NDA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	NDA 211358/ S-004
Priority or Standard	Priority
Submit Date(s)	March 4, 2022
Received Date(s)	March 4, 2022
PDUFA Goal Date	September 4, 2022
Division/Office	Pulmonology, Allergy, and Critical Care (DPACC)/Immunology and Inflammation (OII)
Review Completion Date	August 23, 2022
Established/Proper Name	Lumacaftor/ivacaftor
(Proposed) Trade Name	Orkambi
Pharmacologic Class	Unclassified / cystic fibrosis transmembrane conductance regulator (CFTR) potentiator
Applicant	Vertex Pharmaceuticals Incorporated
Dosage form	Oral Granules
Applicant proposed Dosing Regimen	Every 12 hours: 7 to 9 kg: one packet (lumacaftor 75 mg/ivacaftor 94 mg) 9 to 14 kg: one packet (lumacaftor 100 mg/ivacaftor 125 mg) >14 kg: one packet (lumacaftor 150 mg/ivacaftor 188 mg)
Applicant Proposed Indication(s)/Population(s)	Age 1 to < 2 years age
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	190905008 |Cystic fibrosis (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Patients with cystic fibrosis (CF) in patients 1 year old to less than 2 years of age, homozygous for the *F508del*-CFTR mutation in the CFTR gene
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	
Recommended Dosing Regimen	• LUM75/IVA94 mg every 12 hours for patients 7 to <9kg, • LUM100/IVA125 mg every 12 hours for patients 9 to <14 kg, and • LUM150/IVA188 mg every 12 hours for patients ≥14kg

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Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

Signatures

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
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 Harmonisation
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 (also known as Patient Information)
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

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.

NDA 211358 was submitted for a new LUM/IVA formulation (granules). On August 7, 2018, the indication was expanded 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.

This NDA efficacy supplement is submitted to expand the indication to include the 1 to less than 2 year old age group at a dose of LUM75/IVA94 mg every 12 hours for patients 7 to <9 kg; LUM100/IVA125 mg every 12 hours for patients 9 to <14 kg; and LUM150/IVA188 mg every 12 hours for patients ≥14 kg.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for LUM/IVA granules at a dose of:

- LUM75/IVA94 mg every 12 hours for patients 7 to <9 kg;
- LUM100/IVA125 mg every 12 hours for patients 9 to <14 kg; and
- LUM150/IVA188 mg every 12 hours for patients ≥ 14 kg,

for the treatment of cystic fibrosis in patients 1 to less than 2 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. LUM/IVA granules (NDA 211358) are approved for the treatment of CF patients aged 2 to less than 6 years of age who are homozygous for the *F508del* mutation in the CFTR gene. In this NDA efficacy supplement, the Applicant has submitted data from a pharmacokinetic, pharmacodynamic, and safety study (Study 122) to support the use of LUM/IVA granules in patients 1 to less than 2 years of age who are homozygous for the *F508del* mutation in the CFTR gene.

Study 122 was a phase 3, two-part, open-label PK (part A, 15-day duration, n=14) and safety (part B, 24-week duration, n=46) study in patients 1 to less than 2 years of age. Results demonstrated that when LUM/IVA was administered to patients at the proposed weight-based doses 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 1 to less than 2 year old population, efficacy in the proposed age group can be extrapolated from the adolescent/adult population where efficacy has been demonstrated in randomized, placebo-controlled clinical trials. Additionally, Week 24 data from Part B demonstrated improvements in sweat chloride and markers of pancreatic function/inflammation and intestinal inflammation, including fecal elastase-1 (FE-1), serum immunoreactive trypsinogen (IRT), and fecal calprotectin, suggesting a pharmacodynamic response to the LUM/IVA granule treatment. Study 122 did not reveal any new safety signals.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lumacaftor/Ivacaftor (LUM/IVA) tablets and granules (trade name: Orkambi) are approved for the treatment of CF in patients ≥2 years of age who are homozygous for the *F508del* mutation in the CFTR gene. In this NDA efficacy supplement, the Applicant has submitted data from a pharmacokinetic/safety study (Study 122) to support the use of LUM/IVA granules in patients 1 to less than 2 years of age at a dose of:

- LUM75/IVA94 mg every 12 hours for patients 7 to <9 kg;
- LUM100/IVA125 mg every 12 hours for patients 9 to <14 kg; and
- LUM150/IVA188 mg every 12 hours for patients ≥14 kg.

The recommended regulatory action is approval of LUM/IVA granules for the treatment of cystic fibrosis patients aged 1 to less than 2 years of age who are homozygous for the *F508del* mutation in the CFTR gene.

CF results from mutations in 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 with cystic fibrosis carry at least one *F508del* allele, and approximately 50% of patients with cystic fibrosis are homozygous for the *F508del* mutation. Currently, in addition to treatments targeting the symptoms and sequelae of cystic fibrosis, Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) are the only FDA-approved drugs that target the underlying cause of CF in patients who are homozygous for the *F508del* mutation in the CFTR gene.

Study 122 was an open-label, uncontrolled, two-part pharmacokinetic (part A, 15-day duration, n=14) and safety (part B, 24-week duration, n=46) study in patients 1 to less than 2 years of age who are homozygous for the *F508del* mutation in the CFTR gene. PK results demonstrated that when LUM75/IVA94 mg was administered every 12 hours to patients 7 to <9 kg; and LUM100/IVA125 mg was administered every 12 hours to patients 9 to <14 kg; and LUM150/IVA188 mg was administered every 12 hours to patients ≥14 kg, 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 1 to less than 2 year old population, efficacy in the proposed age group can be extrapolated from the adolescent/adult population (≥12 years of age) where efficacy has been demonstrated in randomized, placebo-controlled clinical trials. In part B, the changes from baseline in sweat chloride, a pharmacodynamic endpoint, were seen in all LUM/IVA granule treatment groups, which is consistent with that observed in LUM/IVA tablet clinical trials.

With regard to safety, in part B of Study 122, no deaths were reported and 5 patients experienced SAEs. Of the five subjects who had an SAE, three patients had pulmonary exacerbations of CF, one subject had post-procedural fever, and one subject had distal intestinal obstruction syndrome (DIOS). The most common AEs were cough, pulmonary exacerbation of CF, fever, vomiting, upper respiratory tract infection, constipation, ear infection, positive *Pseudomonas* test, and rhinorrhea. Overall, the AEs were generally consistent with common manifestations of CF disease or common illnesses in patients 1 to less than 2 years of age. Five patients had liver transaminase elevations of >3x ULN. Of these patients, 1 had a value >8x ULN. None had elevations of total bilirubin >2x ULN. One patient had a respiratory event, specifically dyspnea, that led to treatment interruption. No patients developed cataracts. Overall, the safety profile in the 1 to less than 2 year old age group was consistent with the older age groups and no new safety signals were identified in Study 122.

In summary, efficacy in the proposed age group was extrapolated from the previous LUM/IVA tablet randomized, controlled trials in adolescents and adults ≥12 years of age. Decreases in sweat chloride from baseline were seen in all 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 122. The demonstration of an acceptable safety profile along with the extrapolated efficacy and the change of sweat chloride as a pharmacological response to the treatment supports the recommendation of Approval.

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, Kalydeco (ivacaftor) is the only CFTR modulators approved for CF patients <2 years of age. Kalydeco is approved for CF patients 4 months of age and older for certain genotypes, but not for CF patients homozygous for F508del mutations. Currently, there is no approved CFTR modulator therapy available for CF patients homozygous for *F508del* aged <2 years of age.	There is no approved CFTR modulator therapy available for CF patients homozygous for *F508del* aged <2 years of age. Therefore, treatment options for this age group are needed.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Based on results from Study 122, the Applicant has demonstrated that when lumacaftor/ivacaftor granules were administered to CF patients homozygous for the *F508del* mutation who were aged 1 to less than 2 years of age, systemic exposures were comparable to that observed in the population ≥12 years of age. Decreases in the pharmacodynamic endpoint of sweat chloride level were also observed in study patients.	Lumacaftor/ivacaftor granules provide a clinically relevant treatment benefit for *F508del* homozygous CF patients 1 to less than 2 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 that in 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.
Risk and Risk Management	• The adverse events observed in this study were consistent with common manifestations of CF disease or common illnesses in patients 1 to less than 2 years of age. Five out of a total of 46 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. One patient had a maximum on-treatment transaminase elevation of >8x ULN, but without bilirubin elevation; one patient had a respiratory event. 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 122. 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

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

☐	**The patient experience data that were submitted as part of the application include:**			Section of review 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):		
☐	**Patient experience data that were not submitted in the application, but were considered in this review:**			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
X	**Patient experience data was not submitted as part of this application.**			

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, and approximately 70,000 children and adults worldwide. CF affects all ethnic and racial groups, but it 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 mid-to-late 30s.

CF results from mutations in 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. 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. Ultimately, these deficiencies result in a relatively severe disease phenotype.

2.2. Analysis of Current Treatment Options

While Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) are approved for a limited number of CFTR mutation subpopulations, there are no other FDA-approved products available that are directed at the cause of cystic fibrosis (i.e. 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, as well as currently approved CFTR modulators, are summarized in Table 1. Note

that not all are FDA-approved for use in CF.

Table 1. Treatments for Cystic Fibrosis (CF)

Active Ingredient	Trade Name	FDA-Approved for CF indication?
CFTR Modulators		
Ivacaftor	Kalydeco	Yes; patients with CF aged 4 months and older who have one of 97 specified mutations (not including *F508del*)
Lumacaftor/ivacaftor	Orkambi	Yes; patients with CF aged 2 years and older who are homozygous for *F508del* mutation
Tezacaftor/ivacaftor	Symdeko	Yes; patients with CF aged 6 years and older who have one of 154 specified mutations (including *F508del*)
Elexacaftor/tezacaftor/ivacaftor	Trikafta	Yes; patients with CF aged 6 years and older who have at least one copy of *F508del* mutation or at least one copy of 177 specified mutations
Inhaled Antibiotics for the Treatment of Pseudomonas aeruginosa		
Tobramycin (inhaled)	Bethkis	Yes
Tobramycin (inhaled)	Kitabis Pak	Yes
Tobramycin (inhaled)	TOBI	Yes
Aztreonam (inhaled)	Cayston	Yes
Polymyxin E (IV form given via nebulizer)	Colistin	No
Mucolytics		
Dornase alpha	Pulmozyme	Yes
Hypertonic saline (3%, 7%)	N/A	No
Oral Pancreatic Enzyme Supplementation		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase	Yes
Inhaled Bronchodilators		
Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol	Approved as bronchodilator
Levalbuterol hydrochloride	Xopenex	Approved as bronchodilator
Oral Anti-Inflammatory Agents		
Azithromycin	Zithromax	No
Ibuprofen (high-dose)	Motrin, Advil	No

Abbreviations: cystic f brosis transmembrane conductance regulator

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Sponsor proposes to expand the indication for LUM/IVA granules to include the 1 to less than 2 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 CF patients aged 6 to less than 12 years of age. On August 7, 2018, LUM/IVA granules were approved for CF patients aged 2 to 5 years of age. In the LUM/IVA 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

LUM/IVA tablets were granted Fast Track Designation on January 17, 2008 (IND 79521), Breakthrough Therapy Designation on December 7, 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. This approval was based on the demonstration of efficacy in replicate phase 3 safety/efficacy trials. On August 31, 2016, the indication was expanded to include CF patients 6 to less than 12 years of age. This approval was based on results from a pharmacokinetic/safety trial and extrapolation of efficacy. On August 8, 2018, LUM/IVA granules were approved for CF patients 2 to 5 years of age. 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)

An inspection of the bioanalytical site was requested for Study 122, and the Office of Study Integrity and Surveillance recommended accepting the Applicant's data without a site inspection as the site was recently inspected and the inspectional outcome was adequate.

4.2. Product Quality

CMC

Vertex Pharmaceuticals Incorporated (Vertex) has submitted an efficacy supplement to NDA 211358 for Orkambi® (lumacaftor / ivacaftor combination therapy) to support a label expansion

for the treatment of cystic fibrosis (CF) in patients 1 to <2 years of age who are homozygous for the F508del mutation in the CFTR gene.

The proposed strength for LUM/IVA granules is LUM 75-mg/IVA 94-mg oral granules for patients weighing 7kg to <9kg; LUM 100-mg/IVA 125-mg oral granules for patients weighing 9 kg to <14kg and LUM 150-mg/IVA 188-mg oral granules for patients weighing ≥14 kg.

The 75mg lumacaftor / 94mg ivacaftor FDC granules drug product consists of granules in a sachet for oral administration. The granules are a FDC product of the active ingredients lumacaftor and ivacaftor in a single oral dosage form. (b) (4)

The Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA) are the same for the three strengths of the lumacaftor/ivacaftor FDC granules drug product.

All three strengths of the lumacaftor/ivacaftor FDC drug product (b) (4) have the same packaging configuration. Therefore all stability conclusions from the 100/125mg and 150/188mg granule strengths are applicable to the 75/94mg granules.

The proposed shelf life of 48 months at USP controlled room temperature is supported by available 75/94 mg, 100/125 mg, and 150/188 mg FDC granules stability data described in the stability summary.

Overall Manufacturing Inspection Recommendation: Approval

Biopharmaceutics

The Biopharmaceutics review is focused on the evaluation and acceptability of the dissolution method and acceptance criteria for the new strength of Lumacaftor/Ivacaftor granules (75mg/94mg).

The proposed dissolution method and acceptance criteria for the new strength are same as approved for the higher strengths, 100mg/125mg and 150mg/188mg. Complete multipoint dissolution data for batches used in the clinical studies and stability were provided in response to an information request. Dissolution data demonstrate that all batches are rapidly dissolving and met the proposed dissolution acceptance criteria for each 2 component of the Orkambi granules (Q= (b) (4)% in 20 minutes for Lumacaftor, and Q= (b) (4)% in 15 minutes for Ivacaftor). The dissolution method and acceptance criteria presented in this submission for Lumacaftor/Ivacaftor granules (75mg/94mg) are acceptable.

Biopharmaceutics recommendation: Approval

4.3. Clinical Microbiology

No new data was submitted or required because the microbiology data was previously reviewed.

4.4. Devices and Companion Diagnostic Issues

Not applicable

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Refer to NDA 206038 for an extensive discussion of pharmacology and toxicology of the lumacaftor/ivacaftor combination product. The discussion below is limited to the expansion for the treatment of cystic fibrosis (CF) in patients 1 to <2 years of age who are homozygous for the F508del mutation in the CFTR gene.

The lumacaftor/ivacaftor drug product intended for the 1 to <2 year old population under the current NDA consists of granules in a sachet for oral administration. As shown in Table 2, the levels of each excipient in this fixed-dose combination (FDC) are below the levels found in FDA-approved products, 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

Table 1 Composition of Lumacaftor/Ivacaftor FDC Granules

Component	Quality Standard	Component Function	Amount per Sachet (mg)			Content (% w/w)
			75/94 mg	100/125 mg	150/188 mg	
Lumacaftor drug substance	Internal standard	Active Ingredient	75.0	100.0	150.0	30.2
Ivacaftor (b) (4) (b) (4)	Internal standard	(b) (4)				(b) (4)
Croscarmellose sodium	USP/NF, Ph. Eur.					
Microcrystalline cellulose	USP/NF, Ph. Eur.					
Povidone (b) (4)	USP/NF, Ph. Eur.					
Sodium lauryl sulfate	USP/NF, Ph. Eur.					
						(b) (4)
Total	---	---	248.7	331.1	497.4	100.0
(b) (4)						
(b) (4)						

Excerpted from Sponsor's submission, SD#377-M2-23-qos-dp-description-and-composition, pg 1 and 2

No new nonclinical study reports were submitted in this NDA submission. The juvenile animal studies (JAS) required for the approval of the proposed patients population (less than 2 y.o.) was submitted to NDA 211358 and reviewed by Dr. Andrew Goodwin dated September 14, 2016. The findings were briefly summarized by Dr. Dong Zhao, dated August 07, 2018, under NDA 211358 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 observed on PND 10. The pup was observed with a thin, pale, yellow body and 25% weight loss. The clinical signs observed 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 observed 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 1-2 years old receiving Orkambi.

Table 3. Lumacaftor-Ivacaftor Exposure Comparison

			Exposure Margins for Patients Aged 1 to <2 Years, By Weight		
Juvenile Rat Toxicity Study	**Dose (mg/kg)**	**$AUC_{0\text{-}24h}$ µg.hr/ml**	**BW 7 to <9 kg, L75/l94^ $AUC_{0\text{-}24}$: 468(L)/16.0(l)***	**BW 9 to <14 kg, L100/l125^ $AUC_{0\text{-}24}$: 382(L)/10.7(l)***	**BW ≥14 kg, L150/l188^ $AUC_{0\text{-}24}$: 232(L)/11.6(l)***
Lumacaftor, oral	125	964	2.1	2.5	4.2
	250 (NOAEL)	1300	2.8	3.4	5.6
	500	1700	3.6	4.5	7.3
Ivacaftor, oral	10	26	1.6	2.4	2.2
	50	156	9.8	14.6	13.4

^ L75/l94: 75 mg lumacaftor, 94 mg ivacaftor; L100/l125: 100 mg lumacaftor, 125 ivacaftor; L150/l188: 150 mg lumacaftor, 188 mg ivacaftor
* PK data (mean $AUC_{0\text{-}24}$ = 2 x $AUC_{0\text{-}12}$, µg·hr/mL) from Study 122. Sources: Report R231/Tables 6-11 and 6-12, and Report N329/Tables 7-4 and 7-7.
Abbreviations: AUC, area under the curve; BW, body weight

There are no outstanding pharmacology-toxicology issues.

6. Clinical Pharmacology

6.1. Executive Summary

In this supplement, the Applicant submitted an open label safety and PK trial (Study 122) in children 1 to <2 years old. Study 122 is a 24-week, phase 3, 2-part, open-label study to evaluate the safety and PK of lumacaftor/Ivacaftor in children 1 to <2 years of age with cystic fibrosis, homozygous for *F508del*. The Applicant investigated a bodyweight-tiered dosing regimen (the same as the proposed dosing regimen) in children aged 1 to <2 years old in Study 122. The studied dosing regimen demonstrated a matched steady state AUC ($AUC_{0\text{-}12,ss}$) with the observed $AUC_{0\text{-}12,ss}$ in adults. The matched systemic exposure levels established a scientific bridge that supports the approval of the proposed dosing regimen in children 1 to <2 years old.

An inspection of the bioanalytical site was requested for Study 122, and the Office of Study Integrity and Surveillance recommended accepting the Applicant's data without a site inspection as the site was recently inspected and the inspectional outcome was adequate.

The Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology (DIIP) and Division of Pharmacometrics (DPM) have reviewed the PK and PD results included in this sNDA submission and recommend for approval.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

In Study 122, following oral administration of Orkambi granules (lumacaftor 100 mg/ivacaftor 125 mg) every 12 hours in children 1 to <2 years old with body weight 9 to <14 kg, the estimated mean (SD) AUCss of lumacaftor and ivacaftor are 191 (40.6) µg/mL*h and 5.35 (1.61) µg/mL*h, respectively. Following oral administration of Orkambi granules (lumacaftor 150 mg/ivacaftor 188 mg) every 12 hours in children 1 to <2 years old with body weight ≥14 kg, the estimated AUCss of lumacaftor and ivacaftor are 116 µg/mL*h and 5.82 µg/mL*h, respectively. Following oral administration of Orkambi granules (lumacaftor 75 mg/ivacaftor 94 mg) every 12 hours in children 1 to <2 years old with body weight 7 to <9 kg, the estimated AUCss of lumacaftor and ivacaftor are 234 µg/mL*h and 7.98 µg/mL*h, respectively. These mean values match with the mean AUCss of lumacaftor [198 (64.8) µg/mL*h] and ivacaftor [3.66 (2.25) µg/mL*h] in subjects 12 years and older administered ORKAMBI tablets following lumacaftor 400 mg/ivacaftor 1250 mg every 12 hours treatment.

Changes in sweat chloride in response to lumacaftor/ivacaftor were also evaluated in Study 122. Treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at Week

4 which was sustained through Week 24. The mean absolute change from baseline in sweat chloride at Week 24 was -29.1 mmol/L (95% CI: -34.8, -23.4). In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The mean absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 27.3 mmol/L (95% CI:22.3, 32.3).

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed dose of lumacaftor/ivacaftor for patients 1 to <2 years of age is:

Pediatric patients aged 1 through 2 years and weighing 7 kg to < 9 kg: one packet of granules (each containing lumacaftor 75 mg/ivacaftor 94 mg) mixed with 1 teaspoon (5 mL) of soft food or liquid and administered orally every 12 hours with fat containing food.

Pediatric patients aged 1 through 2 years and weighing 9 kg to < 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 aged 1 through 2 years and weighing 14 kg and 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 1 to <2 years of age are predicted to have generally comparable exposure ($AUC_{0\text{-}12,ss}$) of lumacaftor and ivacaftor as patients 12 years and older following the proposed dosing regimens. See Section 6.3.2 for details.

Therapeutic Individualization

Based on the hepatic impairment PK study in adults, children aged 1 to <2 years old with moderate to severe hepatic impairment require dose adjustment. A modeling/simulation approach based on adults and pediatric PK results was used to inform the dose adjustment in children aged 1 to <2 years old with moderate to severe hepatic impairment. The proposed dose adjustment strategy is listed in Table 4. The proposed dose adjustment is consistent with the previously approved dose adjustment in children 2 to <6 years old with moderate to severe hepatic impairment.

Table 4. Recommended Dosage for Patients With Hepatic Impairment

Hepatic Impairment	Age Group	Weight	Morning	Evening
Mild	1 through 2 years	7 kg to <9 kg 9 kg to <14 kg ≥14 kg	No dose adjustment	No dose adjustment
Moderate	1 through 2 years	7 kg to <9 kg 9 kg to <14 kg ≥14 kg	1 packet of oral granules	1 packet of oral granules every other day
Severe	1 through 2 years	7 kg to <9 kg 9 kg to <14 kg ≥14 kg	1 packet of oral granules*	No dose

* or less frequently.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

General pharmacology and PK of lumacaftor/ivacaftor have 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?

There were two parts (Part A and Part B) of Study 122. Part A consisted of 15-day treatment period with 10-day follow up period. Children were sequentially enrolled in Part A as following:

- Cohort 1: subjects aged 18 to <24 months
- Cohort 2: subjects aged 12 to <18 months

PK samples from Part A were collected at following time points: 3-4 hour post-dose following the first dose (on Day 1); 2 and 3-4 hour post-dose following the morning dose on Day 15; and pre-dose samples on Day 8 and Day 15. Children enrolled in Part A did not roll over to Part B. The PK and safety results of Part A resulted in some modifications of body weight cutoffs in Part B (Table 5).

Part B consisted of 24-week treatment period followed by 2-week washout period and an extension period. PK samples from Part B were collected at following time points: pre-dose and one 2-6 post-dose on Days 15 and at Week 4; and pre-dose at Week 12 and 24.

Table 5. Investigated Dose by Body Weight Group in Study 122

Study Part/Cohort (Age Group)	Weight Range at Screening	Dosing Regimen
Part A Cohort 1 (18 to <24 months)	10 to <14 kg	L100/I125 q12h
	≥14 kg	L150/I188 q12h
Part A Cohort 2 (12 to <18 months)	7 to <10 kg	L75/I94 q12h
	10 to <14 kg	L100/I125 q12h
	≥14 kg	L150/I188 q12h
Part B (12 to <24 months)	7 to <9 kg[a]	L75/I94 q12h
	9[a] to <14 kg	L100/I125 q12h
	≥14 kg	L150/I188 q12h

[a] During Part B, a review of safety and PK data in Part A (Cohorts 1 and 2) and a subset of subjects in Part B was completed and incorporated into the PopPK models. The updated PopPK models supported a decrease in the upper weight bound for the L75/I94 dose and the lower weight bound for the L100/I125 dose from 10 kg to 9 kg.
Abbreviations: PK, pharmacokinetics; PopPK, population PK; q12h: every 12 hours

A total of 14 children were enrolled and received at least one dose of Orkambi in Part A. There was an equal number of subjects (7) in each cohort. Thirteen (92.9%) subjects completed study drug treatment and completed the study; 1 (14.3%) of the 7 subjects in Cohort 1 discontinued both LUM/IVA treatment and the study due to AE. Some key baseline demographic information is summarized in Table 6.

Table 6. Key Baseline Demographic Information in Part A of Study 122

Characteristic	Cohort 1 N = 7	Cohort 2 N = 7	Total N = 14
Sex, n (%)			
Male	4 (57.1)	3 (42.9)	7 (50.0)
Female	3 (42.9)	4 (57.1)	7 (50.0)
Age at baseline (months)			
n	7	7	14
Mean (SD)	20.3 (2.0)	14.1 (1.7)	17.2 (3.6)
Median	20.0	14.0	17.0
Min, max	18, 23	12, 16	12, 23
Weight (kg)			
n	7	7	14
Mean (SD)	11.5 (0.8)	9.1 (0.5)	10.3 (1.4)
Median	11.7	9.2	10.0
Min, max	10.2, 12.4	8.1, 9.7	8.1, 12.4

Source: Table 10-2 and 10-3 on pages 40 and 41 of CSR 122.

A total of 46 children were enrolled and received at least one dose of Orkambi in Part B. 45 (97.8%) subjects completed study drug treatment; one subject discontinued due to an AE (increased ALT and AST). 43 (93.5%) subjects completed the study; the reasons for discontinuing the study for the three subjects were AE, withdrawal of consent (not due to AE), and other reason. A total of 40 (87%) subjects rolled over into the extension study (Study 124). Some key baseline demographic information is summarized in Table 7.

Table 7. Key Baseline Demographic Information in Part B of Study 122

Characteristic	Total N = 46
Sex, n (%)	
Male	22 (47.8)
Female	24 (52.2)
Age at baseline (months)	
n	46
Mean (SD)	18.1 (3.5)
Median	18.5
Min, max	12, 23
Age group at baseline	
12 to <18 months	21 (45.7)
18 to <24 months	25 (54.3)
Dosing group at enrollment	
LUM 75 mg/IVA 94 mg q12h	1 (2.2)
LUM 100 mg/IVA 125 mg q12h	44 (95.7)
LUM 150 mg/IVA 188 mg q12h	1 (2.2)
Weight (kg)	
n	46
Mean (SD)	11.3 (1.3)
Median	11.4
Min, max	8.6, 15.2

Source: Table 10-6 and 10-7 on pages 43, 44, and 45 of CSR 122.

The estimated systemic exposure of lumacaftor and ivacaftor in children 1 to 2 years old in Part B are listed in Table 8 and Table 9, respectively.

Table 8. Summary of Lumacaftor PK Exposures by Dose Group

Parameter / Units			Dose Group A. 12-<24mo (L75/I94)	Dose Group B. 12-<24mo (L100/I125)	Dose Group C. 12-<24mo (L150/I188)
N	Subjects		1	44	1
LUM AUC_{0-12h}	µg·h/mL	Min	234.	104.	116.
		Median	234.	185.	116.
		Max	234.	306.	116.
		Mean	234.	191.	116.
		SD		40.6	
LUM C_{max}	µg/mL	Min	23.7	13.2	15.6
		Median	23.7	20.4	15.6
		Max	23.7	31.6	15.6
		Mean	23.7	20.8	15.6
		SD		3.68	
LUM C_{min}	µg/mL	Min	14.7	4.26	4.21
		Median	14.7	10.2	4.21
		Max	14.7	18.5	4.21
		Mean	14.7	10.5	4.21
		SD		2.98	

Notes: Exposure metrics were derived from individual EBEs from the final population PK model (250)
Abbreviations: I, ivacaftor; L, lumacaftor; max, maximum range of exposures; min, minimum range of exposures; N, number of subjects in the summary; SD, standard deviation

Table 9. Summary of Ivacaftor PK Exposures by Dose Group

Parameter / Units			Dose Group A. 12-<24mo (L75/I94)	Dose Group B. 12-<24mo (L100/I125)	Dose Group C. 12-<24mo (L150/I188)
N	Subjects		1	44	1
IVA AUC_{0-12h}	µg·h/mL	Min	7.98	3.18	5.82
		Median	7.98	5.08	5.82
		Max	7.98	11.3	5.82
		Mean	7.98	5.35	5.82
		SD		1.61	
IVA C_{max}	µg/mL	Min	1.06	0.557	0.964
		Median	1.06	0.817	0.964
		Max	1.06	1.52	0.964
		Mean	1.06	0.854	0.964
		SD		0.194	
IVA C_{min}	µg/mL	Min	0.284	0.0780	0.156
		Median	0.284	0.139	0.156
		Max	0.284	0.406	0.156
		Mean	0.284	0.150	0.156
		SD		0.0630	

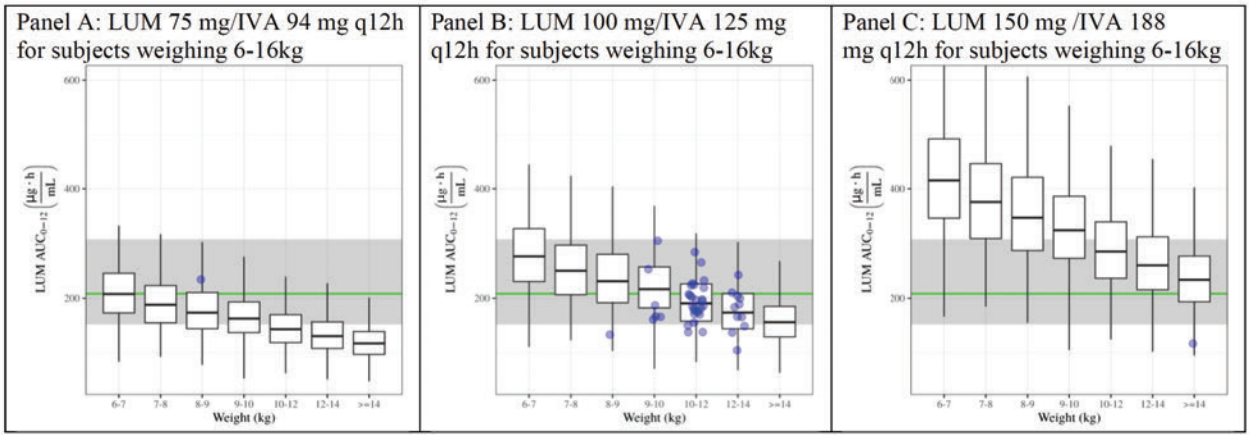
Notes: Exposure metrics were derived from individual EBEs from the final population PK model (1770)
Abbreviations: I, ivacafor; L, lumacaftor; max, maximum range of exposures; min, minimum range of exposures; N, number of subjects in the summary; SD, standard deviation

See pharmacometrics review for the assessment of population pharmacokinetic models in Section 15.3.1.

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

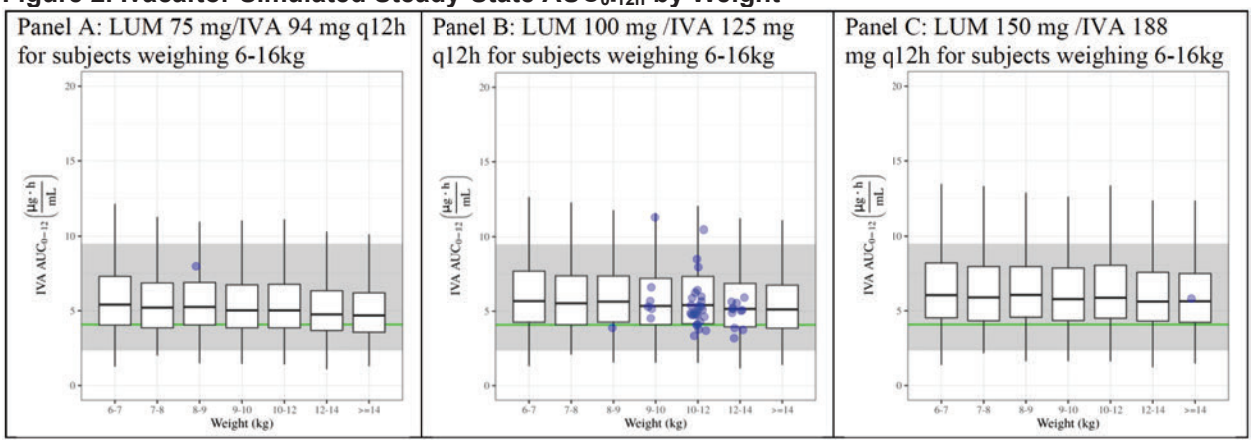
Yes. Based on the estimated $AUC_{0\text{-}12,ss}$ in children 1 to 2 years old, the proposed dosing regimen resulted in a similar exposure level to the observed $AUC_{0\text{-}12,ss}$ in adult subjects with CF following the approved dosing regimen (lumacaftor 400 mg/ivacaftor 250 mg q12h). See clinical pharmacology review by Dr. Jianmeng Chen in the original NDA submission in DARRTS dated 05/08/2015 for details of PK characteristics in adults. A comparison between observed, simulated $AUC_{0\text{-}12,ss}$ in children 1 to <2 years old with the observed range of $AUC_{0\text{-}12,ss}$ in adults are depicted in Figure 1 and Figure 2 for lumacaftor and ivacaftor, respectively.

Figure 1. Lumacaftor Simulated Steady-State $AUC_{0\text{-}12h}$ by Weight



Source: Figure 10-5 LUM Simulated Steady State $AUC_{0\text{-}12}$ by Weight in Study Report R231
Notes: Individual data points representing predicted $AUC_{0\text{-}12h}$ are shown for Study 122 Part B subjects 12 to < 24 months of age (blue circles). Dose of LUM/IVA given every 12 hours is provided in the title of each panel. Boxplots present exposures from simulated subjects based on the WHO growth charts. The median is represented by a horizontal line, and the interquartile range (IQR) is represented by a box. The whiskers represent the largest and smallest values within 1.5×IQR. Gray area in the left panel represents the 5th to 95th percentiles of LUM $AUC_{0\text{-}12h}$ exposures (151.5 ug.h/mL, 308.6 ug.h/mL) in the adult population receiving LUM 400 mg q12h. Green lines represent the median $AUC_{0\text{-}12h}$ exposures (208.4 ug.h/mL) in the same adult population.
Abbreviations: IQR, interquartile range; IVA, ivacaftor; LUM, lumacaftor

Figure 2. Ivacaftor Simulated Steady-State $AUC_{0\text{-}12h}$ by Weight



Source: Figure 10-6 IVA Simulated Steady State $AUC_{0\text{-}12}$ by Weight in Study Report R231
Notes: Individual data points representing predicted $AUC_{0\text{-}12h}$ are shown for Study 122 Part B subjects 12 to < 24 months of age (blue circles). Dose of LUM/IVA given every 12 hours is provided in the title of each panel. Boxplots present exposures from simulated subjects based on the WHO growth charts. The median is represented by a horizontal line, and the interquartile range (IQR) is represented by a box. The whiskers represent the largest and smallest values within 1.5×IQR. Gray area represents the 5th to 95th percentiles of IVA $AUC_{0\text{-}12h}$ exposures (2.3 ug.h/mL, 9.5 ug.h/mL) in the adult population receiving IVA 250 mg q12h. Green lines represent the median $AUC_{0\text{-}12h}$ exposures (4.1 ug.h/mL) in the same adult population
Abbreviations: IQR, interquartile range; IVA, ivacaftor; LUM, lumacaftor

The matched exposure levels between children 1 to <2 years old and adults supported the PK bridging between adults and children 1 to 2 years old.

The reviewer noticed that the proposed lower body weight cutoff of the children 1 to 2 years old with the lowest body weight group is 7 kg. However, the lowest body weight recorded at screening visit in Study 122 was 8.1 kg. In a response to Information Request dated June 17, 2022, the Applicant justified that growth of infants and young children with cystic fibrosis is often below what is expected for the US population. Per Patient Registry for patients with CF, homozygous for the F508del-CFTR mutation (Table 10), the lower weight cutoff of 7 kg was selected because patients weighing <7 kg are below the 5th percentile weight-for-age for this age group (12 to <24 months). The reviewer considers the Applicant's justification acceptable.

Table 10. Weights for CF Patients, Homozygous for *F508del*, 12 to <24 Months of Age and Born in 2016 or 2017 in the US

Age	N	Mean (SD) (kg)	Median (Min, Max) (kg)
12 to <15 months	72	9.4 (1.0)	9.4 (5.9, 11.7)
15 to <18 months	78	10.4 (1.2)	10.4 (7.7, 13.1)
18 to <21 months	77	11.2 (1.3)	11.0 (8.4, 14.3)
21 to <24 months	40	11.7 (1.5)	11.6 (9.0, 15.8)

Source: US CFF Patient Registry Data, 2017 from page 1 of clin-info-amend.pdf submitted on June 17, 2022.
Abbreviations: CF, cystic f brosis; CFF, Cystic Fibrosis Foundation; F508del, CFTR gene mutation with an in-frame deletion of a phenylalanine codon corresponding to position 508 of the wild-type protein; max, maximum; min, minimum; N, total sample size; SD, standard deviation; US, United States

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

Yes. As demonstrated in the original NDA submission, hepatic impairment has effects on lumacaftor and ivacaftor systemic exposure. See original NDA review by Dr. Jianmeng Chen in DARRTS dated 05/28/2015. In the current supplement, the Applicant proposed a similar dose adjustment strategy in children 1 to <2 years old with hepatic impairment to the approved dose adjustment strategy in children 2 to <6 years old.

A simulation study was conducted in children 1 to 2 years old with moderate hepatic impairment. Per the hepatic impairment study in adult, moderate hepatic impairment increases lumacaftor AUC by 1.47-fold and ivacaftor AUC by 1.96-fold. The PopPK simulation assumed the same 1.47-fold effect on lumacaftor and 1.96-fold effect on ivacaftor in in children 1 to <2 years old. The Applicant simulated four different dosing regimens to determine the appropriate dose adjustment, including A) without hepatic impairment following the proposed dosing regimen; B) with moderate hepatic impairment receiving no dose adjustment; C) with moderate hepatic impairment receiving a 50% dose reduction; D) with moderate hepatic impairment receiving a 25% dose reduction (morning dose daily and evening dose every other day). See Table 11 for details.

Table 11. Lumacaftor/Ivacaftor Dosing Scenarios for Cystic Fibrosis Patients 12 to <24 Months of Age With or Without Moderate Hepatic Impairments

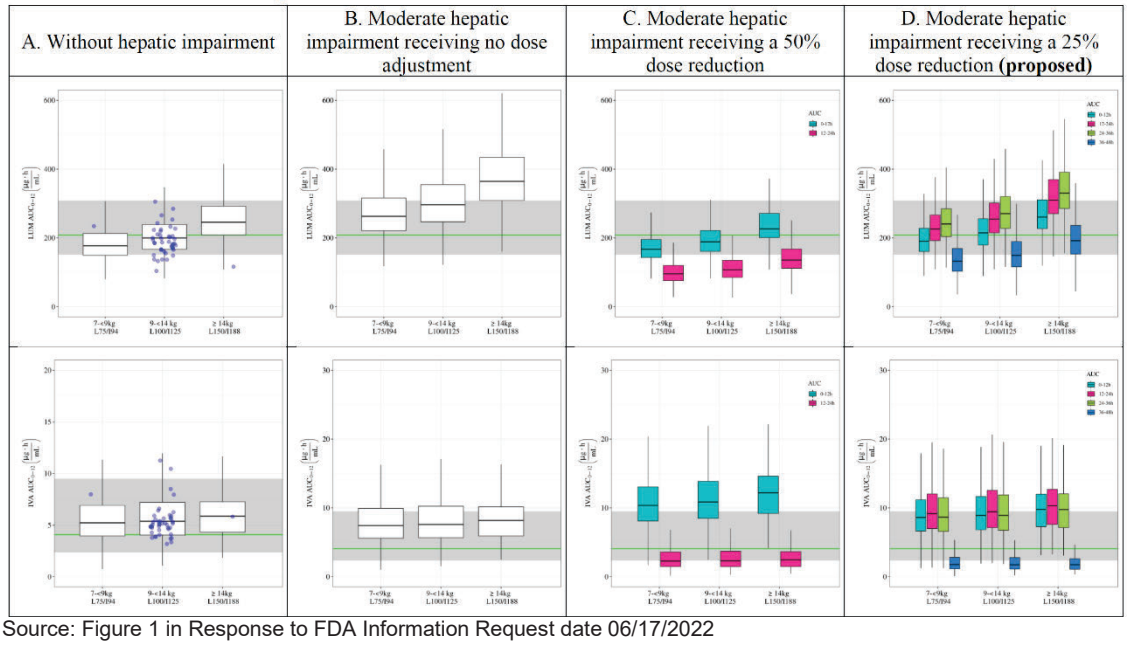
Weight group	A. Without hepatic impairment	B. MHI receiving no dose adjustment	C. MHI receiving a 50% dose reduction	D. MHI receiving a 25% dose reduction (proposed)
7 to <9 kg	LUM 75 mg/IVA 94 mg q12h	LUM 75 mg/IVA 94 mg q12h	LUM 75 mg/IVA 94 mg qd	LUM 75 mg/IVA 94 mg every morning and every other evening
9 to <14 kg	LUM 100 mg /IVA 125 mg q12h	LUM 100 mg /IVA 125 mg q12h	LUM 100 mg /IVA 125 mg qd	LUM 100 mg /IVA 125 mg every morning and every other evening
≥14 kg	LUM 150 mg /IVA 188 mg q12h	LUM 150 mg /IVA 188 mg q12h	LUM 150 mg /IVA 188 mg qd	LUM 150 mg /IVA 188 mg every morning and every other evening

Source: Table 2 in Response to FDA Information Request date 06/17/2022
Abbreviations: CF, cystic f brosis; IVA, ivacaftor; LUM, lumacaftor; MHI, moderate hepatic impairment; q12h, every 12 hours; qd, once daily

The estimated $AUC_{0\text{-}12,ss}$ and $AUC_{0\text{-}48,ss}$ are depicted in Figure 3 and Figure 4, respectively. In children with moderate hepatic impairment, the twice daily dosing regimen resulted in a consistently higher lumacaftor exposure, and the daily dosing regimen resulted in a consistently lower lumacaftor exposure in each bodyweight subgroup. The alternative dosing regimen provided a better exposure matching for lumacaftor. Regardless of the dosing regimens, the exposure of ivacaftor could be matched.

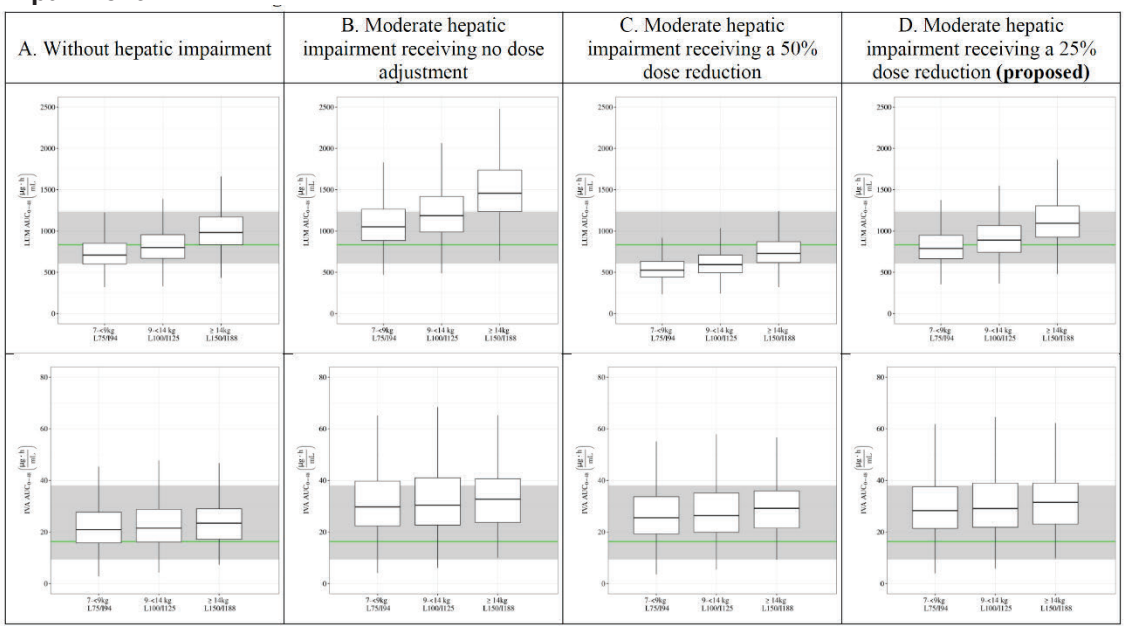
Among the three dosing regimens estimated in children with moderate hepatic impairment, the alternative dosing regimen (receiving 25% dose reduction) provided the best exposure matching with observed data in adults. Therefore, the alternative dosing regimen is recommended in children with moderate hepatic impairment.

Figure 3. Steady-State Lumacaftor and Ivacaftor AUC in 12 Hour Increments Over the Dosing Interval for Cystic Fibrosis Patients 12 to <24 Months of Age With or Without Moderate Hepatic Impairment



Source: Figure 1 in Response to FDA Information Request date 06/17/2022
Notes: Individual data points representing predicted $AUC_{0\text{-}12h}$ are shown for Study 122 Part B subjects 12 to < 24 months of age (blue circles). Dose of LUM/IVA (L/I) are provided below each weight bound. Boxplots present exposures from simulated subjects based on the WHO growth charts. The median is represented by a horizontal line, and the IQR is represented by a box. The whiskers represent the largest and smallest values within 1.5 × IQR. Gray area in the top panel represents the 5th to 95th percentiles of LUM AUC exposures in the adult population receiving LUM 400 mg q12h. Gray area in the bottom panel represents the 5th to 95th percentiles of IVA AUC exposures in the adult population receiving IVA 250 mg q12h. Green lines represent the median AUC exposures in the same adult population
Abbreviations: AUC, area under the curve; CF, cystic fibrosis; IQR, interquartile range; IVA, ivacaftor; L75/I94, lumacaftor 75 mg/ivacaftor 94 mg; L100/I125, lumacaftor 100 mg/ivacaftor 125 mg; L150/I188, lumacaftor 150 mg/ivacaftor 188 mg; LUM, lumacaftor; MHI, moderate hepatic impairment; q12h, every 12 hours; WHO, World Health Organization

Figure 4. Steady-State Lumacaftor and Ivacaftor AUC Over the Common 0 to 48 Hour Dosing Interval for Cystic Fibrosis Patients 12 to <24 Months of Age With or Without Moderate Hepatic Impairment

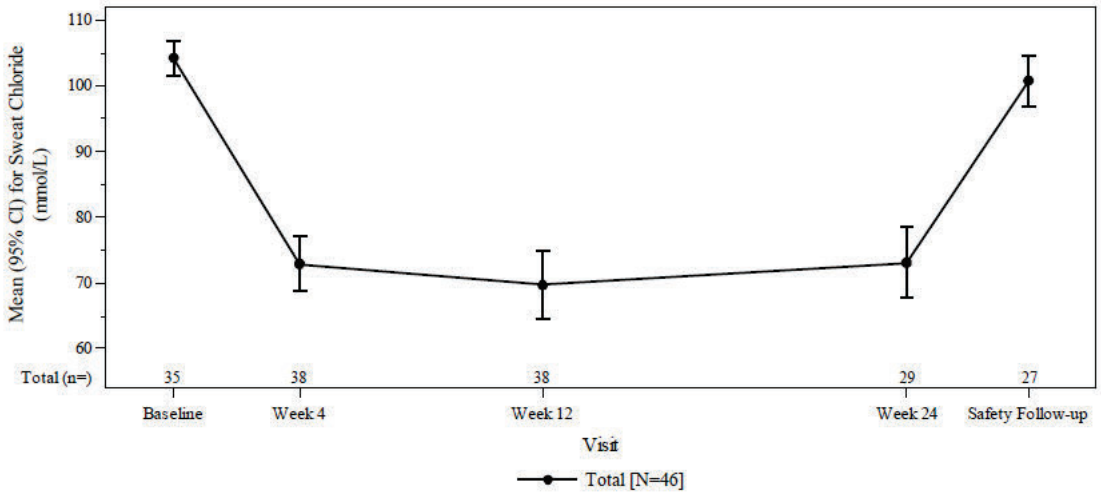


Source: Figure 2 in Response to FDA Information Request date 06/17/2022
Notes: Individual data points representing predicted $AUC_{0\text{-}12h}$ are shown for Study 122 Part B subjects 12 to < 24 months of age (blue circles). Dose of LUM/IVA (L/I) are provided below each weight bound. Boxplots present exposures from simulated patients based on the WHO growth charts. The median is represented by a horizontal line, and the IQR is represented by a box. The whiskers represent the largest and smallest values within 1.5 × IQR. Gray area in the top panel represents the 5th to 95th percentiles of LUM AUC exposures in the adult population receiving LUM 400 mg q12h. Gray area in the bottom panel represents the 5th to 95th percentiles of IVA AUC exposures in the adult population receiving IVA 250 mg q12h. Green lines represent the median AUC exposures in the same adult population.
Abbreviations: AUC, area under the curve; CF, cystic fibrosis; IQR, interquartile range; IVA, ivacaftor; L75/I94, lumacaftor 75 mg/ivacaftor 94 mg; L100/I125, lumacaftor 100 mg/ivacaftor 125 mg; L150/I188, lumacaftor 150 mg/ivacaftor 188 mg; LUM, lumacaftor; MHI, moderate hepatic impairment; q12h, every 12 hours; WHO, World Health Organization

What are the pharmacodynamic characteristics in children 1 to 2 years old?

The sweat chloride results from the Part B of Study 122 were summarized here as a whole regardless of the body weight/dosing groups. Treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at Week 4 which was sustained through Week 24 (Figure 5). The mean absolute change from baseline in sweat chloride at Week 24 was -29.1(13.5) mmol/L (95% CI: -34.8, -23.4). In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The mean (SD) absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 27.3 (11.1) mmol/L (95% CI:22.3, 32.3) (Figure 5). The PD response is similar to adults and children 2 years and older.

Figure 5. Mean (95% CI) for Sweat Chloride (mmol/L) at Each Visit, FAS, Part B



Source: Figure 11-1 in Clinical Study Report 122
Notes: Baseline sweat chloride was defined as the average of the values at screening and the pretreatment measurement on Day 1. If only 1 pre-first dose measurement was available, that measurement was considered the baseline. Analysis included both on-treatment measurements and measurements after treatment discontinuation (Washout Period). The 95% CI are based on the t-distribution.
Abbreviations: FAS, full analysis set; SwCl, sweat chloride

What's the bioanalytical method for lumacaftor and ivacaftor?

Plasma concentrations of lumacaftor and ivacaftor were measured using a validated bioanalytical method. The bioanalytical report is acceptable as the results from calibration standards and quality control samples met the acceptance criteria for the method throughout the analysis period (Bioanalytical Report R024). Calibration curves in human plasma were 2.00 to 2000 ng/mL for IVA, M1-IVA, and M6-IVA; 50.0 to 50000 ng/mL for LUM; and 5.00 to 5000 ng/mL M28-LUM.

The analytical method used to analyze study samples is supported by the following:

- Validation report (b) (4) Vertex Report Number O214) for (b) (4), entitled "Quantitation of VX-770, VRT-837018, VRT-842917, VRT-0995096, and VX-809 in Human Plasma via HPLC with MS/MS Detection" (Dipotassium EDTA) – issued 30 October 2018
  - Addendum report 1 – Analyte stability in frozen adult and pediatric dipotassium EDTA human plasma, analyte stability in frozen adult human plasma (dipotassium EDTA) fortified with azithromycin, salbutamol, and tobramycin, and stability of standards in solution – issued 25 July 2019
  - Addendum report 2 – Adult human plasma (dipotassium EDTA) – Analyte stability in frozen matrix and analyte stability in frozen matrix fortified with azithromycin, salbutamol, and tobramycin – issued 20 April 2020

A summary of the bioanalytical method validation is given in Table 12.

Table 12. Summary of Bioanalytical Parameters and Method Performance From Method Validation (Method Validation Report O214)

Bioanalytical method validation report name, amendments, and hyperlinks	Quantitation of VX-770, VR Human Plasma via HPLC wi		
Method description	Method LCMS P1665.00		
Materials used for standard calibration curve and concentration	VX-770, VRT-837018, and 2000ng/mL); VRT-0995096 VX-809 (50.0, 100, 200, 80(		
Validated assay range	2.00 to 2000 ng/ml for VX-7 ng/mL for VRT-0995096; 5(		
Material used for quality controls (QCs) and concentration	VX-770, VRT-837018, and 0995096 (5.00, 15.0, 240, 2(37,500 ng/mL)		
Minimum required dilutions (MRDs)	N/A		
Source and lot of reagents	Name: VX-770 Lot No.: 17((b) (4) 2018 Name: VRT-837018 Batch No.: REF-16-028, Source: Vertex Pharmaceuticals Incorporated, Retest Date: 31-MAY-2019 Name: VRT-842917, Batch No.: REF-18-002, Source: Vertex Pharmaceuticals Incorporated, Retest Date: 28-FEB-2019 Name: VRT-0995096, Batch No.: REF-10-019, Source: Vertex Pharmaceuticals Incorporated, Retest Date: 31-MAY-2019 Name: VX-809, Batch No.: ASI-599-16-001, Source: Vertex Pharmaceuticals Incorporated, Retest Date: 30-APR-2019		
Regression model and weighting	Linear $1/x^2$		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ for VX-770	14/14	Table 2A of report O214
	Cumulative accuracy (%bias) from LLOQ to ULOQ for VX-770	-1.56 to 1.64%,	Table 2A of report O214
	Cumulative precision (%CV) from LLOQ to ULOQ for VX-770	2.06 to 6.91	Table 2A of report O214
	Number of standard calibrators from LLOQ to ULOQ for VRT-837018	14/14	Table 2B of report O214

Validation parameters	Method validation summary		Source location
	Cumulative accuracy (%bias) from LLOQ to ULOQ for VRT-837018	-1.04 to 1.01	Table 2B of report O214
	Cumulative precision (%CV) from LLOQ to ULOQ for VRT-837018	1.82 to 6.01	Table 2B of report O214
	Number of standard calibrators from LLOQ to ULOQ for VRT-842917	14/14	Table 2C of report O214
	Cumulative accuracy (%bias) from LLOQ to ULOQ for VRT-842917	-0.619 to 0.381	Table 2C of report O214
	Cumulative precision (%CV) from LLOQ to ULOQ for VRT-842917	1.60 to 6.02	Table 2C of report O214
	Number of standard calibrators from LLOQ to ULOQ for VRT-0995096	14/14	Table 2D of report O214
	Cumulative accuracy (%bias) from LLOQ to ULOQ for VRT-0995096	-2.17 to 2.01	Table 2D of report O214
	Cumulative precision (%CV) from LLOQ to ULOQ for VRT-0995096	1.32 to 5.06	Table 2D of report O214
	Number of standard calibrators from LLOQ to ULOQ for VX-809	13/14	Table 2E of report O214
	Cumulative accuracy (%bias) from LLOQ to ULOQ for VX-809	-1.68 to 2.61	Table 2E of report O214
	Cumulative precision (%CV) from LLOQ to ULOQ for VX-809	1.43 to 3.26	Table 2E of report O214
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%bias) in 4 QCs (LLOQ, QCL, QCM, QCH) for VX-770	-3.88 to -0.0618	Table 4A of report O214
	Inter-batch %CV in 4 QCs (LLOQ, QCL, QCM, QCH) for VX-770	2.72 to 6.02	Table 4A of report O214
	Cumulative accuracy (%bias) in 4 QCs (LLOQ, QCL, QCM, QCH) for VRT-837018	-5.01 to -1.50	Table 4B of report O214
	Inter-batch %CV in 4 QCs (LLOQ, QCL, QCM, QCH) for VRT-837018	2.47 to 8.69	Table 4B of report O214
	Cumulative accuracy (%bias) in 4 QCs (LLOQ, QCL, QCM, QCH) for VRT-842917	-4.97 to -1.45	Table 4C of report O214
	Inter-batch %CV in 4 QCs (LLOQ, QCL, QCM, QCH) for VRT-842917	1.80 to 4.77	Table 4C of report O214
	Cumulative accuracy (%bias) in 4 QCs (LLOQ, QCL, QCM, QCH) for VRT-0995096	-4.71 to -1.18	Table 4D of report O214
	Inter-batch %CV in 4 QCs (LLOQ, QCL, QCM, QCH) for VRT-0995096	1.15 to 4.35	Table 4D of report O214
	Cumulative accuracy (%bias) in 4 QCs (LLOQ, QCL, QCM, QCH) for VX-809	-6.59 to -1.97	Table 4E of report O214
	Inter-batch %CV in 4 QCs (LLOQ, QCL, QCM, QCH) forVX-809	1.24 to 4.99	Table 4E of report O214
Matrix effect & Comedication Interference VX-770	No Matrix effect and no Interference		Table 18 A1 to A8/20A of report O214
Matrix effect & Comedication Interference VRT-837018	No Matrix effect and no Interference		Table 18 B1 to B8/20B of report O214
Matrix effect & Comedication Interference VRT-842917	No Matrix effect and no Interference		Table 18 C1 to C8/20C of report O214

Validation parameters	Method validation summary	Source location
Matrix effect & Comedication Interference VRT-0995096	No Matrix effect and no Interference	Table 18 D1 to D8/20D of report O214
Matrix effect & Comedication Interference VX-908	No Matrix effect and no Interference	Table 18 E1 to E8/20E of report O214
Specificity and Interference	There was no interference observed at the retention time of VX770, VRT-837018, and VRT-842917, VRT-0995096 and VX-809 and their internal standards in 6 individual human plasma tested	Table 17A1 - A4/17 B1-B4/17 C1C4/17 D1-D4 and 17 E1-E4 of report O214
Hemolysis effect	There is no effect on Hemolysis on the quantitation of VX-770, VRT-837018, and VRT-842917, VRT-0995096 and VX-809	Table 15A/15B/15C/15D/ and 15E of report O214
Lipemic effect	There is no effect on Lipemic on the quantitation of VX-770, VRT837018, and VRT-842917, VRT-0995096 and VX-809	Table 16A/16B/16C/16D/ and 16E of report O214
Dilution linearity	VX-770 (Adult Plasma) 800 ng/mL diluted five-fold 4000 ng/mL diluted 10-fold 20000 ng/mL diluted 20-fold (Pediatric Plasma)- 800 ng/mL diluted 10-fold	Table 6A of report O214
	VRT-837018 (Adult Plasma) 800 ng/mL diluted five-fold 4000 ng/mL diluted 10-fold 20000 ng/mL diluted 20-fold (Pediatric Plasma)- 800 ng/mL diluted 10-fold	Table 6B of report O214
	VRT-842917 (Adult Plasma) 800 ng/mL diluted five-fold 4000 ng/mL diluted 10-fold 20000 ng/mL diluted 20-fold (Pediatric Plasma)- 800 ng/mL diluted 10-fold	Table 6C of report O214
	VRT-0995096 (Adult Plasma) 2000 ng/mL diluted five-fold 10000 ng/mL diluted 10-fold 50000 ng/mL diluted 20-fold; Pediatric Plasma) 2000 ng/mL diluted ten-fold	Table 6D of report O214
	VX-809 (Adult Plasma) 20000 ng/mL diluted five-fold 100000 ng/mL diluted 10-fold 500000 ng/mL diluted 20-fold; Pediatric Plasma) 20000 ng/mL diluted ten-fold	Table 6E of report O214
Bench-top/process stability	VX-770, VRT-837018, and VRT-842917, VRT-0995096 and VX-809 Bench-top stability: 24.1 Hours at Room Temperature & Process Stability: 104.7 hours at 2 to 8 °C	Table 9 (A – E)/10 (A-E) of report O214
Freeze-Thaw stability	5 Cycles at -25ºC, 5 Cycles at -80ºC for VX-770, VRT-837018, and VRT-842917, VRT-0995096 and VX-809	Table 8 A-1 to 8 E-1 & 8 A-2 to 8 E-2 of report O214

Validation parameters	Method validation summary	Source location
Long-term storage	Long-term storage stability in human plasma containing dipotassium EDTA in the presence of tobramycin, azithromycin, and salbutamol was demonstrated for at least 368 days at -80 °C and -25 °C. Additionally, supplemental long-term storage stability in pediatric human plasma was demonstrated for at least 210 days at -80 °C and -25°C.	Tables 3A-9/10, 3B-7/8, 3C-7/8, 3D-7/8, 3E-7/8, Addendum 1 of the report O214 Tables 4A (1-4), 4B (1-4), 4C (1-4), 4D (1-4) and 4E (1-4) of Addendum 2 of the report O214
Parallelism	N/A	N/A
Carry over	Carryover was less than 20% of LLOQ after injecting ULOQ in 8 out of 10 runs for all analytes. For VX-770, in 1 out of 10 runs, carryover is greater than 20% of LLOQ after ULOQ (33.2%). For VRT0995096 in 2 out of 10 runs carryover is greater than 20% of LLOQ after ULOQ (20.2% and 33.7% respectively).	

Abbreviation: EDTA, ethylenediaminetetraacetic acid; HPLC, high-perfomrance liquid chromatography; LCMS, liquid chromatography mass spectrometry; LLOQ, lower limit of quantitation; MS/MS, tandem mass spectrometry; ULOQ, upper limit of quantitation

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 1 to less than 2 year old population, the Applicant submitted clinical data from Study 122 (Table 13).

Table 13. Summary of Clinical Studies Included in This Submission

Study Number	Study Type/Design	CF Mutation	Population	n	Treatment Arms	Countries
122	Open-label Safety and PK	Homozygous *F508del* mutation	1 to less than 2 years	Part A: 14 Part B: 46	LUM75/IVA94 mg q12h (7 to <9 kg) LUM100/IVA125 mg q12h (9 to <14 kg) LUM150/IVA188 mg q12h (≥14 kg)	USA, Canada

Abbreviations: CF, cystic f brosis; IVA, ivacaftor; LUM, lumacaftor; PK, pharmacokinetics; q12h, every 12 hours

7.2. Review Strategy

The Applicant submitted clinical data from Study 122 to support expansion of the indication to include patients 1 to less than 2 years of age. Study 122 was an open-label pharmacokinetic (PK) and safety study in patients 1 to less than 2 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 1 to less than 2 year old population was extrapolated from the older population.

The protocol for Study 122 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 122

Title: A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age with Cystic Fibrosis, Homozygous for *F508del*.

- Study start date: September 7, 2018
- Study completion: October 29, 2021
- Study report date: January 31, 2022
- 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 1 to less than 2 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 LUM75/IVA94 mg (7 to <10 kg), LUM100/IVA125 mg (10 to <14 kg), or LUM150/IVA188 mg (≥14 kg) q12 hours. During the 15-day treatment period, PK samples were collected 3-4 hours after the morning dose on Day 1; within 60 minutes before the morning

dose on Day 8; and within 60 minutes before the morning dose, at 2 hours, and 3-4 hours after the morning dose on Day 15. Ophthalmologic exam was performed at screening.

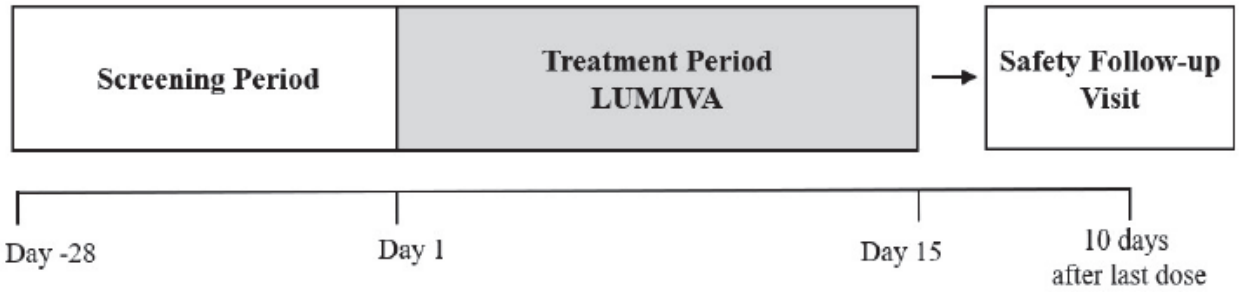
In Part A, two cohorts were enrolled sequentially in the following order:

- Cohort 1: subjects aged 18 to <24 months
- Cohort 2: subjects aged 12 to <18 months

A review of safety, tolerability, and available PK data was completed after each cohort to confirm the doses and weight bounds for Cohort 2 and Part B.

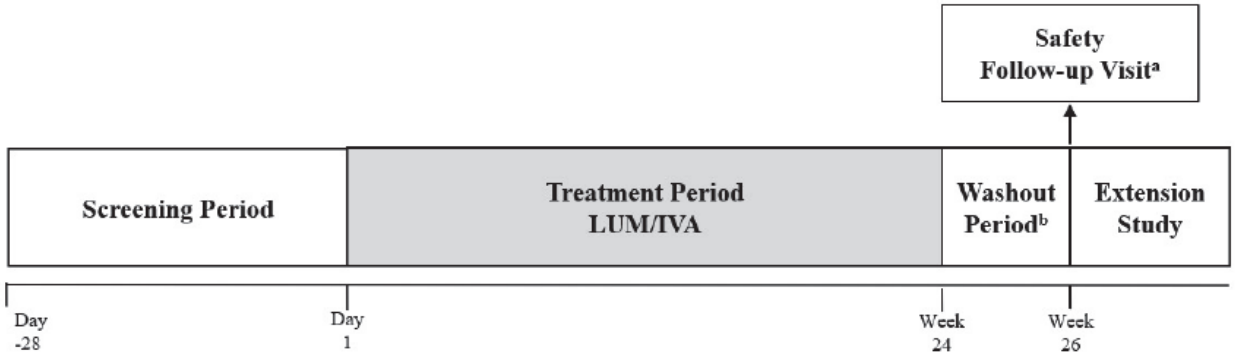
In Part B, there was also a 28-day screening period. This was followed by a 24-week open-label treatment period. Study visits occurred on Day 1, Day 15, and on Weeks 4, 8, 12, 16, and 24. There was a safety follow-up visit at Week 26. PK blood samples were collected on Day 15 (within 60 minutes before the morning dose and 2-6 hours post-dose), Week 4 (within 60 minutes before the morning dose and 2-6 hours post-dose), Week 12 (within 60 minutes before the morning dose), and Week 24 (within 60 minutes before the morning dose and 2-6 hours post-dose). An ophthalmologic exam was conducted before the first dose and anytime within 12 days of the Week 24 visit through 18 days after the last dose. Following the treatment period, all patients were allowed to continued in the open-label extension study (124). The trial schematic for Parts A and B are summarized in Figure 6 and Figure 7, respectively.

Figure 6. Part A Study Design



Source: Study 122 Clinical Study Report, Figure 9-1

Figure 7. Part B Study Design



Source: Study 122 Clinical Study Report, Figure 9-2

Objectives/Rationale

Part A:

- Primary Objective
  - To evaluate the pharmacokinetics (PK) of lumacaftor/ivacaftor in subjects 1 to <2 years of age with CF, homozygous for *F508del*
- Secondary Objectives
  - To evaluate the safety of lumacaftor/ivacaftor in subjects 1 to <2 years of age with CF, homozygous for *F508del*
  - To evaluate the PK of the metabolites of lumacaftor and ivacaftor in subjects 1 to <2 years of age with CF, homozygous for *F508del*

Part B:

- Primary Objective
  - To evaluate the safety of lumacaftor/ivacaftor in subjects 1 to <2 years of age with CF, homozygous for *F508del*
- Secondary Objectives
  - To evaluate the pharmacodynamics (PD) of lumacaftor/ivacaftor in subjects 1 to <2 years of age with CF, homozygous for *F508del*
  - To evaluate the PK of lumacaftor and ivacaftor and their respective metabolites in subjects 1 to <2 years of age with CF, homozygous for *F508del*

Trial Population

This trial included 14 (Part A) and 46 (Part B) CF patients 1 to less than 2 years of age who were homozygous for the *F508del* mutation.

Key Inclusion Criteria

1. Male or female age 1 to less than 2 years of age with a confirmed diagnosis of CF at the screening visit. CF was defined as follows:
   a. Two CF-causing mutations; AND
   b. One of the following two criteria:
      - Chronic sinopulmonary disease or gastrointestinal/nutritional abnormalities; OR
      - A sweat chloride value $\geq$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 homogyzous for the *F508del* mutation

3. Weight at the Screening Visit must be within the weight limits as defined for the study drug dose levels.

Key Exclusion Criteria

1. History of any comorbidity reviewed at the Screening Visit that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject.
2. An acute upper or lower respiratory infection, pulmonary exacerbation, 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:
    a. Hemoglobin <9.5 g/dL
    b. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin >2x upper limit of normal (ULN)
    c. Estimated glomerular filtration rate <60 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 $\geq$8 x ULN
- ALT or AST $\geq$5 x ULN for more than 2 weeks
- ALT or AST $\geq$3 x ULN in association with total bilirubin $\geq$2x ULN and/or clinical jaundice

If no alternative etiology (i.e. acetaminophen use or 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 clinical trials in the older population. It is reasonable to extrapolate efficacy in the proposed age group from the older population (≥12 years of age).

Treatments

The LUM/IVA granule doses in Study 122 were:

- LUM75/IVA94 mg q12h for patients 7 to <10 kg;

- LUM100/IVA125 mg q12h for patients 10 to <14kg;
- LUM150/IVA188 mg q12h for patients ≥14kg.

Prohibited Medications

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

Study Endpoints

Primary Endpoints

- Part A
  - PK parameters of LUM and IVA
- Part B
  - Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values (serum chemistry and hematology), standard 12-lead ECGs, vital signs, pulse oximetry, and ophthalmologic examinations

Secondary Endpoints

- Part A
  - Safety and tolerability assessments based on AEs, clinical laboratory values (serum chemistry and hematology), standard 12-lead ECGs, vital signs, and pulse oximetry
  - PK parameters of the metabolites of LUM and IVA
- Part B
  - Absolute change from baseline in sweat chloride at Week 24
  - PK parameters of LUM, IVA, and their respective metabolites

Additional pharmacodynamic endpoints are summarized in Table 14.

Table 14. PD/Efficacy Endpoints and Statistical Methods

Endpoint (Data Set/Analysis Set)	Method of Analysis
Secondary PD Endpoints	
Absolute change from baseline in **SwCl** at Week 24 (FAS)	Descriptive summary statistics, 95% CI
Additional PD Endpoints	
Absolute change from baseline in **weight-for-length z-score, BMI-for-age z-score, BMI, weight-for-age z-score, weight, length-for-age z-score, and length** at Week 24 (FAS)	Descriptive summary statistics, 95% CI
Absolute change from baseline in **FE-1 levels** at Week 24 (FAS)	
Absolute change from baseline in serum **IRT levels** at Week 24 (FAS)	
Absolute change from baseline in **fecal calprotectin levels** at Week 24 (FAS)	
Number of PEx and **CF-related hospitalizations** through Week 24 (FAS)	• Summary of number of events through Week 24 (inclusive) • Normalized by the time spent in the study
Change from baseline in **microbiology cultures** at Week 24 (FAS)	Descriptive summary statistics
Absolute change from baseline in **LCI** at Week 24 (LCI Substudy Set)	Individual subject data listing
Absolute change in **SwCl from Week 24 at Week 26** (FAS)	Descriptive summary statistics, 95% CI

Source: Study 122 Clinical Study Report, Figure 9-3
Abbreviations: BMI, body mass index; CF, cystic f brosis; CI, confidence interval; FAS, full analysis set; FE-1, fecal elastase-1; IRT, immunoreactive trypsinogen; LCI, lung clearance index; PD, pharmacodynamic; PEx, pulmonary exacerbation; SwCl, sweat chloride

Statistical Analysis Plan

Analysis of safety was descriptive with no formal statistical testing.

Protocol Amendments

This protocol was amended one time:

- Version 1.0: March 7, 2018 (original protocol)
- Version 2.0: December 4, 2019

Keys changes included:

- Updated the planned dosing regimen based on the PK results from Part A Cohort 1 as follows:
  - Added a lower dose of LUM 75 mg/IVA 94 mg for subjects who weigh 7 to <10 kg at screening for Part A and Part B.
  - Updated the lower weight bound from 8 kg to 10 kg for the LUM 100 mg/IVA 125 mg dose in Part B.
  - Updated the rationale for the dosing regimen adjustments based on the PK results from Part A Cohort 1.

  - For Part B, added guidance that doses may be adjusted upward based on consistent weight gain, but that no downward dose adjustments will be made if a subject's weight decreases.

- For LFT testing, removed requirement that subjects have clinical symptoms in addition to new alanine transaminase (ALT) or aspartate transaminase (AST) elevations of ≥3 × upper limit of normal (ULN) to align with VX-770 studies in this age group. The updated language states "[s]ubjects with new ALT or AST elevations of ≥3 × ULN will be followed closely…"
- Clarified documentation of ongoing adverse events based on regulatory agency input.

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 (Section 5.2), within the electronic submission.

> "This study was conducted in accordance with GCP as described in Integrated Addendum to ICH Guideline E6 (R2), Good Clinical Practice (November 2016). The ICH GCP guideline is consistent with the World Medical Association Declaration of Helsinki."

Financial Disclosure

See Section 15.2.

Patient Disposition

Patient disposition is summarized in Table 15. Of the 46 patients who received at least 1 dose of study drug, 45 (97.8%) patients completed LUM/IVA treatment, and 43 (93.5%) patients completed the study. One patient prematurely discontinued LUM/IVA treatment due to an AE (ALT and AST increased). 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 15. Study 122 Patient Disposition

Disposition	Total N=46 n (%)
Completed study	43 (93.5)
Prematurely discontinued treatment	3 (6.5)
Reason for discontinuation from study	
Adverse event	1 (2.2)
Withdrawal of consent (not due to AE)	1 (2.2)
Other	1 (2.2)

Disposition	Total N=46 n (%)
Last completed on-treatment scheduled visit	
Day 1	0
Day 3	0
Day 15	0
Week 4	0
Week 8	1 (2.2)
Week 12	0
Week 16	0
Week 20	0
Week 24	0
Rollover to extension study	
Yes	40 (87.0)
No	6 (13.0)

Source: Study 122 CSR; table 14.1.1b; pp122
Abbreviations: AE, adverse event

Protocol Violations/Deviations

In Part A, there were no important protocol deviations.

In Part B, there was 1 important protocol deviation:

- 1 subject did not meet eligibility requirements due to the subject turning 2 years of age by Day 1. This subject was enrolled, but was never dosed.

In both Part A and Part B, there were subject visits that were impacted by the COVID-19 pandemic, however, they did not impact completion of study visits or study results.

Table of Demographic Characteristics

Baseline demographic characteristics of the Study 122, Part B population are included in Table 16. In summary, 78.3% of patients enrolled in the study were white, which reflects the fact that CF is most common in Caucasians. 22 (47.8%) were male, and 25 (54.3%) were ≥18 months of age. The mean BMI was 17.17 kg/m^2, and the mean sweat chloride level (104.2 mmol/L) was significantly higher than normal. The BMI and mean sweat chloride level values are consistent with those seen in CF patients aged 1 to less than 2 years of age who are homozygous for the *F508del* mutation in the CFTR gene.

Table 16. Study 122. Baseline Characteristics

Characteristics	Total N=46
Sex, n (%)	
Male	22 (47.8)
Female	24 (52.2)

Characteristics	Total N=46
Race, n (%)	
White	36 (78.3)
Black or African-American	1 (2.2)
Asian	1 (2.2)
American Indian or Alaska Native	3 (6.5)
Native Hawaiian or Other Pacific Islander	1 (2.2)
Not collected per local regulations	7 (15.2)
Other	1 (2.2)
Age at baseline (months)	
Mean	18.1
Median	18.5
Age group at baseline, n (%)	
≥12 to <18 months	21 (45.7)
≥18 to <24 months	25 (54.3)
Dosing group at enrollment, n (%)	
LUM75/IVA94 mg q12h	1 (2.2)
LUM100/IVA125 mg q12h	44 (95.7)
LUM150/IVA188 mg q12h	1 (2.2)
Mean BMI (kg/m^2)	17.17
Mean sweat chloride (mmol/L)	104.2
Mean fecal elastase-1 levels (mg/kg)	9.7

Source: study 122 CSR; tables 14.1.2b and 14.1.3b; pp123-126
Abbreviations: BMI, body mass index; IVA, ivacaftor; LUM, lumacaftor; q12h, every 12 hours

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

The most common medical history conditions (≥20% by preferred term) of these patients were:

- Pancreatic failure (100%)
- CF lung (95.7%)
- Gastroesophageal reflux disease (23.9%)

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 99.9%. 100% of subjects were ≥80% compliant with study drug.

All patients used concomitant medication. The most common concomitant medications were:

- Pancreatin (67.4%)
- Salbutamol (60.9%)
- Sodium chloride (58.7%)
- Dornase alfa (54.3%)
- Multivitamins (34.8%)
- Pancrelipase (32.6%)
- Paracetamol (32.6%).

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 March 4, 2022. The submission was appropriately indexed and completed to allow for review. A Core Data Fitness assessment was conducted through the FDA Office of Computational Science and identified no significant 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 from baseline in sweat chloride from Week 24 at Week 26
- Absolute change from basleine in weight-for-length z-score, BMI-for-age z-score, BMI, weight-for-age z-score, weight, length-for-age z-score, and length at Week 24
- Absolute change from baseline in fecal elastase-1 levels at Week 24
- Absolute change from baseline in serum immunoreactive trypsin levels at Week 24
- Absolute change from baseline in fecal calprotectin levels at Week 24
- Number of pulmonary exacerbations and CF-related hospitalizations through Week 24
- Change from baseline in microbiology cultures at Week 24
- Absolute change from baseline in lung clearance index at Week 24
- Acceptability/palatability of LUM/IVA granules at Day 1

Decreases in sweat chloride were seen 4 weeks after treatment (-30.4 mmol/L) and were sustained over the 24 weeks of treatment (-32.3 mmol/L at Week 12; -29.1 mmol/L at Week 24) (Figure 5). After a 2-week Washout Period, sweat chloride levels returned to baseline. While there is no placebo control for comparison, these data would imply that LUM/IVA granules in this age group have a pharmacodynamic effect.

Absolute mean increases in weight (1.3 kg) and height (5.1 cm) were observed at Week 24. 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. The mean change in BMI from baseline was -0.20 kg/m^2 at Week 24.

The Applicant analyzed other secondary endpoints, including exacerbations and CF-related hospitalizations. While these results were reported, it is difficult to make any definitive conclusions, given the lack of placebo, active, or historical control group. The Applicant assessed the change from baseline in qualitative microbiology cultures; no notable changes were observed.

The Applicant reported change from baseline in fecal elastase and immunoreactive trypsinogen

(IRT). The mean absolute change in FE-1 from baseline at Week 24 was 73.1 mg/kg. the mean absolute change in serum IRT from baseline at Week 24 was -295.5 µg/L. While there were changes in these values, the clinical relevance of these changes is unknown.

Dose/Dose Response

While this trial included three doses of LUM/IVA granules, based on weight, all doses yielded similar systemic exposures. As such, exploration for dose response was neither indicated nor performed.

Durability of Response

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 the study drug.

Persistence of Effect

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.

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

The Applicant submitted data from a pharmacokinetic, pharmacodynamic, and safety study (Study 122) to support the use of LUM/IVA granules in patients 1 to less than 2 years of age who were homozygous for the *F508del* mutation in the CFTR gene.

Study 122 was a two-part, non-randomized, uncontrolled, open-label PK (part A, 15-day duration, n=14) and safety (part B, 24-week duration, n=46) study in patients 1 to less than 2 years of age. In part A, results demonstrated that when LUM75/IVA94 mg was administered to patients 7 to <9 kg, LUM100/IVA125 mg was administered to patients 9 to <14 kg, and LUM150/IVA188 mg was administered to patients ≥14 kg 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 1 to less than 2 year old population, efficacy in the proposed age group was extrapolated from the LUM/IVA tablet development program (≥12 years of age). Additionally, Week 24 data from part B demonstrated that decreases in the the pharmacodynamic endpoint of sweat chloride levels were observed, suggesting a pharmacodynamic response to LUM/IVA treatment.

In summary, efficacy of LUM/IVA granules in *F508del* homozygous patients aged 1 to less than 2

years has been demonstrated based on extrapolation from the older population.

8.2. Review of Safety

The Applicant has submitted data from Study 122 to support the safety of LUM/IVA granules in CF patients 1 to less than 2 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.

8.2.1. Safety Review Approach

The clinical safety review is based on clinical data from Study 122, which was a 2-part (A and B) open-label, non-randomized study in 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 46 patients were exposed to LUM/IVA granules in study 122, part B:

- 1 patient who weighed between 7 and <9 kg was administered LUM75/IVA94 mg every 12 hours;
- 44 patients who weighed between 9 and <14 kg were administered LUM100/IVA125 mg every 12 hours; and
- 1 patient who weighed 14kg or greater received LUM150/IVA188 mg every 12 hours.

Since 44 of the 46 patients received the LUM100/IVA125 mg dose, safety tables do not break down adverse events by dose received. The majority of patients was exposed to LUM/IVA granules for 16-24 weeks. The extent of exposure in Study 122 is summarized in Table 17.

Table 17. Study 122. Extent of Exposure

	Total (N=46)
Extent of exposure (days)	
Mean (SD)	166.5 (16.3)
Median (min, max)	168.5 (60, 175)
Duration of exposure, n (%)	
>0 to ≤2 weeks	0
>2 to ≤4 weeks	0
>4 to ≤8 weeks	0
>8 to ≤16 weeks	1 (2.2)
>16 to ≤24 weeks	22 (47.8)
>24 weeks	23 (50.0)

Source: Study 122 CSR; table 14.1.7b; pp170
Abbreviations: SD, standard deviation

Adequacy of the Safety Database

Part B of Study 122 included a 24-week treatment period where safety was assessed. The safety database was adequate to review the safety of LUM/IVA granules in children 1 to <2 years of age.

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, EKG, 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 24.1.

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 in this study (Study 122 CSR, Section 14.3 Safety Data Summary).

8.2.4. Safety Results

Deaths

There were no deaths in Study 122.

Serious Adverse Events

In general, the serious adverse events (SAEs) reported were what would be expected in a CF

population. A total of 5 patients experienced SAEs. Three patients had SAEs of infective pulmonary exacerbation of CF, 1 patients had an SAE of post procedural fever, and 1 patient had an SAE of distal intestinal obstruction syndrome (DIOS). These results are summarized in Table 18. SAE data did not reveal new safety concerns.

Table 18. Study 122 Nonfatal Serious Adverse Events (SAEs)

System Organ Class Preferred Term	Total N=46, n (%)
Subjects with any SAEs	5 (10.9)
Infections and infestations	3 (6.5)
Infective pulmonary exacerbation of cystic fibrosis	3 (6.5)
Gastrointestinal disorders	1 (2.2)
Distal intestinal obstruction syndrome	1 (2.2)
Injury, poisoning, and procedural complications	1 (2.2)
Post procedural fever	1 (2.2)

Source: study 122 CSR; table 14.3.2.6b; pp354

Dropouts and/or Discontinuations Due to Adverse Effects

Forty-six patients were enrolled and received at least 1 dose of LUM/IVA. Forty-five (97.8%) patients completed the LUM/IVA treatment, and forty-three (93.5%) patients completed the study. One (2.2%) patient discontinued LUM/IVA treatment due to AEs (ALT and AST increased). Two (4.3%) patients interrupted LUM/IVA treatment due to AEs (1 subject had an SAE of distal intestinal obstruction syndrome and 1 subject had an AE of dyspnea). At the time of reporting, the AEs of transaminase elevations were considered not resolved.

Significant Adverse Events

In Study 122, a total of 2 (4.3%) patients had treatment emergent adverse events (TEAEs) that were grade 3 (severe). No grade 4 life-threatening TEAEs were reported. One patient had pulmonary exacerbation of CF; one patient had transaminase elevations. 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 treatment-emergent adverse events are summarized in Table 19. The TEAEs reported were generally consistent with common manifestations of CF disease or common illnesses in patients 1 to less than 2 years of age. No new safety signals were identified.

Table 19. Study 122 TEAEs With a Frequency of At Least 5% at the Preferred Term (PT) Level Overall by SOC and PT

System Organ Class Preferred Term	Total N=46, n (%)
Subjects with any TEAEs	44 (95.7)
Infections and infestations	30 (65.2)
Infective pulmonary exacerbation of CF	10 (21.7)
Upper respiratory tract infection	6 (13.0)
Ear infection	5 (10.9)
Viral upper respiratory tract infection	5 (10.9)
Nasopharyngitis	4 (8.7)
Respiratory, thoracic and mediastinal disorders	22 (47.8)
Cough	16 (34.8)
Rhinorrhea	5 (10.9)
Nasal congestion	4 (8.7)
Gastrointestinal disorders	20 (43.5)
Vomiting	8 (17.4)
Constipation	5 (10.9)
Abdominal pain	3 (6.5)
Diarrhea	3 (6.5)
Investigations	15 (32.6)
Pseudomonas test positive	5 (10.9)
Alanine aminotransferase increased	4 (8.7)
General disorders and administration site conditions	11 (23.9)
Pyrexia	10 (21.7)
Skin and subcutaneous tissue disorders	10 (21.7)
Rash	4 (8.7)

Source: study 122 CSR; table 14.3.1.8b; pp332
Abbreviations: CF, cystic f brosis; SOC, System Organ Class; TEAE, treatment-emergent adverse event

Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology and serum chemistries, including liver transaminases. No laboratory abnormalities resulted in study drug discontinuation, aside from the 1 case of drug discontinuation due to transaminase elevation described in the section on hepatic safety.

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, QRS duration, QTcF interval, QT interval, and RR interval were provided by the Applicant. No clinical relevant changes from baseline were noted.

QT

No clinical 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 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 the older populations, the Applicant assessed AE and clinical lab data for transaminase abnormalities in this study. In study 122, five (10.9%) patients had ALT or AST >3x ULN, two (4.3%) subjects had ALT or AST >5x ULN, and one (2.2%) subject had ALT or AST >8x ULN. One (2.2%) subject had an alkaline phosphatase level >1.5x ULN. No subjects had total bilirubin >2x ULN. These results are summarized in Table 20.

Table 20. Study 122. Maximum On-Treatment Transaminase Results

Maximum On-Treatment	Total N=46, n (%)
ALT	
≤3x ULN	41 (89.1)
>3x ULN	5 (10.9)
>5x ULN	2 (4.3)
>8x ULN	1 (2.2)
AST	
≤3x ULN	44 (95.7)
>3x ULN	2 (4.3)
>5x ULN	0
>8x ULN	0
ALT or AST	
ALT>3x ULN or AST>3x ULN	5 (10.9)
ALT>5x ULN or AST>5x ULN	2 (4.3)
ALT>8x ULN or AST>8x ULN	1 (2.2)
ALP	
>1.5x ULN	1 (2.2)
Total Bilirubin	
>1.5x to ≤2x ULN	0
>2x ULN	0

Source: study 122 CST; table 14.3.4.3b; pp514

One case of transaminase elevations of >8x ULN is reviewed below:

Patient (b) (6):
This was a 21-month-old male assigned to the LUM100/IVA125 mg treatment group. The patient had a history of cystic fibrosis (homozygous for *F508del*), dysphagia, gastroesophageal

reflux disease, and pancreatic failure. The patient had previous ALT and AST levels that were elevated based on the reference ranges used in this study. ALT and AST were within normal range at the screening visit. On study day 56, the patient had an elevated ALT of 126 U/L (>3x ULN) and an elevated AST of 156 U/L (>2x ULN). On study day 59, ALT and AST levels peaked at 312 U/L (>8x ULN) and 266 U/L (>3x ULN), respectively. He was treated with ursodeoxycholic acid. Study drug dosing was discontinued. On study day 60, the patient received the last dose of study drug. On study day 72, AST levels decreased to within normal range; however, ALT was still elevated at 78 U/L (>2x ULN). Both ALT and AST levels increased again (312 U/L and 151 U/L, respectively) until the Early Termination Visit. At the time of reporting, the transaminase elevations were considered not resolved. The transaminase elevations were considered by the investigator to be severe in intensity and related to study drug.

Respiratory Safety

The Applicant performed a safety analysis grouping together PTs meant to represent respiratory symptoms and respiratory events (adverse events of special interest, AESI). One (2.2%) patient had an AE of dyspnea that led to treatment interruption. The AE of dyspnea occurred on study day 1 and was assessed by the investigator to be moderate in severity and possibly related to study drug. The evening dose of study drug was interrupted, and the event resolved with bronchodilator treatment. Study drug was resumed on study day 2, and the event did not recur.

Cataracts

No patients developed cataracts during the study.

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 1 to less than 2 years of age, no safety analyses by demographic subgroups were performed.

8.2.8. Specific Safety Studies/Clinical Trials

Study 122 part B was a safety study and has been discussed.

8.2.9. Additional Safety Explorations

Pediatrics and Assessment of Effects on Growth

This trial included pediatric patients of 1 to less than 2 years 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

Based on the Periodic Safety Update Report 10 (July 12, 2022), the estimated post-marketing exposure to Orkambi is (b) (4) patients, representing (b) (4) patient-years. No new safety issues have been identified, beyond that already in labeling, that would alter the risk-benefit profile for the approved indication.

Expectations on Safety in the Postmarket Setting

The patient population included in Study 122 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 patients 1 to <2 years of age, in conjunction with the known safety profile of LUM/IVA granules and tablets in patients ≥2 years of age, was sufficient to assess the safety of LUM/IVA granules in the CF patient population aged 1 to less than 2-years of age. In Study 122 part B, which included 46 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 granules and tablets, specific safety analyses were also performed to assess for liver-related toxicity, occurrence of respiratory related adverse events, cataracts, and changes in blood pressure. These safety analyses did reveal new safety concerns and were consistent with the known safety profile of LUM/IVA. Overall, the LUM/IVA granule safety profile in CF patients aged 1 to less than 2-years is favorable.

8.3. Statistical Issues

None. Since Study 122 was a safety and efficacy study, only descriptive statistics are used.

8.4. Conclusions and Recommendations

The recommend regulatory action is Approval for LUM/IVA granules at doses of:

- LUM75/IVA94 mg for patients 7 to <9kg,
- LUM100/IVA125 mg for patients 9 to <14 kg, and
- LUM150/IVA188 mg for patients ≥14kg

every 12 hours for the treatment of cystic fibrosis in patients 1 to less than 2 years of age who are homozygous for the *F508del* mutation.

In this efficacy supplement, the Applicant has submitted data from a pharmacokinetic, pharmacodynamic, and safety study (study 122) to support the use of LUM/IVA granules in patients 1 to less than 2 years of age who are homozygous for the *F508del* mutation in the CFTR gene.

Study 122 was a two-part, non-randomized, uncontrolled, open-label PK (part A, 15-day duration, n=14) and pharmacodynamic/safety (part B, 24-week duration, n=46) study in patients 1 to less than 2 years of age. Results demonstrated that when LUM100/IVA125 mg was administered to patients 9 to <14 kg every 12 hours, systemic exposures were comparable to that observed in the adolescent/adult population at the approved dose (of note, only 1 patient 7 to <9 kg and 1 patient ≥14 kg were enrolled in study 122 and administered LUM75/IVA94 mg and LUM150/IVA188 mg, respectively). Because of the comparable systemic exposures and because the disease process in the adolescent and adult population (≥12 years of age) is the same as that in the 1 to less than 2 year old population, efficacy in the proposed aged 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 (-29.1 mmol/L), suggesting a pharmacodynamic response to LUM/IVA granule treatment. Safety findings from study 122 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.

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 labeling submitted by the Applicant on March 4, 2022 is the final accepted labeling.

Section	Proposed Labeling	Approved Labeling
1	(b) (4)	ORKAMBI is indicated for the treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the F508del mutation in the CFTR gene. If the patient's genotype is unknown, an FDA cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene. *Removed* (b) (4) *from the Indication statement.*
2		Added an introductory sentence that recommended dosage is based on age and weight with reference to Table 1. Added the total dose for dosages that require 2 tablets of ORKAMBI. For clarity, Table 2 for Recommended Dosage for Patients with Hepatic Impairment was revised to include specific dosage recommendations (b) (4)
3		Added new strength for oral granules: lumacaftor 75 mg/ivacaftor 94 mg
6		• In a 24-week, open-label, multicenter study in 46 patients aged 1 through 2 years with CF who are homozygous for the F508del-CFTR mutation (Trial 7) the safety profile was similar to that observed in studies in patients aged 2 years and older *[see Clinical Pharmacology (12.2)]*. • During the 24-week, open-label clinical trial in 46 patients aged 1 through 2 years (Trial 7), the incidence of maximum transaminase (ALT or AST) levels >8, >5, and >3 x ULN was 2.2% (1/46), 4.3% (2/46), and 10.9% (5/46), respectively. No patients had total bilirubin levels >2 x ULN. One patient discontinued lumacaftor/ivacaftor treatment permanently due to transaminase elevations.

Section	Proposed Labeling (b) (4)	Approved Labeling
8		The safety and effectiveness of ORKAMBI in pediatric patients aged one year of age and older have been established. Use of ORKAMBI in these age groups is supported by evidence from adequate and well-controlled studies of ORKAMBI in patients 12 years of age and older *[see Clinical Studies (14) and Adverse Reactions (6.1)]* with additional data as follows: • Extrapolation of efficacy in patients aged 12 years and older homozygous for the F508del mutation in the CFTR gene to pediatric patients aged 1 through 11 years with support from population pharmacokinetic analyses showing similar drug exposure levels in patients aged 12 years and older and in pediatric patients aged 1 through 11 years *[see Clinical Pharmacology (12.3)]*… *Subsection 8.4 was revised because the pediatric use statement must be included when a drug is approved in pediatric patients for an indication that is the same as an approved indication in adults along with the basis for approval; 21 CFR 201.57(c)(9)(iv)(D)(1).*
12		Changes in sweat chloride in response to lumacaftor/ivacaftor were evaluated in a 24-week, open-label, clinica trial (Trial 7) in 46 patients with CF, aged 1 through 2 years (homozygous for F508del) who received lumacaftor 75 mg/ivacaftor 94 mg (patient weighing 7 kg to <9 kg at screening), lumacaftor 100 mg/ivacaftor 125 mg (patient weighing 9 kg to <14 kg at screening), lumacaftor 150 mg/ivacaftor 188 mg (patient weighing ≥14 kg at screening), every 12 hours for 24 weeks. Treatment with lumacaftor/ivacaftor demonstrated a reduction in sweat chloride at Week 4 which was sustained through Week 24. The mean absolute change from baseline in sweat chloride at Week 24 was -29.1 mmol/L (95% CI: -34.8, -23.4). In addition, sweat chloride was also assessed after a 2-week washout period to evaluate the off-drug response. The mean (SD) absolute change in sweat chloride from Week 24 at Week 26 following the 2-week washout period was 27.3 mmol/L (95% CI:22.3, 32.3).

Section	Proposed Labeling	Approved Labeling
	(b) (4)	
17		Section 17 was revised consistent with Patient Counseling Information Section of Labeling (final guidance). The section is intended for topics for counseling discussions between healthcare providers and patients after a prescribing decision has been made.

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 (Clinical) Comments

The submitted clinical program is adequate to support the efficacy and safety of lumacaftor/ ivacaftor granules at a dose of:

- LUM75/IVA94 mg every 12 hours for patients 7 to <9 kg;
- LUM100/IVA125 mg every 12 hours for patients 9 to <14 kg; and
- LUM150/IVA188 mg every 12 hours for patients ≥14 kg.

every 12 hours for the treatment of cystic fibrosis in patients 1 to <2 years of age who are homozygous for the *F508del* mutation.

The submitted clinical program consisted primarily of a clinical pharmacology study, Study 122. Study 122 was an open-label, uncontrolled, two-part pharmacokinetic (part A, 15-day duration, n=14) and safety study (part B, 24-week duration, n=46) study in patients 1 to less than 2 years of age who were homozygous for the *F508del* mutation in the CFTR gene. PK results demonstrated that when lumacaftor/ivacaftor 100/125 mg was administered to patients 9 to <14 kg every 12 hours (n=44), systemic exposures were comparable to that observed in the adult/adolescent population ≥12 years of age, 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 1 to <2 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). 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.**

15. Appendices

15.1. References

None

15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): VX16-809-122

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 146		
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 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)

15.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

15.3.1. Population Pharmacokinetics Model

The Applicant developed a PopPK model to describe the PK in children 1 to 2 years old.

A list of the studies included in this population pharmacokinetic analysis is provided below:

1. VX16-809-122 (Study 122): A Phase 3, 2-part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor in Subjects 1 to Less Than 2 Years of Age with Cystic Fibrosis, Homozygous for F508del.
2. VX15-809-115 (Study 115): A Phase 3, 2-Part, Open-label Study to Evaluate the Safety and Pharmacokinetics of Lumacaftor/Ivacaftor Combination Therapy in Subjects Aged 2 Through 5 Years with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation.
3. VX14-809-109 (Study 109): A Phase 3, Double-Blind, Placebo-Controlled, Parallel- Group Study to Evaluate the Efficacy and Safety of Lumacaftor in Combination with Ivacaftor in Subjects Aged 6 Through 11 Years with Cystic Fibrosis, Homozygous for the F508del-CFTR Mutation.
4. VX13-809-011 (Study 011): A Phase 3 open-label study to evaluate the pharmacokinetics, safety, and tolerability of Lumacaftor in combination with Ivacaftor in subjects 6 through 11 years of age with CF, homozygous for the F508del-CFTR mutation.

A summary of the studies included in the PopPK analysis is given in Table 21.

Table 21. Summary of the included Lumacaftor/Ivacaftor Data for the Population PK Analysis

Study	Phase	Cohort	LUM Dose (mg)	IVA Dose (mg)	PK Sampling Scheme Frequency	Number of subjects	Population
VX16-809-122	3	Part A Cohort 1: 18-<24 mo	100 q12h 10-<14 kg 150 q12h ≥14kg	125 q12h 10-<14 kg 188 q12h ≥14kg	D1 3-4h post D8 pre-dose D15 pre-dose, 2h (±15min) and 3-4h post	7	CF, Homozygous *F508del*
		Part A Cohort 2: 12-<18 mo	75 q12h 7-<10 kg 100 q12h 10-<14 kg 150 q12h ≥14kg	94 q12h 7-<10 kg 125 q12h 10-<14 kg 188 q12h ≥14kg		7	CF, Homozygous *F508del*
		Part B: 12-<24 mo	75 q12h 7-<9 kg 100 q12h 9-<14 kg 150 q12h ≥14kg	94 q12h 7-<9 kg 125 q12h 9-<14 kg 188 q12h ≥14kg	D15 pre-dose and 2-6h post Wk4 pre-dose and 2-6h post Wk12 pre-dose Wk24 at the same time as other blood collections	46	CF, Homozygous *F508del*
VX15-809-115	3	2-5 yo	100 mg q12h 10-<14 kg 150 q12h ≥14kg	125 q12h 10-<14 kg 188 q12h ≥14kg	Same as Study 122	62	CF, Homozygous *F508del*
VX14-809-109	3	6-11yo	200 mg q12h	250 mg q12h	D1 pre-dose and 3-6h post D15 3-6h post Wk4 pre-dose, 1-2h and 3-6h post Wk24 pre-dose and at the same time as other blood collections	103	CF, Homozygous *F508del*
VX13-809-011	3	6-11 yo	200 mg q12h	250 mg q12h	Part A: D1 pre-dose; and 2, 4, 6, and 12h post D7 pre-dose D14 pre-dose, and 4, 6, 12, and 24-96h post Part B: D1 pre-dose and 3-6h post D15 3-6h post Wk4 pre-dose and 3-6h post Wk16 pre-dose Wk24 morning (no dose administered)	62	CF, Homozygous *F508del*

Source: Table 4-1 Summary of the included LUM/IVA Data for the Population PK Analysis in Study Report R321: LUM/IVA Population Pharmacokinetic Analysis in Subjects 12 To Less Than 24 months of Age with Cystic Fibrosis, Homozygous for F508del, in Part B of Study 122
Abbreviations: CF, cystic f brosis; D, day; IVA, ivacaftor; LUM, lumacaftor; mo, months; post, post-dose (after the morning dose); pre-dose, within 60 minutes before the morning dose; Wk, week; yo, years old

BLQ data were handled according to the "M1" methodology (Beal (2001)). This approach excludes the BLQ data for the population PK analysis.

The final LUM dataset used for model development included 1599 LUM plasma concentration measurements from 287 CF subjects, including 62 LUM plasma concentration measurements from 14 unique 12 to <24 months CF subjects in Part A and 259 LUM plasma concentration measurements from 46 unique 12 to <24 months CF subjects in Part B. Overall, the percentage of BLQ observations was small: 2 out of 1,602 observations, or <0.1%.

The final IVA dataset used for model development included 1,579 IVA plasma concentration measurements from 287 CF subjects, including 62 IVA plasma concentration measurements from 14 unique 12 to <24 months CF subjects in Part A and 258 IVA plasma concentration measurements from 46 unique 12 to <24 months CF subjects in Part B. Overall, the percentage of BLQ observations was small: 3 out of 1,588 observations, or <0.01%.

A summary of baseline demographics in the PopPK analysis is given in Table 22.

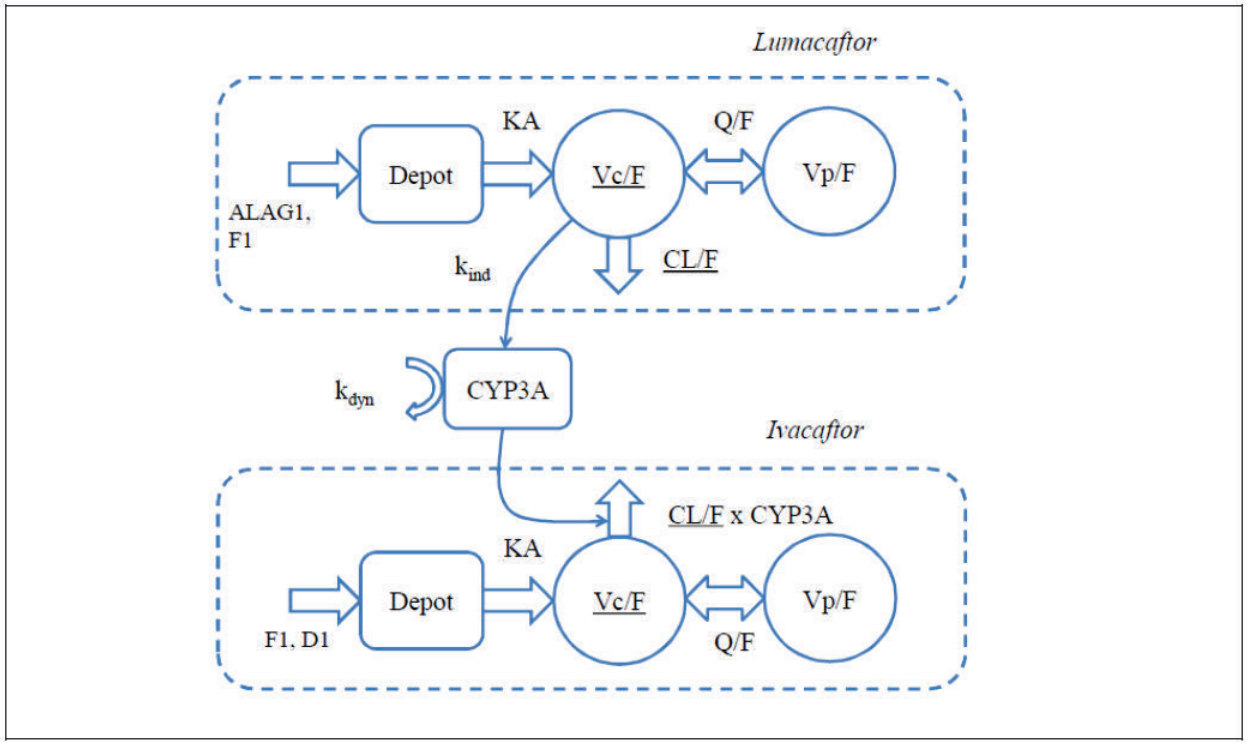
Table 22. Summary of Covariates in the PK Analysis Dataset by Study

Study	VX13-809-011	VX14-809-109	VX15-809-115	VX16-809-122	Overall
N	62	103	62	60	287
Male	30	40	32	29	131
Female	32	63	30	31	156
White	62	100	61	48	271
Other	0	3	1	12	16
Age, year (median [min, max])	9 [6, 12]	9 [6, 11]	3 [2, 5]	1.5 [1, 1.9]	7 [1, 12]
Age, year (mean [SD])	9.2 [1.5]	8.7 [1.6]	3.2 [1.1]	1.5 [0.29]	6.1 [3.5]
Age, months (median [min, max])	110 [72, 140]	110 [72, 130]	36 [24, 60]	18 [12, 23]	84 [12, 140]
Age, months (mean [SD])	110 [18]	100 [19]	39 [13]	18 [3.5]	73 [42]
Body weight, kg (median [min, max])	31 [18, 57]	28 [18, 47]	16 [9.4, 24]	11 [8.1, 15]	24 [8.1, 57]
Body weight, kg (mean [SD])	32 [6.7]	29 [6.5]	16 [2.8]	11 [1.4]	23 [10]

max: maximum value; min: minimum value; N: total sample size; SD: standard deviation.
Notes: Total number of subjects (N) represent *unique* subject in the study. For those subjects who enrolled in Parts A and B in Studies 011 and 115, only baseline demographics from Part B are reported.

The Applicant adopted the previously devleoped structural PK model from adults and chldren with CF.(Figure 8) A stepwise approach was used to estimate the parameters in children 1 to 2 years old for lumacaftor first and then for ivacaftor.

Figure 8. Lumacaftor and Ivacaftor PopPK Model Schematic



Source: Figure 5-1 in Modeling and Simulation Report R231
Notes: Depot refers to the depot compartments; IIV was included onto Vc/F and CL/F
Abbreviations: : ALAG1, lag time into LUM depot compartment; CL/F, (central) clearance; CYP3A, relative increase of CYP3A production compared to homeostasis; D1, zero order duration; F1, relative bioavailability for granulation formulation; KA, first-order absorption; K_{dyn}, dynamic response rate of CYP3A production and degradation; K_{ind}, degree of LUM induction of CYP3A; Vc/F, central volume; Q/F, intercompartmental clearance; Vp/F, peripheral volume

To account for the age changes throughout the study, AGEM at each visit was calculated as follows:
$AGEM$ (months) = $BAGE$ (months) +TIME (h) / (24h/d $*$ 30.4167 d/month) where BAGE is the baseline age and TIME is the time after the first dose, noting the unit conversion from hours to months. The maturation effect on clearance was described by the equation below:

$$F_{CL} = \left[1 - (1 - \beta_{CL}) \times exp\left(-(AGE) \times \frac{Ln(2)}{T_{CL}}\right)\right]$$

βCL and TCL were fixed to 0.35 and 3 months for both lumacaftor and ivacaftor, respectively, and were similar to maturation effects reported for gentamicin (Germovsek E., 2017).
The final parameter estimated for lumacaftor and ivacaftor are given in Table 23 and Table 24, respectively.

Table 23. Lumacaftor Population Pharmacokinetic Final Model (250) Parameter Estimates

Parameter	Units	Estimate	RSE (%)	95% CI
Apparent oral clearance, CL/F	L/h	1.56	11.1	[1.41,1.72]
Apparent central volume, V_c/F	L	18.3	2.30	[16,20.8]
Apparent intercompartmental clearance, Q/F	L/h	0.256	12.0	[0.185,0.353]
Apparent peripheral volume, V_p/F	L	56.5	4.78	[38.7,82.4]
First-order absorption rate constant, KA	1/h	0.746	40.0	[0.593,0.939]
Zero-order infusion duration, D1	h	0.0100		
Relative bioavailability of the tablet formulation, F1	-	1.00		
Relative bioavailability of the granule formulation, Granule_F1	-	0.925		
Absorption lag, ALAG1	h	0.678		
Allometric exponent (weight effect) for CL/F & Q/F	-	0.630	6.09	[0.555,0.705]
Allometric exponent (weight effect) for V_c/F & V_p/F	-	0.687	7.31	[0.589,0.785]
Fractional clearance at birth, β_{CL}	-	0.350		
Maturational half-life of the age-related changes of CL, T_{CL}	mo	3.00		
IIV on CL/F, $\omega^2_{CL/F}$		0.0674	11.3	[0.0524,0.0823]
IIV on Vc/F, $\omega^2_{Vc/F}$		0.0455	30.2	[0.0185,0.0725]
Covariance between CL/F-Vc/F, Cov($\omega_{CL/F}$, ω_V)		0.0227	36.2	[0.0066,0.0387]
Proportional residual error, $\sigma^2_{proportional}$		0.112	4.57	[0.102,0.122]

Source: Table 6-5 in Modeling and Simulation Report R231
Notes: The reference subject is a CF subject weighing 70kg taking the tablet formulation. Inter-individual variability and residual error estimates are reported as variances ω^2, σ^2 respectively.
Model: 250.mod
[a] Parameter IIV CV% = square-root of the parameter IIV $*$ 100
[b] Proportional Error SD = square-root of the proportional error variance
Abbreviations: CI: confidence interval; cov, covariance; mo, months; RSE, relative standard error; σ^2, variance of proportional error

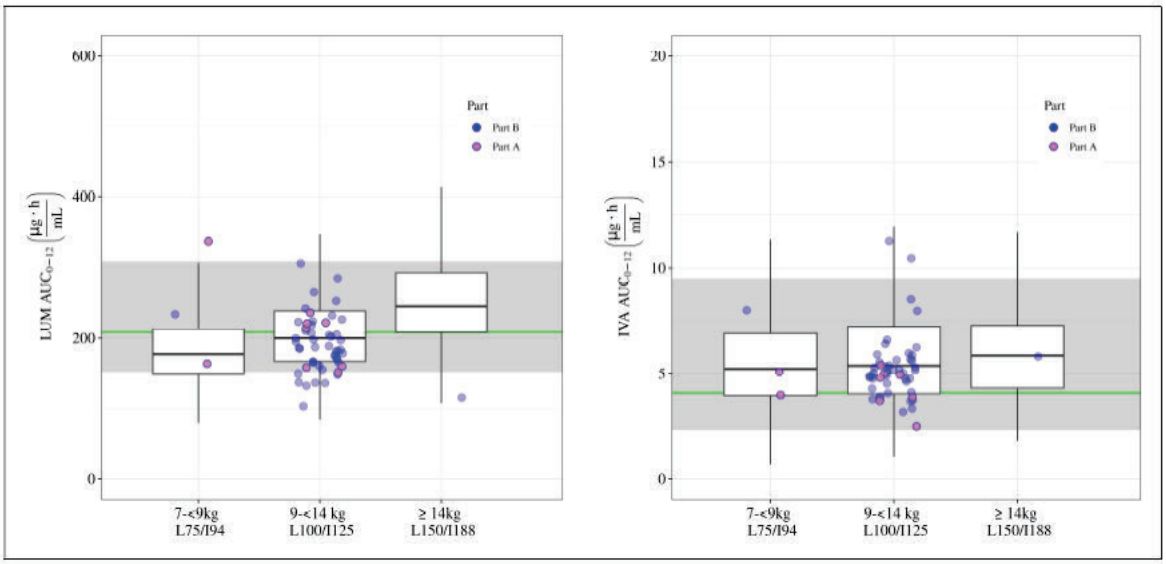
Table 24. Ivacaftor Population Pharmacokinetic Final Model (1770) Parameter Estimates

Parameter	Units	Estimate	RSE (%)	95% CI
Apparent oral clearance, CL/F	L/h	14.8	2.88	[12.7,17.3]
Apparent central volume, V_c/F	L	92.3	3.40	[68.2,125]
Apparent intercompartmental clearance, Q/F	L/h	4.74	21.4	[2.47,9.1]
Apparent peripheral volume, V_p/F	L	1470.	6.29	[597,3610]
First-order absorption rate constant, KA	1/h	0.217	3.82	[0.194,0.243]
Zero-order infusion duration, D4	h	0.959	15.1	[0.676,1.24]
Dynamic response rate of CYP3A production and degradation, KENZ1	1/h	0.0517	84.2	[-0.0336,0.137]
Degree of LUM induction of CYP3A, SLOPE	-	0.224		
Relative bioavailability of the granule formulation to the tablet, F4	-	0.988		
Allometric exponent (weight effect) for CL/F and Q/F	-	0.575	9.91	[0.463,0.686]
Allometric exponent (weight effect) for V_c/F and V_p/F	-	0.852	14.3	[0.613,1.09]
Half-maximal time for CYP3A induction delay, IND	h	105.	3.31	[77.4,142]
Fractional clearance at birth, β_{CL}	-	0.350		
Maturational half-life of the age-related changes of CL, T_{CL}	mo	3.00		
IIV on CL/F, $\omega^2_{CL/F}$		0.139	11.4	[0.108,0.17]
IIV on Vc/F, $\omega^2_{Vc/F}$		0.144	32.3	[0.0529,0.236]
Covariance between CL/F-Vc/F, Cov($\omega_{CL/F}$, $\omega_{Vc/F}$)		-0.0224	90.5	[-0.0621,0.0173]
Proportional residual error, $\sigma^2_{proportional}$		0.208	4.70	[0.189,0.228]

Source: Table 6-9 in Modeling and Simulation Report R231
Notes: The reference subject is a CF subject weighing 70kg taking the tablet formulation. Interindividual variability and residual error estimates are reported as variances ω^2, σ^2 respectively.
Model: run1770.mod
[a] Parameter IIV CV% = square-root of the parameter IIV * 100
[b] Proportional Error SD = square-root of the proportional error variance.
Abbreviations: CI, confidence interval; cov, covariance; F4, granule effect; mo, months; RSE, relative standard error; σ^2, variance of proportional error

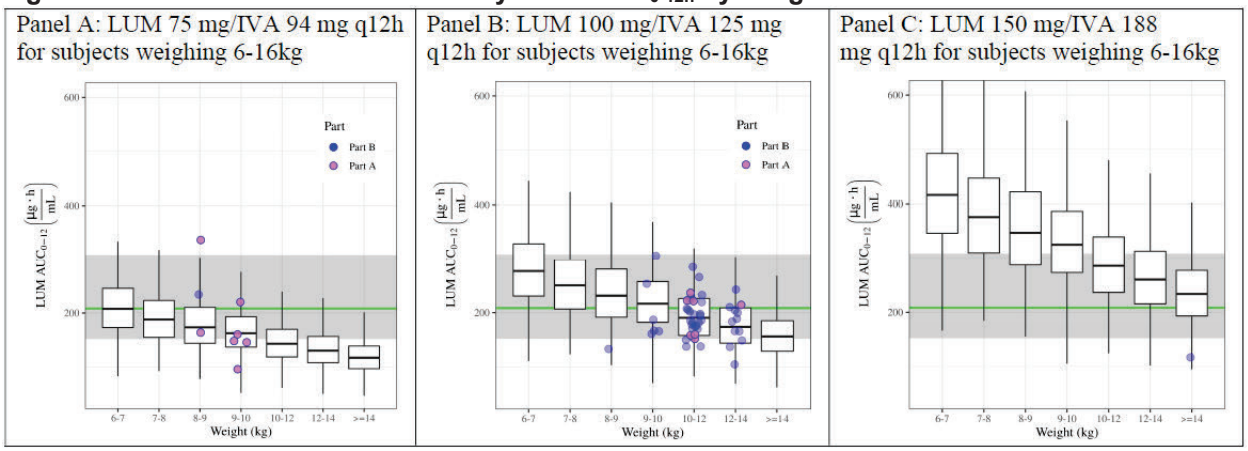
Based on the final PopPK model, the Applicant estimated the $AUC_{0\text{-}12,ss}$ for both lumacaftor and ivacaftor. The estimated and simulated $AUC_{0\text{-}12,ss}$ are depicted in Figure 9, Figure 10, and Figure 11.

Figure 9. Predicted Lumacaftor (Left) and Ivacaftor (Right) AUC at Steady State for Cystic Fibrosis Subjects 12 to <24 Months of Age



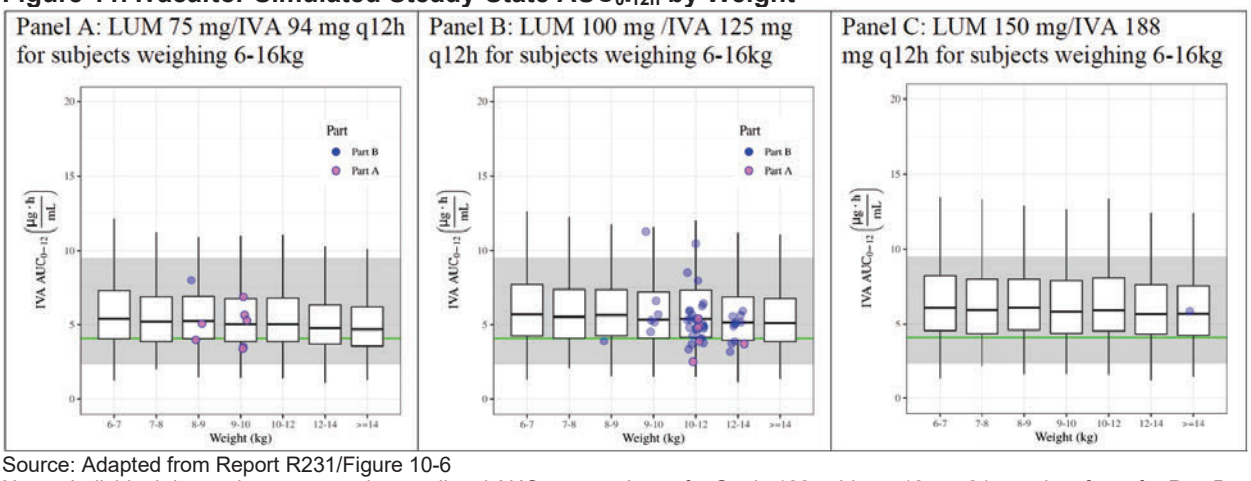
Source: Adapted from Report R231/Figure 6-21
Notes: Individual data points representing predicted $AUC_{0\text{-}12h}$ are shown for Study 122 subjects 12 to <24 months of age from Part B (blue circles) and Part A (red circles). Dose of LUM/IVA (L/I) given every 12 hours is provided below each weight bound. Boxplots present exposures from simulated subjects based on the WHO growth charts. The median is represented by a horizontal line, and the IQR is represented by a box. The whiskers represent the largest and smallest values within 1.5×IQR. Gray area in the left panel represents the 5th to 95th percentiles of LUM $AUC_{0\text{-}12h}$ exposures in the adult population receiving LUM 400 mg q12h. Gray area in the right panel represents the 5th to 95th percentiles of IVA $AUC_{0\text{-}12h}$ exposures in the adult population receiving IVA 250 mg q12h. Green lines represent the median $AUC_{0\text{-}12h}$ exposures in the same adult population. Part A subjects weighing 9-<10kg received the LUM 75 mg/IVA 94 mg q12h (L75/I94) dose and are not included in these plots.
Abbreviations: AUC, area under the concentration curve; IQR, interquartile range; IVA, ivacaftor; LUM, lumacaftor; q12h, every 12 hours

Figure 10. Lumacaftor Simulated Steady-State $AUC_{0\text{-}12h}$ by Weight



Source: Adapted from Report R231/Figure 10-5
Notes: Individual data points representing predicted $AUC_{0\text{-}12h}$ are shown for Study 122 subjects 12 to <24 months of age for Part B (blue circles) and Part A (red circles). Dose of LUM/IVA given every 12 hours is provided in the title of each panel. Boxplots present exposures from simulated subjects based on the WHO growth charts. The median is represented by a horizontal line, and the interquartile range (IQR) is represented by a box. The whiskers represent the largest and smallest values within 1.5×IQR. Gray area in the left panel represents the 5th to 95th percentiles of LUM $AUC_{0\text{-}12h}$ exposures in the adult population receiving LUM 400 mg q12h. Green lines represent the median $AUC_{0\text{-}12h}$ exposures in the same adult population. No Study 122 Part A subjects received the LUM 150 mg/IVA 188 mg q12h dose.
Abbreviations: AUC, area under the concentration curve; IQR, interquartile range; IVA, ivacaftor; LUM, lumacaftor; q12h, every 12 hours

Figure 11. Ivacaftor Simulated Steady-State AUC_{0-12h} by Weight



Source: Adapted from Report R231/Figure 10-6
Notes: Individual data points representing predicted AUC_{0-12h} are shown for Study 122 subjects 12 to <24 months of age for Part B (blue circles) and Part A (red circles). Dose of LUM/IVA given every 12 hours is provided in the title of each panel. Boxplots present exposures from simulated subjects based on the WHO growth charts. The median is represented by a horizontal line, and the interquartile range (IQR) is represented by a box. The whiskers represent the largest and smallest values within 1.5×IQR. Gray area represents the 5th to 95th percentiles of IVA AUC_{0-12h} exposures in the adult population receiving IVA 250 mg q12h.
Green lines represent the median AUC_{0-12h} exposures in the same adult population. No Study 122 Part A subjects received the LUM 150 mg/IVA 188 mg q12h dose.
Abbreviations: AUC, area under the concentration curve; IQR, interquartile range; IVA, ivacaftor; LUM, lumacaftor; q12h, every 12 hours

<u>Reviewer's assessment:</u>

The applicant's PopPK models for lumacaftor and ivacaftor were acceptable. The estimated PK parameters are consistent with previously observed PK characteristics in children 2 years and above. The Applicant revised the previously developed PopPK models for lumacaftor and ivacaftor to account for the PK characteristics in children 1 to 2 years old. In the revised PopPK models, an age dependent maturation function was introduced to account for the age effect on PK. However, based on the PK samples collected in Study 122, age has limited effect on lumacaftor and ivacaftor PK in addition to body weight in children 1 to 2 years old. Therefore, a PopPK model without age effect may also adequately characterize the PK in children 1 year and older.

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