NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	sNDA
Application Number(s)	206038/S018 and 211358/S006
Priority or Standard	Priority
Submit Date(s)	June 21, 2024
Received Date(s)	June 21, 2024
PDUFA Goal Date	December 21, 2024
Division/Office	Division of Pulmonology, Allergy, and Critical Care
Review Completion Date	December 12, 2024
Established/Proper Name	Lumacaftor/ivacaftor
(Proposed) Trade Name	Orkambi
Pharmacologic Class	Cystic Fibrosis Transmembrane Conductance Regulatory (CFTR) potentiator
Code name	VX-809/VX-770
Applicant	Vertex Pharmaceutical Incorporated
Dosage form	Oral Tablets and granules
Applicant proposed Dosing Regimen	LUM75/IVA94 mg q12h (7 to <9 kg) LUM100/IVA125 mg q12h (9 to <14 kg) LUM150/IVA188 mg q12h (≥14 kg)
Applicant Proposed Indication(s)/Population(s)	Treatment of cystic fibrosis (CF) in patients aged 1 year and older who are homozygous for the *F508del* mutation in the CFTR gene
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 aged 1 year and older who are homozygous for the *F508del* mutation in the CFTR gene
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	190905008 |Cystic fibrosis (disorder)|
Recommended Dosing Regimen	LUM75/IVA94 mg q12h (7 to <9 kg) LUM100/IVA125 mg q12h (9 to <14 kg) LUM150/IVA188 mg q12h (≥14 kg)

Table of Contents

Table of Tables

Table of Figures

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OPQ=Office of Pharmaceutical Quality
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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
CF	Cystic Fibrosis
CFR	Code of Federal Regulations
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
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
ELX	elexacaftor
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
IVA	Ivacaftor
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
TEZ	tezacaftor

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 facilitates 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 cystic fibrosis (CF) in patients ≥ 12 years of age who are homozygous for the *F508del* mutation in the CFTR gene at a dose of LUM 400 mg/IVA250 mg every 12 hours with a fat-containing food. On August 31, 2016, the indication was expanded to include CF patients 6 to less than 12 years of age at a dose of LUM 200 mg/IVA 250 mg every 12 hours.

On February 7, 2018, NDA 211358 was submitted for a new granule formulation for LUM/IVA. On August 7, 2018, the indication was expanded to include the 2 to less than 6 year old age group at a dose of LUM 150 mg/IVA 188 mg for patients ≥ 14kg and LUM 100 mg/IVA 125 mg for patients < 14 kg every 12 hours.

NDA 211358 S004 was submitted and approved to expand the indication to include the 1 to less than 2 year old age group at a dose of LUM 75 mg/IVA 94 mg every 12 hours for patients 7 to <9 kg; LUM 100 mg/IVA 125 mg every 12 hours for patients 9 to < 14 kg; and LUM 150 mg/IVA 188 mg every 12 hours for patients ≥ 14 kg.

The Agency issued a Pediatric Written Request (PWR) on January 4, 2018 requesting that the applicant conduct 3 pediatric studies. The following are the studies conducted by the Applicant to fulfill the Written Request:

Study 1 (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 To Less Than 6 Years With Cystic Fibrosis, Homozygous for the *F508del*-CFTR Mutation

Study 2 (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*

Study 3 (Study 124): Phase 3, Open-label, Rollover study that Evaluated the Long Term Safety and Tolerability of Lumacaftor/Ivacaftor (LUM/IVA) Treatment in Subjects with Cystic Fibrosis Who are Homozygous for *F508del* and 12 to < 24 Months of Age at Treatment Initiation

Studies 1 and 2 were previously completed and submitted as part of previous sNDA submissions. The results of Study 1 were submitted as part of the original NDA 211358 submission for the granule formulation which was approved in pediatric patients 2 to < 6 years old on August 7, 2018. The results of Study 2 were submitted as a supplemental NDA (NDA 211358 S004) and approved on September 2, 2022, expanding the indication to include patients 12 to < 24 months of age.

In these current supplements (NDA 206038 S018 and NDA 211358 S006), the Applicant has submitted the results of the final pediatric study (Study 124) and proposes the fulfillment of the Pediatric Written Request (PWR) as well as pediatric exclusivity for the conducted pediatric studies.

1.1. Conclusions

In these supplements, the final PWR study (Study 124), a phase 3, open-label, rollover study that evaluated the long-term safety and tolerability of LUM/IVA treatment in pediatric patients aged 1 to < 2 years with cystic fibrosis who are homozygous for F508del was evaluated. This study was a rollover of the previous study (Study 122 evaluated in previous supplement NDA 211358 S004) which was an open label, 24-week, PK and safety study. Thirty nine patients were rolled over from Study 122 and 13 patients were Orkambi-naïve patients. With regard to safety, no deaths were reported and 12 patients experienced serious adverse events (SAEs) which were not deemed related to study drug. Overall, the adverse events seen in Study 124 were generally consistent with common manifestations of CF disease or common illness in patients 1 to < 2 years of age. Nine patients had liver transaminase increases of > 3xULN. Three patients had a respiratory event and no patients developed cataracts. Overall, the safety profile in the 1 to less than 2 year old age group was consistent with the previous study in this age range. No new safety signals were identified in Study 124.

All 3 pediatric studies have met the criteria detailed in the PWR. The Pediatric Exclusivity Board took place on November 13, 2024 and it was determined that the Sponsor has met the criteria outlined in the PWR. Therefore, the PWR has been fulfilled. The Applicant has proposed labeling changes to include the open label rollover study in the prescribing information. While the Division typically would not include data from such an open-label rollover study, as the

product is already approved for chronic use in the 1 to less than 2 year old population and as the study did not identify new safety concerns, a brief description of this study will be included in section 8.4 of the label given that the results from this study fulfilled a PWR. The proposed regulatory action is Approval.

1.2. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Lumacaftor/Ivafaftor (LUM/IVA) (tradname: Orkambi) is approved for the treatment of CF in patients 1 year and older who are homozygous for the *F508del* mutation in the CFTR gene. LUM/IVA tablets are approved for pediatric patients ≥ 6 years of age and LUM/IVA granules are approved for pediatric patients 1 to 5 years of age. In this supplement, the Applicant submitted the results from an open-label rollover study (Study 124) assessing the long-term safety of LUM/IVA granules in patients 1 to less than 2 years of age in order to fulfill their Pediatric Written Request. The recommended regulatory action is Approval of the supplement and fulfillment of the Pediatric Written Request.

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 124 was an open-label, rollover, long-term (96 weeks) safety study in 52 CF patients 1 to less than 2 years of age who are homozygous for the *F508del* mutation in the CFTR gene. This study was a rollover of the previous study (Study 122) which was an open-label, 24-week, PK and safety study. Thirty nine patients were rolled over from Study 122 and 13 patients were Orkambi-naïve patients. With regard to safety, no deaths were reported and 12 patients experienced serious adverse events (SAEs) which were not deemed related to study drug. SAEs consisted of infections (8 subjects), constipation (1 subject), distal intestinal obstruction syndrome (1 subject), near drowning (1 subject), analphylaxis (1 subject), post procedural pain (1 subject), and atopic dermatitis (1 subject). The 5 most common AEs were cough, pulmonary exacerbation of CF, COVID-19, upper respiratory tract infection, and rhinorrhea. Overall, the AEs were generally consistent with the known safety profile of LUM/IVA, common manifestations of CF disease, or common illness in patients 1 to < 2 years of age. Nine (9) patients had liver transaminase increases of > 3xULN. Of these, 3 patients had ALT or AST > 8xULN and 5 patients had ALT or AST > 5xULN. None had elevations of total bilirubin > 1.5xULN. Three patients had a respiratory event and no patients developed cataracts. Overall, the safety profile in the 1 to less than 2 year old age group was consistent with the previous study in this age range, as well as those patients 2 years of age and older. No new safety signals were identified in Study 124. Study 124 was not designed to assess efficacy. The efficacy of Orkambi has already been established via extrapolation.

Because of the comparable systemic exposures and because the disease process in the adolescent/adult population is the same, efficacy in patients with CF less than 12 years old was extrapolated from the adolescent/adult population. While Study 124 was not designed for efficacy, decreases in sweat chloride concentrations were observed in this age population.

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.	This mutation represents most patients with CF in the US.
Current Treatment Options	In addition to the treatments of the symptoms and sequelae of the disease, Kalydeco and Orkambi are the only CFTR modulators approved for CF patients aged 1 to < 2 years of age. Kalydeco is approved for CF patients 1 months of age and older for certain genotypes, but not for CF patients homozygous for *F508del* mutations. Orkambi is the only CFTR modulator approved for CF patients homozygous for *F508del* aged 1 and older.	CF patients will need long term therapy. Given the young age of the indicated population, safety data to support long term use of this CFTR modulator are critical.
Benefit	While Study 124 was an open label rollover long term safety study and was not designed for efficacy, decreases in the pharmacodynamic endpoint of sweat chloride was observed.	This 96 week study provides long term data for the use of Orkambi. While only descriptive statistics were used, the study results showed that there is a persistence of effect on the drug on sweat chloride concentrations. The efficacy of Orkambi has already been established via extrapolation. Because of the comparable systemic exposures and because the disease process in the adolescent/adult population is the same, efficacy in patients with CF less than 12 year olds was extrapolated from the adolescent/adult population.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	The TEAEs observed in this study were consistent with common manifestations of CF disease or common illness in patients 1 to < 2 years of age. No deaths were reported. 12 SAEs were reported but were not likely related to Orkambi. Specific safety analyses were done for hepatic safety. Findings were similar to the previous 24 week study (Study 122) in the same age population.	No new safety signals were identified in Trial 124. The risks of LFT elevation, development of cataracts, and blood pressure changes are currently being managed through existing labeling and routine pharmacovigilance. A REMS is not required.

1.3. 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 40s[1].

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, there are over 700 mutations in the CFTR gene that are associated with CF disease causation although over 2,000 mutations in CFTR have been identified[2].

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),

[1] Cystic Fibrosis Foundation. Cystic Fibrosis Foundation. United States, 2002. Web Archive. CF Foundation 2022 Annual Report
[2] The Clinical and Functional TRanslation of CFTR (CFTR2) Database; Available at http://cftr2.org.

and Trikafta (elexacaftor/tezacaftor/ivacaftor) are approved for a 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. Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) are specifically approved for patients who are homozygous for the *F508del* mutation, the most common genotype. 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: Available Treatments for Cystic Fibrosis (CF)

Active Ingredient	Trade Name	FDA-Approved for CF Indication?
Targeting CFTR Dysfunction		
Ivacaftor (IVA)	Kalydeco Tablets and Granules	Yes; patients with CF aged 1 month and older who have one of 97 specified CFTR mutations (not including *F508del*)
Lumacaftor/ivacaftor (LUM/IVA)	Orkambi Tablets and Granules	Yes; patients with CF aged 1 year and older who are homozygous for *F508del* mutation
Tezacaftor/ivacaftor (TEZ/IVA)	Symdeko Tablets	Yes; patients with CF aged 6 years and older who have one of 154 specified mutations (including those homozygous for *F508del*)
Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)	Trikafta Tablets	Yes; patients with CF aged 2 years and older who have at least one copy for *F508del* or at least one copy of 177 specified mutations
Inhaled antibiotics for the treatment of Pseudomonas aeruginosa		
Tobramycin (inhalation solution, dry powder)	Bethkis, Kitabis, TOBI, Tobi podhaler, tobramycin generic solution	Yes (ages 6 years and older)
Aztreonam (inhalation solution)	Cayston	Yes (ages 7 years and older)
Polymyxin E/colistimethate (IV form given via nebulizer)	Colistin	No
Mucolytics		
Dornase alfa (inhalation)	Pulmozyme	Yes
Hypertonic saline solution (3%, 7% inhaled)	HyperSal	No
Mannitol (inhaled)	Bronchitol	Yes (ages 18 years and older)
Pancreatic Enzyme Replacement Therapy		
Pancrease, pancrelipase	Creon, Pancreaze, Zenpep, Pancrelipase, Pertzye, Viokace, Ultresa	Yes
Inhaled Bronchodilators		

Albuterol sulfate	Pro-Air, Ventolin, Proventil, Albuterol, and others	No
Levalbuterol	Xopenex	No
Oral Anti-Inflammatory Agents		
Azithromycin	Zithromax	No
Ibuprofen (high dose)	Motrin, Advil	No

Source: Approved labeling data from Drugs@FDA.gov (accessed on July 24, 2024)
Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ELX, elexacaftor; avenous; IVA, ivacaftor; LUM, lumacaftor; TEZ, tezacaftor

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

LUM/IVA tablets (NDA 206038) were initially 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 for LUM/IVA tablets was expanded to include CF patients 6 to less than 12 years of age. On August 8, 2018, LUM/IVA granules (NDA 211358) were approved for CF patients 2 to 5 years of age. The indication for LUM/IVA granules was further expanded to the 1 to < 2 year age group on September 2, 2022.

3.2. Summary of Presubmission/Submission Regulatory Activity

Prior to the submission of these supplements, LUM/IVA has been the subject of multiple regulatory proceedings. LUM/IVA tablets were granted Fast Track Designation on January 17, 2008 (IND 79521), Breakthrough Therapy Designation on December 7, 2012, and Orphan Drug Designation (Designation No. 14-4348) on June 30, 2014. Given the orphan designation status, pediatric assessments were not required for the approval of the original application for LUV/IVA tablets in patients ≥ 12 years of age.

While pediatric assessments were not required, the Applicant submitted a Proposed Pediatric Study Request (PPSR). The Agency issued a PWR on January 4, 2018 requesting that the Applicant conduct 3 pediatric studies. The 3 pediatric studies requested by the Agency were as follows:

Study 1: A two-part (A and B) open-label pharmacokinetic (part A) and safety (part B) study in CF patients ages 2 through 5 years who are homozygous for the *F508del* mutation. The pharmacokinetic (PK) portion of the study (A) must establish dosing based on matching PK parameters with the approved dose in the approved age groups. The safety portion of the study (B) must be 24 weeks in length.

Study 2: A two part (A and B) open label pharmacokinetic (part A) and safety (part B) study in CF patients ages 12 to 24 months who are homozygous for the *F508del* mutation. The PK portion of the study (A) must establish dosing based on matching PK parameters with the approved dose in the approved age groups. The safety portion of the study (B) must be 24 weeks in length.

Study 3: An open-label study to evaluate the safety of long-term treatment with lumacaftor/ivacaftor combination therapy in patients with CF who are homozygous for the *F508del*-CFTR mutation. This study will enroll pediatric patients who are less than 24 months of age at treatment initiation. Patients will be followed for at least 2 years. Study assessments will include ophthalmologic examinations, clinical labs, growth parameters, hospitalizations, exacerbations, and death. This study may include patients from Study 2.

Study 3 will be initiated after dosing is confirmed in Study 2.

Studies 1 and 2 were previously completed and submitted as part of previous sNDA submissions. The results of Study 1 were submitted as part of the original NDA 211358 submission for the granule formulation for patients 2 to < 6 years of age and was approved on August 7, 2018. The results of Study 2 were submitted as a supplemental NDA (NDA 211358 S004) and approved on September 2, 2022, expanding the indication to include patients 12 to < 24 months of age.

In these current supplements (NDA 206038 S018 and NDA 211358 S006), the Applicant has submitted their final pediatric study (Study 3 of 3, Study 124) and to fulfill the Pediatric Written Request (PWR). In addition, the Applicant requests pediatric exclusivity for the studies that were conducted in pediatrics. No changes to the indication are being proposed. The Applicant proposes labeling changes to include Study 3.

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

4.1. Office of Scientific Investigations (OSI)

No inspections were requested for this open label rollover study because this is an approved product in this patient population and for this age group.

4.2. Product Quality

No new product quality information submitted.

4.3. Clinical Microbiology

No new microbiology information submitted.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Nonclinical data was not submitted nor required for this supplement. Updates to Section 8.1 of the label were made to conform with 21CFR201.57(c)(9)(i)(D)(4). Specifically, the doses administered to animals in the studies were added as well as the presence of maternal toxicity in embryofetal toxicity studies with lumacaftor and ivacaftor.

6 Clinical Pharmacology

6.1. Executive Summary

Clinical Pharmacology data was not submitted nor required for this supplement

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 2: Summary of Clinical Study VX19-809-124 (Study 124)

Study Number	Study Type/Design	CF Mutation	Population	N	Treatment Arms	Countries
124	Open-label Extension, Rollover, Safety Study	Homozygous *F508del* mutation	1 to < 2 years of age	52	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 fibrosis; IVA, ivacaftor; LUM, lumacaftor; q12h, every 12 hours

7.2. Review Strategy

The Applicant submitted clinical data from Study VX19-809-124 (referred to as Study 124 in this review) which was the final study required under the Applicant's Pediatric Written Request. Study 124 was an open-label rollover, long-term (96 week) safety study in pedatric patients 1 to less than 2 years of age. The primary objective of Study 124 was to evaluate safety and tolerability with long-term treatment with Orkambi. The Applicant also submitted data for the pharmacodynamic endpoint of sweat chloride concentrations and exploratory endpoints for growth, fecal elastase, immunoreactive trypsin and trysinogen, calprotectin, lipase and amylase. However, this study was primarily reviewed to assess safety as the study was not designed to evaluate efficacy. Note that efficacy in the 1 to less than 2 year old population was previously extrapolated from the older population in a previous supplement. The protocol for Study 124 is discussed in Section 8.1 and the safety data is discussed 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 VX19-809-124 (Study 124)

Study Title

A Phase 3, Open-label, and Rollover Study to Evaluate the Long-term Safety and Tolerability of Lumacaftor/Ivacaftor Treatment in Subjects With Cystic Fibrosis Who Are Homozygous for *F508del* and 12 to <24 Months of Age at Treatment Initiation.

Study Dates

Study initiation (date first eligible subject signed the informed consent form): February 24, 2020

Study completion (date last subject completed the last visit): August 21, 2023

Clinical study report: December 14, 2023

Study Sites

All subjects were enrolled at sites in the US and Canada.

Study Objectives

Primary:

To evaluate the safety and tolerability of long-term LUM/IVA treatment in subjects with CF who are homozygous for *F508del* and 12 to < 24 months of age at treatment initiation.

Secondary:

To evaluate the pharmacodynamics (PD) of long-term LUM/IVA treatment in subjects with CF who are homozygous for *F508del* and 12 to < 24 months of age at treatment initiation.

Study Design and Conduct

Study 124 was a phase 3, multicenter, open label study that evaluated the safety and tolerability of LUM/IVA treatment over a 96-week treatment period in subjects with CF who are homozygous for *F508del* and 12 to < 24 months of age at treatment initiation.

The target enrollment for this study was approximately 50 subjects. The subjects enrolled in this study included rollover subjects who participated in Study VX16-809-122 Part B (Study 122B) and completed the Study 122B Safety Follow-up Visit and met all eligibility requirements

(rollover subjects) as well as LUM/IVA-naïve subjects who did not participate in Study 122B and were 12 to < 24 months of age at Study 124 Day 1.

For rollover subjects, there was a 2-week washout period (from Study 122B) followed by a 96-week open-label treatment period, where eligible patients received weight-based dosing of study treatment: LUM 75 mg/IVA 94 mg (7 to < 9 kg), LUM 100mg/IVA 125mg (9 to < 14 kg), or LUM 150 mg/IVA 188 mg (≥ 14 kg) every 12 hours. Subjects who received LUM/IVA in Study 124 could have received treatment for up to 120 weeks (for rollover subjects: 24 weeks in Study 122B and 96 weeks in Study 124; for LUM/IVA-naïve subjects: 96 weeks in Study 124). During the treatment period, PK samples were collected on Day 15, Weeks 12, 24, 36, 48, 60, 72, 84, and 96, after the last dose, and after safety follow-up according to Figure 1. Safety follow-up occurred 2 weeks after the last dose. An ophthalmalogic examination was done on Day 1 and 24 weeks after the last dose.

Figure 1: SCHEDULE OF ASSESSMENTS for Rollover Subjects

	Treatment Period (Day 1 Through Week 96)					ETT Visit	SFU Visit	Follow-up OE
Event/ Assessment	Day 1	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 12, 24, 36, 48, 60, 72, and 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon As Possible After Last Dose	2 Weeks (± 4 Days) After Last Dose	24 Weeks (± 14 Days) After Last Dose
Informed consent	X							
Inclusion/exclusion criteria confirmation	X							
Telephone contact		X						
Clinic visit	X		X	X	X	X	X	
Length/height and weight	X		X	X	X	X	X	
Vital signs	X		X	X	X	X	X	
Pulse oximetry	X		X	X	X	X	X	
Ophthalmological examination	X			Weeks 24, 48, 72	X	X[e]		X
Physical examination	X			X	X	X	X	
12-lead ECGs	X			Weeks 24, 48	X	X	X	
Serum chemistry and hematology	X		X (LFTs only)	X	X	X	X	
IRT	X			X	X	X	X	
Sweat chloride	X			Weeks 24, 48	X	X		
Fecal sample collection	X			Weeks 24, 48	X	X		

LUM/IVA dosing	**LUM/IVA q12h**						
Study drug count			X	X	X	X		
Medications, treatments, and procedures review	Continuous from signing of ICF through the SFU Visit						
AEs	Continuous from signing ICF through the SFU Visit						*Ocular AEs only*

AE: adverse event; ETT: Early Termination of Treatment; ICF: informed consent form; IRT: immunoreactive trypsinogen and trypsin; IVA: ivacaftor; LFT: liver function test; LUM: lumacaftor; OE: ophthalmological examination; q12h: every 12 hours; SFU: Safety Follow-up

For LUM/IVA-naïve subjects, there was a 28-day screening period followed by a 96-week open-label treatment period, where eligible patients received weight-based dosing of study treatment: LUM 75 mg/IVA 94 mg (7 to < 9 kg), LUM 100 mg/IVA 125 mg (9 to < 14 kg), or LUM 150 mg/IVA 188 mg (≥ 14 kg) every 12 hours. During the treatment period, PK samples were collected on Day 15, Weeks 4, 8, 12, 16, 24, 36, 60, 72, 84, and 96, after the last dose, and after safety follow-up according to the Schedule of Assessments. Safety follow-up occurred 2 weeks after the last dose. An opthalmalogic examination was done on Day 1 and 24 weeks after the last dose. The schedule of assessments is displayed in Figure 2.

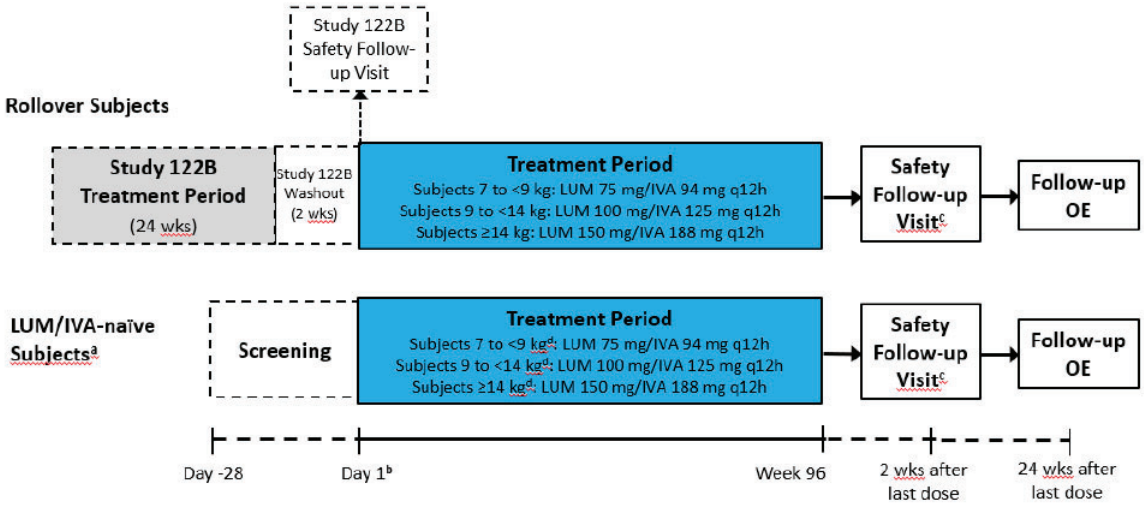
Figure 2: SCHEDULE OF ASSESSMENTS LUM/IVA-naïve subjects

	Screening	Treatment Period (Day 1 Through Week 96)							ETT Visit	SFU Visit	Follow-up OE
Event/Assessment	Days -28 Through -1	Day 1	Day 3 (± 1 Day)	Day 15 (± 3 Days)	Weeks 4, 8, 12, and 16 (± 5 Days)	Week 20 (± 5 Days)	Weeks 24, 36, 48, 60, 72, and 84 (± 7 Days)	Week 96 (± 7 Days)	As Soon As Possible After Last Dose	2 Weeks (± 4 Days) After Last Dose	24 Weeks (± 14 Days) After Last Dose
Informed consent	X										
Inclusion/exclusion criteria	X										
Clinic visit	X	X		X	X		X	X	X	X	
Telephone contact			X			X					
Demographics	X										
Medical history	X										
CFTR genotype	X										
Length/height and weight	X	X		X	X		X	X	X	X	
Vital signs	X	X		X	X		X	X	X	X	
Pulse oximetry	X	X		X	X		X	X	X	X	
Ophthalmological examination	X						Weeks 24, 48, 72	X	X[d]		X
Physical examination (PE)	X	X		Abbrev	Week 12		X	X	X	X	
Standard 12-lead ECG	X				Weeks 4, 12		Weeks 24, 48	X	X	X	
Serum chemistry and hematology	X	X		X (LFTs only)	X		X	X	X	X	
IRT	X				Weeks 4, 12		X	X	X	X	
Sweat chloride	X	X			Weeks 4, 12		Weeks 24, 48	X	X		

Abbrev: abbreviated; AE: adverse event; BMI: body mass index; CF: cystic fibrosis; *CFTR*: CF transmembrane conductance regulator gene; ETT: Early Termination of Treatment; ICF: informed consent form; IRT: immunoreactive trypsin and trypsinogen; IVA: ivacaftor; LFT: liver function test; LUM: lumacaftor; OE: ophthalmological examination; PE: physical examination; q12h: every 12 hours; SFU: Safety Follow-up

The study schematic, including dosage regimens, is displayed in Figure 3.

Figure 3: Study Schematic



Source: Clinical Study Report (dated December 14, 2023), Figure 9-1, p. 16
Abbreviations: IVA, ivacaftor; kg, kilograms; LUM, lumacaftor; mg, milligrams; OE, ophthalmological examination; q12h, once every 12 hours; wks, weeks

Key Inclusion Criteria

- Subjects (male or female) aged 12 to < 24 months on Study 124 Day 1
- Weight at screening within the weight limits defined for the study drug dose levels
- Confirmed diagnosis of CF at screening, defined as:
    - 2 CF-causing mutations as documented in the subject's medical records (subjects confirmed to be homozygous for *F508del* at screening); AND one of the following:
        - Chronic sinopulmonary disease or gastrointestinal/nurtitonal abnormalities; OR
        - A sweat chloride value ≥ 60 mmol/L as documented in the subject's medical records or from the sweat chloride test result obtained at screening
- Subjects with stable CF disease at screening, as deemed by the Investigator

Key Exclusion Criteria

- Prematurely discontinued LUM/IVA treatment in Study 122B
- History of any comorbidity or laboratory abnormality that might confound the results of the study or pose an additional risk in administering LUM/IVA to the subject (e.g.,

cirrhosis with portal hypertension)
- History of drug intolerance or other serious reactions to LUM/IVA in Study 122B that would pose an additional risk to the subject
- Subjects with a history of allergy or hypersensitivity to LUM/IVA
- Liver function test (LFT) abnormality meeting criteria for LUM/IVA treatment interruption at the completion of Study 122B, for which no convincing alternative etiology is identified
- QTc value at the completion of Study 122B that would pose an additional risk to the subject (e.g., remained above the threshold value [> 45 ms from baseline or > 500 ms] on repeated measurement or was noted on 2 or more occasions with no identified alternative etiology for the increased QTc)

Prohibited Medications

No strong CYP3A4 inducers or inhibitors were allowed within 14 days before the first dose of study treatment.

Study Drug Discontinuation Criteria

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

- ALT or AST > 8 x ULN
- ALT or AST > 5 x ULN for more than 2 weeks
- ALT or AST > 3 x ULN in association with total bilirubin >2 x 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.

Study Endpoints

Primary:

Safety and tolerability assessments based on adverse events (AEs), clinical laboratory tests (serum chemistry and hematology), standard 12-lead ECGs, vital signs, pulse oximetry, and ophthalmological examinations (OEs)

Secondary**:**

Absolute change from baseline in sweat chloride (SwCl)

Exploratory**:**

- Absolute change from baseline in growth parameters, including the following:
    - Body mass index (BMI)
    - Weight (in kg)
    - Length (in cm)
- Absolute change from baseline in the following markers of pancreatic function:
    - Fectal elastase (FE-1) levels
    - Serum immunoreactive trypsin and trypsinogen (IRT) levels
- Absolute change from baseline in fecal calprotectin, a marker of intestinal inflammation

Statistical Analysis Plan (SAP)

The final SAP is dated August 3, 2023, and contains the information outlined below.

Analysis Sets:

All Subjects Set: All subjects who are enrolled or dosed in Study 124. This analysis set will be used for individual subject data listings and disposition summary tables unless otherwise specified

Safety Set: All subjects who are exposed to any amount of study drug in Study 124. This analysis set will be used for all safety analysis unless otherwise specified

Full Analysis Set: All subjects who are enrolled and dosed in Study 124. This analysis set will be used for all analysis of PD and exploratory endpoints unless otherwise specified

Sample Size Considerations:

No formal sample size calculations have been performed for this study. The study will enroll approximately 50 subjects to provide data for the assessment of long-term safety in the target patient population, as requested by a regulatory agency.

Statistical Analyses:

All endpoints were analyzed descriptively with no formal statistical testing. Therefore, no multiplicity adjustment was performed.

Continuous variables were summarized using the following summary statistics: number of subjects, mean, standard deviation (SD), standard error (SE), median, and minimum and maximum value. Categorical variables were summarized using counts and percentages. Baseline value will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected on or before the first dose. Absolute change from baseline were calculated as post-baseline value – baseline value.

Protocol Amendments

There was a single protocol amendment dated February 12, 2021, which added the new dose of LUM 75 mg/IVA 94mg and adjusted the lower weight bound for the LUM 100 mg/IVA 125 mg dose.

8.1.2. Study Results

Compliance with Good Clinical Practices (GCP)

The Applicant states that the study was conducted in accordance with ICH E5 GCP Guidelines in the clinical study report. The protocol, amendments, informed consent form, and any other necessary documents were reviewed and approved by the respective independent ethics committee (IEC) / institutional review board (IRB) before study initiation.

Financial Disclosure

Not applicable per 21 C.F.R. § 54.2(e)

Subject Disposition

All 52 enrolled subjects (39 rollover subjects and 13 LUM/IVA-naïve subjects) were included in the All Subjects, Full Analysis, and Safety Sets. Of them, 38 subjects (73%) completed study drug treatment and 14 subjects (27%) prematurely discontinued study drug treatment. The reasons for discontinuation were as follows: 2 subjects (4%) experienced AEs, 4 subjects (8%) refused further dosing (not due to an AE), 1 subject (2%) was lost to follow-up, and a commercial drug (NDA 211358/S004 for LUM/IVA granules was approved on September 2, 2022, which was during the conduct of Study 124) became available for 7 subjects (13%).

Protocol Violations/Deviations

There were no important protocol deviations. Some subject visits were impacted by the COVID-19 pandemic. However, they did not impact the completion of study visits or the study results.

Baseline Demographics and Clinical Characteristics

Subject demographics at baseline are provided in Table 3. The study population included slightly more men (54%) than women (46%) and was predominantly 18 to < 24 months of age (average baseline age was 23 months), white (77%), not Hispanic or Latino (83%), and located in the US (75%). The baseline demographics of the study population were generally consistent with the overall CF population.

Table 3: Baseline Demographics (Full Analysis Set, Study 124)

Demographic	LUM/IVA N=52
Sex, n (%)	
Female	24 (46.2)
Male	28 (53.8)
Age (months)	
Mean (SD)	23.3 (3.5)
Median (Min, Max)	23 (18, 29)
Age group, n (%)	
12 to <18 months	18 (34.6)
18 to <24 months	34 (65.4)
Race, n (%)	
American Indian or Alaska Native	1 (1.9)
White	40 (76.9)
Other	1 (1.9)
Multiple	2 (3.9)
Not collected per local regulations	8 (15.4)
Ethnicity, n (%)	
Hispanic or Latino	1 (1.9)
Not Hispanic or Latino	43 (82.7)
Not collected per local regulations	8 (15.4)
Site location, n (%)	
Canada	13 (25)
United States	39 (75)

Source: Statistical reviewer; Clinical Study Report (dated December 14, 2023), Table 10-2, p. 22-23
Abbreviations: IVA, ivacaftor; LUM, lumacaftor; Max, maximum; Min, minimum; n, number of subjects in the respective category; N, number of subjects in the Full Analysis Set; SD, standard devation

Subject clinical characteristics at baseline are summarized in Table 4. The average sweat chloride, BMI, and weight at baseline among all enrolled subjects with a baseline value was 101.6 mmol/L, 16.6 kg/m^2, and 12.2 kg, respectively. Additionally, the average FE-1, serum IRT, and fecal calprotectin levels at baseline were 13.8 mg/kg, 625.5 µg/L, and 216.4 mg/kg, respectively, and a considerable portion of subjects had a history of pancreatic failure (100%), CF lung (96%), constipation (29%), and gastroesophageal reflux disease (25%). The baseline clinical characteristics were generally consistent with the patients with CF homozygous for *F508del.*

Table 4: Baseline Clinical Characteristics (Full Analysis Set, Study 124)

Clinical Characteristic	LUM/IVA N=52
Sweat Chloride (mmol/L)	
n (%)	35 (67.3)
Mean (SD)	101.6 (8.9)
Median (Min, Max)	100.5 (87, 130)
BMI (kg/m^2)	
n (%)	47 (90.4)
Mean (SD)	16.6 (1.5)
Median (Min, Max)	16.6 (13.8, 23.5)
Weight (kg)	
n (%)	47 (90.4)
Mean (SD)	12.2 (1.6)
Median (Min, Max)	12 (9.5, 19.2)
FE-1 level (mg/kg)	
n (%)	29 (55.8)
Mean (SD)	13.8 (25.6)
Median (Min, Max)	7.5 (7.5, 143)
Serum IRT level (µg/L)	
n (%)	41 (78.8)
Mean (SD)	625.5 (460.4)
Median (Min, Max)	644.1 (36.5, 1200)
Fecal calprotectin level (mg/kg)	
n (%)	28 (53.8)
Mean (SD)	216.4 (480)
Median (Min, Max)	62 (2.5, 1870)
Medical history conditions[a] (%)	
Pancreatic failure	100
CF lung	96.2
Constipation	28.8
Gastroesophageal reflux disease	25

Source: Statistical reviewer; Clinical Study Report (dated December 14, 2023), Table 10-3 (p. 23-25) and Table 14.1.4 (p. 55)

[a] Includes conditions in ≥25% of all enrolled subjects

Abbreviations: BMI, body mass index; CF, cystic fibrosis; FE-1, fecal elastase-1; IVA, ivacaftor; IRT, immunoreactive trypsin and trypsinogen; kg, kilograms; L, liters; LUM, lumacaftor; m, meters; Max, maximum; mg, milligrams; Min, minimum; mmol, millimoles; n, number of subjects with a baseline value for the respective clinical characteristic; N, number of subjects in the Full Analysis Set; SD, standard deviation

Treatment Compliance

Study drug compliance was calculated as follows:

100 x (1 – [total number of days of study drug interruption in the treatment-emergent period] / [duration of study drug exposure])

The treatment-emergent (TE) period started on or after the first dose of study drug in Study 124 to 18 days (inclusive) after the last dose date of study drug in Study 124 or up to the last day in Study 124, whichever occurred first. The total number of days of study drug interruption was defined as the sum of the number of days of each study drug interruption in the TE period, where the number of days of each study drug interruption was defined as the interruption end date – the corresponding interruption start date + 1.

In general, treatment compliance was high. The mean study drug compliance was 99.87%, and all subjects were ≥ 80% compliant.

Concomitant Medications

The most commonly reported concomitant medications were paracetamol (44.2%), amoxicillin/clavulanate potassium (38.5%), salbutamol (34.6%), and sodium chloride (30.8%), ibuprofen (26.9%), influenza vaccine (26.9%), sulfamethoxazole/trimethoprim (23.1%), tobramycin (23.1%), cefdinir (21.2%), macrogol 3350 (21.2%), cefalexin (19.2%), pancreatin (19.2%), amoxicillin (17.3%), multivitamin (17.3%), dornase alfa (15.4%), pancrelipase (15.4%), prednisolone (15.4%) . These medications are typically used for CF management in younger age groups.

Efficacy Results – Primary Endpoint

This was a long-term, open-label safety study; the primary endpoint evaluated safety, not efficacy. The safety findings are discussed in Section 8.2.

Efficacy Results – Secondary and Other Relevant Endpoints

Other relevant endpoints included the absolute change from baseline to Week 96 in SwCl (secondary) and the absolute change from baseline to Week 96 in BMI, weight, and FE-1, serum IRT, and fecal calprotectin levels (exploratory). Mean increases in sweat chloride (-21 mmol/L), BMI (-0.65 kg/m^2), and weight (4.1 kg) from baseline were observed at Week 96 (see Table 5).

Table 5: Change from Baseline to Week 96 in Sweat Chloride, BMI, and Weight (Full Analysis Set, Study 124)

Parameter Statistic	LUM/IVA N=52
Sweat Chloride (mmol/L)	

Parameter Statistic	LUM/IVA N=52
n (%)	22 (42.3)
Mean (SD)	-21 (14.9)
95% CI	-27.6, -14.3
Median (Min, Max)	-23.3 (-47.5, 14)
BMI (kg/m^2)	
n (%)	31 (59.6)
Mean (SD)	-0.65 (1.05)
95% CI	-1.04, -0.27
Median (Min, Max)	-0.66 (-2.19, 1.77)
Weight (kg)	
n (%)	32 (61.5)
Mean (SD)	4.1 (0.9)
95% CI	3.8, 4.4
Median (Min, Max)	4.1 (2.6, 6.7)

Source: Statistical reviewer; Clinical Study Report (dated December 14, 2023), Table 11-1 (p. 27-28) and Table 11-2 (p. 30-31)
Abbreviations: BMI, body mass index; CI, confidence interval; IVA, ivacaftor; kg, kilograms; L, liters; LUM, lumacaftor; m, meters; Max, maximum; Min, minimum; mmol, millimoles; n, size of subsample; N, number of subjects in the Full Analysis Set; SD, standard deviation

While the assessment is limited without a comparator arm, compared to CDC growth charts for healthy children (average weight gain is 2.27 kg per 1 year and average length increases is 10-12 cm per year), there did not appear to be detrimental effects on growth. See Table 10 in Section 8.2.9 for more information.

The Applicant reported change from baseline in fecal elastase and immunoreactive trypsinogen (IRT). The mean absolute change in FE-1 from baseline at Week 96 was 102.0. The mean absolute change in serum IRT from baseline at Week 96 was -255.4 (SD 268.2) µg/L. While there were changes in these values, the clinical relevance of these changes is unknown.

Data Quality and Integrity

This NDA was submitted on June 21, 2024. The application was appropriately indexed and complete to allow for review.

Durability of Response

The absolute changes of sweat chloride, a pharmacodynamic endpoint, from baseline were noted at the end of the treatment period (Week 96). These changes were also observed at earlier weeks, suggesting that the drug response was durable while on the drug.

8.1.3. Assessment of Efficacy Across Trials

Study 124 was not designed for efficacy. Therefore, this section is not applicable.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical safety review is based on clinical data from Study 124, which was a 96-week open-label rollover study from the previous Study 122 reviewed under NDA 211358 S004.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database includes a total of 52 subjects who were exposed to LUM/IVA granules in Study 124:

- 1 patient between 7 and < 9 kg was administered LUV 75 mg/IVA 94 mg every 12 hours
- 49 subjects who weighed between 9 and <14 kg were administered LUM 100 mg/IVA 125 mg every 12 hours
- 2 subjects who weighed between 14 kg and greater were administered LUM 150 mg/IVA 188 mg every 12 hours

The majority of subjects were exposed to LUM/IVA granules for 72 to 96 weeks. The extent of exposure in Study 124 is summarized in Table 6.

Table 6: Summary of Exposure, Safety Set

	Total N = 52
Total exposure (PY)	92.4
Exposure duration (days)	
N	52
Mean (SD)	597.2 (162.0)
SE	22.5
Median	668.0
Min, max	89, 699
Exposure duration by interval (weeks), n (%)	
> 0 to ≤ 8	0
>8 to ≤ 24	3 (5.8)
>24 to ≤ 48	3 (5.8)
>48 to ≤ 72	3 (5.8)
>72 to ≤ 96	27 (51.9)
>96	16 (30.8)

Source: Study 124; Clinical Study Report Table 12-1.

N: total sample size; n: size of subsample; PY: patient-year; SD: Standard Deviation
Notes: Duration of study drug exposure (days) = last dose date of Study 124 - first dose date of Study 124 + 1 day, regardless of any dose interruptions. One PY was defined as 1 subject with 48 weeks of treatment.

Adequacy of the safety database:

Study 124 included a 96-week treatment period where safety was assessed. The safety database was adequate in the context of the overall program and for the purposes of this review.

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 subject during the study that does not necessarily have a causal relationship with the treatment. This included any newly occurring event or worsening of a pre-existing condition after the informed consent form was signed. Any abnormal laboratory tests, ECGs, PEs, or vital signs that were deemed to have clinically significant worsening from baseline was considered an AE. Adverse events were classified using MeDRA Version 26.0.

The treatment emergent period started on or after the first dose date of study drug in Study 124 to 18 days (inclusive) after the last dose date of study drug in Study 124 or up to the last day in Study 124, whichever occurred first.

The Applicant graded AE severity using the FDA Guidance for Industry, *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (September 2007).

Routine Clinical Tests

Routine clinical tests included AEs, clinical laboratory measurements, standard 12-lead ECGs, Vital Signs, physical examinations, pulse oximetry, and ophthalmology examinations.

8.2.4. Safety Results

Deaths

There were no deaths in Study 124.

Serious Adverse Events

A total of 12 (23.1%) subjects experienced a serious adverse events (SAE) in this 96-week open-label study. In general, the SAEs reported were what would be expected in a CF population in a long-term safety study and did not reveal new safety concerns. These events are summarized in Table 7.

Table 7: Study 124 Subjects Experiencing Serious Adverse Events (SAEs)

Serious Adverse Event	Total N = 52
System Organ Class Preferred Term	n (%)
Subjects with any serious TEAEs	12 (23.1)
Infections and infestations	8 (15.4)
Infective pulmonary exacerbation of cystic fibrosis	6 (11.5)
COVID-19	1 (1.9)
Cellulitis orbital	1 (1.9)
Lower respiratory tract infection viral	1 (1.9)
Oral herpes	1 (1.9)
Parainfluenzae virus infection	1 (1.9)
Sinusitis	1 (1.9)
Gastrointestinal disorders	3 (5.8)
Constipation	2 (3.8)
Distal intestinal obstruction syndrome	1 (1.9)
Injury, poisoning and procedural complications	2 (3.8)
Near drowning	1 (1.9)
Procedural pain	1 (1.9)
Immune system disorders	1 (1.9)
Anaphylactic reaction	1 (1.9)
Skin and subcutaneous tissue disorders	1 (1.9)
Atopic Dermatitis	1 (1.9)

Source: Table 14.3.2.3 Sponsor Table CSR

Dropouts and/or Discontinuations Due to Adverse Effects

One subject discontinued study drug due to AEs of increases in ALT and AST.

In addition, there were 6 patients (11.5%) who interrupted study drug due to AEs (3 patients due to ALT increases, 2 patients due to AST increases, 1 patient due to *Ecoli* gastroenteritis, 1 patient due to lower respiratory tract infection, 1 patient due to oral herpes, and 1 patient due to dermatitis atopic).

Significant Adverse Events

In Study 124, a total of 6 patients had Grade 3/4 TEAEs that were not considered related to study drug. One subject had a life threatening (Grade 4) AE of near drowning. There were 5 patients who experienced severe (Grade 3) AEs. The severe TEAEs included constipation, distal intestinal obstruction syndrome, COVID-19, infective pulmonary exacerbation of cystic fibrosis, lower viral respiratory tract infection, oral herpes, ALT increases, and AST increases.

Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events occurring in at least 5% of patients are summarized in Table 8. Differences noted in this TEAE analysis compared to the Applicant's data were related to the grouping of similar preferred terms (e.g., cough and productive cough, COVID-19 and SARS-COV-2). The TEAEs reported were generally consistent the known safety profile of LUM/IVA, with common manifestations of CF disease, or common illnesses in this age population. No new safety signals were identified.

Table 8: AEs Occurring in at least 5% of Subjects by Preferred Term, Trial 124

Adverse Event by Preferred Term	N=52 (n, %)
Cough[a]	28 (53.8%)
Infective pulmonary exacerbation of cystic fibrosis	17 (32.7%)
COVID-19[b]	18 (34.6%)
Upper respiratory tract infection	15 (28.8%)
Rhinorrhoea	15 (28.8%)
Pyrexia	14 (26.9%)
Constipation	14 (26.9%)
Vomiting	13 (25%)
Ear Infection	11 (21.2%)
Rash	9 (17.3%)
Alanine aminotransferase increased	9 (17.3%)
Nasal Congestion	8 (15.4%)
Otitis Media	8 (15.4%)
Pseudomonas test positive	8 (15.4%)
Aspartate aminotransferase increased	7 (13.5%)
Diarrhoea	7 (13.5%)
Respiratory syncytial virus test positive	5 (9.6%)
Abdominal pain/discomfort[c]	5 (9.6%)
Sinusitis	4 (7.7%)
Conjunctivitis	4 (7.7%)
Bronchitis	4 (7.7%)

Blood creatinine phosphokinase increased	3 (5.8%)
Skin laceration	3 (5.8%)
Viral upper respiratory infection	3 (5.8%)
Urinary tract infection	3 (5.8%)
Nasopharyngitis	3 (5.8%)
Molluscum contagiosum	3 (5.8%)

[a]Cough includes preferred terms (PT) cough and productive cough
[b]COVID-19 includes preferred terms (PT) COVID-19, SARS-CoV-2 test positive, SARS-CoV2 antibody test positive
[c]Abdominal pain/discomfort includes preferred terms (PT) abdominal discomfort, abdominal pain, and abdominal pain upper.
Note: AEs were coded using MedDRA 26.0. A subject with multiple events within a category was counted only once in that category. Sponsor uses the term "dictionary-derived term" for preferred terms.
Source: Clinical Reviewer calculated using JMP 17.0 analysis datasets ADAE selecting Safety Population Flag and Treatment Emergent Analysis Flag by Unique Subject Identifier.
Abbreviations: COVID-19, coronarvirus disease of 2019, SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Laboratory Findings

Routine clinical testing for this safety study included evaluations of hematology and serum chemistries, including liver transaminases. Excluding transaminases, no laboratory abnormalities resulted in treatment interruptions or discontinuations. See Section 8.2.5 for a more detailed evaluation of liver transaminases.

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 clinically relevant QT changes from baseline were noted.

Immunogenicity

Not Applicable

8.2.5. Analysis of Submission-Specific Safety Issues

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

Hepatic Safety

Given the known incidences of transaminase increases for Orkambi, the Applicant assessed clinical lab data and adverse events for transaminase abnormalities in this study.

In this study, nine patients (17.3%) had ALT or AST > 3 times the upper limit of normal (ULN). Five patients (9.6%) had ALT or AST > 5xULN. Three (5.8%) patients had ALT or AST > 8xULN. No patients had total bilirubin > 2xULN. See Table 9.

Table 9: Threshold Analysis of Laboratory Tests for Hepatic Safety, n/N1 (%)

Parameter	**Total N=52**
ALT	**n(%)**
≤3 × ULN	43 (83%)
>3xULN to ≤5 × ULN	4 (8%)
>5xULN to ≤8 × ULN	2 (4%)
>8xULN	3 (6%)
AST	
≤3xULN	48 (92%)
>3xULN to ≤5xULN	2 (4%)
>5xULN to ≤8xULN	1 (2%)
>8xULN	1(2%)
ALT or AST	
ALT >3 × ULN or AST >3 × ULN	9 (17.3%)
ALT >5 × ULN or AST >5 × ULN	5 (9.6%)
ALT >8 × ULN or AST >8 × ULN	3 (5.8%)
ALP	
>1.5 × ULN	2 (4%)
Total Bilirubin	
>1.5 × to ≤2 × ULN	0 (0%)
>2 × ULN	0 (0%)

Source: Reviewer calculated using ADLB in JMP 17 selecting SAFFL(Y), by USUBJID, MCRIT1ML, PARAM, AVAL.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate transferase; ULN, upper limit of normal.

As previously noted in section 8.2.4, there were 5 patients (11.5%) who interrupted study drug due to AEs (3 patients due to ALT increases; 2 patients due to AST increases).

It is worth noting that one patient who interrupted study drug due to elevations in AST/ALT was later permanently discontinued due to granulomatous liver disease and portal fibrosis which were mild in severity. This 23-month old patient had a complex medical history which included CF gastrointestinal disease, CF lung disease, failure to thrive, hypovitaminosis, intestinal operation, and meconium ileus. He was also reported to have had a history LFT elevations prior to initiation of Orkambi. Given this patient's complex medical history and also considering that the event that lead to permanent discontinuation occurred 123 days after last treatment with drug, casuality to drug cannot be definitively assessed.

Overall, these findings are consistent with the known liver safety profile of Orkambi.

Respiratory Safety

Three patients had AESIs of respiratory events and/or symptoms (mild in severity). 1 subject experienced dyspnea and 2 experienced wheezing. None of these events/symptoms led to treatment interruption or discontinuation.

Ophthalmological

Risk of cataracts is currently included in Section 5.7 of the Orkambi PI. This trial included ophthalmologic examinations at screening and approximately 24 weeks after the last dose of LUM/IVA. There were no patients who 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 size of this study, additional safety analyses by demographic subgroup were not performed.

8.2.8. Specific Safety Studies/Clinical Trials

Study 124 was an open label long term safety study and is the only study (discussed above).

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Human carcinogenicity studies have been performed in this study.

Human Reproduction and Pregnancy

The use of LUM/IVA during pregnancy and lactation has not be evaluated in this study.

Pediatrics and Assessment of Effects on Growth

This trial included pediatric patients of 1 to less than 2 years old. Height, weight, and BMI were included as exploratory endpoints (discussed in Section 8.1.1). The mean change (and standard

deviation) at 96 weeks from baseline were as follows in Table 10:

Table 10: Effects on Growth. Study 124	
Growth Parameter	Mean Change at Week 96 (SD)
BMI	-0.65 (1.05)
BMI-for-age z score	- 0.19 (0.79)
Weight (kg)	4.1 (0.9)
Weight-for-age z-score	-0.06 (0.52)
Length (cm)	15.6 (1.9)
Length-for-age z-score	0.14 (0.54)

While the assessment is limited without a comparator arm, compared to CDC growth charts for healthy children (average weight gain is 2.27 kg per 1 year and average length increases is 10-12 cm per year), 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 12 submitted on July 26, 2024, the estimated post-marketing exposure to Orkambi is 25,763 subjects, representing 48,139.4 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. At the time of this review, there are currently 3 ongoing NISS evaluations for psychiatric disorders, intracranial disorders, and drug induced liver injury (NISS 1005257, NISS 1005337, NISS1005364).

Expectations on Safety in the Postmarket Setting

The patient population (1 to < 2 years of age) included in Study 124 is already indicated for LUM/IVA since September 21, 2022. Therefore, no substantial differences in post marketing experience 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 124, which included 52 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, as only descriptive statistics were used in this study.

8.4. Conclusions and Recommendations

The recommended regulatory action is Approval. In these current supplements (NDA 206038 S018 and NDA 211358 S006), the Applicant has submitted the results of the final pediatric study (Study 3 of 3) and proposes the fulfillment of the Pediatric Written Request as well as pediatric exclusivity for the conducted pediatric studies. Studies 1 and 2 were previously completed and submitted as part of previous sNDA submissions. The results of Study 1 were submitted as part of the original NDA 211358 submission for the granule formulation which was approved on August 7, 2018. The results of Study 2 were submitted as a supplemental NDA (NDA 211358 S004) and approved on September 2, 2022, expanding the indication to include patients 12 to < 24 months of age. All 3 pediatric studies have met the criteria detailed in the PWR. Therefore, the PWR has been fulfilled. The Applicant has proposed labeling changes to include the open label rollover study in the prescribing information. The proposed regulatory action is Approval.

9 Advisory Committee Meeting and Other External Consultations

Not Applicable

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. However, 3 studies were conducted under a Pediatric Written Request, which is considered to be fulfilled with the submission of this third and last study.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant proposed revisions to add results from Study 124 to [redacted] (b) (4) 8.4.

DPACC recommended the addition of the following language related to Study 124 for Section 8.4 only:

- Safety was evaluated from a 96-week open-label clinical trial (Trial 8) in 52 patients (39 rolled over from Trial 7 and 13 ORKAMBI naïve) aged 1 to 2 years. Adverse reactions from Trial 8 were generally similar to those reported in Trial 7.

While the Division typically would not include in the label data from such an open-label rollover study, as the product is already approved for chronic use in the 1 to less than 2 year old population and as the study did not identify new safety concerns, data from this study will be included in section 8.4 of the label given that the results from this study were part of a PWR.

Additional edits to Section 8.1 regarding embryo-fetal toxicity was recommended by DPACC to conform to labeling practices per 21CFR201.57(c)(9)(i)(D)(4) as well as PLLR guidance.

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 Deputy Director (designated signatory authority) Comments

Vertex Pharmaceuticals has submitted the results of the final study (Study 124) as outlined in a Pediatric Written Request for lumacaftor/ivacaftor (LUM/IVA). The results of this study are submitted as supplemental NDAs to both the granules and tablet formulations (NDA 206038/S-018 and NDA 211358/S-006). With the completion of this study, the Applicant proposes fulfillment of the PWR and requests pediatric exclusivity.

Study 124 was a phase 3, open-label, rollover study that evaluated the long-term safety and tolerability of LUM/IVA treatment in pediatric patients aged 1 to < 2 years with cystic fibrosis who are homozygous for the F508del mutation in the CFTR gene. This study was a rollover of

the previous study (Study 122) which was an open-label, 24-week, PK and safety study. Thirty nine patients were rolled over from Study 122 and 13 patients were Orkambi-naïve patients. Overall, no new safety signals were identified and the safety profile in this age group was consistent with what has been previously noted with Orkambi.

Study 124 is the third of three studies conducted under the pediatric written request (PWR). With submission of the results of this study, the PWR is fulfilled. There are no outstanding issues from any review disciplines. I concur with the content of the various discipline assessments and the recommendation of approval. The Agency and the Applicant have also agreed upon the final labeling language. The action for this application will be **Approval.**

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ROBERT H LIM
12/12/2024 08:33:32 AM