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APPLICATION NUMBER:

217660Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review

Clinical Review

Non-Clinical Review

Statistical Review

Clinical Pharmacology Review

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	217660
Priority or Standard	Priority
Submit Date(s)	October 28, 2022
Received Date(s)	October 28, 2022
PDUFA Goal Date	April 28, 2023
Division/Office	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Review Completion Date	April 20, 2023
Established/Proper Name	Elexacaftor (ELX)/Tezacaftor (TEZ)/Ivacaftor (IVA)
(Proposed) Trade Name	Trikafta
Pharmacologic Class	CFTR Modulator
Code name	VX-445/VX-661/VX-770
Applicant	Vertex Pharmaceuticals Incorporated
Dosage form	Oral Granules
Applicant proposed Dosing Regimen	<14 kg: ELX 80mg/TEZ 40mg/IVA 60 mg qAM and IVA 59.5mg qPM ≥14 kg: ELX 100mg/TEZ 50mg/IVA 75mg qAM and IVA 75mg qPM
Applicant Proposed Indication(s)/Population(s)	Treatment of cystic fibrosis (CF) in patients 2 to less than 6 years of age who have at least one <i>F508del</i> mutation or a CFTR mutation that is responsive based on in vitro data
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)	Treatment of cystic fibrosis (CF) in patients 2 to less than 6 years of age who have at least one <i>F508del</i> mutation or a CFTR mutation that is responsive based on in vitro data
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	190905008 Cystic fibrosis (disorder)
Recommended Dosing Regimen	<14 kg: ELX 80mg/TEZ 40mg/IVA 60 mg qAM and IVA 59.5mg qPM ≥14 kg: ELX 100mg/TEZ 50mg/IVA 75mg qAM and IVA 75mg qPM

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OPQ=Office of Pharmaceutical Quality

OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations

OSE= Office of Surveillance and Epidemiology

DEPI= Division of Epidemiology

DMEPA=Division of Medication Error Prevention and Analysis

DRISK=Division of Risk Management

Signatures

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	Signature:			

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

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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 NDA submission (NDA 217660) is for the proposed product, Trikafta granules, which is a new formulation of the fixed dose combination of elexacaftor, tezacaftor, and ivacaftor (ELX/TEZ/IVA). The chemical name for elexacaftor (ELX) is N-(1,3-dimethyl-1H-pyrazole-4-sulfonyl)-6-[3-(3,3,3-trifluoro-2,2-dimethylpropoxy)-1H-pyrazol-1-yl]-2-[(4S)-2,2,4-trimethylpyrrolidin-1-yl]pyridine-3-carboxamide. The chemical name for tezacaftor (TEZ) is 1-[2,2-difluoro-2H-1,3-benzodioxol-5-yl]-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-[1-hydroxy-2-methylpropan-2-yl]-1H-indol-5-yl}cyclopropane-1-carboxamide. Both ELX and TEZ are orally bioavailable small molecules 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-Ditert-butyl-5-hydroxyphenyl)-1,4-dihydro-4-oxoquinoline-3-carboxamide. IVA is an orally bioavailable small molecule that is a potentiator of the CFTR chloride channel present on the epithelial cell membrane. IVA facilitates increased chloride transport by potentiating the channel-open probability of CFTR.

ELX/TEZ/IVA tablets (NDA 212273, Trikafta tablets) were approved on October 21, 2019 for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who have at least one deletion of phenylalanine 508 mutation (*F508del*) in the CFTR gene. The indication was expanded on December 5, 2020 to also include treatment of CF in patients aged 12 years and older with 177 additional CFTR mutations based on *in vitro* assay data, and on June 8, 2021 to include CF patients 6 to 11 years of age. There is currently no approved granule formulation for ELX/TEZ/IVA.

This submission, NDA 217660, proposes a new granule formulation for the ELX/TEZ/IVA fixed-dose combination product and to expand the indication to include cystic fibrosis (CF) in patients 2 to <6 years with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data. The proposed dose for patients ≥ 14 kg is ELX 100mg/TEZ 50mg/IVA 75mg in the morning and IVA 75mg in the evening; for patients <14kg the dose is ELX 80mg/TEZ 40mg/IVA 60mg in the morning and IVA 59.5 mg in the evening. The granule formulation is more age appropriate for this new younger age group.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The recommended regulatory action is Approval for orally administered Elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) (Trikafta) granules for the treatment of cystic fibrosis patients ages 2 to <6 years of age with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data. This recommendation is based on the extrapolation of efficacy from existing data in the adolescent and adult population, supportive pharmacodynamic data in the 2 to <6 year old age group, and a review of safety in the 2 to <6

year old population. Extrapolation of efficacy from the adolescent and adult population is appropriate for this age group for this medication given comparable systemic exposures compared to the adolescent and adult populations and because the disease process is the same between populations.

Elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) tablets are approved (NDA 212273) for the treatment of CF patients aged 6 years and older with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data. In this NDA, the Applicant submitted data from a pharmacokinetic (PK) and safety study (VX20-445-111, Trial 111) to support the use of ELX/TEZ/IVA granules in patients 2 to <6 years of age with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data.

Trial 111 was a two-part, non-randomized, uncontrolled, open-label PK (Part A, 15-day duration, n=18) and safety (Part B, 24-week duration, n=75) study in patients 2 to <6 years of age. Results demonstrated that when this product was given to patients <14kg at a dose of ELX 80 mg/ TEZ 40 mg/IVA 60 mg qAM and IVA 59.5 mg qPM and to patients ≥ 14 kg at a dose of ELX 100 mg/TEZ 50 mg/IVA 75mg qAM and IVA 75 mg qPM , systemic exposures were comparable to those observed in the adolescent and adult population at the approved dose. Because of the comparable systemic exposures and because the disease process in the adolescent and adult population is the same as in the 2 to <6 year old population, efficacy in the proposed age group can be extrapolated from the adolescent and adult population where efficacy has been previously demonstrated in placebo-controlled clinical trials.

Additionally, Week 24 data from Trial 111 Part B demonstrated within group improvements in the pharmacodynamic parameter of sweat chloride, suggesting a clinically meaningful response to the ELX/TEX/IVA treatment. Trial 111 did not reveal any new safety signals other than those identified in the adolescent, adult, and 6 to 11 year old clinical development programs. The benefit-risk assessment in this population is favorable. The recommended action is Approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Elexacaftor (ELX)/Tezacaftor (TEZ)/Ivacaftor (IVA) tablets, tradename Trikafta (NDA 212273), are approved for the treatment of CF in patients ≥ 6 years of age who have at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data. In this NDA (217660), the Applicant submitted data from a PK/safety study (Trial VX20-445-111) to support the use of ELX/TEZ/IVA granules in patients 2 to <6 years of age at a dose of ELX 80 mg/TEZ 40 mg/IVA 60 mg qAM and 59.5 mg qPM for patients <14 kg and an ELX/TEZ/IVA dosage of 100 mg/TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM for patients ≥ 14 kg. The recommended regulatory action is Approval of ELX/TEZ/IVA granules for the treatment of CF in patients ≥ 2 years of age who have at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data.

CF results from mutations in the CFTR gene which leads to a decreased amount or abnormal function of the CFTR protein. The most common CFTR mutation is *F508del*. In the United States, approximately 85% of patients carry at least one *F508del* allele and approximately 45% of patients are homozygous for the *F508del* mutation. Currently, in addition to the treatments of the symptoms and sequelae of the disease, ELX/TEZ/IVA is the only drug that is currently FDA-approved for targeting the underlying cause of CF in patients who are heterozygous for the *F508del* allele.

Trial 111 was a two-part, non-randomized, uncontrolled, open-label PK (Part A, 15-day duration, $n=18$) and safety (Part B, 24-week duration, $n=75$) study in CF patients 2 to <6 years of age. Results demonstrated that when an ELX/TEZ/IVA dosage of 80 mg/TEZ 40 mg/IVA 60 mg qAM and 59.5 mg qPM was administered to patients 10-14 kg and when an ELX/TEZ/IVA dosage of 100 mg/TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM was administered to patients ≥ 14 kg, systemic exposures were comparable to those observed in the adolescent and adult population at the approved dose. Because of the comparable systemic exposures and because the disease process in the adolescent and adult population is the same as in the 2 to <6 year old population, efficacy in the proposed age group can be extrapolated from the adolescent and adult population where efficacy has been previously demonstrated in placebo-controlled clinical trials. In addition, the within group improvements in sweat chloride through 24 weeks support a clinically meaningful response to the ELX/TEZ/IVA treatment and are consistent with that observed in previous ELX/TEZ/IVA clinical trials.

With regards to safety, in Part B of Trial 111, no deaths were reported and 2 subjects experienced serious adverse events (hospitalization for a CF pulmonary exacerbation and behavioral changes). The subject experiencing behavioral changes ultimately had to discontinue treatment. The three most common adverse events (AEs) were cough, fever, rhinorrhea, COVID and vomiting. Overall, the adverse events (AEs) were generally

consistent with the common manifestations of CF disease, common illnesses in the 2 to <6 years of age, and AEs previously identified in the ELX/TEZ/IVA development program. In the approved ELX/TEZ/IVA tablet product label, listed Warnings and Precautions include liver-related events, which were specifically evaluated in the safety analysis in Trial 111. Additional adverse events of special interest (AESI) identified in the clinical development program were creatine kinase (CK) elevation, cataracts, and rash events. Six subjects (8.0%) had maximum on-treatment liver transaminase (LFT) elevations of > 3x the upper limit of normal (ULN). None had concurrent elevations of total bilirubin greater than 2x ULN. One subject had transaminase elevations leading to study drug interruption in Trial 111 and during the ongoing Open Label Extension trial; one additional patient ultimately required study drug discontinuation due to transaminitis. Rash AEs occurred in 15 (20%) subjects. One subject (1.3%) was reported as having cataracts or lens opacity. Overall, the safety profile in the 2 to <6 year old age group was consistent with the older age groups and no new safety signals were identified in Trial 111.

Due to comparable systemic exposures between the proposed age group and the older populations and, as the disease process in adolescent and adult population is the same as in the 2 to <6 year old population, efficacy in the proposed age group can be extrapolated from the adolescent and adult population where efficacy has been previously demonstrated in placebo-controlled clinical trials. Efficacy was also supported by improvements in clinical outcomes such as sweat chloride following open-label treatment with ELX/TEZ/IVA. With regard to safety, no new safety signals were identified in Trial 111. The demonstration of an acceptable safety profile, along with the extrapolated efficacy and improvements in sweat chloride levels as a pharmacodynamic response to treatment, and the unmet need supports the recommendation of Approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	CF is a rare, progressive, life shortening autosomal recessive genetic condition that affects approximately 30,000 individuals in the United States. CF results from mutations in the CFTR gene that lead to decreased or dysfunctional CFTR protein. CFTR aids in the regulation of salt and water absorption and secretion throughout the body and the lack of properly functioning CFTR leads to the clinical sequelae of CF disease: malabsorption of nutrients, inability to mobilize tenacious respiratory secretions, recurrent pulmonary infections, irreversible lung damage, and ultimately, premature respiratory failure. The majority of these pathologic changes start at birth. The median age of survival for a patient with CF is in the mid-	CF is a rare, progressive, and usually fatal genetic disease. The pathologic changes start early in life. The CFTR mutations included in the proposed indication represents the majority of patients with CF in the United States.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	to-late 30's. The most common CFTR mutation is <i>F508del</i> – in the United States, approximately 85% of CF patients carry at least one allele and 45% are homozygous for this mutation.	
<u>Current Treatment Options</u>	- While no cure exists, there are currently two approved therapies (Kalydeco and Orkambi) aimed at modulating CFTR anion transport in CF patients aged 2 to <6 years. These available options are only approved for a subset of CFTR mutations. - There remains a significant unmet medical need for those patients in this age range who do not have available options for medications that modulate CFTR anion transport. ELX/TEZ/IVA is unique in that it both is active against a larger proportion of CFTR mutations than the currently available medications for this population (e.g., heterozygous <i>F508del</i>) and it is considered to have a greater treatment effect for certain subsets of CF patients who are eligible for currently available therapies (e.g., homozygous <i>F508del</i>) - The remainder of treatment options are aimed at managing the symptoms and sequelae of the underlying CF disease	There are two approved therapies for specific subpopulations of CF patients in this age range. However, there remains an unmet need for those patients in this age group not covered by currently approved therapies and for additional treatment options.
<u>Benefit</u>	- Based on the results from Trial 111, the Applicant demonstrated that when ELX/TEZ/IVA was administered to CF patients aged 2 to <6 years of age who have at least one copy of the <i>F508del</i> CFTR mutation or a CFTR mutation that is responsive based on <i>in vitro</i> data, systemic exposures were comparable to that observed in the adolescent and adult populations. - Improvements in the pharmacodynamic endpoint of sweat chloride levels were also observed in study patients and comparable to changes seen in the adolescent and adult populations.	ELX/TEZ/IVA provides a clinically relevant treatment benefit for CF patients aged 2 to <6 years with at least one copy of the <i>F508del</i> CFTR mutation based on extrapolation of efficacy from the adolescent/adult population. Efficacy can be extrapolated as the disease process in this age group is similar to the older age group, efficacy has been previously demonstrated in the older age group, and systemic exposures are comparable between these age groups. Additionally, a decrease in

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
		sweat chloride level from baseline after ELX/TEZ/IVA treatment provides supportive evidence of efficacy response.
Risk and Risk Management	The AEs observed in this study were consistent with common manifestations of CF disease or common illnesses in patients 2 to <6 years of age. No deaths were reported. Two SAEs were reported. Specific safety analyses were performed which included analyses for LFT elevation, rash, CK elevation, behavioral changes, and drug-drug interaction. Findings of these analyses were generally consistent with the approved tablet formulation. No REMS is proposed at this time	No new safety signals were identified in Trial 111. The potential risks of LFT elevation, rash, CK elevation, behavioral changes and drug-drug interactions can be managed through labeling and routine pharmacovigilance. A REMS is not required at this time. No new safety signals were identified in the clinical development program that outweigh the potential benefit.

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):	
☒	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 disease, affecting approximately 30,000 people in the U.S. and about 70,000 people worldwide (CF Foundation 2021 Annual Report). CF is caused by mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein, an anion channel in the apical cellular membrane. In the lungs, alterations in anion and fluid transport result in the accumulation of thick, tenacious mucus leading to a chronic cycle of inflammation, obstruction, and infection that ultimately progresses to premature respiratory failure. Patients with CF also experience significant extrapulmonary manifestations, including malabsorption, chronic sinus disease, poor bone health, liver dysfunction, and diabetes. Although recent scientific advances have significantly improved the overall health of patients born with CF, the median life expectancy CF remains only in the mid-40s (CF Foundation 2021 Annual Report).

There are over 400 mutations in the CFTR gene that are associated with CF disease causation although over 2,000 mutations have been identified (CFTR2 Database). The most prevalent CF-causing mutation is *F508del*, with approximately 85% of people with CF in the U.S. carrying at least one copy of the *F508del* mutation and 44% of individuals are *F508del* homozygous (CF Foundation 2021 Annual Report). The *F508del* mutation results in improper protein folding and degradation, leading to both less CFTR protein at the cell surface and decreased protein function.

While disease severity and presentation vary between individuals, the early stages of pulmonary dysfunction CF are noted not long after birth with elevations in the lung clearance index, a marker of ventilation heterogeneity, and hyperinflation noted as early as 3 months (Ho, et al. 2012). As children with CF age, pulmonary function and structure decline progressively even during the preschool years (Kerby et al. 2011; VanDevanter et al. 2015). Generally, children with CF who are formally diagnosed earlier in life and are able to initiate CF directed care have improved pulmonary function and overall survival compared to those who were diagnosis is delayed, which supports that earlier intervention helps modify overall disease progression in these patients (Lai et al. 2005).

2.2. Analysis of Current Treatment Options

Ivacaftor (IVA, Trade name: Kalydeco), the first medication to target the underlying defect in CFTR function, was initially approved in 2012. Ivacaftor and other similar medications (i.e., ivacaftor, tezacaftor/ivacaftor, lumacaftor/ivacaftor, elexacaftor/tezacaftor/ivacaftor) that have been subsequently approved, have provided significant clinical benefits to many patients with CF (Volkova et al. 2019).

The remainder of the medications used to treat and manage patients with CF include drugs that

aim to relieve the symptoms and sequelae of the disease. This includes some medications approved for other diseases processes. Table 1 summarizes the current treatments available for patients with CF although not all therapies are approved for specifically for 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 4 months and older who have one of 97 specified CFTR mutations (not including <i>F508del</i>)
Lumacaftor/ivacaftor (LUM/IVA)	Orkambi Tablets and Granules	Yes; patients with CF aged 1 year and older who are homozygous for <i>F508del</i> 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 <i>F508del</i>)
Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA)	Trikafta Tablets	Yes; patients with CF aged 6 years and older who have at least one copy for <i>F508del</i> or at least one copy of 177 specified mutations
Inhaled antibiotics for the treatment of <i>Pseudomonas aeruginosa</i>		
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 December 23, 2022)

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; ELX, elexacaftor; IV, intravenous; IVA, ivacaftor; LUM, lumacaftor; TEZ, tezacaftor

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

ELX/TEZ/IVA fixed dose combination tablets were initially approved on October 21, 2019 for the treatment of CF in individuals ≥ 12 years of age with at least one *F508del* mutation in the CFTR gene (NDA 212273). On December 21, 2020, the Agency approved a supplement expanding the indication to include CF patients who have a mutation in the CFTR gene that is responsive to ELX/TEZ/IVA based on *in vitro* data. The indication for the tablet formulation was further expanded to include CF patients 6-11 years on June 8, 2021.

This application, NDA 217660, proposes a new granule formulation of ELX/TEZ/IVA fixed dose combination for the treatment of CF in individuals aged 2 to <6 years old with at least one *F508del* CFTR mutation or a CFTR mutation that is responsive to ELX/TEZ/IVA based on *in vitro* data.

3.2. Summary of Presubmission/Submission Regulatory Activity

Prior to submission of this NDA, ELX/TEZ/IVA has been the subject of multiple regulatory proceedings. ELX and the ELX/TEZ/IVA combination were initially developed under IND 132547). As noted above, the ELX/TEZ/IVA tablets were initially approved on 10/21/2019. The following is a summary of key regulatory history during the product's development.

- Fast Track Designation (2/8/2017)
- Breakthrough Therapy Designation (5/15/2018)
- Orphan Drug Designation, ODD 18-6476 (8/29/2018)

The initial Pediatric Study Plan (iPSP) for use of ELX/TEZ/IVA in the pediatric CF population was submitted on June 25, 2020. In the agreed iPSP, to support safety and efficacy in the population aged 2 to <6 years of age, the Applicant proposed Trial VX20-445-111 (Trial 111) for the evaluation of PK and safety and Trial VX20-445-112 (Trial 112) as the long-term safety open-label extension.

At the time of approval of ELX/TEZ/IVA tablets (NDA 212273), the Applicant was issued a Postmarketing Requirement (PMR 3718-1) to conduct a carcinogenicity study in rats. This was submitted on 7/22/2021 and the nonclinical review was completed on 7/21/2022. Following review, the Applicant was instructed by the Division to submit a labeling supplement which incorporates this data (see letter dated 8/1/2022). To satisfy this request, the Applicant incorporated these data into the NDA 217660 submission. Simultaneous to submission of NDA 217660, the Applicant also submitted supplemental NDA 212273/S-009 for the tablet formulation to harmonize the tablet and granule labels.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical

Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

An Office of Study Integrity and Surveillance (OSIS) inspection was not conducted. However, the relevant sites had relatively recent OSIS inspections as listed:

- [REDACTED] (b) (4) – OSIS concluded that data from the reviewed studies were reliable.
- [REDACTED] (b) (4) – Initial report with failure to report several failed runs in the method validation and analytical study reports and failure to use objective criteria established in an SOP to determine failed runs. After review of inspection findings, OSIS concluded that the data from the reviewed studies were reliable.

4.2. Product Quality

Chemistry, Manufacturing and Control information was submitted with this NDA to support the ELX/TEZ/IVA granule formulation. Based on the review of these materials, the CMC team recommends Approval. See separate CMC Integrated Quality Assessment for additional information.

4.3. Clinical Microbiology

None

4.4. Devices and Companion Diagnostic Issues

None

5 Nonclinical Pharmacology/Toxicology

Executive Summary

Vertex submitted NDA 217660 for a new granule formulation of Trikafta (elexacaftor/tezacaftor/ivacaftor) and to extend the indication to cystic fibrosis (CF) patients 2 to <6 years of age. No new nonclinical studies were submitted. Nonclinical pharmacology and toxicology studies conducted with Trikafta were previously reviewed under NDA 212273. The Applicant submitted nonclinical-related labeling changes for section 8.4 Pediatric Use and section 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility. The Applicant fulfilled a PMR under NDA 212273 to conduct a 2-year carcinogenicity study with elexacaftor in rats. The 2-year carcinogenicity study with rats was reviewed under NDA 212273.

Juvenile rat studies can assess potential toxicity that might be relevant to pediatric patients (e.g., treatment starting on postnatal day (PND) 7 corresponds to an infant at birth and on PND 21 corresponds to a 2- to 3-year old child). Pediatric patients represent a population different from adults when considering the rapid growth and postnatal development of several organ systems. Lung development in the juvenile rat parallels lung development over the first 1 to 2 years of life for a child (e.g., increased alveolization and surface area that occur in both species).

Juvenile animal studies with ivacaftor were previously reviewed under NDA 203188 and NDA 207925 Kalydeco (ivacaftor) and NDA 212273 Trikafta tablets (ELX/TEZ/IVA). Cataracts were seen in juvenile rats dosed with ivacaftor from postnatal day 7-35 at dose levels of 10 mg/kg/day and higher. This finding has not been observed in older animals.

In a toxicology study with juvenile rats treated with elexacaftor (ELX) from PND 7 to PND 70, findings were limited to small increases of total bilirubin and ALT and CK activities without correlating histopathological findings.

Potential concerns of neuropsychiatric adverse events (AEs) with the CFTR modulators have been reported in the literature and AE reporting. CNS toxicity was evident in the juvenile rat toxicology studies with tezacaftor (TEZ). Tezacaftor toxicity was characterized in juvenile rats starting from PND 7, PND 14, or PND 21 and ending on PND 35, PND 42, or PND 49, respectively. The doses evaluated were 0, 10, 20, 30, 60, and/or 100 mg/kg/day. When administered starting at PND 7 (the equivalent of a human newborn) at doses of 10 to 100 mg/kg/day, multiple deaths/euthanasia, lower body weight gains, and adverse central nervous system (CNS) clinical signs including convulsions, hypoactivity, repetitive movement of the mouth, head tilt, small stature, and cool and/or thin body were observed at doses $\geq$ 30 mg/kg/day. The NOAEL was identified at 10 mg/kg/day. When administered starting at PND 21 (the equivalent of a human 2-3 years of age) at doses of 30 to 100 mg/kg/day, multiple deaths/euthanasia and convulsions occurred at doses of 100 mg/kg/day and lower body weight gains occurred at doses $\geq$ 60 mg/kg/day, which were considered adverse. The NOAEL was identified at 30 mg/kg/day. The effects on body weight and adverse CNS-related clinical signs in juvenile rats were dose-related and generally more severe when administration was initiated

earlier in the postnatal period. In the definitive GLP study, juvenile rats received oral doses of 0, 20, and 30 mg/kg/day TEZ from PND 14 to PND 42 or 0, 30, 30 (+10 mg/kg/day IVA), and 60 mg/kg/day TEZ from PND 21 to PND 49. No treatment-related deaths or adverse clinical signs were observed in animals administered up to 30 mg/kg/day TEZ. However, for PND 21-49, body weight gain for males at 60 mg/kg/day TEZ was reduced to 89.5% of the control. Body weight gain was unaffected for females at 60 mg/kg/day. No adverse findings were identified in juvenile rats administered with the combination of 30 mg/kg/day TEZ and 10 mg/kg/day IVA. The NOAELs of TEZ in juvenile rats were identified as 30 mg/kg/day (AUC_{0-24} : 107.8 h• μ g/mL) from PND 14-42 and 30 mg/kg/day (AUC_{0-24} : 106 h• μ g/mL) from PND 21-49. In juvenile rats from PND 14-42, the AUC_{0-24} of metabolites M1-661 and M2-661 were 47.4 h• μ g/mL and 4.35 h• μ g/mL, respectively. In juvenile rats from PND 21-35, the AUC_{0-24} of metabolites M1-661 and M2-661 were 51.6 h• μ g/mL and 3.87 h• μ g/mL, respectively.

Higher brain levels of TEZ and its two metabolites in younger rats dosed starting from PND 7-9 and PND 14-16 might explain the observed CNS toxicity (clonic convulsions and other CNS-related clinical observations) of TEZ. The increased brain levels of TEZ and its metabolite in the younger juvenile rats may be explained by the lower activity levels of the efflux transporter protein, P-glycoprotein (P-gp), in the brain of younger juvenile rats. TEZ and M1-661 are both substrates for P-gp. Toxicity observed in juvenile rats appeared to correlate to the developmental stage of the blood brain barrier (i.e., P-gp activity). The decreased activity of P-gp in younger juvenile pups would lead to higher brain levels of TEZ, M1-661, and M2-661. The blood-brain barrier (BBB) in rats in terms of P-gp activity is not fully developed until approximately PND 21 – PND 35, whereas in humans the BBB in terms of P-gp activity reaches adult levels at approximate 3-6 months of age as measured by P-gp activity and expression. In general, P-gp activity appears to only be a safety concern for children less than 1 year of age and is unlikely to be a concern for children 2 through <6 years of age.

The results of juvenile rat studies with tezacaftor raise concerns for potential neuropsychiatric AEs. It is unclear if variations in brain levels of p-glycoprotein might be involved in these potential neuropsychiatric AEs.

The application is recommended for approval from the nonclinical perspective.

Table 2: Convulsion for TEZ in juvenile rats and exposure ratios to children 2 to <6 years of age

Juvenile Rat Studies				Exposure Margins to Clinical Dose		Study Report Reference
	Dose (mg/kg/day)	Adverse clinical signs/convulsion	AUC (μ g•hr/mL)	Children 2-<6, <14 kg, 40 mg TEZ AUC: 281.3 μ g•hr/mL	Children 2-<6, >14 kg, 50 mg TEZ AUC: 287.2 μ g•hr/mL	
PNDs 7-35	10 (NOAEL)	No	57.5	0.20	0.20	VX-661-TX-037
	30	Yes	208.9	0.74	0.73	
	60	Yes	447.8	1.59	1.56	
	100	Yes	641.3	2.28	2.23	

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PNDs 21-35	30 (NOAEL)	No	141.7	0.50	0.49	VX-661-TX-069
	60	No	291.6	1.04	1.02	
	100	Yes	500	1.78	1.74	

^bClinical AUC Sources: Report S054/Tables 6-9 and 6-10, Report S055/Tables 6, 14, and 22;

Table 3: Safety Margin for ELX

Juvenile Rat Studies	NOAEL Dose (mg/kg/day)	AUC (µg*hr/mL)	Exposure Margins to Clinical Dose		Study Report Reference
			Children 2-<6, <14 kg, 80 mg AUC: 128 µg*hr/mL	Children 2-<6, >14 kg, 100 mg AUC: 138 µg*hr/mL	
PNDs 7-70	Male: 30 mg	694	5.42	5.03	VX-445-TX-021
	Female: 15 mg	976	7.63	7.07	

^bClinical AUC Sources: Report S054/Tables 6-9 and 6-10, Report S055/Tables 6, 14, and 22;

Table 4: Safety Margin for M23-ELX

Juvenile Rat Studies	NOAEL Dose (mg/kg/day)	AUC (µg*hr/mL)	Exposure Margins to Clinical Dose		Study Report Reference
			Children 2-<6, <14 kg, 80 mg ELX AUC: 56.5 µg*hr/mL	Children 2-<6, >14 kg, 100 mg ELX AUC: 59.0 µg*hr/mL	
PNDs 7-70	Male: 30 mg	40.1	0.71	0.68	VX-445-TX-021
	Female: 15 mg	81.5	1.44	1.38	

^bClinical AUC Sources: Report S054/Tables 6-9 and 6-10, Report S055/Tables 6, 14, and 22;

6 Clinical Pharmacology

6.1. Executive Summary

In this 505(b)(1) NDA submission, the Applicant seeks the marketing approval for elexacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) combination therapy (TRIKAFTA) for “the treatment of cystic fibrosis (CF) in patients aged 2 to less than 6 years old who have at least one *F508del* mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on in vitro data.”

The proposed TRIKAFTA drug product is a granule dosage form of a fixed-dose combination (FDC) of ELX, TEZ and IVA; and a granule dosage form of IVA. The dosing strengths of ELX 100 mg/TEZ 50 mg/IVA 75 mg granules and ELX 80 mg/TEZ 40 mg/IVA 60 mg granules per packet. The dosing strengths of IVA granules are 75 mg and 59.5 mg per packet. The Applicant proposed a bodyweight tiered dosing regimen in children 2 to < 6 years of age, see Table 5 below.

Table 5 Proposed Dosing Regimens in Children 2 to Less Than 6 Years Old

Age	Weight	Morning Dose	Evening Dose
2 to less than 6 years	<14 kg	One packet containing ELX 80 mg/TEZ 40 mg/IVA 60 mg oral granules	One packet containing IVA 59.5 mg oral granules
2 to less than 6 years	≥ 14 kg	One packet containing ELX 100 mg/TEZ 50 mg/IVA 75 mg oral granules	One packet containing IVA 75 mg oral granules

TRIKAFTA should be taken with fat containing food.

Given the similarities in the underlying pathophysiology and clinically presentation of CF in pediatrics and adults, this is reasonable to extrapolate efficacy of TRIKAFTA from older population to the proposed pediatric population based on comparable ELX/TEZ/IVA systemic exposure.

The Clinical Pharmacology review team evaluated the population pharmacokinetic analyses in this review and found the ELX/TEZ/IVA systemic exposure in children 2 to less than 6 years of age with the proposed dosing regimen administered with fat-containing food are generally comparable to that of patients 12 years and older on the approved doses.

Of note, OSI inspection was requested for Study VX20-445-111 Part A and Part B (analytical labs, validation reports and analytical study reports), and the Office of Study Integrity and

Surveillance (OSIS) declined to conduct the inspections and concluded that the data from the reviewed studies were reliable based on the OSIS's inspection histories in (b) (4)

Recommendations: The Office of Clinical Pharmacology Division of Immune and Inflammation Pharmacology and Division of Pharmacometrics have reviewed the information submitted under NDA 217660. This NDA and the proposed dosing regimen for pediatric CF patients are approvable from a clinical pharmacology perspective.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

The comparisons of systemic exposures (AUC) of ELX/TEZ/IVA between children 2 to <6 years of age on the proposed doses and older children/adult on the approved doses are listed in Table 6 based on population PK analysis.

Table 6 Mean (SD) ELX, TEZ and IVA Exposures Observed at Steady State by Age Group and Dose Administered

Age Group	Dose	ELX AUC_{0-24h,ss} (µg·h/mL)	TEZ AUC_{0-24h,ss} (µg·h/mL)	IVA AUC_{0-12h,ss} (µg·h/mL)
Patients aged 2 to less than 6 years weighing less than 14 kg (N = 16)	ELX 80 mg qd/TEZ 40 mg qd/IVA 60 mg qAM and IVA 59.5 mg qPM	128 (24.8)	87.3 (17.3)	11.9 (3.86)
Patients aged 2 to less than 6 years weighing 14 kg or more (N = 59)	ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h	138 (47.0)	90.2 (27.9)	13.0 (6.11)
Patients aged 6 to less than 12 years weighing less than 30 kg (N = 36)	ELX 100 mg qd/TEZ 50 mg qd/IVA 75 mg q12h	116 (39.4)	67.0 (22.3)	9.78 (4.50)
Patients aged 6 to less than 12 years weighing 30 kg or more (N = 30)	ELX 200 mg qd/ TEZ 100 mg qd/ IVA 150 mg q12h	195 (59.4)	103 (23.7)	17.5 (4.97)
Patients aged 12 years and older	ELX 200 mg qd/ TEZ 100 mg qd/ IVA 150 mg q12h	162 (47.5)	89.3 (23.2)	11.7 (4.01)
SD: Standard Deviation; AUC _{ss} : area under the concentration versus time curve at steady state.				

6.2.2. General Dosing and Therapeutic Individualization**General Dosing**

The proposed dose, dosing regimen, and dosage form for ELX/TEZ/IVA in children 2 to <6 years of age are:

Recommended Dosage for Pediatric Patients Aged 2 to less than 6 Years and Older			
Age	Weight	Morning Dose	Evening Dose
2 to less than 6 years	Less than 14 kg	One packet containing ELX 80 mg/TEZ 40 mg/IVA 60 mg oral granules	One packet containing IVA 59.5 mg oral granules
	14 kg or more	One packet containing ELX 100 mg/TEZ 50 mg/IVA 75 mg oral granules	One packet containing IVA 75 mg oral granules

Therapeutic Individualization

The proposed dosing regimen for pediatric patients aged 2 to less than 6 years with body weight greater than or equal to 14 kg is one packet of ELX/TEZ/IVA granules in the morning each containing ELX 100 mg, TEZ 50 mg, and IVA 75 mg, and one packet of IVA granules in the evening containing IVA 75 mg, taken approximately 12 hours apart with fat containing food.

The proposed dosing regimen for pediatric patients aged 2 to less than 6 years with body weight less than 14 kg is one packet of ELX/TEZ/IVA granules in the morning each containing ELX 80 mg, TEZ 40 mg, and IVA 60 mg, and one packet of IVA granules in the evening containing IVA 59.5 mg, taken approximately 12 hours apart with fat containing food.

Outstanding Issues

None.

6.3. Comprehensive Clinical Pharmacology Review

This NDA submission contains the following two clinical studies:

1. VX20-445-012: Phase 1, Open-label, Randomized, Crossover Study to Evaluate the Relative Bioavailability of Fixed Dose Combinations of Elexacaftor, Tezacaftor, and Ivacaftor in Healthy Adult Subjects
2. VX20-445-111: A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age and 6 population pharmacokinetics analysis reports:
 3. R122: Population Pharmacokinetics of Elexacaftor, M23-elexacaftor, and Ivacaftor to Support Dose Selection for Study VX20-445-111 Part B in CF Patients 2 Through 5 Years of Age
 4. R123: Population Pharmacokinetics of Tezacaftor and M1-tezacaftor to Support Dose Selection for Study VX20-445-111 Part B in Subjects 2 Through 5 Years of Age
 5. S052: Population Pharmacokinetics of Elexacaftor and M23-elexacaftor for Subjects 2 Through 5 Years of Age with Cystic Fibrosis with Interim Part B Data from Study VX20-445-111
 6. S053: Population Pharmacokinetics of Tezacaftor, M1-tezacaftor, and Ivacaftor for Subjects 2 Through 5 Years of Age with Cystic Fibrosis with Interim Part B Data from Study VX20-445-111

7. S054: Population Pharmacokinetics of Elexacaftor and M23-elexacaftor for Subjects 2

Through 5 Years of Age with Cystic Fibrosis with Final Part B Data from Study VX20-445-111

8. S055: Population Pharmacokinetics of Tezacaftor, M1-tezacaftor, and Ivacaftor for Subjects 2

Through 5 Years of Age with Cystic Fibrosis with Final Part B Data from Study VX20-445-111

Population PK analysis reports R122, R123, S052, and S053 are interim analysis reports.

Therefore, the pharmacometrics review focused on Population PK analysis reports S054 and S055. See section 15.3.1 Pharmacometrics Review for details.

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

TRIKAFTA is currently approved for the treatment of CF in patients 6 years of age and older who have at least one *F508del* mutation in the CFTR gene or a mutation in the CFTR gene that is responsive based on *in vitro* data.

General pharmacology and PK of TEZ/IVA has been reviewed previously as part of the original NDA 210491 application (clinical pharmacology review by Dr. Jianmeng Chen, DARRTS dated on 2/2/2018) and ELX/TEZ/IVA was reviewed with the original NDA 212273 application (by Dr. Jianmeng Chen, DARRTS dated on 10/21/2019).

ELX and TEZ bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of *F508del*-CFTR to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. IVA potentiates the channel-open probability (or gating) of the CFTR protein at the cell surface.

ELX, TEZ and IVA are primarily metabolized by CYP3A and eliminated in feces following metabolic conversion. M23-ELX was the major metabolite of ELX in human. The *in vitro* potency of M23-ELX is similar to that of ELX and is considered pharmacologically active. M1-TEZ, M2-TEZ, and M5-TEZ were the three major circulating metabolites of TEZ in humans. The *in vitro* potency of M1-TEZ is similar to that of TEZ and is considered pharmacologically active. M1-IVA and M6-IVA are the two major metabolites of IVA in humans. M1-IVA has approximately one-sixth the potency of IVA and is considered pharmacologically active.

6.3.2. Clinical Pharmacology Questions

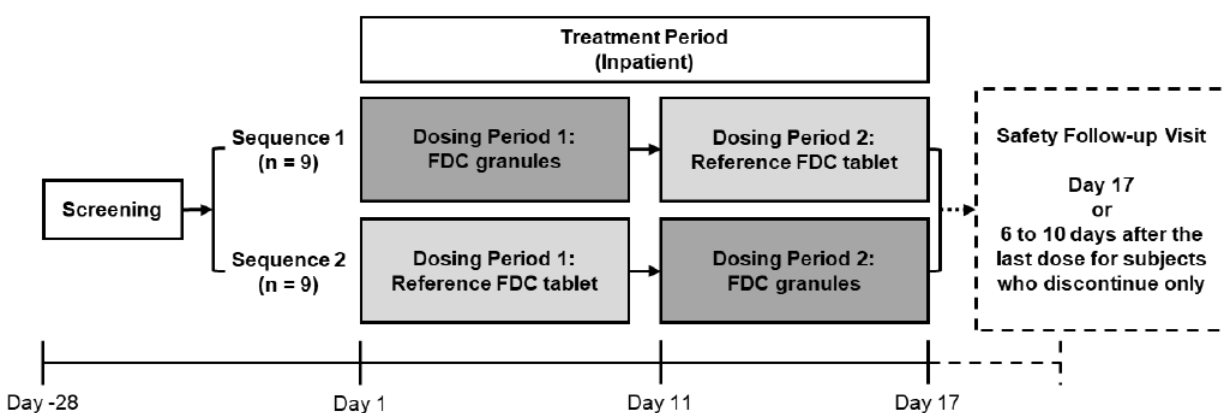
What is the bioavailability of ELX/TEZ/IVA of granule dosage form compared with the previously approved tablet formulation?

The development of granule formulation provides a user-friendly, age-appropriate dosage form in children 2 to < 6 years of age. The relative bioavailability (BA) study VX20-445-012 showed that given the same dose (ELX 100 mg/TEZ 50 mg/IVA 75 mg), the ELX and TEZ systemic exposure following ELX/TEZ/IVA granule dosage form is slight lower than that of the tablet dosage form whereas the bioequivalence was established for IVA component under fed condition. However, the BA results are not clinically relevant as the granule dosage form is not proposed to be used in adults and children 6 years of age older, a population already had

approved tablet dosage form. In addition, the ELX/TEZ/IVA dose of granule dosage form in children 2 to < 6 years of age was sufficiently investigated in study VX20-445-111 and the systemic exposures of ELX/TEZ/IVA were compared to that of adults and adolescents with acceptable results.

Study VX20-445-012 was an open-label, randomized, 2-sequence, 2-period crossover study to evaluate relative BA of ELX/TEZ/IVA FDC. Part A evaluated the relative BA of an ELX 100 mg/TEZ 50 mg/IVA 75 mg FDC granule formulation compared to a reference ELX 100 mg/TEZ 50 mg/IVA 75 mg FDC tablet formulation. Healthy adult subjects received ELX 100 mg/TEZ 50 mg/IVA 75 mg orally in the fed state, either as a single reference ELX 100 mg/TEZ 50 mg/IVA 75 mg FDC tablet or as ELX 100 mg/TEZ 50 mg/IVA 75 mg FDC granules. Part B of the study was not conducted.

Figure 1 VX20-445-012 Study Design



ELX: elexacaftor; FDC: fixed-dose combination; IVA: ivacaftor; n: size of subsample; TEZ: tezacaftor

Note: Reference FDC tablet contains ELX 100 mg/TEZ 50 mg/IVA 75 mg. FDC granules contain ELX 100 mg/TEZ 50 mg/IVA 75 mg.

Source: Figure 2-1 in Clinical Study Report for Study VX20-445-012

PK parameters were determined using standard non-compartmental methods. The BA of the FDC granule formulation relative to the reference FDC tablet formulation was evaluated. The primary comparisons of interest included FDC granules (test) relative to the reference FDC tablet.

After administration of a single oral dose of ELX/TEZ/IVA as FDC granules:

- ELX exposures were approximately 18% to 19% lower relative to the reference FDC tablet.
 - Geometric least squared mean (GLSM) ratio (90% CI): 0.819 (0.763, 0.880) for $AUC_{0-\infty}$ and 0.809 (0.711, 0.922) for C_{max}
- TEZ C_{max} was approximately 13% lower while TEZ $AUC_{0-\infty}$ was similar relative to the reference FDC tablet.
 - GLSM ratio (90% CI): 0.958 (0.913, 1.01) for $AUC_{0-\infty}$ and 0.869 (0.764, 0.988) for C_{max}

- IVA exposures were unchanged relative to the reference FDC tablet.
 - GLSM ratio (90% CI): 0.984 (0.908, 1.07) for AUC_{0-∞} and 0.993 (0.884, 1.12) for C_{max}

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Pharmacokinetics of ELX/TEZ/IVA granules in children 2 to less than 6 years old were evaluate in Study VX20-445-111. Study VX20-445-111 was a Phase 3, 2 part (Parts A and B), multicenter study evaluating the safety, tolerability, PK, PD, and efficacy of ELX/TEZ/IVA in subjects with CF 2 to less than 6 years old. Part A enrolled subjects homozygous for *F508del* (F/F genotype) or heterozygous for *F508del* and a CFTR minimal function mutation (F/MF genotypes). Part B enrolled subjects who have at least 1 *F508del* mutation in the CFTR gene or an ELX/TEZ/IVA-responsive CFTR mutation. A total of 18 subjects were enrolled in Part A, no subjects discontinued treatment or withdrew from the study. A total of 75 subjects were enrolled and received at least 1 dose of study drug in Part B, and 74 (98.7%) subjects completed treatment and the study. The duration of treatment was approximately 15 days in Part A and 24 weeks in Part B. Study drug doses for each part are summarized in Table 7.

Table 7 Part A and B Doses

Subjects Weight at Day 1	ELX Dose	TEZ Dose	IVA Dose
Part A ≥ 14 kg only	100 mg qd	50 mg qd	75 mg q12h
Park B ≥ 14 kg ≥ 10 kg to < 14 kg	100 mg qd 80 mg qAM	50 mg qd 40 mg qAM	75 mg q12h 60 mg qAM 59.5 mg qPM

Source: revised from Table 9-1 in Clinical Study Report for Study VX20-445-111

The generally comparable systemic exposure of ELX/TEZ/IVA in children 2 to <6 years of age on the proposed doses and patients 12 years and older on the approved doses support the extrapolation of efficacy from the older population to children 2 to <6 years of age.

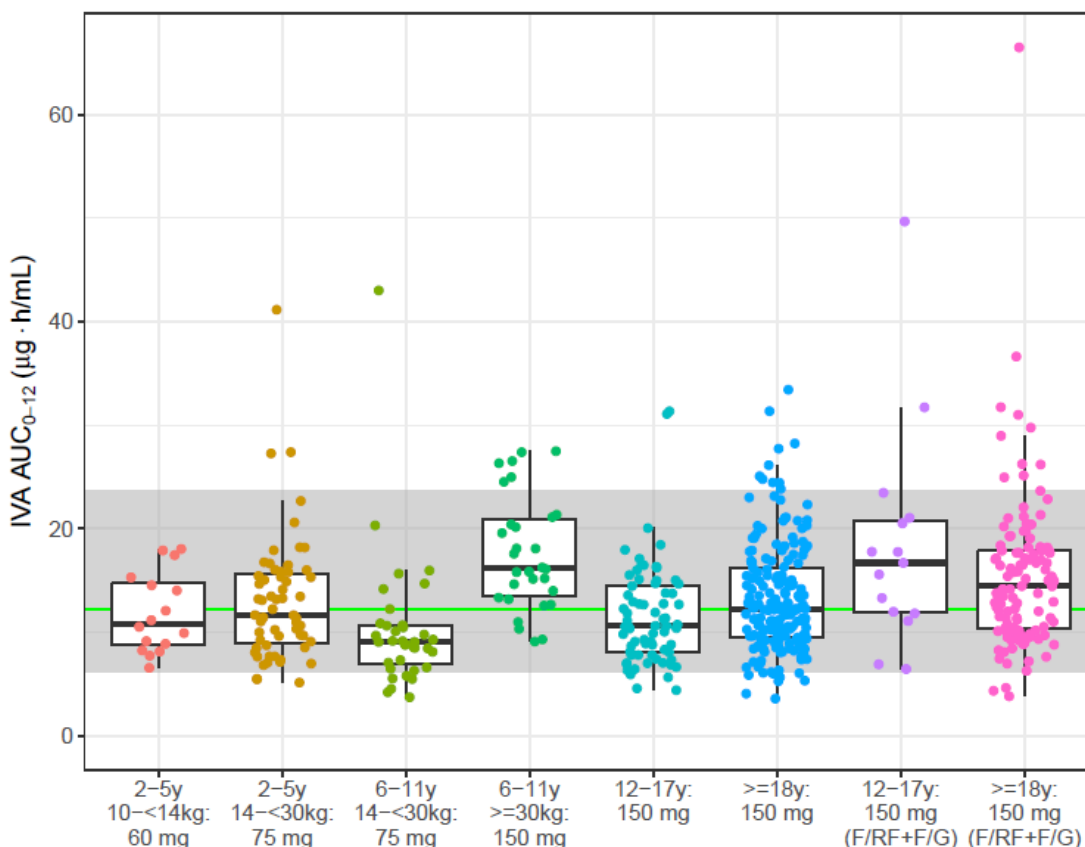
Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dose is reasonable from a clinical pharmacology perspective as the systemic exposure achieved in children 2 to less than 6 years of age are generally comparable to patients 12 years and older. The comparable PK of ELX/TEZ/IVA supports the efficacy extrapolation in patients 2 to less than 6 years of age.

Based on the population pharmacokinetic model predicted AUC at steady state, ELX/TEZ/IVA exposure fell within the adult's 5th and 95th percentile exposure ranges on the approved doses. See section 15.3.1 Pharmacometrics Review for details. A comparison of AUC at steady state

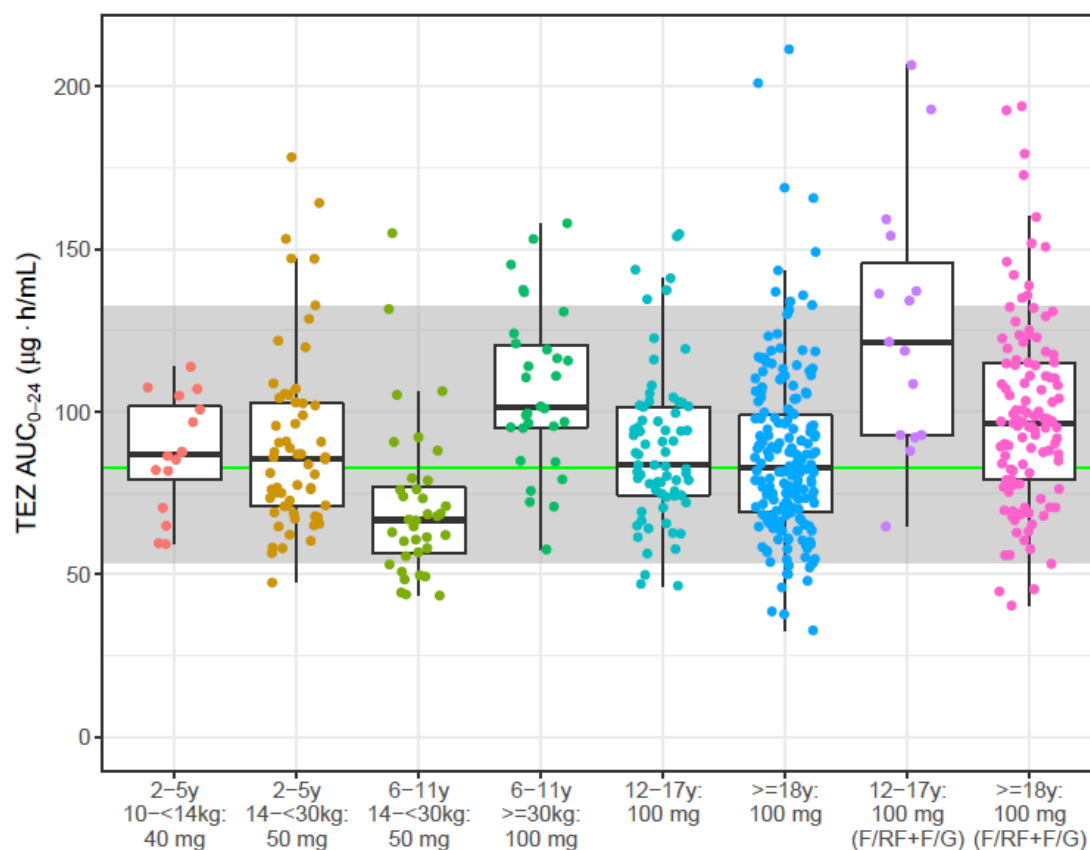
between children 2 to less than 6 years old and patients 6 years and older are depicted in Figure 2, Figure 3, and Figure 4 for IVA, TEZ, and ELX, respectively.

Figure 2 Model Predicted IVA AUC at Steady State in children 2 to less than 6 years old



The points represent individual predicted exposures under the nominal dosing regimen the subject was randomized to in the study. The predictions were made using EBEs from the final population PK model. All individuals had an F/F or F/MF genotype unless otherwise noted. The individual points are summarized and overlaid with a box plot. Median values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to $1.5 \times$ IQR. The green horizontal line represents the median of the adult values and the gray shaded area indicates the 5th and 95th percentiles of the adult values. The reference adult exposures were derived from the “ $\geq 18y$: 150 mg” subject group (i.e., adults that received TC in Studies 445-102 and 445-103). AUC_{0-12} = area under the plasma drug concentration-time curve at steady state for one dosing interval of 0 to 12 hr.

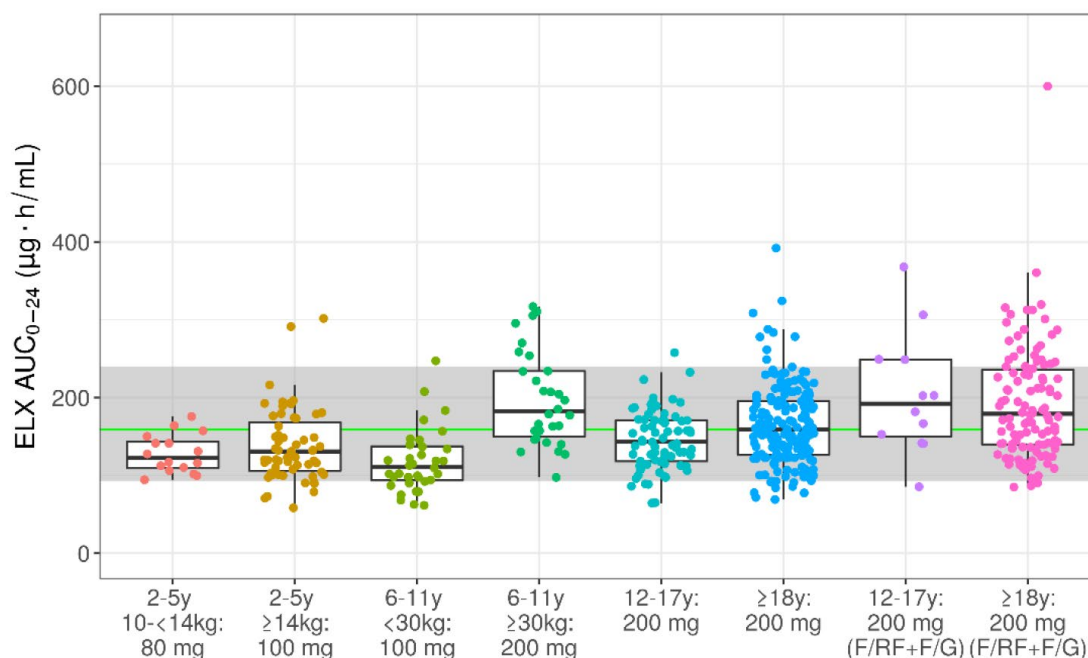
Source: Figure 192 in Population PK report S055

Figure 3 Model Predicted TEZ AUC at Steady State in children 2 to less than 6 years old

The points represent individual predicted exposures under the nominal dosing regimen the subject was randomized to in the study. The predictions were made using EBEs from the final population PK model. All individuals had an F/F or F/MF genotype unless otherwise noted. The individual points are summarized and overlaid with a box plot. Median values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to $1.5 \times$ IQR. The green horizontal line represents the median of the adult values and the gray shaded area indicates the 5th and 95th percentiles of the adult values. The reference adult exposures were derived from the “ $\geq 18y$: 100 mg” subject group (i.e., adults that received TC in Studies 445-102 and 445-103). AUC_{0-24} = area under the plasma drug concentration-time curve at steady state for one dosing interval of 0 to 24 hr.

Source: Figure 56 in Population PK report S055

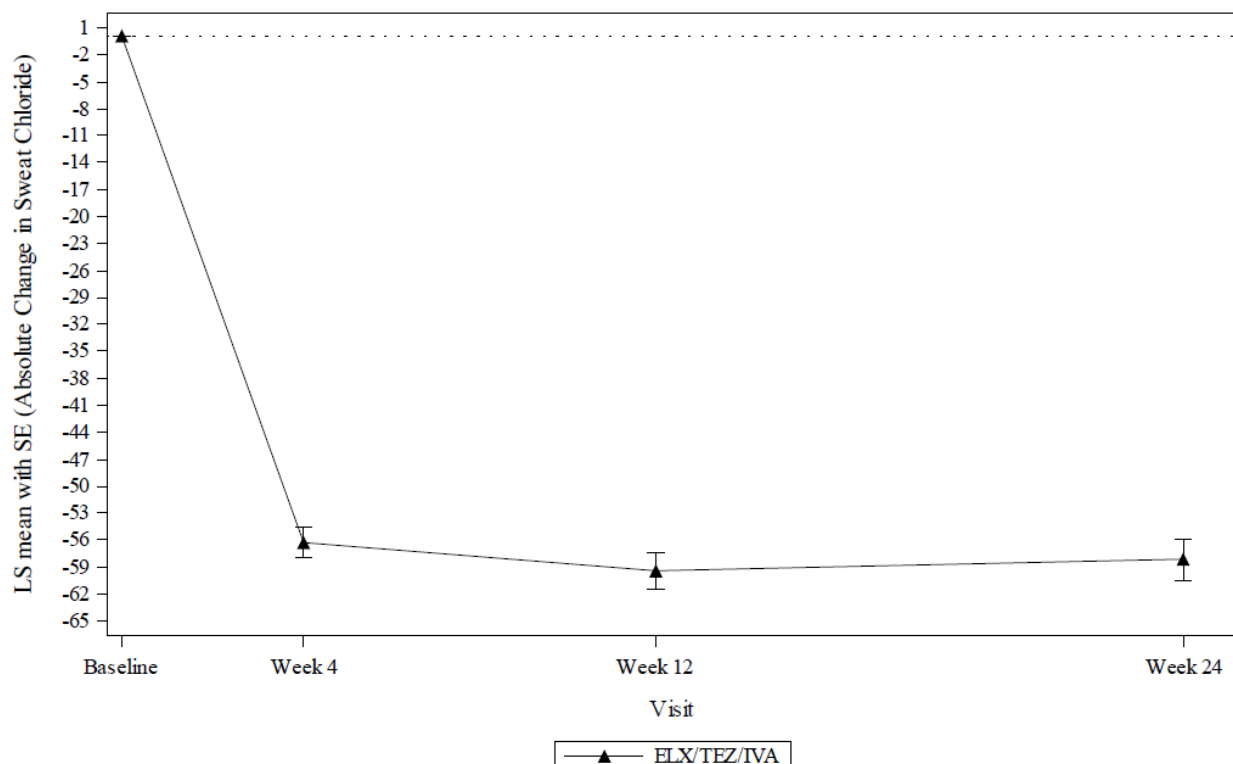
Figure 4 Model Predicted ELX AUC at Steady State in children 2 to less than 6 years old



Notes: Green horizontal line represents the median of the adult values (labeled “≥18y: 200 mg” for the F/F and F/MF genotypes) and the gray shaded area indicates the 5th and 95th percentiles of the adult values. Points represent individual exposures based on the individual EBE values from 2-5y subjects in Study 111 Part B. Boxplots provide statistics of the points, where the median is represented by a horizontal line, and the IQR is represented by a box. The whiskers mark the largest and smallest values within $1.5 \times \text{IQR}$.

Source: Figure 10-5 in Population PK report S054

The mean absolute change in sweat chloride (SwCl) from baseline through Week 24 was -57.9 mmol/L (95% CI: -61.3, -54.6). The absolute change in SwCl from baseline through Week 24 is presented in Figure 5. The absolute change in SwCl was also similar to the previously observed absolute changes in SwCl of -60.9 mmol/L (95% CI: -63.7, 58.2) in patients 6 years to less than 12 years, -41.8 (95% CI: -44.4, -39.3) and -45.1 (95% CI: -50.1, -40.1) in patients 12 years and older.

Figure 5 MMRM Analysis of Absolute Change from Baseline in SwCl (mmol/L) by Visit (FAS, Part B)

ELX: elexacaftor; FAS: Full Analysis Set; F/F: homozygous for F508del; F/MF: heterozygous for F508del and a CFTR minimal function mutation; IVA: ivacaftor; LS: least squares; MMRM: mixed-effects model for repeated measures; SwCl: sweat chloride; TEZ: tezacaftor

Note: Baseline was defined as the most recent non-missing measurement before the first dose of study drug in Part B. MMRM included data from all available visits up to Week 24 in Part B, with visit as fixed effect and baseline SwCl and genotype group (F/F or F/MF) as covariates. A Kenward-Roger approximation was used for denominator degrees of freedom. An unstructured covariance structure was used to model the within subject errors.

Source: Figure 11-1 in Clinical Study Report for Study VX20-445-20-111

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

The hepatic impairment (HI) effect on PK of ELX/TEZ/IVA has not been evaluated in children 2 to less than 6 years old. In a clinical study, following multiple doses of ELX, TEZ and IVA for 10 days, adult subjects with moderate HI (MHI, defined as Child Pugh Class B, score 7 to 9) had 25% higher AUC and 12% higher Cmax for ELX, 73% higher AUC and 70% higher Cmax for M23-ELX, 36% higher AUC and 24% higher Cmax for combined ELX and M23-ELX, 20% higher AUC but similar Cmax for TEZ and 1.5 fold higher AUC and 10% higher Cmax for IVA compared with healthy subjects matched for demographics.

Consistent with the recommendation for patients 6 years of age and older, no dose adjustment is recommended in patients 2 to less than 6 years old with mild HI and dosing is not recommended in patients 2 to less than 6 years old with severe HI. Similarly, dose adjustment is recommended in patients 2 to less than 6 years old with MHI. However, limited to the available dose strengths of the granules, the Applicant proposed a different dose adjustment for patients 2 to less than 6 years old with MHI. The proposed dose adjustment for patients 2 to less than 6 years old with MHI are given in Table 8.

Table 8. Recommended Dosage for Use of TRIKAFTA in Patients with Moderate Hepatic Impairment (Child-Pugh B)

Age	Weight	Morning Dose	Evening Dose
2 to less than 6 years	Less than 14 kg	Weekly dosing schedule as follows: - Days 1-3: One packet (containing elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg) oral granules each day - Day 4: no dose - Days 5-6: One packet (containing elexacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg) oral granules each day - Day 7: no dose	No evening dose of ivacaftor oral granules.
	14 kg or more	Weekly dosing schedule as follows: - Days 1-3: One packet (containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) oral granules each day - Day 4: no dose - Days 5-6: One packet (containing elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) oral granules each day - Day 7: no dose	No evening dose of ivacaftor oral granules.
6 years to less than 12 years	Less than 30 kg	Alternating daily dosing schedule as follows: - Day 1: Two tablets of elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg (total dose of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) - Day 2: One tablet of elexacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg	No evening ivacaftor tablet dose.
	30 kg or more	Alternating daily dosing schedule as follows: - Day 1: Two tablets of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) - Day 2: One tablet elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	No evening ivacaftor tablet dose.

Age	Weight	Morning Dose	Evening Dose
12 years and older		Alternating daily dosing schedule as follows: - Day 1: Two tablets of elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) - Day 2: One tablet elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg	No evening ivacaftor tablet dose.

The proposed dose adjustment in children 2 to less than 6 years old resulted in a similar weekly total dose reduction compared to patients 6 years and older. (Table 9)

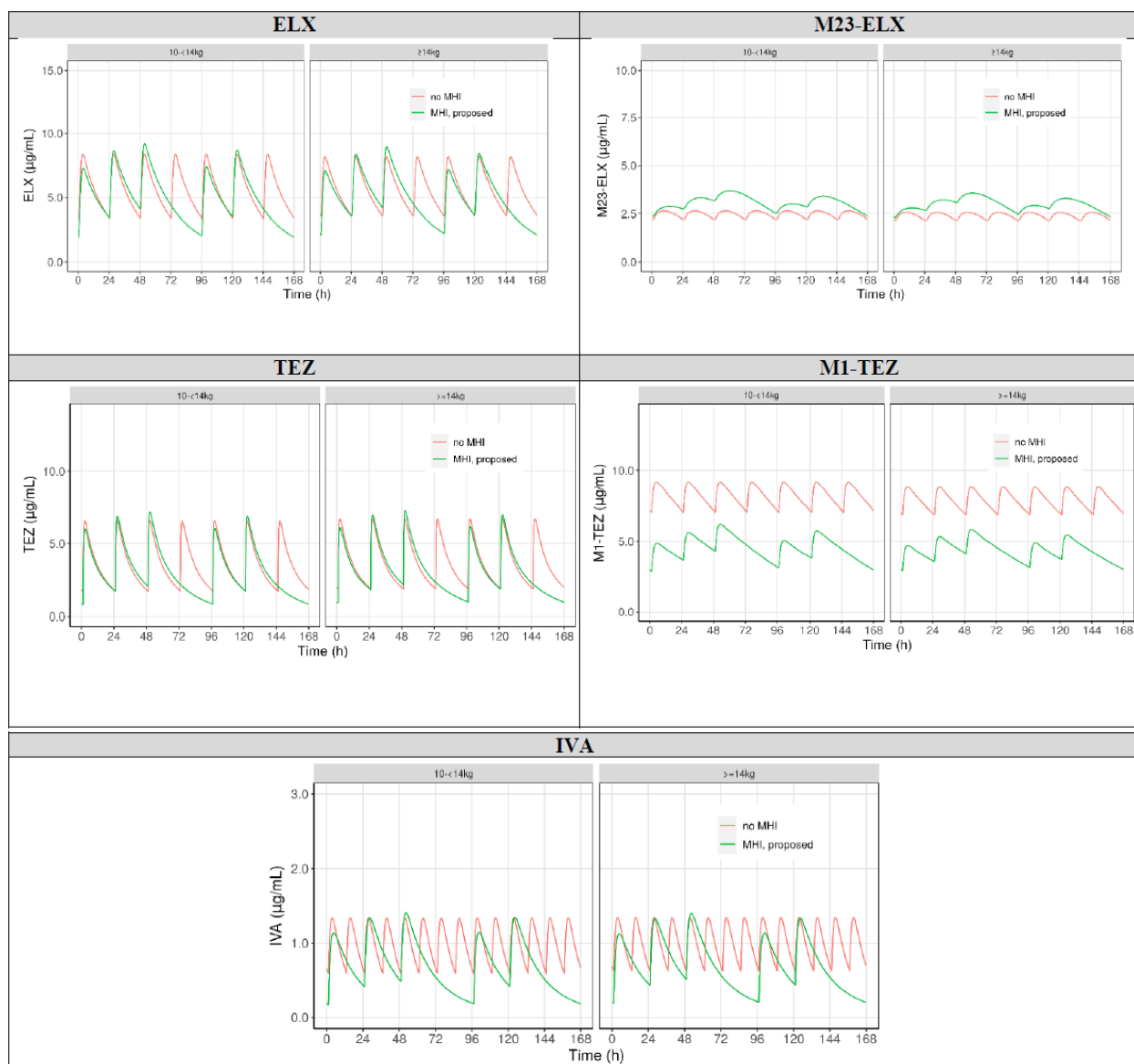
Table 9 Comparison of MHI Dose Reductions for CF Patients 6 Years of Age and Older Compared to CF Patients 2 to Less Than 6 Years Old

	2 to Less Than 6 Years Old Proposed MHI Dose Adjustment (Reduction)	6 Years and Older Approved MHI Dose Adjustment (Reduction)
ELX	28.6%	25%
TEZ	28.6%	25%
IVA	64.3%	62.5%

CF: cystic fibrosis; ELX: elexacaftor; IVA: ivacaftor; MHI: moderate hepatic impairment; TEZ: tezacaftor
 Source: Table 1 in Response to FDA Information Request dated 25 January 2023

To support the proposed dose adjustment, the simulated AUC over a 168-hour (1-week) period in CF patients 2 to less than 6 years old with MHI (with the current proposed dosing adjustment) and without HI are provided in Figure 6. These simulations showed that the proposed dose adjustment for CF patients 2 to less than 6 years of age with MHI provided similar or slightly lower exposures as compared to those without HI. The exposures achieved across the analytes with the proposed dosing adjustment for CF patients 2 to less than 6 years old with MHI are reasonable given the limited available dose strengths of the granules.

Figure 6 Average Concentration-time Profiles For 1-Week Dosing Cycle in CF Patients 2 to Less Than 6 Years Old with MHI (With the Proposed Dose Adjustment) or Without Hepatic Impairment



ELX: elexacaftor; IVA: ivacaftor; MHI: moderate hepatic impairment; TEZ: tezacaftor

Source: Figure 1 in Response to FDA Information Request dated 25 January 2023

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

Table 10 describes the proposed dosage modification for TRIKAFTA when co-administered with strong (e.g., ketoconazole, itraconazole, posaconazole, voriconazole, telithromycin, and clarithromycin) or moderate (e.g., fluconazole, erythromycin) CYP3A inhibitors. The proposed dose modifications in patients 2 to less than 6 years are consistent with the previously

recommended dose modifications in patients 6 years and older. The clinical pharmacology reviewer found the Applicant's proposal acceptable.

Table 10 Dosing Schedule for Concomitant Use of TRIKAFTA with Moderate and Strong CYP3A Inhibitors

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
2 to less than 6 years	Less than 14 kg	Alternating daily dosing schedule is as follows: - Day 1: One packet (containing elixacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg) in the morning - Day 2: One packet (containing ivacaftor 59.5 mg) oral granules in the morning No evening packet of ivacaftor oral granules.	One packet (containing elixacaftor 80 mg/tezacaftor 40 mg/ivacaftor 60 mg) in the morning twice a week, approximately 3 to 4 days apart. No evening packet of ivacaftor oral granules.
	14 kg or more	Alternating daily dosing schedule is as follows: - Day 1: One packet (containing elixacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning - Day 2: One packet (containing ivacaftor 75 mg) oral granules in the morning No evening packet of ivacaftor oral granules.	One packet (containing elixacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning twice a week, approximately 3 to 4 days apart. No evening packet of ivacaftor oral granules.
6 years and older	Less than 30 kg	Alternating daily dosing schedule is as follows: Day 1: Two tablets of elixacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg (total dose of elixacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning	Two tablets of elixacaftor 50 mg/tezacaftor 25 mg/ivacaftor 37.5 mg (total dose of elixacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg) in the morning twice a week, approximately 3 to 4 days apart. No evening ivacaftor tablet dose.

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
		Day 2: One tablet of ivacaftor 75 mg in the morning No evening ivacaftor tablet dose.	
	30 kg or more	Alternating daily dosing schedule is as follows: - Day 1: Two tablets elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) in the morning - Day 2: One tablet of ivacaftor 150 mg in the morning No evening ivacaftor tablet dose.	Two tablets elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) in the morning twice a week, approximately 3 to 4 days apart. No evening ivacaftor tablet dose.
12 years and older		Alternating daily dosing schedule is as follows: - Day 1: Two tablets elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) in the morning - Day 2: One tablet of ivacaftor 150 mg in the morning No evening ivacaftor tablet dose.	Two tablets elexacaftor 100 mg/tezacaftor 50 mg/ivacaftor 75 mg (total dose of elexacaftor 200 mg/tezacaftor 100 mg/ivacaftor 150 mg) in the morning twice a week, approximately 3 to 4 days apart. No evening ivacaftor tablet dose.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

To support the proposed expansion of the indication for ELX/TEZ/IVA to include the 2 to <6 year old population, the Applicant submitted clinical data from Study 111 (Table 11). Additionally, the 90 Day Safety Update report which included data from the Open Label Extension (Trial 112) was submitted on 1/26/2023. Results are presented where appropriate in this review, but the protocol and results were not reviewed in detailed as Trial 112 is still ongoing.

The Applicant also submitted clinical data from Trial VX-445-013, a 9 subject, healthy volunteer human factor study evaluating ELX/TEZ/IVA granules. This trial was not considered in the assessment of safety and efficacy for the purposes of this supplement and was not reviewed.

Table 11: Summary of Clinical Studies Included in this Submission

Trial Identity (Dates)	Trial Design/ Duration	Regimen/Schedule/Route	Study Endpoints	Study population	No. of Centers and Countries
VX20-445-111 (Trial 111) (11/19/2020 – 6/3/2022)	Part A: OL, single arm 15 days	≥14 kg only: ELX 100 mg /TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM Oral granule administration	Primary: PK, safety and tolerability	N=18 CF, 2 to <6y Genotype: F/MF and F/F	US Total sites: 7
NCT No 04537793	Part A: OL, single arm 24 weeks	≥14 kg: ELX 100 mg/TEZ 50 mg /IVA 75 mg qAM and IVA 75 mg qPM ≥10 to <14 kg: ELX 80 mg /TEZ 40 mg/IVA 60 mg qAM and 59.5 mg qPM Oral granule administration	Primary: Safety and tolerability Secondary: PK, PD, efficacy	N = 75 CF, 2 to <6y Genotype: <i>F508del</i> mutation or other responsive CFTR mutation	US, Australia, Canada, Germany, UK Total sites: 22
VX20-445-112 (Trial 112) Ongoing NCT No 05153317	Open label extension 192 weeks (planned)	≥14 kg: ELX 100 mg /TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM ≥10 to <14 kg: ELX 80 mg /TEZ 40 mg/IVA 60 mg qAM and 59.5 mg qPM ≥30 kg ELX 200 mg /TEZ 100 mg /IVA 150 mg qAM and IVA 15 mg qPM Oral granule administration	Long-term safety	N=70 CF, ≥2y previously enrolled in Trial 111 Genotype: <i>F508del</i> mutation or other responsive CFTR mutation	US, Australia, Canada, Germany, UK Total sites: 22

NDA/BLA Multi-disciplinary Review and Evaluation 217660

Trikafta (elexacaftor/tezacaftor/ivacaftor) Oral Granules

Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator protein; ELX, elexacaftor; F/F, *F508del* homozygous; F/MF, *F508del* heterozygous with minimal function CFTR mutation as second allele; IVA, ivacaftor; N, subject number; NCT, National Clinical Trial; No, number; OL, open label; PD, pharmacodynamics; PK, pharmacokinetics; qAM, dose in the morning, qPM, dose in the evening, TEZ, tezacaftor; UK, United Kingdom; US, United States; VX, Vertex Pharmaceuticals; y, years.

Source: Data provided by Applicant

7.2. **Review Strategy**

The Applicant submitted clinical data from Trial 111 to support the granule formulation of ELX/TEZ/IVA and the expansion of the indication to include CF patients 2 to <6 years of age. The study was a two-part, open-label PK and safety study evaluating ELX/TEZ/IVA granules. Part A included a 15-day treatment period focused on PK parameters and Part B was a 24-week open-label treatment period evaluating safety and tolerability in addition to PK. As the majority of the ELX/TEZ/IVA exposure occurred during Part B, the primary focus of the review of safety and efficacy will be on the data submitted for Part B, unless specifically noted. The Applicant has also submitted data supporting the PD and efficacy-related endpoints. As with other similar medications in this population, due to comparable systemic exposures and as the disease process in adolescent and adult population is the same as in the 2 to <6 year old population, efficacy in the proposed age group can be extrapolated from the adolescent and adult population where efficacy has previously been demonstrated in placebo-controlled clinical trials.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial VX20-445-111

Title: A Phase 3 Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Elexacaftor/Tezacaftor/Ivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 2 Through 5 Years of Age

- Study start date: November 19, 2020
- Study completion date: June 3, 2022
- Study report date: September 15, 2022
- Study sites: Part A: 7 sites in US, Part B: 22 sites in North America, Europe, and Australia

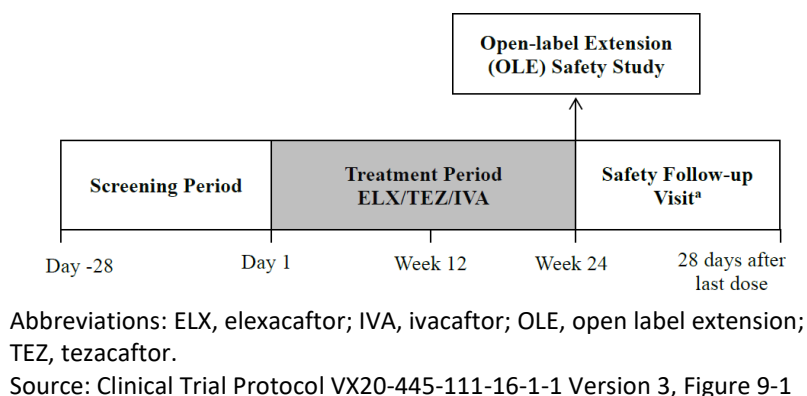
Trial Design and Conduct

Trial VX20-445-111 (Trial 111) was a multinational, pediatric study of elixacaftor (ELX)/tezacaftor (TEZ)/ivacaftor (IVA) in patients with CF aged 2 to <6 years who have at least one copy of the *F508del* CFTR mutation or a mutation in the CFTR gene that is responsive to ELX/TEZ/IVA based on *in vitro* data.

This was a 2-part (Parts A and B) non-randomized, open-label study of ELX/TEZ/IVA granules. In Part A, the PK portion, there was a 28-day screening period, followed by a 15-day treatment period. PK samples collected on Days 1, 8, and 15 of the treatment period. A final safety follow visit occurred 28 days after the last dose. See Section 15.4 for the full assessment schedule. Study participants in Part A were eligible to be screened for enrollment in Part B.

Part B, the primary safety portion, also included a 28-day screening period that was followed by a 24-week treatment period (Figure 7). During the treatment period, subjects received weight-based dosing with ELX/TEZ/IVA for 24 weeks. Study visits occurred at Days 1, 3, 15 and Weeks 4, 8, 12, 16, 20, 24, and 28 (safety follow up visit). Ophthalmologic exams (OE) were performed at screening and at Week 24. Assessments included but were not limited to sweat chloride measurement, multiple breath washout, and obtainment of clinical samples (blood and stool). See the Section 15.4 for the full assessment schedule. Following the treatment periods, all subjects were eligible to continue in the Open-Label Extension Study (VX20-445-112).

Figure 7: Study Schematic, Part B



As is typical in this age range and population, this was an open-label study designed primarily as a PK and safety study with no placebo or comparator arm. Interpretation of efficacy data in this setting will be limited given the lack of control arm; however, given the similarities in the underlying pathophysiology and clinically presentation of CF in pediatrics and adults, this is a reasonable approach as efficacy can be extrapolated from the older population.

Study Population

Key Inclusion Criteria

1. Male or Female, 2 through 5 years of age (inclusive) on date of informed consent
2. Confirmed CF diagnosis with genotype requirements:
 - a. Part A – *F508del* homozygotes (F/F genotype) or *F508del* heterozygotes with an MF mutation that is not responsive to IVA and TEZ/IVA (F/MF genotypes)
 - b. Part B – at least 1 *F508del* mutation or an ELX/TEZ/IVA-responsive CFTR mutation
3. Weight:
 - a. Part A, weight ≥ 14 kg on Day 1
 - b. Part B, weight ≥ 10 kg at the screening visit
4. Stable CF disease and willingness to remain on stable CF medication regimen

Refer to Section 15.5 for the definition and listing of eligible CFTR minimal function (MF) and ELX/TEZ/IVA responsive mutations.

Key Exclusion Criteria

1. History of any illness or any clinical condition that was felt to potentially confounded the results of the study or pose an additional risk in administering study drug(s) to the subject including
 - a. Clinically significant cirrhosis with or without portal hypertension
 - b. Solid organ or hematological transplantation
 - c. Malignancy
2. Any of the following abnormal laboratory values at screening:
 - a. Hemoglobin <10 g/dL

- b. Total bilirubin, aspartate transaminase (AST), or alanine transaminase (ALT) $\geq 2 \times$ upper limit of normal (ULN)
 - c. Part B only, elevated serum ALT or AST $\geq 3 \times$ ULN or total bilirubin $\geq 2 \times$ ULN in the prior year
 - d. Alkaline phosphatase (ALP) or gamma-glutamyl transferase (GGT) $\geq 3 \times$ ULN
 - e. Abnormal renal function defined as glomerular filtration rate ≤ 45 mL/min/1.73 m² (calculated by the Counahan-Barratt equation)
3. An acute upper or lower respiratory infection, Pex, or changes in therapy (including antibiotics) for pulmonary disease within 28 days before Day 1
4. Lung infection with organisms associated with a more rapid decline in pulmonary status including, but not limited to, Burkholderia cenocepacia, Burkholderia dolosa, and Mycobacterium abscessus.
5. An acute illness not related to CF within 14 days

The inclusion and exclusion criteria were reasonable to define the study population and support the proposed indication. The inclusion and exclusion criteria are similar to that used in the ELX/TEZ/IVA and TEZ/IVA Phase 3 studies for older age groups.

Dose and Duration of Treatment

The ELX/TEZ/IVA dosage is summarized below and further discussion of the PK and dosing regimen appears in Section 6. The ELX/TEZ/IVA dose for subjects ≥ 14 kg in Parts A and B is the approved dosage for individuals aged 6-11 years who are less than 30 kg and approved under NDA 212273/S-004. The ELX/TEZ/IVA dose for listed for subjects ≥ 10 kg and < 14 kg was selected based on population-PK modeling using adolescent and adult data.

The investigational drug dose for ELX/TEZ/IVA in Trial 111 Part A and B was as follows:

- Part A:
 - ≥ 14 kg only – ELX 100 mg/TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM
- Part B:
 - ≥ 14 kg – ELX 100 mg/TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM
 - 10 kg to < 14 kg – ELX 80 mg/TEZ 40 mg/IVA 60mg qAM and IVA 59.5 mg qPM

Concomitant Medications

The trial allowed administration of study drug on background standard-of-care CF therapy. Stable medication and supplement regimens were allowed if there were no changes from 28 days before Day 1 through the completion of study participation. No new chronic therapies could be initiated from 28 days prior to the study through the completion of study participation.

Subjects taking chronically inhaled antibiotics (tobramycin or other) remained on their regimen throughout the study. Subjects on rotational inhaled antibiotic regimens were to continue with their prior schedule. The timing of the first dose of study drug was to be as close as possible to the first day in the cycle of the inhaled antibiotics (e.g., not more than ± 3 days). Subjects could receive doses of prednisone or prednisolone up to 10 mg/day chronically or up to 60 mg daily

for 5 days. Bronchodilator use was permitted and documented. Multiple breath washout (MBW) assessments were to be collected prior to use of bronchodilator in subjects who were receiving these medications.

Prohibited medications and medication classes included moderate and strong CYP3A inducers and moderate and strong CYP3A inhibitors (except ciprofloxacin). These medications were not allowed within the 14 days prior to the first dose of study drug on Day 1 and not allowed throughout the completion of the study program. Additionally, investigational or approved medications that modulate CFTR function (e.g., IVA, LUM/IVA) were also not allowed within the 14 days prior to the first dose of study drug on Day 1 and not allowed until after the last dose of the study drug.

Study Drug Interruption and Stopping Rules

Liver Function Tests

Per the protocol, study drug administration was to be interrupted immediately (prior to confirmatory testing) if any of the following criteria are met:

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

An investigation of potential causes was to be conducted with monitoring for clinical progression. Study drug administration was to be discontinued if subsequent ALT or AST values confirm the initial evaluation and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, alcohol ingestion) was identified, regardless of whether transaminase levels have improved. All subjects were to have the levels monitored closely until they levels normalized/returned to baseline.

If an alternative, reversible cause of transaminase elevation with or without increased bilirubin or clinical jaundice was identified, study drug administration could be resumed once the transaminases returned to baseline or were $\leq 2x$ ULN (whichever was higher). Upon resumption of study drug, transaminases and bilirubin were to be assessed weekly for 4 weeks. If a protocol-defined transaminase elevation interruption threshold recurred within 4 weeks of the study drug rechallenge (with confirmation of the initial elevation by repeat testing within 48 to 72 hours), then the study drug was to be permanently discontinued, regardless of the presumed etiology.

Rash

Study drug was to be interrupted if a subject developed a generalized rash Grade 3 or higher or a rash that was considered to be an SAE. Investigators were directed to alert the medical monitor and consider additional evaluations such as laboratory testing, photographs of rash, and dermatology consult. The investigator could consider resumption of study drug if considered clinically appropriate.

Subject Removal Criteria

Subjects were withdrawn from the study for any of the following:

- Any time at the discretion of the investigator or Applicant for safety, behavior, noncompliance with study procedures, or administrative reasons
- Screening CFTR genotype that does not confirm study eligibility
- Meets any of the listed stopping criteria

Study subjects that discontinued study drug were to be followed, provided that the parent/legal guardian did not withdraw consent.

CF Pulmonary Exacerbations

CF Pulmonary Exacerbations (Pex) were defined as a new or changed treatment with oral, inhaled, or IV antibiotics and fulfillment of 1 criterion from List A and 2 criteria from List B (listed below), within the 4 days prior to the antibiotic start date through the antibiotic stop date. It was recommended that study drug not be interrupted during a Pex unless it was deemed in the best interest of the subject by the investigator. This definition for CF pulmonary exacerbations is consistent with prior studies in the CF population in this age range.

- List A
 - Decrease in ppFEV₁ $\geq 10\%$ from the highest value in the past 6 months prior to first dose, unresponsive to albuterol (if applicable)
 - Oxygen saturation $< 90\%$ on room air or $\geq 5\%$ decrease from baseline
 - New lobar infiltrate(s) or atelectasis on chest x-ray
 - Hemoptysis (more than blood-streaked sputum on more than 1 occasion in past week)
- List B
 - Increased work of breathing or respiratory rate (≥ 3 days)
 - New or increased adventitious sounds on lung examination (≥ 3 days)
 - Weight loss $\geq 5\%$ decrease from highest value or decrease across 1 major percentile-for-age in past 6 months
 - Increased cough (≥ 3 days)
 - Increased work of breathing during physical activity (≥ 3 days)
 - Increased chest congestion or change in sputum (≥ 3 days)

Study Endpoints

Primary endpoints

In Part A, the primary endpoints were the PK parameters for ELX, TEZ, IVA, and relevant metabolites. In both Parts A and B, the primary endpoints of safety and tolerability were assessed by AEs, clinically laboratory values, standard 12-lead electrocardiograms (ECGs), vital signs, and pulse oximetry, collected per the assessment schedule (Section 15.4)

Secondary endpoints

In Part B, secondary end points included:

- PK parameters of ELX, TEZ, IVA, and relevant metabolites
- Absolute change in Sweat Chloride (SwCl) from baseline through Week 24
- Absolute change in Lung Clearance Index (LCI)_{2.5} from baseline through Week 24

Additional endpoints evaluated by Part B included:

- Number of pulmonary exacerbations (Pex) and CF-related hospitalizations through Week 24
- Absolute change in weight and weight-for-age z-score from baseline at Week 24
- Absolute change in height and height-for-age z-score from baseline at Week 24
- Absolute change in body mass index (BMI) and BMI-for-age z-score from baseline at Week 24
- Absolute change in fecal elastase-1 (FE-1) levels from baseline at Week 24
- Absolute change in fecal calprotectin levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen (IRT) from baseline at Week 24
- Acceptability and palatability of ELX/TEZ/IVA granules at Day 1 and at Week 24

The lack of control/placebo arm will limit any endpoint evaluation, however the secondary and other efficacy endpoints are appropriate to evaluate a number of clinically relevant factors in patients with CF. These endpoints are consistent with similar CF trials in this age range.

Statistical Analysis Plan

Analysis of safety was descriptive with no formal statistical testing.

Protocol Amendments

The protocol was amended 2 times. Pertinent changes are summarized below.

Amendment 1 (June 29, 2021):

- Updated the dose in Part B to accurately reflect the current granule formulations of the evening dose of IVA
- Updated the sample size for subjects between 2 and 3 years of age (inclusive) in Part B
- Updated exclusion criterion #1 to avoid enrolling subjects with LFT abnormalities in the previous year in the study

Amendment 2 (October 21, 2021):

- Expanded study population in Part B to include subjects who have at least 1 *F508del* CFTR mutation or an ELX/TEZ/IVA-responsive CFTR mutation. Included list of ELX/TEZ/IVA-responsive CFTR mutation (Section 15.5)
- Ophthalmologic examinations were removed as a safety end point and medically relevant findings were to be recorded as a description of ocular AEs

The Applicant also incorporated measures to minimize unnecessary risk to COVID-19 exposure through travel to study sites and included the following

- ICF were able to be provided electronically or via post mail to subjects (and/or caregivers). After the ICF was reviewed with an appropriately qualified member of the investigator's team via telephone or video call, verbal consent was obtained from subjects (and/or caregivers) and by signing and dating the ICF and returning it to the site via post mail
- Study drug was permitted to be shipped directly from the site to the study participant

8.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study was conducted in accordance with Good Clinical Practices as described in Integrated Addendum to ICH Guideline E6 (R2), Good Clinical Practice (Nov 2016). The study protocol and amendments, informed consent, and other necessary documents were reviewed and approved by an Independent Ethics Committee or an Institutional Review Board as appropriate. Written informed consent was obtained prior to study participation.

Financial Disclosure

The Applicant adequately disclosed financial interested and arrangements by clinical investigators as recommended in the guidance for industry Financial Disclosure by Clinical Investigators (Section 15.2)

Subject Disposition

Trial 111 had high completion rates as 74 (98.7%) subjects completed the Trial. One (1.3%) subject prematurely discontinued treatment in Part B due to an adverse event (Section 8.2.4) and 70 (93.3%) subjects in Part B continued to the Open Label Extension study.

Protocol Violations/Deviations

There were no reported protocol deviations reported for Part B. The Applicant provided a list of subject visits impacted by the ongoing COVID-19 outbreak. Twenty-one (21) visits were impacted, but no visits were reported as missed. Three visits were listed as occurring out of window due to this, but there does not appear to have been a significant impact on the study or results interpretability due to COVID-19.

Demographic Characteristics

The average age of subjects in Part B (n=75) was 3.5 years and the population was 54.7% female, 89.3% white, and 8.0% Hispanic or Latino. Race and ethnicity data was not collected in 6 subjects (8.0%) due to local regulations. Demographics for Trial 111 Part B (n=75) are summarized in Table 12. Within the cohort, CFTR genotypes were 30.7% *F508del* homozygous

and 69.3% *F508del* heterozygous. The two most common Minimal Function CFTR Mutations represented were G452X (8.0%) and N1303K (6.7%). Of note, the inclusion criteria also included the potential for enrollment for subjects with other non-*F508del* CFTR mutations that were considered ELX/TEZ/IVA responsive based on *in vitro* testing (Section 15.5) but no subjects were enrolled based on this criteria. The average baseline sweat chloride was 100.7 mmol/L and 10 (13.3%) subjects reported prior use of a medication that modulates the underlying CFTR function. Additionally, 16 (21.3%) subjects were in the lower (10-14) kg weight range for dosing at baseline. The demographics of the study population are typical for CF patients within this age range.

Table 12: Demographics. Trial 111 Part B

	ELX/TEZ/IVA (N=75)
Age (years)	
Mean (SD)	3.5 (0.99)
Median (Min, Max)	3.0 (2, 5)
Sex (n, %)	
Female	41 (54.7)
Male	34 (45.3)
Race (n, %)	
White	67 (89.3)
Black or African American	1 (1.3)
Multiple races	1 (1.3)
Not Reported Per Local Regulations	6 (8.0)
Ethnicity (n, %)	
Not Hispanic or Latino	63 (84.0)
Hispanic or Latino	6 (8.0)
Not Reported Per Local Regulations	6 (8.0)
Region (n, %)	
North America	52 (69.3)
Europe and Australia	23 (30.7)
CFTR Genotype (n, %)	
F/MF	52 (69.3)
F/F	23 (30.7)
Weight Category for Dosing (n, %)	
≥14 kg	59 (78.7)
<14 kg	16 (21.3)
Mean (SD) BMI z-score for age	0.1 (0.85)
Mean (SD) Baseline Sweat Chloride (mmol/L)	100.7 (11.21)
H/o positive <i>Pseudomonas</i> culture	14 (18.7)

Source: OCS Analysis Studio, Custom Table Tool. Data confirmed by reviewer and presented by Applicant in Clinical Trial Protocol (VX20-445-111b) Tables 10-5 and 10-6.

Abbreviations: BMI, Body Mass Index, CFTR, Cystic Fibrosis Transmembrane Conductance Regulator protein; ELX, elexacaftor; F/F, *F508del* homozygous; F/MF, *F508del*/minimal function CFTR mutation, IVA, ivacaftor; SD, Standard Deviation, TEZ, tezacaftor

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

The most commonly reported medical history conditions ($\geq 30\%$) were consistent with a known history of CF. They included pancreatic insufficiency (98.7%) and constipation (30.7%). Other less common but relevant reported medical history included a history of a gastrostomy (4%) and eczema (9.3%).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was calculated as: $1 - \text{total number of days of study drug interruption} / \text{duration of study drug exposure in days}$. Overall compliance was high during Part B with 98.7% of subjects being above 80% compliant with the study drug (mean compliance: 99.5%).

The most common concomitant medications were consistent with the current standards of care for CF in this age range. They included pancreatic enzyme replacement therapy (96.0%), albuterol (72.0%), inhaled sodium chloride (66.7%), and inhaled dornase alfa (44.0%).

Primary Endpoint

The primary endpoint of this trial was safety and is discussed in Section 8.2.

Data Quality and Integrity

This NDA was submitted on 10/28/2022. The application was appropriately indexed and complete 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 of data integrity.

Secondary and other relevant endpoints

Trial 111 Part B evaluated multiple secondary endpoints, but formal evaluation is limited due to the lack of a control group. The non-PK related endpoints reviewed are as follows:

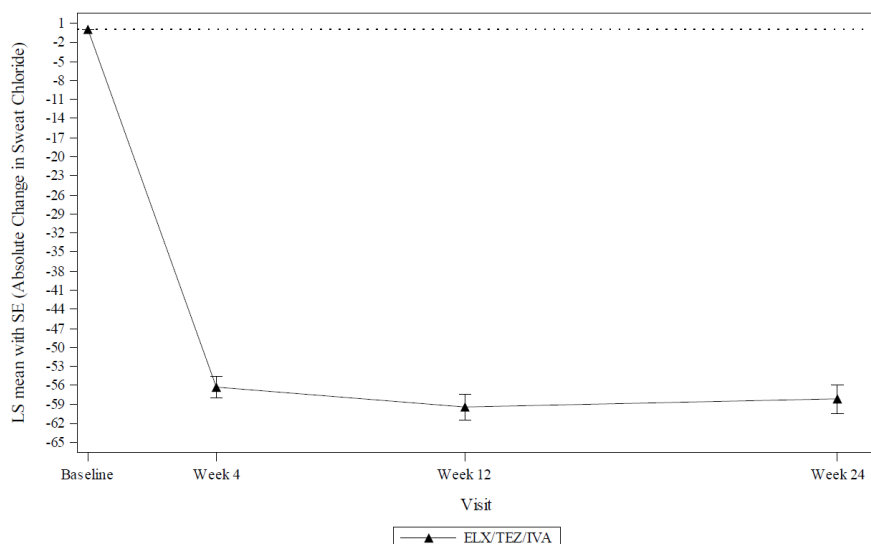
- Absolute change in Sweat Chloride (SwCl)
- Absolute change in Lung Clearance Index ($LCI_{2.5}$)
- Number of Pulmonary exacerbations (PE_x) and CF related hospitalizations
- Absolute change in weight and weight-for-age z-score
- Absolute change in height and height-for-age z-score
- Absolute change in Body Mass Index (BMI) and BMI-for-age z-score
- Absolute change in fecal elastase (FE-1) levels
- Absolute change in fecal calprotectin levels
- Absolute change in serum levels of immunoreactive trypsinogen (IRT)
- Drug acceptability and palatability assessment using Modified Facial Hedonic Scale

Change in SwCl

Decreases in mean SwCl with ELX/TEZ/IVA treatment were noted at the first measurement time point (4 weeks) and were sustained throughout the treatment period. The LS mean decrease at Week 24 was -57.9 (95% CI: -61.3, -54.6) mmol/L. While there is no control group, this decrease

is consistent with previously evaluated age groups and supports the pharmacodynamic effect of ELX/TEZ/IVA in this age group. Post-treatment SwCl levels were not evaluated.

Figure 8: Mixed-Effects Model for Repeated Measures Analysis of Absolute Change from Baseline in Sweat Chloride (mmol/L)



Abbreviations: ELX, elexacaftor; IVA, ivacaftor; LS, least squares; SE, standard error; TEZ, tezacaftor

Source: Applicant provided figure, Clinical Study Report (VX20-445-111), Figure 11-1, page 72. Independently verified by statistical review team.

Change in $LCl_{2.5}$

The protocol also evaluated changes in the lung clearance index ($LCl_{2.5}$), a marker of ventilation heterogeneity (noted to be elevated in the pediatric CF population). The within-group LS mean absolute change from baseline through Week 24 was -0.83 (95% CI: -1.01 to -0.66). This is suggestive of a reduction in ventilation heterogeneity, although what constitutes a clinically meaningful change for this test remains incompletely characterized at this time. Regardless, this is suggestive of a pharmacodynamic effect of ELX/TEZ/IVA treatment in this population although interpretation is limited by the lack of a control group.

Number of CF Pulmonary Exacerbations/Hospitalizations

During the treatment period, 12 (16%) study subjects experienced a CF pulmonary exacerbation, 1 (1.3%) of which required hospitalization and IV antibiotic therapy. Without a control arm for comparison, there are few conclusions that can be drawn from these end points although they seem reasonable for this population over a 24-week time frame.

Change in Weight, Height, and BMI from Baseline at Week 24

Treatment with ELX/TEZ/IVA and other similar medications has been associated with weight gain in the CF population. During the study period, the mean (SD) increase in weight was 1.0 (0.6) kg and 52 subjects (72%) had a $\geq 5\%$ weight gain from baseline. Lack of a control group

makes this difficult to fully interpret, however the average (SD) change in the weight z-score from baseline at Week 24 was 0.02 (0.30) and the average (SD) change in body mass index (BMI) from baseline was 0.03 (0.59) kg/m², suggesting this weight increase was not unexpected in this population. Additional measurements included height: mean (SD) absolute change from baseline at Week 24: 3.1 (0.9) cm and height z-score: mean (SD) absolute change from baseline at Week 24: -0.06 (0.22).

Change in Markers of Pancreatic Function and Inflammation

Additional end points evaluated by the Applicant included fecal elastase (FE-1), fecal calprotectin, and serum IRT. The mean (SD) change in fecal elastase (FE-1) at Week 24 was 39.5 (89.2) mg/kg. The Applicant points out that 4 (5.3%) subjects who had started with baseline FE-1 levels of < 200 mg/kg (pancreatic insufficiency) had Week 24 FE-1 levels ≥ 200 mg/kg (suggestive of pancreatic sufficiency). As with all of the efficacy related endpoints evaluated in Trial 111, the clinical relevance of this difference is unclear in this uncontrolled trial.

Additional evaluations included the mean (SD) change from baseline at Week 24 of fecal calprotectin levels of -289.66 (719.22) mg/kg and the mean (SD) change from baseline at Week 24 of serum IRT of -166.6 (285.0) µg/L.

Dose/Dose Response

This trial included two doses of ELX/TEZ/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

In Trial 111, the absolute changes of sweat chloride, a pharmacodynamic endpoint, from baseline were noted at the end of the treatment period (Week 24). These changes were also observed at earlier weeks, indicating that the drug response was durable while on the drug.

8.1.3. Assessment of Efficacy Across Trials

Not applicable to this review as only one study was included in this NDA submission.

8.1.4. Integrated Assessment of Effectiveness

In this NDA, the Applicant has submitted data from a pharmacokinetic (PK) and safety study (Study 111) to support the use of ELX/TEZ/IVA granules in patients 2 to <6 years of age with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data.

Study 111 was a two-part, non-randomized, uncontrolled, open-label PK (Part A, 15-day duration, n=18) and safety (Part B, 24-week duration, n=75) study in subjects 2 to <6 years of age. In Part B, PK data demonstrated that with the proposed ELX/TEZ/IVA doses (ELX 80 mg/TEZ

40 mg/IVA 60 mg qAM and 59.5 mg qPM in subjects 10-14 kg and ELX 100 mg/TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM in subjects ≥ 14 kg), systemic exposures matched that observed in the adolescent and adult population. Because of the similar systemic exposures and as the disease process in the older population is the same as that in the 2 to <6 year old population, efficacy in the proposed age group was extrapolated from the ELX/TEZ/IVA tablet development program. Additionally, Week 24 data from observed in Part B demonstrated a mean (SD) change in sweat chloride levels of -57.9 (1.7) mmol/L, consistent with both a pharmacodynamic response to the ELX/TEZ/IVA granule treatment and similar to previous trials in which ELX/TEZ/IVA demonstrated efficacy in the adolescent and adult CF population.

In summary, efficacy of ELX/TEZ/IVA granules in CF patients aged 2 to <6 with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data has been demonstrated based on extrapolation of efficacy from the adolescent/adult population.

8.2. Review of Safety

8.2.1. Safety Review Approach

The clinical safety review is based on the clinical data from Trial 111 which was a 2-part, open-label, non-randomized study in CF patients aged 2 to <6 years with at least one copy of the *F508del* CFTR mutation or a CFTR mutation that is responsive based on *in vitro* data. As Part A only included a 15-day treatment period, this safety review will only include a discussion of data from Part B (24-week treatment period) unless otherwise noted. Safety analyses were conducted on the safety analysis set (SAS), defined as all subjects that received at least 1 dose of study drug. Additionally, for the purposes of this review, the safety analysis was not broken down by weight-based dosing subgroup unless otherwise noted as systemic exposure was similar using the weight based dosing.

Section 8.2.4 discusses the safety data from Trial 111, including but not limited to AEs, laboratory parameters, VS, and ECGs. Section 8.2.5 discusses Submission-Specific Safety issues from Trial 111 that were either pre-specified adverse events of special interest (AESI), potential safety issues identified during the ELX/TEZ/IVA development program or known safety issues with related medications. The Applicant identified liver enzyme elevation and rash as AESI in the original ELX/TEZ/IVA development program, and blood creatine kinase (CK) elevation previously emerged as a safety signal during the ELX/TEZ/IVA initial pre-NDA review (NDA 212273). Cataracts are known safety signals with IVA monotherapy and other related products containing IVA such as TEZ/IVA. For a detailed summary of the Trial 111 protocol, refer to Section 8.1.1. Additionally, Section 8.2.8 briefly discusses safety from the ongoing long term extension safety study, Trial 112.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database includes 75 pediatric CF subjects aged 2 to <6 years receiving ELX/TEZ/IVA

granule combination therapy. Dosing was determined by patient weight as outlined. Sixteen subjects (21.3%) were within the 10 and 14 kg weight category and the remainder of subjects (59, 78.7%), weighed greater than or equal to 14 kgs.

- 10 kg to < 14 kg: ELX 80 mg/TEZ 40 mg/IVA 60mg qAM and IVA 59.5 mg qPM
- ≥14 kg: ELX 100 mg/TEZ 50 mg/IVA 75 mg qAM and IVA 75 mg qPM

Overall, subjects in Trial 111 had a mean (SD) exposure of 166.6 (17.0) days or 23.8 (2.4) weeks. One subject (1.3%) had an overall exposure of less than 4 weeks (32 days). Additional information regarding this subject is provided in Section 8.2.4. The remainder of subjects had exposures ≥ 16 weeks as noted in Table 13.

Table 13: Duration of Exposure to ELX/TEZ/IVA, Trial 111

	ELX/TEZ/IVA (10-14 kg) N=16	ELX/TEZ/IVA (≥14 kg) N=59	Total N=75
Extent of Exposure, days			
Mean (SD)	168.6 (3.2)	166.1 (19.1)	166.6 (17.0)
Median (min, max)	168.5 (164, 175)	169.0 (32, 185)	169.0 (36, 185)
Duration of Exposure, n (%)			
>0 to ≤2 weeks	0	0	0
>2 to ≤4 weeks	0	1 (1.7)	1 (1.3)
>4 to ≤8 weeks	0	0	0
>8 to ≤16 weeks	0	0	0
>16 to ≤24 weeks	8 (50.0)	26 (44.1)	34 (45.3)
>24 weeks	8 (50.0)	32 (54.2)	40 (53.3)

Abbreviations: ELX, elexacaftor; IVA, ivacaftor; kg, kilograms; n, number of subjects; SD, standard deviation; TEZ, tezacaftor

Source: Reviewed calculated in JMP 16.0 using ADSL dataset for Part B using variables TRTDURD by WTBLGR1.

Adequacy of the safety database:

Part B of Trial 111 included a 24-week treatment period where safety was assessed. The safety database was adequate to review the safety of ELX/TEZ/IVA in pediatric CF patients 2 to <6 years of age. The safety database is similar to similar therapeutic products reviewed and approved in this population.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The datasets provided by the Applicant were evaluated by the Office of Computational Science as part of this review and no issues were identified.

Categorization of Adverse Events

The Applicant defined an adverse event (AE) as any untoward medical occurrence in a subject during the study, which does not require a causal relationship with the study drug. Any abnormal laboratory assessment, ECG, vital sign, or physical exam finding that was judged by the investigator as clinically significant worsening from baseline was reported as an adverse event. Adverse events were classified using MedDRA Version 25.0. The Applicant graded AE severity using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program or as mild/moderate/severe/life-threatening/death if a term did not appear in the CTCAE. The Applicant's categorization and handling of AEs is consistent with other CF development programs and appropriate for the enrolled subject population.

Routine Clinical Tests

Routine clinical tests included laboratory tests, ECGs, physician exams, VS, and pulse oximetry were conducted as part of the assessment schedule (Appendix 15.4) in this trial.

8.2.4. Safety Results

As noted, the focus of this safety review is on Trial 111 Part B unless otherwise noted.

Deaths

There were no deaths in Trial 111.

Serious Adverse Events

There were 2 (2.7%) SAEs reported in Trial 111. One subject (1.3%) was hospitalized for a CF Pulmonary Exacerbation. This is not uncommon in this population and this SAE is unlikely to be related to study drug. The subject continued on study drug without modification in dose or drug interruption.

The other subject who experienced an SAE was a 3-year-old male with h/o of CF (*F508del/G542X*), pancreatic insufficiency, GERD, poor weight gain, a gastrostomy tube and "well-controlled attention issues" who had reports of urinary incontinence and abnormal behavior (hyperactivity and aggression) that were felt to be inconsistent with prior recent behavioral patterns for this subject. Initial laboratory evaluation was negative. These symptoms (urinary incontinence and abnormal behavior) persisted, and study drug was withheld. Symptoms reportedly resolved and study drug was resumed after 2 days. However, the subject had recurrence of behavior changes (listed as increased aggression and hyperactivity) and urinary incontinence with new onset fecal incontinence and decreased appetite leading to repeat study drug interruption. The reported symptoms again resolved without intervention and study drug was restarted after 25 days. The following day, the subject had recurrence of hyperactivity and aggression and ultimately the study drug was discontinued. The behavioral changes were noted to have resolved 5 days after study drug discontinuation.

It is difficult to formally assess a relationship between the study drug and this SAE in this uncontrolled study particularly as the behaviors reported (including intermittent behavioral changes in urinary incontinence) can be seen in this age group. However, the temporal link with the dechallenge/rechallenge does suggest that study drug may have been a contributing factor.

Dropouts and/or Discontinuations Due to Adverse Effects

One subject (1.3%) discontinued study drug and withdrew from the study for reported behavior changes as noted above. All other subjects completed the study.

Four additional subjects (5.3%) had TEAEs leading to study drug interruptions (listed by PT):

- Increase in aggressive behavior (starting day 5, duration 32 days)
- Rash (starting day 9, duration 21 days)
- Elevated transaminases (ALT, AST, and GGT) (starting day 31, duration 5 days)
- Rash (starting day 9, duration 6 days)

Significant Adverse Events

All other AEs were listed as mild to moderate.

Treatment Emergent Adverse Events and Adverse Reactions

The majority of subjects in Trial 111 were reported as having at least one AE (74, 98.7%) which is consistent with similar prior studies in this population. In the most common AEs recorded were cough (66.7%), fever (36.0%), rhinorrhea/nasal congestion (33.3%), and COVID-19 infection (29.3%). The summary of common AEs occurring in $\geq 5\%$ of subjects grouped by preferred term is shown in Table 14. Differences noted in AE analysis compared to the Applicant provided data were related to grouping of similar preferred terms (e.g. cough and productive cough, COVID-19 and SARS-CoV-2 Positive). Overall, the reported AEs were consistent with manifestations of CF disease, known AEs of ELX/TEZ/IVA, and common illnesses in this age population. No new safety signals were identified. A further discussion of elevations in liver function tests, rashes, and other AEs of special interest is included in Section 8.2.5.

Table 14: AEs Occurring in at least 5% of Subjects by Preferred Term, Trial 111 Part B

Adverse Event by Preferred Term	Part B (n=75) ELX/TEZ/IVA (n, %)
Cough ^a	49 (65.3)
Pyrexia	26 (34.7)
Rhinorrhea	25 (33.3)
COVID-19 ^b	21 (28.0)
Vomiting	21 (28.0)
Rash ^c	14 (18.7)
Nasal congestion	13 (17.3)

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Abdominal discomfort ^d	12 (16.0)
Upper respiratory tract infection	11 (14.7)
Decreased appetite	9 (12.0)
Alanine aminotransferase increased	8 (10.7)
Infective pulmonary exacerbation of cystic fibrosis	8 (10.7)
Headache	7 (9.3)
Constipation	6 (8.0)
Nasopharyngitis	6 (8.0)
Diarrhoea	5 (6.7)
Aspartate aminotransferase increased	4 (5.3)
Gamma-glutamyltransferase increased	4 (5.3)
Irritability	4 (5.3)

^aIncludes PT cough, productive cough; ^bIncludes PT COVID-19, SARS-CoV-2 Positive;

^cIncludes PT rash, rash erythematous, rash macular; ^dIncludes abdominal discomfort, abdominal pain, and abdominal pain upper

Note: AEs were coded using MedDRA 25.0. A subject with multiple events within a category was counted only once in that category.

Source: Clinical Reviewer calculated using JMP 16.0 analysis datasets adae and adsl selecting SAFFL(Y) and TRTEMFL(Y) by USUBJID and AEDECOD.

Abbreviations: COVID-19, coronavirus disease of 2019, ELX, elexacaftor; IVA, ivacaftor; PT, preferred term; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TEZ, tezacaftor

Laboratory Findings

Routine clinical testing for this safety program included evaluations of hematology, serum chemistries, coagulation studies, and urinalyses. Analysis of non-LFT and non-CK chemistry parameters, including mean changes and individual subject shifts from baseline threshold analyses, did not identify any clinically significant changes. Excluding LFTs and CK, 9 subjects (12.0%) had AEs related to laboratory findings, but none led to treatment interruptions or discontinuations. See Section 8.2.5 for a more detailed evaluation of liver transaminase and CK.

Vital Signs

The Applicant presented mean values for heart rate, blood pressure, body temperature, and oxygen saturations. No subjects had AEs reported related to vital sign findings and no clinically relevant changes from baseline were noted. Of note, Section 6 of the ELX/TEZ/IVA US PI already describes increased blood pressure.

Electrocardiograms (ECGs)

Summary statistics of heart rate, PR interval, RR interval, QRS duration, QT interval and QTcF were provided by the Applicant. Two (11.1%) subjects in Part A and 5 (6.7%) subjects in Part B were recorded as having an increase in the total QRS duration of > 89 msec. There were no cardiac or ECG-related AEs recorded during the trial period and no additional clinically 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

Hepatobiliary-Related Labs and Adverse Events

The Applicant prespecified LFT elevations as an AESI, as LFT abnormalities have been well-described with the clinical development programs of ELX/TEZ/IVA and similar medications. The LFT laboratory changes (maximum on-treatment elevations) were independently reviewed and are summarized in Table 15.

Overall rates of LFT abnormalities were similar to the rates seen in the ELX/TEZ/IVA trials in older aged populations with CF. In the overall population, 6 subjects (8.0%) had either an AST or ALT elevation greater than 3 times the upper limit of normal (ULN) and no subjects concurrent elevation in total bilirubin. For ALT and AST, the majority of elevations were between 3 and 5 times the respective ULN.

Narratives for elevations in ALT or AST provided by the Applicant were reviewed. One subject had a significant transaminase elevation that led to study drug interruption (Section 8.2.4). LFTs peaked at ALT > 8x ULN, AST > 20x ULN, GGT > 8x ULN on Day 31. Bilirubin levels were not elevated. Repeat laboratory analysis on day 35 revealed resolution of the transaminitis although the levels did not return entirely to baseline. Study drug was restarted after 5 days and the subject had additional elevations in LFTs although none to the point where the study drug was discontinued or interrupted. An alternative hypothesis of virally mediated transaminitis was proposed by the investigator and Applicant due to preceding pyrexia. While this is a possible etiology, given the known impact of ELX/TEZ/IVA on LFTs, the study drug cannot be ruled out as a causative etiology.

Additionally, one subject had transaminitis leading to study drug discontinuation during the OLE Trial 112 (Section 8.2.8). Note that the liver function testing results from the OLE are not reflected in Table 15.

In Part A, 3 (16.7%) subjects had elevated transaminase levels noted with no reported study drug interruptions or discontinuation although one subject (5.6%) had an elevated ALT (>8x ULN) with ALP <2x ULN, AST <2xULN, GGT >5x ULN, and no elevation in total bilirubin on the final day of the treatment period (day 15) and did not roll over to Part B. LFTs improved on follow up but did not return to baseline.

The impact of ELX/TEZ/IVA and related medications on liver function testing is a well described adverse event and is currently described in the USPI. No new hepatic safety concerns were identified during this review.

Table 15: Maximum Liver Function Test Elevations During the Treatment Emergent Period, Trail 111 Part B

Lab Parameter	Part B (n=75) ELX/TEZ/IVA
ALT (U/L), n (%)	
>3x to ≤5x ULN	4 (5.3)
>5x to ≤8x ULN	1 (1.3)
>8x to ≤20x ULN	1 (1.3)
≥20x ULN	0
AST (U/L), n (%)	
>3x to ≤5x ULN	1 (1.3)
>5x to ≤8x ULN	0
>8x to ≤20x ULN	0
≥20x ULN	1 (1.3)
AST or ALT (U/L), N (%)	
>3x to ≤5x ULN	4 (5.3)
>5x to ≤8x ULN	1 (1.3)
>8x to ≤20x ULN	0
≥20x ULN	1 (1.3)
Alkaline phosphatase (U/L), n (%)	
>1.5x to ≤2.5x ULN	3 (4.0)
≥2.5x ULN	0
GGT (U/L), n (%)	
>2.5x to ≤5x ULN	2 (2.7)
>5x to ≤20x ULN	2 (2.7)
Total Bilirubin (umol/L), n (%)	
>1.5x to ≤2x ULN	1 (1.3)
>2x ULN	0
ALT or AST and total bilirubin, n (%)	
(ALT or AST ≥3x ULN) and bilirubin >2x ULN	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transferase; ELX, elexacaftor; GGT, gamma-glutamyl transferase; IVA, ivacaftor; L, liter; TEZ, tezacaftor; U, units; ULN, upper limit of normal; umol, micromole.

Source: Reviewer calculated using ADLB in JMP 15.0 selecting SAFFL(Y), ONTRTRL(Y) by PARAMCB, USUBJID, MCRIT1ML, AVALC

Skin Related Adverse Events

Rashes have also been identified as a potential safety issue during the original ELX/TEZ/IVA clinical development program. Section 6 of the ELX/TEZ/IVA US PI lists the overall incidence of rash events in adults as 10% with ELZ/TEZ/IVA treatment compared to 5% in the placebo treatment groups. The incidence rash events in adults is also listed to be higher in female ELX/TEZ/IVA treated subjects (16%) than in male ELX/TEZ/IVA treated subjects (5%).

During the Trial 111 treatment period of Part A (15-day, n=18), 4 (22.2%) subjects had reported 6 rash events, none of which were considered serious. All rashes in Part A were reported to have resolved without study drug interruption or discontinuation. During the treatment period for Part B (24 weeks, n=75), 15 (20.0%) subjects were reported as having at least 1 rash event. Two subjects (2.6%) had an interruption in study drug due to reported AEs of rash. Both rashes were reported as moderate in severity, both resolved, and subjects resumed study drug without recurrence.

The incidence of rash in the 2 to <6 year old population appears to be higher than noted in the adolescent/adult clinical development program. There was also an increased incidence of rash events was noted in the 6 to 11 year old population during a similarly designed uncontrolled, 24 week open-label PK and safety trial (Trial 106; NDA 212273/S004).

As the Applicant noted, the rates of rashes due to viral upper respiratory tract infections (URI) are elevated in the 2 to <6 year old this population (and URIs were reported around the time of the rash event in 3 of 18 (16.7%) rash events), however given that this is a known safety issue with this medication, we cannot consider these rash events to be unrelated to ELX/TEZ/IVA treatment. The clinical significance of this elevation in incidence of rash events in this population, as noted in an uncontrolled clinical trial, is not clear. As rashes have been previously well-described and were considered to be self-limited and mild-to-moderate in severity during Trial 111, no labeling changes are proposed as this adverse event has already been described in Section 6 of the US PI.

Creatine Kinase Elevations

Elevations in creatine kinase (CK) have been noted during the ELX/TEZ/IVA development program. During Trial 111, 1 subject (1.3%) had CK elevations between 2.5 and 5 times the upper limit of normal recorded as an AE. There were no recorded subjects with elevations >5x the upper limit of normal and no study drug interruptions/discontinuations due to CK elevations.

Cataracts

Cataracts have been observed in patients, particularly pediatric patients, treated with IVA monotherapy and in juvenile rate toxicology studies with IVA. This risk is currently included in Section 5.4 of the ELX/TEZ/IVA PI. Trial 111 included ophthalmologic exams at screening and either at or up to 4 weeks prior to the Week 24 study visit or at an early termination visit if applicable. One subject (1.3%) was reported as having cataracts or lens opacity. The information submitted from the Open Label Extension (Trial 112) included SAEs and AEs leading to study drug discontinuation and cataracts and/or lens opacities may not be fully reflected in this report at the time of this review.

Neuropsychiatric changes

There have been reports in the postmarketing setting of neuropsychiatric events with ELX/TEZ/IVA that resulted in the opening of a NISS (SSID 1004363). The NISS was unable to confirm the presence of a safety signal and was closed on 7/28/2021. This review also explored AEs in the Psychiatric Disorders and Nervous System System Organ Class by Preferred Term (Table 16). As noted in Section 8.2.4, one subject had an SAE ultimately leading to study drug discontinuation for behavioral changes and another required study drug interruption. The most common neuropsychiatric AEs in Trial 111 were headache (7 subjects, 9.3%) and irritability (4 subjects, 5.3%). Although reports of behavioral changes are difficult to formally assess in this age range, particularly in an uncontrolled trial, it should be noted that 12 subjects (16.0%) were listed as having potential behavioral changes, including the preferred terms – psychomotor activity, aggression, irritability, abnormal behavior, and mood altered. The lack of control arm limits the ability to draw conclusions on these events including on the SAE leading to drug discontinuation but this should continue to be monitored with routine pharmacovigilance. No labeling changes are proposed at this time.

Table 16: Incidence of Neuropsychiatric Adverse Events, Trial 111

Adverse events by System Organ Class Preferred Term	ELX/TEZ/IVA N=75
Nervous System, n (%)	12 (16.0%)
Headache	7 (9.3%)
Psychomotor hyperactivity	3 (4.0%)
Lethargy	1 (1.3%)
Syncope	1 (1.3%)
Psychiatric Disorders, n (%)	12 (16.0%)
Irritability	4 (5.3%)
Insomnia ^a	3 (4.0%)
Aggression	3 (4.0%)
Abnormal behavior	1 (1.3%)
Dysphemia	1 (1.3%)
Mood altered	1 (1.3%)
Restlessness	1 (1.3%)
Sleep terror	1 (1.3%)
Somnambulism	1 (1.3%)

^aIncludes combined terms: Insomnia, initial insomnia, sleep disorder
Abbreviations: ELX, elexacaftor; IVA, ivacaftor; n, number of subjects; SOC, TEZ, tezacaftor

Source: Reviewed calculated in JMP 16.0 using ADAE dataset selecting SAFFL(Y) and TRTEMFL(Y) by USUBJID, AEDECOD, AEBODSYS.

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 size and lack of control arm in this population, additional safety analyses by demographic subgroup were not performed.

8.2.8. Specific Safety Studies/Clinical Trials

On January 26, 2023, the Applicant submitted safety data from an ongoing Open Label Extension (OLE) Trial (VX20-445-112, Trial 112), covering the period of January 17, 2022 through December 31, 2022. Trial 112 is an ongoing Phase 3, open-label, multicenter, rollover study evaluating the long-term (approximately 192 weeks) safety and efficacy of ELX/TEZ/IVA in subjects who have completed Trial 111 Part B. A total of 70 subjects received at least 1 dose of study drug in Trial 112.

The Applicant identified 11 SAEs in 10 subjects during the reporting period including 1 event that led to study drug discontinuation. The narrative provided by the Applicant leading to the study drug discontinuation was reviewed and is summarized below:

- 3-year-old white male with h/o Cystic Fibrosis (*F508del/F508del*) with a history of pancreatic insufficiency, *Pseudomonas* positivity, and poor weight gain. During Trial 111 Part B (initial treatment period), the subject was noted to have elevated transaminases including: ALT > 3x the upper limit of normal (ULN), AST > 3x ULN, GGT > 4x ULN, alkaline phosphatase (ALP) > 1x ULN, with no reported elevation in total bilirubin. These elevations were reported as nonserious, the subject did not receive any treatment for these changes, and the study drug was not interrupted nor dosing changed. At the time, this AE was reported as resolved after 8 days of onset. Later, the study subject had two separate recurrent elevations in LFTs during Trial 111 Part B that were reported as nonserious and mild, but the final AE was not formally considered resolved prior to the subject entering the OLE Trial 112 (at the end of Trial 111 Part B, the Week 24 LFTs were ALT <2x ULN, AST <2x ULN, and GGT <2x ULN). Following persistent elevation of the subject's LFTs (between 1 and 2x the ULN), the decision was made to discontinue the study drug. Follow up data beyond this was not provided to assess for resolution.

While the presence of potential underlying CF-related liver disease confounds the interpretation of narratives such as this, it seems that these changes in liver function testing within this subject have the potential to be related to the administration of ELX/TEZ/IVA. Of note, there had not been study drug discontinuations noted in the initial Trial 111 for this 2 to <6 year old CF population.

The remainder of the reported SAEs that did not lead to study drug discontinuation and appear to be consistent common conditions seen in the CF population and similarly aged populations. The SAEs included 7 CF pulmonary exacerbations, hospitalization for a G-tube insertion, cough, viral tonsillitis, a viral infection, and cough. Overall, the safety update from the ongoing OLE did not reveal any new safety concerns.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

No human carcinogenicity studies have been performed for ELX/TEZ/IVA.

Human Reproduction and Pregnancy

The use of ELX/TEZ/IVA during pregnancy or lactation has not been evaluated in well-controlled trials. No additional findings were reported in this study.

Pediatrics and Assessment of Effects on Growth

This trial included CF pediatric subjects 2 to <6 years of age. Height and weight were included as secondary efficacy endpoints and the discussion is included in Section 8.1.2.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant did not complete studies on potential withdrawal, rebound effects, or systemic examination of abuse potential of ELX/TEZ/IVA, nor were such studies required. Given the mechanism of action and intended use (chronic, life-long), ELX/TEZ/IVA is anticipated to have minimal to no abuse potential.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

ELX/TEZ/IVA was initially approved on 10/21/2019 for CF patients ages 12 years and older with at least one copy of the *F508del* CFTR mutation. Safety concerns identified during the development program and in the postmarketing experience are included in the currently approved label. At the time of this review, there are currently two ongoing NISS evaluations SSID 1004940/Acute pancreatitis and SSID 1004722/Anaphylaxis.

Expectations on Safety in the Postmarket Setting

The patient population included in Trial 111 who received ELX/TEZ/IVA is similar to the target population. Given this fact and the postmarketing experience with ELX/TEZ/IVA, no substantial differences are anticipated.

8.2.11. Integrated Assessment of Safety

The safety data submitted with this application in conjunction with the known safety profile of ELX/TEZ/IVA was sufficient to assess the safety of ELX/TEZ/IVA in the CF patient population aged 2 to <6 years of age. No deaths were reported and the observed SAEs were infrequent. Given the previous clinical experience with ELX/TEZ/IVA tablets, this review explored the clinical safety database to assess for liver related toxicity, rash, CPK elevation, and cataract formation. These safety analyses did not identify any new safety concerns and the safety findings were

consistent with the known safety profile of ELX/TEZ/IVA. Overall, the ELX/TEZ/IVA safety profile in CF patients aged 2 to <6 years of age is favorable.

8.3. Statistical Issues

None. Trial 111 was a PK and safety study and analysis of safety was descriptive.

8.4. Conclusions and Recommendations

The Applicant has demonstrated substantial evidence of effectiveness for ELX/TEZ/IVA granules for the treatment of CF in patients 2 to <6 years of age with at least one *F508del* mutation or a CFTR mutation that is responsive based on *in vitro* data. Given the demonstration of similar systemic exposures and as the disease process in the older population is the same as that in the 2 to <6 year old population, efficacy in the proposed age group was extrapolated from the ELX/TEZ/IVA tablet development program. No new safety signals for ELX/TEZ/IVA were identified. The benefit-risk of this product in the proposed population is favorable. The recommended regulatory action is Approval.

9 Advisory Committee Meeting and Other External Consultations

An advisory committee meeting or other external consultations were not required as part of this application.

10 **Pediatrics**

Cystic Fibrosis (CF) is a rare, orphan disease and thus is not subject to pediatric study requirements as defined under PREA. However, both Phase 3 trials of ELX/TEZ/IVA tablets included CF patients 12 to 17 years of age (NDA 212273) and an additional supplement to that NDA included evaluation of CF patients 6 to 11 years of age. This current NDA includes CF patients 2 to <6 years of age. Efficacy and safety data in the thus far evaluated pediatric age ranges have been consistent with the overall results.

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed updates to the Prescribing Information, Patient Information, and carton and containing labeling that included the trade name TRIKAFTA. The Division of Medical Error Prevention and Analysis also reviewed the proposed PI, container labels, and carton labeling for areas of vulnerability that were conveyed to the Applicant.

Information regarding TRIKAFTA Oral Granules dosing, administration, dose modifications, and use in hepatic impairment was added to Section 2. Section 2 was also revised and reformatted to be consistent with new draft guidance for Dosing and Administration Section of Labeling and the sections on use in Hepatic Impairment (Sections 2.2 and 8.7) were reformatted to provide additional clarity.

Information regarding the clinical trial included in this review (Trial 111) was added. This included information in the population studied (Section 6.1 and 8.4), the pharmacodynamic changes in sweat chloride (Section 12.2), and the pharmacokinetic data (Section 12.3).

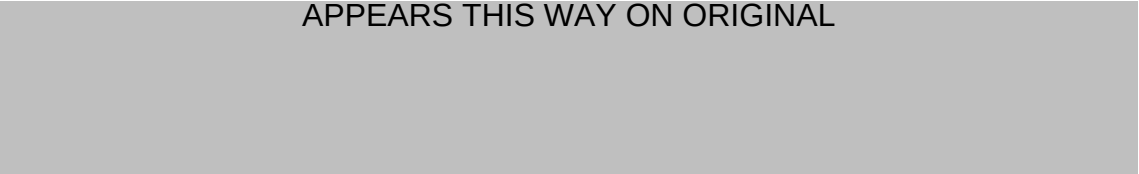
Liver Function Test elevations are a well described adverse reaction already included in Section 6.1. Additional information was added to include the incidence of maximum transaminase elevations seen in Trial 111 and information regarding the subject that discontinued TRIKAFTA during the Open-Label Extension (Trial 112).

Section 8.4 (Pediatric use) was updated to include information regarding use in pediatric patients aged 2 to less than 6 years of age and information on how TRIKAFTA oral granules are supplied and storage requirements were added to Section 16.

Additionally, the Applicant had been issued a PMR (3718-1) to conduct a carcinogenicity study in rats at the time of TRIKAFTA tablet's initial approval (NDA 212273). Results from PMR 3718-1 were submitted on 7/22/2021 and the nonclinical review was completed on 7/21/2022. Following review, the Applicant was instructed by the Division to submit a labeling supplement which incorporates these data (see letter dated 8/1/2022). To satisfy this request, the Applicant incorporated these data into this NDA (217660) submission. Simultaneous to submission of NDA 217660, the Applicant also submitted supplemental NDA 212273/S-009 for the tablet formulation to harmonize the tablet and granule labels. These data were included in Section 13.1.

The Applicant's proposed packaging was also reviewed by DMEPA. To decrease medication error, DMEPA requested the addition of 'morning' and 'evening' to the granule sachets. The Applicant agreed however, requested to use the current pre-printed supply until exhausted. The Division and DMEPA agrees with this plan.

APPEARS THIS WAY ON ORIGINAL



12 Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not deemed necessary for this application.

13 Postmarketing Requirements and Commitment

No additional PMR or PMCs will be issued with this application.

14 Deputy Division Director (designated signatory authority) Comments

Trikafta is a fixed-dose combination of elexacaftor (ELX), tezacaftor (TEZ), and ivacaftor (IVA). IVA is a potentiator of the CFTR chloride channel present on the epithelial cell membrane. ELX and TEZ facilitate the cellular processing and trafficking of defective CFTR protein to the epithelial cell apical surface. Trikafta was approved under NDA 212273 in October 2019 for the treatment of CF in patients 12 years of age and older who have at least one *F508del* mutation in the CFTR gene. In December 2020, based on *in vitro* assay data, the indication was expanded to include 177 additional rare CFTR gene mutations. On June 8, 2021, the indication was again expanded to include CF patients 6 to 11 years of age.

This NDA proposes a new granule formation for the ELX/TEZ/IVA fixed-dose combination product and to expand the indication to include CF patients 2 to < 6 years of age with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data.

The proposed doses are:

- For patients ≥ 14 kg:
 - Morning: ELX 100 mg/TEZ 50 mg/IVA 75 mg
 - Evening: IVA 75 mg
- For patients < 14 kg:
 - Morning: ELX 80 mg/TEZ 40 mg/IVA 60 mg
 - Evening: IVA 59.5 mg

In this NDA, the Applicant submitted data from a PK/safety study – Trial 111 to support the use of ELX/TEZ/IVA in pediatric patients 2 to <6 years of age. Trial 111 was a two-part, non-randomized, uncontrolled, open-label, PK (Part A, 15-day duration, n=18) and safety (Part B, 24-week duration, n=75) study in patients 2 to <6 years of age. Results demonstrated systemic exposures comparable to those observed in the adult/adolescent program when dosed according to the dosing regimen described above. Week 24 data from Part B demonstrated within group improvements in sweat chloride (SwCl), suggesting a clinically meaningful response to the ELX/TEZ/IVA treatment. Because of the comparable systemic exposures and because the disease process in the older population is the same as that in the ≥ 12 -year-old population, efficacy in the proposed age group was extrapolated from the ≥ 12 -year-old age group where efficacy had been demonstrated in clinical trials. No new safety signals were identified.

The Agency and the Applicant have also agreed upon the final labeling language. Of note, DMEPA has asked the Applicant to update labeling on the sachets to indicate “Morning” or “Evening” doses. The Applicant has already pre-printed the sachets but has agreed to the change once their current pre-printed supply is exhausted. The Division and DMEPA agree with this plan, and provisions for this will be outlined in the approval letter, to which the final approved labeling will be attached.

I have reviewed the recommendations of all disciplines. The submitted clinical program is adequate to support the efficacy and safety of ELX/TEZ/IVA for the treatment of pediatric patients 2 to < 6 years of age with at least one *F508del* mutation or a mutation in the CFTR gene that is responsive based on *in vitro* data. The granule formulation is more age appropriate for this new younger age group. The action for this application will be **Approval**.

15 Appendices

15.1. References

Clinical and Functional Translation of CFTR (CFTR2). Accessed from <https://cftr2.org/> on 12/30/2022.

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15.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): VX20-445-111 Parts A and B

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>140</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>5</u>		
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: <u>0</u> Significant payments of other sorts: <u>5</u> Proprietary interest in the product tested held by investigator: <u>0</u> Significant equity interest held by investigator in Sponsor of covered study: <u>0</u>		
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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

The Applicant certified the absence of financial arrangements for 135 of the principal investigators and sub-investigators in the Trial 111. There were 5 investigators with significant payments of other sorts: (b) (6) and (b) (6). These significant payments of other sorts were determined not to have a significant impact upon the conduct of this study. The primary outcome measurements of note (PK and Sweat Chloride) are objective and unlikely to be impacted the significant payments of other sorts. Additionally, enrollment at any particular site (1 to 6 subjects at each of the 22 sites) was relatively small compared to the overall number of patients. As noted in the review,

efficacy was extrapolated from the adolescent and adult CF population and removal of any site's subjects would be unlikely to impact the safety analysis in this NDA.

15.3. OCP Appendices (Technical documents supporting OCP recommendations)

15.3.1. Pharmacometrics Review

The pharmacokinetics of ELX, TEZ, and IVA in patients 2 to less than 6 years old were characterized in Study VX20-445-111. Sparse PK samples were collected to determine plasma concentrations of ELX, M23-ELX, TEZ, M1-TEZ, IVA, and M1-IVA. Population pharmacokinetics models were developed to describe the PK characteristics in patients 2 to less than 6 years old. Population pharmacokinetics analysis reports R122, R123, S052, S053 are interim analysis reports, the final population pharmacokinetics analysis results are presented in reports S054 and S055. Therefore, the following pharmacometrics review included the results presented in report S054 for ELX and M23-ELX, and report S055 for TEZ, M1-TEZ, and IVA. All the five PopPK models adequately described the PK characteristics of ELX, M23-ELX, TEZ, M1-TEZ, and IVA in children 2 to less than 6 years old.

15.3.1.1. ELX Population PK Model

The final ELX dataset used for model development included 3,988 ELX plasma concentration measurements from 622 CF subjects, including 531 ELX plasma concentration measurements from 83 unique 2 to less than 6 years old CF subjects. A summary of demographics and disease characteristics are given in Table 17.

Table 17 Summary of Covariates in the ELX PK Analysis Dataset

Study	001	102	103	104	106 Part A	106 Part B	111 Part A	111 Part B	Overall
N (%)	95 (100%)	199 (100%)	52 (100%)	122 (100%)	16 (100%)	66 (100%)	18 (100%)	75 (100%)	622 (100%)
Male (%)	52 (54.7%)	103 (51.8%)	22 (42.3%)	61 (50%)	5 (31.2%)	27 (40.9%)	7 (38.9%)	34 (45.3%)	303 (48.7%)
Female (%)	43 (45.3%)	96 (48.2%)	30 (57.7%)	61 (50%)	11 (68.8%)	39 (59.1%)	11 (61.1%)	41 (54.7%)	319 (51.3%)
CF, F/MF (%)	74 (77.9%)	199 (100%)	0 (0%)	0 (0%)	9 (56.2%)	37 (56.1%)	11 (61.1%)	52 (69.3%)	368 (59.2%)
CF, F/F (%)	21 (22.1%)	0 (0%)	52 (100%)	0 (0%)	7 (43.8%)	29 (43.9%)	7 (38.9%)	23 (30.7%)	132 (21.2%)
CF, F/G (%)	0 (0%)	0 (0%)	0 (0%)	38 (31.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	38 (6.1%)
CF, F/RF (%)	0 (0%)	0 (0%)	0 (0%)	84 (68.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	84 (13.5%)
White (%)	92 (96.8%)	184 (92.5%)	51 (98.1%)	113 (92.6%)	16 (100%)	57 (86.4%)	18 (100%)	67 (89.3%)	577 (92.8%)
Black or African American (%)	1 (1.1%)	3 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)	5 (0.8%)
Asian (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiple (%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)	1 (1.3%)	3 (0.5%)
Other (%)	2 (2.1%)	11 (5.5%)	1 (1.9%)	9 (7.4%)	0 (0%)	8 (12.1%)	0 (0%)	6 (8%)	37 (5.9%)
Age, years (median [min, max])	30 [18, 58]	24 [12, 59]	27 [12, 53]	36.5 [12, 66]	8.5 [6, 11]	9 [6, 11]	3.5 [3, 5]	3.0 [2, 5]	23 [2, 66]
Age, years (mean [SD])	30.8 [8.8]	25.1 [9.7]	28.3 [11.8]	37.2 [14.3]	8.4 [1.9]	8.7 [1.8]	3.7 [0.8]	3.5 [1.0]	23.9 [14.8]
Body weight, kg (median [min, max])	63 [44, 111.1]	58 [29, 108]	59.5 [36, 83]	66.8 [37, 125.2]	28.5 [18.1, 42.8]	29 [18.1, 53.6]	16 [14.2, 21.9]	16.3 [10.8, 26]	55 [10.8, 125.2]
Body weight, kg (mean [SD])	63.1 [11.1]	59.8 [12.9]	59.6 [12.2]	69.3 [16.9]	29.3 [6.7]	30 [7.7]	16.6 [2]	16.5 [3.2]	53 [21.7]

max: maximum value; min: minimum value; N: total sample size; SD: standard deviation.

Note: 11 subjects were enrolled in both Parts A and B in Study 106, their baseline covariates were counted separately in each part. 10 subjects were enrolled in both Parts A and B in Study 111, their baseline covariates were counted separately in each part. In the overall, the covariates for these crossover subjects were only counted once.

Source: Table 6-1 in in Population PK report S054

The ELX final model was a linear, two-compartment PopPK model with four-transit compartments; first-order absorption; IIV on CL, V2 and KTR; and additive and proportional errors. The model had the following covariate effects:

- weight on clearance, inter-compartmental clearance, and volumes;
- formulation on the absorption rate and bioavailability;
- age on the absorption transit rate; and
- genotype on clearance.

The final parameter estimates are given in Table 18, and an age stratified prediction corrected Visual Predictive Checks (pcVPCs) plot is depicted in Figure 9.

Table 18 ELX Population Pharmacokinetic Final Model Parameter Estimates

NDA/BLA Multi-disciplinary Review and Evaluation 217660
Trikafta (elexacaftor/tezacaftor/ivacaftor) Oral Granules

Parameters	Unit	Estimate	Relative Standard Error (%)	95% CI	IIV %CV or SD
Central clearance, CL	L/h	1.09	28.2	[1.04,1.14]	34.7 (CV% ^a)
Central volume, V2	L	33.9	2.69	[28.2,40.8]	36.2 (CV% ^a)
Absorption rate, KA	1/h	0.622	26.3	[0.301,0.943]	
Total bioavailability, F (fixed)		0.802			
Inter-compartmental clearance, Q	L/h	2.85	28.9	[1.57,5.14]	
Peripheral volume, V3	L	13.6	11.3	[7.62,24.2]	
Transit rate constant, KTR	1/h	3.72	8.29	[3.01,4.61]	53.9 (CV% ^a)
Weight saturation on CL and Q	kg	46.4	1.18	[42.4,50.7]	
Allometric exponent for CL and Q (fixed)		0.75			
Allometric exponent for V2 and V3 (fixed)		1			
Formulation on KA, KATABLET		0.884	45.9	[0.0896,1.68]	
Age effect on transit rate constant, AGEKTR		-0.308	16.3	[-0.406,-0.21]	
Residual Function or Gating mutation on Clearance, GTNCL (prop)		0.816	4.22	[0.749,0.884]	
Granule formulation on bioavailability, FORMFTOT (fixed)		0.821			
ω^2_{CL}		0.12	7.18	[0.103,0.137]	
ω^2_{V2}		0.131	32.2	[0.0482,0.213]	
ω^2_{KTR}		0.291	14.0	[0.211,0.371]	
Residual variability, proportional		0.0548	11.3	[0.0427,0.067]	23.4 (CV% ^a)
Residual variability, additive	(ng/mL) ²	181000	36.9	[50000,312000]	425 (SD ^b)

Notes: Inter-individual variability estimates are reported as variances and prop indicates that the value is multiplicative of the typical value.

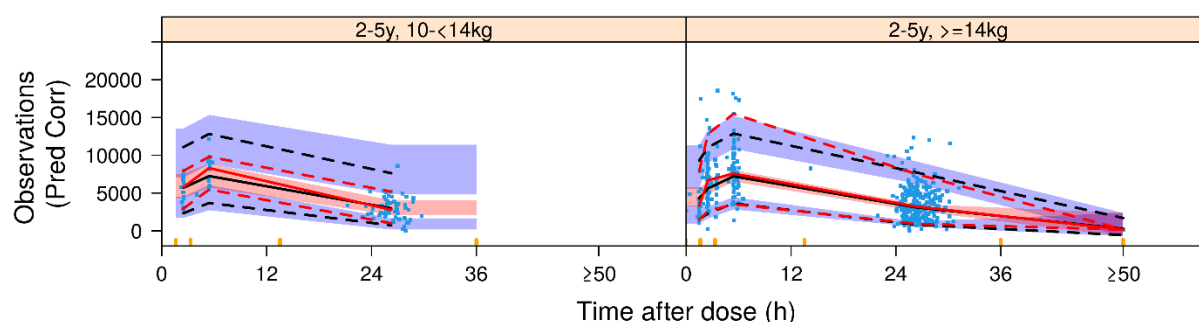
Model: run103.mod

^aParameter IIV CV% = square-root of the parameter IIV * 100

^bAdditive Error SD = square-root of the additive error variance.

Source: Table 6-3 in Population PK report S054

Figure 9 Prediction-Corrected Visual Predictive Checks (pcVPCs) of the ELX Final Population PK Model



Source: Figure 6-8 Panel E in Population PK Analysis report S054

15.3.1.2. M23-ELX Population PK Model

The final M23-ELX dataset used for model development included 3,888 M23-ELX plasma concentration measurements from 621 CF subjects, including 530 M23-ELX plasma concentration measurements from 83 unique 2 to less than 6 years old CF subjects. A summary of demographics and disease characteristics are given in Table 19.

Table 19 Summary of Covariates in the M23-ELX PK Analysis Dataset

Study	001	102	103	104	106 Part A	106 Part B	111 Part A	111 Part B	Overall
N (%)	95 (100%)	198 (100%)	52 (100%)	122 (100%)	16 (100%)	66 (100%)	18 (100%)	75 (100%)	621 (100%)
Male (%)	52 (54.7%)	102 (51.5%)	22 (42.3%)	61 (50%)	5 (31.2%)	27 (40.9%)	7 (38.9%)	34 (45.3%)	302 (48.6%)
Female (%)	43 (45.3%)	96 (48.5%)	30 (57.7%)	61 (50%)	11 (68.8%)	39 (59.1%)	11 (61.1%)	41 (54.7%)	319 (51.4%)
CF, F/MF (%)	74 (77.9%)	198 (100%)	0 (0%)	0 (0%)	9 (56.2%)	37 (56.1%)	11 (61.1%)	52 (69.3%)	367 (59.1%)
CF, F/F (%)	21 (22.1%)	0 (0%)	52 (100%)	0 (0%)	7 (43.8%)	29 (43.9%)	7 (38.9%)	23 (30.7%)	132 (21.3%)
CF, F/G (%)	0 (0%)	0 (0%)	0 (0%)	38 (31.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	38 (6.1%)
CF, F/RF (%)	0 (0%)	0 (0%)	0 (0%)	84 (68.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	84 (13.5%)
White (%)	92 (96.8%)	183 (92.4%)	51 (98.1%)	113 (92.6%)	16 (100%)	57 (86.4%)	18 (100%)	67 (89.3%)	576 (92.8%)
Black or African American (%)	1 (1.1%)	3 (1.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (1.3%)	5 (0.8%)
Asian (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Multiple (%)	0 (0%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)	1 (1.5%)	0 (0%)	1 (1.3%)	3 (0.5%)
Other (%)	2 (2.1%)	11 (5.6%)	1 (1.9%)	9 (7.4%)	0 (0%)	8 (12.1%)	0 (0%)	6 (8%)	37 (6%)
Age, years (median [min, max])	30 [18, 58]	24 [12, 59]	27 [12, 53]	36.5 [12, 66]	8.5 [6, 11]	9 [6, 11]	3.5 [3, 5]	3.0 [2, 5]	23 [2, 66]
Age, years (mean [SD])	30.8 [8.8]	25.1 [9.7]	28.3 [11.8]	37.2 [14.3]	8.4 [1.9]	8.7 [1.8]	3.7 [0.8]	3.5 [1.0]	23.9 [14.8]
Body weight, kg (median [min, max])	63 [44, 111.1]	58 [29, 108]	59.5 [36, 83]	66.8 [37, 125.2]	28.5 [18.1, 42.8]	29 [18.1, 53.6]	16 [14.2, 21.9]	16.3 [10.8, 26]	55 [10.8, 125.2]
Body weight, kg (mean [SD])	63.1 [11.1]	59.9 [12.9]	59.6 [12.2]	69.3 [16.9]	29.3 [6.7]	30 [7.7]	16.6 [2]	16.5 [3.2]	53 [21.7]

max: maximum value; min: minimum value; N: total sample size; SD: standard deviation.

Note: 11 subjects were enrolled in both Parts A and B in Study 106, their baseline covariates were counted separately in each part. 10 subjects were enrolled in both Parts A and B in Study 111, their baseline covariates were counted separately in each part. In the overall, the covariates for these crossover subjects were only counted once.

Source: Table 6-5 in Population PK report S054

The M23-ELX final model was a linear, two compartment PopPK model with IIV on CLM and V2M, additive and proportional errors, and the following covariate effects:

- weight on CLM, QM, V2M, and V3M;
- adult female gender on CLM; and
- genotype on clearance.

The final parameter estimates are given in Table 20, and an age stratified pcVPCs plot is depicted in Figure 10.

Table 20 M23-ELX Population Pharmacokinetic Final Model Parameter Estimates

Parameters	Unit	Estimate	Relative Standard Error (%)	95% CI	IIV %CV or SD
Fraction metabolized, FM (fixed)		0.574			
Central clearance, CLM	L/h	1.75	5.28	[1.65,1.86]	53.7 (CV% ^a)
Central volume, V2M	L	11.6	2.95	[10.1,13.4]	60.9 (CV% ^a)
Intercompartmental clearance, QM	L/h	9.05	8.06	[6.39,12.8]	
Peripheral volume, V3M	L	20.0	3.54	[16.2,24.6]	
Weight cut point on allometric scaling	kg	53.6	0.108	[53.1,54.1]	
Allometric exponent for CLM and QM, POWCLM (fixed)		0.75			
Allometric exponent for V2M and V3M, POWV2M		0.768	10.3	[0.614,0.923]	
Adult female gender on Clearance, GENCL		-0.25	14.4	[-0.321,-0.18]	
Residual Function or Gating mutation on Clearance, GTNCL (prop)		0.71	5.83	[0.629,0.792]	
ω^2_{CL}		0.289	7.61	[0.246,0.332]	
ω^2_{V2}		0.371	19.0	[0.233,0.509]	
Residual variability, proportional		0.0724	5.6	[0.0644,0.0803]	26.9 (CV% ^a)
Residual variability, additive	(ng/mL) ²	73.6	43.4	[11,136]	8.58 (SD ^b)

Notes: Inter-individual variability estimates are reported as variances and prop indicate that the value is multiplicative of the typical value.

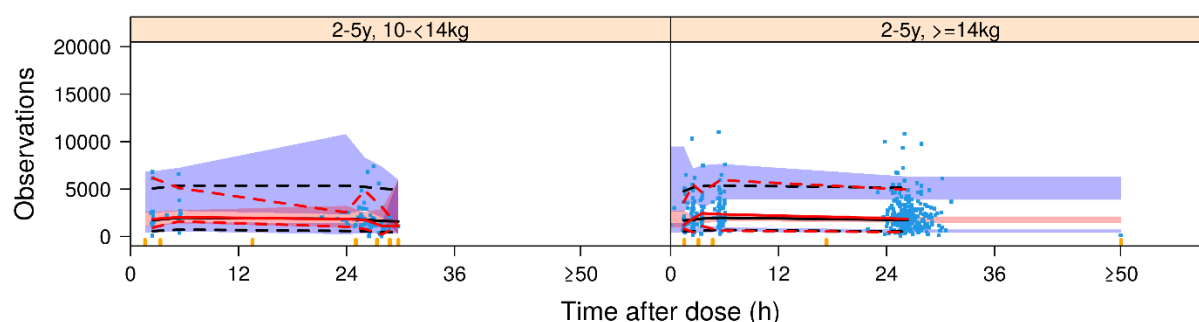
Model: run100.mod

^aParameter IIV CV% = square-root of the parameter IIV * 100

^bAdditive Error SD = square-root of the additive error variance.

Source: Table 6-7 in Population PK report S054

Figure 10 Prediction-Corrected Visual Predictive Checks (pcVPCs) of the M23-ELX Final Population PK Model



Source: Figure 6-14 Panel E in Population PK Analysis report S054

15.3.1.3. TEZ Population PK Model

The final TEZ population PK dataset was composed of 655 subjects contributing 4193 analyzable PK observations for model development. A summary of the demographics and disease characteristics are given in Table 23 and Table 26.

Table 21 TEZ: Baseline categorical covariate summary after all data exclusions

Study	n	Genotype				Sex	
		F/MF	F/F	F/G	F/RF	female	male
445-001	95	74 (77.9)	21 (22.1)	0 (0.0)	0 (0.0)	43 (45.3)	52 (54.7)
445-102	200	200 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	96 (48.0)	104 (52.0)
445-103	55	0 (0.0)	55 (100.0)	0 (0.0)	0 (0.0)	31 (56.4)	24 (43.6)
445-104	130	0 (0.0)	0 (0.0)	41 (31.5)	89 (68.5)	65 (50.0)	65 (50.0)
445-106, Part A	16	9 (56.2)	7 (43.8)	0 (0.0)	0 (0.0)	11 (68.8)	5 (31.2)
445-106, Part B	66	37 (56.1)	29 (43.9)	0 (0.0)	0 (0.0)	39 (59.1)	27 (40.9)
445-111, Part A	18	11 (61.1)	7 (38.9)	0 (0.0)	0 (0.0)	11 (61.1)	7 (38.9)
445-111, Part B	75	52 (69.3)	23 (30.7)	0 (0.0)	0 (0.0)	41 (54.7)	34 (45.3)
All data	655	383 (58.5)	142 (21.7)	41 (6.3)	89 (13.6)	337 (51.5)	318 (48.5)

Source: Table 3 in Population PK Analysis report S055

Table 22 TEZ: Baseline continuous covariate summary after all data exclusions

Study	n	Mean	Median	SD	Min	Q25	Q75	Max
Age (year)								
445-001	95	30.8	30.0	8.85	18.0	23.0	36.5	58.0
445-102	200	25.6	24.4	9.70	12.1	17.4	32.0	59.9
445-103	55	28.8	27.4	11.5	12.7	17.9	38.1	54.1
445-104	130	37.2	37.0	14.8	12.0	25.0	49.0	69.0
445-106, Part A	16	8.44	8.50	1.86	6.00	6.75	10.0	11.0
445-106, Part B	66	8.74	9.00	1.82	6.00	7.00	10.0	11.0
445-111, Part A	18	3.72	3.50	0.826	3.00	3.00	4.00	5.00
445-111, Part B	75	3.53	3.00	0.991	2.00	3.00	4.00	5.00
<i>All data</i>	655	23.7	23.0	15.1	2.00	11.0	34.0	69.0
Weight (kg)								
445-001	95	63.1	63.0	11.1	44.0	55.0	69.0	111
445-102	200	59.8	58.0	12.9	29.0	51.0	68.0	108
445-103	55	59.9	59.0	12.7	36.0	50.5	67.5	91.2
445-104	130	69.4	67.1	16.7	37.0	56.2	79.0	125
445-106, Part A	16	29.3	28.4	6.73	18.1	24.9	33.0	42.8
445-106, Part B	66	30.0	29.0	7.74	18.1	24.1	34.7	53.6
445-111, Part A	18	16.6	16.0	1.97	14.2	15.2	17.7	21.9
445-111, Part B	75	16.5	16.3	3.21	10.8	14.4	18.6	26.0
<i>All data</i>	655	52.3	55.0	22.1	10.8	35.8	67.0	125

Source: Table 3 in Population PK Analysis report S055

The structural component of the final TEZ population PK model was a two-compartment model with first-order absorption and an absorption lag time and was parameterized in terms of apparent clearance after oral dosing (CL/F), apparent central volume of distribution after oral dosing (Vc/F), apparent peripheral volume of distribution after oral dosing (Vp/F), apparent intercompartmental clearance after oral dosing (Q/F), first-order absorption rate constant (ka), and oral absorption lag time (ALAG).

The final parameter estimates are given in Table 23, and an age stratified prediction corrected Visual Predictive Checks (pcVPCs) plot is depicted in Figure 11.

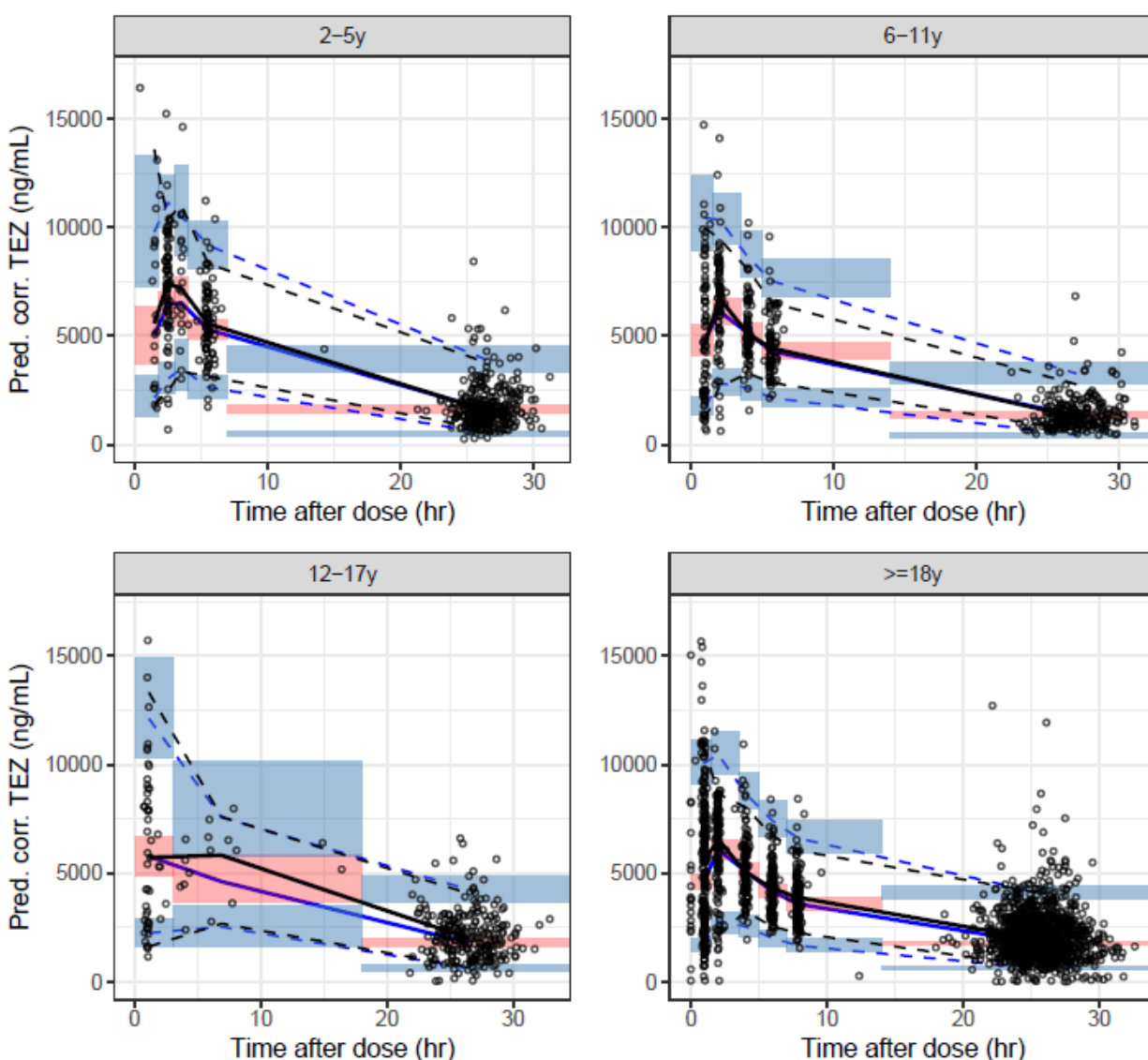
Table 23 TEZ Final model PK parameter estimates

NDA/BLA Multi-disciplinary Review and Evaluation 217660
Trikafta (elexacaftor/tezacaftor/ivacaftor) Oral Granules

			Estimate	%RSE	95% CI	SHK (%)
Structural model parameters						
CL/F (L/hr)	θ_1	Apparent clearance	1.36	1.98	1.31, 1.41	-
Vc/F (L)	θ_2	Apparent central volume	1.89	10.8	1.49, 2.29	-
Vp/F (L)	θ_3	Apparent peripheral volume	31.3	6.77	27.1, 35.4	-
Q/F (L/hr)	θ_4	Apparent intercompartmental clearance	2.93	9.54	2.38, 3.47	-
k_a (hr ⁻¹) [≥6y/tablet]	θ_5	First order absorption rate constant for age ≥6y and tablet	0.272	7.51	0.232, 0.312	-
k_a (hr ⁻¹) [<6y/granule]	θ_6	First order absorption rate constant for age <6y and granule	0.215	6.77	0.186, 0.244	-
ALAG (hr) [≥6y/tablet]	θ_7	Absorption lag time for age ≥6y and tablet	0.722	1.12	0.707, 0.738	-
ALAG (hr) [<6y/granule]	θ_8	Absorption lag time for age <6y and granule	1.25	3.99	1.15, 1.34	-
Covariate effect parameters						
CL _{WT} [WT≤CLWTCUT]	θ_9	Weight effect on CL/F for WT≤CLWTCUT	0.643	4.20	0.590, 0.696	-
CL _{WT} [WT>CLWTCUT]	θ_{10}	Weight effect on CL/F for WT>CLWTCUT	0.00	-	FIXED	-
CLWTCUT (kg)	θ_{11}	Weight cut point for CL/F effect	65.0	0.523	64.3, 65.7	-
CL _{GEN}	θ_{12}	F/RF or F/G genotype effect on CL/F	0.791	3.58	0.735, 0.846	-
Vc _{WT}	θ_{13}	Weight effect on Vc/F	0.914	11.6	0.707, 1.12	-
Vp _{WT}	θ_{14}	Weight effect on Vp/F	1.00	-	FIXED	-
Q _{WT}	θ_{15}	Weight effect on Q/F	0.750	-	FIXED	-
Interindividual variance parameters						
IIV-CL/F	$\Omega_{(1,1)}$	Variance of CL/F	0.0908 [CV%=30.8]	7.64	0.0772, 0.104	6.64
IIV-Vc/F	$\Omega_{(2,2)}$	Variance of Vc/F	1.66 [CV%=207]	11.2	1.30, 2.03	31.1
Residual variance						
Proportional	$\Sigma_{(1,1)}$	Variance	0.0787 [CV%=28.0]	5.10	0.0708, 0.0865	-
Additive	$\Sigma_{(2,2)}$	Variance	4.15e+04 [SD=204]	20.8	2.46e+04, 5.84e+04	-

Source: Table 4 in Population PK Analysis report S055

Figure 11 TEZ Final model: Prediction-corrected VPC: stratified by age group



Observed concentrations at steady state are plotted (black circles) vs. time after dose with the 5th (black dashed line), 50th (black solid line), and 95th percentiles (black dashed line) of the observed data. The red shaded area represents the 90% prediction bands of the 50th percentile of the simulated data (blue solid line). The blue shaded area represents the 90% prediction bands of the 5th and 95th percentiles of the simulated data (blue dash lines).

Source: Figure 53 in Population PK Analysis report S055

15.3.1.4. M1-TEZ Population PK Model

The final M1-TEZ population PK dataset was composed of 655 subjects contributing 4188 analyzable PK observations for model development. A summary of the demographics and disease characteristics are given in Table 24 and Table 25.

Table 24 M1-TEZ: Baseline categorical covariate summary after all data exclusions

Study	n	Genotype				Sex	
		F/MF	F/F	F/G	F/RF	female	male
445-001	95	74 (77.9)	21 (22.1)	0 (0.0)	0 (0.0)	43 (45.3)	52 (54.7)
445-102	200	200 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	96 (48.0)	104 (52.0)
445-103	55	0 (0.0)	55 (100.0)	0 (0.0)	0 (0.0)	31 (56.4)	24 (43.6)
445-104	130	0 (0.0)	0 (0.0)	41 (31.5)	89 (68.5)	65 (50.0)	65 (50.0)
445-106, Part A	16	9 (56.2)	7 (43.8)	0 (0.0)	0 (0.0)	11 (68.8)	5 (31.2)
445-106, Part B	66	37 (56.1)	29 (43.9)	0 (0.0)	0 (0.0)	39 (59.1)	27 (40.9)
445-111, Part A	18	11 (61.1)	7 (38.9)	0 (0.0)	0 (0.0)	11 (61.1)	7 (38.9)
445-111, Part B	75	52 (69.3)	23 (30.7)	0 (0.0)	0 (0.0)	41 (54.7)	34 (45.3)
All data	655	383 (58.5)	142 (21.7)	41 (6.3)	89 (13.6)	337 (51.5)	318 (48.5)

Source: Table 10 in Population PK Analysis report S055

Table 25 M1-TEZ: Baseline continuous covariate summary after all data exclusions

Study	n	Mean	Median	SD	Min	Q25	Q75	Max
Age (year)								
445-001	95	30.8	30.0	8.85	18.0	23.0	36.5	58.0
445-102	200	25.6	24.4	9.70	12.1	17.4	32.0	59.9
445-103	55	28.8	27.4	11.5	12.7	17.9	38.1	54.1
445-104	130	37.2	37.0	14.8	12.0	25.0	49.0	69.0
445-106, Part A	16	8.44	8.50	1.86	6.00	6.75	10.0	11.0
445-106, Part B	66	8.74	9.00	1.82	6.00	7.00	10.0	11.0
445-111, Part A	18	3.72	3.50	0.826	3.00	3.00	4.00	5.00
445-111, Part B	75	3.53	3.00	0.991	2.00	3.00	4.00	5.00
<i>All data</i>	655	23.7	23.0	15.1	2.00	11.0	34.0	69.0
Weight (kg)								
445-001	95	63.1	63.0	11.1	44.0	55.0	69.0	111
445-102	200	59.8	58.0	12.9	29.0	51.0	68.0	108
445-103	55	59.9	59.0	12.7	36.0	50.5	67.5	91.2
445-104	130	69.4	67.1	16.7	37.0	56.2	79.0	125
445-106, Part A	16	29.3	28.4	6.73	18.1	24.9	33.0	42.8
445-106, Part B	66	30.0	29.0	7.74	18.1	24.1	34.7	53.6
445-111, Part A	18	16.6	16.0	1.97	14.2	15.2	17.7	21.9
445-111, Part B	75	16.5	16.3	3.21	10.8	14.4	18.6	26.0
<i>All data</i>	655	52.3	55.0	22.1	10.8	35.8	67.0	125

Source: Table 11 in Population PK Analysis report S055

The structural component of the final M1-TEZ model was a two-compartment model parameterized in terms of CL/F, Vc/F, Vp/F, and Q/F.

The final parameter estimates are given in Table 26, and an age stratified prediction corrected Visual Predictive Checks (pcVPCs) plot is depicted in Figure 12.

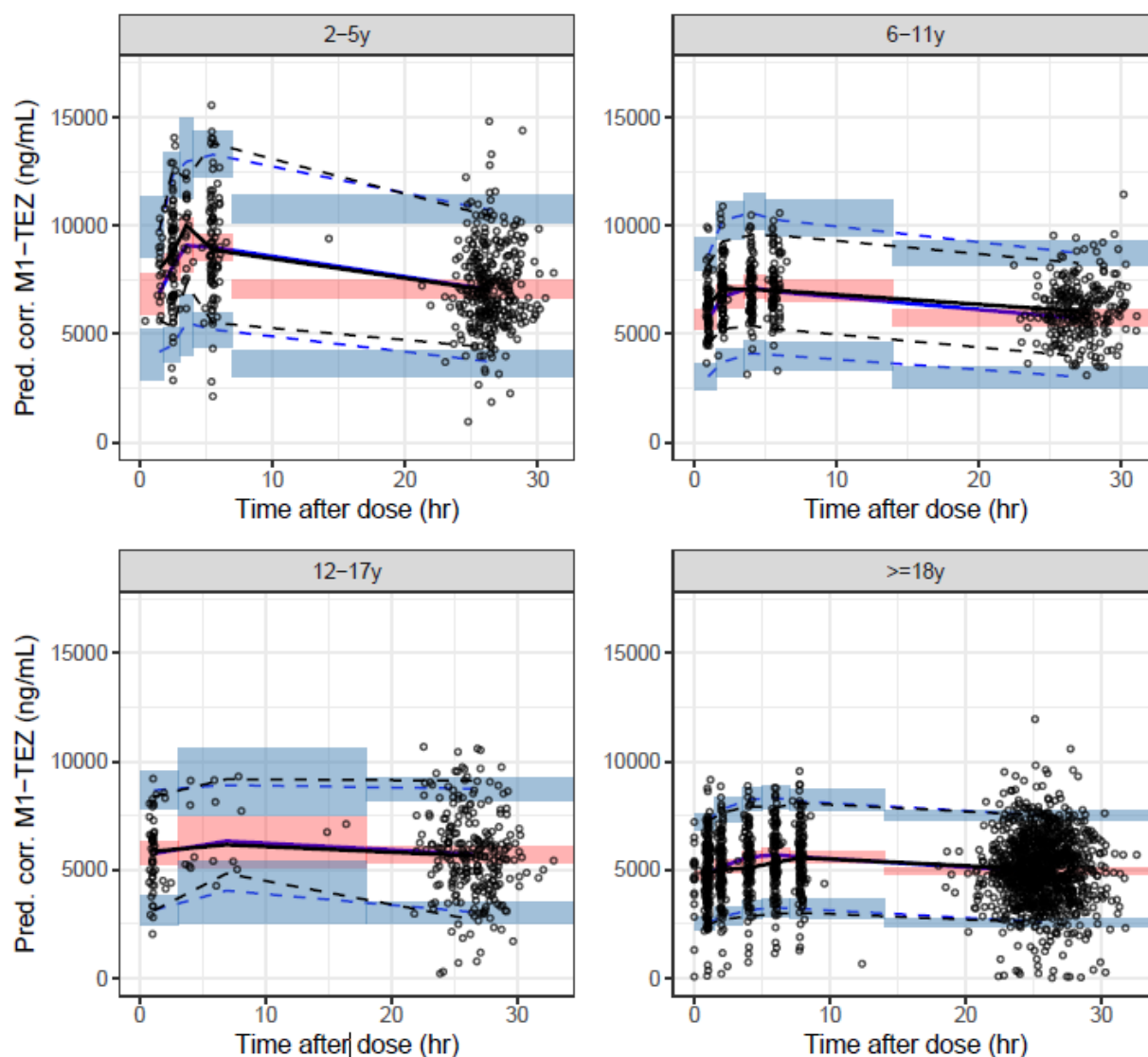
Table 26 M1-TEZ Final model PK parameter estimates

NDA/BLA Multi-disciplinary Review and Evaluation 217660
Trikafta (elexacaftor/tezacaftor/ivacaftor) Oral Granules

			Estimate	%RSE	95% CI	SHK (%)
Structural model parameters						
CL/F (L/hr)	θ_1	Apparent clearance	0.673	1.64	0.652, 0.695	-
Vc/F (L)	θ_2	Apparent central volume	7.64	5.77	6.78, 8.51	-
Q/F (L/hr)	θ_3	Apparent intercompartmental clearance	2.26	4.98	2.04, 2.48	-
Vp/F (L)	θ_4	Apparent peripheral volume	52.5	8.53	43.7, 61.3	-
FM1	-	Fraction of TEZ converted to M1-TEZ	0.8	-	FIXED	-
Covariate effect parameters						
CL _{WT}	θ_5	Weight effect on clearance parameters CL/F and Q/F	0.845	2.42	0.805, 0.885	-
V _{WT}	θ_6	Weight effect on volume parameters Vc/F and Vp/F	1.26	7.21	1.08, 1.44	-
CL _{GEN}	θ_8	F/RF or F/G genotype effect on CL/F	0.800	2.45	0.762, 0.839	-
Interindividual variance parameters						
BC for IIV-CL/F	θ_7	Box-Cox transformation factor	1.43	15.0	1.01, 1.85	-
IIV-BC-CL/F	$\Omega_{(1,1)}$	Variance of Box-Cox transformed CL/F	0.0596	8.93	0.0491, 0.0700	6.52
IIV-Vc/F	$\Omega_{(2,2)}$	Variance of Vc/F	0.364 [CV%=66.2]	19.1	0.227, 0.500	34.4
Interindividual covariance parameters						
CL/F-Vc/F	$\Omega_{(2,1)}$	Covariance of CL/F-Vc/F	0.0658 [Corr=0.447]	-	0.0469, 0.0847	-
Residual variance						
Proportional	$\Sigma_{(1,1)}$	Variance	0.0247 [CV%=15.7]	7.12	0.0213, 0.0282	-
Additive	$\Sigma_{(2,2)}$	Variance	3.10e+05 [SD=556]	17.4	2.04e+05, 4.15e+05	-

Source: Table 12 in Population PK Analysis report S055

Figure 12 M1-TEZ: Final model: Prediction-corrected VPC: stratified by age group



Observed concentrations at steady state are plotted (black circles) vs. time after dose with the 5th (black dashed line), 50th (black solid line), and 95th percentiles (black dashed line) of the observed data. The red shaded area represents the 90% prediction bands of the 50th percentile of the simulated data (blue solid line). The blue shaded area represents the 90% prediction bands of the 5th and 95th percentiles of the simulated data (blue dash lines).

Source: Figure 121 in Population PK Analysis report S055

15.3.1.5. IVA Population PK Model

The final TEZ population PK dataset was composed of 634 subjects contributing 3974 analyzable PK observations for model development. A summary of the demographics and disease characteristics are given in Table 27 and Table 28.

Table 27 IVA: Baseline categorical covariate summary after all data exclusions

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Study	n	Genotype				Sex	
		F/MF	F/F	F/G	F/RF	female	male
445-001	74	53 (71.6)	21 (28.4)	0 (0.0)	0 (0.0)	33 (44.6)	41 (55.4)
445-102	200	200 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	96 (48.0)	104 (52.0)
445-103	55	0 (0.0)	55 (100.0)	0 (0.0)	0 (0.0)	31 (56.4)	24 (43.6)
445-104	130	0 (0.0)	0 (0.0)	41 (31.5)	89 (68.5)	65 (50.0)	65 (50.0)
445-106, Part A	16	9 (56.2)	7 (43.8)	0 (0.0)	0 (0.0)	11 (68.8)	5 (31.2)
445-106, Part B	66	37 (56.1)	29 (43.9)	0 (0.0)	0 (0.0)	39 (59.1)	27 (40.9)
445-111, Part A	18	11 (61.1)	7 (38.9)	0 (0.0)	0 (0.0)	11 (61.1)	7 (38.9)
445-111, Part B	75	52 (69.3)	23 (30.7)	0 (0.0)	0 (0.0)	41 (54.7)	34 (45.3)
All data	634	362 (57.1)	142 (22.4)	41 (6.5)	89 (14.0)	327 (51.6)	307 (48.4)

Source: Table 18 in Population PK Analysis report S055

Table 28 IVA: Baseline continuous covariate summary after all data exclusions

Study	n	Mean	Median	SD	Min	Q25	Q75	Max
Age (year)								
445-001	74	30.9	30.5	8.72	18.0	23.0	35.8	58.0
445-102	200	25.6	24.4	9.70	12.1	17.4	32.0	59.9
445-103	55	28.8	27.4	11.5	12.7	17.9	38.1	54.1
445-104	130	37.2	37.0	14.8	12.0	25.0	49.0	69.0
445-106, Part A	16	8.44	8.50	1.86	6.00	6.75	10.0	11.0
445-106, Part B	66	8.74	9.00	1.82	6.00	7.00	10.0	11.0
445-111, Part A	18	3.72	3.50	0.826	3.00	3.00	4.00	5.00
445-111, Part B	75	3.53	3.00	0.991	2.00	3.00	4.00	5.00
<i>All data</i>	634	23.5	22.4	15.2	2.00	11.0	33.6	69.0
Weight (kg)								
445-001	74	63.2	63.5	10.2	44.0	55.0	69.8	86.6
445-102	200	59.8	58.0	12.9	29.0	51.0	68.0	108
445-103	55	59.9	59.0	12.7	36.0	50.5	67.5	91.2
445-104	130	69.4	67.1	16.7	37.0	56.2	79.0	125
445-106, Part A	16	29.3	28.4	6.73	18.1	24.9	33.0	42.8
445-106, Part B	66	30.0	29.0	7.74	18.1	24.1	34.7	53.6
445-111, Part A	18	16.6	16.0	1.97	14.2	15.2	17.7	21.9
445-111, Part B	75	16.5	16.3	3.21	10.8	14.4	18.6	26.0
<i>All data</i>	634	52.0	55.0	22.2	10.8	35.0	67.0	125

Source: Table 19 in Population PK Analysis report S055

The structural component of the final model was a one-compartment model with first-order absorption and an absorption lag time parameterized in terms of CL/F, apparent volume of distribution after oral dosing (V/F), k_a , and ALAG.

The final parameter estimates are given in Table 29, and an age stratified prediction corrected Visual Predictive Checks (pcVPCs) plot is depicted in Figure 13.

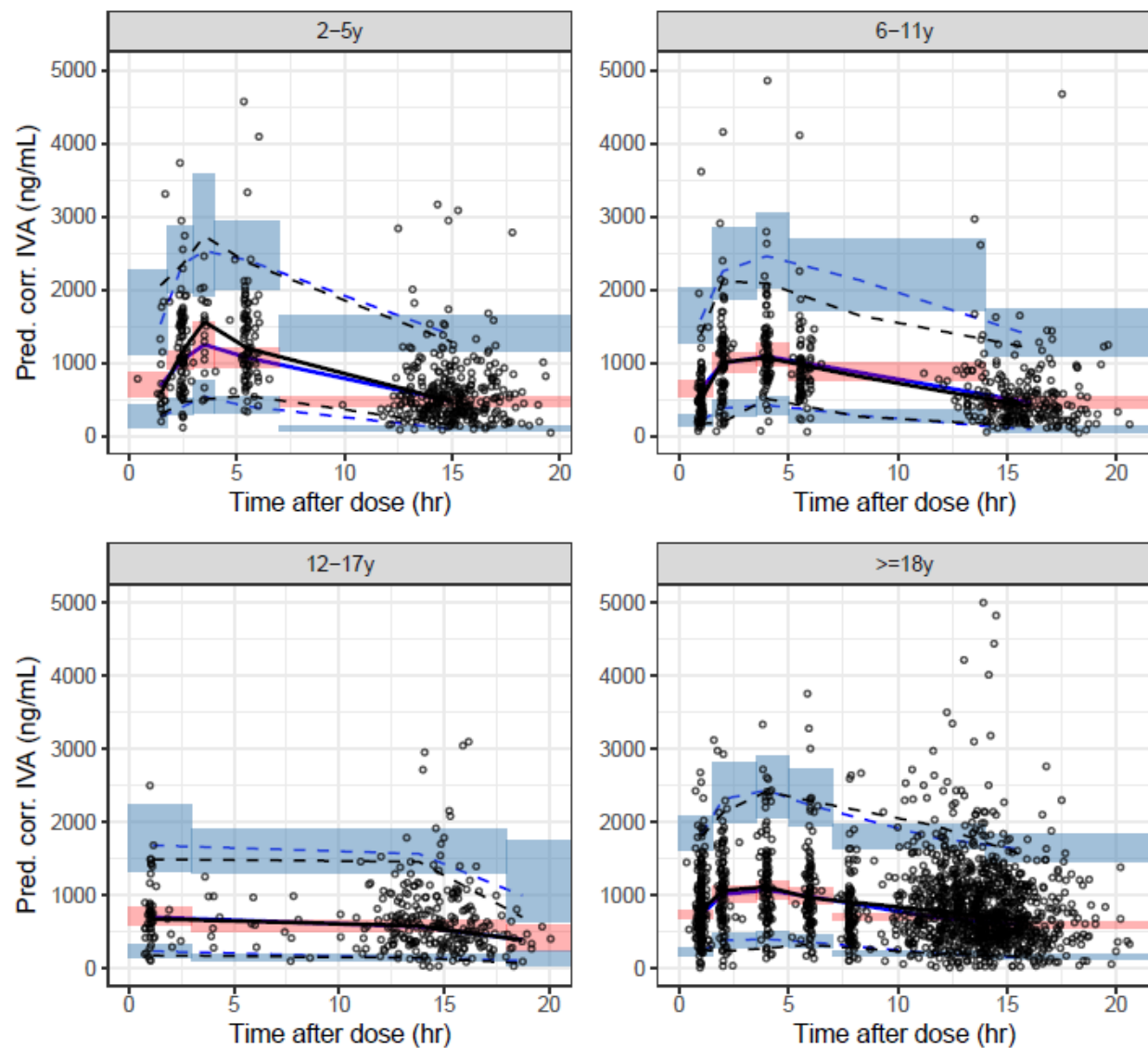
Table 29 IVA Final model PK parameter estimates

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			Estimate	%RSE	95% CI	SHK (%)
Structural model parameters						
CL/F (L/hr)	θ_1	Apparent clearance	13.6	3.07	12.7, 14.4	-
V/F (L)	θ_2	Apparent volume	234	5.67	208, 260	-
k_a (hr ⁻¹)	θ_3	First order absorption rate constant	0.751	8.46	0.627, 0.876	-
ALAG (hr)	θ_4	Absorption lag time	0.674	5.34	0.603, 0.744	-
Covariate effect parameters						
CL _{WT} [WT≤CLWTCUT]	θ_5	Weight effect on CL/F for WT≤CLWTCUT	0.750	-	FIXED	-
CL _{WT} [WT>CLWTCUT]	θ_6	Weight effect on CL/F for WT>CLWTCUT	0.00	-	FIXED	-
CLWTCUT (kg)	θ_7	Weight cut point for CL/F effect	44.2	5.98	39.0, 49.4	-
CL _{FD}	θ_8	First dose effect on CL/F	1.20	6.11	1.05, 1.34	-
CL _{GEN}	θ_9	F/RF or F/G genotype effect on CL/F	0.779	4.64	0.708, 0.849	-
V _{WT}	θ_{10}	Weight effect on V/F	0.856	5.93	0.756, 0.955	-
F _{age,SS}	θ_{11}	6-11y, steady-state Frel adjustment	1.22	4.70	1.11, 1.34	-
ALAG _{age,formulation}	θ_{12}	<6y/granule effect on ALAG	1.76	9.37	1.44, 2.09	-
Interindividual variance parameters						
IIV-CL/F	$\Omega_{(1,1)}$	Variance of CL/F	0.215 [CV%=48.9]	8.31	0.180, 0.249	7.57
IIV-V/F	$\Omega_{(2,2)}$	Variance of V/F	0.257 [CV%=54.1]	12.7	0.193, 0.321	28.3
Interindividual covariance parameters						
CL/F-V/F	$\Omega_{(2,1)}$	Covariance of CL/F-V/F	0.137 [Corr=0.586]	-	0.102, 0.173	-
Residual variance						
Proportional	$\Sigma_{(1,1)}$	Variance	0.0825 [CV%=28.7]	7.49	0.0704, 0.0946	-
Additive	$\Sigma_{(2,2)}$	Variance	1.34e+04 [SD=116]	14.3	9.65e+03, 1.72e+04	-

Source: Table 20 in Population PK Analysis report S055

Figure 13 IVA: Final model: Prediction-corrected VPC: stratified by age group



Source: Figure 189 in Population PK Analysis report S055

15.4. Schedule of Assessments

Part A

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Table 30: Study 111 Part A - Screening Period

Event/Assessment	Screening Visit Day -28 to Day -1	Comments
Informed consent (and assent)	X	
Demographics	X	Section 11.1
Medical history	X	Section 11.1
Ophthalmologic examination	X	Conducted by an ophthalmologist or optometrist (Section 11.5.5)
Full physical examination	X	Section 11.5.3
Weight and height	X	Measured with shoes off (Section 11.4.3)
Vital signs and pulse oximetry	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Standard 12-lead ECG	X	Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4)
CF genotype (all subjects)	X	If the <i>CFTR</i> genotype result is not received before the first dose of study drug, a previous <i>CFTR</i> genotype laboratory report may be used to establish eligibility (Section 8.1). Subjects who have been enrolled whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9).
Serum chemistry	X	Section 11.5.2
Hematology	X	
Coagulation	X	
Urinalysis	X	
Medications review	X	Information regarding medications taken within 56 days before the Screening Visit will be collected (Section 9.5)
Adverse events	Continuous, From Signing of ICF through Completion of Study Participation	Section 13.1; completion of study participation is defined in Section 9.1.6.

AE: adverse event; *CFTR*: cystic fibrosis transmembrane conductance regulator gene; ECG: electrocardiogram; HR: heart rate; ICF: informed consent form; SAE: serious adverse event

Source: VX20-445-111 Protocol, Table 3-1

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Table 31: Study 111 Part A - Treatment Period and Safety Follow-up Visit

Assessment ^a	Day 1	Day 2 and Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)	Comments
Clinic visit	X		X	X	X	X	See Section 9.1.8 for use of remote measures in extenuating circumstances.
Telephone contact		X					Assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
Safety Assessments							
Full physical examination	X			X	X	X	Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator (Section 11.5.3).
Weight and height	X			X	X	X	Measured with shoes off (Section 11.4.3).
Vital signs and pulse oximetry	X		X	X	X	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3).
Standard 12-lead ECG	X		X	X	X	X	Days 1 and 8: before the AM dose Day 15: before the AM dose and 4 hours (± 30 min) after the AM dose Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Serum chemistry	X		X	X	X	X	Section 11.5.2
Hematology	X		X	X	X	X	
Coagulation	X			X			
Observation 4 hours after the AM dose	X						Section 9.6.1
Medications review	Continuous, From Signing of ICF Through Completion of Study Participation						Completion of study participation is defined in Section 9.1.6.
Treatments and procedures review							
Adverse events	Continuous, From Signing of ICF Through Completion of Study Participation						Section 13.1; completion of study participation is defined in Section 9.1.6.

^a All assessments will be performed before study drug dosing (within 60 minutes) unless noted otherwise.

Assessment ^a	Day 1	Day 2 and Day 4 (± 1 Day)	Day 8 (± 1 Day)	Day 15 (± 1 Day)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After Last Dose of Study Drug)	Comments
PK Assessments							
PK sampling	X		X	X			Day 1: before the AM dose, and at 2 hours after the AM dose Day 8: before the AM dose, and at 1.5 hours after the AM dose Day 15: before the AM dose, and at 3.5 and 6 hours after the AM dose If study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug), only 1 PK blood sample will be collected. See Table 11-1 for details.
Study Drug Administration							
Study drug dosing	ELX/TEZ/IVA (Day 1 through Day 15; AM dose only on Day 15)						Administered within approximately 30 minutes of consuming fat-containing food (e.g., standard "CF" meal or snack) (Section 9.6.1). On scheduled visits, the AM dose of study drug will be administered at the site after predose assessments have been completed.
Study drug count			X	X	X		Section 10.4

AE: adverse event; AM: morning; ECG: electrocardiogram; ELX: elexacaftor; ETT: early termination of treatment; HR: heart rate; ICF: informed consent form; IVA: ivacaftor; PK: pharmacokinetic; SAE: serious adverse event; TEZ: tezacaftor

Source: VX20-445-111 Protocol, Table 3-2

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Part B

Table 32: Study 111, Part B - Screening Period

Event/Assessment	Screening Visit Day -28 to Day -1	Comments
Informed consent (and assent)	X	
Demographics	X	Section 11.1
Medical history	X	Section 11.1
Ophthalmologic examination	X	Conducted by an ophthalmologist or optometrist (Section 11.5.5)
Full physical examination	X	Section 11.5.3
Weight and height	X	Measured with shoes off (Section 11.4.3)
Vital signs and pulse oximetry	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3)
Standard 12-lead ECG	X	Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4)
Multiple-breath washout	X	Performed in multiple replicates pre- or post-bronchodilator in subjects ≥ 3 years of age at screening (Section 11.4.2).
Sweat chloride	X	Section 11.4.1
CF genotype (all subjects)	X	If the <i>CFTR</i> genotype result is not received before the first dose of study drug, a previous <i>CFTR</i> genotype laboratory report may be used to establish eligibility (Section 8.1). This assessment does not need to be repeated for confirmed subjects in Part A who wish to participate in Part B. Subjects who have been enrolled whose screening genotype does not confirm study eligibility must be discontinued from the study (Section 9.9). If a subject weighs < 11 kg at the Screening Visit and requires an additional blood sample for a deletion/duplication assay, this second tube should be drawn at the Day 1 Visit.
Fecal sample collection	X	Collected at the study site during the study visit; alternatively, samples may be collected by the subject's caregiver up to 24 hours before the Day 1 visit at home and brought to the study visit (Section 11.3.1).
Serum chemistry	X	Must be obtained from a blood draw taken up to 9 days before Day 1 dosing. The results must be received and reviewed before the first dose of study drug (Section 11.5.2).
Hematology	X	A single set of pre-dose hematology and coagulation assessments will be obtained from a blood draw taken up to 9 days before Day 1 dosing. The results must be received and reviewed before the first dose of study drug (Section 11.5.2).
Coagulation	X	
Urinalysis	X	Section 11.5.2
Medications review	X	Information regarding medications taken within 56 days before the Screening Visit will be collected (Section 9.5)
Adverse events	Continuous, From Signing of ICF through Completion of Study Participation	Section 13.1; completion of study participation is defined in Section 9.1.6.

AE: adverse event; CFTR: cystic fibrosis transmembrane conductance regulator gene; ECG: electrocardiogram; HR: heart rate; ICF: informed consent form; SAE: serious adverse event

Source: VX20-445-111 Protocol, Table 3-3

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Table 33: Study 111, Part B - Treatment Period and Safety Follow-up Visit

Event/ Assessment ^a	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug ^b)	Comments
Clinic visit	X		X	X	X	X	X		X	X	X	See Section 9.1.8 for use of remote measures in extenuating circumstances.
Telephone contact		X						X				Assess the subject's status, any AEs, concomitant medications, treatments, and procedures.
Safety and Efficacy Assessments												
Ophthalmologic examination								X at or up to 4 weeks before		X		Section 11.5.5
Full physical examination	X					X			X	X		Symptom-directed physical examinations will occur at any time during the study if deemed necessary by the investigator (Section 11.5.3).
Weight and height	X		X	X	X	X	X		X	X	X	Measured with shoes off (Section 11.4.3).

^a All assessments will be performed before study drug dosing unless noted otherwise. For any assessments with multiple time points for an individual visit, only 1 set of assessments will be collected if study drug is not administered on the day of the visit (i.e., study drug interruption or permanent discontinuation of study drug).

^b The Safety Follow-up Visit is not required for subjects who complete the Week 24 Visit and enroll in the open-label extension (OLE) safety study within 28 days after the last dose.

Event/ Assessment ^a	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug ^b)	Comments
Vital signs and pulse oximetry	X		X	X	X	X	X		X	X	X	Performed after the subject has been at rest for at least 5 minutes (Section 11.5.3).
Standard 12-lead ECG	X		X			X			X	X	X	Performed before any other procedures that may affect heart rate (HR), such as blood draws, and in the supine position after the subject has been at rest for at least 5 minutes (Section 11.5.4).
Sweat chloride	X			X		X			X	X		Section 11.4.1
Multiple-breath washout	X			X		X			X	X		Performed in multiple replicates pre-bronchodilator in subjects ≥3 years of age at screening (Section 11.4.2).

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Event/ Assessment ^a	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug ^b)	Comments
Serum chemistry	X		X	X	X	X	X	X	X	X	X	Serum chemistry will be drawn prior to study drug dosing on Day 1. Liver function testing (ALT, AST, GGT, ALP, and total bilirubin) must be performed at the scheduled visits and at Week 20 (a minimum of every 4 weeks after Week 4). A local laboratory may be used for the Week 20 sample if a subject cannot return to the study site for the blood draw (Section 11.5.2).
Hematology			X	X ^c	X	X	X		X	X	X	Section 11.5.2
Coagulation									X	X	X	
Urinalysis	X								X	X		

^c It is recommended that subjects weighing <10.4 kg do not complete the Week 4 hematology blood draw.

Event/ Assessment ^a	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug ^b)	Comments
Observation 4 hours after the AM dose	X											Section 9.6.1
Other events related to outcome	Continuous, From Signing of ICF Through Completion of Study Participation											Includes PEX, administration of antibiotic therapy for sinopulmonary signs/symptoms, and hospitalizations for CF (Section 11.4.4). Completion of study participation is defined in Section 9.1.6.
Medications review	Continuous, From Signing of ICF Through Completion of Study Participation											Completion of study participation is defined in Section 9.1.6.
Treatments and procedures review												
Adverse events	Continuous, From Signing of ICF Through Completion of Study Participation											Section 13.1; completion of study participation is defined in Section 9.1.6.

Event/ Assessment ^a	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug ^b)	Comments
Biomarker Assessments												
Fecal sample collection	X		X	X		X			X	X		Samples may be collected by the subject's caregiver up to 24 hours before the study visit at home and brought to the study visit (Section 11.3.1). Samples may be collected pre- or postdose. Subjects who provide a fecal sample at the Screening Visit do not need to provide a sample on Day 1.
Blood biomarker sample (IRT)	X		X		X	X			X	X		The Day 1 blood biomarker sample (IRT) may be drawn at screening to minimize the total amount of blood taken at the Day 1 Visit (results not expected before the first dose; Section 11.3.1)

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Event/ Assessment ^a	Day 1	Day 3 (± 1 day)	Day 15 (± 3 days)	Week 4 (± 5 days)	Week 8 (± 5 days)	Week 12 (± 5 days)	Week 16 (± 5 days)	Week 20 (± 5 days)	Week 24 (± 5 days)	ETT Visit	Safety Follow-up Visit (28 ± 7 Days After the Last Dose of Study Drug ^b)	Comments
PK Assessments												
PK sampling			X	X		X	X			X		Day 15, Week 12, and Week 16: before the AM dose Week 4: before the AM dose, and at 2.5 and 5.5 hours after the AM dose. See Table 11-1 for details.
Study Drug Administration												
Study drug dosing	ELX/TEZ/IVA (Day 1 through evening before Week 24 Visit)											Administered within approximately 30 minutes of consuming fat-containing food (e.g., standard "CF" meal or snack) (Section 9.6.1). On scheduled visits, the AM dose of study drug will be administered at the site after predose assessments have been completed.
Acceptability/palatability assessment	X								X			Section 11.3.2
Study drug count			X	X	X	X	X		X	X		Section 10.4

AE: adverse event; ALP: alkaline phosphatase; ALT: alanine transaminase; AST: aspartate transaminase; ECG: electrocardiogram; ELX: elexacaftor; ETT: early termination of treatment;
GGT: gamma-glutamyl transferase; HR: heart rate; ICF: informed consent form; IRT: immunoreactive trypsinogen; IVA: ivacaftor; PEx: pulmonary exacerbation; PK: pharmacokinetic;
SAE: serious adverse event; TEZ: tezacaftor

Source: VX20-445-111 Protocol, Table 3-4

15.5. Eligible CFTR Mutations

The protocol defined minimal function (MF) mutations as a subset of CFTR mutations that are non-responsive to IVA and TEZ/IVA. A mutation is considered a MF mutation if it meets at least 1 of the following criteria

- No biologic plausibility of translated protein (genetic sequence predicts the complete absence of CFTR protein)
- In vitro testing supports lack of responsiveness to IVA and TEZ/IVA

The Applicant considered mutations as MF mutations based on in vitro testing that met the following criteria:

- Baseline Cl⁻ transport <10% of wildtype CFTR
- Increase in Cl⁻ transport <10% over baseline following the addition of IVA and TEZ/IVA in the assay

The non-exhaustive list of MF CFTR mutations provided by the Applicant is included in Table 34. Investigators were to contact the medical monitor to discuss other mutations not included on this list to assess for potential study eligibility.

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Table 34: Non-exhaustive List of Minimal Function CFTR mutations Eligible for Study 111

Q2X	L218X	Q525X	R792X	E1104X
S4X	Q220X	G542X	E822X	W1145X
W19X	Y275X	G550X	W882X	R1158X
G27X	C276X	Q552X	W846X	R1162X
Q39X	Q290X	R553X	Y849X	S1196X
W57X	G330X	E585X	R851X	W1204X
E60X	W401X	G673X	Q890X	L1254X
R75X	Q414X	Q685X	S912X	S1255X
L88X	S434X	R709X	Y913X	W1282X
E92X	S466X	K710X	Q1042X	Q1313X
Q98X	S489X	Q715X	W1089X	Q1330X
Y122X	Q493X	L732X	Y1092X	E1371X
E193X	W496X	R764X	W1098X	Q1382X
W216X	C524X	R785X	R1102X	Q1411X
185+1G>T	711+5G>A	1717-8G>A	2622+1G>A	3121-1G>A
296+1G>A	712-1G>T	1717-1G>A	2790-1G>C	3500-2A>G
296+1G>T	1248+1G>A	1811+1G>C	3040G>C (G970R)	3600+2insT
405+1G>A	1249-1G>A	1811+1.6kA>G		3850-1G>A
405+3A>C	1341+1G>A	1811+1643G>T	3120G>A	4005+1G>A
406-1G>A	1525-2A>G	1812-1G>A	3120+1G>A	4374+1G>T
621+1G>T	1525-1G>A	1898+1G>A	3121-2A>G	
711+1G>T		1898+1G>C		
182delT	1119delA	1782delA	2732insA	3791delC
306insA	1138insG	1824delA	2869insG	3821delT
365-366insT	1154insTC	1833delT	2896insAG	3876delA
394delTT	1161delC	2043delG	2942insT	3878delG
442delA	1213delT	2143delT	2957delT	3905insT
444delA	1259insA	2183AA>G ^a	3007delG	4016insT
457TAT>G	1288insTA	2184delA	3028delA	4021dupT
541delC	1343delG	2184insA	3171delC	4022insT
574delA	1471delA	2307insA	3171insC	4040delA
663delT	1497delGG	2347delG	3271delGG	4279insA
849delG	1548delG	2585delT	3349insT	4326delTC
935delA	1609del CA	2594delGT	3659delC	
1078delT	1677delTA	2711delT	3737delA	
CFTRdele1	CFTRdele16-17b	991del5		
CFTRdele2	CFTRdele17a,17b	1461ins4		
CFTRdele2,3	CFTRdele17a-18	1924del7		
CFTRdele2-4	CFTRdele19	2055del9>A		
CFTRdele3-10,14b-16	CFTRdele19-21	2105-2117del13insAGAAA		
CFTRdele4-7	CFTRdele21	2372del8		
CFTRdele4-11	CFTRdele22-24	2721del11		
CFTR50kdel	CFTRdele22,23	2991del32		
CFTRdup6b-10	124del23bp	3121-977_3499+248del2515		
CFTRdele11	306delTAGA	3667ins4		
CFTRdele13,14a	602del14	4010del4		
CFTRdele14b-17b	852del22	4209TGTT>AA		
A46D	V520F	Y569D	N1303K	
G85E	A559T	L1065P		
R347P	R560T	R1066C		
L467P	R560S	L1077P		
I507del	A561E	M1101K		

CFTR: cystic fibrosis transmembrane conductance regulator gene

Source: CFTR2.org. Clinical and functional translation of CFTR. The Clinical and Functional Translation of CFTR (CFTR2), US Cystic Fibrosis Foundation, Johns Hopkins University, the Hospital for Sick Children. Available at: <http://www.cftr2.org>. Accessed 15 February 2016.

^a Also known as 2183delAA>G.

Source: VX20-445-111 Protocol, Appendix A

Table 35 lists the CFTR mutations other than *F508del* that are considered to be responsive to ELX/TEZ/IVA based on *in vitro* data.

Table 35: CFTR Mutations Responsive to ELX/TEZ/IVA Based on *in vitro* Data

3141del9	G126D	R334L	S549R	H939R	W1098C
S46insCTA	H139R	R334Q	G551D	S945L	F1099L
P5L	I148T	I336K	G551S	M952I	M1101K
S13F	M152V	T338I	R553Q	M952T	I1139V
L15P	Y161D	S341P	A554E	L967S	D1152H
G27R	Y161S	L346P	V562I	G970D	V1153E
R31L	L165S	R347H	Y563N	S977F	S1159P
A46D	R170H	R347L	P574H	D979V	S1159P
E56K	I175V	R347P	F575Y	I980K	R1162L
E60K	G178E	A349V	G576A	L997F	V1240G
P67L	G178R	R352Q	G576A;R668C [†]	A1006E	G1244E
R74Q	F191V	R352W	D579G	Y1014C	G1249R
R74W	D192G	Q359R	E588V	F1016S	S1251N
R74W;V201M [†]	E193K	W361R	S589N	I1027T	S1255P
R74W;V201M;D1270N [†]	G194R	S364P	I601F	Y1032C	I1269N
R74W;D1270N [†]	G194V	E403D	D614G	T1036N	D1270N
R75Q	H199Y	D443Y;G576A;R668C [†]	I618T	F1052V	W1282R
G85E	V201M	D443Y	G622D	T1053I	R1283M
E92K	P205S	L453S	G628R	H1054D	R1283S
Q98R	L206W	A455E	R668C	K1060T	Q1291R
Y109N	V232D	V456A	S737F	G1061R	V1293G
D110E	A234D	V456F	R751L	R1066H	L1324P
D110H	Q237E	G463V	V754M	A1067T	L1335P
E116K	Q237H	E474K	R792G	G1069R	G1349D
R117C	R258G	G480C	I807M	R1070Q	I1366N
R117G	M265R	S492F	E822K	R1070W	H1375P
R117H	F311del	I502T	D836Y	F1074L	L1480P
R117L	F311L	F508C	S912L	L1077P	
R117P	G314E	F508C;S1251N [†]	D924N	H1085P	
A120T	L320V	S549N	R933G	H1085R	

[†] Complex/compound mutations where a single allele of the *CFTR* gene has multiple mutations; these exist independent of the presence of mutations on the other allele.

Source: VX20-445-111, Appendix B

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