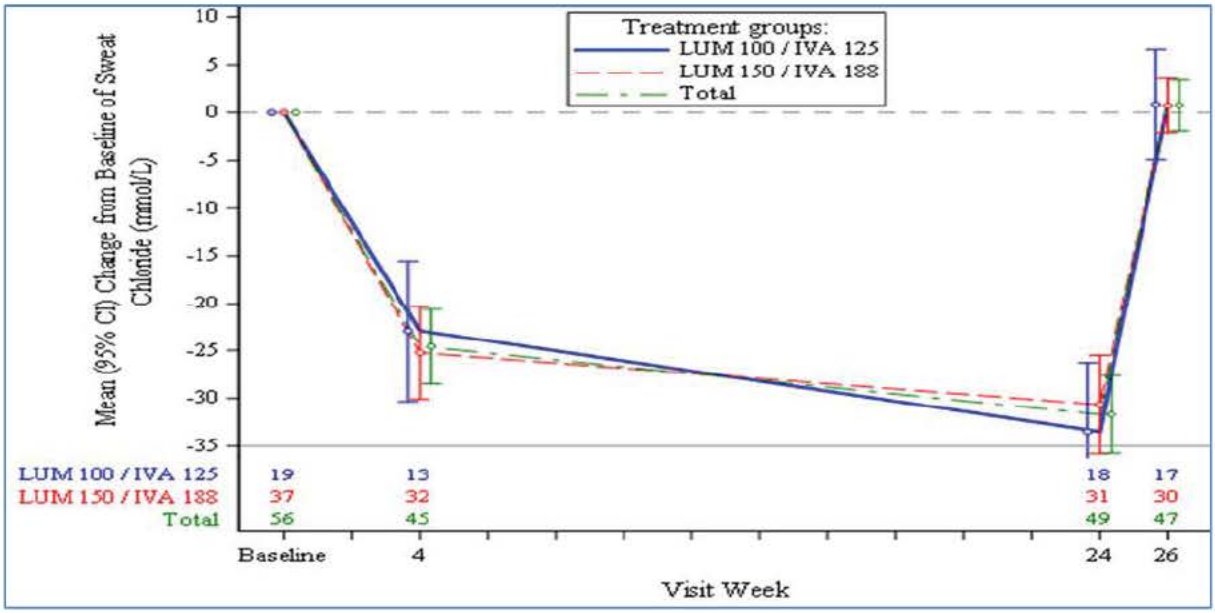
Efficacy Results – Secondary and other relevant endpoints

The non-PK related secondary endpoints were as follows:

- Absolute change from baseline in sweat chloride at Week 24
- Absolute change in sweat chloride from Week 24 at Week 26
- Absolute change from baseline in BMI and BMI-for-age z-score at Week 24
- Absolute change from baseline in weight and weight-for-age z-score at Week 24
- Absolute change from baseline in stature and stature-for-age z-score at Week 24
- Absolute change from baseline in LCI2.5 at Week 24
- Absolute change from baseline in LCI5.0 at Week 24
- Time-to-first pulmonary exacerbation through Week 24
- Number of pulmonary exacerbations through Week 24
- Number of CF-related hospitalizations through Week 24
- Absolute change in FE-1 levels from baseline at Week 24
- Absolute change in serum levels of IRT from baseline through Week 24
- Change in microbiology cultures from baseline at Week 24
- Absolute change from baseline in ppFEV1 at Week 24

For sweat chloride, decreases from baseline were seen in both LUM/IVA granule treatment groups 4 weeks after treatment (LUM100/IVA125 mg = - 22.9 mmol/L; LUM150/IVA188 mg = -25.2 mmol/L). This initial decrease was sustained over the 24-week treatment period (LUM100/IVA125 mg = -33.5 mmol/L; LUM150/IVA188 mg = -30.7 mmol/L). After a 2-week washout period, the sweat chloride levels returned to baseline. Sweat chloride results are summarized in Figure 6.

Figure 6. Study 115. Sweat chloride changes



Source: FDA statistician, Dr. Mingyu Xi

While there is no placebo control for comparison, these data would imply that LUM/IVA granules in this age group have a pharmacodynamic effect. This change is consistent with previous LUM/IVA tablet studies in which LUM/IVA tablets demonstrated efficacy, although smaller than the sweat chloride responses observed in patients 6 to less than 12 years of age (LUM200/IVA250 mg = -24.8 mmol/L) who were administered LUM/IVA tablets.

With regard to absolute change from baseline in weight at Week 24, both LUM/IVA dose groups demonstrated absolute mean increases in weight compared to their own baseline (LUM100/IVA125 mg = 1.4kg; LUM150/IVA188 mg = 1.5 kg). At Week 24, absolute mean increases in stature were also observed (LUM100/IVA125 mg =4.1 cm; LUM150/IVA188 mg =3.4 cm). However, whether or not this was related to treatment is uncertain, as there was no placebo group and as the studied age group is actively growing. Based on CDC growth charts for healthy children, the average weight gain during every 6-month period for children between the age of 2-6 years is approximately 1 kg and for stature approximately 3-4 cm[5]. As such, the observed absolute increases in weight and stature may reflect normal development, rather than a treatment effect. With regard to BMI, the mean change from baseline was 0.22 kg/m^2 and 0.29 kg/m^2 for the LUM100/IVA125 mg and LUM150/IVA188 mg groups, respectively.

The Applicant also assessed weight, stature, and BMI in terms of age adjusted z-scores. At baseline, mean values in both LUM/IVA dose groups showed weight, stature, and BMI that were within one standard deviation of normal as evidenced by baseline z-scores bounded by -1 and 1. At Week 24 of treatment, results were similar with z-scores still bounded by -1 and 1. This would suggest that during the 24-week treatment period, growth was similar to what one would expect in this age group. The results at baseline and Week 24 are summarized in Table

13.

Table 13. Study 115. Weight, Stature, and BMI for age z-scores

	Weight for age z-score		Stature for age z-score		BMI for age z-score	
	Baseline	Week 24	Baseline	Week 24	Baseline	Week 24
LUM100/IVA125 mg (N=19)	-0.70	-0.26	-0.84	-0.65	-0.10	0.26
LUM150/IVA188 mg (N=41)	0.21	0.41	0.09	0.17	0.30	0.55
Total (N=60)	-0.08	0.19	-0.20	-0.10	0.17	0.45

Source: study 115 CSR; table 14.2.1.2.2b, 14.2.1.3.2b and 14.2.1.4.2b; pp233-236, 241-244 and 249-252

The Applicant also reported absolute change from baseline for z-scores. Change from baseline in weight for age z-score at Week 24 was 0.44 and 0.17 for the LUM100/IVA125 mg and LUM150/IVA188 mg groups, respectively. Change from baseline in stature for age z-scores at Week 24 were 0.19 and 0.04 for the LUM100/IVA125 mg and LUM150/IVA188 mg groups, respectively. For BMI, they were 0.36 and 0.26 for the LUM100/IVA125 mg and LUM150/IVA188 mg groups, respectively. Overall, the changes in z-scores were small which may imply that the changes were related to normal growth. However, without a placebo group for comparison, these data are difficult to interpret as these data represent change from baseline in z-scores rather than z-scores for change from baseline. As such, the change from baseline cannot be interpreted in relationship to normal values.

The Applicant also analyzed other secondary endpoints including exacerbation, CF-related hospitalizations, and LCI. While these results were reported, it is difficult to make any definitive conclusions given the lack of a placebo, active, or historical control group. The Applicant also assessed the change from baseline in qualitative microbiology cultures, and no trends for increased or decreased growth were noted.

The Applicant also reported change from baseline in PPFEV1 for those patients who could perform spirometry. Of the 60 patients, twelve patients in the LUM150/IVA188 mg group had PPFEV1 measurements at baseline and at Week 24. At Week 24, the change from baseline in PPFEV1 was 0.5% in this groups, which was not clinically meaningful. Additionally, given the age of the patients, the reliability of the spirometry data is questionable.

The Applicant also reported change from baseline in fecal elastase, and immunoreactive trypsinogen (IRT). For fecal elastase, values were increased at Week 24, and for IRT values were decreased at Week 24. While there were changes in these values, the clinical relevance of these changes is unknown.

Dose/Dose Response

While this trial included two doses of LUM/IVA granules, both doses yielded similar systemic exposures. As such, exploration for dose response was not possible.

Durability of Response

In this study, the absolute changes of sweat chloride, a pharmacodynamic endpoint, from baseline were noted at Week 24 when LUM/IVA treatment was completed. These changes were also observed at earlier weeks, indicating that the drug response was durable while on drug.

Persistence of Effect

In this study, the sweat chloride levels returned to baseline after a 2-week washout period, suggesting that there was no persistence of LUM/IVA effect on this pharmacodynamic endpoint once the treatment was stopped.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

None

Additional Analyses Conducted on the Individual Trial

None

Integrated Review of Effectiveness

Only one study was included to assess efficacy in this NDA. Refer to Section 8.1.1 and 8.1.2 for the review of effectiveness.

8.1.3. Assessment of Efficacy Across Trials

Not applicable to this review as only one study was included

8.1.4. Integrated Assessment of Effectiveness

In this NDA, the Applicant has submitted data from a pharmacokinetic (PK) and safety study (study 115) to support the use of LUM/IVA granules in patients 2 to less than 6 years of age who were homozygous for the *F508del* mutation in the CFTR gene.

Study 115 was a two-part, non-randomized, uncontrolled, open-label PK (part A, 15-day duration, n=12) and safety (part B, 24-week duration, n=60) study in patients 2 to less than 6 years of age. In part A, results demonstrated that when LUM150/IVA188 mg was administered to patients ≥14kg and LUM100/IVA125 mg administered to patients <14kg every 12 hours, systemic exposures matched that observed in the adolescent/adult population. Because of the similar systemic exposures and because the disease process in the older population is the same as that in the 2 to less than 6 year old population, efficacy in the proposed age group was extrapolated from the LUM/IVA tablet development program. Additionally, Week 24 data from part B demonstrated that for the pharmacodynamic endpoint of sweat chloride decreases were

observed in both LUM/IVA granule treatment groups (LUM100/IVA125 mg = -33.5 mmol/L; LUM150/IVA188 mg = -30.7 mmol/L), suggesting a pharmacodynamic response to the LUM/IVA granule treatment.

In summary, efficacy of LUM/IVA granules in *F508del* homozygous patients aged 2 to less than 6 years has been demonstrated based on extrapolation from the older population.

8.2. Review of Safety

The Applicant has submitted data from study 115 to support the safety of LUM/IVA granules in CF patients 2 to less than 6 years of age who were homozygous for the *F508del* mutation in the CFTR gene. In the LUM/IVA tablet label, the listed Warnings and Precautions include liver-related events, respiratory events, increased blood pressure and cataracts, which were specifically assessed in this study. In addition, there were concerns regarding significant drug-drug interactions with CYP3A inducers, inhibitors, and substrates.

8.2.1. Safety Review Approach

The clinical safety review is based on the clinical data from study 115 that was a 2-part (A and B) open-label, non-randomized study in CF patients who were homozygous for the *F508del* mutation. As Part A only included a 15-day treatment period, this section will only include a discussion of safety data from Part B which included a 24-week treatment period.

8.2.2. Review of the Safety Database

Overall Exposure

A total of 60 patients were exposed to LUM/IVA granules in study 115. Nineteen patients who weighed less than 14kg were administered LUM100/IVA125 mg every 12 hours, while forty-one patients who weighed 14kg or greater received LUM150/IVA188 mg every 12 hours. The majority of patients were exposed to LUM/IVA granules for 16-24 weeks. The extent of exposure in study 115 is summarized in Table 14.

Table 14. Study 115. Extent of exposure

	LUM100/IVA125 mg N=19	LUM150/IVA188 mg N=41	Total N=60
Extent of Exposure (days)			
Mean (SD)	165.8 (7.11)	156.9 (37.27)	159.7 (31.22)
Median (min, max)	168.0 (138, 171)	168.0 (23, 174)	168.0 (23, 174)
Duration of Exposure, n(%)			
>0 to ≤2 weeks	0	0	0
>2 to ≤4 weeks	0	3 (7.3)	3 (5.0)
>4 to ≤8 weeks	0	0	0
>8 to ≤16 weeks	0	0	0
>16 to ≤24 weeks	18 (94.7)	30 (73.2)	48 (80.0)
>24 weeks	1 (5.3)	8 (19.5)	9 (15.0)

Source: Study 115 CSR; table 12-2; pp107

Relevant characteristics of the safety population:

Refer to Table 5 in section 8.1.2.

Adequacy of the safety database:

Part B of study 115 included a 24-week treatment period where safety was assessed. The safety database was adequate to review the safety of LUM/IVA granules.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

None

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 was to be reported as an adverse event. Adverse events were classified using MedDRA Version 20.0.

In addition, treatment emergent adverse events (TEAEs) in this study were defined as any AE during the treatment period from initial dosing of LUM/IVA in the respective part to 14 days after the last dose of LUM/IVA in the corresponding part. In this review, TEAEs are assessed in the following safety analysis. The grading of AE severity was determined as mild (Grade 1, mild level of discomfort and does not interfere with regular activities), moderate (Grade 2, moderate level of discomfort and significantly interferes with regular activities), severe (Grade 3, significant level of discomfort and prevents regular activities) or life-threatening (Grade 4, any

adverse drug event that places the subject, in the view of the investigator, at immediate risk of death).

Routine Clinical Tests

The standard battery of routine clinical tests including physical exam, vital signs and clinical laboratory testing were conducted as part of the assessment schedule (Table 20 in appendix 15) in this study.

8.2.4. Safety Results

Deaths

There were no deaths in study 115.

Serious Adverse Events

In general, the serious adverse events (SAE) reported were what would be expected in a CF population. A total of 4 patients experienced SAEs. One patient each had gastroenteritis viral and constipation, and two patients had pulmonary exacerbations of CF. These results are summarized in Table 15. SAE data did not reveal new safety concerns.

Table 15. Study 115. Nonfatal serious adverse events

System Organ Class Preferred Term	LUM100/IVA125 mg N=19, n(%)	LUM150/IVA188 mg N=41, n(%)	Total N=60, n(%)
Subjects with any SAEs	2 (10.5)	2 (4.9)	4 (6.7)
Infections and infestations	1 (5.3)	2 (4.9)	3 (5.0)
Infective PEx of CF	0	2 (4.9)	2 (3.3)
Gastroenteritis viral	1 (5.3)	0	1 (1.7)
Gastrointestinal disorders	1 (5.3)	0	1 (1.7)
Constipation	1 (5.3)	0	1 (1.7)

Source: study 115 CSR; table 12-13; pp121

Dropouts and/or Discontinuations Due to Adverse Effects

Sixty patients were enrolled and received at least 1 dose of LUM/IVA. Fifty-six (93.3%) patients completed the LUM/IVA treatment, and fifty-seven (95.0%) patients completed the study. One patient in the LUM100/IVA125 mg q12h group prematurely discontinued the LUM/IVA treatment 1 month early due to a miscommunication, but this patient continued in the study. Three patients in the LUM150/IVA188 mg q12h group prematurely discontinued from both the LUM/IVA treatment and the study because of AEs of AST or ALT elevations >8x ULN. The transaminase elevations were not associated with total bilirubin elevations. All transaminase elevations returned to close to baseline after drug discontinuation.

Three (5.0%) patients had AEs that led to LUM/IVA interruption. In the LUM100/IVA125 mg q12h group, one patient had transaminase elevation, and one patient had constipation. In the LUM150/IVA188 mg q12h group, transaminase elevations occurred in one patient. All AEs that led to LUM/IVA interruption had an outcome of resolved.

Significant Adverse Events

In study 115, a total of 5 (8.3%) patients had treatment emergent adverse events (TEAEs) that were grade 3 (severe). No grade 4 life-threatening TEAEs were reported. In the LUM100/IVA125 mg q12h group, one patient each had severe gastroenteritis viral and constipation. In the LUM150/IVA188 mg q12h group, transaminase elevations occurred in two patients and one patient had pulmonary exacerbations of CF. These severe adverse events were consistent with common manifestations of CF disease and no new safety signals were identified.

Treatment Emergent Adverse Events and Adverse Reactions

Common adverse events are summarized in Table 16. The AEs reported were generally consistent with common manifestations of CF disease or common illnesses in patients 2 to less than 6 years of age. No new safety signals have been identified.

Table 16. Study 115. AEs With a Frequency of At Least 5% at the Preferred Term (PT) Level Overall by SOC and PT

System Organ Class Preferred Term	LUM100/IVA125mg N = 19, n (%)	LUM150/IVA188mg N = 41, n (%)	Total N = 60, n (%)
Subjects with any AEs	19 (100.0)	40 (97.6)	59 (98.3)
Respiratory, thoracic, and	17 (89.5)	28 (68.3)	45 (75.0)
Cough	12 (63.2)	26 (63.4)	38 (63.3)
Rhinorrhea	8 (42.1)	7 (17.1)	15 (25.0)
Nasal congestion	4 (21.1)	6 (14.6)	10 (16.7)
Oropharyngeal pain	1 (5.3)	3 (7.3)	4 (6.7)
Productive cough	2 (10.5)	2 (4.9)	4 (6.7)
Dyspnea	1 (5.3)	2 (4.9)	3 (5.0)
Wheezing	1 (5.3)	2 (4.9)	3 (5.0)
Infections and infestations	14 (73.7)	22 (53.7)	36 (60.0)
Upper respiratory tract	3 (15.8)	7 (17.1)	10 (16.7)
Ear infection	3 (15.8)	4 (9.8)	7 (11.7)
Sinusitis	2 (10.5)	3 (7.3)	5 (8.3)
Infective pulmonary exacerbation of cystic	0	4 (9.8)	4 (6.7)
Otitis media	0	4 (9.8)	4 (6.7)
Viral upper respiratory tract	2 (10.5)	2 (4.9)	4 (6.7)
Pharyngitis streptococcal	2 (10.5)	1 (2.4)	3 (5.0)
Rhinitis	1 (5.3)	2 (4.9)	3 (5.0)
Gastrointestinal disorders	11 (57.9)	19 (46.3)	30 (50.0)
Vomiting	6 (31.6)	11 (26.8)	17 (28.3)
Constipation	3 (15.8)	4 (9.8)	7 (11.7)
Diarrhea	2 (10.5)	4 (9.8)	6 (10.0)
Abdominal pain	1 (5.3)	3 (7.3)	4 (6.7)
Nausea	1 (5.3)	2 (4.9)	3 (5.0)
Steatorrhea	2 (10.5)	1 (2.4)	3 (5.0)
Investigations	10 (52.6)	10 (24.4)	20 (33.3)
ALT increased	3 (15.8)	5 (12.2)	8 (13.3)
AST increased	2 (10.5)	4 (9.8)	6 (10.0)
Pseudomonas test positive	3 (15.8)	2 (4.9)	5 (8.3)
General disorders and administration site	8 (42.1)	10 (24.4)	18 (30.0)
Pyrexia	7 (36.8)	10 (24.4)	17 (28.3)
Nervous system disorders	1 (5.3)	5 (12.2)	6 (10.0)
Headache	0	4 (9.8)	4 (6.7)

Source: study 115 CSR; table 12-6; pp112

Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries including liver transaminases, coagulation studies, and urinalyses. No laboratory

abnormalities resulted in study drug discontinuation, aside from the 3 cases of drug discontinuation due to transaminase elevations described in section on hepatic safety above.

Vital Signs

The Applicant presented mean values for heart rate, blood pressure, body temperature, and oxygen saturations. No clinically relevant changes from baseline were noted.

Electrocardiograms (ECGs)

Summary statistics of heart rate, PR interval, RR interval, QRS duration, QT and QTcF for each LUM/IVA granule treatment group was provided by the Applicant. No clinically relevant changes from baseline were noted. Shift table analysis was also unrevealing.

QT

No clinically relevant QT changes from baseline were noted.

Immunogenicity

Not applicable

8.2.5. Analysis of Submission-Specific Safety Issues

Given the listed Warnings and Precautions included in the approved LUM/IVA tablet label, specific safety analyses were performed for hepatic safety, respiratory safety, cataracts and blood pressure changes.

Hepatic safety
Due to the increases in AST and ALT observed in the LUM/IVA tablet phase 3 clinical trials in older population, we specifically assessed AE and clinical lab data for transaminase abnormalities in this study. In study 115, nine patients (15%) had maximum on-treatment transaminase elevations of >3x ULN. Of these patients, five had values which were >8x ULN. All these patients had normal or slightly higher than normal baseline transaminases, except for one patient that had baseline ALT =2x ULN. These results are summarized in Table 17.

Table 17. Study 115. Maximum on-treatment transaminase results

Maximum on-treatment	LUM100/IVA125 mg N=19, n(%)	LUM150/IVA188 mg N=41, n(%)	Total N=60, n(%)
ALT			
≤3x ULN	18 (94.7)	33 (80.5)	51 (85.0)
>3 × ULN	1 (5.3)	8 (19.5)	9 (15.0)
>5 × ULN	1 (5.3)	6 (14.6)	7 (11.7)
>8 × ULN	1 (5.3)	4 (9.8)	5 (8.3)
AST			
≤3x ULN	19 (100.0)	36 (87.8)	55 (91.7)
>3 × ULN	0	5 (12.2)	5 (8.3)
>5 × ULN	0	2 (4.9)	2 (3.3)
>8 × ULN	0	1 (2.4)	1 (1.7)
ALT or AST			
≤3x ULN	18 (94.7)	33 (80.5)	51 (85.0)
>3x ULN	1 (5.3)	8 (19.5)	9 (15.0)
>5x ULN	1 (5.3)	6 (14.6)	7 (11.7)
>8x ULN	1 (5.3)	4 (9.8)	5 (8.3)

Source: study 115 CSR; table 12-16; pp125

The five cases of transaminase elevations of >8x ULN are reviewed below:

Patient (b) (6):
This was a 3-year-old male (wt.13.2 kg) assigned to the LUM100/IVA125 mg treatment group. The patient had a history of pancreatic insufficiency, infective PEx of CF, and gastrostomy. Transaminases were within normal range at baseline. However, 29 days after the first dose of study drug (b) (6)), ALT and AST were found to be elevated (ALT>8x ULN, AST>2x ULN), and LUM/IVA granules were interrupted on (b) (6). When transaminases were reassessed on (b) (6), ALT was slightly elevated (1.2x ULN), but AST was within normal range and remained within normal range for the remainder of the study. LUM/IVA granules were resumed on (b) (4). The ALT value normalized on (b) (4) and remained within normal range for the remainder of the study except for a transient elevation on (b) (6). The AE of increased ALT was considered by the investigator to be related to study drug, and the AE of increased AST was considered by the investigator to be possibly related to study drug.

Patient (b) (6):
This patient was a 2-year-old male (wt.14.1 kg) assigned to the LUM150/IVA188 mg treatment group and had a history of pancreatic insufficiency, gastroesophageal reflux disease, constipation, seasonal allergy, asthma, and tracheomalacia. At screening (b) (6), this patient had an elevation of ALT (=2x ULN). 29 days after the first dose of study drug (b) (6), ALT, AST and gamma-glutamyl transferase (GGT) were found to be elevated (ALT>8x ULN, AST>3x ULN, GGT>1.09x ULN), and LUM/IVA granules were interrupted on (b) (6). On (b) (6), ALT value decreased but remained elevated (>2x ULN) and AST normalized. The AEs of increased ALT and AST after LUM/IVA granule administration were considered by the investigator to be possibly related to study drug. On (b) (6), the patient

started to retake the study drug until (b) (6) when the patient received the last dose. On (b) (6), mild increased ALT (>2x ULN) and AST (>1.2x ULN) were reported, which remained ongoing at the time of last report (b) (6). Increased ALT and AST after the patient resumed the study drug were considered by the investigator to be unlikely related to study drug.

Patient (b) (6):
This patient was a 5-year-old female (wt.19.4 kg) assigned to the LUM150/IVA188 mg treatment group and had a history of pancreatic insufficiency, impetigo, and sinusitis. Transaminases were within normal range at baseline. On (b) (6) (26 days after the first dose), ALT, AST and GGT were found to be elevated (ALT>8x ULN, AST>8x ULN, GGT>2x ULN), and LUM/IVA granules were discontinued on the same day. After drug withdrawal, transaminase levels gradually decreased. On (b) (6), slightly increased ALT (>1x ULN), normal AST and slightly increased GGT (>1.1x ULN) were reported. The AE of increased transaminases was considered by the investigator to be possibly related to study drug.

Patient (b) (6):
This patient was a 4-year-old male (wt.16.3 kg) assigned to the LUM150/IVA188 mg treatment group and had a history of pancreatic insufficiency and gastroesophageal reflux disease. Before the patient received the first dose of study drug on (b) (6), ALT values were occasionally slightly higher than normal. On (b) (6) (29 days after the first dose), ALT and AST values were found to be elevated (ALT>8x ULN, AST>1.9x ULN), and LUM/IVA granules were discontinued on the same day. On (b) (6), increased ALT (>3.8x ULN) and normal AST were reported. Increased ALT remained ongoing at the time of reporting (b) (6). The AE of increased transaminases was considered by the investigator to be possibly related to study drug.

Patient (b) (6):
This patient was a 5-year-old male (wt.19.9 kg) assigned to the LUM150/IVA188 mg treatment group and had a history of CF hepatic disease, pancreatic insufficiency, constipation, allergy to egg and milk, eosinophilic esophagitis, asthma, sinus disorder, Port-A-Cath insertion, and gastrostomy tube due to abdominal surgery. The patient also had a history of elevated liver enzymes (resolved). Before the patient received the first dose of study drug on (b) (6), ALT values were slightly higher than normal. On (b) (6)(15 days after the first dose), ALT and AST values were first found to be elevated (ALT>4x ULN, AST>2x ULN). The ALT and AST values remained elevated and reached peak values of ALT > 8 X ULN and AST >5 × ULN on (b) (6). LUM/IVA granules were discontinued on (b) (6). On (b) (6), the AST value normalized and remained within normal range for the remainder of the study. The ALT value also decreased but remained elevated until (b) (6). The AE of increased transaminases was considered by the investigator to be possibly related to study drug.

In all 5 cases of transaminase elevations >8x ULN in this study, associated increases in total bilirubin were not observed. After drug withdrawal, transaminase levels decreased and no

clinical jaundice was observed. Overall these findings are consistent with the known safety profile of LUM/IVA.

Respiratory safety
In the development program of LUM/IVA tablets, respiratory adverse events, were observed more commonly in patients in the treatment group compared to those who received placebo. Therefore, the Applicant performed a safety analysis grouping together PTs meant to represent respiratory symptoms and respiratory events [adverse events of special interest (AESI)]. A total of 3 (5.0%) patients had AESIs of respiratory symptoms, defined as the PTs chest discomfort, dyspnea, or respiratory abnormal. By PT, dyspnea occurred in 3 (5.0%) patients and respiratory abnormal occurred in 1 (1.7%) patient. The mean time-to-onset of the first event was 10.3 days, and the mean duration of events was 2.3 days. These results are summarized in Table 18.

Table 18. Study 115. Adverse Events of Special Interest (AESI) of respiratory symptoms

AESI Preferred Term	LUM100/IVA125 mg N=19, n(%)	LUM150/IVA188 mg N=41, n(%)	Total N=60, n(%)
Subjects with any AESI of respiratory symptoms	1 (5.3)	2 (4.9)	3 (5.0)
Chest discomfort	0	0	0
Dyspnea	1 (5.3)	2 (4.9)	3 (5.0)
Respiration abnormal	0	1 (2.4)	1 (1.7)
Time-to-onset of the first event (days)			
Mean	28.0	1.5	10.3
Median	28.0	1.5	2.0
Duration of events (days)			
Mean	1.0	2.7	2.3
Median	1.0	2.0	1.5

Source: study 115 CSR; table 12-11; pp118

A total of 6 (10.0%) patients had AESIs of respiratory events, defined as respiratory symptoms (chest discomfort, dyspnea, respiratory abnormal as noted above) along with the PTs asthma, bronchial hyperreactivity, bronchospasm, or wheezing. The patients with respiratory symptoms were described above. No patients reported asthma, bronchial hyperreactivity or bronchospasm. However, wheezing occurred in 3 (5.0%) patients. The mean time-to-onset of the first event was 23.2 days, and the mean duration of events was 6.1 days. These results are summarized in **Table 19**.

Table 19. Study 115. Adverse Events of Special Interest (AESI) of respiratory events

AESI Preferred Term	LUM100/IVA125 mg N=19, n(%)	LUM150/IVA188 mg N=41, n(%)	Total N=60, n(%)
Subjects with any AESI of respiratory events	2 (10.5)	4 (9.8)	6 (10.0)
Chest discomfort	0	0	0
Dyspnea	1 (5.3)	2 (4.9)	3 (5.0)
Respiration abnormal	0	1 (2.4)	1 (1.7)
Asthma	0	0	0
Bronchial hyperreactivity	0	0	0
Bronchospasm	0	0	0
Wheezing	1 (5.3)	2 (4.9)	3 (5.0)
Time-to-onset of the first event (days)			
Mean	14.5	27.5	23.2
Median	14.5	9.0	9.0
Duration of events (days)			
Mean	4.3	7.2	6.1
Median	4.0	5.0	4.5

Source: study 115 CSR; table 12-12; pp120

Note that no patients had AESIs of respiratory symptoms or events that led to interruption or discontinuation of treatments. Additionally, none were serious in nature.

Cataract
As lens opacities/cataracts were noted in ivacaftor juvenile animal studies and have been observed in patients taking LUM/IVA and IVA, study 115 included ophthalmologic evaluations pre-dose and at Week 24 (or at Week 26). No patients developed lens opacities during the study.

Blood pressure
Increased blood pressures had been observed in some patients treated with LUM/IVA tablets, and it is recommended that blood pressures be monitored periodically in all patients being treated with LUM/IVA tablets. As such, systolic and diastolic blood pressures were measured and no clinically meaningful changes of blood pressures from baseline were observed.

Overall, these specific analyses did not reveal new safety concerns.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

This study did not include clinical outcome assessments.

8.2.7. Safety Analyses by Demographic Subgroups

Given the limited number of patients included, all of whom were 2 to less 6 years of age, no safety analyses by demographic subgroups were performed.

8.2.8. Specific Safety Studies/Clinical Trials

Study 115 part B was a safety study and has been discussed. The Applicant also submitted safety data from an ongoing study 116. Study 116 is a Phase 3, open-label, multicenter, rollover study in patients who completed Study VX15-809-115 Part B designed to evaluate the safety of long-term (approximately 96 weeks) LUM/IVA combination therapy in CF patients 2 years and older. These data did not reveal any new safety concerns.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Not performed

Human Reproduction and Pregnancy

Not applicable

Pediatrics and Assessment of Effects on Growth

This trial included pediatric patients of 2 to less than 6 year old. Compared to historical controls (CDC growth charts), there did not appear to be detrimental effects on growth.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not applicable

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

There is no post-marketing experience with LUM/IVA granules. However, LUM/IVA tablets were initially approved on 07/02/2015 for CF patients aged 12 years and older who are homozygous for the *F508del* mutation. Since that time until the date of this review, no new issues have been identified that would alter the risk-benefit profile for the approved indication.

Expectations on Safety in the Postmarket Setting

The patient population included in study 115 who received LUM/IVA granules is similar to the target population. Given this fact and the postmarketing experience with LUM/IVA tablets, no substantial differences are anticipated.

8.2.11. Integrated Assessment of Safety

The safety data submitted with this application for the LUM/IVA granules, in conjunction with the known safety profile of LUM/IVA tablets, was sufficient to assess the safety of LUM/IVA granules in the CF patient population aged 2 to less than 6-years of age. In study 115 part B, which included 60 patients all treated with LUM/IVA, no deaths were reported, and the observed SAEs were consistent with the disease process and were not frequent. Given the previous clinical experience with LUM/IVA tablets, specific safety analyses were also performed to assess for liver-related toxicity, occurrence of respiratory related adverse events, cataract, and changes in blood pressure. These safety analyses did reveal new safety concerns and were consistent with the known safety profile of LUM/IVA tablets. Overall, the LUM/IVA granule safety profile in CF patients aged 2 to less than 6-years is favorable.

SUMMARY AND CONCLUSIONS

8.3. Statistical Issues

None. Study 115 was a PK/safety study and analysis of safety was descriptive.

8.4. Conclusions and Recommendations

The recommend regulatory action is Approval for LUM/IVA granules at a dose of LUM150/IVA188 mg for patients ≥14kg and LUM100/IVA125 mg for patients <14kg every 12 hours for the treatment of cystic fibrosis in patients 2 to less than 6 years of age who are homozygous for the *F508del* mutation.

In this NDA, the Applicant has submitted data from a pharmacokinetic (PK)/safety study (study 115) to support the use of LUM/IVA granules in patients 2 to less than 6 years of age who are homozygous for the *F508del* mutation in the CFTR gene.

Study 115 was a two-part, non-randomized, uncontrolled, open-label PK (part A, 15-day duration, n=12) and safety (part B, 24-week duration, n=60) study in patients 2 to less than 6 years of age. Results demonstrated that when LUM150/IVA188 mg was administered to patients ≥14kg and LUM100/IVA125 mg was administered to patients <14kg every 12 hours, systemic exposures were comparable to that observed in the adolescent/adult population at the approved dose. Because of the comparable systemic exposures and because the disease process in the adolescent adult population is the same as that in the 2 to less than 6 year old population; efficacy in the proposed age group can be extrapolated from the adolescent/adult population where efficacy had been demonstrated in placebo controlled clinical trials. Additionally, Week 24 data from part B demonstrated decreases in the pharmacodynamic endpoint of sweat chloride in both LUM/IVA granule treatment groups (LUM100/IVA125 mg = -33.5 mmol/L; LUM150/IVA188 mg = -30.7 mmol/L), suggesting a pharmacodynamic response to the LUM/IVA granule treatment. Safety findings from study 115 were consistent with that observed in the older populations. No new safety signals were revealed. The overall risk-benefit assessment supports approval of LUM/IVA granules. The clinical recommendation is Approval.

X Liangfeng Han -S
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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Liangfeng Han -S, 0.9.2342.19200300.100.1.1=2002375346
Date: 2018.07.31 14:55:29 -04'00'

X Robert H. Lim -S
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Date: 2018.08.07 07:57:42 -04'00'

Liangfeng Han, MD
Primary Clinical Reviewer

Robert Lim, MD
Clinical Team Leader

9 Advisory Committee Meeting and Other External Consultations

An advisory meeting was not convened, nor required, for this application.

10 Pediatrics

Lumacaftor and Ivacaftor combination therapy was granted Orphan Drug Designation (Designation No. 14-4348) on 30 June 2014. PREA requirements do not apply to this orphan drug product.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The new LUM/IVA formulation (granules) proposes to expand the LUM/IVA indication to include the 2 to less than 6 year old age group at a dose of LUM150/IVA188 mg for patients ≥14kg and LUM100/IVA125 mg for <14kg every 12 hours. The expanded age range and dose for the age range were added (b) (4)

Summary of Significant Labeling Changes (High level changes and not direct quotations)		
Section	**Proposed Labeling**	**Approved Labeling**
1 Indication and Administration	Added patients 2 to less than 6 years old added.	The information is included
2.1 Dosing information	Added granule formulation and dosage for patients 2 to less than 6 year old.	The information is included.
(b) (4)	(b) (4)	

12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary for this application.

13 Postmarketing Requirements and Commitment

No postmarketing requirements and commitments are requested.

14 Division Director (DPARP)

The submitted clinical program is adequate to support the efficacy and safety of lumacaftor/ivacaftor granules at a dose of lumacaftor/ivacaftor 150/188 mg for patients ≥ 14 kg and of lumacaftor/ivacaftor 100/125 mg for patients < 14 kg every 12 hours for the treatment of cystic fibrosis in patients 2 to 6 years of age who are homozygous for the *F508del* mutation.

The submitted clinical program consisted primarily of a clinical pharmacology study, Study 115. Study 115 was an open-label, uncontrolled, two-part pharmacokinetic (part A, 15-day duration, n=12) and safety study (part B, 24-week duration, n=60) study in patients 2 to less than 6 years of age who were homozygous for the *F508del* mutation in the CFTR gene. PK results demonstrated that when lumacaftor/ivacaftor 150/188 mg was administered to patients ≥ 14 kg and lumacaftor/ivacaftor 100/125 was administered to patients < 14 kg every 12 hours, systemic exposures were comparable to that observed in the adult/adolescent population, in whom this drug is already approved. Because the disease process in the adult/adolescent population is the same as that in the proposed age group, efficacy in 2 to 6 year olds can be extrapolated from the older age groups where efficacy has been demonstrated in placebo-controlled clinical trials, based on comparable systemic exposures. In addition, changes from baseline in sweat chloride, a pharmacodynamic endpoint, were seen in both dose groups, which is consistent with the results of previous trials, demonstrating a pharmacodynamic response to lumacaftor/ivacaftor granule treatment.

Patients with moderate/severe hepatic impairment will require dose reduction (consistent with current labeled dosing recommendations), which will be stated in term of packets of granules, rather than tablets in the package insert. No new safety signals were identified. The product quality is also adequate. There are no outstanding issues from any review disciplines. I concur with the content of various discipline assessments and the recommendation of approval. The Agency and the Applicant have also agreed upon final labeling language. The action for this application will be **Approval.**

X Banu A. Karimi-shah -S

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DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=13004 06057, cn=Banu A. Karimi-shah -S
Date: 2018.08.07 08:43:48 -04'00'

Banu A. Karimi-Shah, MD
Clinical Team Leader, DPARP
Signing for Dr. Sally Seymour, Acting Division Director

15 Appendices

15.1. 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. http://www.cdc.gov/growthcharts/clinical_charts.htm

15.2. Financial Disclosure

Clinical Investigator Financial Disclosure
Review Template

Application Number: 211358

Submission Date(s): 02/07/2018

Applicant: Vertex

Product: Orkambi granules (LUM/IVA)

Reviewer: Liangfeng Han

Date of Review: 05/15/2018

Covered Clinical Study (Name and/or Number): 115

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 94		

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): 2		
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: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in S 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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

From study (b) (6), the Applicant certified the absence of financial arrangements for (b) (6) of the primary investigators and sub-investigators. In study (b) (6) there was two principle investigators with significant payments of other sorts (b) (6). These significant payments of other sorts were determined to not have a significant impact upon the conduct of this study. Enrollment at any particular site ((b) (6)) was relatively small compared to the overall number of patients. Additionally, removal of patients from these sites would not have affected interpretation of safety and efficacy was based on extrapolation from the older population.

15.3. Nonclinical Pharmacology/Toxicology

NA

15.4. OCP Appendices (Technical documents supporting OCP recommendations)

Population PK Analyses

Population PK analyses were conducted by Applicant based on pooled data from Study 115, Study 109, and Study 011 to characterize the exposure of lumacaftor (LUM) and ivacaftor (IVA) in cystic fibrosis (CF) subjects 2 through 11 years of age.

Study 115 was a Phase 3, open-label study that evaluated LUM/IVA in CF subjects 2 through 5 years of age for 15 days in Part A and for 24 weeks in Part B. Subjects who weighed <14 kg at screening received L100/I125 every 12 hours (q12h). Subjects who weighed ≥14 kg at screening received L150/I188 q12h. A total of 62 subjects were enrolled in the study. For Part A, PK samples were collected at 3-4 hours on Day 1, prior to morning dose on Day 8, prior to morning dose, 2 hours and 3-4 hours on Day 15. For Part B, PK samples were collected at prior to morning dose and 2-6 hours on Day 15 and Week 4.

Study 109 was a Phase 3, double-blind, randomized, placebo-controlled study that evaluated LUM/IVA in CF subjects 6 through 11 years of age for 24 weeks. Subjects received L200/I250q12h or placebo. A total of 103 subjects were enrolled in Study 109.PK samples were collected at prior to morning dose at Day1, Week 4, and Week 24, and 3 to 6 hours on Day 1, Day 15 and Week 4.

Study 011 was a 2-part, open-label study that evaluated LUM/IVA in CF subjects 6 through 11 years of age for 15 days in Part A (Phase 1) and 24 weeks in Part B (Phase 3). All subjects received L200/I250q12h. A total of 62 subjects were enrolled in Study 011. For Part A, PK samples were collected at prior to morning dose on Day 1, Day 7, and Day 14, 2, 4, 6, and 12 hours on Day 1, and 4, 6, 12, and 24-96 hours on Day 14. For Part B, PK samples were collected at prior to morning dose on Day 1, Week 4, and Week 16, 3 to 6 hours on Day 1, Day 15, and Week 4, and an additional dose in the morning on Week 24.

Table 1 summarizes the baseline continuous and categorical covariates for subjects who received LUM/IVA in Studies 011, 109, and 115.

Table 1 Summary of Covariates in the PK Analysis Set by Study

Reference ID: 4303047

Covariate	Statistic	6 Through 11 Years of Age		2 Through 5 Years of Age
		Study 011	Study 109	Study 115
Age (year)	N	62	103	62
	Mean (SD)	9 (1.7)	8.7 (1.6)	3.2 (1.1)
	Min	6	6	2
	Median	9	9	3
	Max	12[a]	11	5
Weight (kg)	Mean (SD)	31.7 (6.9)	29.4 (6.5)	15.6 (2.8)
	Min	18.2	17.7	9.4
	Median	30.6	28.4	15.6
	Max	57	47.4	23.9
Sex	Male (%)	30 (48.4)	40 (38.8)	32 (51.6)
	Female (%)	32 (51.6)	63 (61.2)	30 (48.4)
Race	Caucasian	62	100	61
	Other	0	3	1

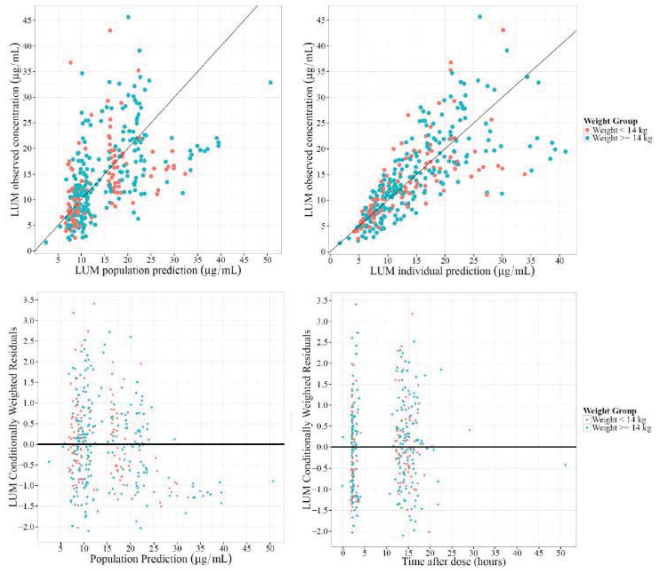
Source: Applicant's pop PK analysis report, Page 20, Table 7-1

4.2.1 Population PK Analysis for LUM

A 2-compartment linear model with first-order absorption and elimination was developed to describe the PK profile of LUM in CF subjects aged 2-11 years. F1 was fixed to 1 for the formulation evaluated in Studies 011 and 109 and the relative bioavailability was estimated for the granule formulation in Study 115. Body weight was found as a significant covariate on clearance (CL) and central compartment volume distribution (Vc). The power was finally fixed to 0.75 and 1 for CL and Vc, respectively.

The diagnostic plots for the final model was plotted in subjects 2 through 5 years as shown in Figure 1. The final parameter estimates for LUM model is listed in Table 2.

Figure 1. Diagnostic plots for the final model of LUM in subjects 2 through 5 years



Source: Applicant's pop PK analysis report, Page 34-37, Figures 7-8 and 7-9

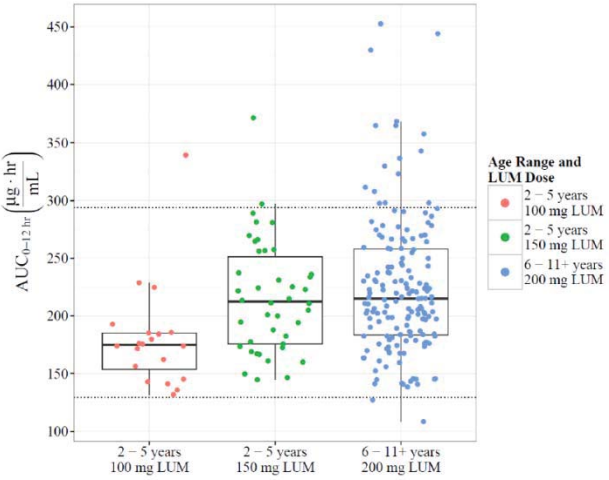
Table 2. Final parameter estimates for LUM model

Fixed Parameter Estimates				
Parameter	**Units**	**Estimate**	**%RSE**	**95% CI**
CL/F	L/hr	1.76*	4.2	(1.68, 1.84)
Vc/F	L	3.38*	16.2	(2.29, 4.98)
Q/F	L/hr	0.16	14.0	(0.09, 0.26)
Vp/F	L	27.93	3.2	(22.6, 34.51)
KA	1/hr	0.11	4.3	(0.09, 0.13)
Granule F1	-	0.87	5.1	(0.78, 0.96)
ALAG	hr	0.87	46.1	(0.77, 0.99)
Random Effect Parameter Estimates				
Parameter		**Estimate**	**%RSE**	**%CV**	**% Shrinkage[3]**
ω^2 CL/F		0.062	13.9	24.99	10.0
ω^2 Vc/F		0.829	24.1	91.04	24.5
ω^2 KA		0.112	33.2	33.46	20.4
Cov($\omega_{CL/F}$, $\omega_{Vc/F}$)		0.131	24.2	NA	NA
Cov($\omega_{CL/F}$, ω_{KA})		0.059	21.2	NA	NA
Cov($\omega_{Vc/F}$, ω_{KA})		0.238	34.5	NA	NA
Residual Variance				
Parameter		**Estimate**	**%RSE**	**% Shrinkage**	
σ^2 (proportional)		0.11	5.2	9.8	

Source: Applicant's pop PK analysis report, Page 40, Tables 7-3

The predicted LUM $AUC_{0–12h}$ exposure for subjects in Studies 011, 109, and 115 are shown in Figure 2.

Figure 2. Predicted LUM $AUC_{0\text{-}12h}$ at steady-state for subjects 2 through 11 years of age



Dashed lines represent 90% confidence interval for AUC0 - 12hr of subjects greater than 12 years of age receiving L400 q12h. Each point represents the individual $AUC_{0\text{-}12hr}$ prediction for a subject
Source: Applicant's pop PK analysis report, Page 41, Figure 7-11

Table 3 summarizes the LUM exposures for subjects in 4 age populations.

Table 3. Summary of LUM exposures

Age and Dose	Mean $AUC_{0\text{-}12hr}$ (µg·hr/mL)	Standard Deviation	Median $AUC_{0\text{-}12hr}$ (µg·hr/mL)	Range $AUC_{0\text{-}12hr}$ (µg·hr/mL)	N
2 through 5 years of age L100 q12h	180.27	45.51	174.94	[131.41, 339.03]	20
2 through 5 years of age L150 q12h	216.62	48.59	212.37	[144.79, 371.60]	42
6 through 11 years of age L200 q12h	224.30	59.05	215.13	[108.45, 452.40]	165
12 through 17 years of age L400 q12h	241.49	61.36	241.15	[129.92, 496.45]	98
18 years and older L400 q12h	216.53	47.92	209.09	[122.31, 418.41]	264

Source: Applicant's pop PK analysis report, Page 42, Table 7-4

4.2.2 Population PK Analysis for IVA

A 2-compartment linear mammillary model with first-order absorption and elimination was developed to describe the PK profile of IVA in CF subjects aged 2-11 years. F1 was fixed to 1 for the formulation evaluated in Studies 011 and 109 and the relative bioavailability was estimated for the granule formulation in Study 115. Body weight was found as a significant covariate on CL, Vc and peripheral compartment volume distribution (Vp). The power was finally fixed to 0.75, 1, and 1 for CL, Vc, and Vp, respectively. The effect of LUM exposure on IVA disposition was incorporated by making IVA's CL/F proportional to CYP3A, a term which quantifies the degree of CYP3A induction by LUM according to Equations below:

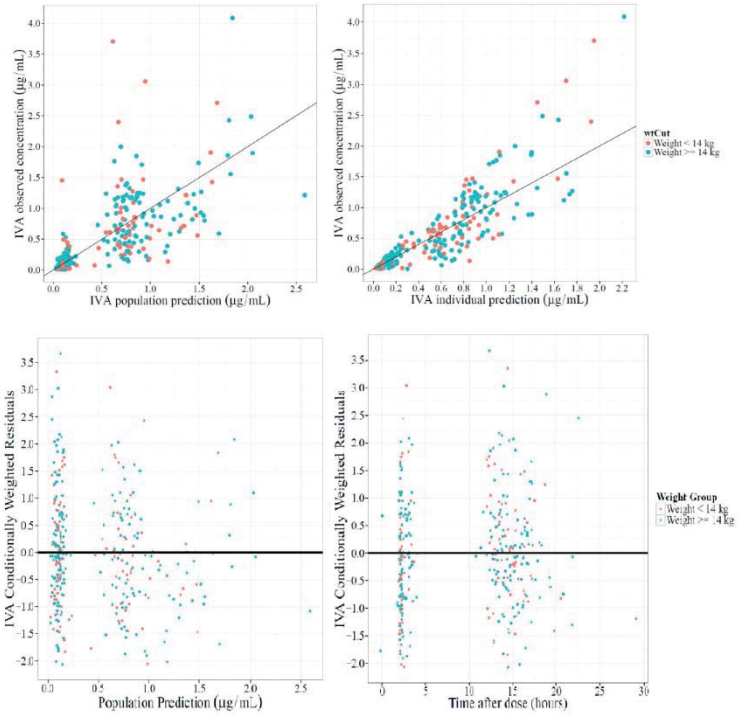
$$\frac{dCYP3A}{dt} = k_{dyn} \times (1 + k_{ind} \times LUM - CYP3A)$$

$$\frac{da_c}{dt} = a_{dep} \times KA + Q \times (C_p - C_c) - CL \times CYP3A \times C_c$$

where kdyn is the dynamic response rate of CYP3A production and degradation; kind is the degree of LUM induction of CYP3A (kind was fixed at 0.224 to aid in stability, which was the same value used for CF subjects 12 years of age and older); and LUM is the predicted LUM plasma concentration, ac is the IVA amount in the central compartment, adep is the IVA amount in the depot compartment, Cp is the IVA concentration in the peripheral compartment, Cc is the IVA concentration in the central compartment.

The diagnostic plots for the final model was plotted in subjects 2 through 5 years as shown in Figure 3.

Figure 3. Diagnostic plots for the final model of IVA in subjects 2 through 5 years



Source: Applicant's pop PK analysis report, Page 53-56, Figures 7-18 and 7-19

Table 4 listed the final parameter estimates for IVA model.

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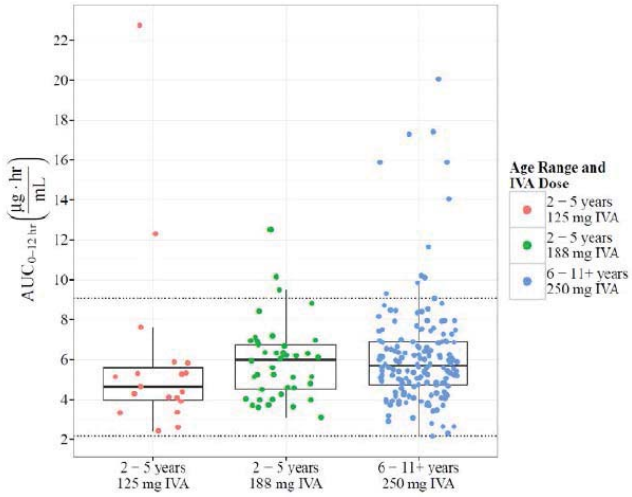
Table 4. Final parameter estimates for IVA model

Fixed Parameter Estimates					
Parameter	**Units**	**Estimate**	**%RSE**	**95% CI**	
CL/F	L/hr	17.36*	1.4	(16.05, 18.79)	
Vc/F	L	41.74*	12.4	(16.86, 103.31)	
Vp/F	L	30.99*	15.9	(10.64, 90.22)	
Q/F	L/hr	21.69	37.7	(2.24, 209.54)	
D1	hr	1.23	39.9	(1.05, 1.44)	
KA	1/hr	0.175	1.4	(0.166, 0.183)	
Kdyn	1/hr	0.066	2.6	(0.062, 0.069)	
Granule F1	-	0.79	6.6	(0.69, 0.9)	
Random Effect Parameter Estimates					
Parameter		**Estimate**	**%RSE**	**%CV**	**% Shrinkage**
ω^2 CL/F		0.183	9.1	42.75	8.9
ω^2 Vc/F		0.398	66.8	63.05	45.9
ω^2 KA		0.030	21.8	17.18	29.9
Cov($\omega_{CL/F}$, $\omega_{Vc/F}$)		-0.111	53.5	NA	NA
Cov($\omega_{CL/F}$, ω_{KA})		-0.024	58.5	NA	NA
Cov($\omega_{Vc/F}$, ω_{KA})		0.012	259.7	NA	NA
Residual Variance					
Parameter		**Estimate**	**%RSE**	**% Shrinkage**	
σ^2 (proportional)		0.19	5.1	10.2	

kdyn: dynamic response rate of CYP3A production and degradation
Source: Applicant's pop PK analysis report, Page 59, Tables 7-6

The predicted IVA AUC0–12h exposure for subjects in Studies 011, 109, and 115 are shown in Figure 4.

Figure 4. Predicted IVA $AUC_{0\text{-}12h}$ at steady-state for subjects 2 through 11 years of age



Dashed lines represent 90% confidence interval for $AUC_{0\text{-}12hr}$ of subjects greater than 12 years of age receiving I250 q12h. Each point represents the individual $AUC_{0\text{-}12hr}$ prediction for a subject.
Source: Applicant's pop PK analysis report, Page 60, Figure 7-21

Table 5 summarizes the IVA exposures for subjects in 4 age populations.

Table 5 Summary of IVA exposure

Age and Dose	Mean $AUC_{0\text{-}12hr}$ (µg·hr/mL)	Standard Deviation	Median $AUC_{0\text{-}12hr}$ (µg·hr/mL)	Range $AUC_{0\text{-}12hr}$ (µg·hr/mL)	N
2 through 5 years of age I125 q12h	5.92	4.61	4.64	[2.41, 22.75]	19
2 through 5 years of age I188 q12h	5.9	1.93	5.99	[3.09, 12.51]	42
6 through 11 years of age I250 q12h	6.17	2.68	5.69	[2.16, 20.04]	161
12 through 17 years of age I250 q12h	3.89	1.56	3.58	[1.78, 10.26]	98
18 years and older I250 q12h	3.8	1.94	3.41	[1.35, 17.31]	264

Source: Applicant's pop PK analysis report, Page 60, Table 7-7

4.2.3 Evaluate the Impact of Hepatic impairment in subjects 2 Through 5 Years

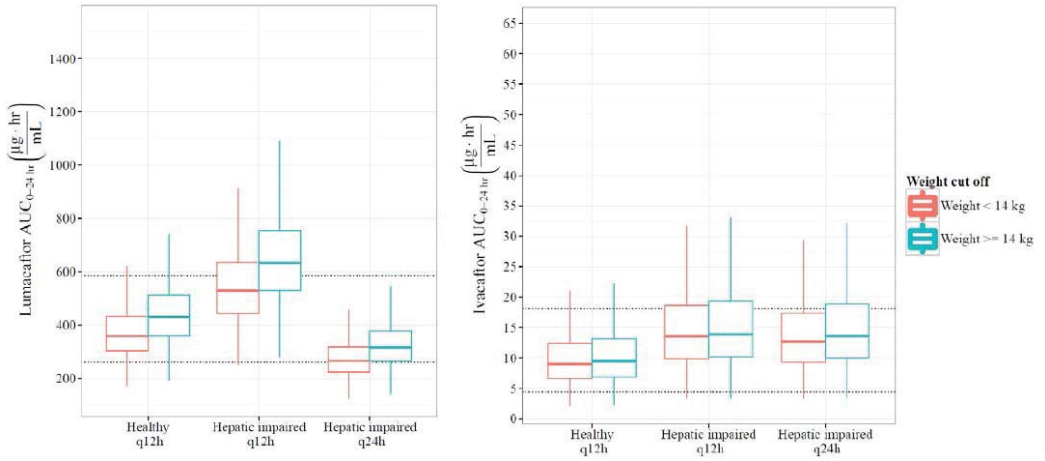
A dose adjustment is required for patients 6 years of age and older with moderate or severe hepatic impairment. This recommendation was based on the observed increase in exposure of LUM and IVA in a Phase 1, hepatic impairment study in adults. The final LUM and IVA PK models for subjects 2 through 5 years of age were used to predict the potential impact on exposure from moderate hepatic impairment. Phase 1 studies in subjects with moderate hepatic impairment (MI) showed LUM AUC in subjects with MI to be 1.47-fold higher than healthy adult subjects and IVA AUC in subjects with MI to be 1.96-fold higher than healthy adult subjects who received IVA monotherapy. Assuming the exposure differences are caused by the changes in CL and that the magnitude of the change is the same for the 2-through 5-year old population, the clearances for subjects with MI 2 through 5 years of age were adjusted as follows:

$$CL_{MI,LUM} = \frac{CL_{healthy,LUM}}{1.47}$$

$$CL_{MI,IVA} = \frac{CL_{healthy,IVA}}{1.96}$$

The result of simulation shows without any dose adjustment (i.e., same q12h dosing regimen), there is an increase in LUM and IVA exposure in the hepatic impairment population, which exceeds the prior clinical experience with LUM, particularly for subjects ≥14 kg (Figure 5).

Figure 5. Simulated LUM (left) and IVA (right) steady state daily $AUC_{0\text{-}24h}$ comparison between CF subjects 2 through 5 years of age with or without moderate hepatic impairment



Dash lines represent the AUC range in adults
Source: Applicant's pop PK analysis report, Page 62-63, Figures 7-22 and 7-23

Table 6 summarizes the predicted LUM and IVA steady state exposures after administration of an adjusted dose regimen (every 24 hours; q24h) in CF subjects 2 through 5 years of age with or without moderate hepatic impairment. For the adjusted dose regimen (q24h), the LUM steady state AUCs are relatively lower in CF subjects with hepatic impairment compared to CF subjects with normal hepatic function; however, the LUM AUCs were still in a reasonable range compared to adult AUCs.

Table 6. Summary of the predicted LUM and IVA steady state daily exposure in CF subjects 2 through 5 years of age with or without moderate hepatic impairment

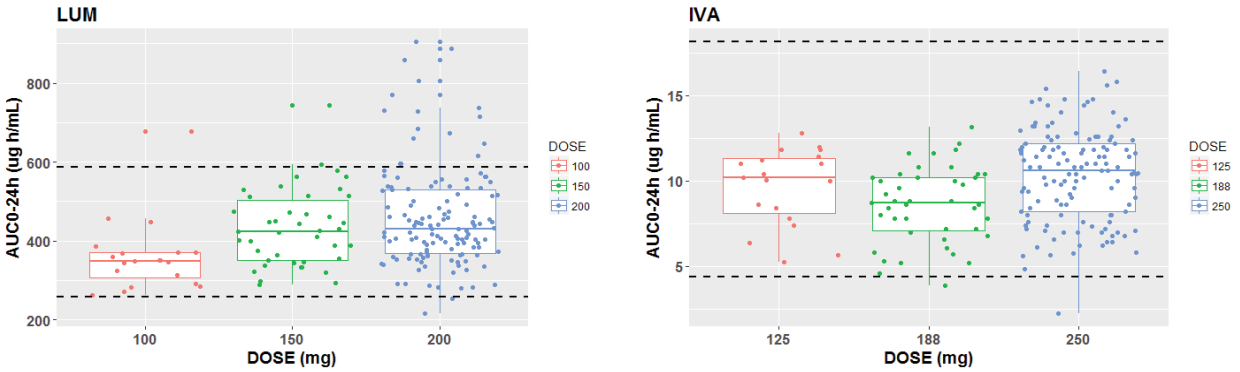
Age and Dose	Mean daily LUM $AUC_{0\text{-}24hr}$ (µg·hr/mL)	LUM $AUC_{0\text{-}24hr}$ Standard Deviation	Mean daily IVA $AUC_{0\text{-}24hr}$ (µg·hr/mL)	IVA $AUC_{0\text{-}24hr}$ Standard Deviation
CF Subjects 2 Through 5 Years of Age Without Hepatic Impairment				
L100/I125 q12h	361.9	100.9	8.96	4.6
L150/I188 q12h	430.6	117.8	9.42	5.0
CF Subjects 2 Through 5 Years of Age With Hepatic Impairment				
L100/I125 q24h	266.0	74.2	12.7	6.5
L150/I188 q24h	316.5	86.6	13.5	7.2

Source: Applicant's pop PK analysis report, Page 62, Table 7-8

The simulated IVA steady state AUCs were higher in CF subjects with moderate hepatic impairment compared to CF subjects with normal hepatic function. Reduction of the LUM dose results in lower systemic LUM exposure and less CYP3A induction, resulting in slower IVA clearance. Thus, the combination of the dose adjustment and the drug-drug interaction results in a negligible difference in exposures between a q12h and a q24h regimen for IVA. The proposed dosing regimen for IVA is expected to remain within prior clinical exposures observed for LUM/IVA and IVA. For IVA monotherapy, the mean steady state $AUC_{0\text{-}24h}$ values in subjects 2 through 5 years of age (21 µg·hr/mL) was higher than the simulated mean steady state AUCs for CF subjects 2 through 5 years of age with moderate hepatic impairment administered a reduced dose regimen of q24h.

Reviewer's comments: The population PK model appears to be acceptable from pharmacometrics perspective. An independent analysis was conducted by the Reviewer. The results show the exposure in patients aged 2 to 5 years were comparable with that in patients aged 6 to 11 years for both LUM and IVA (Figure 6). The exposure in patients aged 2 to 5 years were also well within the exposure range in patients aged 12 years and above. There findings suggest the studied dose is reasonable.

Figure 6. Comparison of AUC_{0-24h} at steady-state for patients aged 2 to 5 years and patients aged 6 to 12 years for LUM (left) and IVA (right)

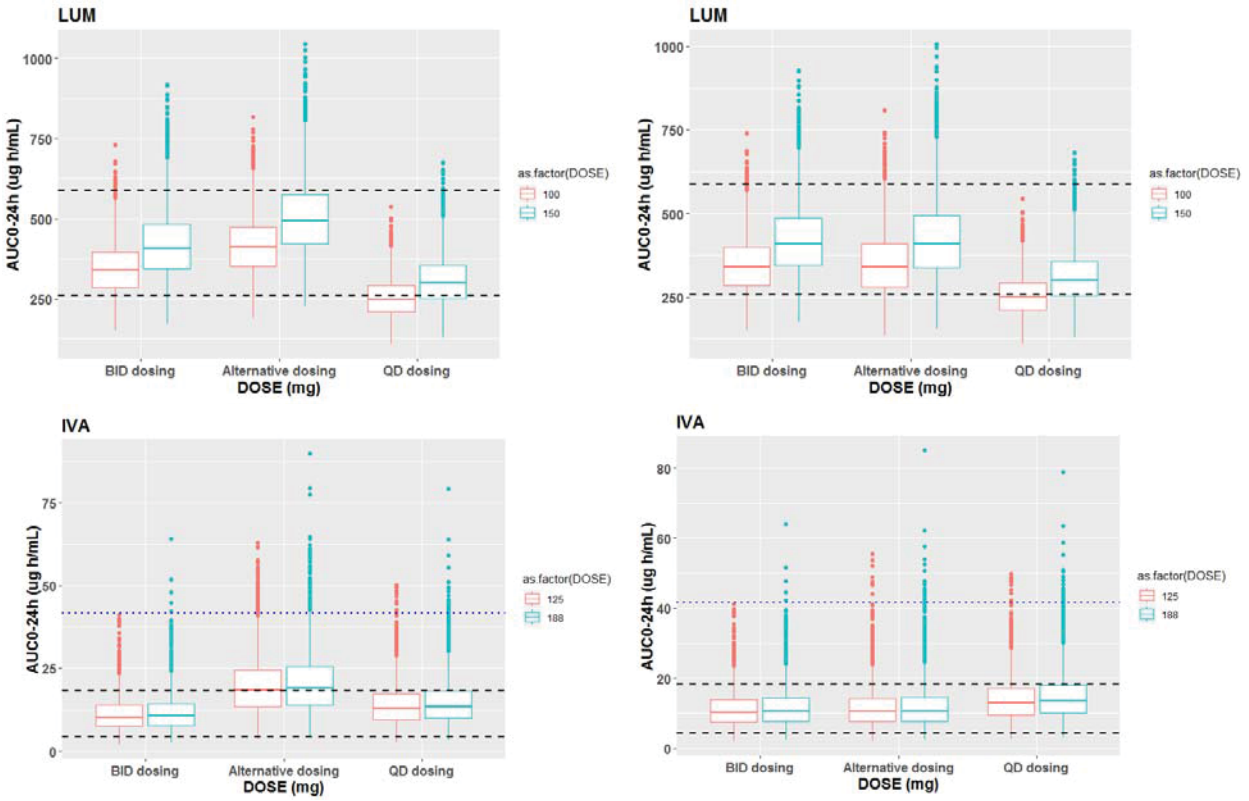


Black dashed lines on the left represent the 90% confidence interval for AUC0 - 24h of subjects aged 12 years and above receiving L400 q12h, L600 q24h, or I250 q12h
Source: Reviewer's independent analysis

Dosing regimen in pediatric patients aged 2 to 5 years with moderate hepatic impairment
The results show that BID dosing on day 1 and QD dosing on day 2 may result in comparable steady state LUM exposure in patients aged 2 to 5 years with moderate hepatic impairment compared to that in patients aged 2 to 5 years with normal hepatic function. While the steady state LUM exposure was lower with [redacted] (b) (4) *on both 1st dosing day and 2nd dosing day. Assuming a similar exposure-response relationship in patients aged 2 to 5 years and patients aged 6 years and above, the lower exposure may be associated to efficacy loss. On the other hand, BID dosing on day 1 and QD dosing on day 2 may result in higher exposure of IVA on the 1st dosing day in patients aged 2 to 5 years with moderate hepatic impairment compared to that in patients aged 2 to 5 years with normal renal function. But it is still lower than the maximum steady state AUC_{0-24h} in patients aged 2 to 5 years with normal hepatic function who received IVA monotherapy in the Phase 3 study. Safety may not be a concern for BID dosing on Day 1 and QD dosing on day 2. Therefore, BID dosing on day 1 and QD dosing on day 2 is more reasonable than QD dosing every day in this population from efficacy and safety perspectives. However, it is worth noting that few pediatric patients aged 2 to 5 years are expected to have impaired hepatic function*

Reference ID: 4303047

Figure 7 Steady State AUC_{0-24h} comparison in patients aged 2 to 5 years with normal hepatic function or moderate hepatic impairment on 1st dosing day (left) and 2nd dosing day (right)



BID dosing represents BID dosing in patients aged 2 to 5 years with normal hepatic function; Alternative dosing represents BID dosing on day 1 and QD dosing on day 2 in patients aged 2 to 5 years with moderate hepatic impairment; QD dosing represent the QD dosing in patients aged 2 to 5 years with moderate hepatic impairment; black dashed lines represent the 90% confidence interval for AUC0 - 24h of subjects aged 12 years and above receiving L400 q12h, L600 q24h, or I250 q12h; blue dashed lines represent the maximum steady state AUC_{0-24h} in patients aged 2 to 5 years with normal hepatic function who received IVA monotherapy in the Phase 3 study; blue boxes represent the patients with body weight ≥14 kg and red boxes represent the patients with body weight <14 kg
Source: Reviewer's independent analysis

The results show that BID dosing on day 1 and QD dosing on day 2 would result in comparable steady state LUM exposure in patients aged 2 to 5 years with moderate hepatic impairment compared to that in patients aged 2 to 5 years with normal hepatic function. While the steady state LUM exposure was low with proposed dosing by Applicant (QD dosing). On the other hand, the exposure of IVA is relatively higher for the first day with BID dosing, it is still lower than the maximum steady state AUC_{0-24h} in patients aged 2 to 5 years with normal hepatic function who received IVA monotherapy in the Phase 3 study. Therefore, BID dosing on day 1 and QD dosing on day 2 is more reasonable than BID dosing every day in this population.

However, it is worth noting that few pediatric patients aged 2 to 5 years are expected to have impaired hepatic function.

15.5. Additional Clinical Outcome Assessment Analyses

None

15.6. Study 115 Assessment Schedules

Table 20. Study 115. Part B Screening Assessments

Assessment	Screening Period (Day -28 through Day -1)
Informed consent/assent	X
Demographics	X
Medical and ophthalmological history	X
Stature, weight, and vital signs[a,b]	X
Pulse oximetry[b]	X
Ophthalmologic examination[c]	X
Full physical examination	X
Standard 12-lead ECG[d]	X
CFTR genotype[e]	X
Serum chemistry[f]	X
Hematology[f]	X
Coagulation studies[f]	X
Urinalysis[f]	X
Sweat chloride[g]	X
LCI (optional)[h]	X
Spirometry[i]	X
Medications review[j]	Continuous from signing of ICF through Safety Follow up Visit[k]
Adverse events	Continuous from signing of ICF through Safety Follow up Visit[k]

BMI: body mass index; ICF: informed consent form; LCI: lung clearance index; OE: ophthalmologic examination

[a] If children could stand unassisted and follow directions, stature was measured as height; otherwise, stature was measured as length. Stature and weight were measured with shoes off and while wearing light clothing. BMI was derived from this assessment. Refer to Section 9.5.6.3 for details.

[b] The subject rested for at least 5 minutes before having vital signs and pulse oximetry measured. Refer to Section 9.5.8.4 for details.

[c] An OE was conducted by a licensed ophthalmologist. The examination did not need to be repeated if there was documentation of an examination that met protocol criteria and that was conducted within 3 months before the Screening Visit. Subjects with documented bilateral lens removal did not need the OE. Refer to Section 9.5.8.6 for details.

[d] A standard 12-lead ECG was performed. The subject was instructed to rest in the supine position for at least 5 minutes, if possible, before having an ECG performed. The ECG was performed before any other procedures that could affect heart rate, such as blood draws. Refer to Section 9.5.8.5 for details.

[e] All subjects were tested to assess *CFTR* genotype, regardless of availability of a previous *CFTR* genotype laboratory report. Refer to Section 9.5.8.2 for details. However, this assessment did not need to be repeated for confirmed subjects in Part A who participated in Part B.

[f] Refer to Section 9.5.8.2 for details.

[g] If an eligible historical sweat chloride result was documented in the subject's medical record, that result alone (and not the Screening Visit result) could be used to determine eligibility. For subjects using an historical sweat chloride value documented in their medical record to determine eligibility, the sweat chloride test at the Screening Visit was still required. At screening, 2 samples could be collected, 1 sample from each arm (left and right).

[h] The LCI assessment (subjects ≥3 years of age at screening who consented/assented to the optional LCI Substudy) could be performed pre- or post-bronchodilator. The assessment was performed in multiple replicates and before the spirometry assessment. Refer to Section 9.5.6.2 for details.

[i] Spirometry (subjects ≥3 years of age at screening only) could be performed pre- or post-bronchodilator. Refer to Section 9.5.8.7 for details.

[j] Refer to Section 9.3.4.2 for details.

[k] If required.

Table 21. Study 115. Part B Treatment Period Assessment Schedule

Event/Assessment[a]	Treatment Period									ETT Visit[b]	Safety Follow-up Visit (Week 26 [2 weeks ± 4 days After Last Dose])[c,d]
	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)		
Clinic visit	X		X	X	X		X		X	X	X
Telephone contact[e]		X				X		X			
Stature and weight[f]	X		X	X	X		X		X	X	X
Vital signs[g,h]	X[i]		X	X	X		X		X	X	X
Pulse oximetry[g]	X		X	X	X		X		X	X	X
Ophthalmologic examination									X[i]	X[i]	X[i]

[a] All assessments were performed before LUM/IVA dosing unless noted otherwise (Appendix 16.1.1/Protocol Version 3.0/Section 11.1). When repeats of an assessment were required postdose at a given visit, the assessment was collected only once if LUM/IVA was not administered on the day of the visit (i.e., LUM/IVA interruption or permanent LUM/IVA discontinuation).

[b] Subjects who prematurely discontinued LUM/IVA treatment were asked to complete the ETT Visit, to remain on study, and to complete the study assessments from the time of LUM/IVA treatment discontinuation through the Week 24 Visit and Safety Follow-up Visit, if applicable. The ETT Visit was scheduled as soon as possible after the subject decided to terminate LUM/IVA treatment. If the ETT Visit occurred 10 days or later following the last dose of LUM/IVA, then the ETT Visit replaced the Safety Follow-up Visit (i.e., the assessments performed were those specified for the ETT Visit), and a Safety Follow-up Visit was not required. Subjects who became eligible to receive commercially-available LUM/IVA by prescription of a physician, and who chose to continue onto commercially-available LUM/IVA before completion of Part B, remained on study-supplied LUM/IVA through the ETT Visit, and could only initiate treatment with commercially-available LUM/IVA after completion of this visit.

[c] The Safety Follow-up Visit was not required for subjects who permanently discontinued LUM/IVA treatment before or at the Week 16 Visit if they returned for the Week 24 Visit. The Safety Follow-up Visit was not required for subjects who continued onto commercially-available LUM/IVA by prescription of a physician within 2 weeks (± 4 days) of completing LUM/IVA treatment at Week 24 or at the ETT Visit.

[d] The Safety Follow-up Visit, if applicable, was the last visit for Part B, and should also be the Day 1 Visit in the Extension Study (refer to Appendix 16.1.1/Protocol Version 3.0/Section 8.1.2 and the Extension Study for details).

[e] Telephone contacts were made to assess the subject's status, any AEs, concomitant medications, treatments, and procedures.

[f] If children could stand unassisted and follow directions, stature was measured as height; otherwise, stature was measured as length. Stature and weight were measured with shoes off and while wearing light clothing. BMI was derived from this assessment. Refer to Section 9.5.6.3 for details.

[g] The subject rested for at least 5 minutes before having vital signs and pulse oximetry measured. Refer to Section 9.5.8.4 for details.

[h] Vital signs were measured predose and at 1 hour (± 15 minutes), 2 hours (± 15 minutes), and 4 hours (± 15 minutes) postdose on Day 1.

[i] An OE was conducted by a licensed ophthalmologist at the Week 24 Visit OR the Safety Follow-up Visit OR the ETT Visit, as applicable. Subjects with documented bilateral lens removal did not need the OE. Refer to Section 9.5.8.6 for details.

Reference ID: 4303047

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/s/

BANU A KARIMI SHAH
08/07/2018