

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218730Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	218730
Priority or standard	Priority voucher redemption
Submit date(s)	5/2/2024
Received date(s)	5/2/2024
PDUFA goal date	1/2/2025
Division/office	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Review completion date	12/20/2024
Established/proper name	ALYFTREK
(Proposed) proprietary name	vanzacaftor/tezacaftor/deutivacaftor
Pharmacologic class	Unclassified / Unclassified / CFTR potentiator
Other product name(s)	vanzacaftor/tezacaftor/deutivacaftor
Applicant	VERTEX PHARMACEUTICALS INC
Dosage form(s)/formulation(s)	TABLET
Dosing regimen	6 to less than 12 years old (less than 40 kg): Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50mg once daily 6 to less than 12 years old (greater than or equal to 40 kg): (b) (4) [REDACTED] 12 years and older (any weight): (b) (4) [REDACTED]
Applicant-proposed indication(s)/ population(s)	Treatment of cystic fibrosis (CF) in patients with CF aged 6 years and older who have at least one <i>F508del</i> mutation or another responsive mutation in the <i>CFTR</i> gene
SNOMED CT code for proposed indication disease term(s)¹	190905008 Cystic Fibrosis (Disorder)
Regulatory action	Approval
Approved dosage (if applicable)	6 to less than 12 years old (less than 40 kg): Three tablets of vanzacaftor 4 mg/tezacaftor 20 mg/deutivacaftor 50mg once daily 6 to less than 12 years old (greater than or equal to 40 kg): (b) (4) [REDACTED] 12 years and older (any weight): (b) (4) [REDACTED]
Approved indication(s)/ population(s) (if applicable)	For the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one <i>F508del</i> mutation or another responsive mutation in the <i>CFTR</i> gene
SNOMED CT code for approved indication disease term(s)¹	190905008 Cystic Fibrosis (Disorder)

¹ For internal tracking purposes only.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC _{inf}	area under the concentration-time estimated to infinity
AUC _{tau}	area under the concentration-time curve over the dosing interval
BA	bioavailability
BMI	body mass index
CF	cystic fibrosis
CFQ-R	cystic fibrosis questionnaire-revised
CFTR	cystic fibrosis transmembrane conductance regulator
CL	clearance
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMV	cytomegalovirus
COVID-19	coronavirus disease of 2019
CTCAE	Common Terminology Criteria for Adverse Events
C _{trough}	plasma concentration observed at the end of dosing interval
CYP	cytochrome P450
DARS	Division of Applied Regulatory Science
DDI	drug-drug interaction
DHN	Division of Hepatology and Nutrition
DILI	drug-induced liver injury
D-IVA	deutivacaftor
ECG	electrocardiogram
ELX	elexacaftor
E-R	exposure-response
F	<i>F508del</i>
FAS	full analysis set
FDA	Food and Drug Administration
FDC	fixed-dose combination
FEV ₁	forced expiratory volume in one second
FRT	Fischer Rat Thyroid
G	gating
GLP	good laboratory practice
GLSM	geometric least squares mean
HBE	human bronchial epithelial
HI	hepatic impairment
IC ₅₀	half maximal inhibitory concentration
ICH	International Council for Harmonisation

NDA 218730

ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

IND	investigational new drug
IR	immediate release
IVA	ivacaftor
LC-MS/MS	liquid chromatography–mass spectrometry
LFT	liver function test
K ₂ -EDTA	dipotassium-ethylenediaminetetraacetic acid
LS	least squares
MedDRA	Medical Dictionary for Regulatory Activities
MF	minimal function
MHI	moderate hepatic impairment
MMRM	mixed-effects model for repeated measures
MRHD	maximum recommended human dose
NCS	noncanonical splice
NDA	new drug application
NI	noninferiority
NISS	newly identified safety signal
NOAEL	no observed adverse effect level
OAT	organic anion transporter
PBPK	physiologically based pharmacokinetic
PBS	phosphate-buffered saline
PD	pharmacodynamic
P-gp	P-glycoprotein
PI	Prescribing Information
PK	pharmacokinetic
PE _x	pulmonary exacerbation
ppFEV ₁	percent predicted forced expiratory volume in 1 second
popPK	population pharmacokinetic
PT	preferred term
QD	once daily
q12h	every 12 hours
RD	respiratory domain
RF	residual function
RH	relative humidity
RI	renal impairment
SAE	serious adverse event
SDD	spray-dried dispersion
SEE	substantial evidence of effectiveness
SOC	system organ class
SSID	safety signal identification
SwCl	sweat chloride
TC	triple combination
TCR	triple combination responsive
TE	treatment-emergent
TEZ	tezacaftor
TRA	total radioactivity
ULN	upper limit of normal

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

USPI	United States Prescribing Information
VNZ	vanzacaftor
WRO	written responses only

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

The Applicant, Vertex Pharmaceuticals, submitted a new drug application (NDA) for the novel oral fixed-dose combination of vanzacaftor (VNZ), tezacaftor (TEZ), and deutivacaftor (D-IVA) for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* (F) variant¹ or another response variant in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. The NDA was reviewed by a multidisciplinary team. Each team recommends approval for patients with CF aged 6 years and older with at least one *F508del* variant or another responsive variant in the *CFTR* gene, and the signatory authority for this application concurs with these recommendations.

To support the NDA for VNZ/TEZ/D-IVA, the Applicant submitted the results from two phase 3, randomized, double-blind, noninferiority trials: VX20-121-102 (Trial 102) and VX20-121-103 (Trial 103). Both trials demonstrated the noninferiority of VNZ/TEZ/D-IVA to elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), the current standard of care in this population, as measured by pulmonary function in subjects aged 12 years and older with CF. The primary endpoint was percent predicted forced expiratory volume in 1 second (ppFEV₁) through 24 weeks, an established endpoint for this indication. Additional secondary endpoints supported these results. The efficacy of VNZ/TEZ/D-IVA is extrapolated to patients aged 6 through 11 years of age from the adolescent and adult populations of Trials 102 and 103. Additional support comes from exploratory efficacy endpoint data from the open-label trial, Trial VX21-121-105 (Trial 105), in the 6- to 11-year-old population.

The available safety database was adequate for review and demonstrated that VNZ/TEZ/D-IVA is safe for its intended use as labeled. The data support that the risks of VNZ/TEZ/D-IVA are comparable to those of ELX/TEZ/IVA and include the potential risk for drug-induced liver injury and liver failure. The risk of hepatotoxicity will be managed by the inclusion of a Boxed Warning in labeling and increased monitoring through an enhanced pharmacovigilance strategy that will attach to this approval. The remaining observed adverse reactions were like those for ELX/TEZ/IVA and will be addressed through labeling and routine pharmacovigilance.

The NDA also included appropriate preapproval nonclinical and clinical pharmacology studies. A nonclinical postmarketing requirement and clinical pharmacology drug-drug interaction postmarketing requirement will attach to this approval.

¹ Throughout this review the term “variant” will be used per the most recent American College of Genetics and Genomics (ACMG) standards ([Richards et al. 2015](#); [den Dunnen et al. 2016](#)). Note that in the United States Prescribing Information (USPI) for VNZ/TEZ/D-IVA and Applicant materials, the term “mutation” is used. In the context of this review, these terms are synonymous.

The review team concludes that the benefit of VNZ/TEZ/D-IVA, based on noninferiority to ELX/TEZ/IVA as measured by pulmonary function, outweighs the risks when VNZ/TEZ/D-IVA is used as recommended in the approved labeling. There are no outstanding issues from any review discipline. The signatory concurs with the content of the various discipline assessments and their recommendations for approval. The Agency and Applicant have agreed upon the final labeling language. The submitted clinical program is adequate to support the efficacy and safety of VNZ/TEZ/D-IVA for the treatment of CF in patients 6 years of age and older with a copy of the *F508del* variant or another responsive *CFTR* variant. VNZ/TEZ/D-IVA will offer an alternative, once-daily therapy for many patients with CF and will be a new therapy for some patients with certain *CFTR* variants. The action for this application will be Approval.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

To support the proposed indication for VNZ/TEZ/D-IVA, the Applicant completed two phase 3 efficacy and safety trials, Trials 102 and 103. The trials demonstrated SEE for VNZ/TEZ/D-IVA in subjects with CF with a responsive *CFTR* variant. The determination of efficacy is based on demonstration of the noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA on the primary endpoint of the absolute change from baseline in the ppFEV₁ through 24 weeks. Evaluation of in vitro data from Ussing chamber electrophysiology experiments demonstrated greater activity for the triple drug combination, VNZ/TEZ/D-IVA, compared to the mono-components and dual-components.

The proposed indication includes 303 variants in the *CFTR* gene, representing over 90% of the U.S. CF population. To support the inclusion of the individual *CFTR* variants, the Applicant submitted a combination of clinical data, in vitro data, and a proposal for the extrapolation of safety and efficacy to rare noncanonical splice (NCS) variants. The data types and the conclusions on their contributions to SEE are reviewed below and summarized in [Table 2](#).

Table 2. Data Source Used to Support *CFTR* Variant Based Indication for VNZ/TEZ/D-IVA

Data Source and Variant/Variant Grouping^a	Number of <i>CFTR</i> Variants	Comparison to ELX/TEZ/IVA Indication
Clinical data		
F508del	1	Included
Other ^b	23	Included
In vitro data (FRT cells)		
Responsive to TEZ/IVA or IVA monotherapy	130	Included
Triple combination responsive	24	Included
Not previously tested with ELX/TEZ/IVA	74	Included ^c
Not responsive to ELX/TEZ/IVA	31	Not included
In vitro data (HBE cells)		
N1303K	1	Included ^c

Data Source and Variant/Variant Grouping^a	Number of <i>CFTR</i> Variants	Comparison to ELX/TEZ/IVA Indication
Extrapolation of efficacy Nonconical splice variants	19	Included ^c

Source: Clinical reviewer based on Applicant data
^a See [Table 196](#) in Section 16 for additional information regarding responsive variants
^b Includes *CFTR* variants based on data from subjects enrolled in phase 3 trials without a *F508del* variant, all variants previously included in ELX/TEZ/IVA indication supported by in vitro (FRT) data
^c Added to indication for ELX/TEZ/IVA on Dec 11, 2024 (sNDAs 212273/S012 and 217660/S003; DARRTS ID: 5493844)
Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; ELX, elxacaftor; FRT, Fischer rat thyroid; HBE, human bronchial epithelial; IVA, ivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

Trials 102 and 103 were adequate and well-controlled phase 3 trials that enrolled 971 subjects aged 12 years and older with CF. Among the enrolled population, 95.7% of subject had a *CFTR* genotype that included at least one copy of the *F508del* variant, the most common variant in the U.S. CF population. Both Trials 102 and 103 demonstrated the noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA with respect to the ppFEV₁ through 24 weeks. The noninferiority trial design and margin selected were reasonable.

In addition, Trials 102 and 103 enrolled 42 subjects with 23 non-*F508del* triple combination responsive (i.e., responsive to ELX/TEZ/IVA based on in vitro data) variants. The subgroup analysis of these subjects was limited by sample size but was consistent with the overall population and supportive of the noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA in this population. Approval for this group of variants is also supported by in vitro data from prior development programs.

To support an additional 259 *CFTR* variants, the Applicant submitted in vitro data utilizing the Fischer Rat Thyroid (FRT) cell system, a type of Ussing Chamber electrophysiology assay the Division has experience leveraging for regulatory actions for CF therapies. These data supported the inclusion of 154 *CFTR* variants that were previously demonstrated to be responsive to ELX/TEZ/IVA, TEZ/IVA, and/or IVA. These data also supported 31 new *CFTR* variants not responsive to currently approved therapies, as well as 74 *CFTR* variants that were recently added to the ELX/TEZ/IVA indication as part of a supplemental NDA uploaded to DARRTS on December 11, 2024 (DARRTS ID: 5493844).

Additional in vitro data utilizing a human bronchial epithelial (HBE) cell system, another Ussing Chamber assay, supported the inclusion of a single variant, *N1303K*. HBE cells were used instead of FRT because the *N1303K* variant is not responsive to ELX/TEZ/IVA in the FRT system. A regulatory threshold to define effectiveness for this assay was established as part of the recently approved efficacy supplement for ELX/TEZ/IVA. The determination of effectiveness was made by comparing the response to VNZ/TEZ/D-IVA with the response to TEZ/IVA in *F508del*/*F508del* HBE cells.

The efficacy and safety for 19 NCS variants were extrapolated from the overall population evaluated in Trials 102 and 103. These variants are expected to result in the production of small quantities of wild-type (normal function) *CFTR*, and extrapolation was supported, in part, by in vitro FRT data demonstrating that VNZ/TEZ/D-IVA augments wild-type *CFTR* function. In addition, there is clinical data demonstrating the benefit of ELX/TEZ/IVA in certain variants included in this group (Trial VX21-445-124, supplemental NDAs 212273/S012 and 217660/S003, uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]). Together,

these data support the conclusion that the expected response to treatment and benefits of VNZ/TEZ/D-IVA would translate to patients with these rare variants.

In addition, the efficacy and safety of VNZ/TEZ/D-IVA were extrapolated from the adolescent and adult population to CF patients aged 6 through 11 years of age with a responsive *CFTR* variant. Extrapolation is supported by comparable drug systemic exposures between the 6- to 11-year-old population and the adolescent and adult population and the knowledge that CF is the same disease across age groups.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 3. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- CF is a rare, progressive, life-shortening autosomal recessive genetic condition that affects approximately 33,000 individuals in the United States. CF results from pathologic variants in the <i>CFTR</i> gene that lead to decreased or dysfunctional CFTR protein. CFTR aids in the regulation of salt and water absorption and secretion throughout the body. 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-40s. - The most common <i>CFTR</i> variant is <i>F508del</i>. In the United States, approximately 85% of CF patients carry at least one allele and 45% are homozygous for this variant.	CF is a rare, progressive, and life-shortening genetic disease. The pathologic changes associated with CF start early in life. The <i>CFTR</i> variants included in the proposed indication represent the majority of patients with CF in the United States.

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- Although no cure exists, there are currently four therapies that affect CFTR processing or function that are approved for some of the CF population, including: ELX/TEZ/IVA (TRIKAFTA), TEZ/IVA (SYMDEKO), LUM/IVA (ORKAMBI), and IVA (KALYDECO). - The majority of CF patients in the United States are <i>CFTR</i> genotype eligible for at least one of the approved therapies; however, there remains a significant unmet need for alternative CF therapies, both for patients who are not currently eligible based on <i>CFTR</i> genotype as well as patients who are intolerant of the currently approved medications or with persistent symptom burden despite treatment. - The remainder of treatment options are aimed at managing the symptoms and sequelae of the underlying CF disease.	There remains an unmet need for therapies for CF patients who are not currently eligible for or are intolerant of an approved therapy that affects CFTR function or processing. There remains an additional need in patients with persistent symptom burden despite therapy with an approved medication.
Benefit	- Trials 102 and 103 demonstrated the noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA with respect to pulmonary function as measured by the absolute change from baseline in the ppFEV₁. Supportive secondary endpoints included change from baseline in SwCl, an important pharmacodynamic measure of CFTR function, and other endpoints that are clinically meaningful in a CF population (e.g., rate of pulmonary exacerbations, CFQ-R respiratory domain). - In vitro testing using the FRT system demonstrated an increase in chloride transport by ≥10% from baseline with treatment of VNZ/TEZ/D-IVA or its components in certain <i>CFTR</i> variants. - Additional in vitro testing in CF HBE cells demonstrated the responsiveness of the tested variant by showing an increase in chloride transport comparable to that in other variants for which clinical efficacy data exists.	The clinical benefit of VNZ/TEZ/D-IVA was demonstrated to be noninferior to ELX/TEZ/IVA for CF patients aged 12 years and older with a <i>F508del</i> variant or other responsive <i>CFTR</i> variant. VNZ/TEZ/D-IVA offers a once daily dosing regimen, compared to the twice daily dosing schedule of ELX/TEZ/IVA. Efficacy in CF patients aged 6 through 11 years can be extrapolated from Trials 102 and 103 because of comparable systemic exposures between the 6- to 11-year-old population and the adolescent and adult populations and the knowledge that CF is the same disease across age groups. Results of exploratory efficacy endpoints from the open label trial in the 6- to 11-year-old population further support this conclusion. The Applicant provided adequate data to support all proposed <i>CFTR</i> variants, which included clinical data, in vitro responsiveness data in FRT and HBE systems, and adequate support for the extrapolation of efficacy data in rare noncanonical splice variants not feasible to enroll in clinical trials because of rarity and not amenable to established in vitro systems.

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	- The VNZ/TEZ/D-IVA AEs observed were generally consistent with the known safety profile of ELX/TEZ/IVA. - Specific safety analyses were performed, including analyses for liver function test elevation, rash, creatinine phosphokinase elevation, and neuropsychiatric events. - The safety data submitted suggest that VNZ/TEZ/D-IVA conveys a similar risk to ELX/TEZ/IVA, although the overall analysis is limited by the lack of placebo arm to assess the baseline rates of events. - A new signal for life-threatening drug-induced liver injury was recently characterized for ELX/TEZ/IVA, and the available data for VNZ/TEZ/D-IVA suggest the risk is likely similar. Limitations of the available data include lack of placebo arm and the ELX/TEZ/IVA run-in period for both Trials 102 and 103, which resulted in only ELX/TEZ/IVA-tolerant subjects eligible for enrollment. - The potential for DILI related to VNZ/TEZ/D-IVA was carefully evaluated in consultation with the Division of Hepatology and Nutrition. Rates of maximum transaminase elevations were greater for VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA. We also identified five cases of nonjaundiced DILI events that were adjudicated as probably or possibly related to VNZ/TEZ/D-IVA. - The safety results from Trial 105 did not reveal any new safety signals or identify imbalances in AEs to suggest differential risks for children compared to adolescents or adults. However, given the single arm design and small sample size, interpretation of these results is limited.	The safety profile of VNZ/TEZ/D-IVA appears similar to that of ELX/TEZ/IVA and includes the potential risk for DILI and liver failure. A Boxed Warning for drug-induced liver injury and liver failure will be included in labeling, and increased postmarket surveillance will occur through an enhanced pharmacovigilance strategy. A REMS is not indicated at this time. There were no safety signals identified in the development program for VNZ/TEZ/D-IVA that outweigh the potential benefit for the treatment of CF. Safety for the 6- through 11-year-old CF population was extrapolated from the adolescent and adult populations enrolled in the phase 3 development program based upon comparable systemic exposures.

Abbreviations: AE, adverse event; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R, cystic fibrosis questionnaire-revised; DILI, drug-induced liver injury; D-IVA, deutivacaftor; ELX, elxacaftor; FRT, Fischer Rat Thyroid; HBE, human bronchial epithelial; IVA, ivacaftor; LUM, lumacaftor; ppFEV₁, percent predicted forced expiratory volume in 1 second; REMS, Risk Evaluation and Mitigation Strategies; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

2.2. Conclusions Regarding Benefit-Risk

CF is a rare, progressive genetic condition that leads to premature respiratory failure caused by pathologic variants in the *CFTR* gene. The majority of patients in the United States are currently eligible for one of the four approved medications that affect CFTR processing or function [Table 4](#). There remains an unmet need for new therapies for patients with CF, including those with ineligible *CFTR* variants and those who are intolerant of or incompletely treated by currently available therapies. VNZ/TEZ/D-IVA is a fixed-dose combination product with the same mechanism of action as ELX/TEZ/IVA. D-IVA increases the channel open probability of the CFTR channel, and VNZ and TEZ improve intracellular protein processing to allow for increased protein expression at the cell surface, thus resulting in an increase in overall apical anion transport.

To support the NDA for VNZ/TEZ/D-IVA, the Applicant submitted the results from two phase 3, randomized, double-blind, ELX/TEZ/IVA-controlled, noninferiority trials. Both trials, VX20-121-102 (Trial 102) and VX20-121-103 (Trial 103) evaluated subjects with CF aged 12 years and older over 52 weeks and demonstrated the noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA with respect to pulmonary function as measured by the absolute change in ppFEV₁ through 24 weeks. Additional secondary endpoints, including the rate of CF pulmonary exacerbations and the change in the cystic fibrosis questionnaire-revised respiratory domain, support the efficacy of VNZ/TEZ/D-IVA. Interpretation of these endpoints is limited by lack of multiplicity control, but the results are generally supportive of VNZ/TEZ/D-IVA and are discussed in more detail in [Section 6](#).

In addition, the Applicant submitted the results of secondary endpoints related to sweat chloride (SwCl) concentrations. SwCl is an important pharmacodynamic marker of CFTR function; however, endpoints based on SwCl are not clinically meaningful as they do not measure how a patient feels, functions, or survives and have not been validated as surrogate endpoints. As such, they cannot be used to demonstrate comparative efficacy. Both phase 3 trials demonstrated a statistically significant reduction in the change from baseline in SwCl with VNZ/TEZ/D-IVA treatment compared to ELX/TEZ/IVA; however, it is unclear how these changes translate to clinically meaningful outcomes. The Applicant also submitted results of responder analyses assessing the proportion of subjects with a week 24 SwCl below 60mmol/L and below 30mmol/L, which were also statistically significant in the prespecified analyses. The data submitted to support the clinical relevance of these responder analyses, however, was insufficient. Overall, the SwCl endpoints support that VNZ/TEZ/D-IVA has comparable on target pharmacodynamic effects to ELX/TEZ/IVA. For additional discussion of SwCl, refer to [Section 6.3.2](#).

There was an adequate safety database to support this review. However, a significant limitation of the safety database stemmed from the noninferiority design, which eliminated a placebo arm and necessitated enrolled subjects be tolerant of ELX/TEZ/IVA, including during a four-week run-in period. Since 86.3% of the population had been prescribed ELX/TEZ/IVA or a medication containing its components prior to enrollment, the generalizability of safety results to ELX/TEZ/IVA naïve or intolerant patients is limited. Overall, the available data support that the safety of VNZ/TEZ/D-IVA is similar to that of ELX/TEZ/IVA. The potential risk of liver injury

related to VNZ/TEX/D-IVA was a major focus of the safety review. Overall, there were higher rates of transaminase elevation and liver-related adverse events leading to drug discontinuation in subjects treated with VNZ/TEZ/D-IVA compared to ELX/TEZ IVA. There were no cases of Hy's Law or liver failure reported, but there were five cases of nonjaundiced drug-induced liver injury adjudicated as probably or possibly related to VNZ/TEZ/D-IVA exposure. A multidisciplinary team recommended that the potential risk for drug-induced liver injury and liver failure with VNZ/TEZ/D-IVA be communicated to prescribers in a Boxed Warning with further monitoring through an enhanced pharmacovigilance strategy. Refer to Section [7.7.2](#) for details.

The efficacy and safety of VNZ/TEZ/D-IVA were extrapolated to the 6- to 11-year-old population from the adolescent and adult population studied in Trials 102 and 103. The Applicant submitted an interim report of the final clinical data from the 6- to 11-year-old cohort from Trial VX21-121-105 (Trial 105), an open-label, multicohort, 2-part trial in pediatric CF subjects aged 1 through 11 years. Extrapolation of efficacy and safety in this population is justified because systemic exposures between the 6- to 11-year-old population and the adolescent and adult populations are comparable and because CF is the same disease across age groups. Exploratory efficacy endpoints from Trial 105 were also supportive of the efficacy of VNZ/TEZ/D-IVA in this population, and a review of safety data from Trial 105 did not reveal any new concerning safety signals in this population.

The data submitted to support the satisfaction of 21 Code of Federal Regulations 300.50, the 'combination rule' was considered adequate and included the clinical demonstration of noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA, as well as the available historical clinical trial data with IVA, TEZ/IVA, and ELX/TEZ/IVA. Further support comes from in vitro data demonstrating a greater effect of the VNZ/TEZ/D-IVA triple combination versus the mono-components and dual-components alone. Refer to Section [6.3.1](#) for further discussion.

To support the *CFTR* variant based indication, the Applicant submitted adequate data for the individual variants. This included in vitro electrophysiology models utilizing FRT and CF HBE cells, as well as adequate support to justify the potential for benefit in 19 rare NCS variants that are not amenable to enrollment in clinical trials because of relative rarity and cannot be evaluated in existing in vitro models. Refer to Section [6.3.3](#) for further discussion.

The overall risk-benefit assessment supports the approval of VNZ/TEZ/D-IVA for the treatment of CF in patients aged 6 years and old with a copy of *F508del* or other responsive variants in the *CFTR* gene.

II. Interdisciplinary Assessment

3. Introduction

Cystic fibrosis (CF) is an autosomal recessive, progressive disease affecting over 33,000 people in the United States and 90,000 people worldwide ([CFF 2023](#)). CF is caused by pathologic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that leads to decreased or dysfunctional CFTR protein, an anion channel in the apical epithelial membrane. In the lungs, the CF-mediated 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, the leading cause of death in this population ([CFF 2023](#)). In addition, there are significant extrapulmonary manifestations characteristic of CF, including malabsorption, chronic sinus disease, poor bone health, liver dysfunction, and a form of diabetes ([CFF 2023](#)).

There are over 700 variants in the *CFTR* gene that are associated with CF disease causation, although over 2,000 variants have been identified ([CFF; JHU; and HSC 2024](#)). The most common CF-causing variant in the United States is *F508del* (F), a variant that results in improper protein folding leading to increased degradation ([Cheng et al. 1990](#)). In CF patients with genotype information available in the United States, approximately 85% of individuals are heterozygous for *F508del* and 44% of individuals are *F508del* homozygous ([CFF 2023](#)). The reported prevalence of the next most commonly reported *CFTR* variants in the United States is significantly lower with no other variant reported in >5.0% of the population in 2023 ([CFF 2023](#)).

Currently, there is no cure for CF and, historically, CF-directed therapies were focused on the relief of symptoms and sequelae of the disease. More recently, medications targeting the underlying pathophysiologic defect in CFTR function and general intracellular protein processing of CFTR have been developed and approved for CF subpopulations based on *CFTR* variants as reviewed below in [Table 4](#).

Table 4. Medications Approved for the Treatment of CF That Affect CFTR Processing or Function

Active Ingredient	Trade Name	FDA-Approved Indication
Ivacaftor (IVA)	KALYDECO tablets and granules	Treatment of CF in patients aged 1 month and older who have at least one mutation in <i>CFTR</i> gene that is responsive to IVA based on clinical and/or in vitro data ^a
Lumacaftor/Ivacaftor (LUM/IVA)	ORKAMBI tablets and granules	Treatment of CF in patients aged 1 year and older who are homozygous for the <i>F508del</i> mutation in the <i>CFTR</i> gene
Tezacaftor/Ivacaftor (TEZ/IVA)	SYMDEKO tablets	Treatment of CF in patients aged 6 years and old who are homozygous for <i>F508del</i> mutation or who have at least on mutation in <i>CFTR</i> gene that is responsive to TEZ/IVA based on in vitro data and/or clinical evidence ^b
Elexacaftor/Tezacaftor/Ivacaftor (ELX/TEZ/IVA)	TRIKAFTA tablets and granules	Treatment of CF in patients aged 2 years and older who have at least one <i>F508del</i> mutation in the <i>CFTR</i> gene or another mutation in the <i>CFTR</i> gene that is responsive based on in vitro data

Source: Clinical Review from Drugs@FDA, accessed on Oct 3, 2024

^a Does not include *F508del*

^b Does not include patients heterozygous for *F508del* without another responsive *CFTR* mutation

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

Ivacaftor (IVA, Trade name: KALYDECO), the first medication targeting CFTR function, was approved in 2012 but limited at that time to patients aged 6 years and older with a *G551D* *CFTR* variant, the third most prevalent *CFTR* variant reported in the United States ([Vertex Pharmaceuticals 2012](#)). Initial expansion of the IVA indication to additional variants was based on clinical data; however, given the rarity of remaining variants, subsequent indication expansions were based on in vitro studies leveraging Ussing chamber electrophysiology experiments with Fischer Rat Thyroid (FRT) cells expressing normal and mutant CFTR protein ([Durmowicz et al. 2018](#)). Subsequently, all other medications that directly affect CFTR processing or function have had the indications expanded to include additional variants using FRT data that demonstrate an increase in chloride transport by $\geq 10\%$ of normal from baseline. At the time of this review, approximately 92% of U.S. CF patients are eligible for a medication that affects CFTR processing or function based on their genotype and age ([CFF 2023](#)).

Elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA), approved in 2019 ([Vertex Pharmaceuticals 2019](#)), accounted for 93% of prescriptions for medications that affect CFTR processing or function reported in 2023 and is standard-of-care therapy for those with eligible *CFTR* variants ([CFF 2023](#)). It is the most effective therapy for CF that targets the underlying defect in the disease.

These medications have provided significant clinical benefits to many patients with CF with responsive *CFTR* variants ([Volkova et al. 2020](#)). However, despite these advances, there remains a significant ongoing disease burden in CF and the CF population would benefit from safe and effective alternative therapies.

Vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA), an oral fixed-dose combination (FDC) tablet, has the same mechanism of action as ELX/TEZ/IVA. As part of its clinical development program, ELX/TEZ/IVA had demonstrated a large, sustained clinical effect on the forced

expiratory volume in 1 second (FEV₁), a clinically meaningful endpoint for which there is regulatory precedent in CF ([Heijerman et al. 2019](#); [Middleton et al. 2019](#)). Given the severity of the underlying disease, the effect size of ELX/TEZ/IVA, and its market prevalence within the CF population, the Applicant and Division agreed upon a clinical development program that included two pivotal trials designed to assess the noninferiority of VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA. The trial design and assessment of the noninferiority margin are reviewed in Section [6.2.2.1](#) with an in-depth review of the clinical protocols included in Section [15.1](#).

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Satisfaction of 21 CFR 300.50, the “Combination Rule”

3.1.1.2. Clinical Relevance of Sweat Chloride Concentration Efficacy Endpoints

3.1.1.3. Additional Data Used to Support Indication Based on *CFTR* Variant

3.1.2. Key Safety Review Issues

3.1.2.1. Assessment of Safety in Subjects Intolerant of ELX/TEZ/IVA

3.1.2.2. Risk for Hepatotoxicity With VNZ/TEZ/D-IVA

3.2. Approach to the Clinical Review

The Applicant submitted data from two phase 3 clinical trials, Trials 102 and 103, as the primary support for the safety and efficacy of VNZ/TEZ/D-IVA in CF. These trials were both international, multicenter, randomized, double-blind, ELX/TEZ/IVA-controlled trials evaluating the efficacy and safety of VNZ/TEZ/D-IVA over 52 weeks. The design of the phase 3 clinical development program is reasonable. The in-depth review of the clinical protocols is included in Section [15.1](#).

In addition, the Applicant submitted an interim analysis from Trial 105 to support the use of VNZ/TEZ/D-IVA in pediatric CF patients ages 6 through 11. Trial 105 is an ongoing, two-part, open-label, multicohort, pediatric, pharmacokinetic (PK) and safety study of VNZ/TEZ/D-IVA in CF subjects 1 through 11 years of age. The submitted interim analysis included the final clinical data for the 6- to 11-year-old cohorts (Cohorts A1 and B1). An in-depth review of the

clinical protocol for Trial 105 is included in Section [15.2](#). As with other similar medications in this population, the efficacy and safety in the 6- to 11-year-old CF population is primarily extrapolated from adolescents and adults. The efficacy-related endpoints and safety profile from the 6- to 11-year-old cohorts were also reviewed in comparison to the adolescent and adult data to assess for consistency or the presence of new signals.

FDA biostatisticians performed efficacy analyses to confirm the data shown in support of the Applicant's primary and secondary efficacy endpoints. The review of the efficacy of VNZ/TEZ/D-IVA is in Section [6](#). The clinical reviewer and FDA clinical data scientist performed the safety review, found in Section [7](#). The clinical pharmacology team, including reviewers from the Division of Applied Regulatory Science, reviewed dose ranging trials and in vitro analyses used to support efficacy as well as data supporting the contribution of each component to the fixed-dose combination, found in Section [6.3.1](#).

The approach to establishing substantial evidence of effectiveness (SEE) is reviewed in Section [3.3](#), and a summary of the clinical trials submitted by the Applicant in support of the efficacy and safety of VNZ/TEZ/D-IVA is reviewed below in [Table 5](#).

3.3. Approach To Establishing Substantial Evidence of Effectiveness

- (1) Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

The treatment of cystic fibrosis (CF) in patients with CF aged 6 years and old who have at least one *F508del* mutation or another responsive mutation in the *CFTR* gene.

- (2) SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)

- a) Adequate and well-controlled clinical investigation(s):

- (i) ☒ Two or more adequate and well-controlled clinical investigations, **OR**
- (ii) ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

- b) ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{2,3,4}

² FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* ([December 2019](#))

³ FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* ([May 1998](#))

⁴ FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* ([September 2023](#))

OR

- c) ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²

(3) Complete response, if applicable

- a) ☐ SEE was established
- b) ☐ SEE was not established (*if checked, omit item 2*)

Table 5. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for VNZ/TEZ/D-IVA

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
VX20-121-102 (Trial 102) NCT 05076149	Phase 3, CF subjects, ≥12 years F/MF	Control type: Active (ELX/TEZ/IVA) control Randomization: 1:1 Blinding: Double-blind Innovative design features: Noninferiority design (margin - 3.0% FEV ₁)	Drug: VNZ/TEZ/D-IVA Dosage: VNZ 20 mg QD/TEZ 100 mg daily/D-IVA 250 mg QD; or ELX 200 mg QD/TEZ 100 mg QD/IVA 150 mg q12h Number treated: 398 subjects Duration (quantity and units): 56 wk	Primary: Absolute change from baseline in ppFEV ₁ through Week 24 Key Secondary: Absolute change from baseline in SwCl through Week 24 Proportion of subjects with SwCl <60mmol/L through Week 24 Proportion of subjects with SwCl <30mmol/L through Week 24	Number planned: 400 subjects; Number randomized: 405 subjects	126 centers in 12 countries (U.S. and ex-U.S.)

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Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
VX20-121-103 (Trial 103) NCT 05076149	Phase 3, CF subjects, ≥12 years F/F, F/G, F/RF, or TCR/non-F	Control type: Active (ELX/TEZ/IVA) controlled Randomization: 1:1 Blinding: Double-blind Innovative design features: Noninferiority design (margin - 3.0% FEV ₁)	Drug: VNZ/TEZ/D-IVA Dosage: VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 250 mg QD; or ELX 200 mg QD/TEZ 100 mg QD/IVA150 mg q12h Number treated: 573 subjects Duration (quantity and units): 56 wk	Primary: Absolute change from baseline in ppFEV ₁ through Week 24 Secondary: Absolute change from baseline in SwCl through Week 24 Proportion of subjects with SwCl <60mmol/L through Week 24 Proportion of subjects with SwCl <30mmol/L through Week 24	Number planned: 550 subjects Number randomized: 574 subjects	159 centers in 20 countries (U.S. and ex-U.S.)
VX20-121-104 (Trial 104) NCT 05444257	Phase 3, open-label extension (ongoing)	Control type: Uncontrolled Randomization: N/a	Drug: VNZ/TEZ/D-IVA Dosage: VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 250 mg QD Number treated: 850 planned Duration (quantity and units): 96 wk	Primary: Safety and tolerability Secondary: Absolute change in ppFEV ₁ Absolute change in SwCl Number of PEx	Number planned: 850 subjects Number enrolled: 822 subjects	207 centers in 23 countries (U.S. and ex-U.S.)

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Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
VX21-121-105 (Trial 105) NCT 05422222	Phase 3, open-label pediatric PK, safety, efficacy, and tolerability CF, cohorts A1 and B1 ages 5 to 11 years with at least 1 TCR variant	Control type: Open-label Randomization: N/a Blinding: N/a Innovative design features: ELX/TEZ/IVA 4-week run-in period	Drug: VNZ/TEZ/D-IVA Dosage: Cohort A1 (all subjects): VNZ 10 mg QD/TEZ 50 mg QD/D-IVA 125 mg QD. Cohort B1 (subjects <40 kg): VNZ 12 mg QD/TEZ 60 mg QD/D-IVA 150 mg QD. Cohort B1 (subjects ≥40 kg): VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 250 mg QD Number treated: Cohort A1: 17 subjects. Cohort B1: 78 subjects Cohort A1 Duration (quantity and units): 22 d Cohort B1 Duration (quantity and units): 28 wk	Primary (part B): Safety and tolerability Secondary (Part B): Absolute change in SwCl through week 24 PK parameters of VNZ, TEZ, D-IVA and relevant metabolites Absolute change in ppFEV ₁	Number planned Cohort A1: 12-20 subjects Actual number enrolled Cohort A1: 17 subjects Number planned Cohort B1: 65 subjects. Actual number enrolled Cohort B1: 78 subjects	Cohort A1: 8 centers in U.S. Cohort B1: 33 centers in 8 countries (U.S. and ex-U.S.)

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Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized	Number of Centers and Countries
VX22-121-106 (Trial 106) NCT 05844449	Phase 3, open-label extension Cohort 1 (ongoing) Ages 6-11 years	Control type: Uncontrolled Randomization: N/a	Drug: VNZ/TEZ/D-IVA Dosage: Cohort 1 (subjects <40 kg): VNZ 12 mg QD/TEZ 60 mg QD/D-IVA 150 mg QD. Cohort 1 (subjects ≥40 kg): VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 250 mg QD Number treated: 65 subjects Duration (quantity and units): 96 wk	Primary: Safety and tolerability Secondary: Absolute change in SwCl Absolute change in ppFEV ₁ Number of PEx and CF-related hospitalizations	Number enrolled: 75 subjects	32 centers in 8 countries (U.S. and ex-U.S.)

Source: Clinical reviewer.

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

Abbreviations: BID, twice daily; CF, cystic fibrosis; CFQ-R, Cystic Fibrosis Questionnaire-revised; CFTR, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; d, day; DB, double-blind; ELX, elxacaftor; F, *F508del CFTR* variant; G, gating *CFTR* variant; IVA, ivacaftor; LTE, long-term extension; MC, multicenter; MF, minimal function *CFTR* variant; N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PEx, pulmonary exacerbation; PG, parallel group; PK, pharmacokinetic; ppFEV₁, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; QD, once daily; R, randomized; RD, respiratory domain; RF, residual function *CFTR* variant; SwCl, sweat chloride; U.S., United States; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor; VNZ, vanzacaftor; wk, week(s); y, year(s)

4. Patient Experience Data

Table 6. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Sections 6.2 and 16.1
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: (please specify)	
	- Externally-Led Patient-Focused Drug Development Session (CFRI 2018) - Patient Listening Session (Emily's Entourage 2021)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

VNZ and TEZ bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including *F508del*-CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. Similar to IVA, deuterated ivacaftor (D-IVA) potentiates the channel open probability (or gating) of the CFTR protein at the cell surface. The combined effect of VNZ, TEZ, and D-IVA is increased quantity and function of CFTR at the cell surface, resulting

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in increased CFTR activity as measured by CFTR-mediated chloride transport in CF human bronchial epithelial (HBE) cell cultures derived from donor CF lungs.

In vivo pharmacodynamic studies were not performed. The totality of in vitro pharmacology data submitted was considered sufficient to characterize the pharmacological activity of VNZ, TEZ, and IVA and inform labeling for the indication of CF.

5.2. Clinical Pharmacology / Pharmacokinetics

Table 7. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	VNZ/TEZ/D-IVA is a combination of deutivacaftor, a CFTR potentiator, tezacaftor, and vanzacaftor, indicated for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one <i>F508del</i> variant in the <i>CFTR</i> gene or a variant in the <i>CFTR</i> gene.
Mechanism of action	VNZ and TEZ bind to different sites on the CFTR protein and have an additive effect in facilitating the cellular processing and trafficking of select mutant forms of CFTR (including <i>F508del</i> -CFTR) to increase the amount of CFTR protein delivered to the cell surface compared to either molecule alone. D-IVA potentiates the channel open probability (or gating) of the CFTR protein at the cell surface.
Active moieties	The active moieties are VNZ, TEZ, M1-TEZ (similar potency compared to TEZ), D-IVA, and M1-D-IVA (20% of potency compared to D-IVA).
QT prolongation	Following a single dose of 60 mg VNZ (Form A, which resulted in six times the C_{max} value when compared to the C_{max} following 20 mg VNZ dose in Form D in FDC tablet), no clinically relevant effects on prolongation of the QTc interval were observed in the thorough QT study, Study VX22-121-013. Refer to the approved label of ELX/TEZ/IVA (Trade name: TRIKAFTA). At doses up to three times the maximum recommended dose of TEZ and IVA, the QT/QTc interval in healthy subjects was not prolonged to any clinically relevant extent. In vitro results showed that IVA inhibits about 22% of hERG current at 8 μ M. Given the hydrogen to deuterium replacements from IVA to D-IVA, which is unlikely to change its 3-dimensional conformation, the high plasma protein binding of IVA and D-IVA (>99%), and the in vivo $C_{max,ss}$ value around 3 – 6 μ M for IVA and D-IVA, it is reasonable to extrapolate the in vivo QT results from IVA to D-IVA following the therapeutic dose of VNZ/TEZ/D-IVA.

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Characteristic	Drug Information																				
	General Information																				
Bioanalysis	Methods for the quantitation of VNZ in human K ₂ -EDTA plasma using LC-MS/MS Detection were developed and validated. A method for the quantitation of VNZ in human urine using LC/MS/MS was developed and validated. The bioanalytical assays were considered acceptable. Validation reports for D-IVA and TEZ were previously reviewed and found adequate in the original application for NDA 210491 TEZ/IVA and NDA 212273 ELX/TEZ/IVA.																				
Healthy subjects versus patients	The popPK estimated effect does not necessarily suggest a PK difference between healthy subjects and CF Patients. This observation is likely attributable to the relatively small number of healthy subjects in the final data and confounding due to healthy subjects receiving only VNZ Form A.																				
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	<table><tr><th colspan="5">Table 8. Drug Exposure Values</th></tr><tr><th>General Information</th><th>Vanzacaftor</th><th>Tezacaftor</th><th colspan="2">Deutivacaftor</th></tr><tr><td>Mean (SD) C_{max,ss}, mcg/mL</td><td>0.812 (0.344)</td><td>6.77 (1.24)</td><td colspan="2">2.33 (0.637)</td></tr><tr><td>Mean (SD) AUC_{0-24h,ss}, mcg·h/mL</td><td>18.6 (8.08)</td><td>89.5 (28.0)</td><td colspan="2">39.0 (15.3)</td></tr></table> Source: Clinical pharmacology reviewer Abbreviations: AUC_{0-24h,ss}, area under the concentration-time curve from time 0 to 24 hours at steady-state; C_{max}, maximum plasma concentration at steady-state; SD, standard deviation	Table 8. Drug Exposure Values					General Information	Vanzacaftor	Tezacaftor	Deutivacaftor		Mean (SD) C _{max,ss} , mcg/mL	0.812 (0.344)	6.77 (1.24)	2.33 (0.637)		Mean (SD) AUC _{0-24h,ss} , mcg·h/mL	18.6 (8.08)	89.5 (28.0)	39.0 (15.3)	
Table 8. Drug Exposure Values																					
General Information	Vanzacaftor	Tezacaftor	Deutivacaftor																		
Mean (SD) C _{max,ss} , mcg/mL	0.812 (0.344)	6.77 (1.24)	2.33 (0.637)																		
Mean (SD) AUC _{0-24h,ss} , mcg·h/mL	18.6 (8.08)	89.5 (28.0)	39.0 (15.3)																		
Range of effective dose(s) or exposure	In a phase 2 dose-ranging study for VNZ (Study VX18-121-101), VNZ [Form A] 10 mg showed the numerically greatest improvement of ppFEV₁ response compared to placebo group when compared to 5 mg and 20 mg. In a phase 2 dose-ranging study for D-IVA (Study VX18-561-101), D-IVA 250 mg and D-IVA 150 mg QD resulted in similar absolute change from baseline in ppFEV₁ compared to IVA 150 mg Q12h treatment, active control. In addition, treatment with D-IVA 250 mg QD yielded numerically greater improvements in SwCl response compared to D-IVA 150 mg QD. In the pivotal phase 3 trials (Trials VX20-121-102 and VX20-121-103), VNZ [Form D] 20 mg/TEZ 100 mg/D-IVA 250 mg FDC QD was evaluated and demonstrated noninferiority to ELX/TEZ/IVA, the current standard of care, on the primary efficacy endpoint of absolute change from baseline in ppFEV₁ through Week 24. Pediatric PK and safety trial (Trial VX21-121-105) demonstrated that the exposures (trough concentrations) of each APIs and their active metabolites in subjects aged 6 through 11 years following the proposed doses (VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg for body weight ≥40 kg and VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg for body weight <40 kg) were generally within the range of adults and adolescents following VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg.																				
Maximally tolerated dose or exposure	VNZ [Form A] up to 60 mg QD for 10 days was investigated in healthy subjects in Study VX17-121-001. Up to 300 mg once daily dose of TEZ for 7 days has been investigated in QT Study VX15-661-010. A single dose of D-IVA 300 mg was the maximally tolerated dose in healthy subjects in Study CP656.1001.																				

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Characteristic	Drug Information
Dose proportionality	Study VX17-121-001 Part A showed that using suspension formulation, VNZ exposure increases dose proportionally from 5 to 60 mg following single dose administration (i.e., AUC_{inf} increases 14.6-fold when dose increases 12-fold) in healthy subjects. Part B from the same study showed VNZ exposure increases slightly greater than dose proportionally following administration of multiple oral doses of VNZ QD for 10 days, which VNZ AUC_{tau} increased 8.5-fold from 10 mg QD to 60 mg QD. Refer to the clinical pharmacology review of TEZ/IVA (dated Feb 2, 2018), exposures of tezacaftor (administered alone or in combination with ivacaftor) increase in an approximately dose proportional manner with increasing doses from 10 mg to 300 mg once daily. Study VX18-561-001 showed that D-IVA exposure increases dose proportionally with ascending dose from 50 to 250 mg following 5 days once daily treatment (AUC_{tau} increases 6-fold).
Accumulation	Study VX17-121-001 showed accumulation ratio of AUC_{tau} ranged 3.5-5.5 for VNZ in healthy subjects. Study VX18-561-001 showed accumulation ratio of AUC_{tau} ranged 1.2-1.7 for D-IVA in healthy subjects. Refer to the approved label of TRIKAFTA, the accumulation ratio of TEZ is 2.1 at steady state following 100 mg once daily dosing regimen.
Time to achieve steady-state	Study VX17-121-001 Part C showed that following once daily regimen in the context of TC, the VNZ C_{trough} value was stabilized by Day 10 in healthy subjects. Trial VX20-121-102 showed that VNZ C_{trough} value was stabilized since Day 15 (i.e., the earliest PK sampling time from this trial) following the to-be-marketed FDC tablet once daily administration in subjects with CF. Given the effective elimination half-life of 93 hours for VNZ, it is reasonable to conclude that the steady state of VNZ is reached on Day 10. Study VX18-561-001 showed that following once daily regimen, D-IVA C_{trough} value was stabilized around Days 4-5 in healthy subjects, Trial VX20-121-102 and 103 showed that D-IVA C_{trough} value was stabilized since Day 15 (i.e., the earliest PK sampling time from these trials) following the to-be-marketed FDC tablet once daily administration in subjects with CF. Given the effective elimination half-life of 19 hours for D-IVA, it is reasonable to conclude that the steady state of D-IVA is reached no later than Day 5. Study VX17-121-001 Part C showed that following once daily regimen in the context of TC, TEZ C_{trough} value was stabilized on Day 7. Trials VX20-121-102 and VX20-121-103 showed that TEZ C_{trough} value was stabilized since Day 15 (i.e., the earliest PK sampling time from these trials) following the to-be-marketed FDC tablet once daily administration in subjects with CF. Given the elimination half-life of 22 hours for TEZ, it is reasonable to conclude that the steady state of TEZ is reached no later than Day 7.
Bridge between to-be-marketed and clinical trial/study formulations	To-be-marketed formulation VNZ [Form D]/TEZ/D-IVA FDC tablet (dosing strength of 10 mg/50 mg/125 mg and 3 mg/20 mg/50 mg) was used in pivotal phase 3 trials and pediatric Trial 105. During the development, VNZ [Form A] was used in phase 1 and phase 2 studies. Studies VX19-121-003 and VX21-121-005 demonstrated that the VNZ C_{max} and AUC from Form D (to-be marketed) was approximately 50% of that from Form A. The results from Studies VX19-121-003 and VX21-121-005 supported the dose selection of 20 mg VNZ [Form D] in phase 3 trials.

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Characteristic	Drug Information
	Absorption
Bioavailability	Absolute bioavailability of VNZ, TEZ, and D-IVA were not determined.
T _{max}	The median (min, max) of T _{max} of VNZ and D-IVA were 10 (4, 12) hours (Study VX17-121-001, Part B) and 4 (3, 6) hours (Study VX18-561-001), respectively.
Food effect (fed/fasted)	In Study VX21-121-005, food effect (high- and low-fat) on VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg FDC tablet was evaluated. High-fat food increases AUC and C _{max} of VNZ by 5.8- and 6.3-fold, TEZ by 1.2- and 1.1-fold, D-IVA by 4.2- and 5.4-fold, respectively. Low-fat food increases AUC and C _{max} of VNZ by 3.7- and 3.9-fold, TEZ by 1.1- and 1.2-fold, D-IVA by 3.3- and 3.4-fold, respectively. Food did not relevantly change T _{max} of VNZ/TEZ/D-IVA.
	Distribution
Volume of distribution	After a single oral dose of 2 VNZ 10-mg/TEZ 50-mg/D-IVA 125-mg FDC tablets, the mean (SD) apparent volumes of distribution were 90.4 (31.3) L for VNZ, 123 (43.2) L for TEZ, and 157 (47.3) L for D-IVA.
Plasma protein binding	Plasma protein binding of VNZ and D-IVA are greater than 99%. Plasma protein binding of TEZ is approximately 99%.
Drug as substrate of transporters	Based on in vitro data, VNZ is not a substrate of P-gp, BCRP, OATP1B1, or OATP1B3. Based on in vitro data, D-IVA and M1-D-IVA are substrates of P-gp and BCRP but are not substrates of OATP1B1 or OATP1B3. Refer to the approved label of ELX/TEZ/IVA, TEZ is a substrate for P-gp and BCRP, but not a substrate of OATP1B1 or OATP1B3.
	Elimination
Mass balance results	Unchanged VNZ accounted for most of the total circulating radioactivity in plasma and there were no major circulating metabolites of VNZ. VNZ was mainly cleared by metabolism in humans. The total excretion (in urine and feces) of the radiolabeled dose over 408 hours (17 days) was approximately 92.1%, with fecal excretion being the major route of elimination accounting for 91.6% and urinary excretion accounting for 0.5% (Study VX20-121-004). Refer to the mass balance Study VX13-661-005, the recovery rate of ¹⁴C-labeled TEZ is 85.9% at 21 days post-single dose with 72.2% and 13.7% excreted in feces and urine, respectively. No unchanged TEZ is detected in urine and unchanged TEZ only constitute 30.1% of the dose in feces. A human mass balance trial of D-IVA was not performed. However, it is expected that the excretion pathway for D-IVA is similar to IVA. Refer to the approved label of IVA (trade name: KALYDECO), following oral administration, the majority of ivacaftor (87.8%) is eliminated in the feces after metabolic conversion. There was minimal urinary excretion of ivacaftor as unchanged parent.

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Characteristic	Drug Information
Clearance	Mean (SD) apparent clearance were 1.18 (0.455) L/hr for VNZ, 0.937 (0.338) L/hr for TEZ, and 6.52 (2.77) L/hr for D-IVA
Half-life	Mean (% CV) of the elimination half-life of VNZ and D-IVA were 50.4 (32.3) hours (Study VX17-121-001, Part B) and 21.8 (28.1) hours (Study VX18-561-001), respectively. The effective half-life of VNZ, TEZ, and D-IVA are 92.8 (30.2), 22.5 (5.9), and 19.2 (8.7) hours, respectively.
Metabolic pathway(s)	VNZ, TEZ, and D-IVA are primarily metabolized by CYP3A4/5.
<i>Intrinsic Factors and Specific Populations</i>	
Body weight and age	Pediatric PK and safety trial (Study VX21-121-105) demonstrated that the exposures (trough concentrations) of each APIs and their active metabolites in subjects aged 6 through 11 years following the proposed doses (VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg for body weight $\geq$40 kg and VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg for body weight <40 kg) were generally within the range of adults and adolescents following VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg. Weight was identified as the main factor contributing to the differences in the PK between adult and pediatric subjects. Age was not identified as a significant covariate after the body weight adjustment
Renal impairment	No dedicated renal impairment study has been conducted for VNZ/TEZ/D-IVA FDC tablet. It is reasonable that no dose adjustment for subjects with mild or moderate renal impairment due to the minimal renal excretion for all three active ingredients. In addition, popPK showed similar exposure of VNZ/TEZ/F-IVA between healthy subjects and subjects with mild/moderate renal impairment. Therefore, the proposal for use with caution in people with CF with severe RI or end-stage renal disease is also reasonable.
Hepatic impairment	Following administration of a single dose of VNZ 10mg/TEZ 50 mg/D-IVA 125 mg in hepatic impairment (HI) Study VX21-121-008, the total exposure (AUC_{inf}) of VNZ, TEZ, and D-IVA decreased 30%, remained comparable, and decreased 20%, respectively, in subjects with moderate hepatic impairment when compared to matched subjects with normal hepatic function. Similarly, the free drug exposure ($AUC_{u,inf}$) of VNZ and D-IVA decreased 20% and 40%, respectively, in subjects with moderate HI when compared to matched subjects with normal hepatic function Based on these results and hepatotoxicity of VNZ/TEZ/D-IVA, it is reasonable that no dosage adjustment in patients with mild hepatic impairment is proposed. It is reasonable that the Applicant proposed VNZ/TEZ/D-IVA use in patients with moderate HI should only be considered when there is a clear medical need, and the benefit exceeds the risk. If used, no dose adjustment is recommended. VNZ/TEZ/D-IVA use is not recommended in patients with severe hepatic impairment.

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Characteristic	Drug Information
Moderate or strong CYP3A4 inhibitor	Clinical DDI studies evaluated the effects of the strong CYP3A inhibitor itraconazole on the PK of VNZ, TEZ and D-IVA. Coadministration with itraconazole increased VNZ AUC by 3.5- to 10.5-fold, TEZ AUC by 4.0- to 4.5-fold and D-IVA AUC by 11-fold. PBPK analysis was used to predict the interaction effect of moderate CYP3A inhibitors. Simulations indicated that coadministration with moderate CYP3A inhibitors may increase the AUC of VNZ, TEZ, and D-IVA by approximately 2.4- to 4-fold, 2-fold, and 3- to 5-fold, respectively. Simulations indicated that predicted fold changes in AUC with moderate and strong CYP3A inhibitors were similar between children aged 6 through 11 years and adults at the proposed therapeutic doses of VNZ and D-IVA, assuming the exposure levels of CYP34 inhibitors are similar between adults and pediatrics. The dose of VNZ/TEZ/D-IVA should be reduced when coadministered with strong and moderate CYP3A inhibitors, as follows:

Table 9. Recommended Dosage for Pediatric Patients Aged 6 Years and Older

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
(b) (4)			

Source: Clinical pharmacology reviewer
 Abbreviations: CYP, cytochrome P450

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Characteristic	Drug Information
	<i>Drug Interaction Liability (Drug as Perpetrator)</i>
Inhibition/induction of metabolism	D-IVA may inhibit CYP2C9 (in vitro IC₅₀ value of 15.6 µM with R value of 1.03). The risk for clinical inhibition was not ruled out using PBPK analysis. Therefore, monitoring of the international normalized ratio (INR) during coadministration of VNZ/TEZ/D-IVA with warfarin is recommended. Other medicinal products for which exposure may be increased by VNZ/TEZ/D-IVA include glimepiride and glipizide; these medicinal products should be used with caution. Based on in vitro and in vivo results, VNZ, TEZ, and D-IVA have low potential to inhibit other CYP enzymes. VNZ, TEZ, and D-IVA have low induction potential for CYP enzymes at clinically relevant exposures.
Inhibition/induction of transporter systems	In vitro studies indicate VNZ is not a substrate of P-gp, BCRP, OATP1B1, and OATP1B3. In vitro studies indicate D-IVA is a substrate of P-gp (efflux ratio of 6.7 at 1 µM, which is similar to value 5.6 of IVA) and BCRP (net efflux ratio of 42.1 at 50 µM, which is similar to value of 32.5 of IVA), but not OATP1B1 and OATP1B3. In vitro studies indicate TEZ is a substrate of P-gp (efflux ratio of 4.18), BCRP (efflux ratio of 4.62), and OATP1B1, but not OATP1B3. In vitro results showed that VNZ has potential to inhibit BCRP transporter (I_{gut}/IC₅₀=532) following the recommended dose (i.e., 20 mg). Therefore, a postmarketing requirement DDI study to evaluate the effect of VNZ on PK of a sensitive BCRP substrate is recommended. In vitro results showed that TEZ has low potential to inhibit P-gp, BCRP, OCT2, OAT1, or OAT3. In vitro results showed similar P-gp and BCRP inhibition potencies between IVA and D-IVA. Study VX14-661-006 showed that coadministration of ivacaftor or tezacaftor/ivacaftor with digoxin, a sensitive P-gp substrate, increased digoxin AUC by 1.3-fold, consistent with weak inhibition of P-gp by ivacaftor. Therefore, the review team agree that a similar P-gp DDI-related language can applied from IVA to D-IVA (i.e., when used concomitantly with digoxin or other substrates of P gp with a narrow therapeutic index such as cyclosporine, everolimus, sirolimus, and tacrolimus, caution and appropriate monitoring should be used).
	<i>Immunogenicity (if Applicable)</i>
Bioanalysis	NA
Incidence	NA
Clinical impact	NA

Source: Clinical pharmacology reviewer

Abbreviations: API, active pharmaceutical ingredient(s); AUC, area under the concentration-time curve; AUC_{inf}, area under the concentration-time estimated to infinity; AUC_{tau}, area under the concentration-time curve during the dosing interval; BCRP, breast cancer resistance protein; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; C_{max}, maximum plasma concentration; C_{max,ss}, maximum plasma concentration at steady-state; C_{trough}, lowest plasma concentration at steady-state; CV, coefficient of variation; CYP, cytochrome P450; DDI, drug-drug interaction; D-IVA, deutivacaftor; ELX, elexacaftor; FDC, fixed-dose combination; hERG, human ether-à-go-go-related gene; HI, hepatic impairment; IC₅₀, half maximal inhibitory concentration; IVA, ivacaftor; LC-MS/MS, liquid chromatography with tandem mass spectrometry; M, metabolite; NA, not applicable; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein; PBPK, population-based pharmacokinetics; PK, pharmacokinetic; popPK, population pharmacokinetics; ppFEV₁, percent predicted forced expiratory volume in 1 second; Q12h, once every 12 hours; QD, once daily; QT, QT interval; QTc, corrected QT interval; RI, renal impairment; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor; T_{max}, time to maximum concentration; VNZ, vanzacaftor

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The proposed dose of VNZ/TEZ/D-IVA FDC product is VNZ [Form D] 20 mg/TEZ 100 mg/D-IVA 250 mg once daily (QD) for subjects 12 years of age or older and subjects 6 through 11 years with body weight ≥ 40 kg; and VNZ [Form D] 12 mg/TEZ 60 mg/D-IVA 150 mg QD for subjects 6 through 11 years with body weight < 40 kg.

The dose selection of VNZ and D-IVA for phase 3 trials were primarily determined based on the two phase 2 dose-ranging studies (Study VX18-121-101 and Study VX18-561-101 for VNZ and D-IVA, respectively), and two phase 1 relative bioavailability studies (Study VX19-121-003 and Study VX21-121-005). The dose selection of TEZ is based on the approved TEZ dose of ELX/TEZ/IVA (Trade name: TRIKAFTA, NDA 212273 and NDA 217660) for the treatment of CF.

The proposed pediatric dose for subjects 6 through 11 years of age was primarily supported by Trial VX22-121-105 and population PK modeling and simulations.

6.1.1. Dose Selection of Vanzacaftor

Dose-ranging results from part 1 of the phase 2 study, Study VX18-121-101, demonstrated a numerically higher percent predicted forced expiratory volume in 1 second (ppFEV₁) improvement from baseline on Day 29 following VNZ [Form A] 10 mg QD when compared to other VNZ doses in the context of triple combination (TC) with TEZ 100 mg QD and IVA 150 mg every 12 hours (q12h) in CF subjects with *F508del* /minimal function (MF) variants. In addition, a near maximal response on sweat chloride (SwCl) reduction was observed between 10 mg [Form A] and 20 mg [Form A]. Therefore, a dose of 10 mg VNZ [Form A] QD was selected for further evaluation in phase 3 studies. However, (b) (4)

Additional PK bridging studies (Study VX19-121-003 and Study VX21-121-005) were conducted between the two forms, and the results showed that the bioavailability of VNZ [Form D] was only about 50% of that of VNZ [Form A] following the same dose administration. Based on these results, a dose of 20 mg VNZ [Form D] QD was eventually selected and carried into phase 3 trials.

VNZ Dose-Ranging Study VX18-121-101 (Study 101)

Study 101 provided primary support for VNZ dose selection for the pivotal phase 3 studies. Study 101 was a 2-part, randomized, double-blind, placebo- (Part 1) or TEZ/IVA-controlled (Part 2), proof-of-concept trial of VNZ in CF subjects. VNZ [Form A] was used in both Part 1 and Part 2 of this trial.

The primary endpoint was the absolute change in ppFEV₁ through Day 29. Key secondary endpoints were the absolute change from baseline in SwCl and the absolute change from baseline in cystic fibrosis questionnaire-revised (CFQ-R) respiratory domain (RD) score at Day 29.

In Part 1, CF subjects with *F508del*/MF variants were enrolled. The treatment groups were VNZ [Form A] 5, 10, and 20 mg QD in the context of TC with TEZ 100 mg QD and IVA 150 mg q12h in comparison to triple-placebo for 4 weeks. Subjects with no previous treatment with medications that affect CFTR processing or function within 28 days before the first dose were randomized in a 2:2:1:1 ratio to the TC-VNZ 20 mg, TC-VNZ 10 mg, TC-VNZ 5 mg, and placebo arms. In total, 58 subjects were randomized and received at least 1 dose of trial drug. In Part 2, CF subjects with *F508del*/*F508del* variant with no previous treatment with a medication that affects CFTR processing or function within 28 days before the start of TEZ/IVA run-in period (4 weeks) were enrolled. VNZ [Form A] 20 mg QD/TEZ 100 mg QD/IVA 150 mg q12h was evaluated in comparison to TEZ 100 mg QD/IVA 150 mg q12h. Subjects were randomized in a 2:1 ratio to the TC-VNZ 20 mg and TEZ/IVA arms. Twenty-nine (29) subjects were enrolled and 28 completed the treatment.

VNZ/TEZ/D-IVA treatment for 4 weeks in CF subjects with *F508del*/MF or *F508del*/*F508del* genotypes resulted in improvements in ppFEV₁, SwCl, and CFQ-R RD score (secondary efficacy endpoints) from the respective baseline when compared to the control groups (placebo for Part 1 and TEZ/IVA for Part 2) as presented in [Table 10](#). In Part 1, among three doses of VNZ [Form A], the 10 mg dose showed the numerically greatest improvement in ppFEV₁ response compared to placebo group, versus VNZ 5 mg and 20 mg.

Table 10. Efficacy Results of VNZ Dose Ranging Study VX18-121-101

Study Part	Treatment Group	Absolute Change From Baseline in ppFEV ₁ Through Day 29 in percentage points	Absolute Change From Baseline in SwCl Through Day 29 in mmol/L	Absolute Change From Baseline in CFQ-R RD Score At Day 29 in points
Part 1; LS mean (SE)	TC-5 mg	4.6 (3.0)	-42.8 (4.4)	17.6 (7.0)
	TC-10 mg	14.2 (2.1)	-45.8 (3.0)	21.2 (4.7)
	TC-20 mg	9.8 (2.0)	-49.5 (3.2)	29.8 (4.4)
	Placebo	1.9 (3.0)	2.3 (4.6)	3.3 (6.7)
Part 2; LS mean (SE)	TC-20 mg	15.9 (2.3)	-45.5 (2.0)	19.4 (4.3)
	TEZ/IVA	-0.1 (3.0)	-2.6 (2.8)	-5.0 (5.8)

Source: Table 11-10 CSR VX18-121-101

Notes: Within-group LS means (SE) compared to baseline are presented. Baseline in Part 2 was established after a 4-week TEZ/IVA Run-in Period.

Abbreviations: CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; CSR, clinical study report; IVA, ivacaftor; LS, least squares; ppFEV₁, percent predicted forced expiratory volume in 1 second; SE, standard error; SwCl, sweat chloride; TC, triple combination; TEZ, tezacaftor; VNZ, vanzacaftor

The clinical pharmacology review team acknowledges that Study VX21-121-006 demonstrated VNZ maximum plasma concentration (C_{max}) and area under the concentration-time curve (AUC) increased 48% and 54%, respectively, when VNZ was administered in TC with TEZ/D-IVA compared to VNZ administered alone. There is a concern whether this increase of VNZ systemic exposure up to 50% may change the efficacy/safety profile of VNZ in the TC context. However, since the dose ranging trial of VNZ (Study 101) was conducted in the TC context, the dose

ranging results directly support the 10 mg VNZ [Form A] dose in the TC context that was used in the phase 3 trials.

Therefore, the Applicant's decision to carry 10 mg VNZ [Form A] (later translated into 20 mg VNZ [Form D], see below) into phase 3 trials is reasonable.

VNZ Formulation Bridging Study VX19-121-003 (Study 003)

VNZ dose selection was also based on an assessment of the relative bioavailability of VNZ [Form A] physical formulation compared to VNZ [Form D] physical formulation in Study 003. Study 003 was a phase 1, open-label, randomized, 2-sequence, 2-period crossover study to evaluate the relative bioavailability of a single dose FDC tablet of VNZ [Form D] 20 mg/TEZ 100 mg/D-IVA 150 mg (test) compared to single dose VNZ [Form A] 20 mg, TEZ 100 mg, and D-IVA 150 mg coadministered as separate tablets (reference) under fed conditions.

Twenty healthy subjects were randomized and received at least one dose of study drug. The PK metrics and relative bioavailability of VNZ (Form A versus Form D), TEZ, and D-IVA after single-dose administration as an FDC tablet or as separate tablets was statistically evaluated. The geometric least squares mean ratios and their associated 90% CIs are provided for exposure of each active pharmaceutical ingredient (API) in [Table 11](#). The exposure (AUC and C_{max}) of VNZ following Form A was approximately 50% of the exposure following FDC tablet, which contained VNZ Form D. Based on these results, a dose of VNZ [Form D] 20 mg QD provides similar exposure as the VNZ [Form A] 10 mg QD dose, which was evaluated in VNZ dose-ranging trial, Study 101.

Table 11. Summary of PK Metrics (Mean [CV%]) and Relative BA Assessment of VNZ, TEZ, and D-IVA Exposures After Administration as an FDC Tablet (20 mg VNZ [Form A]) or as Separate Tablets (20 mg VNZ [Form D]), Study 003

Analyte	N	PK Metric	FDC Tablet	Separate Tablet	GLSM Ratio ¹ (90% CI)
VNZ	20	C_{max} (µg/mL)	0.168 (33.1)	0.368 (28.1)	0.452 0.412, 0.497
	20	AUC_{tlast} (µg·h/mL)	17.9 (49.0)	34.6 (35.1)	0.498 0.462, 0.536
	20	AUC_{inf} (µg·h/mL)	17.7b (40.1)	35.1 ² (34.3)	0.495 (0.461, 0.532)
TEZ	20	C_{max} (µg/mL)	5.37 (24.3)	5.40 (20.7)	0.991 (0.925, 1.06)
	20	AUC_{tlast} (µg·h/mL)	103 (33.5)	106 (22.7)	0.950 (0.915, 0.986)
	20	AUC_{inf} (µg·h/mL)	111 (33.6)	114 (23.6)	0.948 (0.915, 0.982)
D-IVA	20	C_{max} (µg/mL)	1.03 (32.9)	0.965 (26.5)	1.06 (0.972, 1.15)
	20	AUC_{tlast} (µg·h/mL)	22.0 (65.4)	19.8 (46.6)	1.07 (0.972, 1.17)
	20	AUC_{inf} (µg·h/mL)	22.2 (64.9)	20.0 (46.0)	1.06 (0.971, 1.17)

Source: Tables 11-1 and 11-2 in CRS VX19-121-003

¹ FDC tablet/Separate tablets

² N=19

Note: Separate tablets were VNZ 20 mg Form A, TEZ 100 mg, and D-IVA 150 mg; FDC tablet was VNZ 20 mg Form D/TEZ 100 mg/D-IVA 150 mg.

Abbreviations: AUC, area under the concentration-time curve; AUC_{inf} , area under the concentration-time curve estimated to infinity; AUC_{tlast} , area under the concentration-time curve to the last measurable concentration; C_{max} , maximum plasma concentration; BA, bioavailability; CI, confidence interval; C_{max} , maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; FDC, fixed-dose combination; GLSM, geometric least squares mean; N, number of subjects; PK, pharmacokinetic; TEZ, tezacaftor; VNZ, vanzacaftor

VNZ Formulation Bridging Study VX21-121-005 (Study 005)

Relative bioavailability (BA) of VNZ [Form A] physical formulation compared to VNZ [Form D] physical formulation was further evaluated at steady state in Part A of Study 005. Study 005 Part A was a phase 1, open-label, randomized, 2-sequence, 2-period, crossover trial to evaluate the relative bioavailability of FDC tablet of VNZ [Form D] 20 mg/TEZ 100 mg /D-IVA 250 mg (test) compared to single dose VNZ [Form A] 10 mg, TEZ 100 mg, and D-IVA 250 mg coadministered as separate tablets (reference) at steady-state. Trial drug was given under fed conditions.

Eighteen healthy subjects were randomized and received at least one dose of trial drug. The PK metrics and relative BA of VNZ (Form A versus Form D), TEZ, and D-IVA after single-dose administration as an FDC tablet or as separate tablets was statistically evaluated. The geometric least squares mean ratios and their associated 90% CIs are provided for exposure of each API in [Table 12](#). Exposures of VNZ 20 mg [Form D], TEZ 100 mg, and D-IVA 250 mg were similar when trial drug was given as FDC tablets relative to when it was given as separate tablets as VNZ 10 mg [Form A], TEZ 100 mg, and D-IVA 250 mg.

Table 12. Summary of PK Metrics (Mean (CV%)) and Relative BA Assessment of VNZ, TEZ, and D-IVA Exposures After Administration as an FDC Tablet (10 mg VNZ [Form A]) or as Separate Tablets (20 mg VNZ [Form D]), Study 005

Analyte	N	PK Metric	FDC Tablet	Separate Tablet	GLSM Ratio ¹ (90% CI)
VNZ	18	C _{max} (µg/mL)	0.185 ² (31.3)	0.198 (18.7)	91.6 (82.6,102)
	18	AUC _{last} (µg·h/mL)	18.0 ² (28.9)	18.3 (21.0)	97.6 (86.9, 110)
	18	AUC _{inf} (µg·h/mL)	18.7 ² (28.3)	19.1 (21.6)	97.5 (86.9, 109)
TEZ	18	C _{max} (µg/mL)	5.29 (19.3)	5.44 (13.4)	96.9 (88.6,106)
	18	AUC _{last} (µg·h/mL)	109 (24.0)	107 (20.4)	99.8 (91.5, 109)
	18	AUC _{inf} (µg·h/mL)	115 (24.5)	114 (21.6)	99.8 (91.8, 109)
D-IVA	18	C _{max} (µg/mL)	1.74 (21.6)	1.81 (16.2)	97.1 (87.7,107)
	18	AUC _{last} (µg·h/mL)	42.6 (30.0)	41.5 (23.6)	102 (91.4, 114)
	18	AUC _{inf} (µg·h/mL)	42.8 (29.9)	41.7 (23.5)	102 (91.4, 114)

Source: Tables 11-1 and 11-1 in CRS VX21-121-005

¹ FDC tablet/Separate tablets

² N=16, two subjects who presented carryover for VNZ in the FDC tablets treatment group were excluded from that period

Note: Separate tablets were VNZ 10 mg Form A, TEZ 100 mg, and D-IVA 250 mg, FDC tablet was VNZ 20 mg Form D/TEZ 100 mg/D-IVA 250 mg.

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{last}, area under the concentration-time curve to the last measurable concentration; BA, bioavailability; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; FDC, fixed-dose combination; GLSM, geometric least squares mean; N, number of subjects; PK, pharmacokinetic; TEZ, tezacaftor; VNZ, vanzacaftor

Based on the relative BA results from Study 003 and 005, a single dose of VNZ [Form D] 20 mg achieves similar exposure compared to a single dose of 10 mg VNZ [Form A] in the context of TC. Therefore, the decision to carry 20 mg VNZ [Form D] into phase 3 trials is considered reasonable by the clinical pharmacology review team.

Exposure-response analysis (Report t299) showed VNZ doses of 5, 10, and 20 mg daily administered with TEZ/D-IVA were associated with no additional increase in ppFEV₁ beyond the increases achieved with ELX/TEZ/IVA treatment during the run-in period. The VNZ 20 mg dose administered in combination with TEZ/D-IVA was associated with a reduction of up to 7.11mmol/L in SwCl beyond the reduction achieved by ELX/TEZ/IVA. The clinical meaning of

this small numerical difference is unclear. In addition, the analysis showed a numerically greater reduction of SwCl from baseline by VNZ/TEZ/D-IVA and ELX/TEZ/IVA in subjects with *F508del/F508del* and *F508del/MF* variants than other genotypes (e.g., *F508del/gating* [G] or *F508del/residual function* [RF]), probably related to higher SwCl baseline levels in subjects with *F508del/F508del* and *F508del/MF* variants. Refer to Section 6.2.3.2. for additional definitions of these variant types.

6.1.2. Dose Selection of Deutivacaftor

The dose of D-IVA 250 mg QD was selected for the phase 3 trials in subjects ≥ 12 years of age because this dose resulted in numerically greater improvements in SwCl response with similar ppFEV₁ response when compared to D-IVA 150 mg QD in the dose-ranging study, Study VX18-561-101.

Study VX18-561-101 (Study 561-101)

Study 561-101 was a phase 2, randomized, double-blind, parallel-group, and active-controlled study of D-IVA monotherapy in CF subjects who have a gating variant and were previously taking a stable dose of IVA. Four dose levels of D-IVA (25, 50, 150, and 250 mg) were evaluated to provide a broad range of exposure for exposure-response analyses.

The primary endpoint was the absolute change in ppFEV₁ at Week 12. Key secondary endpoint was the absolute change from baseline in SwCl at Week 12.

In total, 77 subjects who were on stable IVA treatment were randomized and 75 received at least one dose of study drug. Two lower dose treatment groups (25 mg and 50 mg) were prematurely discontinued because of high drop-off rate, which was presumably related to insufficient CFTR modulation. Results from Study 561-101 demonstrated treatment with either D-IVA 250 mg QD or D-IVA 150 mg QD resulted in similar absolute values of ppFEV₁ change from baseline compared to IVA 150 mg q12h treatment (Table 13). However, treatment with D-IVA 250 mg QD resulted in numerically greater improvements in SwCl response compared to D-IVA 150 mg QD. Therefore, the Applicant's choice of D-IVA 250 mg QD for further evaluation in phase 3 trials was reasonable.

Table 13. Efficacy and PD of D-IVA Treatment Relative to IVA Baseline, Study 561-101

Treatment Group	Absolute Change in ppFEV₁ in percentage points at Week 12 (LS mean [95% CI])	Absolute Change in SwCl in mmol/L at Week 12 (LS mean [95% CI])
D-IVA 250 mg qd	2.7 (-1.0, 6.5)	-6.5 (-14.1, 1.2)
D-IVA 150 mg qd	3.1 (-0.8, 7.0)	3.3 (-4.6, 11.2)
IVA 150 mg q12h	-0.8 (-6.2, 4.7)	0.9 (-9.5, 11.3)

Source: Table 11-4 CSR VX18-561-101

Abbreviations: CI, confidence interval; D-IVA, deutivacaftor; IVA, ivacaftor; LS, least squares; PD, pharmacodynamic; ppFEV₁, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; qd, once daily; SwCl, sweat chloride

The clinical pharmacology review team acknowledges that Study VX21-121-006 demonstrated D-IVA C_{max} and AUC increased 18% and 27%, respectively, when D-IVA was administered in TC with VNZ/TEZ compared to D-IVA administered alone. There is a concern whether this

increase of D-IVA systemic exposure of up to 27% may change the efficacy/safety profile of D-IVA in the TC context. Based on the flat dose-response relationship over D-IVA 150 mg to D-IVA 250 mg on ppFEV₁ response observed from Study 561-101, it is unlikely that observed increase of systemic exposure would contribute additional efficacy of D-IVA in the context of TC.

6.1.3. Dose Selection for Pediatric Subjects 6 Through 11 Years Old

Trial VX21-121-105 (Trial 105)

Trial 105 was an open-label, 2-part (Parts A and B), multicohort (Cohorts 1, 2, and 3), multicenter trial evaluating the PK, safety, tolerability, and efficacy of VNZ/TEZ/D-IVA therapy in CF subjects 1 through 11 years of age who carry at least one triple combination responsive (TCR) *CFTR* variant. Cohorts A1 and B1 evaluated subjects 6 through 11 years of age.

The primary objective of Trial 105 was to evaluate the PK, safety, and tolerability of VNZ/TEZ/D-IVA and relevant metabolites when dosed in TC in pediatric CF subjects.

Subjects in Cohort A1 received VNZ 10 mg QD/TEZ 50 mg QD/D-IVA 125 mg QD for 22 days. Subjects who participated in Cohort A1 were permitted to participate in Cohort B1 if they met eligibility criteria (refer to Section 15 for complete enrollment criteria). A review of safety, tolerability, and available PK data was completed by an internal team after Cohort A1 completed treatment to determine the doses and weight cutoffs for Cohort B1.

In Cohort A1, 17 subjects 6 through 11 years of age were randomized and received at least one dose of trial drug. All subjects received VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg QD, which is half the dose for CF subjects ≥ 12 years of age. The comparison results showed that the mean plasma concentration observed at the end of dosing interval (C_{trough}) values in Cohort A1 (on Day 22) of three active ingredients and their active metabolites in subjects 6 through 11 years of age were generally lower than that from adults and adolescents in the pivotal phase 3 Trials 102 and 103 as presented in Table 14.

Therefore, the pediatric VNZ/TEZ/D-IVA doses were increased in both body weight tiers in Cohort B1 with the same adult/adolescent dose for subjects ≥ 40 kg and VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg for subjects < 40 kg. Following the new dosing algorithm, overall trough concentrations were within the range for each of the analytes previously observed in CF subjects ≥ 12 years of age in pivotal phase 3 Trials 102 and 103.

Table 14. Trough Concentrations (Mean [SD]) Observed in CF Subjects 6 Through 11 Years of Age in Trial 105 Compared to Those Values in Trials 102 and 103

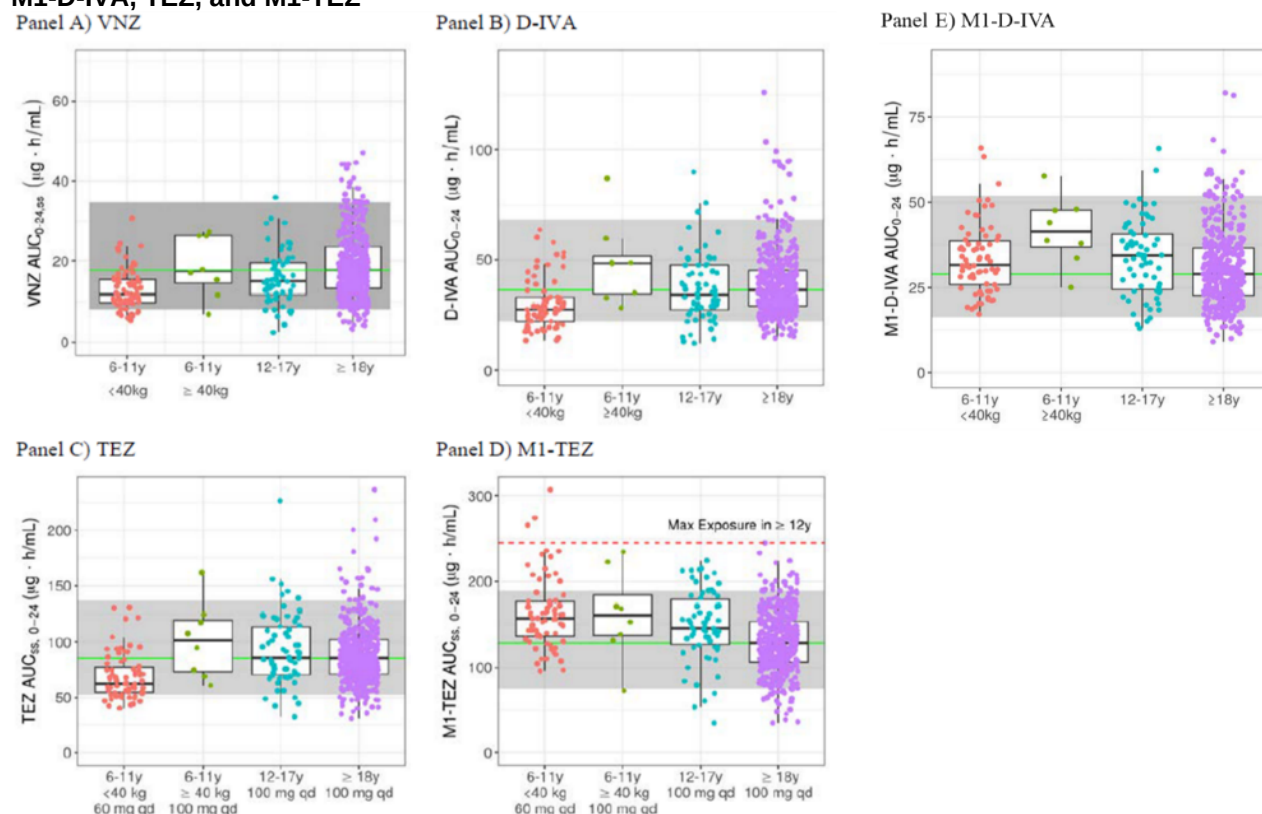
Dosing Group	Dose	VNZ	TEZ	M1-TEZ	D-IVA	M1-D-IVA
Trial 105						
Cohort A1 ^a (N=17) 6 - 11 years	VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg	0.43 (0.19)	1.55 (1.01)	5.14 (1.89)	0.63 (0.44)	0.7 (0.44)
Cohort B1 (N=67) 6 - 11 years, <40 kg	VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg	0.46 (0.22)	1.5 (0.82)	5.91 (2.09)	0.65 (0.47)	0.72 (0.45)
Cohort B1 (N=7) 6 - 11 years, ≥40 kg	VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg	0.68 (0.32)	2.86 (1.59)	6.32 (2.73)	1.59 (1.15)	1.17 (0.36)
Trials 102 and 103						
12 - 17 years (N=58)	VNZ 20 mg/ TEZ 100 mg/ D-IVA	0.58 (0.34)	2.32 (1.61)	5.5 (2.17)	0.87 (0.74)	0.81 (0.62)
≥18 years (N=394)	250 mg	0.77 (0.44)	2.26 (1.29)	4.86 (1.64)	1.12 (0.86)	0.85 (0.63)

Source: Reviewer's analysis using adpc.xpt from Trials 102, 103, and 105

^a Trough concentrations were measured at Day 22 because the duration of treatment was for 3 weeks.

Abbreviations: CF, cystic fibrosis; D-IVA, deutivacaftor; M, metabolite; N, number of subjects; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

The population PK-predicted steady-state AUC values of VNZ, TEZ, M1-TEZ, and D-IVA in CF pediatric subjects 6 through 11 years of age, adolescents, and adults are summarized in [Figure 1](#).

Figure 1. Comparison of PopPK-Predicted Steady-State AUC Versus Age Group for VNZ, D-IVA, M1-D-IVA, TEZ, and M1-TEZ

Source: Figure 22 from page 72 of Summary of Clinical Pharmacology Studies

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. Points represent values from individual subjects. Boxplots represent the 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 $1.5 \times \text{IQR}$.

Abbreviations: AUC, area under the concentration-time curve; $\text{AUC}_{\text{ss},0-24}$, area under the concentration-time curve from time 0-24 hours at steady-state; D-IVA, deutivacaftor; IQR, interquartile range; m, metabolite; max, maximum; popPK, population pharmacokinetic; qd, once daily; TEZ, tezacaftor; VNZ, vanzacaftor; y, year

Overall, the distributions of observed pediatric C_{trough} and predicted AUC values of three active ingredients and their active metabolites in subjects 6 through 11 years old following the proposed doses (i.e., VNZ 20 mg/TEZ 100 mg/ D-IVA 250 mg for subjects ≥ 40 kg and VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg for subjects <40 kg) were within the range of those in adults and adolescents. The review team acknowledges the pediatric exposure values of VNZ/TEZ/D-IVA in subjects <40 kg were at the lower end of the adult/adolescent range. However, a consistent and similar trend was observed in subjects 6 through 11 years old with body weight <30 kg in the ELX/TEZ/IVA development program. For details, refer to the supplemental NDA 212273 Unireview dated June 7, 2021.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Results of Pooled Analyses

The evaluation of efficacy was based on the analyses of the individual trials. Pooled efficacy analyses will not be discussed in this review.

6.2.2. Trial VX20-121-102 (Trial 102)

6.2.2.1. Design, Trial 102

Trial VX20-121-102 (Trial 102) was a phase 3, multicenter, randomized, double-blind, parallel-group, ELX/TEZ/IVA-controlled, noninferiority trial evaluating the safety and efficacy of VNZ/TEZ/D-IVA in subjects with CF 12 years of age and older. The trial included a 4-week run-in period during which all subjects received ELX/TEZ/IVA to establish a reliable on-treatment (ELX/TEZ/IVA) baseline for the treatment period. Subjects were then randomized 1:1 to receive VNZ/TEZ/D-IVA or ELX/TEZ/IVA for a 52-week treatment period. Randomization was stratified by: age at screening, ppFEV₁ during the run-in period (Day -14 clinic assessment), SwCl during the run-in period (Day -14 clinic assessment), and prior use of ELX/TEZ/IVA or medications that contain one or more of its components. The full review of the trial protocol design, subject population, objectives, and endpoints is in Section [15.1](#).

The dosages evaluated in the phase 3 trials were:

- Active control: ELX 200 mg QD/TEZ 100 mg QD/IVA 150 mg q12h
- Treatment: VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 250 mg QD

The primary objective of Trial 102 was to evaluate the efficacy of VNZ/TEZ/D-IVA in adolescent and adult CF subjects. The efficacy endpoints are listed below:

Primary Endpoint

- Absolute change from baseline in ppFEV₁ through Week 24

Key Secondary Endpoints

- Absolute change from baseline in sweat chloride (SwCl) through Week 24
- Proportion of subjects with SwCl <60mmol/L through Week 24 (pooled with data from Trials 102 and 103)
- Proportion of subjects with SwCl <30mmol/L through Week 24 (pooled with data from Trials 102 and 103)

Other Secondary Endpoints

- Number of CF pulmonary exacerbations (PE_x) through Week 52
- Absolute change from baseline in CFQ-R RD score through Week 24
- Absolute change from baseline in ppFEV₁ through Week 52
- Absolute change from baseline in SwCl through Week 52
- Proportion of subjects with SwCl <60mmol/L through Week 24
- Proportion of subjects with SwCl <30mmol/L through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, electrocardiograms, vital signs, and pulse oximetry

ELX/TEZ/IVA and other medications that affect CFTR processing or function have contributed to significant clinical benefits in the CF population and are currently used by over 80% of patients in the United States ([CFF 2023](#)). The Applicant designed a noninferiority (NI) trial with ELX/TEZ/IVA as the active control. Given the magnitude of treatment effect and pervasive use of ELX/TEZ/IVA as the standard of care, the Applicant argued use of placebo control would have been unethical and infeasible, with which the Division agreed.

There was not a previously accepted NI margin: i.e., an amount of loss of pulmonary function, as measured by forced expiratory volume in one second (FEV₁) (or any other lung function measure), by which a new drug could be worse than a reference drug with established efficacy to determine noninferiority in CF. The Applicant proposed an NI margin for absolute change in ppFEV₁ of -3.0% supported by data from the ELX/TEZ/IVA development program, which included the following rationale:

- For the population eligible for Trial 102 (*F508del*/MF), the lower bound of the 95% CI of the treatment effect for ELX/TEZ/IVA was approximately 12% for the ppFEV₁. According to the FDA guidance for industry *Non-Inferiority Clinical Trials to Establish Effectiveness* ([November 2016](#)), preservation of at least 50% of the conservative effect of 12% (M1) is recommended as a clinically acceptable NI margin (M2), i.e., ≤6% (equal to 50% of 12% effect size). Thus, the Applicant proposed 3.0% as the NI margin, which the Division agreed is reasonable. Refer to Section [15](#) for additional details on the NI margin.

All other efficacy endpoints were analyzed using superiority comparisons, some of which were controlled for multiplicity (refer to Section [15.1](#) for details). As reviewed in Section [6.3.2](#), the key secondary endpoints were limited to SwCl-based endpoints and were the only secondary endpoints analyzed under multiplicity control. The Division views SwCl as an important pharmacodynamic marker of CFTR function but advised the Applicant to consider additional non-SwCl key secondary endpoint(s) that represent clinically meaningful outcomes (e.g., PE_x, CFQ-R). The Applicant included assessments of these clinically meaningful endpoints, but they were maintained as ‘other’ secondary endpoints and not included in the statistical analysis hierarchy. The results of these other endpoints are reviewed in more detail in Section [6.2.2.4](#) and Section [16.2](#).

Overall, the trial design, endpoint selection, and endpoint classifications were reasonable to demonstrate noninferiority in a CF population with respect to ppFEV₁.

6.2.2.2. Eligibility Criteria, Trial 102

The eligibility criteria for Trial 102 were appropriate for capturing a population of adults and adolescents with stable CF. The *CFTR* variant-based eligibility for Trial 102 included subjects heterozygous for the *F508del* and minimal function (MF) *CFTR* variants, defined as either a variant that results in no translated *CFTR* protein or a variant that is nonresponsive to TEZ, IVA, or TEZ/IVA based on in vitro testing.

The key inclusion criteria included:

- Ages 12 years and older
- Heterozygous *F508del* and a MF *CFTR* variant
- Percent predicted FEV₁ ([Quanjer et al. 2012](#)):
 - Subjects receiving ELX/TEZ/IVA at screening: $\geq 40\%$ and $\leq 90\%$
 - Subjects not receiving ELX/TEZ/IVA at screening: $\geq 40\%$ and $\leq 80\%$

The key exclusion criteria included:

- History of intolerance to trial drug including ELX/TEZ/IVA
- History of comorbidity including but not limited to hepatic cirrhosis, moderate to severe hepatic impairment, solid organ or hematological transplantation
- Acute upper or lower respiratory tract infection, infectious PEx of CF, or changes in therapy (including antibiotics) for sinopulmonary disease

The trial population was consistent with similar clinical development programs in CF, including Trial VX17-445-102 used to support the registration of ELX/TEZ/IVA. These similarities in the population further support the use of a noninferiority trial design with ELX/TEZ/IVA as the active control. The exclusion of subjects unable to tolerate ELX/TEZ/IVA is reasonable and appropriate given the design of the trial; however, this is a significant limitation that affects the generalizability of safety results. Additional information regarding the trial's population is included in Section [15](#).

6.2.2.3. Statistical Analysis Plan, Trial 102

The primary efficacy analysis compared VNZ/TEZ/D-IVA to ELX/TEZ/IVA using a mixed-effects model for repeated measures (MMRM) adjusted for treatment, visit, age at screening (<18 versus ≥ 18 years of age), and treatment-by-visit interaction, with baseline ppFEV₁ and baseline SwCl as continuous covariates. The primary result obtained from the model was the estimated treatment difference through Week 24, which was estimated by averaging Weeks 16 and 24. The adjusted mean difference with a 2-sided 95% CI and the 1-sided P value for NI were provided. The primary null hypothesis was to be rejected, and noninferiority demonstrated, if the

lower bound of the 95% CI was $\geq -3.0\%$. Intercurrent events of premature treatment discontinuation and use of non-trial medications that affect CFTR processing or function for >3 days were handled with a treatment policy strategy. Conditional on the observed data and covariates, missing data was assumed to be missing at random, and its impact was assessed by tipping point analyses. The analysis was conducted on the full analysis set (FAS) population, defined as all randomized subjects who carry the intended *CFTR* genotype and received at least one dose of trial drug.

To address multiplicity in the analysis of the efficacy endpoints, the Applicant pre-specified a hierarchical order for the primary endpoint and key secondary endpoints of absolute change from baseline in SwCl through Week 24, and proportion of subjects with SwCl <60 mmol/L and SwCl <30 mmol/L through Week 24 on the pooled with data from Trials 102 and 103. See Section [15.1](#) for additional information.

6.2.2.4. Results of Analyses, Trial 102

Subject Enrollment and Disposition

A total of 435 subjects were enrolled in Trial 102. During the run-in period, 37 (8.5%) of subjects discontinued the trial and did not enter the treatment period. The most common reason reported for discontinuation (22, 5.1%) during the run-in period was an adverse event of which the majority were related to CF pulmonary exacerbations. Following the run-in period, 405 subjects were randomized and 398 (98.3%) received at least 1 dose of the trial drug and are considered the FAS. A summary of the subject enrollment and disposition is included in [Table 15](#).

Table 15. Subject Enrollment and Disposition, Trial 102

Disposition/Reason	ELX/TEZ/IVA n (%)	VNZ/TEZ/D-IVA n (%)	Total n (%)
All randomized population	205	200	405
Safety analysis set	202	196	398
Full analysis set	202	196	398
Completed treatment	186 (92.1)	181 (92.3)	367 (92.2)
Discontinued treatment	16 (7.9)	15 (7.7)	31 (7.8)
Completed trial	191 (94.6)	184 (93.9)	375 (94.2)
Discontinued trial	11 (5.4)	12 (6.1)	23 (5.8)

Source: Clinical reviewer. Software: JMP v15.0, OCS Analysis Studio. adsl dataset, using SAFFL (Y), EOTSTT, DCTREA1, EOSSTT, DCREAS.

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; n, number of subjects in subset; TEZ, tezacaftor; VNZ, vanzacaftor

The majority of subjects completed treatment (367, 92.2%), and the overall trial (375, 94.2%). The rates of treatment discontinuation were balanced between groups, although there were small numeric differences in the primary reasons for treatment discontinuation (not shown in [Table 15](#)): e.g., adverse events were reported in 10 (5.0%) subjects in the ELX/TEZ/IVA group compared to 4 (2.0%) subjects in the VNZ/TEZ/D-IVA group; subject refusal of further dosing was reported in 2 (1.0%) subjects in the ELX/TEZ/IVA group compared to 5 (2.6%) subjects in the VNZ/TEZ/D-IVA group. Any imbalance between groups is unlikely to affect the analysis given the overall low rate of treatment discontinuation.

The rates of trial discontinuation were also balanced between groups, and the main reasons cited included withdrawal of consent (5 [2.5%] subjects in ELX/TEZ/IVA group and 5 [2.6%] subjects in VNZ/TEZ/D-IVA group) and adverse events (4 [2.0%] subjects in ELX/TEZ/IVA group and 4 [2.0%] subjects in VNZ/TEZ/D-IVA group). The rates of treatment and trial discontinuation were low. Rates of trial completion and treatment discontinuation in Trial 102 were similar to other phase 3 programs in this population.

Subject Demographics

The population enrolled in Trial 102 had a mean age of 30.8 years (range 12.2 to 71.6 years), was 59.0% male, and 14.3% adolescents (12 to <18 years). The mean age of Trial 102 was older than phase 3 trials from the ELX/TEZ/IVA program, but not unreasonable based on the known demographics of the CF population. The baseline subject demographics are shown in [Table 16](#).

Table 16. Baseline Subject Demographics (FAS), Trial 102

Demographic	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
Sex, n (%)			
Male	119 (58.9)	116 (59.2)	235 (59.0)
Female	83 (41.1)	80 (40.8)	163 (41.0)
Age, years			
Mean (SD)	30.9 (11.4)	30.8 (10.5)	30.8 (11.0)
Median (min, max)	31.3 (12.2, 71.6)	30.3 (12.4, 61.7)	31.0 (12.2, 71.6)
Age category at screening visit, n (%)			
12 to <18 years	31 (15.3)	26 (13.3)	57 (14.3)
≥18 years	171 (84.7)	170 (86.7)	341 (85.7)
Race, n (%)			
White	197 (97.5)	191 (97.4)	388 (97.5)
Black/African American	1 (0.5)	4 (2.0)	5 (1.3)
Asian	0	1 (0.5)	1 (0.3)
Other	1 (0.5)	0	1 (0.3)
More than one race reported	3 (1.5)	0	3 (0.8)
Ethnicity, n (%)			
Not Hispanic or Latino	190 (94.1)	183 (93.4)	373 (93.7)
Hispanic or Latino	11 (5.4)	13 (6.6)	24 (6.0)
Not reported per local regs	1 (0.5)	0	1 (0.3)
Geographic region, n (%)			
North America	91 (45.0)	87 (44.4)	178 (44.7)
Rest of the world	111 (55.0)	109 (55.6)	220 (55.3)

Source: Clinical reviewer. Software: JMP v15.0, OCS Analysis Studio. adsl dataset, using FASFL(Y), SEX, AAGE, RACE, ETHNIC, REGION1, COUNTRY.

Abbreviations: D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects in subset; SD, standard deviation, TEZ, tezacaftor; VNZ, vanzacaftor

The majority of subjects were White (388, 97.5%) and non-Hispanic (372, 93.7%), reflecting the demographics of the CF patient population ([CFE 2023](#)). The trial enrolled 220 (55.5%) subjects at international sites, which is similar to other trials of CF therapeutics. There were no significant imbalances in baseline demographics noted between the treatment groups.

The overall population had an average baseline ppFEV₁ of 67.1% with an average SwCl of 53.9mmol/L. The average ppFEV₁ was higher and the average SwCl was lower than the phase 3

registrational trials for ELX/TEZ/IVA. These differences are likely reflective of the ELX/TEZ/IVA treatment effect, since 347 (87.2%) of subjects reported prior use of ELX/TEZ/IVA or medications that contain one or more of its components. Baseline CF disease characteristics are reviewed in [Table 17](#).

Table 17. Baseline Disease Characteristics (FAS), Trial 102

Parameter/Characteristic	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
ppFEV ₁ at baseline ^a , percentage points			
Mean (SD)	67.2 (14.6)	67.0 (15.3)	67.1 (15.0)
Median (min, max)	68.1 (31.0, 100.1)	67.7 (28.0, 108.6)	68.0 (28.0, 108.6)
ppFEV ₁ by severity group at baseline ^a , n (%)			
<40%	3 (1.5)	6 (3.1)	9 (2.3)
≥40 to <70%	111 (55.0)	95 (48.5)	206 (51.8)
≥70 to <90%	79 (39.1)	85 (43.4)	164 (41.2)
>90%	8 (4.0)	7 (3.6)	15 (3.8)
Missing data	1 (0.5)	2 (1.5)	3 (1.0)
SwCl at baseline ^b , mmol/L			
Mean (SD)	54.3 (18.2)	53.6 (17.0)	53.9 (17.6)
Median (min, max)	54.2 (10.0, 113.5)	52.0 (20.5, 106.8)	53.8 (10.0, 113.5)
SwCl category at baseline ^b , n (%)			
<30mmol/L	19 (9.4)	17 (8.7)	36 (9.0)
≥30 to <60mmol/L	105 (52.0)	114 (58.2)	219 (55.0)
≥60mmol/L	77 (38.1)	63 (32.1)	140 (35.2)
Missing	1 (0.5)	2 (1.0)	3 (0.8)
Prior use of a medication that affects CFTR processing or function ^c , n (%)			
No	25 (12.4)	26 (13.3)	51 (12.8)
Yes	177 (87.6)	170 (86.7)	347 (87.2)
CFQ-R RD score at baseline, points			
Mean (SD)	82.9 (15.7)	85.8 (14.7)	84.4 (15.3)
Prior medication use ^d , n (%)			
Dornase alfa	136 (67.3)	123 (62.8)	259 (65.1)
Azithromycin	82 (40.6)	88 (44.9)	170 (42.7)
Inhaled antibiotic	91 (45.0)	81 (41.3)	172 (43.2)
Any bronchodilator	178 (88.1)	172 (87.8)	350 (87.9)
Inhaled hypertonic saline	135 (66.8)	118 (30.2)	253 (63.6)
<i>Pseudomonas aeruginosa</i> colonization ^e , n (%)			
Positive	112 (55.4)	113 (57.7)	225 (56.5)

Parameter/Characteristic	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
Height and weight, mean (SD)			
Weight, kg	64.5 (13.7)	65.1 (13.3) ^f	64.8 (13.5)
Height, cm	166.9 (9.5)	168.8 (9.5)	167.8 (9.5)
BMI, kg/m ²	23.0 (3.8)	22.7 (3.4) ^f	22.9 (3.6)
BMI z-score for subjects <20y, n	40	32	72
BMI z-score for subjects <20y, kg/m ²	-0.14 (0.88)	-0.36 (1.09)	-0.24 (0.97)

Source: Clinical reviewer. Software: JMP v15.0. adsl dataset using FASFL(Y), PPFEV1BL, SWBL, CFQRRBL, PSEUBL, WTBL, HTBL, BMIBL, ZBMIBL, PMEDFL

^a Baseline FEV₁ measurements were defined as the predose Day 1 value. If missing, the most recent predose, nonmissing value on or after the Day -14 visit was used as baseline.

^b Baseline SwCl measurements were defined as the average of the two most recent predose, nonmissing values on or after the Day -14 visit. If only one nonmissing value was available during this interval, the available value was considered as baseline.

^c Medications that affect CFTR processing or function include ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, and IVA

^d Medications administered with 56 days before first dose of treatment in the Treatment Period excluding the ones started in the Run-in Period

^e *Pseudomonas aeruginosa* colonization defined as respiratory tract culture positivity within 2 years prior to screening

^f One subject without recorded baseline weight or BMI values

Abbreviations: BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LUM, lumacaftor; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects in subset; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation, SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor; y, year

Overall, the baseline CF disease characteristics were balanced between the treatment groups and reasonable for a stable adolescent and adult CF population. The overall use of other CF background symptomatic therapies was lower than the phase 3 trials for ELX/TEZ/IVA, with the exception of inhaled hypertonic saline and inhaled bronchodilators. This difference is not unexpected and is likely reflective of changes in prescribing practices over time in the context of ELX/TEZ/IVA availability. The rate of positive *Pseudomonas aeruginosa* culture within the last 2 years was also lower than the phase 3 trials of ELX/TEZ/IVA and is consistent with recently published data about the overall CF population ([CFF 2023](#)). These differences in baseline disease characteristics are not significant enough to affect the appropriateness of the reference trials for the noninferiority comparison.

Trial 102 limited enrollment to subjects who were heterozygous for *F508del* and an MF variant. The past medical history and concomitant medications were reviewed and are consistent with a CF adult and adolescent population and balanced between treatment groups. Additional information regarding subject genotype, past medical history, and concomitant medications is included in Section [16.1.1](#).

Analysis of Efficacy – Primary Endpoint

Trial 102 was designed as a noninferiority trial with a designated margin of -3.0% for the primary endpoint of ppFEV₁. The least squares (LS) mean difference for change from baseline in ppFEV₁ through Week 24 was 0.2% (95% CI: -0.7%, 1.1%) in VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA based on the FAS population, as shown in [Table 18](#). Since the lower bound of the 95% CI was greater than -3.0%, VNZ/TEZ/D-IVA was demonstrated to be noninferior to ELX/TEZ/IVA in ppFEV₁.

Table 18. Change From Baseline in ppFEV₁ Through Week 24 (FAS), Trial 102

Endpoint/Parameter	ELX/TEZ/IVA (N=202)	VNZ/TEZ/D-IVA (N=196)
Absolute CFB ^a in ppFEV ₁ through Week 24 ^b		
n	193	187
LS mean (SE)	0.3 (0.3)	0.5 (0.3)
95% CI of LS mean	-0.3, 0.9	-0.1, 1.1
LS mean difference (95% CI)		0.2 (-0.7, 1.1)
1-sided p-value for noninferiority vs ELX/TEZ/IVA		<0.00001

Source: Statistical analyst. Software: R. adsl and adsp datasets

^a Baseline ppFEV₁ measured at Day 1. If predose Day 1 was missing, the most recent predose, nonmissing value on or after Day -14 visit was used.

^b ppFEV₁ through Week 24 (estimated by averaging Weeks 16 and 24)

Abbreviations: CFB, change from baseline; CI, confidence interval; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; n, number of subjects included in analysis; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation, SE, standard error; TEZ, tezacaftor; VNZ, vanzacaftor; vs, versus

The Applicant specified that the primary endpoint would be analyzed through Week 24, defined as the average of the values from Weeks 16 and 24. During the development of VNZ/TEZ/D-IVA, the Division recommended the use of a landmark analysis at Week 24 to better capture durability of treatment effect. The Applicant maintained the through 24-week analysis; therefore, the statistical reviewer and analyst performed an additional landmark analysis using an MMRM analysis for change from baseline in ppFEV₁ at Week 24. The landmark analysis at Week 24 resulted in an LS mean difference (95% CI) of 0.3% (-1.3%, 0.8%), which supported the noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA, as well. In addition, the robustness of the analysis results regarding missing data was supported by the tipping point sensitivity analysis. See Section 16.2 for details.

Although the landmark analysis was post hoc and exploratory, the results were supportive of the treatment effect of VNZ/TEZ/D-IVA. For future development programs, the Division continues to recommend landmark analyses for ppFEV₁ endpoints.

Analysis of Efficacy – Secondary Endpoints

The results of a key secondary endpoint, the absolute change from baseline in the SwCl through 24 weeks, is shown in Table 19.

Table 19. Change From Baseline in SwCl (mmol/L) Through Week 24 (FAS), Trial 102

Sweat Chloride Values	ELX/TEZ/IVA (N=202)	VNZ/TEZ/D-IVA (N=196)
Baseline SwCl (SD), mmol/L	54.3 (18.2)	53.6 (17.0)
n	194	184
LS mean CFB through Week 24 (SE)	0.9 (0.8)	-7.5 (0.8)
LS mean difference (95% CI)		-8.4 (-10.5, -6.3)
p-Value		<0.0001

Source: Statistical analyst. Software: R. adsl and adsw datasets.

Abbreviations: CFB, change from baseline; CI, confidence interval; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; n, number of subjects included in analysis; SD, standard deviation; SE, standard error; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

VNZ/TEZ/D-IVA led to a statistically significant decrease from baseline in SwCl through Week 24 compared to ELX/TEZ/IVA with a mean difference (95% CI) of -8.4 (-10.5, -6.3)

mmol/L (p-value<0.0001). Since SwCl is a pharmacodynamic marker and not a predictive marker of disease response to treatment, the clinical implications of a treatment difference of approximately 8mmol/L in change from baseline are unclear at this time. This is discussed further in Section 6.3.2. Other secondary endpoints based on SwCl, including pooled and individual trial analyses of the proportion of subjects who achieved SwCl <60mmol/L and <30mmol/L through Week 24, are also discussed in Section 6.3.2.

Selected other secondary endpoints from Trial 102 are shown below in Table 20 and include the number of CF pulmonary exacerbations through Week 52 and the absolute change from baseline in the CFQ-R RD score through Week 24. These are both clinically relevant endpoints for a CF population, which are currently described in Section 14 of United States Prescribing Information (USPI) for ELX/TEZ/IVA.

Table 20. Select Other Secondary Endpoints (FAS), Trial 102

Endpoint	VNZ/TEZ/D-IVA (N=196) vs. ELX/TEZ/IVA (N=202)	
	Parameter	Result (95% CI)
Number of PEx through Week 52	Rate difference	-0.10 (-0.24, 0.04)
Absolute CFB in CFQ-R RD score through Week 24	LS mean diff	2.3 (-0.6, 5.2)

Source: Statistical analyst. Software: R. adsl, adcfqr, and adce datasets.

Abbreviations: CF, cystic fibrosis; CFB, change from baseline; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; CI, confidence interval; D-IVA, deutivacaftor; diff, difference; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; PEx, pulmonary exacerbation; TEZ, tezacaftor; VNZ, vanzacaftor; vs., versus

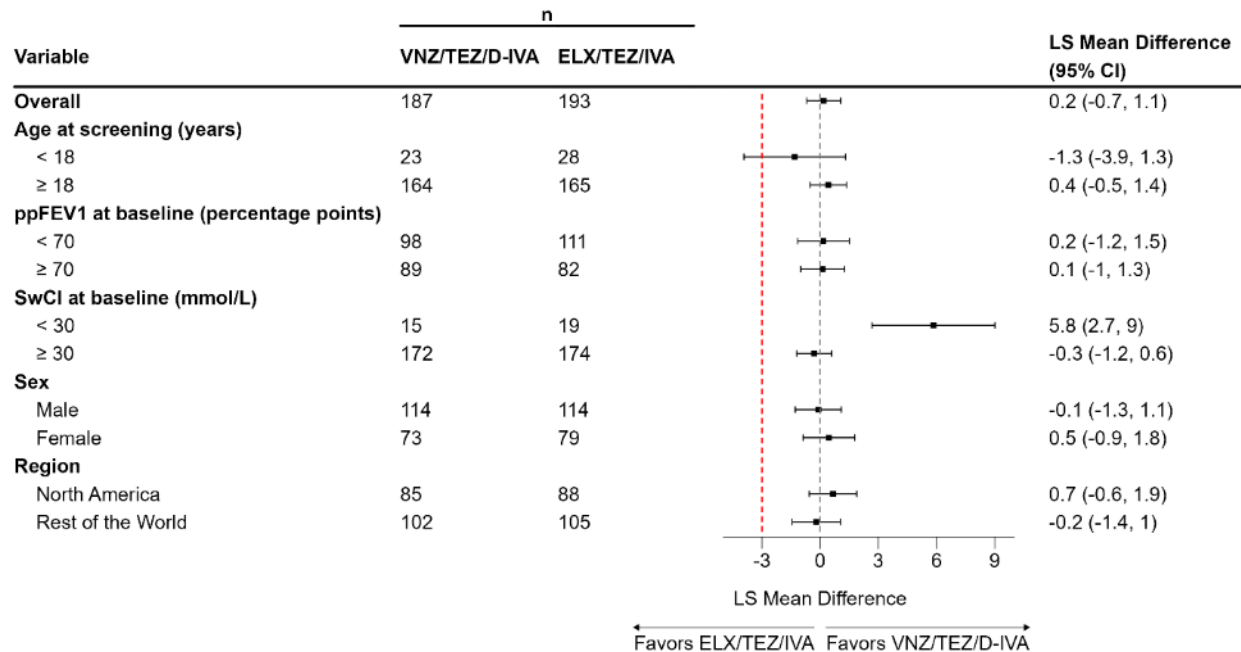
In subjects treated with VNZ/TEZ/D-IVA, the rate difference (95% CI) in number of CF PEx through Week 52 was -0.10 (-0.24, 0.04) and the mean difference (95% CI) in absolute change from baseline in CFQ-R RD score through Week 24 was 2.3 (-0.6, 5.2) points compared to treatment with ELX/TEZ/IVA. The results were similar between the VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups; however, the interpretation of these endpoints is limited because they were analyzed without control for multiplicity.

Additional discussion of the secondary endpoints is included in Section 16.2. Overall, the secondary endpoints appear supportive of efficacy for VNZ/TEZ/D-IVA in patients with CF.

Efficacy Subgroup Analyses

The Applicant performed multiple subgroup analyses for the primary endpoint, including age, ppFEV₁ at baseline, SwCl at baseline, sex, and geographic region. Overall, the subgroups evaluations were generally consistent with the overall population. Select subgroup analyses are summarized in Figure 2.

Figure 2. Subgroup Analyses of Change From Baseline in ppFEV₁ Through Week 24 (FAS), Trial 102



Source: Statistical analyst. Software: R. adsl and adsp datasets.

Abbreviations: CI, confidence interval; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; n, number of subjects in subset; ppFEV₁, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

For the adolescent subgroup (subjects with an age at screening of <18 years), the LS mean difference of the ppFEV₁ between VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups was -1.3% (95% CI: -3.9%, 1.3%). The point estimate numerically favors ELX/TEZ/IVA treatment and the lower bound of the 95% CI is smaller than the NI margin of -3.0%. Interpretation of results in the adolescent subgroup is limited by the wide 95% CI, likely because of the small sample size.

In subjects with a SwCl of <30mmol/L at baseline, the 95% confidence interval of the LS mean difference in ppFEV₁ between the VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment groups ruled out the NI margin and excluded the null. However, the interpretation of this finding is limited by a small sample size, as it represents less than 10% of the overall population; therefore, the clinical meaning of this finding is unclear.

6.2.3. Trial VX20-121-103 (Trial 103)

6.2.3.1. Design, Trial 103

The overall design and endpoint selection for Trial 103 were the same as Trial 102 (reviewed in Section 6.2.2.1 and Section 15.1). The dosages evaluated in Trial 103 were also the same as Trial 102. The Applicant proposed a noninferiority margin of absolute change in FEV₁ of -3.0% supported by data from the ELX/TEZ/IVA development program that included a similar rationale as for Trial 102:

- For the population eligible for Trial 103 (F/F and others), there were no historical placebo-controlled trials to derive a NI margin by the usual approach. The Applicant employed a novel method based on Bucher's network indirect comparison approach to come up with 12% as M1 ([Bucher et al. 1997](#)). Then similarly, the Applicant proposed 3.0% as the NI margin, and the Division generally agreed with the proposal, acknowledging the lack of historical placebo-controlled data. See Section [15.1](#) for additional information on the NI margin.

As in Trial 102, all other efficacy endpoints were analyzed using superiority comparisons, some of which were controlled for multiplicity (refer to Section [15.1](#) for details).

6.2.3.2. Eligibility Criteria, Trial 103

The eligibility criteria for Trial 103 were also very similar to Trial 102 (reviewed in Section [6.2.2.1](#) and Section [15.1](#)) with the exception of the *CFTR* variant based inclusion criteria.

Trial 103 enrolled subjects with the following *CFTR* genotypes:

- Homozygous for *F508del* (F/F)
- Heterozygous for *F508del* and a gating variant (F/G)
- Heterozygous for *F508del* and a residual function variant (F/RF)
- At least one other TCR *CFTR* variant identified as responsive to ELZ/TEZ/IVA and no *F508del* variant (TCR/non-F)

G variants and RF variants, also referred to as conduction variants, are classified as pathologic *CFTR* variants in which *CFTR* protein is created and trafficked to the cell surface but chloride transport through the protein channel is decreased because the channel does not open or function properly ([CFF 2024](#)). A summary of the G and RF variants eligible for Trial 102 provided by the Applicant is included in Section [15.1](#). Note there can be overlap of certain variants between these two *CFTR* classification groups.

6.2.3.3. Statistical Analysis Plan, Trial 103

The statistical analysis plan for Trial 103 was the same as Trial 102 (reviewed in Section [6.2.2.3](#) and Section [15.1](#)), with the exception of sample size that was powered at 95% for Trial 103 compared to 90% for Trial 102.

6.2.3.4. Results of Analyses, Trial 103

Subject Enrollment and Disposition

A total of 597 subjects were enrolled in Trial 103. During the run-in period, 24 (4.0%) subjects discontinued the trial. The primary reason listed for trial discontinuation was "other" (11 subjects, 1.8%) and included reasons such as subject preference and antibiotic requirements for CF pulmonary exacerbations. Following the run-in period, 574 subjects were randomized and

573 (99.8%) received at least 1 dose of the trial drug and are considered the FAS. A summary of the subject enrollment and disposition is included in [Table 21](#).

Table 21. Subject Enrollment and Disposition, Trial 103

Disposition/Reason	ELX/TEZ/IVA n (%)	VNZ/TEZ/D-IVA n (%)	Total n (%)
All randomized population	289	285	574
Safety analysis set	289	284	573
Full analysis set	289	284	573
Completed treatment	273 (94.5)	259 (91.2)	532 (92.8)
Discontinued treatment	16 (5.5)	25 (8.8)	41 (7.2)
Completed trial	279 (96.5)	264 (93.0)	543 (94.8)
Discontinued trial	10 (3.5)	20 (7.0)	30 (5.2)

Source: Clinical reviewer. Software: JMP v15.0, OCS Analysis Studio. adsl dataset using SAFFL(Y), EOTSTT, DCTREA1, EOSSTT, DCREAS.

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; n, number of subjects in subset; TEZ, tezacaftor; VNZ, vanzacaftor

As with Trial 102, the majority of subjects in Trial 103 completed treatment (532, 92.8%) and the trial (543, 94.8%). There were numerically more subjects in the VNZ/TEZ/D-IVA group that discontinued both treatment (25, 8.8%) and the trial (20, 7.0%) than in the ELX/TEZ/IVA group (discontinued treatment: 16, 5.5%; discontinued trial: 10, 3.5%), as shown in [Table 21](#). The main reason listed for treatment and trial discontinuation was adverse events, reviewed in more detail in Section [7.6.1.4](#). This numerical difference is unlikely to affect the analysis given the overall low rates of discontinuation. The trial completion and discontinuation rates were similar to Trial 102 and other phase 3 programs in this population.

Subject Demographics

The population randomized in Trial 103 had a mean age of 33.7 years (range 12.2 to 71.2 years), was 51.1% male, and 13.8% adolescents (12 to <18 years), similar to Trial 102. The baseline subject demographics are shown in [Table 22](#).

Table 22. Baseline Subject Demographics (FAS), Trial 103

Demographic	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	Total N=573
Sex, n (%)			
Male	144 (49.8)	149 (52.5)	293 (51.1)
Female	145 (50.2)	135 (47.5)	280 (48.9)
Age, years			
Mean (SD)	34.0 (12.4)	33.3 (12.6)	33.7 (12.5)
Median (min, max)	33.8 (12.7, 63.4)	32.6 (12.2, 71.2)	33.1 (12.2, 71.2)
Age category at screening visit, n (%)			
12 to <18 years	38 (13.1)	41 (14.4)	79 (13.8)
≥18 years	251 (86.9)	243 (85.6)	494 (86.2)

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Demographic	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	Total N=573
Race, n (%)			
White	262 (90.7)	270 (95.1)	532 (92.8)
Black/African American	0	0	0
Asian	1 (0.3)	1 (0.4)	2 (0.3)
American Indian or Native Alaskan	1 (0.3)	0	1 (0.2)
Other	1 (0.3)	1 (0.4)	2 (0.3)
More than one race reported	1 (0.3)	2 (0.7)	3 (0.5)
Not reported per local regulations	23 (8.0)	10 (3.5)	33 (5.8)
Ethnicity, n (%)			
Not Hispanic or Latino	261 (90.3)	265 (93.3)	526 (91.8)
Hispanic or Latino	5 (1.7)	4 (1.4)	9 (1.6)
Not reported per local regulations	23 (8.0)	15 (5.3)	38 (6.6)
Geographic region, n (%)			
North America	103 (35.6)	114 (41.1)	217 (37.9)
Rest of the world	186 (64.4)	170 (59.9)	356 (62.1)

Source: Clinical reviewer. Software: JMP v15.0, OCS Analysis Studio. adsl dataset using FASFL(Y), SEX, AGE, RACE, ETHNIC, REGION1, COUNTRY.

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor, FAS, full analysis set; IVA, ivacaftor; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects in subset; SD, standard deviation, TEZ, tezacaftor; VNZ, vanzacaftor

The majority of subjects were White (532, 92.8%) and non-Hispanic (526, 91.8%), reflecting the demographics of the CF patient population ([CFF 2023](#)). The Trial enrolled 356 (62.1%) subjects from international sites, which is a numerically higher proportion than Trial 102 but remains reasonable. Any imbalances in the subject demographics between the treatment groups were minor and unlikely to affect the overall analysis.

The enrolled population had an average ppFEV₁ of 66.8% and an average SwCl of 42.8mmol/L. Similar to Trial 102, the majority of subjects were previously prescribed drugs that affect CFTR processing or function (491, 85.7%) the most common of which was ELX/TEZ/IVA (389, 67.9%). The baseline average SwCl in Trial 103 is lower than in Trial 102, which is reflective of the differences in CFTR variant eligibility criteria. The baseline CF disease characteristics are reviewed in [Table 23](#).

Table 23. Baseline Disease Characteristics (FAS), Trial 103

Parameter/Characteristic	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	Total N=573
ppFEV ₁ at baseline ^a (percentage points)			
Mean (SD)	66.4 (14.9)	67.2 (14.6)	66.8 (14.7)
Median (min, max)	66.9 (36.4, 104.6)	66.9 (38.3, 112.5)	66.9 (36.4, 112.5)
ppFEV ₁ by severity group at baseline ^a , n (%)			
<40%	7 (2.4)	5 (1.8)	12 (2.1)
≥40 to <70%	160 (55.4)	149 (52.5)	309 (53.9)
≥70 to <90%	107 (37.0)	112 (39.4)	219 (38.2)
>90%	12 (4.2)	13 (4.6)	25 (4.4)
Missing data	3 (1.0)	5 (1.8)	8 (1.4)
SwCl at baseline ^b (mmol/L)			
Mean (SD)	42.1 (17.9)	43.4 (18.5)	42.8 (18.2)
Median (min, max)	41.6 (10.0, 109.2)	43.0 (10.0, 113.2)	42.4 (10.0, 113.2)

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ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Parameter/Characteristic	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	Total N=573
SwCl category at baseline ^b , n (%)			
<30mmol/L	80 (27.7)	72 (25.4)	152 (26.5)
≥30 to <60mmol/L	154 (53.3)	158 (55.6)	312 (54.5)
≥60mmol/L	48 (16.6)	52 (18.3)	100 (17.5)
Missing data	7 (2.4)	2 (0.7)	9 (1.6)
Prior use of medication that affects CFTR processing or function ^c , n (%)			
No	39 (13.5)	43 (15.1)	82 (14.3)
Yes	250 (86.5)	241 (84.9)	491 (85.7)
CFQ-R RD score at baseline, points			
Mean (SD)	85.6 (13.2)	85.7 (13.2)	85.7 (13.2)
Prior medication use ^d , n (%)			
Dornase alfa	179 (61.9)	177 (62.3)	356 (62.1)
Azithromycin	109 (37.7)	113 (39.8)	222 (38.7)
Inhaled antibiotic	106 (36.7)	93 (32.7)	199 (34.7)
Any bronchodilator	242 (83.7)	254 (89.4)	496 (86.6)
Inhaled hypertonic saline	159 (55.0)	144 (50.7)	303 (52.9)
Pseudomonas colonization ^e , n (%)			
Positive	153 (52.9)	156 (54.9)	309 (53.9)
Height and weight, mean (SD)			
Weight, kg	65.0 (13.3)	66.6 (14.0)	65.8 (13.7)
Height, cm	167.8 (10.1)	168.7 (9.4)	168.3 (9.8)
BMI, kg/m ²	22.9 (3.3)	23.3 (4.0)	23.1 (3.7)
BMI z-score for subjects <20y, n	42	53	95
BMI z-score for subjects <20y, units	-0.30 (0.98)	-0.17 (0.95)	-0.23 (0.96)

Source: Clinical reviewer. Software: JMP v15.0. adsl dataset using FASFL(Y), PPFEV1BL, SWBL, CFQRRBL, PSEUBL, WTBL, HTBL, BMIBL, ZBMIBL, PMEDFL, GENOGR1

^a Baseline FEV₁ measurements were defined as the predose Day 1 value. If missing, the most recent predose, nonmissing value on or after the Day -14 visit was used as baseline.

^b Baseline SwCl measurements were defined as the average of the 2 most recent predose, nonmissing values on or after the Day -14 visit. If only one nonmissing value was available during this interval, the available value was considered as baseline.

^c Medications that affect CFTR processing or function include ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, and IVA

^d Medications administered with 56 days before first dose of treatment in the Treatment Period excluding the ones started in the Run-in Period

^e Pseudomonas aeruginosa colonization defined as respiratory tract culture positivity within 2 years prior to screening

Abbreviations: BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R RD, cystic fibrosis questionnaire respiratory domain; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LUM, lumacaftor; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects in subset; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation, SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor; y, years

Overall, the baseline CF disease characteristics were balanced between the treatment groups and reasonable for capturing a stable adolescent and adult CF population. As noted in Trial 102, the use of CF background therapy and rates of *P. aeruginosa* culture positivity in the enrolled population were lower than those of the phase 3 trials used to support the registration of ELX/TEZ/IVA but remains consistent with recently published data about the overall CF population ([CFF 2023](#)).

Trial 103 enrolled primarily subjects who are homozygous for *F508del* (446, 77.8%), and the enrollment by genotype group is shown in [Table 24](#) (see Section [15](#) for additional information regarding *CFTR* genotype eligibility criteria).

Table 24. Subjects by *CFTR* Genotype Group (FAS), Trial 103

<i>CFTR</i> Genotype Group	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	Total N=573
F/F, n (%)	224 (77.5)	222 (78.2)	446 (77.8)
F/G, n (%)	20 (6.9)	19 (6.7)	39 (6.8)
F/RF, n (%)	23 (8.0)	23 (8.1)	46 (8.0)
TCR/non-F, n (%)	22 (7.6)	20 (7.0)	42 (7.3)

Source: Clinical reviewer, Software: JMP v15.0 adsl.xpt using FAS(Y), GENOGR1.

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; ELX, ellexacaftor; F, *F508del* variant; FAS, full analysis set; G, gating *CFTR* variant; IVA, ivacaftor; N, number of subjects in treatment group; n, number of subjects in subset; RF, residual function *CFTR* variant; TCR, triple combination responsive; TEZ, tezacaftor; VNZ, vanzacaftor

Trial 103 also enrolled a subgroup of subjects with *CFTR* variants that are triple combination responsive (i.e., responsive to ELX/TEZ/IVA on in vitro testing and included in the *CFTR*-variant-based indication on the ELX/TEZ/IVA USPI). The list of in vitro ELX/TEZ/IVA responsive variants in subjects enrolled in Trial 103 without a copy of *F508del* is included in [Table 25](#).

Table 25. Triple Combination *CFTR*-Responsive Variants in Enrolled Subjects Without a Copy of *F508del* (FAS), Trial 103

<i>CFTR</i> Variant							
A455E	D1152H	G1244E	G551D	G85E	H1054D	I336K	L1077P
L206W	M1101K	R1066H	R352Q	R75Q	S1159F	S1251N	S549N
S549R	S945L	V562I	V754M	W1098C	W1282R	Y563N	

Source: Clinical reviewer from Applicant provided data.

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; FAS, full analysis set

The past medical history and concomitant medications were reviewed and are consistent with a CF adult and adolescent population and balanced between treatment groups. Additional information regarding subject genotype, past medical history, and concomitant medications is included in Section [16.1.2](#).

Analysis of Efficacy – Primary Endpoint

Trial 103 was also designed as noninferiority trial with a designated margin of -3.0%. Through Week 24, treatment with VNZ/TEZ/D-IVA was also noninferior to ELX/TEZ/IVA in the absolute change from baseline in ppFEV₁, the primary efficacy endpoint. The LS mean difference was 0.2% (95% CI: -0.5%, 0.9%) in the FAS population, as shown in [Table 26](#).

Table 26. Change From Baseline in ppFEV₁ Through Week 24 (FAS), Trial 103

Endpoint/Parameter	ELX/TEZ/IVA (N=289)	VNZ/TEZ/D-IVA (N=284)
Absolute CFB ^a in ppFEV ₁ through Week 24 ^b		
n	276	268
LS mean (SE)	0.0 (0.2)	0.2 (0.3)
95% CI of LS mean	-0.5, 0.5	-0.3, 0.7
LS mean difference (95% CI)		0.2 (-0.5, 0.9)
1-sided p-value for noninferiority vs ELX/TEZ/IVA		<0.00001

Source: Statistical analyst. Software: R. adsl and adsp datasets.

^a Baseline ppFEV₁ measured at Day 1. If predose Day 1 was missing, the most recent predose, nonmissing value on or after Day 14 visit was used.

^b ppFEV₁ through Week 24 (estimated by averaging Weeks 16 and 24)

Abbreviations: CFB, change from baseline; CI, confidence interval; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; n, number of subjects included in analysis; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation, SE, standard error; TEZ, tezacaftor; VNZ, vanzacaftor

Similar to Trial 102, the Applicant specified that the primary endpoint would be analyzed through Week 24, defined as the average of the values from Week 16 and 24. The statistical reviewer and analyst preformed a landmark analysis at Week 24 that resulted in an LS mean difference (95% CI) of 0.2% (-0.6%, 1.0%). Although the landmark analysis was post hoc and exploratory, the results were supportive of the treatment effect of VNZ/TEZ/D-IVA. The robustness of the analysis result regarding missing data was supported by the tipping point sensitivity analysis. See Section [16.2](#) for additional information.

Analysis of Efficacy – Secondary Endpoints

The summary of a key secondary endpoint, the absolute change from baseline in the SwCl through 24 weeks, is shown in [Table 27](#).

Table 27. Change From Baseline in SwCl (mmol/L) Through Week 24 (FAS), Trial 103

Sweat Chloride Values	ELX/TEZ/IVA (N=289)	VNZ/TEX/D-IVA (N=284)
Baseline SwCl (SD)	42.1 (17.9)	43.4 (18.5)
n	276	270
LS mean CFB (SE)	-2.3 (0.7)	-5.1 (0.7)
LS mean difference (95% CI)		-2.8 (-4.7, -0.9)
p-Value		0.0034

Source: Statistical analyst. Software: R. adsl and adsw datasets.

Abbreviations: CFB, change from baseline; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; CI, confidence interval; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; n, number of subjects included in analysis; SD, standard deviation, SE, standard error; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

As with Trial 102, treatment with VNZ/TEZ/D-IVA led to a statistically significant decrease from baseline in SwCl through Week 24 compared to ELX/TEZ/IVA with a mean difference (95% CI) of -2.8 (-4.7, -0.9) mmol/L (p-value=0.0034) in Trial 103. The clinical implications of a treatment difference of approximately 3mmol/L in change from baseline are unclear at this time. The overall change from baseline in SwCl as well as the responder analyses are discussed in more detail in Section [6.3.2](#).

Selected other secondary endpoints from Trial 103 are reviewed below in [Table 28](#) and include the number of CF pulmonary exacerbations through Week 52 and the absolute change from baseline in the CFQ-R RD score through Week 24.

Table 28. Select Other Secondary Endpoints (FAS), Trial 103

Endpoint	VNZ/TEZ/D-IVA (N=289) vs. ELX/TEZ/IVA (N=284)	
	Parameter	Result (95% CI)
Number of PEx through Week 52	Rate difference	0.03 (-0.07, 0.13)
Absolute CFB in CFQ-R RD score through Week 24	LS mean diff (95% CI)	-0.1 (-2.3, 2.1)

Source: Statistical analyst. Software: R. adsl, adcfqr, and adce datasets.

Abbreviations: CF, cystic fibrosis CFB, change from baseline; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; CI, confidence interval; D-IVA, deutivacaftor; diff, difference; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; PEx, pulmonary exacerbation; TEZ, tezacaftor; VNZ, vanzacaftor; vs., versus

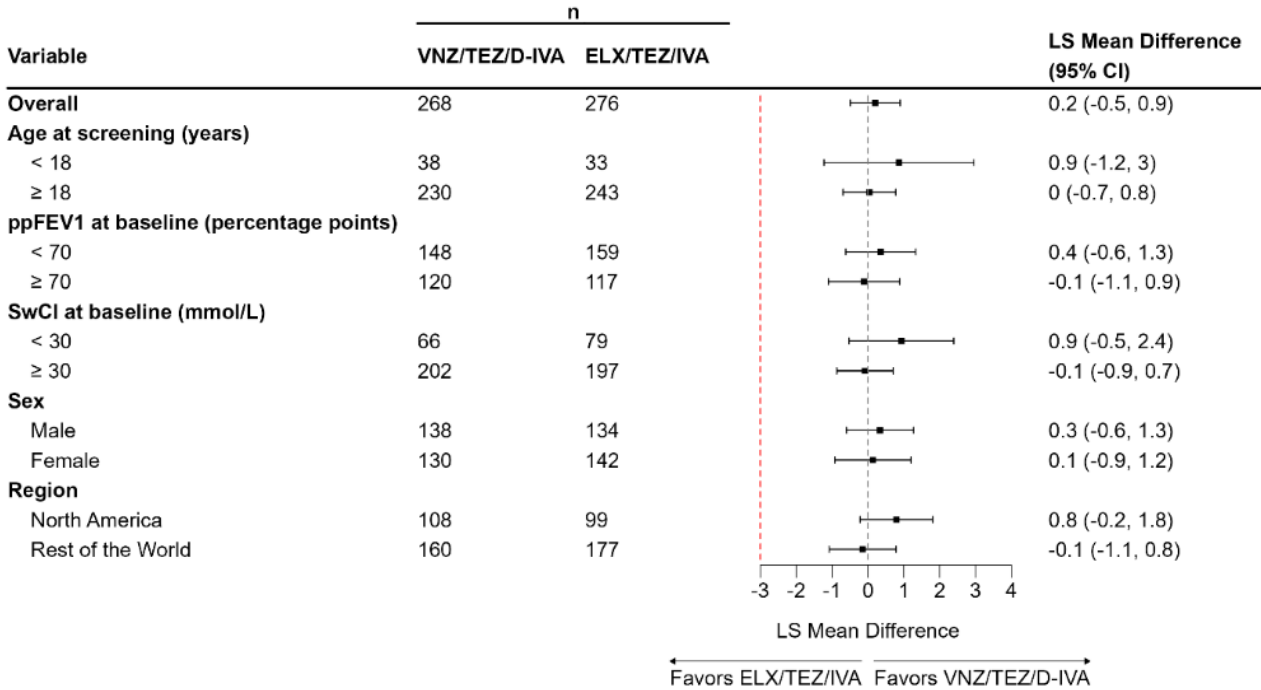
In subjects treated with VNZ/TEZ/D-IVA compared to those treated with ELX/TEZ/IVA, the rate difference (95% CI) in the number of CF PEx through Week 52 was 0.03 (-0.07, 0.13) and the mean difference (95% CI) in absolute change from baseline in CFQ-R RD score through Week 24 was -0.1 (-2.3, 2.1). As noted with Trial 102, the results were similar between the VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment arms; however, the interpretation of these endpoints is limited because they were analyzed without control for multiplicity.

Additional discussion of the secondary endpoints is included in Section [16.2](#). Overall, the secondary endpoints support the efficacy for VNZ/TEZ/D-IVA in patients with CF.

Efficacy Subgroup Analyses

As with Trial 102, the Applicant performed multiple subgroup analyses on the primary endpoint including age, ppFEV₁ at baseline, SwCl at baseline, sex, and geographic region. Overall, the subgroups evaluations were generally consistent with the overall population. Select subgroup analyses are summarized in [Figure 3](#).

Figure 3. Subgroup Analyses of Change From Baseline in ppFEV₁ Through Week 24 (FAS), Trial 103

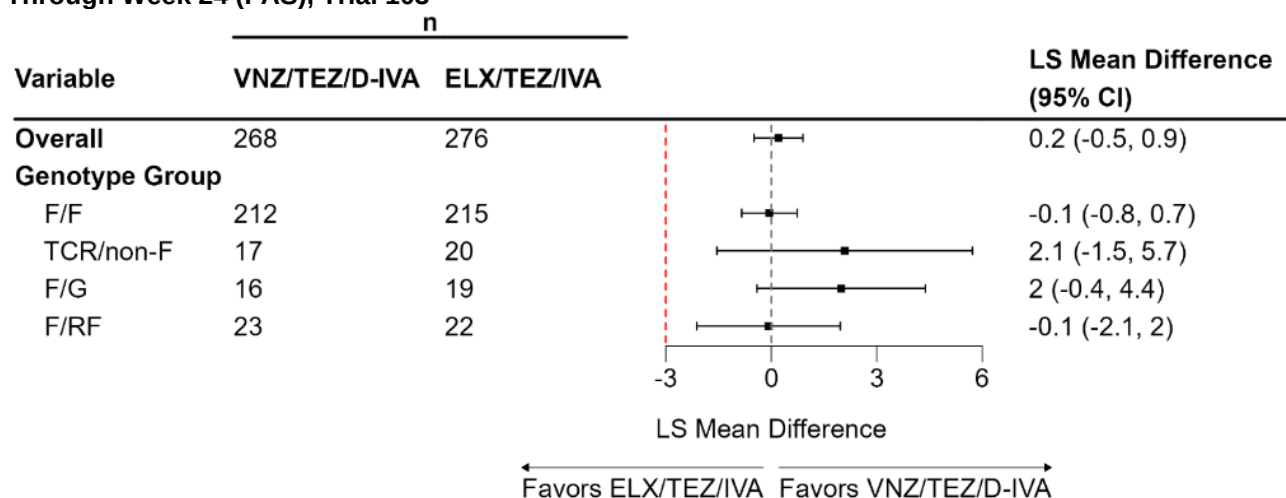


Source: Statistical analyst. Software: R. adsl and adsp datasets.
Abbreviations: CI, confidence interval; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; n, number of subjects in subset; ppFEV₁, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

For the adolescent subgroup (subjects with an age at screening of <18 years), the point estimate of the LS mean difference was consistent with the overall population. This finding helps address some of the uncertainty regarding the point estimate and wide confidence intervals observed for the adolescent population noted in Trial 102 (Section 6.2.2.4). Point estimates from all other subgroups were also supportive of the efficacy of VNZ/TEZ/D-IVA.

Additional analyses based on *CFTR* genotype subgroup were also performed as shown in [Figure 4](#).

Figure 4. *CFTR* Genotypic Subgroup Analysis of Absolute Change From Baseline in ppFEV₁ Through Week 24 (FAS), Trial 103



Source: Statistical analyst. Software: R. adsl and adsp datasets.

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; D-IVA, deutivacaftor; ELX, elxacaftor; F, *F508del* variant; FAS, full analysis set; G, gating variant; IVA, ivacaftor; LS, least squares; n, number of subjects in subset; ppFEV₁, percent predicted forced expiratory volume in 1 second; RF, residual function variant; SwCl, sweat chloride concentration; TCR, triple combination responsive variant; TEZ, tezacaftor; VNZ, vanzacaftor

The majority of subjects enrolled in Trial 103 were homozygous for *F508del*, and the efficacy analysis for this subgroup was consistent with the overall population. The analyses of the remaining of the *CFTR* genotype subgroups, including subjects heterozygous for *F508del* and a gating or residual function variant or subjects with a non-*F508del* triple combination responsive variant, were limited because of small sample sizes; however, they are generally supportive of the efficacy of VNZ/TEZ/D-IVA.

6.2.4. Trial VX21-121-105 (Trial 105)

6.2.4.1. Design, Trial 105 (Cohorts A1 and B1)

Trial 105 was a phase 3, 2-part (Parts A and B), multicenter, multicohort, open-label trial in pediatric CF subjects. Cohorts A1 and B1 enrolled subjects 6 through 11 years of age and the final analysis results are presented below. The remainder of the cohorts in Trial 105 are either ongoing or have not yet begun enrollment. Ultimately, Trial 105 will enroll CF subjects 1 through 11 years of age (inclusive).

Part A (PK)

There was a 28-day screening period followed by a 15-day treatment period. A review of safety, tolerability, and available PK data was completed by the Applicant after Cohort A1 completed treatment to determine the doses and weight cutoffs for Cohort B1.

Primary Endpoints

- PK parameters of VNZ, TEZ, D-IVA, and relevant metabolites
- Safety and tolerability as determined by AEs, clinical laboratory values, standard 12-lead electrocardiograms, vital signs, and pulse oximetry

All subjects in Cohort A1 received VNZ 10 mg QD/TEZ 50 mg QD/D-IVA 125 mg QD.

Part B (Safety and Tolerability)

Part B also included a 28-day screening period with a 28-day ELX/TEZ/IVA run-in period to establish an on-treatment (ELX/TEZ/IVA) baseline. The run-in period was waived for subjects already receiving stable ELX/TEZ/IVA prior to enrollment. The screening and run-in (if applicable) periods were followed by a 24 Week treatment period, during which all subjects received VNZ/TEZ/D-IVA.

The primary endpoint of Part B was safety and tolerability of VNZ/TEZ/D-IVA. Additional efficacy endpoints from Trials 102 and 103 were examined in exploratory analyses. A full review of the trial protocol design, trial population, objectives, and endpoints is included in Section [15.2](#). In general, the trial design and population were consistent with previous trials in the CF pediatric population for other similar medications.

The doses of trial drug for Cohort B1 are reviewed in [Table 29](#).

Table 29. Run-In and Treatment Period Doses, Trial 105 (Cohort B1)

Cohort B1 Run-In Period			
Weight at Day -28	ELX	TEZ	IVA
<30 kg	100 mg QD	50 mg QD	75 mg q12h
≥30 kg	200 mg QD	100 mg QD	150 mg q12h
Cohort B1 Treatment Period			
Weight at Day 1	VNZ	TEZ	D-IVA
<40 kg	12 mg QD	60 mg QD	150 mg QD
≥40 kg	20 mg QD	100 mg QD	250 mg QD

Source: Clinical Reviewer based on Applicant Provided data

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; q12h, dose every 12 hours; QD, once daily; TEZ, tezacaftor; VNZ, vanzacaftor

6.2.4.2. Eligibility Criteria, Trial 105

The eligibility criteria for Cohorts A1 and B1 of Trial 105 were reasonable for a stable CF population aged 6 through 11 years. The *CFTR*-variant based eligibility included at least one TCR variant, including *F508del*, in the *CFTR* gene.

The key inclusion criteria included:

- Ages 6 through 11 years (inclusive) on the date of informed consent
- Weight between 5th and 9th percentile (inclusive) for weight-for-age at screening
- At least one TCR *CFTR* variant, including *F508del*
- FEV₁ ≥ 60% predicted at screening
- Stable CF disease judged by the investigator

The key exclusion criteria included:

- History of intolerance to trial drug including ELX/TEZ/IVA
- History of comorbidity including but not limited to hepatic cirrhosis, moderate to severe hepatic impairment, chronic kidney disease, solid organ, or hematological transplantation
- Acute upper or lower respiratory tract infection, infectious PEx of CF, or changes in therapy (including antibiotics) for sinopulmonary disease

The trial population in Cohorts A1 and B1 of Trial 105 were reasonable and similar to other pediatric CF development programs.

6.2.4.3. Statistical Analysis Plan, Trial 105

Since Cohort A1 was for PK assessment, the statistical analysis plan is described for Cohort B1. For change from baseline endpoints, a MMRM approach was employed. The primary result obtained from the model was the average treatment effect through Week 24. The estimated mean change from baseline through Week 24 along with the corresponding 2-sided 95% CI were provided. For the number of events variables, a descriptive summary along with the observed event rate was provided. The number and proportion of subjects with SwCl < 60 mmol/L was descriptively summarized with the 2-sided 95% CI based on Clopper-Pearson method.

6.2.4.4. Results of Analyses, Trial 105

Subject Enrollment and Disposition

In Trial 105, Cohort A1 enrolled 17 subjects and all subjects completed treatment and the trial cohort. Cohort B1 enrolled 78 subjects: 17 (21.8%) entered the treatment period after completion of the ELX/TEZ/IVA run-in period, and the remaining 61 (78.2%) subjects directly entered the treatment period following screening, since they were on stable commercial ELX/TEZ/IVA for at least 28 days prior to screening.

Cohort B1 enrolled 78 subjects and all subjects completed the trial. The majority of subjects also completed treatment with VNZ/TEZ/D-IVA with the exception of 1 (1.3%) subject who discontinued treatment due to an adverse event (reviewed in Section [7.6.2.4](#)). The rates of completion of the trial and treatment were consistent with other similarly designed trials in this

population. The majority of VNZ/TEZ/D-IVA exposure occurred in Cohort B1, and this will be the focus of the remainder of this section of the review unless otherwise noted.

Subject Demographics

The population enrolled in Trial 105 Cohort B1 had a mean age of 9.1 years (range 6.2 to 12.0 years) and was 56.4% male. The baseline subject demographics for are shown in [Table 30](#).

Table 30. Baseline Subject Demographics (FAS), Trial 105 (Cohort B1)

Parameter	Total N=78
Sex, n (%)	
Male	44 (56.4)
Female	34 (43.6)
Age, years	
Mean (SD)	9.1 (1.7)
Median (min, max)	9.3 (6.2, 12.0)
Race, n (%)	
White	71 (91.0)
Black/African American	1 (1.3)
More than one race reported	1 (1.3)
Not reported per local regulations	5 (6.4)
Ethnicity, n (%)	
Not Hispanic or Latino	62 (79.5)
Hispanic or Latino	9 (11.5)
Not reported per local regs	7 (9.0)
Geographic Region, n (%)	
North America	47 (60.3)
Rest of the World	31 (39.7)

Source: Clinical reviewer, Software: JMP v15.0, OCS Analysis Studio. adsl dataset using FASFL(Y), SEX, AGE, RACE, ETHNIC, REGION1, COUNTRY.

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects in subset; SD, standard deviation, TEZ, tezacaftor; VNZ, vanzacaftor

As with the phase 3 adult and adolescent trials, the majority of subjects were White (71, 91.0%) and non-Hispanic (79.5, 79.5%), reflective of the demographics of CF. Trial 105 enrolled 31 (39.7%) subjects from international sites which is similar to other trials of CF therapeutics.

The population in Trial 105 had an average baseline ppFEV₁ of 99.7% and an average SwCl of 40.4mmol/L. The baseline CF disease characteristics are reviewed in [Table 31](#).

Table 31. Baseline Disease Characteristics (FAS), Trial 105 (Cohort B1)

Parameter/Characteristic	Total N=78
ppFEV ₁ at baseline ^a (percentage points)	
Mean (SD)	99.7 (15.1)
Median (min, max)	100.5 (29.3, 146.0)

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Parameter/Characteristic	Total N=78
ppFEV ₁ by severity group at baseline ^a , n (%)	
<40%	1 (1.3)
≥40 to <70%	1 (1.3)
≥70 to <90%	15 (19.2)
>90%	60 (76.9)
Missing data	1 (1.3)
SwCl at baseline ^a (mmol/L)	
Mean (SD)	40.4 (20.9)
Median (min, max)	39.0 (11.5, 109.5)
SwCl category at baseline ^a , n (%)	
<30mmol/L	30 (38.5)
≥30 to <60mmol/L	35 (44.9)
≥60mmol/L	12 (15.4)
Missing	1 (1.3)
Prior use of a medication that affects CFTR processing or function ^b , n (%)	
No	12 (15.4)
Yes	66 (84.6)
CFQ-R RD score at baseline, points	
Mean (SD)	84.8 (16.1)
Prior medication use ^c , n (%)	
Dornase alfa	49 (62.8)
Azithromycin	10 (12.8)
Inhaled antibiotic	3 (3.8)
Any bronchodilator	61 (78.2)
Inhaled hypertonic saline	58 (74.4)
Pseudomonas aeruginosa colonization ^d , n (%)	
Positive	10 (12.8)
Height and weight, mean (SD)	
Weight, kg	30.2 (7.5)
Height, cm	133.0 (10.5)
BMI, kg/m ²	16.8 (2.1)
BMI z-score, units	0.07 (0.87)
Weight category	
<40 kg	70 (89.7)
≥40 kg	8 (10.3)

Source: Clinical reviewer. Software: JMP v15.0. adsl dataset using FASFL(Y), PPFEV1BL, SWBL, CFQRRBL, PSEUBL, WTBL, HTBL, BMIBL, ZBMIBL, PMEDFL, GENOGR1

^a Baseline FEV₁ and SwCl measurements were defined as the predose Day 1 value. If missing, the screening assessments will be used as baseline.

^b Medications that affect CFTR processing or function include ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, and IVA

^c Medications administered with 56 days before first dose of treatment in the Treatment Period excluding the ones started in the Run-in Period

^d Pseudomonas aeruginosa colonization defined as respiratory tract culture positivity within 2 years prior to screening
Abbreviations: BMI, body mass index; CFTR, cystic fibrosis transmembrane conductance regulator; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; LUM, lumacaftor; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects in subset; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

The baseline pulmonary function was higher than the phase 3 adolescent and adult trials (note that both these trials had a limit on the upper bound of ppFEV₁ in the eligibility criteria) and the ELX/TEZ/IVA trial of the 6- to 11-year-old CF population. Similarly, the SwCl was lower than the adult and adolescent phase 3 trials and the ELX/TEZ/IVA trial in the 6- to 11-year-old CF

population (Trial VX18-445-106). These differences are not unexpected as 84.6% of the subjects enrolled had previously been prescribed medications that affect CFTR processing or function.

As also noted in the adolescent and adult phase 3 trials, fewer subjects were receiving symptomatic background CF (with the exception of inhaled hypertonic saline), and fewer subjects had a positive *Pseudomonas* respiratory tract culture in the prior 2 years compared to the initial ELX/TEZ/IVA trial in the 6- to 11-year-old CF population (Trial VX18-445-106). Overall, the baseline CF disease characteristics for the subjects in Cohort B1 were reasonable and consistent with reported data in this population ([CFF 2023](#)).

The *CFTR*-variant eligibility criteria for Trial 105 included subjects with any triple combination responsive variant including *F508del*. The *CFTR* genotype breakdown for Cohort B1 is shown in [Table 32](#).

Table 32. *CFTR* Genotype Group (FAS) Trial 105 (Cohort B1)

<i>CFTR</i> Genotype Group, n (%)	Total N=78
F/MF	24 (30.8)
F/F	37 (47.4)
F/G	3 (3.8)
F/RF	1 (1.3)
F/other	2 (2.6)
TCR/F	5 (6.4)
TCR/non-F	6 (7.7)

Source: Clinical reviewer. Software: JMP v15.0. adsl dataset using FASFL(Y), PPFEV1BL, SWBL, CFQRRBL, PSEUBL, WTBL, HTBL, BMIBL, ZBMIBL, PMEDFL, GENOGR1.
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; F, *F508del* variant; FAS, full analysis set; G, gating variant; MF, minimal function *CFTR* variant; N, number of subjects in treatment group; n, number of subjects in subset; RF, residual function *CFTR* variant; SD, standard deviation, TCR, triple combination responsive *CFTR* variant

The distribution of *CFTR* genotypes was consistent with the overall CF population and was generally reasonable. Additional information regarding subject genotype, past medical history, and concomitant medications is included in [Section 16.1.3](#).

Analysis of Efficacy-Related Endpoints

Trial 105 was designed primarily as a PK, safety, and tolerability trial in pediatric CF subjects. Trial 105 Cohort B1 also evaluated multiple secondary endpoints related to the efficacy of VNZ/TEZ/D-IVA, but interpretation is limited because of the lack of a control group. A summary of select non-PK related efficacy endpoints is shown in [Table 33](#).

Table 33. Select Secondary Efficacy Endpoints (FAS), Trial 105 (Cohort B1)

Endpoint	n	Parameter	VNZ/TEZ/D-IVA N=78
			Result (95% CI)
CFB in SwCl through Week 24, mmol/L	77	LS mean	-8.6 (-11.0, -6.3)
Absolute CFB in ppFEV ₁ through Week 24, %	74	LS mean	0.0 (-2.0, 1.9)
CFB in CFQ-R RD ^a score through Week 24, points	75	LS mean	3.9 (1.5, 6.3)

Source: Statistical analyst using Applicant provided data (CSR VX21-121-105, Tables 11-3, 11-5, 11-7)

^a CFQ-R RD, Child's version

Abbreviations: CFB, change from baseline; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; CI, confidence interval; D-IVA, deutivacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; N, number of subjects in treatment group; n, number of subjects in subset; ppFEV₁, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

The secondary endpoints generally support the effectiveness of VNZ/TEZ/D-IVA in the 6-to-11-year-old CF population and include a change from ELX/TEZ/IVA treatment baseline of -8.6mmol/L (95% CI: -11.0, -6.3) in SwCl. The results also demonstrate stability in the ppFEV₁ (LS mean 0.0%, 95% CI: -2.0, 1.9). The findings are consistent with the treatment effects seen in the adolescent and adult trials and supportive of the efficacy of VNZ/TEZ/D-IVA. Additional review of secondary efficacy endpoints in Trial 105 is included in Section [16.2.2](#).

6.2.4.5. Pediatric (6 Through 11 Years of Age) Efficacy Summary

The PK data for VNZ/TEZ/D-IVA administration, reviewed in Section [14.2.6](#), demonstrated that systemic exposures were comparable to those observed in the adolescent and adult population. Because of the similar systemic exposures and because the disease process in the older population is the same as that in the 6- to 11-year-old population, efficacy in this age group was extrapolated from the VNZ/TEZ/D-IVA adolescent and adult development program.

6.3. Key Efficacy Review Issues

6.3.1. Satisfaction of 21 CFR 300.50, the “Combination Rule”

Issue

VNZ/TEZ/D-IVA is a FDC drug product. The Applicant has proposed to use a combination of clinical and in vitro data to support satisfaction of 21 CFR 300.50, i.e., to demonstrate the contribution of each active ingredient to the claimed effects of the combination product.

Background

The regulatory evidentiary standard to support approval for a new fixed drug combination product must consider 21 CFR 300.50(a), often referred to as the “combination rule,” which states that, “two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosage of each...is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy...”.

Often, the Agency relies on factorial design clinical trials to evaluate and support the contribution of each component in the combination product. However, there is no single regulatory framework for satisfying the combination rule, and the Agency may exercise flexibility, particularly in cases when the beneficial treatment effect of a particular drug class is well understood and established.

During the development of VNZ/TEZ/D-IVA, the Applicant proposed to leverage a combination of in vitro and clinical data to demonstrate the individual contributions of VNZ, TEZ, and D-IVA to the efficacy of the FDC product, rather than rely on a full factorial design approach. The Division agreed this approach was reasonable. There is regulatory precedent for this approach, which is similar to that used to support the approval of ELX/TEZ/IVA.

Assessment

The Division completed a multidisciplinary review of the clinical and in vitro data to evaluate the contributions of VNZ, TEZ, and D-IVA, which included the various types of evidence described below. For additional details of the clinical pharmacology assessment, refer to Section [14](#).

The Mechanism of Action or Action Site

- VNZ and TEZ both facilitate the cellular processing and trafficking of select *CFTR* variants (including *F508del*-CFTR). The binding sites of VNZ and TEZ on the CFTR protein are different, and in vitro pharmacology results demonstrate that VNZ and TEZ work synergistically.
- Similar to IVA, D-IVA is a CFTR potentiator that increases the CFTR channel open probability at the cell surface and facilitates increased chloride ion transport.

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ORIGINAL

The Contribution of D-IVA in the Treatment of CF

- The D-IVA dose-ranging trial (Study VX18-561-101) demonstrated that D-IVA 150 mg or 250 mg QD resulted in a sustained ppFEV₁ response over 12 weeks in CF subjects with gating *CFTR* variants who were responsive to and prescribed a stable dose of IVA monotherapy. In addition, the ppFEV₁ change from baseline values following 12-week treatment with D-IVA 150 mg or 250 mg QD were comparable to CF subjects who were treated with IVA monotherapy for 12 weeks. The results indicate the similar treatment effect between D-IVA and IVA on a clinically meaningful endpoint.
- The following in vitro electrophysiology studies demonstrated the similar CFTR potentiating potencies between D-IVA and IVA:
 - Study PH-088 demonstrated that D-IVA and IVA have similar effects in increasing *G551D/F508del* CFTR chloride transport in HBE cells.
 - Study PH-045 demonstrated that D-IVA and IVA have similar effects in increasing *G551D* CFTR chloride transport in FRT cells.
 - Study PH-043 demonstrated that D-IVA and IVA have similar effects in increasing *F508del/F508del* CFTR chloride transport in HBE cells.
 - Study Q-142 demonstrated that D-IVA and IVA have almost identical concentration-response relationship to increase *F508del/F508del* and *F508del*/minimal function (MF) CFTR chloride transport when in combination with IVA and TEZ in HBE cells.

The Contribution of TEZ in the Treatment of CF

- In the development program of TEZ/IVA (NDA 210491), Trial VX14-661-108 demonstrated that TEZ 100 mg QD/IVA 150 mg q12h was superior in improving ppFEV₁ from baseline compared to IVA 150 mg q12h monotherapy in CF subjects with *F508del*/residual function variants. The results indicate the contribution of TEZ in treatment of CF on IVA background therapy on a clinically meaningful endpoint.
- The following in vitro electrophysiology studies demonstrated the contribution of TEZ in increasing CFTR chloride transport:
 - Factorial Study N035 demonstrated synergistic effect between TEZ and IVA where a greater *F508del/F508del* CFTR chloride transport was observed with TEZ/IVA compared to TEZ or IVA alone in HBE cells. In addition, both TEZ or IVA alone increased chloride transport when compared to vehicle control.
 - Study S525 demonstrated an increase of *F508del/F508del* and *F508del*/MF variant CFTR chloride transport with TEZ/VNZ in HBE cells compared to VNZ alone, indicating the additional contribution of TEZ on background VNZ treatment.

The Contribution of VNZ in the Treatment of CF

- In the development program of ELX/TEZ/IVA (NDA 212273), the phase 3 trial (VX17-445-103) demonstrated that ELX/TEZ/IVA is superior compared to TEZ/IVA with respect to the absolute change from baseline in ppFEV₁ at Week 4 in *F508del* homozygous subjects. This supports the contribution of ELX to the full efficacy of ELX/TEZ/IVA.
- In VNZ/TEZ/D-IVA program, Trials 102 and 103 demonstrated noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA as measured by the absolute change from baseline in ppFEV₁ through Week 24. The results from these trials, taken together, indicate the necessity of VNZ to contribute to the full efficacy of VNZ/TEZ/D-IVA because the dose of TEZ is the same between VNZ/TEZ/D-IVA and ELX/TEZ/IVA and because D-IVA 250 mg QD and IVA 150 mg q12h have a similar treatment effect (see above).
- The following in vitro electrophysiology studies demonstrated the contribution of VNZ in the increase in CFTR chloride transport:
 - Study S525 demonstrated a concentration-response relationship for VNZ to increase *F508del/F508del* and *F508del/MF* variant CFTR chloride transport in HBE cells.
 - Study S525 demonstrated an increase of *F508del/F508del* and *F508del/MF* variant CFTR chloride transport with VNZ/TEZ/D-IVA compared to TEZ/IVA in HBE cells.
 - Study U020 demonstrated that VNZ/TEZ/D-IVA and ELX/TEZ/IVA have similar effects increasing *N1303K/N1303K* and *N1303K/minimal function* variant CFTR chloride transport in HBE cells, and both triple combinations are superior to effect of TEZ/IVA.

Conclusion

The following data sources demonstrate the contribution of each component of VNZ/TEZ/D-IVA to the effect of the combination product: the demonstration of noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA in two phase 3 clinical trials; the available historical clinical trial data with IVA, TEZ/IVA, and ELX/TEZ/IVA; the support of electrophysiology in vitro data. The Division concludes that there is adequate data from the VNZ/TEZ/D-IVA development program to satisfy the combination rule (21 CFR 300.50).

6.3.2. Clinical Relevance of Sweat Chloride Concentration Efficacy Endpoints

Issue

SwCl concentrations are pharmacodynamic measurements of CFTR function. The phase 3 development program for VNZ/TEZ/D-IVA included secondary endpoints related to SwCl, including the change from baseline in SwCl and responder analyses for the proportion of subjects with SwCl below 60mmol/L and 30mmol/L, which are used clinically as the CF diagnostic threshold and the normal range threshold, respectively ([Farrell et al. 2017](#)). Most results of the SwCl analyses were statistically significant, favoring VNZ/TEZ/D-IVA compared to ELX/TEZ/IVA; however, the clinical meaningfulness of the SwCl results is not established at this time.

Background

SwCl concentration measurements have been secondary endpoints in multiple clinical development programs for CF, including ELX/TEZ/IVA. The Division views SwCl as an important pharmacodynamic measurement for drugs that act on CFTR. However, as SwCl measurements do not reflect how a patient feels, functions, or survives, they are not considered clinically meaningful endpoints, nor have they been validated as surrogate endpoints. (b) (4)

(see Section 6.2.2).

SwCl concentrations are part of the CF diagnostic algorithm (Farrell et al. 2017) but are not used clinically as prognostic or predictive markers. There are no clinical care guidelines that recommend serial SwCl measurements after diagnosis of CF or recommend repeating SwCl measurements following initiation of therapy to assess response to intervention. Therefore, information about post-treatment SwCl is of unclear meaning to prescribers and patients.

(b) (4) the Applicant cited data regarding the natural history of CF, drawn primarily from the U.S. Cystic Fibrosis Foundation Patient Registry, which suggests SwCl levels at diagnosis may be prognostic for clinical outcomes, including rate of pulmonary function decline and mortality (McKone et al. 2015). However, other studies that have evaluated whether SwCl may predict severity of CF phenotype have shown inconsistent results (Wilschanski et al. 1995; Davis et al. 2004). In addition, there is no evidence to support that post-treatment SwCl concentrations will have predictive value for clinically meaningful outcomes, such as rate of lung function decline or mortality.

We note that the clinical development program for ELX/TEZ/IVA established a large and sustained treatment effect as measured by the ppFEV₁ for the overall phase 3 population enrolled in the registrational trials. In a postmarket study that evaluated both the change in ppFEV₁ and change in SwCl six months after initiation of ELX/TEZ/IVA, there was a wide range of variability in the correlation between outcomes, i.e., subjects with minimal SwCl changes with a large FEV₁ response and subjects with large SwCl changes with a minimal FEV₁ response (Nichols et al. 2022). These data suggest that reliance on changes in SwCl alone will not predict clinically meaningful outcomes.

Additional published data from an observational study comparing pre- and post-ELX/TEZ/IVA SwCl levels also demonstrate heterogeneity in SwCl response to treatment. This study included variations in post-ELX/TEZ/IVA SwCl levels between *CFTR* genotype groupings (e.g., *F508del*/MF versus *F508del*/*F508del*, in which patients had one versus two ELX/TEZ/IVA responsive variants, respectively) as well as variation in response within a *CFTR* genotype grouping (Zemanick et al. 2024). These data further limit the potential for SwCl as a predictive marker in this context.

Assessment

Trials 102 and 103 included multiple key and other secondary endpoints related to SwCl concentration measurements. A summary of baseline SwCl measurements in the trial population and SwCl-based secondary endpoint results are included in Table 34.

Table 34. Sweat Chloride Endpoints and Baseline Measurements (FAS), Trials 102 and 103

Sweat Chloride Values	VNZ/TEZ/D-IVA vs. ELX/TEZ/IVA	
	Trial 102	Trial 103
<i>Baseline SwCl measurements</i>		
Mean (SD), mmol/L	53.9 (17.6)	42.8 (18.2)
SwCl ≥60mmol/L at baseline, n (%)	140 (35.2)	100 (17.5)
SwCl <30mmol/L at baseline, n (%)	36 (9.0)	152 (26.5)
<i>Key secondary endpoints</i>		
CFB in SwCl (W24), mmol/L	-8.4 (p<0.0001)	-2.8 (p=0.0034)
Subjects with SwCl <60 (W24), pooled n (%)		399 (85.8) vs 367 (76.6)
OR (p-value)		2.21 (p<0.0001)
Subjects with SwCl <30 (W24), pooled n (%)		142 (30.5) vs 108 (22.5)
OR (p-value)		2.87 (p<0.0001)
<i>Other secondary endpoints</i>		
Subjects with SwCl <60 (W24) n (%)	153 (80.5) vs. 116 (59.2)	246 (89.5) vs. 251 (88.7)
OR (95% CI)	4.28 (2.57, 7.11)	1.10 (0.65, 1.87)
Subjects with SwCl <30 (W24) n (%)	37 (19.5) vs. 13 (6.6)	105 (38.2) vs 95 (33.6)
OR (95% CI)	7.19 (3.54, 14.59)	2.06 (1.33, 3.18)

Source: Statistical analyst. Software: R. adsl and adsw datasets

Abbreviations: CI, confidence interval; CFB, change from baseline; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; n, number of subjects in subset; OR, odds ratio; SD, standard deviation; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor; vs., versus; W, week

Change From Baseline

As shown in [Table 34](#), treatment with VNZ/TEZ/D-IVA led to a statistically significant reduction in SwCl concentration from baseline compared to treatment with ELX/TEZ/IVA in both phase 3 trials, with mean reductions in SwCl from baseline of -8.4mmol/L and -2.8mmol/L in Trials 102 and 103, respectively. The clinical meaningfulness of this change is unclear. Since SwCl is not a clinically meaningful endpoint, there is no established threshold for quantifying what magnitude of change may be clinically significant, nor has the Applicant proposed such a threshold. However, we note that the changes observed are numerically small. The difference in the magnitude of change between the two trials is also of unclear significance and may be a function of genotypic differences in SwCl at baseline, as discussed more below. The Division maintains that these results provide pharmacodynamic information to prescribers demonstrating comparable on-targets effects of VNZ/TEZ/D-IVA and ELX/TEZ/IVA (b) (4)

Responder Analyses <60mmol/L and <30mmol/L

The Applicant also proposed the use of pooled responder analyses (b) (4). As shown in [Table 34](#), subjects treated with VNZ/TEZ/D-IVA were more likely to have a SwCl concentration <60mmol/L or <30mmol/L compared to ELX/TEZ/IVA at 24 weeks, based on pooled responder analyses. These threshold values are based on the CF diagnostic threshold (60mmol/L) and normal SwCl range (<30mmol/L). As discussed above, we do not agree that the thresholds proposed by the Applicant are clinically meaningful—these

thresholds are valid for diagnostic purposes, but their utility in measuring response to treatment is not clear or established within the CF literature.

Furthermore, the Division does not agree that the Applicant's decision to pool data for the responder analyses from Trials 102 and 103 was clinically appropriate. The populations in Trials 102 and 103 had different *CFTR* variant-based eligibility criteria (see Section [15.1](#)). Trial 102 enrolled subjects heterozygous for *F508del* and an MF variant (i.e., subjects with only one variant predicted to be responsive to VNZ/TEZ/D-IVA), whereas Trial 103 enrolled a wide range of *CFTR* genotypes and included many subjects with two responsive variants (i.e., subjects homozygous for *F508del* or heterozygous for *F508del* and another response variant). The available data support that ELX/TEZ/IVA and VNZ/TEZ/D-IVA are clinically effective in patients with one or two responsive variants as measured by FEV₁; however, since SwCl is a pharmacodynamic measurement of CFTR function, differences in both the number and type of *CFTR* variant may result in significant discrepancies and heterogeneity in SwCl levels, as supported by the CF literature and observations from the trial results ([Zemanick et al. 2024](#)). The baseline SwCl levels were different between the populations of the two trials with a mean baseline SwCl of 53.0mmol/L and 42.8mmol/L in Trials 102 and 103, respectively. This difference was, in part, attributable to baseline CFTR genotypic differences. As such, we observed that there was a greater proportion of subjects in Trial 102 with a baseline SwCl ≥ 60 mmol/L compared to Trial 103 (140 [35.2%] and 100 [17.5%] subjects, respectively) and a lower proportion of subjects with a baseline SwCl < 30 mmol/L (36 [9.0%] and 152 [26.5%] subjects, respectively). Thus, as expected, as shown in [Table 34](#), the proportion of responders in Trial 102 is greater than Trial 103, an important distinction that is lost in the pooled analysis. The genotype differences and expected response to therapy between the enrolled populations of the two phase 3 trials do not support pooling of the data.

We also do not agree that pooling these results was appropriate from a statistical perspective in the context of two adequate and well controlled trials submitted to support substantial evidence of effectiveness. (b) (4)

There was no justification from the Applicant for pooling this endpoint based on statistical considerations. Although the Applicant also included the responder analyses for the trials individually as other secondary endpoints, these were conducted outside of multiplicity control. In these exploratory analyses, results were generally consistent with the other SwCl based secondary endpoints but remain of unclear clinical significance.

The Applicant's statistical handling of the responder analyses, pooled and unpooled, included all subjects in the analysis, whether the individual's baseline SwCl was above or below the specified threshold. Only a limited number of subjects had baseline SwCl values > 60 mmol/L in both trials, as shown in [Table 34](#). The Applicant partially addressed this issue by accounting for baseline imbalance via the statistical analysis model; however, we note this as an additional limitation to the interpretability of the results.

Conclusion

(b) (4)
The change from baseline SwCl results provide

pharmacodynamic information on CFTR function and will be communicated in the USPI with appropriate language to convey the uncertainty of the clinical meaning. (b) (4)

6.3.3. Additional Data Sources to Support Indication Based on *CFTR* Variant

Issue

The Applicant submitted multiple types of data, including clinical trial results, in vitro models, and scientific justification for extrapolation, to support the inclusion of a total of 303 *CFTR* variants in the indication for VNZ/TEZ/D-IVA.

Background

There are over 700 variants in the *CFTR* gene that are associated with CF disease causation, although over 2,000 variants have been identified ([CFF; JHU; and HSC 2024](#)). The most common CF-causing variant in the United States is *F508del*. Approximately 85% of individuals with genotype information available are heterozygous for *F508del* and 44% are *F508del* homozygous ([CFF 2023](#)). The reported prevalence of the next most reported *CFTR* variant in the United States is significantly lower with no other variant reported in >5.0% of the population in 2023 ([CFF 2023](#)).

Given the rarity of many *CFTR* variants, relying on clinical trial data alone to demonstrate efficacy is not feasible. In this context, in vitro data have supported the expansion of the indication to additional *CFTR* variants for ELX/TEZ/IVA and other medications that contain one or more of its components. The pathophysiology of CF is well understood, and the in vitro data used has primarily been from an in vitro Ussing chamber assays using the FRT cell system to model electrophysiologic changes ([Durmowicz et al. 2018](#)). Recently, in vitro HBE cells have also been used to support the effectiveness of ELX/TEZ/IVA by demonstrating increased chloride transport in the *N1303K* variant, which was not responsive to ELX/TEZ/IVA when expressed in the FRT system (refer to the supplemental NDAs 212273/S012 and 217660/S003 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]).

In addition, there remain *CFTR* variants that are not amenable to evaluation within these in vitro models and are considered too rare to be easily evaluated in a clinical trial. Some of these variants, including 16 ultra-rare noncanonical splice (NCS) variants, which are expected to result in the presence of wild-type *CFTR* protein in a lower quantity than normal, were recently added to the indication for ELX/TEZ/IVA based on the extrapolation of efficacy and safety from a clinical trial, in which three of these types of variants were enrolled (Trial VX21-445-124). Extrapolation was supported by the knowledge that patients with these variants share a “residual function” clinical phenotype with patients in the clinical trial and that this residual function phenotype results from expression of wild-type *CFTR* protein, for which there is in vitro FRT data demonstrating that ELX/TEZ/IVA robustly augments chloride transport (refer to the supplemental NDAs 212273/S012 and 217660/S003 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]).

Assessment

The Applicant has proposed the inclusion of 303 *CFTR* variants in the indication for VNZ/TEZ/D-IVA. Refer to [Table 2](#) in Section 1.2 and see [Table 196](#) in Section 16.2.3 for additional details on the data sources used to support the individual *CFTR* variants included in the proposed indication for VNZ/TEZ/D-IVA.

Clinical Data

The clinical data relies primarily on the demonstration of efficacy in subjects with at least one copy of the *F508del CFTR* variant, as established by the noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA and the prior demonstration of efficacy of ELX/TEZ/IVA.

For the remaining 302 variants, the data sources are summarized as follows. There is clinical data for an additional 23 variants from Trials 102 and 103, for which there is also nonclinical electrophysiology support.

FRT Data

The Applicant submitted FRT data demonstrating an increase in chloride transport of $\geq 10\%$ over baseline with VNZ/TEZ/D-IVA treatment for 31 *CFTR* variants that were not responsive to ELX/TEZ/IVA. See Section [14.1.2](#) for more details.

In addition, the Applicant submitted FRT data demonstrating a $\geq 10\%$ over baseline in chloride transport with VNZ/TEZ/D-IVA to support 74 variants that were recently added to the indication for ELX/TEZ/IVA on December 11, 2024, based on the FRT data. The threshold of a $\geq 10\%$ over baseline in chloride transport established during the review of existing in vitro FRT data was also leveraged to support a total of 154 *CFTR* variants previously demonstrated to be responsive to ELX/TEZ/IVA, TEZ/IVA, or IVA. The use of this existing FRT data was discussed with the Applicant during the development of VNZ/TEZ/IVA and the Division agreed this was a reasonable approach.

Overall, the FRT data submitted and reference to previously available data are supportive of inclusion of the proposed *CFTR* variants in the indication for VNZ/TEZ/D-IVA.

HBE Data

In vitro data using HBE cells were used to support the inclusion of a single rare variant, *N1303K*, in the indication for ELX/TEZ/IVA (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]). In this instance, HBE cells were used instead of FRT because the *N1303K* variant is not responsive to ELX/TEZ/IVA in the FRT system (see P289v4). At the time, a regulatory threshold to indicate effectiveness for ELX/TEZ/IVA using HBE cells had been not previously established, and the measure of effectiveness was determined by comparing the response of ELX/TEZ/IVA in HBE cells homozygous and heterozygous for *N1303K* to the response of TEZ/IVA in *F508del/F508del* HBE cells.

Similarly, VNZ/TEZ/D-IVA demonstrated an increase in chloride transport in homozygous and heterozygous *N1303K* HBE cells that was greater than the effect of TEZ/IVA on chloride

transport in *F508del/F508del* HBE cells, supporting inclusion of *N1303K* in the indication for VNZ/TEZ/D-IVA. Refer to Section [14.1.1](#) for more details of the clinical pharmacology assessment.

Extrapolation of Efficacy in Noncanonical Splice Variants

The Applicant proposed that the efficacy of VNZ/TEZ/D-IVA be extrapolated to include 19 NCS variants. Based on the available data, these variants result in expression of wild-type CFTR protein at the apical cell surface but at lower levels than normal.

These variants were added to the indication for ELX/TEZ/IVA on December 11, 2024, and included three NCS variants (i.e., *2789+5G>A*, *3272-26A>G*, *3849+10kbC>T*), for which the efficacy of ELX/TEZ/IVA was demonstrated in Trial VX21-445-124, and 16 ultra-rare NCS variants, for which the efficacy and safety of ELX/TEZ/IVA was extrapolated. This extrapolation was based on similarities in clinical phenotype (i.e., “residual function”) with the variants included in Trial VX21-445-124 and in vitro data demonstrating that ELX/TEZ/IVA augments wild-type CFTR function. Refer to Section [14.1.2](#) for additional details.

The data used to support the efficacy of VNZ/TEZ/D-IVA in these NCS variants included the demonstration of the overall clinical noninferiority of VNZ/TEZ/D-IVA to ELX/TEZ/IVA with supportive in vitro FRT data demonstrating that VNZ/TEZ/D-IVA also augments wild-type CFTR function. The data support the extrapolation of efficacy for these 19 *CFTR* variants based on the conclusion that the expected response to and benefits of VNZ/TEZ/D-IVA would translate to patients with these rare NCS variants.

Conclusion

Overall, the data submitted by the Applicant to support the efficacy of VNZ/TEZ/D-IVA in patients with *CFTR* variants where clinical trial data is infeasible to study is sufficient to support their inclusion in the indication for VNZ/TEZ/D-IVA. Refer to Section [14](#) for additional details.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical program for NDA 218730 primarily focused on evaluation of the safety of the new molecular entity VNZ. The Applicant established a scientific bridge to leverage the nonclinical toxicity data from the IVA program (NDA 203188, Trade name: KALYDECO [tablet]) to characterize the safety profile of D-IVA. The potential risks or safety concerns based on nonclinical data for TEZ were previously reviewed in the TEZ/IVA (NDA 210491, Trade name: SYMDEKO) and ELX/TEZ/IVA (NDA 212273, Trade name: TRIKAFTA [tablet]) programs. Overall, the nonclinical program supports the marketing application for NDA 218730.

The nonclinical safety of VNZ was evaluated in safety pharmacology studies in the rat and dog, repeat dose toxicology studies in the rat and dog of up to 26 and 39 weeks duration, respectively;

a full battery of developmental and reproductive toxicology studies in the rat and rabbit; genetic toxicology studies (Ames, in vitro micronucleus, and in vivo rat micronucleus assays); 6-month transgenic mouse carcinogenicity study; a juvenile toxicology study in rats; 13-week combination toxicology study in rats with VNZ/TEZ/D-IVA (see Section [13.1](#)). A 2-year carcinogenicity study in rats will be conducted as a postmarketing requirement (see Section [24](#)).

In the general toxicology program for VNZ in rats, the major target organs of toxicity were the stomach (erosion/ulcers) and liver (hepatocellular vacuolar degeneration, multifocal hepatocellular necrosis) at exposures greater than 20 times (males) and 60 times (females) the exposure at the maximum recommended human dose (MRHD) of 20 mg VNZ. In the general toxicology program for VNZ in dogs, there were no potential safety concerns identified up to 100 times the exposure at the MRHD of VNZ. In a combination repeat dose toxicology study in rats, there were no adverse findings when VNZ, TEZ, and D-IVA were coadministered at doses that produced exposures 4, 1, and 1 times in male animals and 9, 2, and 1 times in female animals compared to the exposures at the MRHD, respectively. Safety pharmacology studies conducted in rats indicated that VNZ does not adversely affect the CNS or respiratory systems. The good laboratory practice human ether-a-go-go related gene assay indicated a potential QTc prolongation risk, which was not observed upon follow-up in the dog repeat dose toxicology studies. VNZ was negative for genotoxicity in the Ames assay, in vitro micronucleus assay in TK6 cells, and in vivo micronucleus assay in male Sprague-Dawley rats. In a 6-month transgenic mouse carcinogenicity study, there were no treatment-related tumor findings. Refer to Section [8.3](#) and Section [8.4](#) for an overview of juvenile and developmental and reproduction toxicity assessment with VNZ.

D-IVA is the deuterated isotopologue of IVA. A scientific bridge was established between D-IVA and IVA in a 13-week repeat dose toxicology study in rats. In this study, the target organs of toxicity for both IVA and D-IVA were the kidney (basophilic tubules, tubular dilatation, and interstitial fibrosis), stomach (increased mucosal thickness), and thyroid (follicular cell hypertrophy). There were no toxicologically significant differences in findings between the same doses of D-IVA and IVA. Therefore, a bridge to the ivacaftor nonclinical program was justified and no further toxicology studies with D-IVA alone were recommended.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

The VNZ/TEZ/D-IVA FDC is not included in a specific drug class. The established pharmaceutical class for D-IVA is a CFTR potentiator. The components VNZ and TEZ remain unclassified but facilitate the cellular processing and trafficking of defective CFTR protein to the cell surface.

We focus this section of the review on ELX/TEZ/IVA because it is the active comparator in Trials 102 and 103 and shares components with VNZ/TEZ/D-IVA. ELX/TEZ/IVA also represents the majority market share in prescriptions among this group of drugs, given its wider variant-based indication and relative greater efficacy ([Heijerman et al. 2019](#); [CFF 2023](#)). In addition, the estimated cumulative worldwide patient exposure from marketing experience is also

significantly higher for ELX/TEZ/IVA at 160,240 person-years, more than double other related medications (information provided by the Applicant).

Recently a Boxed Warning related to drug-induced liver injury and liver failure was added to the United States Prescribing Information (USPI) of ELX/TEZ/IVA following the identification of cases of liver failure leading to death or transplantation in patients without a history of liver disease.⁵ The risk for drug-induced liver injury related to VNZ/TEZ/D-IVA was a major focus of this safety review.

In addition, the USPI of ELX/TEZ/IVA includes the following Warnings and Precautions⁶:

- Hypersensitivity reactions, including anaphylaxis – as reported in postmarketing setting
- Concomitant use with cytochrome P450 (CYP)3A inducers – coadministration is not recommended
- Concomitant use with CYP3A inhibitors – the dose of ELX/TEZ/IVA should be reduced when used concomitantly with moderate or strong CYP3A inhibitors
- Cataracts – cases of noncongenital lens opacities have been reported in pediatric patients treated with IVA-containing regimens

The most common adverse drug reactions listed in the USPI include headache, upper respiratory tract infection, abdominal pain, and diarrhea. Additional adverse reactions include rash, liver function test elevations, increased creatine phosphokinase, and increased blood pressure. The common adverse reactions were evaluated as part of the safety review of VNZ/TEZ/D-IVA, and some were prespecified as adverse events of special interest (AESIs) (e.g., liver function testing elevations, increased creatine phosphokinase, rash events).

In addition, there have been multiple postmarketing safety evaluations of ELX/TEZ/IVA and other similar medications as reviewed below in [Table 35](#).

Table 35. Summary of Postmarketing Safety Evaluations of ELX/TEZ/IVA

Signal (SSID)	Date Opened	Phase/Status
Increased intracranial pressure disorders (1005337)	May 16, 2024	Evaluation/Open
Psychiatric disorders (1005257)	Jan 19, 2024	Evaluation/Open
Cataract congenital (1005079)	Mar 17, 2023	Evaluation/Closed
Acute pancreatitis (1004940)	Sep 12, 2022	Evaluation/Closed
Anaphylactic reaction (1004722)	Jan 18, 2022	Action/Closed
Hypotension (1004367)	Feb 16, 2021	Pre-evaluation/Closed
Tremor (1004366)	Feb 16, 2021	Pre-evaluation/Closed
Seizure (1004365)	Feb 16, 2021	Pre-evaluation/Closed
Hormone level abnormal (1004364)	Feb 16, 2021	Pre-evaluation/Closed
Neuropsychiatric symptoms (1004363)	Feb 16, 2021	Pre-evaluation/Closed
Abnormal weight gain (1004317)	Jan 4, 2021	Pre-evaluation/Closed
Drug induced liver injury (1004310)	Dec 19, 2020	Pre-evaluation/Closed

⁵ For the most current TRIKAFTA label, please refer to the Drugs@FDA website.

⁶ Ibid.

Signal (SSID)	Date Opened	Phase/Status
Severe cutaneous adverse reactions (1004292)	Dec 9, 2020	Pre-evaluation/Closed

Source: Clinical reviewer. LiST data accessed Sep 12, 2024.
Abbreviations: ELX, elexacaftor; IVA, ivacaftor; SSID, safety signal identification; TEZ, tezacaftor

In response to the identification of the drug-induced liver injury (DILI) risk attributed to ELX/TEZ/IVA, a newly identified safety signal (NISS) related to drug-induced liver injury (safety signal identification [SSID] #1005364) was opened on July 2, 2024, to evaluate for medications that share components with ELX/TEZ/IVA. This safety signal assessment is in the action phase pending finalization at the time of this review. Postmarketing safety evaluations ongoing at the time of this review or ones that resulted in labeling changes were also included in the safety evaluation of VNZ/TEZ/D-IVA and are reviewed in Section [7.6.1.6](#) and Section [7.6.1.7](#).

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

7.3.1. Adverse Events Identified in Postmarket Experiences

VNZ/TEZ/D-IVA is not currently approved in the United States or in any other foreign market. No postmarketing experience is available. Relevant information regarding risks identified through postmarketing experience of ELX/TEZ/IVA or medications that contain its components is included in Section [7.2](#).

7.3.2. Expectations on Safety

Not applicable for this review.

7.3.3. Additional Safety Issues From Other Disciplines

Not applicable for this review.

7.4. FDA Approach to the Safety Review

All clinical studies conducted as part of the VNZ/TEZ/D-IVA development program were evaluated for safety. Given the short exposure periods and smaller sample sizes in the phase 1 and 2 studies, the focus of the safety review is on the phase 3 development program, Trials 102 and 103.

Both phase 3 trials included a 4-week ELX/TEZ/IVA run-in period followed by a 52-week treatment period. Given similarities between the trial designs and populations, the safety data from Trials 102 and 103 were pooled for analysis. The safety data were also reviewed from the trials individually, and differences are noted where applicable. For detailed summaries of the trial protocols, refer to Section [15.1](#).

Subjects unable to tolerate ELX/TEZ/IVA were excluded from the trials. Although selecting the population this way was clinically appropriate for the trial design, it adds a significant limitation to the interpretation of VNZ/TEZ/D-IVA safety data, as does the absence of a placebo arm for comparison of baseline rates. As such, the VNZ/TEZ/D-IVA safety data were evaluated in relation to the ELX/TEZ/IVA treatment arms, as well as in the context of the known safety profile of ELX/TEZ/IVA. We are unable to draw conclusions regarding the safety of VNZ/TEZ/D-IVA in patients who have previously been unable to tolerate ELX/TEZ/IVA, as reviewed in Section [7.7.1](#).

The safety for pediatric subjects aged 6 through 11 years is extrapolated from the adolescent and adult data based on comparable systemic exposures and because CF is the same disease process across age groups. The pediatric safety data from the Trial 105 were also reviewed for the presence of additional potential safety signals; however, the lack of a control arm limits the overall interpretation of these data. As most of the VNZ/TEZ/D-IVA exposure occurred in Cohort B1 of Trial 105, this will be the primary focus of the pediatric safety data review.

All safety analyses were conducted in the safety analysis set, defined as all subjects who received at least one dose of trial drug. Unless otherwise noted, all AEs presented are considered treatment emergent adverse events, defined as AEs that started or worsened in severity on or after the first dose of trial medication in the treatment period up until 28 days after the last dose of the trial drug or completion of trial participation date, whichever occurred first. Adverse events that occurred in the run-in period or after the treatment period are reviewed in Section [17](#).

No major data quality or integrity issues were identified that would preclude a safety review for this NDA. There were no major issues identified with respect to recording, coding, and characterizing AEs. The Applicant's translations of verbatim terms into the Medical Dictionary for Regulatory Activities preferred terms for the events reported in the trials were reviewed and found to be acceptable. The definition, grading scheme, and assessment of causality for all AEs and serious adverse event (SAEs) were reviewed and found to be acceptable.

7.5. Adequacy of the Clinical Safety Database

Phase 3 Trials 102 and 103

The pooled safety data included 971 subjects randomized in the phase 3 trials (480 subjects received VNZ/TEZ/D-IVA and 491 subjects received ELX/TEZ/IVA). The duration of exposure for Trials 102 and 103 is presented in [Table 36](#).

Table 36. Duration of Exposure (SAS), Trials 102 and 103

Parameter	Trial 102		Trial 103	
	ELX/TEZ/IVA (N=202)	VNZ/TEZ/D-IVA (N=196)	ELX/TEZ/IVA (N=289)	VNZ/TEZ/D-IVA (N=284)
Duration of treatment ^a , weeks				
Mean (SD)	49.4 (10.0)	50 (7.8)	50.3 (7.6)	49.2 (10.0)
Median (min, max)	52 (0.4, 53.7)	52 (1.3, 54.1)	52 (0.1, 53.3)	52 (0.4, 53.7)

Parameter	Trial 102		Trial 103	
	ELX/TEZ/IVA (N=202)	VNZ/TEZ/D-IVA (N=196)	ELX/TEZ/IVA (N=289)	VNZ/TEZ/D-IVA (N=284)
Subjects treated, by duration, n (%)				
≤1 week	1 (0.5)	0	1 (0.3)	1 (0.4)
>1 to ≤2 weeks	2 (1.0)	1 (0.5)	0	0
>2 to ≤4 weeks	2 (1.0)	0	0	3 (1.1)
>4 to ≤12 weeks	3 (1.5)	0	2 (0.7)	5 (1.8)
>12 to ≤24 weeks	0	6 (3.1)	7 (2.4)	8 (2.8)
>24 to ≤36 weeks	4 (2.0)	5 (2.6)	3 (1.0)	2 (0.7)
>36 to ≤52 weeks	120 (63.9)	115 (58.7)	186 (64.4)	182 (64.1)
>52 weeks	61 (30.2)	69 (35.2)	90 (31.1)	83 (29.2)

Source: Clinical reviewer and clinical data scientist. Software: R and JMP v15.0. adex.xpt and adsl.xpt.

^a Treatment period duration is 52 weeks

Abbreviations: D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects in subset; SAS, safety analysis set; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

The duration of treatment was balanced between treatment arms and similar in both phase 3 trials. The average duration of exposure was 50 weeks, and over 90% of the population was exposed to treatment for at least 36 weeks. Overall, the safety database provided by the Applicant is of sufficient size and duration for a rare disease, such as CF, to assess the safety of the proposed dose of VNZ/TEZ/D-IVA when taken chronically.

Pediatric Trial 105

The safety data from Trial 105 Cohort B1 included 78 subjects and the duration of exposure is shown in [Table 37](#).

Table 37. Duration of Exposure (SAS), Trial 105 (Cohort B1)

Parameter	VNZ/TEZ/D-IVA (N=78)
Duration of treatment ^a , weeks	
Mean (SD)	23.8 (2.1)
Median (min, max)	24.0 (6.3, 25.4)
Subjects treated, by duration, n (%)	
≤1 week	0
>1 to ≤2 weeks	0
>2 to ≤4 weeks	0
>4 to ≤12 weeks	1 (1.3)
>12 to ≤24 weeks	48 (61.5)
>24 weeks	29 (37.2)

Source: Clinical reviewer and clinical data scientist. Software: R and JMP v15.0. adex.xpt and adsl.xpt.

^a Treatment period duration is 24 weeks

Abbreviations: D-IVA, deutivacaftor; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects in subset; SAS, safety analysis set; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

The mean duration of exposure was 23.8 weeks. Overall, the database is adequate for review of additional safety signals of VNZ/TEZ/D-IVA in the pediatric 6- to 11-year-old CF population. The scope of the safety database is consistent with other similar development programs in this population.

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Trials 102 and 103

7.6.1.1. Overview of Adverse Events Summary, Pooled Analyses, Trials 102 and 103

The overview of AEs occurring in the pooled phase 3 trials is provided in [Table 38](#). Over 95% of subjects in both treatment arms experienced an AE, similar to other clinical development programs in the CF population.

Table 38. Overview of Adverse Events During the Treatment Period (Pooled SAS), Trials 102 and 103

	ELX/TEZ/IVA N=491 n (%)	VNZ/TEZ/D-IVA N=480 n (%)
Subjects with Adverse Events		
Subjects with any AE	496 (95.5)	459 (95.6)
Subjects with AE by maximum severity		
Grade 1/Mild	145 (29.5)	166 (34.6)
Grade 2/Moderate	269 (54.8)	239 (49.8)
Grade 3/Severe	54 (11.0)	54 (11.3)
Grade 4/Life-threatening	1 (0.2)	0
Grade 5/Death	0	0
Subjects with AE		
Leading to discontinuation	18 (3.7)	18 (3.8)
Leading to drug interruption	12 (2.4)	19 (4.0)
Subjects with related AE	175 (35.6)	168 (35.0)
Subjects with SAE	81 (16.5)	68 (14.2)
Subjects with AE leading to death	0	0

Source: Clinical reviewer. Software: JMP v15.0 and OCS Analysis Studio. adae.xpt using SAFFL(Y), TRTEMFL(Y), AREL, ATOXGR, AESER, AEACON, TRT01A.

Abbreviations: AE, adverse event; D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

The proportion of subjects experiencing severe AEs was balanced between treatment arms. There was a numerically higher proportion of subjects reported to have AEs leading to drug interruptions in the VNZ/TEZ/D-IVA arm compared to ELX/TEZ/IVA, 19 (4%) vs 12 (2.4%), respectively, which will be reviewed in more detail in Section [7.6.1.4](#). There was a numerically higher proportion of subjects with reported SAEs in the ELX/TEZ/IVA treatment arm as reviewed in more detail in Section [7.6.1.3](#).

An additional review of AEs occurring during the run-in or follow-up periods is included in Section [17](#).

7.6.1.2. Deaths, Pooled Analyses, Trials 102 and 103

There were no reported deaths attributable to adverse events during the treatment period in the pooled phase 3 safety database. There were two deaths in Trial 103, summarized below, that

occurred after the completion of the treatment period. Both subjects were randomized to the ELX/TEZ/IVA treatment arm.

- Subject (b) (6) was a 39-year-old White female with CF complicated by CF-related diabetes and bronchiectasis, asthma, and a history of reported alcohol use/abuse that was in remission at the time of trial enrollment. The subject was on ELX/TEZ/IVA prior to trial enrollment. The trial drug was discontinued on Day 354 for an SAE of distal intestinal obstruction syndrome. In the weeks prior to this, the subject experienced AEs of moderate vomiting and liver function test (LFT) elevations and underwent a magnetic resonance cholangiopancreatography that demonstrated moderate hepatic steatosis, cholelithiasis with gallbladder wall edema or thickening, and an intraductal papillary mucinous neoplasm of the pancreas. The treating hepatologist's impression was that the changes were related to alcoholic steatosis and hepatitis. The subject then experienced pneumonia and a CF pulmonary exacerbation. During this time, commercial ELX/TEZ/IVA was restarted but discontinued again as the subject's LFTs remained elevated. The subject's clinical status continued to deteriorate and progressed to respiratory failure and septic shock. The subject's family decided to withdraw care, and the subject died. The reported immediate cause of death was acute respiratory distress syndrome from pneumonia with liver and renal failure listed as other significant contributing factors.

The data provided do not suggest that this subject's death was attributable to ELX/TEZ/IVA; however, a component of drug contribution to progressive liver failure cannot be excluded.

- Subject (b) (6). 52-year-old White man with CF complicated by pancreatic insufficiency, abdominal pain, and anterior liver nodularity. The subject had not previously received ELX/TEZ/IVA or other similar medication. Trial drug was discontinued on Day 184 for the elevated LFTs. The subject reported 'regular' alcohol use at screening (12 beers per week), which increased because of reported social events. On Day 211, the subject experienced an SAE of hepatic cirrhosis and severe portal hypertension. The following week, the subject was reported to have moderate portal vein thrombosis and a liver mass near the pancreatic head on CT. Subsequent biopsy revealed severe adenocarcinoma of the pancreas. The subject was discharged to home with palliative care and died a few weeks later.

We agree with the Applicant's assessment that the cause of death was not likely related to trial drug.

7.6.1.3. Serious Adverse Events, Pooled Analyses, Trials 102 and 103

[Table 39](#) summarizes the SAEs occurring in ≥ 2 subjects in the pooled phase 3 safety database.

Table 39. SAEs Occurring in ≥ 2 Subjects During the Treatment Period by PT (Pooled SAS), Trials 102 and 103

SAE by PT	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 n (%)	N=480 n (%)
Subjects with any SAE	81 (16.5)	68 (14.2)
Infective pulmonary exacerbation of CF	35 (7.1)	29 (6.0)
Influenza	3 (0.6)	7 (1.5)
Pneumonia	6 (1.2)	4 (0.8)
Hemoptysis	3 (0.6)	3 (0.6)
COVID-19	4 (0.8)	2 (0.4)
DIOS	3 (0.6)	2 (0.4)
ALT increased	2 (0.4)	2 (0.4)
Suicidal ideation	2 (0.4)	2 (0.4)
AST increased	1 (0.2)	2 (0.4)
GGT increased	1 (0.2)	2 (0.4)
Depression	0	2 (0.4)
Syncope	0	2 (0.4)
Cholelithiasis	3 (0.6)	0
Constipation	3 (0.6)	0
Nephrolithiasis	2 (0.4)	0

Source: Clinical reviewer and clinical data scientist. Software: JMP v15.0. adae.xpt using SAS(Y), TRTEMFL(Y), AESER(Y), AEDECOD.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; COVID-19, SARS CoV2 2019; DIOS, distal intestinal obstruction syndrome; D-IVA, deutivacaftor; ELX, elxacaftor; GGT, gamma-glutamyl transferase; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

There was a numerically higher proportion of subjects (81, 16.5%) in the ELX/TEZ/IVA treatment arm than in the VNZ/TEZ/D-IVA treatment arm (68, 14.2%) who experienced an SAE during the treatment period. The most common SAE reported was related to infective pulmonary exacerbation of CF. This finding is not unexpected as pulmonary exacerbations are a common complication of CF and is reviewed in more detail in [Section 7.6.1.5](#).

Influenza was the next most common SAE and occurred in a slightly higher proportion of subjects in the VNZ/TEZ/D-IVA treatment arm (7, 1.5%) compared to those treated with ELX/TEZ/IVA (3, 0.6%). To evaluate this further, the SAEs were also analyzed by system organ class (SOC) (data not shown). The Infections and Infestations SOC was generally balanced between treatment arms – VNZ/TEZ/D-IVA (50, 10.2%), ELX/TEZ/IVA (46, 9.6%). There were also no risk differences calculated for any SOC or individual preferred term (PT) for which the 95% confidence interval excluded the null. Additional review of SAEs related to FDA Medical Query and time to SAE onset did not reveal any additional concerning safety signals.

All SAE narratives were reviewed. The general rates of SAEs in the pooled phase 3 trials were similar to the treatment arm in Trial VX17-445-102 of the phase 3 development for program ELX/TEZ/IVA. The rates of SAEs in Trials 102 and 103 were generally balanced between trials. The small imbalance in SAEs between the pooled treatment arms is unlikely to be of clinical

significance. Additional review of hepatotoxicity, suicidal ideation, infective pulmonary exacerbation of CF, and influenza is included in Section 7.6.1.5 and Section 7.6.1.6.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Pooled Analyses, Trials 102 and 103

The AEs leading to treatment discontinuation or interruption that occurred in ≥ 2 subjects are reviewed in Table 40. The rates of AEs leading to discontinuation were balanced between the treatment arms; however, as reviewed in more detail in Section 7.6.1.6 and Section 7.7.2, a numerically higher proportion of subjects in the VNZ/TEZ/D-IVA treatment arm discontinued the trial drug because of abnormalities in LFTs.

Table 40. AEs Leading to Treatment Discontinuation or Interruption During the Treatment Period Occurring in ≥ 2 Subjects, (Pooled SAS), Trials 102 and 103

AE Leading to Discontinuation by PT	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 n (%)	N=480 n (%)
Subjects with any AE leading to discontinuation	18 (3.7)	18 (3.8)
ALT increased	3 (0.6)	7 (1.5)
AST increased	3 (0.6)	6 (1.3)
Fatigue	2 (0.4)	3 (0.6)
Alkaline phosphatase increased	1 (0.2)	2 (0.4)
Cough	1 (0.2)	2 (0.4)
Anxiety	0	2 (0.4)
Bilirubin increased	0	2 (0.4)
Unconjugated bilirubin increased	0	2 (0.4)
Depression	0	2 (0.4)
Dysphonia	0	2 (0.4)
Pulmonary function decreased	2 (0.4)	0
Subjects with any AE leading to drug interruption	12 (2.4)	19 (4.0)
ALT increased	2 (0.4)	4 (0.8)
AST increased	3 (0.6)	3 (0.6)
Rash	0	2 (0.4)
COVID-19	0	1 (0.2)
Alkaline phosphatase increased	2 (0.4)	1 (0.2)
Nausea	2 (0.4)	0

Source: Clinical reviewer. Software: OCS Analysis Studio. adae.xpt using SAS(Y), TRTEMFL(Y), AEDECOD.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; COVID-19, SARS CoV2 2019; D-IVA, deutivacaftor; ELX, elxacaftor; GGT, gamma-glutamyl transferase; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

The proportion of subjects with an AE requiring trial drug interruption was numerically higher in the VNZ/TEZ/D-IVA treatment arm occurring in 19 (4.0%) versus 12 (2.4%) subjects in the ELX/TEZ/IVA treatment arms. This difference is partially driven by LFT elevations and rashes (reviewed in Section 7.6.1.6). There were no other concerning signals noted in the review of PTs leading to drug interruption or discontinuation. Overall drug discontinuation rates were similar between arms. The clinical significance of the imbalance in drug interruptions is unclear.

7.6.1.5. Adverse Events, Pooled Analyses, Trials 102 and 103

The summary of AEs occurring in $\geq 10\%$ of subjects in the pooled phase 3 trials is included in [Table 41](#). As noted above, the majority of subjects ($>95\%$) experienced an AE. This proportion of subjects with AE is similar to other CF clinical development programs including the phase 3 trials used to support the registration of ELX/TEZ/IVA.

Table 41. AEs by PT During the Treatment Period Occurring in $\geq 10\%$ Subjects (Pooled SAS), Trials 102 and 103

AE by PT	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 n (%)	N=480 n (%)
Subjects with AE	469 (95.5)	459 (95.6)
Infective pulmonary exacerbation of CF	158 (32.2)	133 (27.7)
COVID-19 ^a	139 (28.3)	122 (25.4)
Cough ^b	116 (23.6)	120 (25.0)
Nasopharyngitis	95 (19.3)	102 (21.2)
Upper respiratory tract infection ^c	97 (19.8)	101 (21.0)
Headache	63 (12.8)	76 (15.8)
Oropharyngeal pain	60 (12.2)	69 (14.4)
Diarrhea	59 (12.0)	58 (12.1)
Abdominal pain ^d	53 (10.8)	53 (11.0)
Influenza	26 (5.3)	52 (10.8)
Pyrexia	50 (10.2)	52 (10.8)
Fatigue	46 (9.4)	51 (10.6)
Nasal congestion	47 (9.6)	48 (10.0)
Sputum increased	50 (10.2)	45 (9.6)

Source: Clinical reviewer. Software: OCS Analysis Studio. adae.xpt using SAS(Y), TRTEMFL(Y), AEDECOD.

^a Includes PTs COVID-19, COVID-19 pneumonia, coronavirus test positive, SARS-CoV-2 test positive

^b Includes PTs cough and productive cough

^c Includes PTs upper respiratory tract infection and viral upper respiratory tract infection

^d Includes PTs abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort

Abbreviations: AE, adverse event; CF, cystic fibrosis; COVID-19, SARS CoV2 2019; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

Many of the most common AEs reported are consistent with the known safety profile of ELX/TEZ/IVA and expected event rates in the CF population. The most common AE reported was infective pulmonary exacerbation of CF. There was a numerically higher proportion of subjects in the ELX/TEZ/IVA treatment arm (158, 32.2%) with this AE compared to the VNZ/TEZ/D-IVA treatment arm (133, 27.7%), although the risk difference did not exclude the null (risk difference [95% CI]: -4.5 [-10.2, 1.3]). Pulmonary exacerbations of CF are common in the CF population and were also recorded as other secondary efficacy endpoints. The analysis of the rate differences of pulmonary exacerbations of CF as an efficacy endpoint in both phase 3 trials was supportive of the noninferiority of VNZ/TEZ/D-IVA. The clinical significance of the imbalance in reported AEs related to infective pulmonary exacerbations of CF is unclear.

The noninferiority design of the phase 3 trials and high background rates of AEs related to CF limit the ability to adjudicate adverse reactions related to VNZ/TEZ/D-IVA. To further evaluate the safety profile of VNZ/TEZ/D-IVA, AEs occurring at a higher rate in the VNZ/TEZ/D-IVA arm were reviewed and are outlined in [Table 42](#).

Table 42. AEs Occurring at a Higher Rate in VNZ/TEZ/D-IVA Arm by PT During the Treatment Period in ≥5% Subjects (Pooled SAS), Trials 102 and 103

AE by PT	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 n (%)	N=480 n (%)
Influenza	26 (5.3)	52 (10.8)
Sinus congestion	15 (3.1)	32 (6.7)
Rash	22 (4.5)	37 (7.7)
Headache	63 (12.8)	76 (15.8)
Oropharyngeal pain	60 (12.2)	69 (14.4)
ALT increased	29 (5.9)	38 (7.9)
Nasopharyngitis	95 (19.3)	102 (21.2)
Abdominal pain upper	19 (3.9)	26 (5.4)
Cough ^a	116 (23.6)	120 (25.0)
AST increased	27 (5.5)	33 (6.9)
Upper respiratory tract infection ^b	97 (19.8)	101 (21.0)
Fatigue	46 (9.4)	51 (10.6)
Pyrexia	50 (10.2)	52 (10.8)
Increased creatine phosphokinase	41 (8.4)	43 (9.0)
Nasal congestion	47 (9.6)	48 (10.0)
Abdominal pain ^c	53 (10.8)	53 (11.0)
Diarrhea	59 (12.0)	58 (12.1)

Source: Clinical reviewer and clinical data scientist. Software: R, OCS Analysis Studio, and JMP v15.0. adae.xpt using SAS(Y), TRTEMFL(Y), AEDECOD.

^a Includes PTs cough and productive cough

^b Includes PTs upper respiratory tract infection and viral upper respiratory tract infection

^c Includes PTs abdominal pain, abdominal pain lower, abdominal pain upper, abdominal discomfort

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

The proportion of subjects with an AE related to influenza was higher in the VNZ/TEZ/D-IVA treatment arm (52, 10.8%) compared to those treated with ELX/TEZ/IVA (26, 5.3%). Influenza was one of the few AEs for which the 95% confidence interval of the risk difference excluded the null (risk difference [95% CI]: 5.5% [2.2, 9.1]). As noted in Section 7.6.1.3, the rate of SAEs related to influenza was also numerically higher in the VNZ/TEZ/D-IVA treatment arm. The significance of this difference is unclear. Additional PTs of upper respiratory tract infections and specific viral upper respiratory tract infections were also higher in the VNZ/TEZ/D-IVA arm; however, notably, coronavirus disease of 2019 (COVID-19) occurred at a higher rate in the ELX/TEZ/IVA arm (127, 25.9%) compared to VNZ/TEZ/D-IVA (107, 22.3%). Overall, the viral infections observed did not contribute to increased rates of infective exacerbations of CF or hospitalizations. We also note that rates of AEs related to influenza were also elevated compared to placebo in the clinical development program for ELX/TEZ/IVA, but the clinical relevance of this finding was also considered uncertain at the time.

Adverse events related to rash, transaminase elevations, and increased creatinine phosphokinase are discussed in Section 7.6.1.6. Other AEs reported, including cough, sinus congestion, abdominal pain, and nasal congestion, are often symptoms associated with CF. The interpretation of these, and other reported AEs such as headache and pyrexia, is limited due to the lack of a placebo arm to assess the baseline rate of these events in the trial population.

We note the following AEs occurred at higher rates in the ELX/TEZ/IVA treatment arm with at least a 1% difference in the risk difference: infective pulmonary exacerbation of CF, COVID-19,

sinusitis, vomiting, arthralgia, dyspnea, constipation, and back pain. The clinical implications of these differences between the treatment arms are also unclear.

Review of the phase 3 trials individually and by SOC did not reveal any additional concerning safety signals. Because of the limitations from the trial design and high rate of background AEs related to CF, we recommend the inclusion of all AEs occurring in $\geq 5\%$ of treated subjects occurring at a greater rate in VNZ/TEZ/D-IVA treated subjects compared to ELX/TEZ/IVA be included in the USPI for VNZ/TEZ/D-IVA.

Overall, the review of common AEs did not demonstrate significant new safety concerns for VNZ/TEZ/D-IVA beyond the known safety profile of ELX/TEZ/IVA. The analysis of the data suggests that the safety profile of VNZ/TEZ/D-IVA is very similar to ELX/TEZ/IVA.

7.6.1.6. Adverse Events of Special Interest, Trials 102 and 103

The following adverse events were prespecified as AESIs based on the known safety profile of medications similar to VNZ/TEZ/D-IVA (e.g., ELX/TEZ/IVA) and safety information from the phase 2 development program: liver function test abnormalities, creatine kinase elevations, rash, cataracts, hypoglycemic events, and neuropsychiatric events.

Liver Function Test Abnormalities and Related Events

Transaminase elevations are a well described adverse reaction related to all approved medications that affect CFTR processing or function and have been included as a Warning and Precaution in the USPI of these products since the initial approval of IVA in 2012 ([Vertex Pharmaceuticals 2012](#)). During the course of the NDA review of VNZ/TEZ/D-IVA, an FDA Amendments Act of 2007 safety labeling change dated October 22, 2024, was issued for the addition of a Boxed Warning to the ELX/TEZ/IVA USPI regarding the risk of drug-induced liver injury and liver failure attributable to ELX/TEZ/IVA. This change was based on data from clinical trials submitted to a recent supplemental NDA (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]) and review of the available postmarketing data.

Given the similarities between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, the DILI team in the Division of Hepatology and Nutrition (DHN) was consulted to assist in the review of the potential DILI risk related to VNZ/TEZ/D-IVA. An Information Request was sent to the Applicant on July 16, 2024, to obtain additional information on cases of suspected DILI that were identified in the initial safety review. The DILI team within DHN also assisted the primary review team in the assessment of the individual cases and the risk for VNZ/TEZ/D-IVA-related DILI was discussed at multiple internal meetings within the Division and Office of New Drugs.

There were no cases of liver failure leading to death or liver transplant noted in the phase 3 pooled safety database for VNZ/TEZ/D-IVA. As noted, the review of the safety database is limited both by the lack of a placebo arm and the required exclusion of subjects intolerant of ELX/TEZ/IVA. There were five cases of nonjaundiced DILI that were assessed as ‘probably’ or ‘possibly’ related to VNZ/TEZ/D-IVA, reviewed in more detail below. No subjects exposed to

VNZ/TEZ/D-IVA had transaminase elevations with concurrent elevations in total bilirubin. One ELX/TEZ/IVA exposed subject did meet Hy's Law. Summaries of the cases assessed as probably related to VNZ/TEZ/D-IVA are reviewed below:

- Subject (b) (6) was a 48-year-old White man with CF and Gilbert's syndrome. The subject had been randomized to the ELX/TEZ/D-IVA arm during the treatment period of Trial 102 and continued to the open-label extension (Trial 104) and began treatment with VNZ/TEZ/D-IVA. On Day 256 of Trial 104, the subject's transaminases were >10x the upper limit of normal (ULN) alanine aminotransferase [ALT] 813 U/L [14 x ULN] and aspartate aminotransferase [AST] 395 U/L [11 x ULN]) and the total bilirubin was 2.53 mg/dL (>2 x ULN). The bilirubin elevation noted was of unclear clinical significance because of the subject's history of Gilbert's syndrome. The trial drug was discontinued the following day, and the subject withdrew from the trial on Day 307. Targeted laboratory evaluation that included hepatitis antibodies and antigens and evaluation for cytomegalovirus (CMV) and Epstein-Barr virus was unremarkable. An ultrasound revealed a liver of normal size and morphology. We note that the subject was also reported to have an AE related to a respiratory tract infection (viral respiratory tract infection by metapneumovirus) on Day 268.

We agree with the Applicant's assessment that given the context of an unrevealing work-up and lack of alternative etiology, the elevation in the transaminases is related to hepatocellular injury due to VNZ/TEZ/D-IVA. We are unable to assess the clinically meaningfulness of the elevation in the total bilirubin because of the subject's history of Gilbert's disease. There is no evidence to support this event was related to the metapneumovirus respiratory tract infection.

- Subject (b) (6) was a 40-year-old White man with CF complicated by pancreatic insufficiency who was receiving treatment with IVA monotherapy prior to enrollment. The subject was randomized to the VNZ/TEZ/D-IVA treatment arm. On Day 116, the subject had AEs reported for increased ALT and AST. The initial elevations in the transaminases were >5 x ULN (ALT 371 U/L and AST 189 U/L) and the data available in the case narrative demonstrated that the transaminase levels peaked at on Day 120 (ALT 615 U/L [>10 x ULN] and AST 318 U/L [>8 x ULN]). Total bilirubin levels were within the normal range. Targeted laboratory evaluation that included hepatitis antibodies and antigens, evaluation for CMV and Epstein-Barr virus, and an abdominal ultrasound were unremarkable. The subject received the last dose of trial drug on Day 120 and withdrew consent and discontinued from the trial a few days later.

The Applicant assessed that that the role of VNZ/TEZ/D-IVA in this case cannot be excluded. Addition information was requested from the Applicant on September 16, 2024, to further assess this case but the data available was limited as the follow-up clinical evaluation was done outside of the clinical trial setting. The provided data revealed that the transaminases continued to rise, with a highest ALT of 1130 U/L (>28 x ULN) and a highest AST of 436 U/L (>9 x ULN) and confirmed that the total bilirubin remained within the normal range; however, the data did not reveal a peak bilirubin. No additional follow up information was available. Our assessment of this case is that it is probably hepatocellular injury related to VNZ/TEZ/D-IVA.

- Subject (b) (6) was a 40-year-old White man enrolled in Trial VX23-121-012, a phase 1, randomized, open-label relative bioavailability, food effect, and dose proportionality of a granule formulation of VNZ/TEZ/D-IVA in healthy adult subjects. The subject had a reported past medical history that included hepatitis A, parasitic infection (no other information available), and 'positive' CMV (no other information available). All LFT parameters were reported to be in the normal range at the screening visit prior to the first dose of the trial drug. On Day 20, six days after the second dose of the trial drug, the subject had AEs of increased ALT, AST, and gamma-glutamyl transferase reported. The ALT was 537 U/L ($>8 \times \text{ULN}$), the AST was 219 U/L ($>4 \times \text{ULN}$), and the gamma-glutamyl transferase was 269 U/L ($>3 \times \text{ULN}$). The total bilirubin remained within the normal range. Subsequent follow up laboratory analysis revealed down trending transaminases. Targeted laboratory evaluation that included hepatitis antibodies and antigens and evaluation for CMV and Epstein-Barr virus was unremarkable; however, the available data are limited because no dates were provided by the Applicant. An abdominal ultrasound was notable for mild steatosis.

The Applicant, in conjunction with their hepatology consultant, assessed that the subject likely had underlying nonalcohol steatohepatitis with an acute asymptomatic transaminase elevation that resolved after trial drug discontinuation and that an association with VNZ/TEZ/D-IVA cannot be excluded. Our assessment of this case was that, regardless of potential undiagnosed nonalcohol steatohepatitis, the acute transaminase event was probably hepatocellular injury related to VNZ/TEZ/D-IVA.

The overall assessment of the reviewed cases was that, although there were no cases of concurrent transaminitis and bilirubin elevation, the available data supports that there is a risk of hepatocellular injury associated with VNZ/TEZ/D-IVA.

In addition, the maximum liver function test elevations from baseline occurring during the treatment period were evaluated in the pooled phase 3 safety database and are outlined below in [Table 43](#). The available data to assess for maximum LFT elevations from baseline was limited by the exclusion of subjects with a history of intolerance to ELX/TEZ/IVA. Note that $>85\%$ of the enrolled phase 3 population had documented prior use of ELX/TEZ/IVA or another medication containing its components. These limitations may lead to a rate of LFT elevations in the ELX/TEZ/IVA that is lower than that seen in the ELX/TEZ/IVA registrational trials or observed in clinical care, but we are unable to assess the impact of these limitation on the subjects exposed to VNZ/TEZ/D-IVA.

Table 43. Maximum Liver Function Test Elevation From Baseline During the Treatment Period (Pooled SAS), Trials 102 and 103

Lab Parameter	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 N1 (%)	N=480 N1 (%)
ALT (U/L), n (%)		
$>3x$ to $\leq 5x$ ULN	8 (1.6)	13 (2.7)
$>5x$ to $\leq 8x$ ULN	2 (0.4)	5 (1.0)
$>8x$ to $\leq 20x$ ULN	1 (0.2)	2 (0.4)
$>20x$ ULN	0	0

Lab Parameter	ELX/TEZ/IVA N=491 N1 (%)	VNZ/TEZ/D-IVA N=480 N1 (%)
AST (U/L), n (%)		
>3x to ≤5x ULN	4 (0.8)	10 (2.1)
>5x to ≤8x ULN	5 (1.0)	5 (1.0)
>8x to ≤20x ULN	0	4 (0.8)
>20x ULN	0	1 (0.2)
ALT or AST (U/L), n (%)		
>3x to ≤5x ULN	9 (1.8)	17 (3.5)
>5x to ≤8x ULN	5 (1.0)	6 (1.3)
>8x to ≤20x ULN	1 (0.2)	5 (1.0)
>20x ULN	0	1 (0.2)
ALT or AST (U/L), n (%)		
>3x ULN	15 (3.1)	29 (6.0)
>5x ULN	6 (1.2)	12 (2.5)
>8x ULN	1 (0.2)	6 (1.3)
Total bilirubin (μmol/L), n (%)		
>1.5x to ≤2x ULN	26 (5.3)	14 (2.9)
>2x to ≤3x ULN	21 (4.3)	8 (1.7)
>3x to ≤10x ULN	8 (1.6)	0
>10x ULN	0	0
ALT or AST (U/L) and total bilirubin (μmol/L) ALT or AST >3x ULN and total bilirubin >2x ULN	2 (0.4)	1 (0.2)
GGT (U/L), n (%)		
>2.5x to ≤5x ULN	13 (2.7)	7 (1.5)
>5x to ≤20x ULN	0	4 (0.8)
Alkaline phosphatase (U/L), n (%)		
>1.5x to ≤2.5x ULN	25 (5.1)	28 (16.7)
>2.5x to ≤5x ULN	4 (0.8)	5 (1.0)
>5x to ≤20x ULN	0	5 (1.0)
>20x ULN	1 (0.2)	1 (0.2)

Source: Clinical reviewer. Software: JMP v15.0. adlb.xpt using SAFFL(Y), ONTRTFL(Y), PARAMCD, AVALC, MCRIT1, ANL02FL. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-IVA, deutivacaftor; ELX, elxacaftor; GGT, gamma glutamyl transferase; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; SAS, safety analysis set; TEZ, tezacaftor; ULN, upper limit of normal; VNZ, vanzacaftor; x, times

There was a higher proportion of subjects with transaminase elevations in the VNZ/TEZ/D-IVA treatment arm compared to ELX/TEZ/IVA. When evaluating maximum elevations in either ALT or AST, 29 (6.0%) subjects in the VNZ/TEZ/D-IVA treatment arm had transaminase elevations >3 x ULN compared to 15 (3.1%) in the ELX/TEZ/IVA treatment arm. Similarly, six (1.3%) VNZ/TEZ/D-IVA treated subjects had either ALT or AST elevations >8 x ULN compared to one (0.2%) subject treated with ELX/TEZ/IVA. However, when evaluating for elevations in total bilirubin, a higher proportion of subjects (21, 4.3%) in the ELX/TEZ/IVA treatment arm had elevations in total bilirubin between 2 to 3 x ULN compared to subjects (8, 1.7%) treated with VNZ/TEZ/D-IVA. No subjects treated with VNZ/TEZ/D-IVA had total bilirubin elevations >3 x ULN, compared to 8 (1.6%) subjects treated with ELX/TEZ/IVA.

The clinical implications of the differences between the rates of transaminase and bilirubin elevations between the VNZ/TEZ/D-IVA and ELX/TEZ/IVA treatment arms are unclear, but the overall assessment of the available data is that VNZ/TEZ/D-IVA likely conveys a similar level of risk of liver injury to ELX/TEZ/IVA. An additional analysis of the shift in LFTs from baseline was unrevealing (data not shown).

Additional analysis was performed on transaminase-related AEs as outlined in [Table 44](#).

Table 44. In-Depth AESI Assessment for Elevated Transaminase During the Treatment Period, Grouped Query (Pooled SAS), Trials 102 and 103

	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491	N=480
Adverse Event	n (%)	n (%)
All PTs related to AESI	35 (7.1)	43 (9.0)
Alanine aminotransferase increased	29 (5.9)	38 (7.9)
Aspartate aminotransferase increased	27 (5.5)	33 (6.9)
Hypertransaminasaemia	0	2 (0.4)
Maximum severity		
Mild	20 (4.1)	24 (5.0)
Moderate	13 (2.6)	15 (3.1)
Severe	2 (0.4)	4 (0.8)
SAE	2 (0.4)	2 (0.4)
Resulting in discontinuation	3 (0.6)	7 (1.5)
Relatedness determined by investigator	22 (4.5)	30 (6.2)

Source: Clinical reviewer and clinical data scientist. Software: R. adae.xpt.

Abbreviations: AESI, adverse events of special interest; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

Similar to the analysis of the maximum postbaseline laboratory elevations, subjects treated with VNZ/TEZ/D-IVA were more likely to have transaminase-related AEs recorded (43, 9.0%) compared to ELX/TEZ/IVA treated subjects (35, 7.1%). In general, the transaminase related AEs were also more likely to be severe in the VNZ/TEZ/D-IVA treated subjects: four (0.8%) versus two (0.4%) in the VNZ/TEZ/D-IVA treatment arm and ELX/TEZ/IVA treatment arms, respectively. However, overall SAEs were the same between treatment arms: two (0.4%) VNZ/TEZ/D-IVA exposed subjects versus two (0.4%) ELX/TEZ/IVA exposed subjects. There were also more subjects (7, 1.5%) in the VNZ/TEZ/D-IVA treatment arm with transaminase related AEs leading to treatment discontinuation than those subjects (3, 0.6%) treated with ELX/TEZ/IVA.

The ability to interpret the clinical meaningfulness of the noted differences between treatment arms is limited by the absence of a placebo and the population limited to those tolerant of ELX/TEZ/IVA; however, the data support the conclusion that VNZ/TEZ/D-IVA conveys at least a similar risk of liver injury to ELX/TEZ/IVA. Additional assessment of the potential for VNZ/TEZ/D-IVA induced liver injury including labeling recommendations is included in Section [7.7.2](#).

Creatine Kinase Elevations

Section 6 of the USPI for ELX/TEZ/IVA includes the adverse reaction of ‘increased creatine phosphokinase’ noting that the incidence of maximum creatine phosphokinase was greater in ELX/TEZ/IVA-treated subjects compared to placebo and that some cases were associated with treatment interruption or rhabdomyolysis. Creatine phosphokinase elevation was designated as an AESI in the VNZ/TEZ/D-IVA development program. [Table 45](#) reviews the in-depth assessment of creatine phosphokinase elevations in the pooled phase 3 safety database.

Table 45. In-Depth AESI Assessment for Creatine Phosphokinase Elevation During the Treatment Period (Pooled SAS), Trials 102 and 103

Adverse Event	ELX/TEZ/IVA N=491 n (%)	VNZ/TEZ/D-IVA N=480 n (%)
AE of blood creatine phosphokinase increased (PT)	41 (8.4)	43 (9.0)
Maximum severity		
Mild	28 (5.7)	30 (6.2)
Moderate	11 (2.2)	12 (2.5)
Severe	2 (0.4)	1 (0.2)
SAE	1 (0.2)	1 (0.2)
Resulting in discontinuation	1 (0.2)	1 (0.2)
Relatedness determined by investigator	18 (3.7)	18 (3.8)
Creatine phosphokinase level on chemistry laboratory analysis (U/L)		
>3x ULN	61 (12.4)	57 (11.9)
>5x ULN	32 (6.5)	38 (7.9)
>10x ULN	16 (3.3)	21 (4.4)

Source: Clinical reviewer and clinical data scientist. Software: R. adae.xpt.

Abbreviations: AE, adverse event; AESI, adverse events of special interest; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; ULN, upper limit of normal; VNZ, vanzacaftor; x, times

Overall, there were similar rates of creatine phosphokinase AEs between treatment arms; however, there was a small numerical increase in the overall number of increased blood creatinine phosphokinase AEs reported (VNZ/TEZ/D-IVA 43 [9.0%] subjects compared to ELX/TEZ/IVA 41 [8.4%] subjects). In addition, blood creatine phosphokinase elevations >5 x ULN were higher in subjects treated with VNZ/TEZ/D-IVA (38, 7.9%) compared to those treated with ELX/TEZ/IVA (32, 6.5%). The majority of AEs were mild to moderate. There were two SAEs, one in each treatment arm, leading to trial drug discontinuation and adjudicated as possibly related to trial drug. Both subjects had previously experienced elevations of creatine phosphokinase while on ELX/TEZ/IVA that were attributed to exercise. There were no cases of rhabdomyolysis reported.

It is difficult to assess the clinical implication of the rates of creatine phosphokinase elevations without a placebo, but our review suggests that VNZ/TEZ/D-IVA conveys at least a similar risk to ELX/TEZ/IVA for creatinine phosphokinase elevations. We recommend continued inclusion of this risk in Section 6 of the USPI for VNZ/TEZ/D-IVA.

Cataract Adverse Events

Cataracts have been observed in subjects, particularly pediatric subjects, treated with IVA monotherapy and in juvenile rat toxicology studies with IVA. The risk for cataract is currently included in Section 5 of the USPI for all IVA containing medications including ELX/TEZ/IVA.

Trials 102 and 103 required ophthalmologic exams at screening/baseline and at Week 24 for pediatric subjects <18 years of age. Adverse events related to cataracts, including those occurring in subjects ≥18 years, are reviewed in [Table 46](#).

Table 46. In-Depth AESI Assessment for Cataracts During the Treatment Period (Pooled SAS), Trials 102 and 103

Adverse Event	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 n (%)	N=480 n (%)
PT related to AESI	4 (0.8)	3 (0.6)
Cataract	0	2 (0.4)
Cataract congenital	1 (0.2)	1 (0.2)
Cataract cortical	3 (0.6)	0

Source: Clinical reviewer and data scientist. Software: R. adae.xpt.

Abbreviations: AESI, adverse events of special interest; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

Overall, the rates of AEs related to cataracts were similar between treatment arms. We recommend the continued inclusion of cataracts in Section 5 of the USPI for VNZ/TEZ/D-IVA.

Note that the development of congenital cataracts occurring in infants born to women who had taken ELX/TEZ/IVA or other similar medications was evaluated as a potential postmarket safety signal in 2023 (SSID 1005079). As part of that review, the risk for congenital cataracts was determined to be negligible and no further action was necessary beyond routine pharmacovigilance. The two cases of AEs related to congenital cataracts were recorded in adolescent subjects receiving the trial drug themselves and are not related to this congenital cataract NISS.

Rash-Related Adverse Events

An increased incidence of rash related safety events was initially noted in the development of ELX/TEZ/IVA, and rash reactions are included in Section 6 of the USPI. [Table 47](#) reviews the AEs related to rash or other skin events in the pooled phase 3 safety database.

Table 47. In-Depth AESI Assessment for Rash Events During the Treatment Period (Pooled SAS), Trials 102 and 103

Adverse Event	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 n (%)	N=480 n (%)
PT related to AESI	38 (7.7)	53 (11.0)
Dermatitis	0	2 (0.4)
Dermatitis allergic	1 (0.2)	1 (0.2)
Drug eruption	0	2 (0.4)
Drug hypersensitivity	0	1 (0.2)
Lichen planus	1 (0.2)	0
Perioral dermatitis	1 (0.2)	0
Periorbital dermatitis	1 (0.2)	0
Pityriasis rosea	0	1 (0.2)
Rash	22 (4.5)	37 (7.7)
Rash erythematous	1 (0.2)	2 (0.4)
Rash follicular	0	1 (0.2)
Rash maculo-papular	0	2 (0.4)
Rash papular	2 (0.4)	0
Rash pruritic	0	1 (0.2)
Rash pustular	1 (0.2)	0
Rash vesicular	1 (0.2)	0
Urticaria	7 (1.4)	5 (1.0)

Adverse Event	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=491 n (%)	N=480 n (%)
Maximum severity		
Mild	27 (5.5)	39 (8.1)
Moderate	11 (2.2)	13 (2.7)
Severe	0	1 (0.2)
Resulting in discontinuation	0	1 (0.2)
Relatedness determined by investigator	17 (3.5)	21 (4.4)

Source: Clinical reviewer and clinical data scientist. Software: R. adae.xpt.

Abbreviations: AESI, adverse events of special interest; D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

Overall, the majority of rash-related AEs reported were mild and there were no SAEs or life-threatening AEs related to rashes in either treatment arm. Only one severe event was reported in a subject who was a 28-year-old White female with CF and a history of contact dermatitis and multiple drug hypersensitivity events, previously taking ELX/TEZ/IVA. The subject was randomized to the VNZ/TEZ/D-IVA treatment arm and reported a rash described as maculopapular on Day 8. The following day, the rash had spread to include the feet, legs, chest, back, arm, and face. Symptoms progressed to include dysphonia and the subject described a raspy voice, 'itchy' sensation in her throat, and lip swelling. She was then hospitalized for the SAE of hypersensitivity. This AEs was likely related to the trial drug but appears consistent with the known safety profile of ELX/TEZ/IVA.

There is a numerical increase in rash and other skin-related AEs in the VNZ/TEZ/D-IVA treatment arm compared the ELX/TEZ/IVA arm (risk difference [95% CI]: 3.3% [-0.4,7.1]). It is difficult to assess this safety signal in the absence of a placebo arm and in a population generally tolerant of ELX/TEZ/IVA. The imbalance in rash events between the treatment arms was most pronounced in the first 4-6 weeks of therapy. At Day 40 there were 29 subjects (6.0%) with rash events reported in the VNZ/TEZ/D-IVA arm compared to 10 subjects (2.0%) in the ELX/TEZ/IVA arm (data not shown).

The clinical significance of the increased number of events or timing of events in the VNZ/TEZ/D-IVA treatment arm is not clear. However, the data suggest that VNZ/TEZ/D-IVA conveys at least a similar risk to ELX/TEZ/IVA for rashes and support inclusion of relevant data in Section 6 of the VNZ/TEZ/D-IVA USPI.

Hypoglycemic Events

Hypoglycemic events were noted in the phase 2 program for VNZ/TEZ/D-IVA and designated as an AESI for the phase 3 program. [Table 48](#) reviews the in-depth analysis for hypoglycemic events.

Table 48. In-Depth AESI Assessment for Hypoglycemia Events During the Treatment Period (Pooled SAS), Trial 102 and 103,

	ELX/TEZ/IVA N=491	VNZ/TEZ/D-IVA N=480
Adverse Event	n (%)	n (%)
PT related to AESI	18 (3.7)	8 (1.7)
Blood glucose decreased	6 (1.2)	1 (0.2)
Hypoglycemia	13 (2.6)	7 (1.5)
Maximum severity		
Mild	9 (1.8)	5 (1.0)
Moderate	9 (1.8)	2 (0.4)
Severe	0	1 (0.2)
Resulting in discontinuation	0	0
Relatedness determined by the investigator	8 (1.6)	2 (0.4)

Source: Clinical reviewer and clinical data scientist. Software: R. adae.xpt.

Abbreviations: AESI, adverse events of special interest; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

The overall rates of AEs related to hypoglycemia events were low; however, they were numerically higher in the ELX/TEZ/IVA treatment arm (18, 3.7%) compared to the VNZ/TEZ/D-IVA treatment arm (8, 1.7%). The majority of AEs were mild to moderate, with one subject experiencing a severe AE in the VNZ/TEZ/D-IVA treatment arm.

In the targeted review of the blood glucose laboratory analyses (data not shown), the rates of hypoglycemia <70 mg/dL were higher in the VNZ/TEZ/D-IVA treatment arm compared to the ELX/TEZ/IVA arm (168, 35.0% versus 151, 30.8% respectively); however, the rates of more severe hypoglycemia (<54 and <40 mg/dL) were rare and balanced between treatment arms.

The rates of fasting hyperglycemia ranging from 100 to 125 mg/dL were also elevated in the VNZ/TEZ/D-IVA arm (91, 32.4%) compared to the ELX/TEZ/IVA arm (72, 23.9%), although this was in contrast to the rates of random (i.e., not fasting) hyperglycemia (≥200 mg/dL), that were more elevated in the ELX/TEZ/IVA arm (70, 16.5%) compared to the VNZ/TEZ/D-IVA arm (70, 16.5%).

The clinical implication of the imbalances of serum glucose levels is unclear, particularly with a small overall incidence of related AEs. Overall, these data do not suggest an overt safety concern at this time.

Neuropsychiatric Events

Baseline mental health disorders, including depression and anxiety, are elevated in patients with CF compared to their aged-matched peers. Some published data suggest that medications that affect CFTR processing or function can have a beneficial impact on the mental health of CF patients on a population level ([Piehler et al. 2024](#)). However, there have been postmarketing safety reports suggesting that there may be increased rates of depression, including suicidality, in some CF patients taking these medications. Psychiatric events are also currently being evaluated as a postmarketing safety signal (SSID #1005257), and neuropsychiatric events were included as an AESI for the VNZ/TEZ/D-IVA development program to further evaluate this safety concern. The in-depth assessment of neuropsychiatric AEs is included in [Table 49](#).

Table 49. In-Depth AESI Assessment for Neuropsychiatric Events During the Treatment Period (Pooled SAS), Trials 102 and 103,

	ELX/TEZ/IVA N=491 n (%)	VNZ/TEZ/D-IVA N=480 n (%)
Adverse Event		
PT related to AESI	59 (12.0)	55 (11.5)
Adjustment disorder with anxiety	1 (0.2)	0
Adjustment disorder with depressed mood	1 (0.2)	0
Anger	2 (0.4)	1 (0.2)
Anhedonia	1 (0.2)	0
Anxiety	10 (2.0)	21 (4.4)
Attention deficit hyperactivity disorder	4 (0.8)	1 (0.2)
Behavior disorder	1 (0.2)	0
Brain fog	0	1 (0.2)
Depressed mood	7 (1.4)	4 (0.8)
Depression	10 (2.0)	14 (2.9)
Depression suicidal	1 (0.2)	0
Depressive symptom	3 (0.6)	0
Disturbance in attention	3 (0.6)	0
Generalized anxiety disorder	1 (0.2)	0
Initial insomnia	1 (0.2)	3 (0.6)
Insomnia	22 (4.5)	15 (3.1)
Irritability	2 (0.4)	1 (0.2)
Major depression	0	1 (0.2)
Memory impairment	1 (0.2)	1 (0.2)
Mental fatigue	1 (0.2)	2 (0.4)
Middle insomnia	1 (0.2)	2 (0.4)
Mixed anxiety and depressive disorder	1 (0.2)	0
Physical assault	0	1 (0.2)
Suicidal ideation	4 (0.8)	2 (0.4)
Maximum severity		
Mild	26 (5.3)	28 (5.8)
Moderate	27 (5.5)	23 (4.8)
Severe	6 (1.2)	4 (0.8)
SAE	4 (0.8)	4 (0.8)
Resulting in discontinuation	2 (0.4)	3 (0.6)
Relatedness determined by investigator	32 (6.5)	22 (4.6)

Source: Clinical reviewer and clinical data scientist. Software: R. adae.xpt.

Abbreviations: AESI, adverse events of special interest; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

We note that the AE of anxiety occurred in a greater proportion of subjects in the VNZ/TEZ/IVA treatment arm (21, 4.4%) compared to ELX/TEZ/IVA treatment arm (10, 2.0%), and the 95% CI of the risk difference excluded the null (risk difference [95% CI]: 2.3 [0.1, 4.8]). However, there were similar rates of overall neuropsychiatric events in both treatment arms. The majority of AEs were mild to moderate; however, there were severe events, SAEs, and AEs leading to discontinuation in both treatment arms. There were no deaths or life-threatening events related to neuropsychiatric events reported.

The narratives provided by the Applicant were reviewed and include episodes of depression and suicidality in both treatment arms. Most cases had confounding factors, which, in addition to the lack of a placebo arm, make it difficult to assess causality. These data do not suggest that VNZ/TEZ/D-IVA conveys an increased overall risk for neuropsychiatric events compared to

ELX/TEZ/IVA. Overall, the relationship between these medications and neuropsychiatric events remains incompletely described. This safety signal will be further evaluated in the ongoing NISS (SSID 1005257). Currently, the data do not support inclusion in the USPI.

7.6.1.7. Review of Postmarketing Safety Signals in Similar Drug Products

The phase 3 safety data were also reviewed for signals from ongoing post marketing safety reviews or previous reviews for which labeling changes were issued (outlined in Section 7.2). Note that two open NISS review topics, hepatotoxicity and neuropsychiatric events, were designated as AESIs and are reviewed in more detail in the above Section 7.6.1.6.

Hypersensitivity Reactions (SSID 1004722)

A Warning and Precaution related to hypersensitivity reactions, including anaphylaxis, was added to the USPI for ELX/TEZ/IVA and other medications that contain one or more of its components as result of a safety labeling change issued on August 3, 2023. An evaluation of AEs based on PTs, SOC, FDA medical queries (broad and narrow) was performed. There were no overt cases of anaphylaxis or angioedema reported; however, there were multiple AEs related to hypersensitivity events in both treatment arms, including the case described in Section 7.6.1.6. We recommend that the Warning and Precaution related to hypersensitivity reactions be included in the USPI for VNZ/TEZ/D-IVA based on these hypersensitivity AEs noted, the shared or similar APIs in both FDCs, and the overall similarity in safety profiles between VNZ/TEZ/D-IVA and ELX/TEZ/IVA.

Increased Intracranial Pressure Disorders (SSID 1005337)

A NISS was opened to assess for the presence of increased intracranial pressure disorders on May 16, 2024, and remained under evaluation at the time of this review. To assess this risk in the VNZ/TEZ/D-IVA phase 3 safety database, a review of potential PTs related to increased intracranial pressure disorders included in the nervous system disorders, vascular disorders, and eye disorder SOCs was conducted (data not shown). There did not appear to be any PTs directly related to increased intracranial pressure occurring in either treatment arm in the phase 3 development program for VNZ/TEZ/D-IVA. This signal will continue to be monitored via routine postmarket pharmacovigilance unless otherwise indicated by results of the ongoing NISS.

7.6.1.8. Laboratory Findings, Pooled Analyses, Trials 102 and 103

Analyses of clinical laboratory results including chemistry, hematologic parameters, and total cholesterol, consisting of changes in mean values over time, changes in individual subjects over time, and potentially clinically significant values were conducted. There were no clinically meaningful trends or mean changes from baseline observed. Postbaseline newly occurring or worsening potentially clinically significant values for hematology and clinical chemistry were infrequent and similar between the treatment arms.

7.6.1.9. Vital Signs, Pooled Analyses, Trials 102 and 103

No clinically significant changes in mean vital sign values (systolic and diastolic blood pressure, heart rate, and respiratory rate) over time were identified in the pooled phase 3 safety database. We note an increase rate of diastolic blood pressure readings below 60 mmHg in the VNZ/TEZ/D-IVA treatment arm (141, 29.4%) compared to the ELX/TEZ/IVA treatment arm (111, 22.6%); however, there was a similar proportion of subjects with systolic blood pressure readings <90 mmHg. These readings do not appear clinically significant as there were very low rates of hypotension related AEs reported during the treatment period.

Increased blood pressure is included in Section 6 of the current USPI for ELX/TEZ/IVA. Review of maximum blood pressure readings and AEs related to hypertension did not reveal a significant difference between the treatment arms; however, 90 (18.8%) of subjects treated with VNZ/TEZ/D-IVA had a systolic blood pressure reading over 140 mm Hg compared to 90 (18.3%) in the ELX/TEZ/IVA arm. We recommend that increased blood pressure be included in Section 6 of the USPI of VNZ/TEZ/D-IVA.

Overall, no significant new safety concerns were identified in the analysis of vital signs.

7.6.1.10. Subgroups, Pooled Analyses, Trials 102 and 103

A safety analysis by key demographic subgroup, including age, gender at birth, and region (U.S. and ex-U.S. sites), and *CFTR* genotype was performed ([Table 50](#)). There were no significant differences noted between subgroups.

Table 50. Overview of AEs During the Treatment Period Based on Demographic Subgroup (Pooled SAS), Trials 102 and 103

Demographic	ELX/TEZ/IVA N=491		VNZ/TEZ/D-IVA N=480	
	N in Subgroup	n With AE (%)	N in Subgroup	n With AE (%)
Sex				
Female	228	215 (94.3)	215	201 (93.5)
Male	263	254 (96.6)	265	258 (97.4)
Age group, years				
<18	69	63 (91.3)	67	60 (89.6)
≥18	422	406 (96.2)	413	399 (96.6)
Is in United States				
United States	177	173 (97.7)	189	183 (96.8)
Non-United States	314	296 (94.3)	291	276 (94.8)
<i>CFTR</i> genotype				
F/MF ^a	202	196 (97.0)	196	185 (94.4)
F/F ^b	224	212 (94.6)	222	212 (95.5)
F/G ^b	21	19 (90.5)	19	19 (100)
F/RF ^b	22	20 (90.9)	23	23 (100)
TCR/non-F ^b	22	21 (95.5)	20	20 (100)

Source: Clinical reviewer and clinical data scientist. Software: R. adae.xpt.

^a F/MF subgroup consists of all of Trial 102

^b Data from Trial 103

Abbreviations: AE, adverse event; *CFTR*, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; ELX, elxacaftor; F, *F508del* variant; G, gating variant; IVA, ivacaftor; MF, minimal function variant; N, number of subjects in treatment arm or subgroup; n, number of subjects in subgroup with event; RF, residual function variant; SAS, safety analysis set; TCR, triple combination responsive; TEZ, tezacaftor; VNZ, vanzacaftor

Combined, the F/G, F/RF, and TCR/non-F subgroups accounted for only 13.1% of the overall phase 3 population. Within the limitations of the small sample size, the review of *CFTR* genotype subgroups not including F/F and F/MF, appeared consistent with the overall population. Additional safety analyses of the adolescent subgroup are included in Section [17.1](#).

7.6.2. Safety Results, Trial 105

7.6.2.1. Overview of Adverse Events Summary, Trial 105

The overview of AEs occurring in Trial 105 Cohort B1 is provided in [Table 51](#). Similar to the adolescent and adult population, over 95% of subjects experienced an AE, which is consistent with other development programs for this population.

Table 51. Overview of Adverse Events During the Treatment Period (SAS), Trial 105 (Cohort B1)

	VNZ/TEZ/D-IVA
	N=78
Subjects With Adverse Events	n (%)
Subjects with any AE	75 (96.2)
Subjects with AE by maximum severity	
Grade 1/Mild	39 (50.0)
Grade 2/Moderate	36 (46.2)
Grade 3/Severe	0
Grade 4/Life-threatening	0
Grade 5/Death	0
Subjects with AE	
Leading to discontinuation	1 (1.3)
Leading to drug interruption	1 (1.3)
Subjects with related AE	23 (29.5)
Subjects with SAE	6 (7.7)
Subjects with AE leading to death	0

Source: Clinical reviewer. Software: JMP v15.0, OCS Analysis Studio. adae.xpt using SAFFL(Y), TRTEMFL(Y), AREL, ATOXGR, AESER, AEACON. TRT01A.

Abbreviations: AE, adverse event; D-IVA, deutivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

Overall, the majority of AEs were mild to moderate. SAEs and AEs leading to trial drug discontinuation or interruption are reviewed below (Section [7.6.2.3](#) and Section [7.6.2.4](#) respectively). An additional review of the AEs occurring during the run-in or follow-up periods is included in Section [17](#).

7.6.2.2. Deaths, Trial 105

There were no deaths reported in Trial 105.

7.6.2.3. Serious Adverse Events, Trial 105

The SAEs occurring in Cohort B1 of Trial 105 are reviewed in [Table 52](#).

Table 52. SAEs During the Treatment Period by PT (SAS), Trial 105 (Cohort B1)

VNZ/TEZ/D-IVA	
N=78	
SAE by PT	n (%)
Subjects with any SAE	6 (7.7)
Infective pulmonary exacerbation of CF	2 (2.6)
Adenovirus infection	1 (1.3)
Constipation	1 (1.3)
Cough	1 (1.3)
Failure to thrive	1 (1.3)
Pulmonary function test decreased	1 (1.3)

Source: Clinical reviewer and clinical data scientist. Software: JMP v15.0. adae.xpt using SAS(Y), TRTEMFL(Y), AESER(Y), AEDECOD.

Abbreviations: CF, cystic fibrosis; D-IVA, deutivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

The assessment of SAEs is limited by the open-label, single-arm design of the trial. Overall, the SAEs reported were consistent with what would be expected in a pediatric CF population. The SAE narratives were also reviewed, and, overall, there were no new safety concerns noted in the review of the SAE safety data.

7.6.2.4. Adverse Events Leading to Treatment Discontinuation, Trial 105

Only one subject discontinued treatment due to an AE (cough and fatigue) and one subject had treatment interrupted due to an AE (seizure). There were no new safety concerns noted based on subjects who discontinued or interrupted treatment.

7.6.2.5. Adverse Events, Trial 105

The summary of AEs occurring in $\geq 5\%$ of subjects in Cohort B1 of Trial 105 is reviewed in [Table 53](#).

Table 53. AEs by PT Occurring in $\geq 5\%$ Subjects (SAS), Trial 105 (Cohort B1)

VNZ/TEZ/D-IVA	
N=78	
AE by PT	n (%)
Subjects with AE	75 (96.2)
Cough	36 (46.2)
Pyrexia	16 (20.5)
Headache	14 (17.9)
Infective pulmonary exacerbation of CF	13 (16.7)
Oropharyngeal pain	13 (16.7)
Abdominal pain	9 (11.5)
Nasal congestion	9 (11.5)
Rhinorrhea	9 (11.5)
Vomiting	8 (10.3)
Fatigue	7 (9.0)
Pharyngitis streptococcal	7 (9.0)
Rhinitis	7 (9.0)
Abdominal pain upper	6 (7.7)
Diarrhea	6 (7.7)

	VNZ/TEZ/D-IVA
	N=78
AE by PT	n (%)
Neutrophil count decreased	6 (7.7)
Productive cough	6 (7.7)
Upper respiratory tract infection	6 (7.7)
ALT increased	4 (5.1)
Ear infection	4 (5.1)
Rash	4 (5.1)
White blood cell count decreased	4 (5.1)

Source: Clinical reviewer. Software: OCS Analysis Studio. adae.xpt using SAS(Y), TRTEMFL(Y), AEDECOD.

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; CF, cystic fibrosis; D-IVA, deutivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

The AEs reported were consistent with a pediatric CF population. The most common AE reported was cough, occurring in 36 (46.2%) subjects. The lack of a placebo arm limits the analysis of these data; however, cough may be related to the subjects underlying CF. Notably, unlike the adolescent and adult population, influenza was not a commonly reported AE – only 1 (1.3%) subject had an AE of influenza type B and 1 (1.3%) other subject reported an AE of influenza-like illness. The clinical significance of this is unclear.

Overall, the review of AEs occurring in the pediatric population did not reveal any new safety concerns or identify risks unique to this age cohort.

7.6.2.6. Adverse Events of Special Interest, Trial 105

The AESIs evaluated in Trial 105 were the same as the adolescent and adult phase 3 trials and included LFT abnormalities, creatine kinase elevations, rash, cataracts, hypoglycemic events, and neuropsychiatric events.

Hepatobiliary-Related Labs and Adverse Events

[Table 54](#) reviews the maximum liver function test elevations occurring during the treatment period of Trial 105, Cohort B1.

Table 54. Maximum Liver Function Test Elevation From Baseline During the Treatment Period (SAS), Trial 105 (Cohort B1)

	VNZ/TEZ/D-IVA
	N=78
Post Baseline LFT Threshold Criteria	n (%)
ALT (U/L), n (%)	
>3x to ≤5x ULN	2 (2.6)
>5x to ≤8x ULN	1 (1.3)
>8x to ≤20x ULN	0
>20x ULN	0
AST (U/L), n (%)	
>3x to ≤5x ULN	0
>5x to ≤8x ULN	0
>8x to ≤20x ULN	0
>20x ULN	0

	VNZ/TEZ/D-IVA N=78 n (%)
Post Baseline LFT Threshold Criteria	
GGT (U/L), n (%)	
>2.5x to ≤5x ULN	1 (1.3)
>5x to ≤20x ULN	0
Alkaline phosphatase (U/L), n (%)	
>1.5x to ≤2.5x ULN	4 (5.1)
>2.5x to ≤5x ULN	0
>5x to ≤20x ULN	0
>20x ULN	0

Source: Clinical reviewer. Software: JMP v15.0. adlb.xpt using SAFFL(Y), ONTRTFL(Y), PARAMCD, AVALC, MCRIT1, ANL02FL. Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-IVA, deutivacaftor; ELX, elxacaftor; GGT, gamma glutamyl transferase; IVA, ivacaftor; LFT, liver function test; N, number of subjects in treatment arm; n, number of subjects in subset; SAS, safety analysis set; TEZ, tezacaftor; ULN, upper limit of normal; VNZ, vanzacaftor; x, times

Elevations in ALT were noted during the treatment period of Cohort B1 in Trial 105 with one (1.3%) subject with an elevation of greater than 5x the ULN. There were no subjects with elevations in AST greater than 3x the ULN or elevations in total bilirubin greater than 1.5x the ULN.

As reviewed in [Table 55](#), four (5.1%) subjects in Cohort B1 of Trial 105 had AEs related to transaminase elevations.

Table 55. In-Depth AESI Assessment for Elevated Transaminase During the Treatment Period, Grouped Query (SAS), Trial 105 (Cohort B1)

	VNZ/TEZ/D-IVA N=78 n (%)
Elevated Transaminase Assessment	
PT related to AESI	4 (5.1)
Alanine aminotransferase increased	4 (5.1)
Aspartate aminotransferase increased	2 (2.6)
Maximum severity	
Mild	3 (3.8)
Moderate	1 (1.3)
Severe	0
Resulting in discontinuation	0
Relatedness	4 (5.1)

Source: Clinical reviewer and clinical data scientist. Software: R. adae.xpt. Abbreviations: AESI, adverse events of special interest; D-IVA, deutivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

Additional discussion regarding hepatotoxicity is included in Section [7.7.2](#).

Creatine Kinase Elevations

There were two (2.6%) subjects with the AE of blood creatine phosphokinase increased. Both AEs were mild in severity and deemed related to the treatment by the investigator. On review of laboratory analyses, one (1.3%) subject had a creatine phosphokinase elevation >10 x ULN.

Cataract Adverse Events

There was one subject (1.3%) with an AE of cortical cataract that was considered mild in severity, not clinically significant, and considered possibly related to the treatment by the investigator.

Rash-Related Adverse Events

There were four (5.1%) subjects that experienced a rash event during the treatment period of Cohort B1 of Trial 105. All were assessed as mild in severity.

Hypoglycemic Events

There were no AEs reported for hypoglycemia in Cohort B1 of Trial 105. On review of the clinical laboratory results, 23 (29.5%) subjects had a blood glucose result of <70 mg/dL, although only 1 (1.3%) subject had results <54 mg/dL. The clinical significance of this is unclear without a comparator treatment arm.

Neuropsychiatric Events

There were four (5.1%) subjects that experienced neuropsychiatric AEs that included aggression, anxiety, and initial insomnia. All were assessed as mild, with none resulting in treatment discontinuation or interruption.

Review of the AESIs that occurred in Cohort B1 of Trial 105 did not reveal any new safety concerns.

7.6.2.7. Laboratory Findings, Trial 105

Analysis of clinical laboratory results including chemistry, hematologic parameters, and total cholesterol, consisting of changes in mean values over time, changes in individual subjects over time, and potentially significant values were conducted. There were no clinically meaningful trends or mean changes from baseline were observed. The interpretation of these data is limited by the lack of a comparator, but, overall, the assessment of laboratory findings was reassuring and did not reveal any new safety signals.

7.6.2.8. Vital-Sign Analyses, Trial 105

There were no clinically significant changes in mean vital sign values (systolic and diastolic blood pressure, heart rate, respiratory rate, and temperature) over time that occurred during the treatment period for Cohort B1 of Trial 105. Although limited by the lack of a comparator arm, no significant safety concerns were identified.

7.6.2.9. Subgroup Analyses, Trial 105

A safety analysis by key demographic subgroup, including gender at birth and region (U.S. and ex-U.S. sites) did not reveal any clinically significant differences between subgroups.

An additional subgroup analysis by subject's weight-based dosing cohort at baseline (<40 mg and ≥40 kg) was limited by sample size (baseline weight <40 kg n=70, baseline weight ≥40 kg n=8), but did not reveal a clinically significant difference in the rates of AEs.

7.6.2.10. Pediatric (6 Through 11 Years of Age) Safety Summary

The safety results from Trial 105 did not reveal new safety signals or identify imbalances in AEs to suggest differential risks for children compared to adolescents or adults. However, given the single arm design of the trial and the small sample size, interpretation of these results is limited. Safety for the 6-to-11-year-old CF population was, therefore, extrapolated from the adolescent and adult populations enrolled in the phase 3 development program. Treatment with VNZ/TEZ/D-IVA leads to comparable systemic exposures between populations, and there are sufficient similarities in disease process across age groups to support extrapolation. Such an approach is consistent with the development of related products (e.g., ELX/TEZ/IVA) for pediatric CF patients.

7.7. Key Safety Review Issues

7.7.1. Assessment of Safety in Subjects Intolerant of ELX/TEZ/IVA

Issue

Alternative therapies for CF patients who are unable to tolerate ELX/TEZ/IVA or a medication that contains its components is an area of unmet need for CF therapeutic development. However, to maintain clinical equipoise, the phase 3 development program for VNZ/TEZ/D-IVA required a noninferiority trial design that necessitated the exclusion of subjects intolerant of ELX/TEZ/IVA. The available data do not assess safety and tolerability in the ELX/TEZ/IVA-intolerant population.

Background

ELX/TEZ/IVA and other medications that affect CFTR processing or function have contributed to many clinical benefits in eligible CF patients, and over 80% of the U.S. CF population are prescribed one of these treatments. However, there remains an unmet medical need for alternative CF therapies for patients who are not currently eligible based on *CFTR* genotype as well as for patients who are intolerant of, or with persistent symptoms despite treatment with, the currently approved medications. The CF Foundation estimates that approximately 3,000 patients, almost 10% of the U.S. CF population, are currently genotype eligible but not prescribed one of these therapies ([CFF 2023](#)). Although many reasons contribute to this fact, intolerance to therapy is a primary reason for discontinuation of treatment in these patients.

The Applicant chose a noninferiority trial design with ELX/TEZ/IVA as the active control for the phase 3 development program of VNZ/TEZ/D-IVA. Given the magnitude of treatment effect and pervasive use of ELX/TEZ/IVA as the standard of care, the Division agreed to this design

(reviewed in more detail in Section 6.2.2.1). The noninferiority design necessitated that subjects with a history of intolerance to ELX/TEZ/IVA be excluded. The disadvantages of this approach are the inability to characterize the safety and tolerability in the ELX/TEZ/IVA-intolerant population and the limited generalizability of the observed results.

Assessment

In general, the safety of VNZ/TEZ/D-IVA and ELX/TEZ/IVA appear comparable. As reviewed in Section 7.6.1, there were similar rates of overall AEs, severe AEs, and SAEs. The most common AEs were also similar between the treatment arms, as were the overall rates of AESIs. There were no new safety signals identified. These findings are reassuring since we anticipate that VNZ/TEZ/D-IVA has the potential to replace ELX/TEZ/IVA as the standard of care. However, these similarities in safety profile also suggest that patients intolerant of ELX/TEZ/IVA may experience similar adverse reactions to VNZ/TEZ/D-IVA.

To further characterize the safety profile of VNZ/TEZ/D-IVA, we performed additional subgroup analyses on subjects that had not previously been prescribed ELX/TEZ/IVA or a medication containing its components prior to enrollment. We note that this analysis aims to characterize the safety profile in treatment naïve subjects but will not characterize the safety profile in ELX/TEZ/IVA intolerant patients.

The analysis of the subgroup of subjects not previously prescribed ELX/TEZ/IVA or its components is very limited by sample size, as this subgroup only accounted for 15% of total subjects. In addition, all subjects received ELX/TEZ/IVA for four weeks during the run-in period prior to randomization and were, therefore, not entirely treatment naïve upon starting the treatment period.

Subjects in this subgroup had a baseline mean ppFEV₁ of 71.0% and a mean baseline SwCl of 52.2mmol/L. They were more likely to have a non-*F508del* TCR variant (20% vs 1.8%) and less likely to have F/F or F/MF variants compared to non-naïve subjects. The safety results in this group are summarized in Table 56.

Table 56. Overview of AEs in Subjects Not Previously Prescribed CFTR-Directed Background Medication^a (Pooled SAS), Trials 102 and 103

	Run-in Period (4w)	Treatment Period (52w)	
	ELX/TEZ/IVA N=145 n (%)	ELX/TEZ/IVA N=64 n (%)	VNZ/TEZ/D-IVA N=71 n (%)
Subjects with Adverse Events			
Subjects with any AE	74 (51.0)	55 (85.9)	60 (84.5)
Subjects with AE			
Leading to discontinuation	5 (3.4)	4 (6.2)	2 (2.8)
Leading to drug interruption	1 (0.7)	4 (6.2)	1 (1.4)

	Run-in Period (4w)	Treatment Period (52w)	
	ELX/TEZ/IVA N=145 n (%)	ELX/TEZ/IVA N=64 n (%)	VNZ/TEZ/D-IVA N=71 n (%)
Subjects with Adverse Events			
Subjects with SAE	2 (1.4)	10 (15.6)	6 (8.5)
Most common AEs reported by PT			
Upper respiratory tract infection	0	13 (20.3)	21 (29.6)
COVID-19	1 (0.7)	28 (28.1)	18 (25.4)
Nasopharyngitis	2 (1.4)	12 (18.8)	15 (21.1)
Cough	13 (9.0)	5 (7.8)	13 (18.3)
Infective pulmonary exacerbation of CF	1 (0.7)	15 (23.4)	12 (16.9)
Headache	14 (9.7)	4 (6.2)	11 (15.5)
Diarrhea	11 (7.6)	6 (9.4)	9 (12.7)
ALT increased	1 (0.7)	5 (7.8)	8 (11.3)
AST increased	1 (0.7)	7 (10.9)	8 (11.3)
Pyrexia	1 (0.7)	5 (7.8)	8 (11.3)
Rash	12 (8.3)	4 (6.2)	8 (11.3)
Increased blood creatine phosphokinase	0	9 (14.1)	6 (8.5)

Source: Clinical reviewer. Software: JMP v15.0 and OCS Analysis Studio. adae.xpt.

^a Background medications included ELX/TEZ/IVA, TEZ/IVA, LUM/IVA, or IVA monotherapy

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; COVID-19, SARS CoV2 2019; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; LUM, lumacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; PT, preferred term; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor; w, weeks

In the run-in period, 74 (51%) of subjects in this subgroup experienced an AE over the 4 weeks with two (1.4%) subjects experiencing SAEs, one infective pulmonary exacerbation of CF and one rash. This rate is higher than the rate of AEs in run-in period in the overall population (395, 38.3%) reviewed in Section 17.2. The clinical significance of this is unclear given the limitations of the sample size and duration under observation. The most common AEs reported during the run-in period in treatment naïve subjects were consistent with the known safety profile of ELX/TEZ/IVA and similar to the AEs reported during the treatment period, which included headache, cough, and rash. Infective pulmonary exacerbation of CF was only reported in one (0.7%) subject, which is likely attributable to the short treatment duration of the run-in period. AEs leading to discontinuation in the run-in occurred in five (3.4%) subjects and included COVID-19, influenza, and rash. One (0.7%) additional subject had trial treatment interrupted due to rash.

In the treatment period, the overall rates of AEs were similar between arms—VNZ/TEZ/D-IVA 60 (84.5%) subjects and ELX/TEZ/IVA 55 (85.9%) subjects. We note the proportion of subjects with AEs is lower than the overall population – 459 (95.6%) versus 469 (95.5%) subjects in VNZ/TEZ/D-IVA and ELX/TEZ/IVA, respectively (see Section 7.6.1.5). The clinical significance of this difference is unclear but may be related to underlying differences in baseline CF disease.

There were more subjects experiencing AEs leading to discontinuation in the ELX/TEZ/IVA arm (4, 6.2%) compared to the VNZ/TEZ/D-IVA arm (2, 2.8%). The AEs that led to discontinuation were all related to LFT abnormalities except for one (1.6%) subject in the ELX/TEZ/IVA treatment arm. The clinical implication of this is unclear, since in the overall population, AEs related to LFT abnormalities and leading to treatment discontinuation were higher in the VNZ/TEZ/D-IVA arm. In addition, the rates of LFT elevations in the subgroup of treatment

naïve subjects were higher in the VNZ/TEZ/D-IVA treatment arm compared to the ELX/TEZ/IVA treatment arm (data not shown).

Overall, our assessment of the subgroup of subjects not previously prescribed CFTR-directed therapies supports the conclusion that VNZ/TEZ/D-IVA conveys a similar safety risk profile to ELX/TEZ/IVA.

Conclusion

The available data support that the risks of VNZ/TEZ/D-IVA and ELX/TEZ/IVA are comparable; however, there are no data to characterize the safety of VNZ/TEZ/D-IVA in patients intolerant of ELX/TEZ/IVA or medications that contain its components. The Division recommends labeling strategies to address this uncertainty. We do not recommend a limitation of use since the potential benefit of VNZ/TEZ/D-IVA in this population is substantial. We expect that additional characterization of the safety comparability of these products may only be clarified in the postmarket setting. To guide patients and providers on the risks of VNZ/TEZ/D-IVA in the ELX/TEZ/IVA-intolerant population, we will include a Warning and Precaution that clearly describes the absence of data in patients intolerant of ELX/TEZ/IVA and guides prescribers to weigh benefits and risks before initiating VNZ/TEZ/D-IVA in this population. In addition, as discussed throughout this review, the serious and well-characterized risks of ELX/TEZ/IVA will be retained in the USPI for VNZ/TEZ/D-IVA.

7.7.2. Risk for Hepatotoxicity With VNZ / TEZ / D-IVA

Issue

Transaminase elevations are a well described adverse reaction related to all approved medications that affect CFTR processing or function and have been included as a Warning and Precaution in the USPI since the initial approval of IVA in 2012 ([Vertex Pharmaceuticals 2012](#)). Liver toxicity findings were also noted in the VNZ toxicology program (Section [7.1](#)) and previously documented in the IVA toxicology program (NDA 203188). The risk for potential hepatotoxicity related to VNZ/TEZ/D-IVA was a major focus of the safety review.

Background

The hepatotoxicity risks listed on the USPI for ELX/TEZ/IVA had previously included elevated liver transaminases with and without elevated bilirubin as well as liver failure leading to transplantation in one subject with underlying cirrhosis and portal hypertension. As discussed in Section [7.6.1.6](#), this warning was elevated to a Boxed Warning for DILI and liver failure as part of a recent safety labeling change, dated October 22, 2024. In addition, a NISS (SSID 1005364) was opened to include queries for liver injury data across all approved products containing at least one component of ELX/TEZ/IVA. This NISS is in the action phase pending finalization at the time of this review.

Assessment

To assess the hepatotoxicity risk of VNZ/TEZ/D-IVA, LFT abnormalities were pre-specified as an AESI in the phase 3 development program, and results are reviewed in detail in Section 7.6.1.6.

The rates of transaminase laboratory elevations and AEs related to transaminases were higher in the VNZ/TEZ/D-IVA treatment arm than in the ELX/TEZ/IVA treatment arm (Table 57).

Table 57. Maximum Transaminase Elevation From Baseline During the Treatment Period (Pooled SAS), Trials 102 and 103

	ELX/TEZ/IVA N=491 n (%)	VNZ/TEZ/D-IVA N=480 n (%)
Maximum ALT or AST Elevation		
>3x ULN	15 (3.1)	29 (6.0)
>5x ULN	6 (1.2)	12 (2.5)
>8x ULN	1 (0.2)	6 (1.3)

Source: Clinical reviewer. Software: JMP v15.0. adlb.xpt using SAFFL(Y), ONTRTFL(Y), PARAMCD, AVALC, MCRIT1
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-IVA, deutivacaftor; ELX, elxacaftor;
IVA, ivacaftor; N, number of subjects in treatment arm; n, number of subjects in subset; SAS, safety analysis set; TEZ, tezacaftor;
ULN, upper limit of normal; VNZ, vanzacaftor; x, times

Although it is difficult to interpret this difference given that over 85% of the population had been treated with ELX/TEZ/IVA or its components prior to enrollment, these data suggest that VNZ/TEZ/D-IVA conveys a similar risk of liver injury to ELX/TEZ/IVA.

We further assessed the rates of AST and ALT elevations in subjects that were not previously prescribed ELX/TEZ/IVA or its components (the subgroup described in Section 7.7.1). Elevations in AST or ALT 3 to 5 x ULN were noted in four (5.8%) subjects in the VNZ/TEZ/D-IVA treatment arm compared to one (1.6%) subject in the ELX/TEZ/IVA treatment arm. In addition, one (1.5%) subject in the VNZ/TEZ/D-IVA had an AST or ALT elevation greater than 8x the ULN compared to no subjects treated with ELX/TEZ/IVA. Overall, these data further suggest that VNZ/TEZ/D-IVA conveys at least a similar risk of liver injury to ELX/TEZ/IVA.

On review of the individual cases, there were five cases of nonjaundiced DILI assessed as probably or possibly related to VNZ/TEZ/D-IVA, including a case in a healthy volunteer. Refer to DHN consult dated December 19, 2024, for details (DARRTS ID: 5499379). There were no cases of Hy’s law or documented cases of liver failure attributed to VNZ/TEZ/D-IVA. However, the available phase 3 safety database of VNZ/TEZ/D-IVA is limited to 480 subjects treated for 52 weeks. Although this scope is sufficient to determine the overall safety profile of VNZ/TEZ/D-IVA for chronic use, it is unlikely to capture rare events, particularly when compared to the estimated cumulative exposure of ELX/TEZ/IVA of 160,240 person-years (see Section 7.2).

Finally, we note that the etiology of the liver injury related to ELX/TEZ/IVA has not been established. In the ELX/TEZ/IVA clinical program, the trough concentrations of ELX, TEZ, IVA, and their active metabolites reported from six subjects who experienced hepatotoxicity were all within the therapeutic range (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]). The mechanism of injury is likely an off-target effect, mediated by one or more components of ELX/TEZ/IVA. That VNZ/TEZ/D-IVA shares the same (TEZ) and two highly similar

components (VNZ and ELX, IVA and D-IVA) components also supports that the risk for liver injury is comparable to ELX/TEZ/IVA.

Given the recent addition of the Boxed Warning for DILI and liver failure to the USPI for ELX/TEZ/IVA, there were multidisciplinary discussions held between the Division and DHN and within the Office of New Drugs regarding the assessment of risk related to VNZ/TEZ/D-IVA and how to convey this risk to prescribers. The Division will include a Boxed Warning for potential DILI and liver failure related to VNZ/TEZ/D-IVA. This risk is appropriate for a Boxed Warning since it is not only serious and life-threatening, but also potentially preventable through risk mitigation strategies. This approach is consistent with the FDA guidance for industry *Warning and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format* ([October 2011](#)) for serious risks for which the frequency or severity could be reduced by interventions (e.g., increased monitoring frequency, drug interruption guidelines). The guidance also reviews that there are instances when a Boxed Warning based on an anticipated reaction would be appropriate, as in this case.

Conclusion

There are no data to suggest that the risk of DILI with VNZ/TEZ/D-IVA is different from or lower than the risk with ELX/TEZ/IVA. The Division will include a Boxed Warning, consistent with that in the USPI for ELX/TEZ/IVA, in the USPI for VNZ/TEZ/D-IVA. The Boxed Warning will include recommendations for increased LFT monitoring frequency and duration, guidelines for drug interruption, and considerations for population selection. Additional information regarding labeling is included in Section [23](#). An enhanced pharmacovigilance strategy will attach to the approval of VNZ/TEZ/D-IVA to further evaluate this safety signal in the postmarket setting.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Hepatic Impairment

The Applicant proposed no dose adjustment of VNZ/TEZ/D-IVA FDC tablet for CF patients with mild hepatic impairment (HI) (Child-Pugh Class A) (b) (4). However, the use of VNZ/TEZ/D-IVA in CF patients with MHI is not recommended and should only be considered when there is a clear medical need, and the benefit exceeds the risk. VNZ/TEZ/D-IVA should not be used in CF patients with severe HI (Child-Pugh Class C). The review team agree that this approach is acceptable, and these recommendations will be included in the USPI.

The Applicant conducted a reduced design dedicated HI trial (Study VX21-121-008) to evaluate a single dose of VNZ 10 mg/TEZ 50 mg /D-IVA 125 mg FDC PK in subjects with MHI (n=12) compared to matched healthy subjects (n=12). Results of Study 008 showed that the impact of MHI on TEZ exposure was insignificant, while the mean exposures of VNZ and D-IVA were

lower in subjects with MHI compared to those in matched healthy subjects. The total exposure area under the concentration-time estimated to infinity (AUC_{inf}) of VNZ and D-IVA decreased 30% and 20%, respectively, in subjects with moderate hepatic impairment when compared to matched subjects with normal hepatic function. Similarly, the free drug exposure ($AUC_{unbound, 0-inf}$) of VNZ and D-IVA decreased 20% and 40%, respectively, in subjects with MHI when compared to matched subjects with normal hepatic function.

Based on the hepatotoxicity of VNZ/TEZ/D-IVA (refer to Section [7.7.2](#) and the PK results from the dedicated HI Study VX21-121-008, the clinical pharmacology review team agrees that no dose modification is recommended for CF patients with mild HI; VNZ/TEZ/D-IVA should not be used in CF patients with severe HI, and VNZ/TEZ/D-IVA should only be considered in patients with MHI (without dose adjustment) when there is a clear medical need and the benefit exceeds the risk. Because of hepatotoxicity, the clinical pharmacology review team also agrees liver function tests should be closely monitored in HI patients on VNZ/TEZ/D-IVA treatment.

Renal Impairment

VNZ/TEZ/D-IVA FDC tablet has not been studied in CF patients with any degree of renal impairment (RI) or end-stage renal disease. There were CF subjects with mild RI (n=126) and moderate RI (n=2) in the phase 3 trials. The Applicant proposed no dose adjustment for subjects with mild or moderate renal impairment. The USPI will recommend use with caution in people with CF with severe RI or end-stage renal disease. The review team agrees that this approach is acceptable.

Renal excretion contributed minimally to VNZ elimination (0.5% of the total radioactivity was detected in the urine within 17 days postdose, as indicated by Study 004). Per TEZ/IVA labeling, the contribution of renal route in TEZ excretion is approximately 14% (mostly as M2 metabolite) and <1% of the administered dose was excreted in urine as unchanged TEZ. This result suggests that renal excretion is not the major pathway of TEZ elimination in humans. Although a mass balance study was not conducted for D-IVA, the urine excretion of D-IVA is expected to be low based on in vitro comparison results with IVA (6.6% of IVA dose is excreted in urine). In addition, population PK showed similar exposure of VNZ/TEZ/F-IVA between healthy subjects and subjects with mild/moderate RI.

Overall, these results suggest that renal clearance is likely to play a minimal role in the elimination of VNZ, TEZ, and D-IVA and support the proposed dosing recommendation.

Pediatrics PK

The proposed pediatric doses in children 6 through 11 years of age (i.e., VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg QD for children weighing ≥ 40 kg and VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg QD for children weighing ≥ 40 kg) were studied in Cohort B1 of Trial VX21-121-105 with 78 children.

The comparison of pediatric observed C_{trough} values and population PK-estimated steady state AUC values of VNZ, TEZ, M1-TEZ, D-IVA, and M1-D-IVA following the studied/proposed doses were generally within the range of those in adults and adolescents. For details, refer to Section [6.1.3](#).

8.2. Extrinsic Factors

Food Effect

Study VX21-121-005 (Study 005)

The effect of food consumption on drug exposure was evaluated in Part B of Study 005. Study 005 Part B was a phase 1, randomized, open-label, crossover study with 3-period, 3-sequence design to evaluate the effect of food on the relative bioavailability of VNZ [Form D]/TEZ/D-IVA FDC tablet.

The PK analysis dataset included data from 17 healthy subjects who received VNZ/TEZ/D-IVA FDC tablets in the three dosing periods: FDC Fasted, FDC Low-fat (approximately 400 to 500 kCal including 11 to 14 g of fat [approximately 25% of caloric content]), and FDC High-fat (approximately 800 to 1000 kCal including 55 to 65 g of fat [approximately 50% of caloric content]). The effect of food intake on VNZ, TEZ, and D-IVA PK after a single oral dose of the FDC tablet (VNZ [Form D] 20 mg /TEZ 100 mg/D-IVA 250 mg) under fed conditions compared to fasted conditions was statistically evaluated in [Table 58](#). Administration of a single oral dose of the FDC tablet following a fat containing meal increased VNZ and D-IVA exposures up to 6-fold and 5-fold, respectively, compared to fasted condition. Food intake had no significant impact on TEZ exposures overall.

Table 58. Summary of Mean (CV%) of PK Metrics and Food Effect Assessment on VNZ, TEZ, and D-IVA Exposures After Administration of VNZ [Form D]/TEZ/D-IVA FDC Tablet Under Fasted and Fed (High-Fat and Low-Fat) Conditions

Analyte	PK Metric	Fasted	Low-Fat	High-Fat	GLSM Ratio (%)	
					Low-Fat/Fasted	High-Fat/Fasted
VNZ	C _{max} (µg/mL)	0.0342 (42.3)	0.145 (44.5)	0.219 (32.9)	390 (296, 515)	634 (480, 836)
	AUC _{tlast} (µg·h/mL)	3.62 (48.7)	14.7 (45.1)	21.5 (36.2)	381 (281, 518)	597 (439, 810)
	AUC _{inf} (µg·h/mL)	3.90 (48.5)	15.7 (46.0)	22.7 (37.8)	374 (277, 505)	576 (427, 778)
TEZ	C _{max} (µg/mL)	4.41 (43.0)	5.11 (31.7)	4.52 (29.0)	116 (96.4, 141)	108 (89.6, 130)
	AUC _{tlast} (µg·h/mL)	78.7 (31.4)	91.9 (34.2)	93.9 (29.2)	113 (97.3, 130)	121 (105, 140)
	AUC _{inf} (µg·h/mL)	83.5 (30.5)	96.9 (34.4)	99.9 (29.0)	112 (96.4, 129)	121 (105, 140)
D-IVA	C _{max} (µg/mL)	0.379 (68.5)	1.45 (45.1)	1.72 (40.7)	432 (316, 591)	537 (395, 731)
	AUC _{tlast} (µg·h/mL)	9.63 (58.1)	32.0 (45.6)	38.1 (35.5)	332 (256, 431)	420 (326, 542)
	AUC _{inf} (µg·h/mL)	9.66 (58.0)	32.1 (45.6)	38.1 (35.5)	332 (256, 429)	419 (325, 540)

Source: Tables 11-3 and 11-4 in CRS VX21-121-005

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; AUC_{tlast}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; FDC, fixed-dose combination; GLSM, geometric least squares mean; PK, pharmacokinetic; TEZ, tezacaftor; VNZ, vanzacaftor

Based on the finding in Part B from Study 005, the clinical pharmacology review team agrees with Applicant's recommendation to take VNZ/TEZ/D-IVA FDC with fat-containing food in patients with CF.

Drug Interactions

Effect of VNZ, TEZ, and D-IVA on the PK of Each Other

The PK interactions between 10 mg VNZ [Form A], 100 mg TEZ, and 250 mg D-IVA (in separate tablets) were evaluated in clinical trial in healthy subjects (n=20), Study VX21-121-006.

When coadministered with TEZ and D-IVA, the $C_{max,ss}$ and AUC of VNZ was increased 48% and 54%, respectively compared to VNZ administered alone. When coadministered with VNZ and D-IVA, TEZ $C_{max,ss}$ and AUC increased 29% and 35%, respectively, and M1-TEZ $C_{max,ss}$ and AUC were increased 17% and 11%, respectively. Likewise, D-IVA $C_{max,ss}$ and AUC increased 18% and 27%, respectively, M1-D-IVA $C_{max,ss}$ and AUC increased 27% and 39%, respectively, when D-IVA was administered in TC with VNZ/TEZ compared to D-IVA administered alone.

There is a concern whether this up to 50% increase of systemic exposures of VNZ, TEZ, D-IVA and their active metabolites may change the efficacy/safety profile of each API in the TC context. For VNZ, the dose ranging trial of VNZ (Study 101) was conducted in the TC context, and the dose ranging results directly supported the 10 mg VNZ [Form A] dose in the TC context to be used in phase 3 studies. For D-IVA, although Study 561-101 was conducted on D-IVA mono-component in CF subjects with gating variants, based on the flat dose-response relationship over D-IVA 150 mg to D-IVA 250 mg on ppFEV₁ response observed in Study 561-101, it is unlikely that the observed increase in systemic exposure would contribute additional efficacy of D-IVA in the context of TC.

Effect of Coadministered Drugs on VNZ/TEZ/D-IVA

VNZ/TEZ/D-IVA as Substrates of CYP Enzymes

VNZ, TEZ, and D-IVA are all extensively metabolized by CYP3A.

In vitro metabolizing enzyme profiling results (Study N295) showed VNZ was stable when incubating with recombinant CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 (>95% remaining at the 60-minute time point) as presented in [Table 59](#). The compound exhibited a turnover of >18% in CYP3A4 and CYP3A5 (43.2% and 81.2% remaining, respectively).

Table 59. Summary of Human Recombinant CYP Isozyme Stability Data for VNZ at 1 μ M and Respective Positive Control Compounds After a 60-Minute Incubation at 37°C

VRT-1725010 Initial Concentration	Percent of VRT-1725010 Remaining (Mean $\pm$ SEM) ^a							
	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4	CYP3A5
1 μ M	110 $\pm$ 15.4	108 $\pm$ 8.80	96.2 $\pm$ 9.68	109 $\pm$ 17.3	108 $\pm$ 8.63	104 $\pm$ 10.4	43.2 $\pm$ 4.83	81.2 $\pm$ 12.9
Positive Control	Phenacetin 60 μ M	Bupropion 1 μ M	Amodiaquine 60 μ M	Diclofenac 60 μ M	Amitriptyline 60 μ M	Dextromethorphan 60 μ M	Quinidine 2 μ M	Quinidine 2 μ M
	64.7 $\pm$ 18.3	28.3 $\pm$ 4.38	9.05 $\pm$ 4.44	1.77 $\pm$ 1.53	27.9 $\pm$ 4.33	0.980 $\pm$ 0.243	39.6 $\pm$ 6.26	41.9 $\pm$ 7.94

Source: Table 2 in Nonclinical study report N295

^a Mean $\pm$ SEM, N=3

Abbreviation: CYP, cytochrome P450; N, number of subjects in treatment arm; SEM, standard error of mean; VRT-1725010, VNZ; VNZ, vanzacaftor

In vitro metabolizing enzyme profiling results (Study S286) showed D-IVA was stable when incubating with recombinant CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 (>80% remaining at the 60-minute time point). The compound exhibited a turnover of >20% in CYP3A4 and CYP3A5 (6.00% and 18.6% remaining, respectively) as presented in [Table 60](#).

Table 60. Percent of D-IVA Remaining in Human Recombinant CYPs in the Presence or Absence of NADPH

Cofactor	Percent of VX-561 (1 μ M) Remaining after 60-min Incubation (Mean $\pm$ SD, n=3)							
	Control ^a	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4
+NADPH	95.1 $\pm$ 6.55	105 $\pm$ 10.1	101 $\pm$ 7.79	102 $\pm$ 4.84	97.2 $\pm$ 8.76	111 $\pm$ 5.40	86.8 $\pm$ 5.57	6.00 $\pm$ 0.684
-NADPH	91.1 $\pm$ 9.52	105 $\pm$ 6.42	112 $\pm$ 1.45	98.6 $\pm$ 2.74	93.7 $\pm$ 4.60	108 $\pm$ 10.2	107 $\pm$ 9.51	103 $\pm$ 3.69

Source: Table 1 in Nonclinical study report S286

Abbreviation: CYP, cytochrome P450; D-IVA, deutivacaftor; min, minute; N, number of subjects in treatment arm; NADPH, nicotinamide adenine dinucleotide phosphate; SD, standard deviation; SEM, standard error of mean; VX-561;

The results of D-IVA are similar to the metabolizing profile of IVA (Study B242), showing that CYP3A4 is the major metabolizing enzyme of IVA ([Table 61](#)).

Table 61. Percentage of VRT-813077 Remaining Following Incubation With Recombinant Human CYP450 Isozymes in the Presence of NADPH for 1 Hour at 37°C

	Percent of VRT-813077 Remaining (Mean $\pm$ SD)				
	CYP1A2	CYP2C9	CYP2C19	CYP2D6	CYP3A4
VRT-813077 (0.5 μ M)	78 $\pm$ 5	100 $\pm$ 10	111 $\pm$ 4	88 $\pm$ 13	8.5 $\pm$ 2.6

Source: Table 1-1 from B242-legacy.pdf

Abbreviations: CYP, cytochrome P450; N, number of subjects in treatment arm; NADPH, nicotinamide adenine dinucleotide phosphate; SD, standard deviation; SD, standard deviation; VRT-813077, IVA

In vitro study DM-059 showed that when incubating with CYP3A4 supersomes, the mean half-life of D-IVA and IVA was 8.1 $\pm$ 0.2 and 5.5 $\pm$ 0.1 hours, respectively.

There were two clinical drug-drug interaction (DDI) studies (Study VX21-121-007 and Study VX18-445-006) conducted on VNZ (as mono-component) and D-IVA (in the context of ELX/TEZ/D-IVA), respectively, with itraconazole, a strong CYP3A inhibitor. VNZ exposure was increased ($C_{\max}$ by 1.55-fold, $AUC_{0-\text{tlast}}$ by 5.55-fold, and AUC_{inf} by 6.37-fold) when VNZ

was coadministered with itraconazole compared to VNZ administration alone (Study VX21-121-007). The exposure of D-IVA was increased by 1.96- and 11.1-fold for C_{max} and AUC_{inf} , respectively, in Study VX18-445-006. The DDI study (Study VX14-661-006) under the TEZ/IVA development program indicated that itraconazole increased TEZ AUC and C_{max} by 4.0- and 2.8-fold compared to TEZ administration alone. In addition, DDI study (Study VX13-770-017) under the IVA program indicated that moderate CYP3A4 inhibitor ciprofloxacin did not affect TEZ exposure.

Study VX12-770-017 in the TEZ/IVA program showed that ciprofloxacin, a moderate CYP3A4 inhibitor, had no clinically relevant effect on the PK of TEZ when coadministered with IVA.

Based on the finding in Studies VX21-121-007, VX18-445-006, physiologically based pharmacokinetic evaluation, exposure-response relationship of VNZ and TEZ, and CYP3A4-related DDI evaluation of TEZ under TEZ/IVA and IVA programs, the Applicant proposed to reduce the dose of VNZ/TEZ/D-IVA FDC when it is coadministered with CYP3A inhibitors as presented in [Table 62](#).

Table 62. Dosing Schedule for Concomitant Use of VNZ/TEZ/D-IVA With Moderate or Strong CYP3A Inhibitors

Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors
(b) (4)			

Source: Applicant proposed labeling
Abbreviations: CYP, cytochrome P450; D-IVA, deutivacaftor; QOD, every other day; TEZ, tezacaftor; VNZ, vanzacaftor

VNZ, TEZ, and D-IVA showed linear PK characteristics around the therapeutic dose. Therefore, the proposed dose reduction to 1/3 to 1/4 of the normal dose ([Table 62](#)) is expected to lower the exposures (AUC) of VNZ and D-IVA in patients on CYP3A4 moderate inhibitors (which increase VNZ and D-IVA AUC by 2- to 5-fold) within the range of patients on normal dose without taking CYP3A4 moderate inhibitors (Section [14.5](#)). The extent of the proposed dose reduction of TEZ in the context of TC when coadministered with CYP3A4 moderate inhibitors (1/3 to 1/4) is greater than the approved dose reduction of TEZ in the context of ELX/TEZ/IVA (1/2 of the normal dose), which is expected to result in a lower exposure (Section [14.5](#)). However, the dose-response relationship of TEZ was relatively flat over 30 mg to 150 mg range when coadministered with IVA in patients with F/F, as observed in the TEZ/IVA program (Trial VX11-661-101). Considering the availability of dosing strengths of TC and the unmet medical need of CF, the proposed dose reduction of VNZ/TEZ/D-IVA when coadministered with CYP3A4 moderate inhibitors is reasonable.

Similarly, the proposed dose reduction to ~1/10 to 1/14 of the normal dose ([Table 62](#)) is expected to lower the VNZ and D-IVA AUC in patients on CYP3A4 strong inhibitors (which increase VNZ and D-IVA AUC by 10.5- and 11-fold, respectively) within the range of subjects on normal dose without taking CYP3A4 strong inhibitors (Section [14.5](#)). Thus, the dose reduction for VNZ and D-IVA in the context of TC when coadministered with CYP3A4 strong inhibitors is reasonable. The extent of the proposed dose reduction of TEZ in the context of TC when coadministered with CYP3A4 strong inhibitors (1/10 to 1/14) is greater than the approved

dose reduction of TEZ in the context of ELX/TEZ/IVA (2/7 of the normal dose). However, based on the flat dose-response relationship of TEZ over 30 – 150 mg range (Trial VX11-661-101), the proposed dose reduction of TEZ when coadministered with CYP3A4 strong inhibitors is reasonable.

The proposed pediatric dose adjustments for VNZ and D-IVA when coadministered with CYP3A4 inhibitors are generally reasonable as population PK-simulated results showed the AUC at steady state values after the proposed dose adjustment were within the reference range (Section 14.5). The proposed pediatric dose adjustment for TEZ when coadministered with CYP3A4 inhibitors generally results in a lower exposure compared to the reference range. However, this can be similarly justified by relative flat dose-response curve of TEZ observed in adults.

VNZ and D-IVA are sensitive substrates of CYP3A. The exposure to VNZ and D-IVA was predicted to be reduced with concomitant use of strong or moderate CYP3A inducers. For example, simulations showed significant decrease in exposure to VNZ and D-IVA by 82% and 90%, respectively, when coadministered with rifampin, a strong CYP3A inducer. Moreover, carbamazepine, a strong CYP3A inducer, significantly decreased VNZ and D-IVA exposures by 57% and 76%, respectively. The exposure to VNZ and D-IVA decreased by 69% and 73%, respectively, when coadministered with efavirenz, a moderate CYP3A inducer. Therefore, coadministration of VNZ/TEZ/D-IVA FDC tablet with strong or moderate CYP3A inducers is not recommended.

VNZ/TEZ/D-IVA as Substrates of Transporters

In vitro studies indicate VNZ is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporter (OAT)P1B1, and OATP1B3 (Table 63).

According to the labeling of ELX/TEZ/IVA, TEZ is a substrate of P-gp, BCRP, and OATP1B1. Coadministration of itraconazole (CYP3A4, P-gp, and BCRP triple inhibitor) with TEZ increased AUC and C_{max} of TEZ by 4.0- and 2.8-fold, respectively, compared to TEZ administration alone.

In vitro studies indicate D-IVA is a substrate of P-gp (efflux ratio of 6.7 at 1 μ M, which is similar to value 5.6 of IVA) and BCRP (net efflux ratio of 42.1 at 50 μ M, which is similar to value of 32.5 of IVA), but not OATP1B1 and OATP1B3 (Table 63).

Table 63. Evaluation of VNZ, TEZ, D-IVA and Metabolites as Substrate of Uptake and Efflux Transporters

Compound	OATP1B1	OATP1B3	P-gp	BCRP
VNZ	No	No	No	No
TEZ	Yes	No	Yes	Yes
M1-TEZ	No	No	Yes	NA
M2-TEZ	Yes	Yes	Potentially yes	No
M5-TEZ	No	No	NA	NA
D-IVA	No	No	Yes	Yes
M1-D-IVA	No	No	Yes	Yes
M6-D-IVA	Yes	Yes	No	Yes

Source: Table 26 on page 67 from 2.6.4 Pharmacokinetics Written Summary.pdf

Abbreviations: D-IVA, deutivacaftor M, metabolite; OAT, organic anion transporter; P-gp, P-glycoprotein; TEZ, tezacaftor; VNZ, vanzacaftor

In vitro studies indicate D-IVA is a substrate of P-gp (efflux ratio of 6.7 at 1 μ M, which is similar to value 5.6 of IVA) and BCRP (net efflux ratio of 42.1 at 50 μ M, which is similar to value of 32.5 of IVA), but not OATP1B1 and OATP1B3.

Effect of VNZ/TEZ/D-IVA on Other Drugs

VNZ

The plasma C_{max} of VNZ at steady state following the proposed VNZ 20 mg/TEZ100 mg/D-IVA 250 mg is around 1.35 μ M. That translates to about ≤ 20 nM free C_{max} plasma concentration of VNZ. In vitro results showed that VNZ did not inhibit CYP1A2, CYP2C19, CYP2D6, and CYP3A4, and showed weak inhibition of CYP2B6, CYP2C8, and CYP2C9 with the most potent K_i value as 14.2 μ M (for CYP2B6). The half maximal effective concentration value of VNZ on CYP3A4 mRNA induction was estimated ranging from 0.3 to 1.4 μ M, and an E_{max} ranging from 3.4- to 5.2-fold. Comparison of in vivo C_{max} value and in vitro inhibition/induction values, the in vivo CYP inhibition/induction potential of VNZ is low.

VNZ is a P-gp inhibitor with a half maximal inhibitory concentration (IC_{50}) of 3.80 μ M when digoxin is used as substrate. The calculated induced gut/ IC_{50} value is 35. Given that coadministration of VNZ with TEZ (a P-gp substrate) and D-IVA (a weak P-gp inhibitor) only increased TEZ C_{max} and AUC by 29% and 35%, VNZ is likely having low potential to inhibit P-gp in vivo.

VNZ is a BCRP inhibitor with an IC_{50} of 0.25 μ M when prazosin is used as a substrate. The calculated induced gut/ IC_{50} value is 532, which is almost two magnitudes higher than the cutoff of 10, suggesting VNZ has a potential to inhibit BCRP in vivo. Therefore, a postmarketing requirement study to evaluate the effect of VNZ or VNZ/TEZ/D-IVA on PK of a sensitive BCRP substrate is recommended.

VNZ inhibited OATP1B1- and OATP1B3-mediated atorvastatin uptake with IC_{50} of 45.1 and 61.7 μ M, respectively, in the presence of HBE medium which contained 20% human serum. The

calculated $IC_{50,u}/C_{max,inlet,u}$ (1.47 μM) is smaller than the cutoff value of 10. Therefore, the in vivo OATP1B1- and OATP1B3 inhibition potential of VNZ is low.

TEZ

Refer to the approved drug label of ELX/TEZ/IVA ([Vertex Pharmaceuticals 2019](#)), in vitro results showed that TEZ has low potential to inhibit all the major CYP enzymes. TEZ is not likely to induce CYP3A, CYP1A2 and CYP2B6. TEZ has low potential to inhibit P-gp, BCRP, organic cation transporter 2, OAT1, or OAT3.

D-IVA

Major CYP enzymes inhibition data for D-IVA, M1-D-IVA and M6-D-IVA are summarized in [Table 65](#). In general, CYP3A4, CYP2C8 and CYP2C9 inhibition potencies are similar between IVA and D-IVA, M1-IVA and M1-D-IVA.

Therefore, it is expected that the in vivo CYP3A4, CYP2C8 and CYP2C9 inhibition potential by D-IVA is similar to slightly higher than that of IVA because of the doubling of C_{max} value. Of note, in clinical studies, IVA did not significantly affect the PK of rosiglitazone, a model CYP2C8 substrate, and midazolam, a sensitive CYP3A substrate (Study 770-010 and Study 661-006). (b) (4)

(i.e., D-IVA may inhibit CYP2C9; therefore, monitoring of the international normalized ratio during co administration of VNZ/TEZ/D-IVA with warfarin is recommended). Other medicinal products for which exposure may be increased by VNZ/TEZ/D-IVA include glimepiride and glipizide; these medicinal products should be used with caution.

Table 64. Inhibition of the Human Liver Microsomal CYP Isozymes by IVA, D-IVA, and Their Major Metabolites

Drug/ Metabolite	IC ₅₀ Values (μM)						
	CYP1A2	CYP2B6	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5
D-IVA	>50	>50	9.5	15.6	>50	>50	15.7 ^b 21 ^c
D-IVA R value ^a	NA	NA	1.05	1.03	NA	NA	1.03
M1-D-IVA	>100	23.2	4.8	4.6	46	55.9	24.8 ^b , 17.7 ^b 14.9 ^c
M1-D-IVA R value ^a	NA	1.02	1.08	1.09	1.01	1.01	1.03
M6-D-IVA	>25	>25	>25	>25	>25	>25	>25 ^b , >75 ^b >25 ^c
IVA	>50	45.3	7.9	13.8	>50	>50	17.1 ^c
M1-IVA	>100	23.9	5.9	7.1	43	27	19.2 ^c , 11.7 ^b
M6-IVA	>25	>25	>25	>25	>25	>25	>25 ^b , >25 ^c

Source: Adapted from Table 28 on page 65 from 2.6.4 Pharmacokinetics Written Summary.pdf

^a R = 1 + free C_{max}/free K_i (K_i = IC₅₀ / 2 at substrate concentration close to K_m) for CYPs except CYP3A4/5. R = 1+ free lin, max / free K_i for CYP3A4/5

^b Testosterone as probe substrate

^c Midazolam as probe substrate

Abbreviations: CYP, cytochrome P450; D-IVA, deutivacaftor; IC₅₀, half maximal inhibitory concentration; IVA, ivacaftor; M, metabolite; NA, not applicable

Following individual incubation with increasing concentrations of D-IVA, M1-D-IVA, or M6-D-IVA for 72 hours with plated human hepatocytes, less than 20% (positive threshold) increase of CYP1A2, CYP2B6, or CYP3A4 mRNA relative to positive control were observed in any of the three lots of hepatocytes, suggesting low induction potential for D-IVA, M1-D-IVA, or M6-D-IVA to induce these enzymes.

Transporter inhibition data for D-IVA, M1-D-IVA and M6-D-IVA are summarized in [Table 65](#). In general, the P-gp and BCRP inhibition potencies are similar between IVA and D-IVA, M6-IVA and M6-D-IVA. M1-D-IVA is less potent to inhibit P-gp and BCRP than M1-IVA.

Table 65. Inhibition of the Transporters by D-IVA, IVA, and Their Major Metabolites

Transporters	P-gp	BCRP	OATP- 1B1	OATP- 1B3	OAT1	OAT3	OCT2	OCT1	MATE 1	MATE 2-K	BSEP
Compounds	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)	IC ₅₀ (μM)
D-IVA	3.83	1.19	>100	>100	>100	>100	>100	>100	>100	>100	>10
M1-D-IVA	9.86	9.15	>100	>100	~100	>100	>100	>100	>100	>100	>10
M6-D-IVA	>10	>26.3	>100	>100	~100	>100	>100	>100	>100	>100	>10
IVA	10.6	3.46	>100	>100	>100	>100	>100	>100	>100	>100	>10
M1-IVA	95% inhibition at 10 μM	83% inhibition at 10 μM	>100	>100	~100	>100	>100	>100	>100	>100	>10
M6-IVA	>10	>10	>100	>100	~100	>100	>100	>100	>100	>100	>10

Source: Adapted from Table 30 on page 71 from 2.6.4 Pharmacokinetics Written Summary.pdf

Abbreviations: BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CYP, cytochrome P450; D-IVA, deutivacaftor; IC₅₀, half maximal inhibitory concentration; IVA, ivacaftor; M, metabolite; MATE, multidrug and toxin extrusion transporter; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein

Based on the totality of the DDI evaluation of VNZ/TEZ/D-IVA and their major metabolites, additional in vivo evaluation of VNZ on sensitive BCRP substrate is warranted. Refer to Section [24](#) for a DDI-related postmarketing requirement study.

8.3. Plans for Pediatric Drug Development

CF is a rare, orphan disease and is not subject to pediatric study requirements as defined under the Pediatric Research Equity Act (PREA). However, the Applicant submitted proposals for the inclusion of pediatric subjects within the clinical development program for VNZ/TEZ/D-IVA, and a Pediatric Written Request was issued on December 6, 2023.

Following approval, the indication for VNZ/TEZ/D-IVA will include patients aged 6 years and older. This is based on safety and efficacy data obtained from the phase 3 noninferiority trials, Trials 102 and 103, which enrolled subjects 12 to 17 years of age (reviewed in Sections [6.2.2](#), [6.2.3](#), and [7.6.1](#)). Additionally, a pediatric PK and safety trial, Trial 105, is ongoing to evaluate the PK of VNZ/TEZ/D-IVA when dosed in triple combination in CF subjects 1 through 11 years of age (inclusive) with at least one TCR variant in the *CFTR* gene. In this application, the Applicant submitted interim analysis results using data from subjects 6 through 11 years of age in Cohorts A1 and B1 to support the extrapolation of efficacy and safety in this population (reviewed in Sections [6.2.4](#) and [7.6.2](#)). The remaining cohorts in younger CF subjects 1-5 years of age (Cohorts A2, A3, B2, and B3) are ongoing.

(b) (4)

juvenile toxicology studies were not needed to support this application for subjects aged 6 years and older. In a juvenile rat toxicology study, vanzacaftor had no adverse effects at up to 58 (male)/28 (female) times the exposure at the MRHD. Juvenile animal toxicology studies for IVA and TEZ were previously reviewed under NDA 203188 and NDA 212273, respectively.

8.4. Pregnancy, Lactation, and Females / Males of Reproductive Potential

Clinical Experience

The use of VNZ/TEZ/D-IVA, ELX/TEZ/IVA, or medications containing their components during pregnancy or lactation has not been evaluated in well-controlled trials.

Animal Data

The Applicant conducted a full evaluation of the developmental and reproductive toxicity of VNZ, which included a fertility and early embryonic development study, embryo-fetal development studies in rat and rabbits, pre- and postnatal development study in rats, and a juvenile toxicity study in rats. Additional details are available in Section [13](#). Nonclinical information related to the developmental and reproductive toxicity of TEZ has been previously described under NDA 210491 TEZ/IVA and NDA 212273 ELX/TEZ/IVA. Nonclinical

information from IVA (NDA 203188 IVA) was leveraged to assess the reproductive and developmental toxicity of D-IVA.

Table 66. Nonclinical Data of VNZ Supporting Labeling on Fertility, Pregnancy, Lactation, and Pediatric Use

Labeling Section	Nonclinical Data
8.1 Pregnancy	- In pregnant rats administered VNZ during organogenesis, VNZ did not cause adverse effects to the fetus at maternal exposures up to 30 times the MRHD. - In pregnant rabbits administered VNZ during organogenesis, VNZ did not cause adverse effects to the fetus at maternal exposures up to 22 times the MRHD. The high dose of 70 mg/kg/day (71 times the exposure at the MRHD) produced maternal toxicity (i.e., mortality, abortion, decreased mean body weight or body weight gains) and was associated with findings of increased postimplantation loss, decreased live fetuses, decreased fetal body weight, increased kidney malformations, and increased incidences of skeletal variations. The effects observed at the high dose were related to maternal toxicity and so were not considered relevant to the human risk.
8.3 Females and Males of Reproductive Potential	In a rat fertility study, VNZ had no effects on male and female fertility and reproductive performance indices up to 19 (male)/30 (female) times the exposure at the MRHD.
8.4 Pediatric Use	In a juvenile rat toxicology study, VNZ had no adverse effects at up to 58 (male)/28 (female) times the exposure at the MRHD.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	In a pre- and postnatal development study in pregnant rats, no adverse effects were observed in the offspring exposed daily to VNZ from birth (in utero) through lactation at maternal doses up to approximately 18 times the MRHD.

Source: Reviewer generated table; Applicant provided data

Abbreviation: MRHD, maximum recommended human dose; VNZ, vanzacaftor

Table 67. Reproductive Toxicity Safety Margins

Study	NOAEL (mg/kg)	AUC _{0-24h} (ng·hr/mL)	Exposure Margins ^a (Multiples)
FEED, rat	12.5 (M)/10 (F)	361 (M)/565 (F) ^b	19(M)/30(F)
EFD, rat (maternal and fetal)	10	565	30
EFD, rabbit (maternal and fetal)	40	410	22
Juvenile rat	25 (M)/12.5 (F)	1100 (M)/532 (F)	58(M)/28(F)
PPND, rat (maternal and developmental)	10	339	18

Source: Reviewer generated table; Applicant provided data.

^a Clinical exposure of VNZ in CF subjects at a VNZ/TEZ/D-IVA triple combination treatment with VNZ dose of 20 mg QD. Report T270/Tables 8 and S11; Report T271/Tables 8 and 17; and Report T406/Table 11.7

^b AUC at dose of 10 mg/kg on Day 17 in the EFD study VX-121-TX-005 with rats.

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24h}, area under the concentration-time curve from time 0 extrapolated to 24 hr; CF, cystic fibrosis; D-IVA, deutivacaftor; EFD, embryofetal development; F, female; FEED, fertility and early embryonic development; M, male; NOAEL, no observed adverse effect level; PPND, pre- and postnatal development; QD, once daily; TEZ, tezacaftor; VNZ, vanzacaftor

9. Product Quality

Approval

The Office of Pharmaceutical Quality review team has assessed NDA 218730 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such Office of Pharmaceutical Quality recommends approval of this NDA from a quality perspective.

Drug Substance

The CMC information for two of the APIs, VNZ and D-IVA, is provided in this NDA (NDA 218730). For the remaining API, TEZ, the Applicant has fully cross-referenced their own approved NDA 210491. Four minor issues involving VNZ and D-IVA were identified via our original review of the NDA on September 13, 2024. However, the Applicant's responses on September 20, 2024, have resolved those issues. Thus, the NDA is currently recommended for approval from the API perspectives.

Drug Product

Vertex developed the drug product manufacturing process for an immediate-release, oral formulation. The process involves (b) (4) as outlined in Section 2.3.P.3. A Quality by Design approach was utilized to identify critical quality attributes for efficacy and safety. In-process control and release testing was implemented to monitor these critical quality attributes and ensure consistent product quality.

The drug product specifications were established using a Quality by Design approach, identifying critical quality attributes and referencing international harmonization guidelines and United States Pharmacopeia chapters. Data from development, release testing, stability studies, and manufacturing, were used to establish the specifications. The established specifications ensure the drug product's identity, strength, purity, and overall quality throughout its intended 24-month shelf life.

The noncompendial analytical methods ensure the identity, strength, purity, and quality of the drug product at release and throughout its shelf-life. These methods have been validated according to International Council for Harmonisation (ICH) Q2(R1) guidelines.

The drug product is packaged in a thermoform blister consisting of (b) (4) films with a lidding foil seal. All components comply with relevant regulations, including 21 CFR 174-186 and USP. Container closure system components, including suppliers and specifications, are detailed in the referenced Drug Master Files (b) (4) and (b) (4). The blister packaging passed the ICH Q1B photostability test, ensuring light protection for the tablets throughout their shelf life. Additionally, the proposed container closure system design itself has been previously approved for similar drug products from this Applicant.

The Applicant submitted batch analysis data for the drug product, encompassing five clinical/stability batches of the higher strength (VNZ/TEZ/D-IVA 10/50/125 mg) tablets and three batches of the lower strength (VNZ/TEZ/D-IVA 4/20/50 mg) tablets. All batches were

manufactured using the proposed commercial manufacturing process (Section 3.2.P.3.3) and met the drug product specifications, both those used at the time of testing and those proposed for the commercial drug product.

A stability study, following ICH guidelines was conducted on five clinical/stability batches of the 10/50/125 mg tablets and three batches of the 4/20/50 mg tablets. These batches were evaluated under various storage conditions: long-term (25°C ±2°C, 60% relative humidity (RH) ±5% for 48 months), intermediate (30°C ±2°C/75% RH ±5% for 48 months) and accelerated (40°C ±2°C, 75% RH ±5% for 6 months). All batches were manufactured using the proposed commercial manufacturing process and tested using the proposed analytical methods at the intended testing sites. After 12-18 months of long-term storage and 6 months of accelerated storage, no significant trends were observed in any of the evaluated product attributes.

Shelf-Life: Based on the satisfactory long-term and accelerated stability data, an expiration dating period of 24 months is proposed and granted when stored in the proposed container closure system. The drug product should be stored at 20° to 25°C (68° to 77°F) with excursions permitted from 15°C to 30°C (59°F to 86°F).

Manufacturing

The drug product manufacturer, drug substance manufacturer, primary packaging facility, and contract test laboratories in the application have acceptable cGMP compliance status and experience for the intended functions in the application. The facilities are recommended for approval based on previous history.

The drug product formulation consists of three APIs: VNZ, TEZ, and D-IVA). (b) (4)

(b) (4) The commercial Critical Process Parameters are supported by registration batch data. All registration batches met the amended specification in terms of appearance, identity, assay, degradation products, (b) (4) physical form, (b) (4) and (b) (4). The same specification is proposed for commercial manufacture. The Applicant cross referenced the TEZ (b) (4) CMC information from the approved application NDA 210491.

For drug product manufacture, (b) (4)

(b) (4) A maximum of 4x scale up is proposed for the unit operations. The commercial Critical Process Parameters are supported by process Design of Experiments and the registration batch data. Drug product content uniformity is medium risk due to the low level of VNZ and (b) (4). Acceptable in-process content uniformity test results have been provided on the registration batches which include one commercial scale batch for the 4/20/50 mg and two commercial scale batches for the 10/50/125 mg strength drug products. (b) (4)

(b) (4) All three APIs have low water solubility. (b) (4)

Process Design of Experiments indicated that

dissolution within the drug product specification can be achieved for the proposed tablet

(b) (4)

Biopharmaceutics

From a biopharmaceutics perspective, the application is adequate, and approval is recommended. The to-be-marketed and phase 3 formulations were the same so there was no need for bridging. Based on information provided, the Applicant considers the VNZ and TEZ to be Biopharmaceutical Classification System Class 2 (low solubility/high permeability). D-IVA is considered to be either Biopharmaceutical Classification System Class 2 or 4, as permeability studies were inconclusive. No biowaiver has been requested and both strength combinations were used in the phase 3 clinical study. The Applicant has provided data demonstrating that the dissolution methods are sensitive to material attributes, minor changes in the tablets' composition, as well as variation in the process parameters that could influence the release of VNZ, TEZ, and D-IVA. The methods are considered to be suitable for regulatory purposes. The Applicant has tightened the dissolution acceptance criteria for VNZ and TEZ to be reflective of the associated data and all dissolution acceptance criteria are now adequate.

Labeling

The quality-related labeling review decision is pending for this integrated quality assessment due to ongoing negotiations with the Applicant. There are only minor labeling deficiencies from the CMC perspective, and we expect the Applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

Good Clinical Practice Compliance

The Applicant stated that the trials were conducted in accordance with the current International Council for Harmonisation draft guidance for industry *E6(R3) Good Clinical Practice (GCP) (June 2023)*, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The study protocol and amendments, informed consent, and other necessary documents were reviewed and approved by an Independent Ethics Committee or an International Review Board as appropriate. Written Informed Consent was obtained prior to study participation.

Financial Disclosure

The Applicant adequately disclosed potential financial interests and arrangements by clinical investigators as recommended in the FDA guidance for industry *Financial Disclosure by Clinical Investigators* ([February 2013](#)). See Section [25](#) for more information. In addition, the Applicant stated that no investigators/sub-investigators participating in either trial were part-time or full-time employees.

11. Advisory Committee Summary

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

III. Additional Analyses and Information

12. Summary of Regulatory History

Tezacaftor (TEZ, VX-661)

Tezacaftor was approved on February 12, 2018, as part of new drug application (NDA) 210491 (TEZ/IVA). Vertex submitted a new molecular entity NDA on June 28, 2017, for TEZ/IVA combination therapy “for the treatment for patients with cystic fibrosis (CF) aged 12 years and older who are homozygous for the *F508del* (F) mutation or who have at least one mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene that is responsive to TEZ/IVA based on in vitro data and/or clinical evidence.”

Deutivacaftor (D-IVA, CTP-656)

On December 22, 2015, a Pre-investigational new drug meeting request was received to discuss the plans for CTP-656, a deuterated isotopolog of ivacaftor (IVA) for use in CF patients. In the meeting minutes dated March 11, 2016, the Division provided clinical and clinical pharmacology comments regarding the development program, the comparator arms and wash-out period and stated that the proposed phase 2 study was insufficient to support phase 3 dosing. The Division also noted that the extent of the nonclinical and clinical bridge between D-IVA and IVA was unclear and the need for additional nonclinical studies would be determined by the adequacy of the bridging program.

On November 18, 2016, investigational new drug (IND) 128544 was submitted, for D-IVA, as a once-daily dosing treatment for patients with CF. The submission included phase 1 studies: a single ascending dose study, a multiple ascending dose study, and a bioavailability/food effect study conducted in Australia. The first study under the IND was a phase 2 study in which three doses of D-IVA, placebo, or open-label KALYDECO (IVA) were administered for 28 days. The study was deemed safe to proceed on December 23, 2016, with nonhold comments.

Vertex submitted a chemistry, manufacturing, and controls (CMC) Type C meeting request on August 14, 2017, for D-IVA, being developed in combination with TEZ and either VX-659 or ELX, to discuss an approach to leveraging existing CMC information for IVA to support development of D-IVA. Meeting Minutes were issued on October 18, 2017.

On September 19, 2018, the Division provided feedback for the submission received on July 24, 2018, on the proposed design of a phase 2 study evaluating a range of doses for D-IVA and the commercial dose of IVA. The comments discussed concerns that the proposed dose ranging study alone would not be sufficient to support phase 3 dosing.

Vanzacaftor

On April 10, 2019, IND 142001 for vanzacaftor (VNZ), a new molecular entity, was submitted with the proposed protocol, VX18-121-101 (Study 101) entitled “A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 [VNZ]

Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis.” The submission also included a request for Fast Track designation. The IND was granted Fast Track designation and deemed safe to proceed on May 30, 2019.

Rare Pediatric Disease Designation was granted on October 1, 2020 (RPD-2020-485). On October 26, 2020, Orphan Designation (DRU-2020-772) was granted for VNZ for the treatment of CF.

A Type B end-of-phase 2 meeting request dated December 9, 2020, was submitted to gain agreement on the proposed pivotal clinical development program and to discuss the adequacy of the nonclinical, clinical, and clinical pharmacology data to support initiation of phase 3 studies, as well as an NDA submission for VNZ/TEZ/D-IVA. In the meeting minutes dated March 26, 2021, the following discussions occurred:

- The Division advised Vertex to conduct a dedicated crossover pharmacokinetic (PK) study with four treatment arms (VNZ, TEZ, D-IVA, and VNZ/TEZ/D-IVA) to evaluate the PK interaction potential among the three mono-components before initiation of phase 3 trials, further noting that evaluation of the drug-drug interactions (DDIs) between individual components of a combination product is a required step to satisfy the “combination rule” (21 CFR 300.50).
- The Division raised a concern for the proposed dose for D-IVA, noting the current safety database for D-IVA was limited, and safety for D-IVA should not be borrowed from the IVA program. The Division strongly advised that the safety database should consist of 52 week-controlled data for more complete evaluation of safety.
- The Division acknowledged the justification for noninferiority margin using a meta-analytic approach and noted that substitution of D-IVA for IVA adds uncertainty for indirect comparison. The Division recommend that Vertex submit further biological or clinical justification for the proposed margin.

On April 26, 2021, a Type C meeting request was submitted to discuss Vertex’s approach in demonstrating the contribution of the individual components of the fixed-dose combination therapy VNZ/TEZ/D-IVA and the design of 3-way crossover study to evaluate the PK interaction potential among VNZ, TEZ/D-IVA, and VNZ/TEZ/D-IVA. The Preliminary Comments issued on August 12, 2021, noted that final determination of satisfying the combination rule would depend on the strength of the D-IVA to IVA bridge and that although the proposed 3-period crossover study design for the PK DDI study for individual components was reasonable, the waiver of a DDI study between TEZ and D-IVA should be sufficiently justified. On July 30, 2021, the Division also provided comments on the phase 3 trial protocols submitted on July 8, 2021.

Breakthrough designation request was received on May 27, 2021, and was denied on July 20, 2021, because the data with VNZ/TEZ/D-IVA was limited by small sample size, short study duration, and lack of concurrent standard of care comparison and because the data did not show a substantial improvement over existing therapies.

On October 7, 2021, a Type C meeting request was submitted to discuss the planned pediatric development program, seeking agreement on the proposed study design and the data to support

initiation of Parts A and B of the 6- to 11-year-old cohort. Written responses only (WRO) issued on January 25, 2022, discussed study design, the pediatric indication expansion to younger age groups, and the initiation of 6- to 11-year-old cohorts.

On March 2, 2022, a request for special protocol assessment was submitted under protocol entitled, “*Carcinogenicity Study Protocol: 2-Year Oral Gavage Study in Rats and 6-Month Tg.rasH2 Transgenic Mouse Study.*” Carcinogenicity Assessment Committee provided comments to the proposed mouse and rat study and issued agreement on April 14, 2022.

On April 29, 2022, a Type C WRO meeting was requested to seek feedback on whether the available clinical data (from Studies 103 and 105) and in vitro data are sufficient to support the inclusion of CF subjects with a variant in the *CFTR* gene other than *F508del* in the proposed indication. In a WRO issued on July 11, 2022, the Division provided comments on the proposal to leverage in vitro Fischer Rat Thyroid (FRT) data to support inclusion of *CFTR* variants in the prescribing information for VNZ/TEZ/D-IVA and stated that the final determination would be a review issue.

On January 19, 2023, a CMC meeting request was submitted to seek feedback on proposed VNZ drug substance starting materials, VNZ drug substance impurity control strategy (b) (4) WRO was issued on March 21, 2023.

A Proposed Pediatric Study Request was submitted on July 7, 2023, investigating the potential use of VNZ/TEZ/D-IVA in the treatment of CF patients >1 year of age who have at least one responsive variant in the *CFTR* gene. In response, the Division issued a Pediatric Written Request on December 6, 2023.

On February 7, 2024, the intent to use the priority review voucher (PRV NDA 210941) was received under NDA 218730.

The initial request for Pre-NDA meeting was received on December 15, 2023, then subsequently rescheduled to February 2, 2024. In the Meeting Minutes issued on April 9, 2024, the Division noted that to support priority review, the NDA submission should clearly address the noted review issues: satisfaction of the “combination rule” for all variants whether supported by clinical and/or nonclinical data, dose justification for D-IVA for all age groups, adequacy of in vitro data to support the indication for additional *CFTR* variants, and the adequacy of the safety database. In addition, the application will need to include any clinical or in vitro data in its entirety and a summary table of all *CFTR* variant indications, organized by clinically meaningful groupings, which clearly outlines the origin of primary data to support an indication, as well as any complementary data. The Division also did not agree to the submission of the proposed FRT data during the review period.

On May 2, 2024, Vertex submitted an NDA for VNZ/TEZ/D-IVA, “for the treatment of CF in patients aged 6 years and older who have a least one *F508del* mutation or another responsive mutation in the *CFTR* gene.”

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The Applicant has conducted a comprehensive program of pharmacology, pharmacokinetic, and toxicology studies to support clinical development and the NDA submission of VNZ/TEZ/D-IVA. VNZ is the only component of this triple combination (TC) for which a complete nonclinical program was needed. All pivotal toxicology studies of VNZ have been submitted and reviewed previously under IND 142001. The Applicant performed a bridging study between D-IVA and IVA to leverage existing IVA nonclinical data. The Applicant has also provided combination toxicology studies for the new TC. The impurities studies have been submitted and reviewed under this application. The key findings from the nonclinical studies are cited and summarized in this review to support the approval of NDA 218730.

13.1.1. Pharmacology

Primary pharmacology studies using human bronchial epithelial (HBE) cells from CF donors demonstrated that VNZ was able to improve CFTR glycosylation which would be expected to improve CFTR trafficking to the membrane. VNZ alone did not greatly improve CFTR function as evaluated by chloride (Cl) transport. However, VNZ in combination with TEZ and IVA greatly enhanced CFTR activity. VNZ did not appear to act as a potentiator for CFTR. Secondary pharmacology studies found that VNZ inhibits human prostanoid EP4 (K_i 0.64 μ M), IP (PGI₂) (K_i 0.83 μ M), prostanoid EP3 (K_i 1.27 μ M), prostanoid EP2 (K_i 3.23 μ M), rat adrenergic α_{1A} (K_i 3.48 μ M), and rat adrenergic α_{1B} (K_i 7.46 μ M).

13.1.2. Safety Pharmacology

Safety pharmacology studies indicated that VNZ does not affect the CNS or respiratory systems in rats at doses up to 10 mg/kg. In a good laboratory practice (GLP) human ether-a-go-go related gene assay, VNZ inhibited the channel with a half maximal inhibitory concentration (IC_{50}) of 0.7 μ M. The safety pharmacology study evaluating cardiovascular toxicity in dogs did not note any treatment-related effects. Additionally, the 4-week and 39-week repeat-dose toxicology studies in dogs evaluated electrocardiogram (ECG) parameters and did not find any treatment-related effects. Therefore, the results of the human ether-a-go-go related gene assay were not considered clinically meaningful.

Absorption, Distribution, Metabolism, Excretion/PK

Metabolite profiling using liver microsomes and cryopreserved hepatocytes of human, rat, dog, and monkey origin did not identify any human-specific metabolites. There were also no major metabolites identified in rats, dogs, or monkeys. Cytochrome P450 (CYP)3A4/5 appeared to be the major metabolic enzymes responsible for VNZ metabolism via oxidative metabolism. VNZ does not appear to partition into rat, dog, monkey, or human red blood cells. Plasma binding was high (>99.9% bound) across rats, dogs, monkeys, and humans. Tissue distribution study using

male Sprague-Dawley rats given single oral doses of VNZ (3, 10, and 30 mg/kg), found little drug distribution to the brain, lung, heart, and kidney (tissue to plasma ratios ranged from 0.115-1.18 and did not increase with dose). Liver to plasma ratios were higher than all other tissues and decreased with increasing dose (17.3, 11.53, and 3.16, respectively).

13.1.3. General Toxicology

Repeat Dose Toxicology Studies In Rats

4-Week Rat Study (VRT-1725010-TX-006)

In a GLP study, Sprague Dawley rats (10 animals/sex/group) were administered VNZ by oral gavage once daily at 0 (vehicle), 1, 5, and 20 mg/kg/day in males and at 0, 0.5, 2.5, and 10 mg/kg/day in females for 4 weeks. The sex-specific dosing was due to preliminary studies showing that female rats had twice the exposure of male rats receiving the same dose. There was one low dose female that was euthanized on Day 7 due to shallow, difficult breathing. The cause of death was likely from technical error with the gavage delivery. Hematology noted a dose-dependent decrease in basophil counts in both males and females. Monocyte counts increased in a dose-dependent manner for both sexes. No potential target organs of toxicity were identified. The no observed adverse effect level (NOAELs) were identified as 20 mg/kg (AUC: 418 hr·µg/mL) for males and 10 mg/kg (AUC: 655 hr·µg/mL) for females.

26-Week Rat Study (VX-121-TX-007)

In a GLP study, Sprague Dawley rats (15 animals/sex/group) were administered VNZ by oral gavage once daily at 0 (vehicle), 5, 12, 25, and 125 mg/kg/day in males and 0, 2.5, 6, 12.5, and 30 mg/kg/day in females for 26 weeks with additional animals included in the control and 125(male)/30(female) mg/kg/day groups for a 6-week recovery period. All male rats administered 125 mg/kg/day VNZ were found dead or euthanized by Day 14 of the study due to declining clinical condition. Most of the animals had erosions or ulcers in the nonglandular or glandular stomach. Four female rats in the main and toxicokinetic groups administered 30 mg/kg/day VNZ were euthanized or found dead on Day 98, 136 (2), and 183. A cause of death was not identified for all of the female rats but several had findings in the stomach. Target organs of toxicity were the liver (hepatocellular vacuolar degeneration for males at 25 and 125 mg/kg/day and multifocal hepatocellular necrosis for females at the 30 mg/kg/day), glandular stomach (erosion(s) and severe ulceration for males at 125 mg/kg/day and females at 30 mg/kg/day), nonglandular stomach (ulceration for males at 125 mg/kg/day, hyperplasia and/or hyperkeratosis in males at 125 mg/kg/day and females at 30 mg/kg/day), adrenal gland (hypertrophy for males ≥ 25 mg/kg/day and females ≥ 12.5 mg/kg/day), and decreases in lymphocytes in the spleen, thymus, and lymph nodes for males ≥ 25 mg/kg/day and females ≥ 12.5 mg/kg/day. The NOAELs were identified as 12 mg/kg/day (AUC: 390 µg·hr/mL) for males and 12.5 mg/kg/day (AUC: 1120 µg·hr/mL) for females due to mortality, reduced body weight, multifocal hepatocellular necrosis, ulcers and/or erosions in the glandular and nonglandular stomach for males at 125 mg/kg/day and females at 30 mg/kg/day, and hepatocellular vacuolar degeneration for males at 25 and 125 mg/kg/day.

Repeat Dose Toxicology Studies In Beagle Dogs

4-Week Dog Study (VRT-1725010-TX-007)

In a GLP study, Beagle dogs (4 animals/sex/group) were administered VNZ by oral gavage once daily at 0 (vehicle), 0.3, 1.0, and 4.0 mg/kg for 4 weeks. One high dose female was euthanized on Day 11 due to clinical signs of coughing, lacrimation, decreased activity, emesis with frothy white material that progressed to frothy red material, and red frothy vomitus. At necropsy, the lungs were discolored red which correlated microscopically with hemorrhage. There was also moderate edema and neutrophilic infiltration. These findings were consistent with aspiration of the test article and likely due to a gavage error. There were no adverse findings in the remaining animals at the end of the study. No potential target organs of toxicity were identified. The NOAEL identified as 4.0 mg/kg (AUC: 356 µg·hr/mL, average of males and females).

39-Week Dog Study (VX-121-TX-008)

In a GLP study, Beagle dogs (4 animals/sex/group) were administered VNZ by oral gavage once daily at 0 (vehicle), 1.5, 4, or 10 mg/kg for 39 weeks with additional animals included in the control and 10 mg/kg/day groups for a 6-week recovery period. All dogs were sexually mature based on histopathologic assessment. No potential target organs of toxicity were identified. The NOAEL was identified as 10 mg/kg/day (AUC: 1960 µg·hr/mL, average of males and females).

Special Studies

13-Week Oral Rat Bridging Study for D-IVA

A 13-week oral rat bridging study (VX-561-TX-001) was conducted to compare D-IVA at 0 (vehicle), 8.75, 17.5, 35, or 100 mg/kg/day to IVA at 100 mg/kg/day only. Unscheduled deaths in 19% of 100 mg/kg D-IVA and 11% of 100 mg/kg IVA animals resulted in early termination of both 100 mg/kg groups one week early. Target organs were identified as the kidney (basophilic tubules, tubular dilatation, and interstitial fibrosis), stomach (increased mucosal thickness), and thyroid (follicular cell hypertrophy). There were no toxicologically significant differences in clinical pathology, organ weights, or histopathology at 100 mg/kg/day D-IVA versus IVA. There were no adverse findings at the lower D-IVA doses. The NOAEL was identified as 35 mg/kg/day D-IVA. This study was judged adequate to establish a bridge to the ivacaftor nonclinical program to support the clinical development of D-IVA. No further general toxicology, developmental and reproductive toxicology, or carcinogenicity studies were recommended.

13-Week Combination Rat Study (VX-121-TX-012/VX-661-TX-088/VX-561-TX-001)

In a GLP study, Sprague Dawley rats (10 animals/sex/group) were administered 0 (vehicle), - VNZ (2.5 mg/kg/day) alone or in dual or TC with TEZ (45 mg/kg/day) and/or D-IVA (17.5 mg/kg/day) by oral gavage once daily for 13 weeks. TEZ- and VNZ/D-IVA/TEZ-related clinical chemistry (decreases in triglyceride concentrations) and urinalysis effects (increases in urine volume with concurrent decreases in urine specific gravity) were observed in males. No potential target organs of toxicity were identified. There were no additive toxicity effects when VNZ was administered in combinations with TEZ and/or D-IVA. The NOAELs were identified

as VNZ, TEZ, or D-IVA, alone at 2.5, 45, or 17.5 mg/kg/day, respectively, or in combination at 2.5/17.5 mg/kg/day (VNZ/D-IVA) or 2.5/17.5/45 mg/kg/day (VNZ/ D-IVA/TEZ).

Vanzacaftor Toxicokinetics and Exposure Margins

Adequate exposure margins between the nonclinical general toxicology studies and proposed human doses of VNZ were obtained throughout the clinical development program.

Table 68. Toxicokinetics and Exposure Margins

Study	Species	NOAEL Dose (mg/kg)	AUC _{0-24h} (µg·h/mL)	Exposure Margin ^a
26-week rat study	Rat	VNZ 12 (M)/ 12.5 (F)	390 (M)/ 1120 (F)	20.5 (M)/ 58.9 (F)
39-week dog study	Dog	VNZ 10	1960	103.1
13-week combination rat study	Rat	VNZ/TEZ/D-IVA 2.5/45/17.5	VNZ/TEZ/D-IVA 75.4/309.3/91.4(M) 164.0/464.1/65.1(F)	VNZ/TEZ/D-IVA 4.0/1.4/1.1 (M)/ 8.6/2.1/0.8 (F)

Source: Reviewer generated table; Applicant provided data.

^a Clinical exposure of VNZ in CF subjects at a VNZ/TEZ/D-IVA triple combination treatment with VNZ dose of 20 mg QD. Report T270/Tables 8 and S11; Report T271/Tables 8 and 17; and Report T406/Table 11.7. Clinical exposure values at doses of 20 mg VNZ/100 mg TEZ/250 mg D-IVA were 19.0 µg·h/mL for VNZ, 89.0/130/ µg·h/mL for TEZ/M1-TEZ, and 39.3/30.4/13.3 µg·h/mL for D-IVA/M1-D-IVA/M6-D-IVA.

Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 extrapolated to 24 hr; CF, cystic fibrosis; D-IVA, deutivacaftor; F, female; M, male; M, metabolite; NOAEL, no observed adverse effect level; QD, once daily; TEZ, tezacaftor; VNZ, vanzacaftor

13.1.4. Genetic Toxicology

Vanzacaftor was negative in the Ames assay, in vitro micronucleus assay in TK6 cells, and in vivo micronucleus assay in male Sprague-Dawley rats.

Carcinogenicity

In the 6-month carcinogenicity study, transgenic rasH2 mice were administered 0 (vehicle), 3, 10, and 30 mg/kg/day vanzacaftor by oral gavage. The Applicant did have concurrence from the Executive Carcinogenicity Assessment Committee for dose selection. There were no treatment-related effects on mortality rates and body weights. There were no statistically significant treatment-related tumor findings in male or female mice. All animals in the positive control group (urethane) were observed with neoplastic findings. Non-neoplastic target organs of toxicity were kidney (multifocal unilateral mononuclear cell infiltration) and thymus (minimal hemorrhage).

Developmental and Reproductive Toxicology

Fertility Studies

In a GLP fertility study (Study VX-121-TX-009), VNZ was administered to rats at oral doses of 0 (vehicle), 2.5, 5, and 12.5 (Male, M)/10 (Female, F) mg/kg/day (3, 9, and 19 (M)/30 (F) times the exposure at the maximum recommended human dose [MRHD], respectively). Males were dosed for 28 days prior to mating, throughout mating, and continuing until the day prior to euthanasia. Females were dosed for 14 days prior to mating, throughout mating, and continuing until Gestation Day 7. VNZ had no effects on male and female fertility and reproductive performance indices up to 12.5 (M)/10 (F) mg/kg/day (19 (M)/30 (F) times the exposure at the

MRHD). In conclusion, the NOAEL for fertility in this study was determined to be 12.5 mg/kg in males and 10 mg/kg in females associated with AUC_{0-24h} of 361 and 565 µg·hr/mL, respectively.

Embryofetal Development Studies

In a GLP embryo-fetal development study (Study VX-121-TX-005), pregnant rats were administered VNZ at oral doses of 0 (vehicle), 2.5, 5, and 10 mg/kg/day (4, 10, and 30 times the exposure at the MRHD, respectively) during the period of organogenesis from gestation days 6 to 17. VNZ did not cause adverse effects to the fetus at exposures up to 30 times the MRHD. In conclusion, the NOAEL for maternal and embryo/fetal toxicities was determined to be 10 mg/kg/day (AUC_{0-24h}, 565 µg·hr/mL) in rats.

In a GLP embryo-fetal development study (Study VX-121-TX-006), pregnant rabbits were administered VNZ at oral doses of 0 (vehicle), 10, 40, and 70 mg/kg/day (3, 22, and 71 times the exposure at the MRHD, respectively) during the period of organogenesis from gestation Days 7 to 20. VNZ did not cause adverse effects to the fetus at maternal exposures up to 22 times the MRHD. The high dose of 70 mg/kg/day (71 times the exposure at the MRHD) produced maternal toxicity (i.e., mortality, abortion, decreased mean body weight or body weight gains) and was associated with findings of increased postimplantation loss, decreased live fetuses, decreased fetal body weight, increased kidney malformations, and increased incidences of skeletal variations. The effects observed at the high dose were related to maternal toxicity and so were not considered relevant to the human risk. In conclusion, the NOAEL for maternal and embryo/fetal toxicities was determined to be 40 mg/kg/day (AUC_{0-24h}, 410 µg·hr/mL) in rabbits.

Pre- and Postnatal Development Study

In a GLP pre- and postnatal development study (Study VX-121-TX-017), pregnant rats were administered VNZ at oral doses of 0 (vehicle), 2.5, 5, and 10 mg/kg/day (approximately 2, 7, and 18 times the exposure at the MRHD, respectively) from gestation Day 7 to lactation/postpartum Day 20. No adverse effects were observed in the offspring at maternal doses up to approximately 18 times the MRHD. On PND 14, AUC values of VNZ in dams were 10.0 to 28.6 times greater than that in pups. In conclusion, the NOAEL for maternal and developmental toxicities was determined to be 10 mg/kg/day (AUC_{0-24h}, 339 µg·hr/mL) in rats.

Juvenile Animal Study

In a GLP juvenile animal study (Study VX-121-TX-019), juvenile rats were administered VNZ at oral doses of 0 (vehicle), 2.5, 10 (M)/6 (F), and 25 (M)/12.5 (F) mg/kg/day (approximately 4, 15, and 58 (M)/ 28 (F) times the exposure at the MRHD, respectively) from postnatal Day 7 through postnatal Day 70. No adverse effects were observed at oral doses up to approximately 58 (M)/28 (F) times the MRHD. Increased in white blood cell count, gamma-glutamyl transferase activity, total bilirubin, total bile acids, and phosphorus concentrations and decreased cholesterol and urea were observed in a dose-dependent manner in VNZ-treated groups. Without associated histopathological findings, these findings are not considered adverse. In conclusion, the NOAEL for juvenile toxicities was determined to be 25 mg/kg/day in males and 12.5 mg/kg/day in females, associated with AUC_{0-24h} of 1100 and 532 µg·hr/mL, respectively.

Referenced NDAs, Biologics License Applications, Drug Master Files

- NDA 203188 KALYDECO (IVA) [tablet]
- NDA 210491 SYMDEKO (TEZ/IVA)
- NDA 212273 TRIKAFTA (ELX/TEZ/IVA)

13.2. Individual Reviews of Studies Submitted With the New Drug Application

3.2.S.3.2 Impurities

The Applicant followed the recommendations of the International Council for Harmonisation (ICH) guidance for industry *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* ([March 2018](#)) and evaluated the mutagenic potential of impurities based on literature, internal databases, and in silico assessment including Leadscape Genetox Statistical Models and Derek Nexus. Overall, the proposed impurity specifications are acceptable and there are no outstanding nonclinical safety concerns.

Other identified impurities are appropriately controlled per the ICH guidance for industry *Q3A(R) Impurities in New Drug Substances* ([June 2008](#)), ICH guidance for industry *Q3B(R) Impurities in New Drug Products* ([August 2006](#)), United States Pharmacopeia (USP) Guidelines or qualified in nonclinical toxicology studies.

14. Clinical Pharmacology

Of note, in this review, early development names are also used to refer to active ingredients: VX-445 (Elexacaftor, ELX), VX-121 (vanzacaftor, VNZ), VX-561 (deutivacaftor, D-IVA), VX-770 (ivacaftor, IVA), VX-661 (tezacaftor, TEZ).

14.1. In Vitro Studies

14.1.1. In Vitro ADME Studies

In vitro studies are listed in [Table 69](#).

Table 69. In Vitro Studies (Using Human Biomaterials) of Vanzacaftor, Deutivacaftor and Its Major Metabolites

ADME	Conclusions	Study/Report
<i>Vanzacaftor</i>		
Absorption	VNZ is not a substrate for P-gp.	T327

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

ADME	Conclusions	Study/Report
Distribution	Blood to plasma concentration ratio of VNZ (1 μ M) in human was 0.588 (N309) and 0.513 (N277).	N309, N277
	VNZ exhibited high binding to plasma proteins with average percent bound values of 99.99% for human.	N355
	In vitro, VNZ binds more extensively to human serum albumin (HSA) than α 1-acid glycoprotein (AAG), suggesting that HSA is likely the major human plasma protein for VNZ binding and AAG plays a minor role.	T440
	To estimate the free concentration in the HBE assay, protein binding of VNZ in HBE medium containing 20% human serum was evaluated by equilibrium dialysis. The percent bound value of VNZ in HBE medium containing 20% human serum was 99.89%.	T321
Metabolism	VX121 is stable (>85% remaining) when incubating with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6. The compound shows greater turnover in CYP3A4 (43% remaining) and CYP3A5 (81% remaining), suggesting CYP3A isozymes are primarily responsible for VNZ metabolism.	N295
	In vitro metabolite profiles were qualitatively similar across human, mouse, rat, dog, and monkey. No human-specific metabolites were observed in vitro.	N312
	Metabolic profile of ^{14} C-VX121 was investigated in plasma, urine, and feces samples from the mass balance Study 004. See individual study report for Study 004 for summary of results.	(b) (4) 33036, R190
DDI Potential-CYP Induction	VNZ is predicted to have a low potential for CYP3A4 induction at clinically relevant concentrations.	N322, N189
DDI Potential-CYP Inhibition	The IC ₅₀ values of VNZ for inhibition of CYP1A2, CYP2C19, CYP2D6, and CYP3A, were all greater than 30 μ M, suggesting low potential for inhibition of these enzymes by VNZ.	N189
	Weak inhibition of CYP2B6, CYP2C8, and CYP2C9 was observed (IC ₅₀ =14.2, 18.1, and 18.4 μ M, respectively). Pre-incubation of VNZ with human liver microsomes in the presence of NADPH indicated the potential of VNZ to inactivate CYP3A4/5 in a time-dependent manner was low.	
DDI Potential-Transporter	VNZ is not a substrate of human OATP1B1 or OATP1B3.	T329
	VNZ is neither a human P-gp substrate nor a human BCRP substrate.	T328
	VNZ is a P-gp inhibitor with an IC ₅₀ of 3.80 μ M.	T325
	VNZ has a potential to inhibit BCRP in vivo (IC ₅₀ =0.252 μ M).	T326
	VNZ has low potential to inhibit OATP1B1 and OATP1B3 in vivo at the therapeutic dose.	T330
	VNZ is not expected to cause clinically relevant drug interactions via inhibition of OAT1 in vivo.	T331
	The potential of VNZ to inhibit OAT3 transporter in the clinic is predicted to be low.	T347
	No concentration dependent inhibition of OCT _{1/2} and MATE1/2-K by VNZ was observed in vitro with IC ₅₀ values >81 μ M.	T332, T334
hERG assay	The IC ₅₀ for the inhibitory effect of VNZ on hERG potassium current was 0.7 μ M (Hill coefficient =1.5), which provides >~3800-fold margin over the predicted free C _{max} at the projected therapeutic dose.	VRT-1725010-TX-011
<i>Deutivacaftor</i>		
Absorption	D-IVA is a substrate for P-gp.	T335

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

ADME	Conclusions	Study/Report
Distribution	An in vitro study showed that blood to plasma concentration ratio in human was 0.612-0.738 and 0.869-0.902 for D-IVA and M1-D-IVA, respectively.	S080
	D-IVA and M1-D-IVA exhibited high binding to human plasma protein, with average percent bound values of 99.93% and 99.24%, respectively.	T235
	In vitro, D-IVA and M1-D-IVA bind more extensively to HSA than AAG, suggesting that HSA is likely the major human plasma protein for D-IVA and M1-D-IVA binding and AAG plays a minor role.	S079
Metabolism	D-IVA was stable (>85% remaining) when incubating with CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP2D6. D-IVA showed greater turnover in CYP3A4 (6.00% remaining), and CYP3A5 (18.6% remaining), indicating that CYP3A isozymes are primarily responsible for D-IVA metabolism.	S286
	Metabolism of D-IVA in human liver microsomes and human hepatocytes involved oxidation of the deuterated tert-butyl to form M1-D-IVA and its sequential metabolite, M6-D-IVA.	CTP-656 DM-087, D-IVA DM-046
	D-IVA exhibited an approximately 2.5 times longer $t_{1/2}$ than IVA (12.2 vs 4.8 minutes) in human recombinant CYP3A4 in vitro.	S109
DDI Potential-CYP Induction	D-IVA, M1-D-IVA, and M6-D-IVA are predicted to have low induction potential for CYP1A2, CYP2B6, and CYP3A4.	CNCT-1005
DDI Potential-CYP Inhibition	In vitro inhibition data indicate low potential for inhibition of CYP1A2, CYP2B6, CYP2C19, and CYP2D6 by D-IVA, M1-D-IVA, and M6-D-IVA.	D-IVA DM-058, CTP-656 DM-085, S016
	D-IVA and M1-D-IVA have comparable inhibition potency of CYP2C8, CYP2C9, and CYP3A.	D-IVA DM-058, CTP-656 DM-085
	The potential of D-IVA to inactivate CYP3A4/5 in a time-dependent manner was low.	S016
DDI Potential-Transporter	D-IVA and M1-D-IVA are not substrates of OATP1B1 or OATP1B3, but they are substrates of P-gp and BCRP, whereas M6-D-IVA is a substrate of OATP1B1, OATP1B3, and BCRP but not a substrate of P-gp.	T335, T336, T366, CTP-656 DM-090
	D-IVA and M1-D-IVA inhibits P-gp with IC_{50} s of 3.83 and 9.86 μ M, respectively. D-IVA and M1-D-IVA inhibits BCRP with IC_{50} s of 1.19 and 9.15 μ M, respectively.	S082, T324, T348, T450, CTP-656 DM-090
	No dose-dependent inhibition of OATP1B1/3, OAT1/3, OCT $_{1/2}$, and MATE1/2-K, by D-IVA, M1-D-IVA and M6-D-IVA was observed with all IC_{50} values >100 μ M. D-IVA, M1-D-IVA and M6-D-IVA had a weak inhibition of BSEP in vitro with IC_{50} values >10 μ M.	
hERG assay	D-IVA inhibited hERG current with an IC_{20} of 0.86 μ M, which provides >200 fold margin of exposure over the proposed therapeutic dose of 250 mg QD.	CTP-656-SP-024

Source: Reviewer's summary

Abbreviations: ADME, absorption, distribution; metabolism; and excretion; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; C_{max} , maximum plasma concentration; CYP, cytochrome-P450; D-IVA, deutivacaftor; DDI, drug-drug interaction; HBE, human bronchial epithelial; hERG, human ether-à-go-go-related gene; IC_{50} , half maximal inhibitory concentration; M, metabolite; MATE, multidrug and toxin extrusion transporter; NADPH, nicotinamide adenine dinucleotide phosphate; OAT, organic anion transporter; OCT, organic cation transporter; P-gp, P-glycoprotein; VNZ, vanzacaftor

14.1.2. In Vitro Electrophysiology Studies

Regulatory History

There is regulatory precedent for using in vitro data from the Ussing chamber assays to support expansion of approval for IVA (NDA 203188 KALYDECO), TEZ/IVA (NDA 210491 SYMDEKO), and ELX/TEZ/IVA (NDA 212273 TRIKAFTA) to *CFTR* variants when the clinical data for that variant was not available. For the combination products, Ussing chamber data have also been leveraged to understand the contribution of each drug component to the overall treatment effect.

For IVA, the Applicant has previously provided Ussing chamber data obtained from CF patient-derived primary HBE cells and FRT cells genetically engineered to express different variant forms of human *CFTR* proteins. The Ussing chamber data for supporting TEZ/IVA and ELX/TEZ/IVA were generated from FRT cell lines mostly, and from HBE cells for limited variants (i.e., *F508del/F508del*, *F508del/minimal function (MF)*, *N1303K/N1303K*, and *N1303K/MF*).

The Applicant also submitted in vitro Western Blot data to demonstrate the treatment effect on the level of mature *CFTR* proteins delivered to the cell membrane. Western Blot data are useful to understand the mechanism-of-action of TEZ, ELX, and VNZ, which affect processing and trafficking dysfunctions. However, Western Blot data have not been used to identify whether a *CFTR* variant is a “responder” to treatment. For this purpose, direct measurement of chloride transport using the Ussing chamber assay is used.

Background for the Current Application

The currently approved triple combination therapy for CF patients carrying treatment-responsive *CFTR* variants is ELX/TEZ/IVA. NDA 218730 is for a new triple combination that includes a new molecular entity VNZ to replace ELX, and a deuterated isotopologue of IVA (D-IVA) to replace IVA. VNZ performs the same function as ELX to help processing and trafficking of mutant *CFTR* proteins, thereby increasing their surface expression. D-IVA performs the same function as IVA to increase the amount of time that *CFTR* channels stay in the open state, thereby allowing more ions to pass through. The Applicant has identified 303 variants to be responsive to VNZ/TEZ/D-IVA, based on the following evidence or rationale:

Clinical Data (24 Variants Total)

- Twenty-four variants, including *F508del* and 23 other triple combination-responsive variants are supported with clinical data. These variants are already indicated for ELX/TEZ/IVA.

In Vitro FRT Data (257 Variants Total)

- One hundred and twenty-nine (129) variants respond to TEZ/IVA or IVA. These have not been tested with VNZ/TEZ/D-IVA directly. The rationale that they will respond to VNZ/TEZ/D-IVA is based on data that shows functional equivalence of D-IVA and IVA, and the idea that further functional correction, hence additional clinical benefit, can be expected by the additional drug components in the new triple combination.
- Seventy-four (74) variants that were recently shown to respond to ELX/TEZ/IVA (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]; source: U032) are now shown to respond to VNZ/TEZ/D-IVA (source: U015).
- Twenty-three (23) variants that were previously shown to respond to ELX/TEZ/IVA (source: P289v4) but not to TEZ/IVA or IVA are now shown to respond to VNZ/TEZ/D-IVA (source: U015).
- Thirty-one (31) variants did not respond to ELX/TEZ/IVA. These are now shown to respond to VNZ/TEZ/D-IVA (source: U015).

In Vitro HBE Data (One Variant: N1303K)

- N1303K did not respond to ELX/TEZ/IVA when expressed in the FRT system. HBE cells from homozygous and heterozygous N1303K CF donors (the latter with minimal function on the 2nd allele not expected to produce CFTR proteins) are used to demonstrate positive response to ELX/TEZ/IVA and VNZ/TEZ-D-IVA through comparisons with data from *F508del/F508del* and *F508del/MF* HBE cells in response to TEZ/IVA treatment (source: U020 and S525).

Splice Variants (19 Variants Total)

- The rationale for including these noncanonical splice (NCS) variants is that clinical data showed that these variants have phenotype of residual function (RF) (interpreted as the presence of a small number of wild-type CFTR proteins in these subjects) and in vitro FRT data demonstrating VNZ/TEZ/D-IVA increased chloride transport on wild-type CFTR proteins (source: U015).

In Vitro Electrophysiology Data That Directly Compared the Effects of D-IVA and IVA on Chloride Transport

For D-IVA, deuterium is substituted with nine hydrogens at the primary site of metabolism for IVA (on the tert-butyl group adjacent to the hydroxyl group of the phenol) (b) (4)

This strategy is based on the rationale that even though deuterium has similar chemical properties as hydrogen, carbon-deuterium bonds are stronger than corresponding carbon-hydrogen bonds. (b) (4)

Five pieces of in vitro electrophysiology data directly compared the effects of D-IVA and IVA on increasing CFTR-mediated chloride transport. These data are derived from the following experiments and study reports:

For experiments conducted using HBE cells from CF donors

- *G551D/F508del*-HBE cells treated with D-IVA or IVA (source: PH-088)
- *F508del/F508del*-HBE cells pretreated with lumacaftor and then acutely treated with D-IVA or IVA (source PH-088)
- *F508del/F508del*-HBE cells treated with D-IVA or IVA (source: PH-043)
- *F508del*/minimal function variant treated with D-IVA or IVA, in the presence of VNZ/TEZ (source: Q142)

For experiments conducted using FRT cells expressing human *CFTR* variants

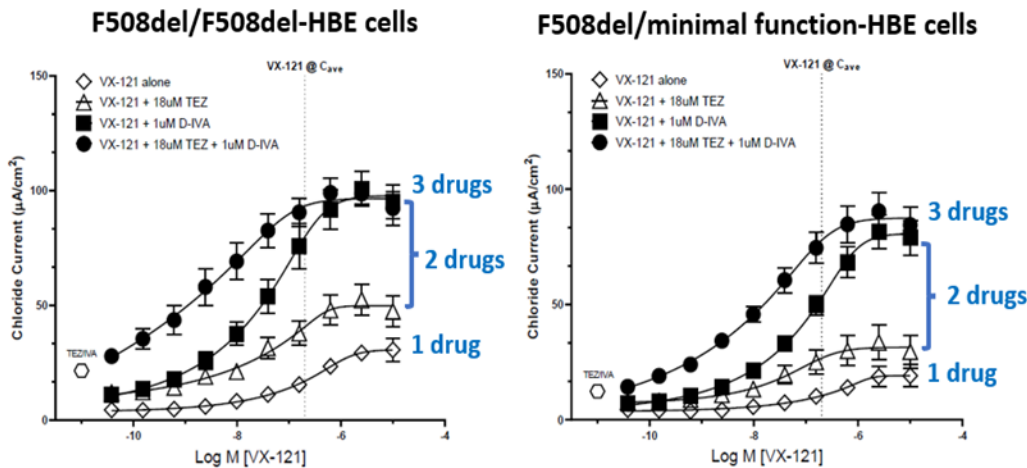
- *G551D CFTR* variant treated with D-IVA or IVA (source: PH-045)

Results from these experiments showed that D-IVA and IVA have similar potencies on increasing CFTR-mediated current or produced similar magnitude of CFTR-mediated chloride transport, supporting the functional equivalence of D-IVA and IVA. The variants studied in these experiments are carried by approximately 85% of CF patients.

In Vitro Electrophysiology Data That Demonstrated Contributions of Individual Drug Components to VNZ/TEZ/D-IVA Triple Combination

Per 21 CFR 300.50(a), “two or more drugs may be combined in a single dosage form when each component makes a contribution to the claimed effect and the dosage of each...is such that the combination is safe and effective for a significant patient population requiring such concurrent therapy...” Two pieces of in vitro electrophysiology data were submitted by the Applicant that can be used to support the benefit of individual drug components in the VNZ/TEZ/D-IVA combination. [Figure 5](#) below shows experiments conducted on HBE cells from CF donors carrying *F508del/F508del* or *F508del/MF* variant. VNZ was tested across multiple concentrations alone, in the presence of TEZ (18 μ M), in the presence of D-IVA (1 μ M), or in the presence of both TEZ/D-IVA. Comparing the magnitudes of chloride transport at the vertical dotted lines in this figure (which correspond to VNZ plasma concentration following an efficacious dose in a phase 2 study), the following order of treatment efficacy can be derived from the comparison of their in vitro potency (from highest to lowest): VNZ/TEZ/D-IVA > VNZ/D-IVA > VNZ/TEZ > VNZ. Note that the TEZ/IVA single-concentration (i.e., 18 μ M/1 μ M) data are displayed to the lower left corner for reference. Given that IVA and D-IVA are demonstrated to be functionally equivalent (see section above), the potency of TEZ/IVA on increasing chloride transport is expected to be similar to TEZ/D-IVA (i.e., 18 μ M/1 μ M).

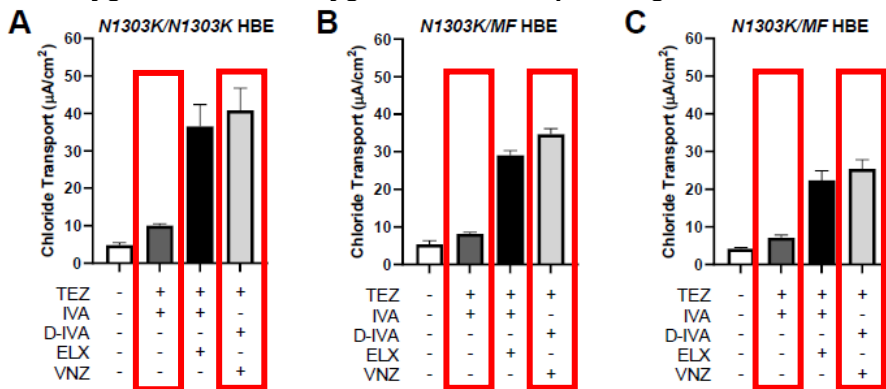
Figure 5. Chloride Transport Measured From Homozygous and Heterozygous *F508del*-Containing HBE Cells to Evaluate the Effects of VNZ, TEZ, and D-IVA in Different Combinations



Source: Modified Figure 3 from Report S525
Abbreviations: C_{avg} , average concentration at steady-state; D-IVA, deutivacaftor; HBE, human bronchial epithelial; TEZ, tezacaftor; VNZ, vanzacaftor; VX-121, vanzacaftor

Figure 6 below summarizes results from experiments conducted on HBE cells from CF donors carrying *N1303K/N1303K* or *N1303K/MF* variants. These experiments allowed for comparisons of chloride transport measured in the presence of VNZ (0.22 μ M), TEZ (18 μ M), and D-IVA (1 μ M) to that measured in the presence of TEZ (18 μ M) and IVA (1 μ M). VNZ/TEZ/D-IVA elicited greater chloride transport than TEZ/IVA. As stated earlier, D-IVA and IVA are considered functionally equivalent in augmenting chloride transport. Altogether, data presented in Figure 5 and Figure 6 illustrate contributions of individual drug components in VNZ/TEZ/D-IVA to the overall effect of this triple combination on increasing chloride transport. The variants covered by experiments presented in Figure 5 and Figure 6 are carried by approximately 85% of CF population.

Figure 6. Comparison of the Effects TEZ/IVA and VNZ/TEZ/D-IVA on Chloride Transport in Homozygous and Heterozygous *N1303K*-Expressing HBE Cells



Source: Modified Figures 3 from Report U020
Panels A, B, and C each summarizes data obtained using cells from one donor.
Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; HBE, human bronchial epithelial; IVA, ivacaftor; MF, minimal function *CFTR* variant; TEZ, tezacaftor; VNZ, vanzacaftor

In Vitro Electrophysiology Data to Support Effectiveness of VNZ/TEZ/D-IVA on Select CFTR Variants

As mentioned above, 257 rare *CFTR* variants are proposed to be responsive to VNZ/TEZ/D-IVA based on in vitro electrophysiology data. Except for 31 variants that were previously found not to respond to ELX/TEZ/IVA, all are included in the ELX/TEZ/IVA label, either currently or proposed in the efficacy supplement under review (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]; source: U032; ELX/TEZ/IVA-responsive variants are listed in p289v4 and U032). The Division of Applied Regulatory Science (DARS) from the Office of Clinical Pharmacology thus focused on these 31 *CFTR* variants for data analysis.

Study Design: Methods of Ussing Chamber Assay

Ussing chamber assays were performed to determine the baseline level of CFTR-mediated chloride transport for mutants and wild-type CFTR proteins, as well as the effect of treatment in increasing CFTR-mediated chloride transport. For *CFTR* variants included in U015, VNZ was tested at 6 concentrations (0, 0.1, 0.3, 1, 3, and 10 μM ; note that only 3 μM data were submitted when the FDA requested raw data for independent analysis through “Information Request” – see below). TEZ (10 μM) and D-IVA (1 μM) were tested at one concentration each. The 3 μM concentration of VNZ was chosen to determine responsiveness. When administered, VNZ, TEZ, and D-IVA were added 18–24 hours prior to electrophysiology recording. During the recording, CFTR-mediated chloride transport was evoked by adding forskolin (10 μM), then verified by eliminating the recorded current using a cocktail of CFTR inhibitors. The current mediated by CFTR channels is calculated as the peak forskolin-evoked response minus the minimum stable chloride current that remained after adding the CFTR inhibitor cocktail (see [Figure 7](#)). The same experimental design was used to study *CFTR* variants included in P289v4 and U032. For the FRT system, *CFTR* variants are defined as responsive to treatment if they exhibit a ≥ 10 percent point increase in chloride transport expressed as percent change of normal over baseline.

For U020, Ussing chamber assays were performed on HBE cells derived from CF donors who were either homozygous or heterozygous for *N1303K* with a MF variant on the other allele that does not produce CFTR protein and is not expected to respond to medications that affect CFTR processing or function. For S525, Ussing chamber assays were performed on HBE cells derived from CF donors who were either homozygous or heterozygous for *F508del* where the variant on the other allele is a MF and does not produce CFTR protein, thus is not expected to respond to medications that affect CFTR processing or function. The N1303K-HBE cells were treated with 18 μM TEZ/1 μM IVA, 3.3 μM ELX/18 μM TEZ/1 μM IVA, or 0.22 μM VNZ/18 μM TEZ/1 μM D-IVA for 18 – 24 hours prior to electrophysiology recording. The F/F- and F/MF-HBE cells were treated with 18 μM TEZ/1 μM IVA for 18 – 24 hours. For electrophysiology recording, chloride transport was evoked with forskolin then eliminated with the CFTR inhibitor cocktail as stated above for the FRT system.

Results: Review of the Ussing Chamber Data

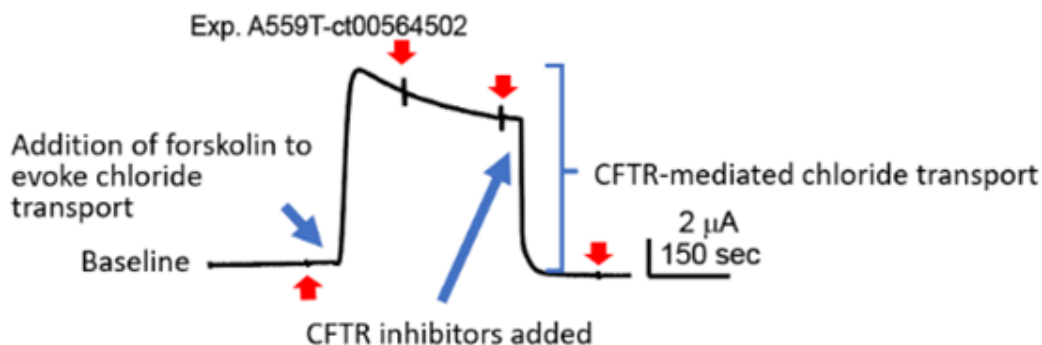
An Information Request was sent to the Applicant to obtain the raw electrophysiology records for the following 15 *CFTR* variants previously demonstrated to not respond to ELX/TEZ/IVA and wild-type *CFTR* channels:

- For U015 that used FRT cells: H119R, G91R, R1066C, Y569C, Q452P, A559T, I506T, A561E, 3195del6, L102R, R560T, I1234Vdel6aa, A559V, I1398S, R1066L, and wild-type *CFTR*

For U020 that used HBE cells from CF donors homozygous or heterozygous for N1303K variant, and for S525 that used HBE cells from CF donors homozygous or heterozygous for *F508del*-variant, DARS had requested the original source waveforms for these experiments and completed data analysis to support the current efficacy supplements for ELX/TEZ/IVA (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]; source: U032). DARS data analysis had been complete, leading to the conclusion that results from U020 and S525 could be used as they are.

The submitted Ussing chamber data by the Applicant were organized in the following manner for every experiment: a column of datapoints for time, and a column of datapoints for chloride transport. Plotting data from these two columns enabled DARS' electrophysiologists to visualize the signal recorded from the epithelial cell layer for the duration of the recording. [Figure 7](#) shows an exemplar recording from one epithelial cell layer of A559T *CFTR* variant.

Figure 7. Transmembrane Current Recorded From the Cells That Expressed A559T Variant



Source: DARS reviewer's analysis

Forskolin was added to elevate cAMP level, leading to activation of the *CFTR* channels. *CFTR* inhibitors were then added to eliminate the current. *CFTR* current amplitude was estimated as the difference between the maxima and minima of the recorded current. Red arrows indicate signals used to assess transmembrane resistance, a data quality metric to ensure preparation health.

Abbreviations: cAMP, cyclic adenosine monophosphate; *CFTR*, cystic fibrosis transmembrane conductance regulator; Exp., expressed; sec, second

These Ussing chamber experiments are high throughput in nature, with each execution testing 96 different epithelial cell layers on a recording plate that can be of different *CFTR* variants and/or treated with different drug combinations. For each variant studied using the FRT system and presented in U015, six experimental replicates were performed, each in a 96-well plate and with three to four technical replicates to assess drug effect and two to 20 technical replicates to measure baseline (no drug) response. The Applicant submitted raw data for recordings on the recording plate, and a plate map for unblinding to identify which recordings corresponded to

CFTR variants identified in U015. DARS electrophysiologists were blinded to treatment conditions and *CFTR* variants tested during the data analysis process, hence analyzed all the submitted recordings. In total, 9,216 electrophysiology recordings were analyzed. The analysis steps are as follows: 1) reconstruct the electrical waveforms and check data quality to verify epithelial cell membrane integrity; 2) quantify treatment effects using DARS own criteria, and 3) after extracting chloride transport measurements, unblind using the plate maps to summarize drug effects on each variant. This process evaluates whether any electrophysiologist would arrive at the same conclusion as the Applicant based on examining the original recorded signals alone.

Summary of DARS Analysis

[Table 70](#) below summarizes the results of DARS measurements (labeled as Office of Clinical Pharmacology “OCP analysis”) versus values presented in U015 study report. Numerical differences in the mean chloride transport and standard deviation (SD) are to be expected, given that the Applicant and DARS have different methods of signal averaging and peak detection to estimate drug response. The closeness of the values, including variability, indicates that DARS independent data analysis performed on the original electrophysiology waveforms reproduced Applicant’s reported values.

Table 70. Evaluation of VNZ/TEZ/D-IVA on Select *CFTR* Variants in Report U015

CFTR Variant	Treatment	OCP analysis		U015 study report	
		$\mu\text{A}/\text{cm}^2$		$\mu\text{A}/\text{cm}^2$	
		Mean	SD	Mean	SD
Q452P*	VNZ/TEZ/D-IVA	92	14	96	8
	no drug	3	0	3	0
A561E	VNZ/TEZ/D-IVA	24	4	24	4
	no drug	2	0	2	0
I1234Vdel6aa	VNZ/TEZ/D-IVA	21	2	21	2
	no drug	2	0	2	0
R560T	VNZ/TEZ/D-IVA	19	3	19	3
	no drug	3	0	3	0
A559T	VNZ/TEZ/D-IVA	52	10	52	10
	no drug	3	1	3	1
R1066L	VNZ/TEZ/D-IVA	41	16	42	15
	no drug	2	0	3	1
R1066C	VNZ/TEZ/D-IVA	131	27	132	27
	no drug	3	1	3	1
H199R	VNZ/TEZ/D-IVA	178	30	180	32
	no drug	3	1	4	1

CFTR Variant	Treatment	OCP analysis		U015 study report	
		$\mu\text{A}/\text{cm}^2$		$\mu\text{A}/\text{cm}^2$	
		Mean	SD	Mean	SD
Wild-type	VNZ/TEZ/D-IVA	437	20	452	30
	no drug	169	29	169	29
G91R	VNZ/TEZ/D-IVA	174	33	174	33
	no drug	4	2	4	2
Y569C	VNZ/TEZ/D-IVA	97	9	97	8
	no drug	4	3	3	1
A559V	VNZ/TEZ/D-IVA	53	12	53	12
	no drug	3	0	3	1
I506T	VNZ/TEZ/D-IVA	50	7	50	7
	no drug	3	0	3	1
3195del6	VNZ/TEZ/D-IVA	39	6	39	6
	no drug	3	0	3	0
I1398S	VNZ/TEZ/D-IVA	22	9	23	9
	no drug	3	0	4	1
L102R	VNZ/TEZ/D-IVA	19	2	19	2
	no drug	2	0	2	0

For Q452P-treated group, dropping one technical replicate that suggested drugs were not added as intended (given no evidence of chloride transport, consistent with Q452P being a MF), then the DARS' mean $\pm$ SD is close to sponsor's reported value (97 $\pm$ 9 for DARS vs 96 $\pm$ 8 in U015).

Source: DARS independent analysis values versus those extracted from Report U015.

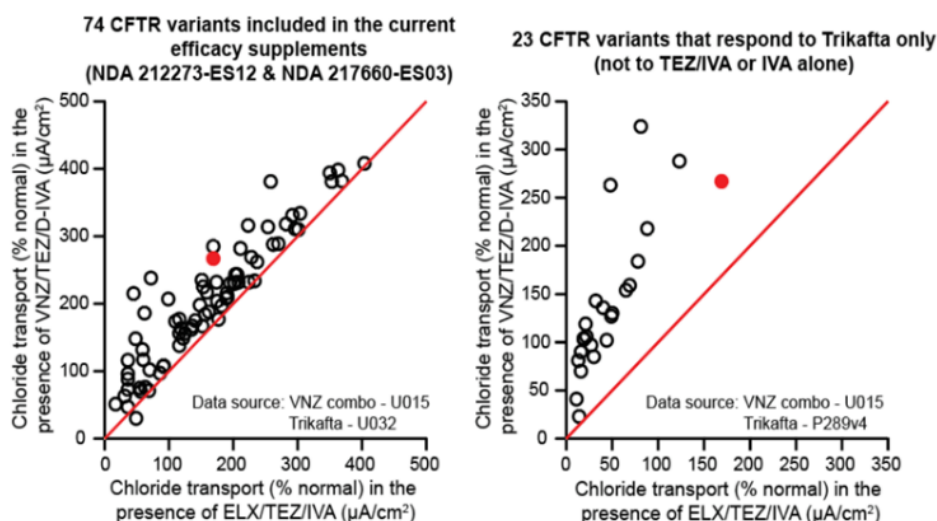
Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; MF, minimal function *CFTR* variant; OCP, Office of Clinical Pharmacology; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor; vs, versus

Comparisons Between the Effects of VNZ/TEZ/D-IVA and ELX/TEZ/IVA on Increasing Chloride Transport in FRT Cells for Select *CFTR* Variants

As stated in the [Background for the Current Application](#) subheading of this section, 97 *CFTR* variants tested in the in vitro FRT systems have both ELX/TEZ/IVA and VNZ/TEZ/D-IVA data. These variants include 74 that are included in the current efficacy supplement (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024

[DARRTS ID: 5493844]) and 23 that responded to ELX/TEZ/IVA but not TEZ/IVA or IVA. [Figure 8](#) below shows this comparison. The red line drawn on each graph indicates where datapoints would lie if ELX/TEZ/IVA and VNZ/TEZ/D-IVA elicited equal magnitude of chloride transport for these *CFTR* variants. Nearly all datapoints lie above the red diagonal lines, indicating that VNZ/TEZ/D-IVA elicits a trend of numerically greater chloride transport than ELX/TEZ/IVA for these *CFTR* variants.

Figure 8. VNZ/TEZ/D-IVA Versus ELX/TEZ/IVA on Chloride Transport for 97 *CFTR* Variants and Wild-Type *CFTR*



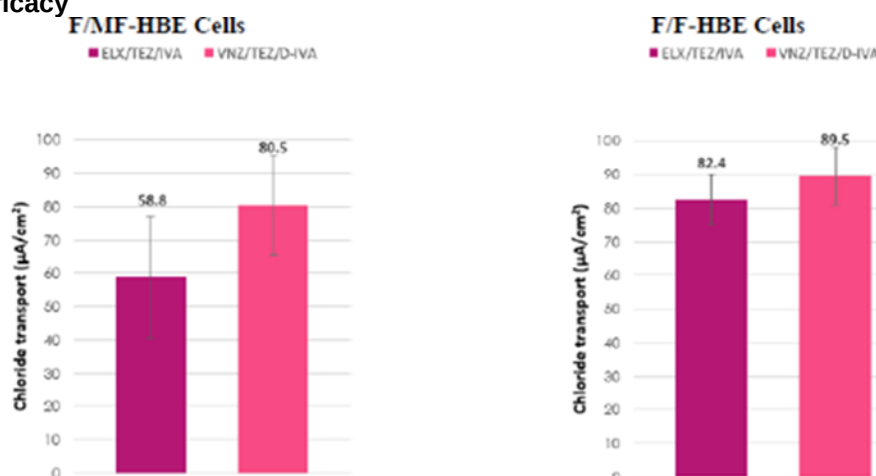
Source: DARS reviewer's analysis

Each open symbol represents a different *CFTR* variant. Wild-type *CFTR* data are shown as solid red symbols.

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

In comparison with the FRT data presented in [Figure 8](#), electrophysiology recordings obtained from HBE cells from *F508del/F508del* and *F508del/MF* CF donors ([Figure 9](#)) and 1303K/N1303K and N1303K/MF CF donors ([Figure 6](#)) showed equivalence of ELX/TEZ/IVA and VNZ/TEZ/D-IVA on increasing chloride transport in these variants.

Figure 9. Noncanonical Splice *CFTR* Variants Without Clinical and Ussing Chamber Data to Support Efficacy



Source: Figure 3, page 24 from 2.5 clinical-overview-us.pdf

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; ELX, elxacaftor; F, *F508del* variant; HBE, human bronchial epithelial; IVA, ivacaftor; MF, minimal function *CFTR* variant; TEZ, tezacaftor; VNZ, vanzacaftor

Justification of Effect of VNZ/TEZ/D-IVA on *CFTR* NCS Variants

Nineteen NCS variants are proposed to be responsive to VNZ/TEZ/D-IVA. Among them, three are supported by clinical data with ELX/TEZ/IVA. Sixteen ultra-rare ones, however, have neither clinical data nor Ussing chamber HBE or FRT data. In general, splice variants result in errors during the mRNA splicing process that then leads to improper intron retention or exon removal. The reason for the lack of FRT data for these splice variants is that the FRT system relies on *CFTR* cDNAs exogenously delivered by DNA vectors. The *CFTR* cDNA sequences do not contain introns, and the system is not suitable to evaluate errors during the mRNA splicing process. These 16 NCS variants are thought to produce a limited amount of wild-type *CFTR* proteins based on some clinical phenotype results. In vitro results showed that wild-type *CFTR* proteins have high baseline activity level and respond robustly to VNZ/TEZ/D-IVA treatment (167% increase in chloride transport over normal in U015, in contrast to the 70%-point increase in chloride transport over normal for ELX/TEZ/IVA in Report P289v4) may be used to support that these splice variants would benefit from VNZ/TEZ/D-IVA treatment. This approach is consistent with the rationale to expand the indication for ELX/TEZ/IVA to this group of variants (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]).

CFTR Variants That Were Evaluated in Clinical Trials for VNZ/TEZ/D-IVA

The Applicant stated in the “Clinical Overview-US” (p. 30, first paragraph) that for the 24 *CFTR* variants evaluated in the phase 3 clinical program (*F508del* and 25 other ELX/TEZ/IVA-responsive variants), there are also data demonstrating response to VNZ/TEZ/D-IVA in the FRT system. Variants studied in the phase 3 clinical program include the following:

- A445E, G1244E, H1054D, L1077P, R1066H, R75Q, S549N, V562I, W1282R, D1152H, G551D, I336K, L206W, S1159F, S549R, V754M, Y563N, *F508del*, G85E, M1101K, R352Q, S1251N, S945L, and W1098C

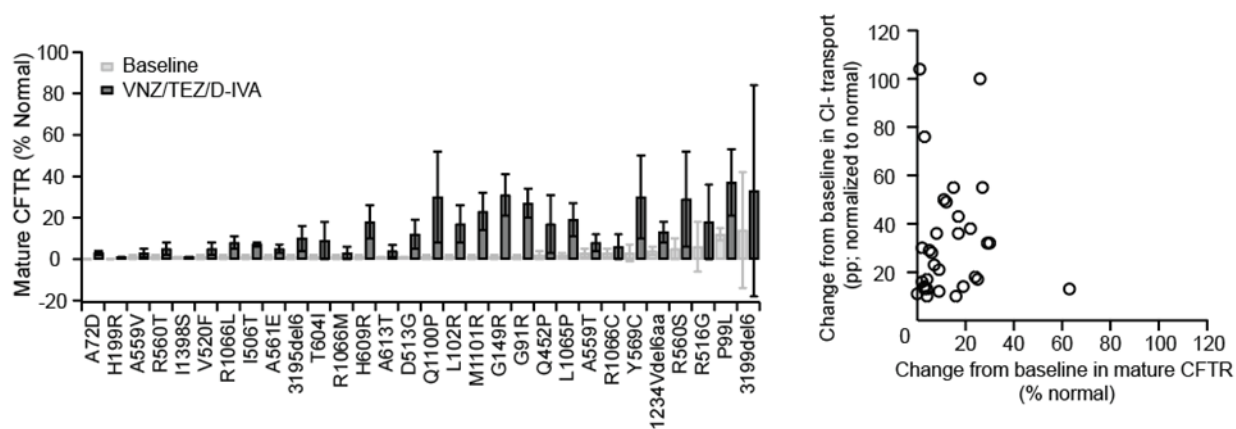
Therefore, U015 study report does not contain effects of VNZ/TEZ/D-IVA for these variants studied in the clinical trials. An updated comparison to capture nonclinical-to-clinical data translation is unlikely needed.

Western Blot Analysis

As stated above in “Regulatory history”, the Applicant also submitted Western Blot data to demonstrate the effect of VNZ/TEZ/D-IVA on the *CFTR* variants. Although useful to understand mechanism-of-action for ELX, TEZ, and VNZ, Western Blot data have not been used to identify treatment-responsive variants because an increase in mature *CFTR* proteins does not necessarily translate to an increase in function.

DARS analyzed the Western Blot data submitted in U015 for the 31 variants responsive to VNZ/TEZ/D-IVA that were not responsive to ELX/TEZ/IVA. The ratios of mature to total *CFTR* proteins indicate that the treatment was effective at improving the maturation of *CFTR* for most variants ([Figure 10](#), left panel). The relationship between the changes induced VNZ/TEZ/D-IVA in maturation of *CFTR* proteins and increase in chloride transport was also analyzed. The right panel of [Figure 10](#) shows that the Western Blot and Ussing chamber data are not strictly correlated, supporting the choice of Ussing chamber functional data over Western Blot data to identify treatment-responsive variants.

Figure 10. Western Blot Results by *CFTR* Variants



Source: Reviewer's analysis

Left panel, mature/total *CFTR* proteins before and after treatment for the 31 variants responsive to VNZ/TEZ/D-IVA that were not responsive to ELX/TEZ/IVA. Right panel, the percent changes from baseline in Ussing chamber experiments for the 31 variants responsive to VNZ/TEZ/D-IVA that were not responsive to ELX/TEZ/IVA were plotted against the percent changes from baseline in mature *CFTR* proteins after treatment in Western Blot experiments. Each circle represents data from a CF variant. There was a lack of correlation between the effects of the triple combination on chloride transport and *CFTR* maturation for these variants. Data source: U015; graphs: DARS reviewer.

Abbreviations: CF, cystic fibrosis; *CFTR*, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; D-IVA, deutivacaftor; ELX, elxacaftor; IVA, ivacaftor; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

Conclusions

- (1) In vitro electrophysiology data obtained in the HBE and FRT systems support functional equivalence of IVA and D-IVA on increasing chloride transport.
- (2) Individual drug components of VNZ/TEZ/D-IVA contribute to the overall effect of the new triple combination on increasing chloride transport.
- (3) The original electrophysiology source waveforms obtained from *CFTR* expressed in FRT cell for 15 variants previously shown not to respond to ELX/TEZ/IVA have been received and independently analyzed by DARS. These recordings are of good quality, performed on uncompromised epithelial cell layers based on transmembrane resistance quality check, and drug effects of VNZ/TEZ/IVA are robust and accurate as reported in U015 nonclinical study report.
- (4) Note that original electrophysiology source waveforms for the HBE experiments performed on *F508del*- and N1303K-containing cells have already been analyzed to support the current efficacy supplements for ELX/TEZ/IVA (refer to the supplemental NDAs 212273/S012 & 217660/S03 uploaded to DARRTS on December 11, 2024 [DARRTS ID: 5493844]). DARS had concluded that these data are adequate and accurate as reflected in the nonclinical study reports U020 and S525.
- (5) Wild-type *CFTR* channels respond to VNZ/TEZ/D-IVA. The results of wild-type *CFTR* have been received and independently analyzed by DARS. These recordings are of good quality, performed on uncompromised epithelial cell layers based on transmembrane resistance quality check, and drug effects of VNZ/TEZ/IVA are robust and accurate as reported in U015 nonclinical study report.

- (6) The rationale for extrapolating wild-type CFTR protein's response toward the new triple combination treatment for the 19 NCS variants is logical from DARS perspective.
- (7) The increases in chloride transport elicited by VNZ/TEZ/D-IVA are generally numerically greater than those elicited by ELX/TEZ/IVA. In vitro electrophysiology data support the clinical conclusion that VNZ/TEZ/D-IVA combination is noninferior in correcting CFTR dysfunction in comparison with ELX/TEZ/IVA combination.

14.2. In Vivo Studies

All clinical pharmacology studies listed in [Table 71](#) were reviewed in this section.

Table 71. Clinical Pharmacology Studies

Study Number	VNZ Drug Substance	Study Description
<i>Studies in healthy subjects</i>		
VX17-121-001	Form A	Part A (SAD, relative BA), B (MAD), C (PK in FDC), and D (PK in CF subjects) of VNZ
VX18-561-001	NA	MAD of D-IVA
VX16-770-018 Part D	NA	Relative BA between IVA and D-IVA
VX19-121-003	Form A, Form D	Relative BA between VNZ formulations, pilot food effect
VX21-121-005	Form A, Form D	Relative BA between separate tablets and FDC, food effect on FDC
VX22-121-009	Form D	Relative BA between different FDC strengths
VX21-121-006	Form A	DDI between VNZ, TEZ, and D-IVA
VX21-121-007	Form A	DDI evaluating itraconazole effect on VNZ
VX18-445-006	Form A	DDI evaluating itraconazole effect on D-IVA
VX20-121-004	Form A	VNZ mass balance study
VX21-121-008	Form D	VNZ hepatic impairment study
VX22-121-013	Form A	VNZ tQT study
<i>Studies in subjects with CF</i>		
VX18-121-101	Form A	VNZ dose-ranging study
VX18-561-101	NA	D-IVA dose-ranging study
VX21-121-105	Form D	Pediatric PK and safety trial

Source: Reviewer's summary

Abbreviations: BA, bioavailability; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; ELX, elexacaftor; FDC, fixed-dose combination; IVA, ivacaftor; MAD, multiple ascending dose; PK, pharmacokinetic; SAD, single ascending dose; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

Majority of the clinical pharmacology studies for TEZ and IVA have been reviewed previously under NDA 203188 (refer to the clinical pharmacology review archived on January 18, 2012) and NDA 210491 (refer to the clinical pharmacology review archived on February 2, 2018).

Excretion of D-IVA in human was not evaluated in a formal human absorption, distribution, metabolism, and excretion (ADME) study.

14.2.1. Single and Multiple Ascending Dose Studies

14.2.1.1. Study VX17-121-001 (Study 001)

Title

A Phase 1/2 Study of VX-121 [VNZ] in Healthy Subjects and in Subjects With Cystic Fibrosis

Study Period

March 20, 2018 to May 3, 2019

Objective

Primary Objectives

- **Part A**: To evaluate the safety and tolerability of single ascending doses of VNZ in healthy subjects
- **Part B**: To evaluate the safety and tolerability of multiple ascending doses of VNZ for 10 days in healthy subjects
- **Part C**: To evaluate the safety and tolerability of multiple ascending doses of VNZ administered in TC with tezacaftor (TEZ)/ivacaftor (IVA) for 14 days in healthy subjects
- **Part D**: To evaluate the safety and tolerability of VNZ/TEZ/IVA in subjects with CF

Study Design

A 4-part, randomized, double-blind, placebo-controlled, single- and multiple-dose, first-in-human and first-in-patient dose escalation study of VNZ that included an evaluation of relative bioavailability (BA) and the effect of milk on VNZ exposure.

Part A, B, and C

Parts A (exclusive of Cohort A9), B, and C were randomized, double-blind, and placebo-controlled study. Subjects were randomized 3:1 to receive either active study drugs or placebo.

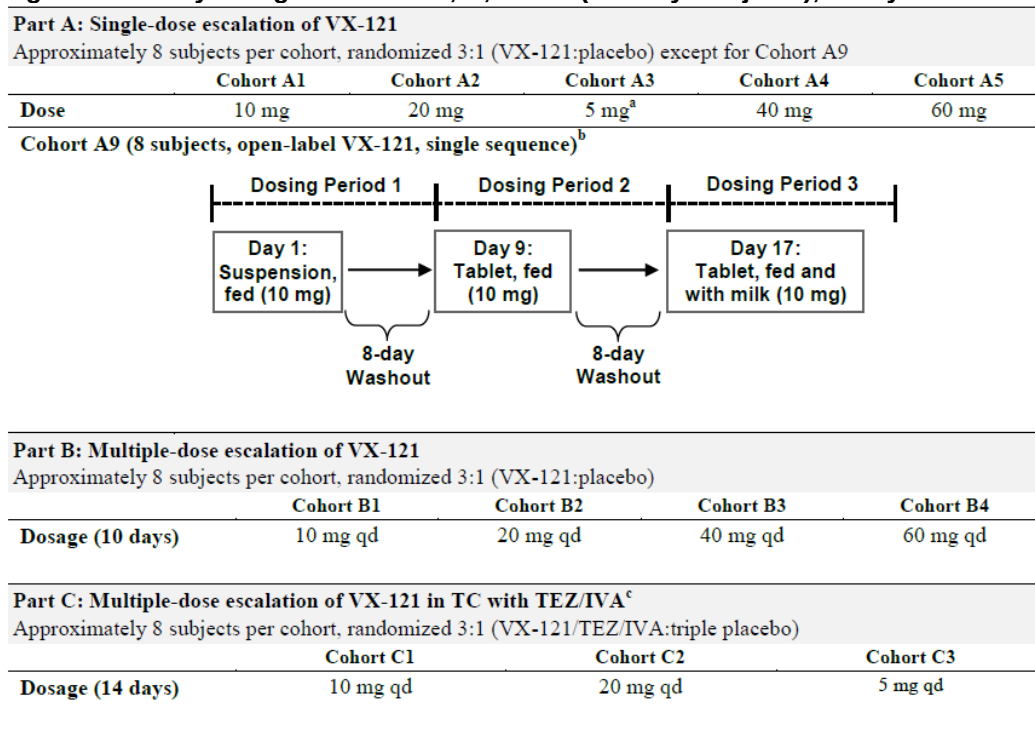
Parts A (exclusive of Cohort A9) and B had a dose-escalation design, with each subject participating in only one cohort (unless at least 21 days had elapsed before participation in another cohort), to avoid PK and/or pharmacodynamic (PD) carryover effects ([Figure 11](#)).

Cohort A9: Subjects in Cohort A9 received three single doses of VNZ to evaluate the BA of a tablet (with calcium restrictions) relative to the suspension formulation (with calcium restrictions) and the effect of milk on the tablet formulation. Each dosing occasion was separated by 8 days.

Part C evaluated the safety, tolerability, and PK of VNZ administered in TC with TEZ/IVA to support potential development of this TC for the treatment of CF. The PK of TEZ and

metabolites, and IVA and metabolites was also evaluated, following administration of VNZ/TEZ/IVA.

Figure 11. Study Design for Parts A, B, and C (Healthy Subjects), Study 001



Source: Figure 2-1 CSR VX17-121-001

^a In addition to randomized study drug administration depicted above, after an 8-day washout, all subjects received an additional 5-mg single dose of open-label VX-121 [VNZ] suspension with milk to evaluate the effect of milk on VX-121 [VNZ] exposure.

^b Subjects received a single dose of VX-121 [VNZ] on three dosing occasions with an 8-day washout between dosing occasions. VX-121 [VNZ] doses included a single oral dose of suspension, a single oral dose of tablet to evaluate the relative BA of the tablet, and a single oral dose of tablet with milk to evaluate the effect of milk on VX-121 [VNZ] exposure.

^c The dosage of TEZ/IVA was TEZ 100mg qd/IVA 150 mg q12h, which was administered as TEZ 100-mg/IVA 150-mg FDC in the morning and IVA 150 mg in the evening.

Abbreviations: BA, bioavailability; FDC, fixed-dose combination; IVA, ivacaftor; q12h, every 12 hours; qd, once daily; TC, triple combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Part D evaluated the safety, tolerability, PK, PD, and efficacy of VNZ/TEZ/IVA in CF subjects who are heterozygous for *F508del* and a MF *CFTR* variants (F/MF genotype) (Figure 12). Because there was no commercially available effective treatment for this population, a placebo arm was included as the control treatment to assess whether any observed effects were treatment-related or simply related to the study conditions.

Figure 12. Study Design, Study 001 (Part D)

Screening Period 4 weeks	Treatment Period ^a 4 weeks	Safety Follow-up Period 4 weeks
N = 9	VX-121 + TEZ/IVA	
N = 3	Placebo	

Source: Figure 9-1 CSR VX17-121-001

^a The dosage of VX-121 [VNZ] was 5-mg QD tablet. The dosage of TEZ/IVA in the TC was TEZ 100 mg QD/IVA 150 mg q12h, which was administered as TEZ 100-mg/IVA 150-mg FDC in the morning and IVA 150 mg in the evening.

Abbreviations: FDC, fixed-dose combination; IVA, ivacaftor; N, number of subjects in treatment group; q12h, every 12 hours; QD, once daily; TC, triple combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Test Drug

VNZ drug substance calcium salt (lot 2460-1802-00337), VNZ 5-mg tablets (lot 2018028), TEZ/IVA 100-mg/150-mg fixed-dose combination tablets (lots 2017016 and 2016051), and IVA 150-mg tablets (lots 3140699R and 3153411R) for oral administration.

Samples

Blood samples for plasma PK analysis of VNZ, TEZ, IVA and their relevant metabolites were collected as below.

- Part A, Cohorts A1, A2, A4, A5, and A6: On Day 1 before dosing and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Day 2), 36 (Day 2), 48 (Day 3), 72 (Day 4), and 96 (Day 5) hours after dosing.
- Part A, Cohort A3: On Days 1 and 9 before dosing (0 hours), and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Days 2, 10), 36 (Days 2, 10), 48 (Days 3, 11), 72 (Days 4, 12), 96 (Days 5, 13), 120 (Days 6, 14), 144 (Days 7, 15), and 168 (Days 8, 16) hours after dosing.
- Part A, Cohort A9: On Days 1, 9, 17 before dosing (0 hours), and at 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24 (Days 2, 10, 18), 36 (Days 2, 10, 18), 48 (Days 3, 11, 19), 72 (Days 4, 12, 20), 96 (Days 5, 13, 21), 120 (Days 6, 14, 22), 144 (Days 7, 15, 23), and 168 (Days 8, 16, 24) hours after dosing.
- Part B: On Days 1 and 5 before dosing (0 hours), 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing (if QD dosing, also at 24 hours [on Day 2 and Day 6]). Before dosing on Days 7, 8, and 9. On Day 10, before dosing (0 hours), 1, 2, 3, 4, 5, 6, 8, 10, 12, 24 (Day 11), 36 (Day 11), 48 (Day 12), 72 (Day 13), and 96 (Day 14) hours after dosing.
- Part C: On Days 1 and 7 before dosing (0 hours) and at 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. Before (morning) dosing on Days 2, 3, 4, 5, 8, 10, and 12, blood samples will be collected. On Day 14, before dosing (0 hours), and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 15), 36 (Day 15), 48 (Day 16), 72 (Day 17), and 96 (Day 18) hours after dosing.
- Part D: On Day 1, before dosing (0 hours) and at 1, 2, 4, and 6 hours after dosing (relative to the morning dose). A predose sample on Days 8 and 29. On Day 15, before dosing (0 hours) and at 1, 2, 4, 6, and 8 hours after dosing.

Results

Parts A, B and C (Healthy Subjects)

VNZ AUC increased approximately dose proportionally when administered orally as single doses between 5 and 60 mg. Summary PK results for Part A are provided in [Table 72](#). When administered as single 10-mg doses in the fed state (Cohort A9), VNZ exposure for the tablet formulation was similar to the suspension as presented in [Table 73](#).

Table 72. Summary of Selected VNZ PK Parameters Following Single Doses, Study 001 (Part A)

Cohort ^a	Formulation	Dose (mg)	N	Median (min, max)	Mean (%CV)				
				t _{max} (h)	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	CL/F (L/h)	Vz/F (L)	t _{1/2} (h)
A1	suspension	10	5	12.02 (12.00, 24.02)	0.134 (22.1)	11.2 (31.8)	0.963 (28.5)	72.1 (21.8)	53.2 (15.1)
A2	suspension	20	6	29.93 (8.08, 36.02)	0.247 (20.9)	29.9 (21.4)	0.692 (20.2)	80.5 (20.2)	83.5 (28.1)
A3	suspension	5	5	12.07 (12.00, 36.00)	0.071 (21.6)	8.90 (63.9)	0.725 (48.5)	69.3 (29.7)	81.0 (54.4)
A3	suspension (administered with milk)	5	5	36.00 (12.00, 36.00)	0.061 (23.3)	6.70 (43.9)	0.856 (39.5)	81.3 (35.6)	68.1 (28.8)
A4	suspension	40	6	10.03 (8.00, 12.00)	0.893 (24.2)	87.8 (43.7)	0.558 (54.3)	49.3 (26.1)	70.3 (38.1)
A5	suspension	60	6	12.00 (8.00, 12.00)	1.04 (25.4)	71.7 (13.3)	0.849 (13.5)	63.8 (27.6)	51.6 (20.0)
A9	suspension	10	8	18.03 (12.00, 36.00)	0.181 (25.3)	20.4 (31.4)	0.554 (42.0)	52.4 (12.0)	74.1 (34.1)
A9	tablet	10	8	12.01 (12.00, 24.03)	0.178 (25.1)	18.4 (31.8)	0.589 (28.4)	57.0 (37.7)	69.1 (33.3)
A9	tablet (administered with milk)	10	8	12.00 (8.05, 35.98)	0.156 (22.6)	16.0 (22.9)	0.652 (22.3)	57.3 (26.5)	62.9 (29.8)

Source: Table 11-1 CSR VX17-121-001

^a Unless otherwise specified, administration of calcium rich foods such as milk and milk products were restricted in all cohorts 4 hours before and after each study drug dose.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; CL/F, apparent clearance at steady-state; C_{max}, maximum plasma concentration; CV, coefficient of variation; h, hour; max, maximum; min, minimum; N, number of subjects in treatment group; PK, pharmacokinetic; t_{1/2}, half-life; t_{max}, time to maximum concentration

Table 73. Relative Bioavailability of VNZ Tablet and Suspension Formulations, Study 001 (Part A; 10-mg Dose)

PK Parameter	N	Reference GLSM	Test GLSM	GLSM	90% CI
		Suspension	Tablet	Ratio	Lower, Upper
C _{max}	16	0.177 µg/mL	0.172 µg/mL	0.976	0.843, 1.13
AUC _{0-∞}	16	19.3 µg·h/mL	17.6 µg·h/mL	0.914	0.801, 1.04
AUC _{0-last}	16	15.2 µg·h/mL	14.1 µg·h/mL	0.929	0.825, 1.05

Source: Table 11-2 CSR VX17-121-001

Note: Tablet strength for VNZ is 5 mg. Administration of calcium rich foods such as milk and milk products were restricted 4 hours before and after each study drug dose.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; GLSM, geometric least squares mean; N, number of subjects in treatment group; PK, pharmacokinetic

Following administration of multiple oral doses of VNZ monotherapy QD for 10 days, area under the concentration-time curve over the dosing interval (AUC_{tau}) increased approximately

dose proportionally between 10 mg QD and 60 mg QD. Based on a visual inspection of plasma concentration observed at the end of dosing interval (C_{trough}) levels, VNZ reached steady-state by Day 10. The mean $t_{1/2}$ was approximately 50 to 60 hours. The mean accumulation ratio of AUC_{tau} ranged from 3.5 to 5.5 following QD administration of VNZ. Summary PK results for Part B are provided in [Table 74](#).

Following administration of multiple oral doses of VNZ QD in TC with TEZ/IVA for 14 days, VNZ AUC_{tau} increased approximately dose proportionally between 5 and 20 mg. VNZ exposures in TC with TEZ/IVA were generally consistent with those observed following VNZ monotherapy. TEZ and IVA exposures in TC with VNZ were generally consistent with those observed historically. Metabolite to parent ratios for M1-IVA, M6-IVA, M1-TEZ, and M2-TEZ were also similar to those observed historically (data are not included).

Table 74. Summary of Selected VNZ PK Parameters Following Multiple Doses for 10 Days, Study 001 (Part B)

Cohort ^a	Formulation	Dose (qd, mg)	N	Day	Median (min, max)	Mean (%CV)					
					t_{max} (h)	C_{max} (µg/mL)	AUC_{0-24h} (µg·h/mL)	CL_{ss}/F (L/h)	Vz/F (L)	$t_{1/2}$ (h)	$AR_{AUC_{0-24h}}$
B1	suspension	10	6	1	23.89 (12.00, 23.97)	0.153 (17.0)	2.62 (16.6)	NR	NR	NR	NR
				5	12.00 (4.00, 23.92)	0.497 (17.9)	10.3 (17.8)	NR	NR	NR	3.96 (14.7)
				10	10.00 (4.00, 12.00)	0.574 (21.3)	11.5 (22.0)	0.913 (25.9)	64.3 (25.9)	50.4 (32.3)	4.41 (19.2)
B2	suspension	20	6	1	23.88 (12.00, 23.88)	0.418 (15.9)	7.11 (17.9)	NR	NR	NR	NR
				5	6.00 (4.00, 12.00)	1.41 (22.5)	30.1 (22.4)	NR	NR	NR	4.28 20.0
				10	7.50 (4.00, 10.02)	1.94 (21.2)	38.2 (24.2)	0.551 (24.8)	45.8 (26.3)	59.5 (29.4)	5.49 (28.5)
B3	suspension	40	5	1	12.00 (8.00, 23.88)	0.803 (6.58)	14.4 (7.53)	NR	NR	NR	NR
				5	4.50 (0.00, 12.00)	2.67 (21.1)	53.8 (19.8)	NR	NR	NR	3.71 (13.7)
				10	4.00 (4.00, 10.00)	3.07 (21.7)	58.7 (21.4)	0.707 (20.9)	56.6 (15.3)	56.6 (15.8)	4.12 (16.1)
B4	suspension	60	5	1	17.94 (12.00, 23.92)	1.43 (15.2)	27.5 (15.7)	NR	NR	NR	NR
				5	6.50 (4.00, 12.00)	4.36 (18.1)	86.6 (19.2)	NR	NR	NR	3.15 (9.7)
				10	5.00 (4.00, 10.00)	5.07 (15.8)	97.5 (17.7)	0.630 (16.9)	52.7 (23.5)	58.7 (27.1)	3.50 (18.1)

Source: Table 11-5 CSR VX17-121-001

^a Administration of calcium rich foods such as milk and milk products were restricted in all cohorts 4 hours before and after each study drug dose.

Abbreviations: AUC_{0-24h} , area under the concentration-time curve from time 0 to 24 hours; CL_{ss} , clearance at steady-state; C_{max} , maximum plasma concentration; CV, coefficient of variation; h, hour; max, maximum; min, minimum; N, number of subjects in treatment group; NR, not reportable; PK, pharmacokinetic; qd, once daily; $t_{1/2}$, half-life; t_{max} , time to maximum concentration

Part D (CF Subjects)

Based on a summary of sparse PK sample concentrations, VNZ, TEZ, and IVA exposures in CF subjects following VNZ/TEZ/IVA administration for 29 days were generally similar to healthy subjects in Part C. Summary PK results for VNZ are provided in [Table 75](#).

Table 75. Summary of Selected VNZ, TEZ, M1-TEZ PK Metrics Following Multiple Doses in TC With TEZ/IVA for 29 Days, Study 001 (Part D)

Analyte	N	Mean (%CV) of C _{trough} (μg/ml)		
		Day 8	Day 15	Day 29
VNZ	9	0.258 (32.3)	0.348 (31.3)	0.323 (34.2)
TEZ	9	1.78 (29.5)	2.01 (27.0)	2.02 (45.8)
M1-TEZ	9	4.15 (15.6)	4.52 (23.4)	5.11 (29.4)
IVA	9	0.873 (42.0)	0.916 (64.0)	0.916 (64.0)
M1-IVA	9	1.38 (30.9)	1.76 (35.2)	1.62 (38.2)

Source: Tables 11-9, 11-10, and 11-11 CSR VX17-121-001

Abbreviations: C_{trough}, lowest plasma concentration at steady-state; CV, coefficient of variation; IVA, ivacافتor; M, metabolite; N, number of subjects in treatment group; PK, pharmacokinetic; TC, triple combination; TEZ, tezacافتor; VNZ, vanzacافتor**Conclusions****Parts A, B, and C (Healthy Subjects)**

VNZ was generally safe and well tolerated at single doses up to 60 mg, at multiple doses up to 60 mg QD for 10 days, and at multiple doses up to 20 mg QD in TC with TEZ/IVA for 14 days. When administered as single and multiple doses as a monotherapy, and in TC with TEZ/IVA, VNZ exposure was approximately dose proportional. Based on observed C_{trough} levels, VNZ reached steady-state by Day 10. The mean accumulation ratio of AUC_{tau} ranged from 3.5 to 5.5 following QD administration of VNZ. VNZ exposures in TC with TEZ/IVA were generally consistent with those observed following VNZ monotherapy and also were consistent with historical exposures.

Part D (CF Subjects)

VNZ/TEZ/IVA for 4 weeks was generally safe and well tolerated in CF subjects. VNZ, TEZ, and IVA exposures in CF subjects were comparable to those in healthy subjects.

14.2.1.2. Study VX18-561-001 (Study 561-001)**Title**

A Phase 1, Randomized, Double-blind, Placebo-controlled, Multiple-ascending Dose Study Evaluating the Safety, Tolerability, and Pharmacokinetics of VX-561 [D-IVA] in Healthy Subjects

Study Period

September 28, 2018 to November 16, 2018

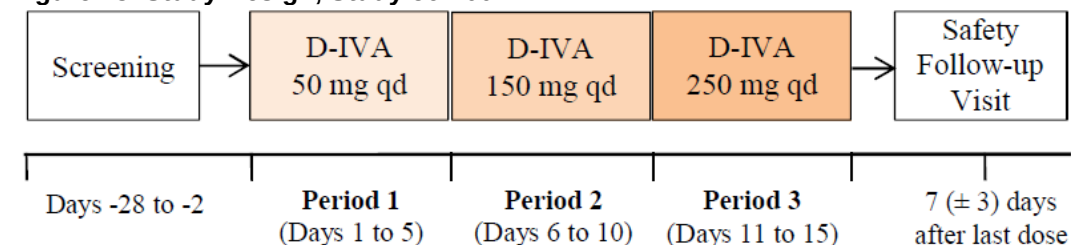
Objective

- To evaluate the PK of deutivacافتor (D-IVA) after administration of multiple ascending doses of D-IVA in healthy subjects
- To evaluate the safety and tolerability of multiple ascending doses of D-IVA in healthy subjects

Study Design

This was a randomized, double-blind, placebo-controlled, multiple-dose, dose escalation study of D-IVA in healthy subjects. Subjects were randomized with 3 (active) to 1 (placebo) ratio. Fixed-sequence study design was chosen to reduce the intersubject variability on PK endpoints. Placebo was chosen as the control treatment to assess whether any observed effects were treatment-related or simply related to the study condition. Study scheme is presented in [Figure 13](#).

Figure 13. Study Design, Study 561-001



Source: Figure 9-1 CSR VX18-561-001

Abbreviations: D-IVA, deutivacaftor; qd, once daily

Test Drug

Study drug details are presented in [Table 76](#). Study drug was administered orally in a fed state that was 30 minutes after the start of breakfast containing approximately 20 g of fat.

Table 76. Study Drug, Study 561-001

Drug Name	Lot Numbers	Strength/Formulation/Route
D-IVA	2017019	50-, 150-, or 250-mg tablets, oral
D-IVA-matching placebo	2017018	0-mg tablet, oral

D-IVA: deutivacaftor

Source: Table 9-2 CSR VX18-561-001

Abbreviations: D-IVA, deutivacaftor

Samples

Blood samples for plasma PK analysis were collected on Days 1, 5, 6, 10, 11, and 15 predose (0 hours) and at 1, 2, 3, 4, 5, 6, 8, 12, 24 hours postdose. Additional 24 (Day 16), 36, 48 (Day 17), and 72 hours (Day 18) post day 15 dose.

Results

A summary of D-IVA, D-M1, and D-M6 PK parameters following multiple doses of 50, 150, and 250 mg QD of D-IVA are presented in [Table 77](#). D-IVA exposure increased proportionally with ascending doses from 50 to 250 mg QD. The D-IVA $t_{1/2}$ was approximately 22 hours. D-IVA t_{max} ranged from 3.0 to 6.0 hours. Steady-state appeared to be reached by Day 5. Accumulation ratios for D-IVA AUC_{tau} ranged from 1.22- to 1.73-fold across doses after 5 days of dosing. Mean metabolite-to-parent ratios were similar across doses and were approximately 1.17 to 1.25 for M1-D-IVA at steady-state.

Table 77. Summary of (A) D-IVA and (B) M1-D-IVA PK Parameters After Multiple Ascending Doses of 50, 150, and 250 mg QD of D-IVA

(A) D-IVA

D-IVA	Day	N	Median (Min, Max)		Mean (CV%)				
			t _{max} (h)	C _{max} (µg/mL)	AUC _τ (µg·h/mL)	CL _{ss} /F (L/hr)	C _{avg,ss} (µg/mL)	AR _{AUCτ}	t _{1/2} (h)
50 mg qd	1	9	5.00 (3.00, 5.00)	0.238 (20.9)	2.80 (27.0)	ND	ND	ND	ND
	5	9	5.00 (3.00, 5.00)	0.367 (31.7)	4.93 (40.7)	23.8 (43.4)	0.205 (40.7)	1.73 (25.7)	ND
150 mg qd	6	9	4.00 (4.00, 5.00)	0.880 (27.6)	11.3 (33.6)	ND	ND	ND	ND
	10	9	5.00 (4.00, 5.00)	1.14 (32.0)	15.9 (41.2)	11.4 (48.2)	0.660 (41.2)	1.37 (15.4)	ND
250 mg qd	11	9	5.00 (3.00, 5.00)	1.74 (36.6)	23.9 (42.1)	ND	ND	ND	ND
	15*	9	3.00 (4.00, 6.00)	2.20 (56.8)	29.5 (44.5)	6.36 (53.6)	1.23 (44.5)	1.22 (14.0)	21.8 (28.1)

(B) M1-D-IVA

D-IVA	Day	N	Median (Min, Max)		Mean (CV%)		
			t _{max} (h)	C _{max} (µg/mL)	AUC _{last} (µg·h/mL)	MR _{Cmax}	MR _{AUC}
50 mg qd	1	9	5.00 (3.00, 5.00)	0.383 (26.0)	3.41 (26.5)	1.61 (16.7)	1.25 (20.7)
	5	9	5.00 (4.00, 5.02)	0.518 (22.3)	5.76 (27.7)	1.47 (19.0)	1.25 (19.1)
150 mg qd	6	9	5.00 (4.00, 5.00)	1.22 (21.0)	12.6 (22.8)	1.45 (24.4)	1.18 (19.5)
	10	9	5.00 (4.00, 6.00)	1.47 (19.3)	17.1 (27.2)	1.37 (24.7)	1.17 (21.2)
250 mg qd	11	9	5.00 (4.00, 5.00)	2.23 (23.9)	24.8 (28.4)	1.36 (20.3)	1.12 (22.4)
	15*	9	5.00 (3.00, 6.00)	2.66 (36.7)	54.9 (32.6)	1.34 (26.7)	1.21 (24.9)

Source: Tables 11-1 and 11-2 CSR VX18-561-001

* AUC₀₋₂₄ was calculated for Day 15 AUC_τ

Abbreviations: AUC_τ, area under the concentration-time curve during the dosing interval; AUC_{last}, area under the concentration-time curve to the last measurable concentration; AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24 h; AR_{AUCτ}, accumulation ratio of area under the concentration-time curve during the dosing interval; C_{avg,ss}, average concentration at steady-state; CL_{ss}, clearance at steady-state; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; D-M1: D-M1-IVA, metabolite of D-IVA; h, hour; max, maximum; MR_{AUC}, mean-metabolite-to-parent ratios for area under the concentration-time curve; MR_{Cmax}, mean-metabolite-to-parent ratios for maximum plasma concentration; min, minimum; N, number of subjects in treatment group; ND, not determined; PK, pharmacokinetic; qd, once daily; t_{1/2}, half-life; t_{max}, time to maximum concentration

Conclusions

D-IVA exposure was dose proportional when administered as multiple-ascending doses from 50 to 250 mg QD. Mean metabolite-to-parent ratios were similar across doses. D-IVA was generally safe and well tolerated at multiple-ascending doses from 50 to 250 mg QD.

14.2.2. Relative Bioavailability Studies

14.2.2.1. Study VX16-770-018 (Study 018; Part D)

Title

A Phase 1, 4-part, Randomized, Open-label Study to Evaluate the Relative Bioavailability and Food Effect of VX-561 [D-IVA] and Extended Release Ivacaftor Formulations in Healthy Adult Subjects

Study Period

December 15, 2016 to June 20, 2017

Objective

Primary Objective

To evaluate the relative BA of D-IVA formulations compared to the immediate release (IR) (commercial) formulation of IVA in the fed condition in healthy subjects

Secondary Objective

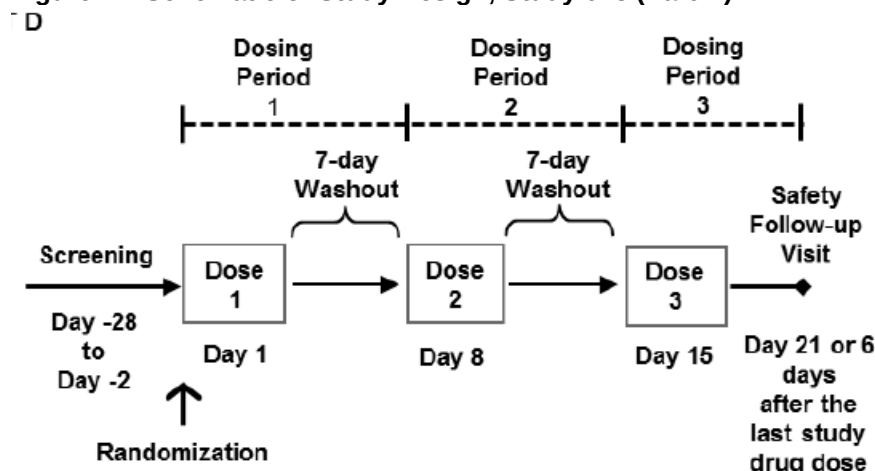
To assess the safety and tolerability of the D-IVA formulations in healthy subjects

Study Design

Part D was a 3-period, 3-sequence, crossover study to assess the relative BA of two D-IVA tablets relative to the IVA IR (commercial) tablet.

A single oral dose of IVA IR tablet, D-IVA Formulation 1 (D-IVA F1; low drug load tablet), or D-IVA Formulation 2 (D-IVA F2; high drug load tablet) was administered on the morning of the first day of each dosing period (Days 1, 8, and 15). Dosing periods were separated by a 7-day washout. The Safety Follow-up Visit assessments were performed on the last day of Dosing Period 4 (Day 21). The study scheme is presented in [Figure 14](#).

Figure 14. Schematic of Study Design, Study 018 (Part D)



Source: Figure 9-1 CSR VX16-770-018

Test Drug

IVA IR tablet (Treatment A), D-IVA F1 (Treatment B), D-IVA F2 (Treatment C) ([Table 78](#))

Table 78. Study Drug, Study 018 (Part D)

Drug Name	Formulation/ Route	Dosage	Packaging (Formulation Provided)	Batch/Lot Numbers
IVA: IR Tablet/Commercial Formulation	Tablet/ Oral	150-mg IVA	150-mg tablets	3140698R
IVA: (b) (4) XR Formulation (XR1)	Tablet/ Oral	400-mg IVA	200-mg tablets	2016042
IVA: (b) (4) XR Formulation (XR2)	Tablet/ Oral	400-mg IVA	200-mg tablets	2016043
IVA: (b) (4) XR Formulation (XR3)	Tablet/ Oral	400-mg IVA	200-mg tablets	2016044
VX-561 F1	Tablet/ Oral	100-mg VX-561	100-mg tablets	16C049
VX-561 F2	Tablet/ Oral	100-mg VX-561	50-mg tablets	2017019

Source: Table 9-4 CSR VX16-770-018

Abbreviations: IR, immediate release; IVA, ivacaftor; VX-561 F1, low drug load tablet; VX-561 F2, high drug load tablet; XR, extended release; XR1, fast release tablet; XR2, medium release tablet; XR3, slow-release tablet; VX-561 [D-IVA], deutivacaftor

Samples

Blood samples for plasma PK analysis were collected on Days 1, 8, and 15 predose (0 hours) and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose.

Results

A summary of the PK metrics for the IVA IR tablet, D-IVA F1, and D-IVA F2 are presented [Table 79](#). D-IVA tablets had longer elimination half-life ($t_{1/2}$) compared to the IVA IR tablet. At

a lower dose of 100 mg, the AUC_{0-∞} of the D-IVA tablets were higher than that of the IVA IR tablet at 150 mg.

Table 79. Mean (CV%) PK Metrics for IVA IR and D-IVA Tablets

PK Parameter	IR Tablet (150 mg) N = 17	VX-561 F1 (100 mg) N = 17	VX-561 F2 (100 mg) N = 17
T _{max} (h) ^a	4.12 (2.00, 8.00)	4.00 (3.00, 6.00)	6.00 (4.00, 6.08)
C _{max} (ng/mL)	721 (27)	801 (22)	550 (25)
AUC _{0-∞} (h·ng/mL)	8150 (33)	13100 (29)	9950 (27)
t _{1/2} (h)	10.6 (19)	14.4 (22)	15.4 (25)

Source: Table 11-6 CSR VX16-770-018

Abbreviation: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; h, hour; IR: immediate release; IVA, ivacaftor; N, number of subjects in treatment group; PK, pharmacokinetic; t_{1/2}, half-life; T_{max}, time to maximum concentration; VX-561 [D-IVA], deutivacaftor; VX-561 [D-IVA] F1, low drug load tablet; VX-561 [D-IVA] F2, high drug load tablet

Analysis of Relative Bioavailability

Total exposures (AUC_{0-∞}) of D-IVA tablets at 100-mg dose were 62% higher (D-IVA F1) and 24% higher (D-IVA F2) than the IVA IR tablet at 150-mg dose. D-IVA F2 maximum plasma concentration (C_{max}) was 32% lower and AUC_{0-∞} was 23% lower than D-IVA F1. Statistical comparison of the relative BA of D-IVA tablets versus the IVA IR tablet is presented in [Table 80](#).

Table 80. Analysis of Relative Bioavailability of D-IVA Compared to the IVA IR Tablet

Test Formulation	PK Parameter	GLSM			
		Reference (IR Tablet, 150 mg) N = 17	Test (VX-561, 100 mg) N = 17	Ratio	90% CI
VX-561 F1	C _{max} (ng/mL)	697	784	1.12	103, 123
	AUC _{0-∞} (h·ng/mL)	7770	12600	1.62	149, 175
VX-561 F2	C _{max} (ng/mL)	697	535	0.767	70.2, 83.8
	AUC _{0-∞} (h·ng/mL)	7770	9620	1.24	114, 134

Source Table 11-7 CSR VX16-770-018

GLSM Ratio = GLSM value for VX-561 [D-IVA] tablet/GLSM value for IR tablet

Abbreviation: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; D-IVA, deutivacaftor; GLSM, geometric least squares mean; IR, immediate release; IVA, ivacaftor; N, number of subjects in treatment group; PK, pharmacokinetic; VX-561 [D-IVA], deutivacaftor; VX-561 [D-IVA] F1, low drug load tablet; VX-561 [D-IVA] F2, high drug load tablet

Conclusions

Both D-IVA tablets (F1 and F2) had longer t_{1/2} but the t_{max} was comparable among the tested tablets. At a lower dose of 100 mg, D-IVA F1 and F2 tablets had higher exposures than the IVA IR tablet at 150 mg. The high drug load tablet of D-IVA (F2) had lower exposures than the low drug load tablet of D-IVA (F1).

14.2.2.2. Study VX19-121-003 (Study 003)

Title

A Phase 1, Open-label, Randomized, Crossover Study to Evaluate the Relative Bioavailability of a Fixed-dose Combination Tablet of VX-121 [VNZ], Tezacaftor, and Deutivacaftor in Healthy Adult Subjects

Study Period

August 4, 2020 to September 26, 2020

Objective

Primary Objective

To evaluate the relative BA of VNZ/TEZ/D-IVA administered as a FDC tablet compared to separate tablets of VNZ, TEZ, and D-IVA, under fed conditions.

Secondary Objective

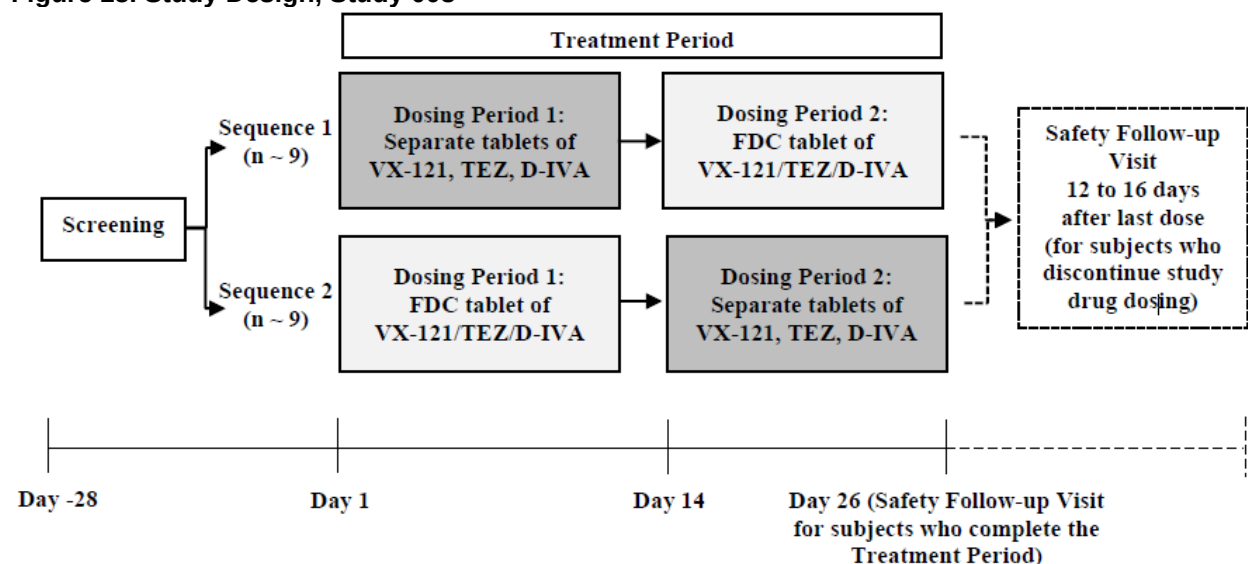
To evaluate the safety and tolerability of VNZ/TEZ/D-IVA administered as an FDC tablet or separate tablets.

Study Design

This was a phase 1, open-label, randomized, 2-sequence, 2-period crossover study to evaluate the relative BA of an FDC tablet of VNZ/TEZ/D-IVA (test formulation) compared to VNZ, TEZ, and D-IVA coadministered as separate tablets (reference formulation). The FDC tablet (test formulation) utilized the VNZ Form D physical formulation, while the separate tablet (reference formulation) utilized the VNZ Form A physical formulation.

At the start of each Dosing Period, healthy adult subjects received a single dose of VNZ 20 mg, TEZ 100 mg, and D-IVA 150 mg orally in the fed state, either as an FDC tablet or as separate tablets ([Figure 15](#)).

Figure 15. Study Design, Study 003



Source: Figure 9-1 CSR VX19-121-003

Abbreviation: D-IVA, deutivacaftor; FDC, fixed-dose combination; n, size of subsample; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Test Drug

VNZ 20 mg [Form D] /TEZ 100 mg/D-IVA 150 mg FDC tablets (test) (Batch 2020010) and VNZ 20 mg tablets [Form A] (Batch 2018028), TEZ 100 mg tablets (Batch 2017015), and D-IVA 150 mg tablets (Batch 2018034) (reference) ([Table 81](#))

Table 81. Study Drugs, Study 003

Drug Name	Dosing Form/Route	Dosage	How Supplied	Batch Numbers
VX-121/TEZ/D-IVA	Tablet ^a /oral	VX-121 20 mg/TEZ 100 mg/ D-IVA 150 mg	Supplied as FDC tablets	2020010
VX-121	Tablet ^b /oral	VX-121 20 mg	Supplied as 5-mg tablets	2018028
TEZ	Tablet/oral	TEZ 100 mg	Supplied as 50-mg tablets	2017015
D-IVA	Tablet/oral	D-IVA 150 mg	Supplied as 50-mg tablets	2018034

Source: Table 9-2 CSR VX19-121-003

^a The VX-121 drug substance in the FDC tablet was provided as Calcium Salt Form D.

^b The VX-121 drug substance in the VX-121 tablet was provided as Calcium Salt Form A.

Abbreviation: D-IVA, deutivacaftor; FDC, fixed-dose combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Samples

Blood samples for plasma PK analysis of VNZ, TEZ, D-IVA and their relevant metabolites were collected on Days 1 and 14 at predose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 96, 144, 192, 240, 288 hours postdose.

Results

[Table 82](#) summarizes the PK parameters of VNZ [Form A and Form D], TEZ, and D-IVA after a single dose of the FDC tablet or separate tablets. Exposures of VNZ were significantly lower while exposures of TEZ and IVA were generally similar after administration of the FDC tablet relative to the separate tablets.

Table 82. Mean (CV%) of VNZ, TEZ, and D-IVA PK Parameters After Administration as an FDC Tablet or as Separate Tablets

Analyte	Formulation	N	t _{max} ^a (h)	C _{max} (µg/mL)	AUC _{0-last} (h*µg/mL)	AUC _{0-∞} (h*µg/mL)	CL/F (L/h)	t _{1/2} (h)
VX-121	FDC tablet	20	24.00 (10.00, 24.10)	0.168 (33.1)	17.9 (49.0)	17.7 ^b (40.1)	1.30 ^b (36.6)	65.5 ^b (29.5)
	Separate tablets	20	12.00 (10.00, 24.10)	0.368 (28.1)	34.6 (35.1)	35.1 ^b (34.3)	0.629 (30.9)	65.6 ^b (22.3)
TEZ	FDC tablet	20	3.00 (2.00, 4.00)	5.37 (24.3)	103 (33.5)	111 (33.6)	0.985 (29.6)	107 (21.1)
	Separate tablets	20	4.00 (2.00, 4.05)	5.40 (20.7)	106 (22.7)	114 (23.6)	0.913 (20.5)	106 (23.8)
D-IVA	FDC tablet	20	4.00 (4.00, 8.00)	1.03 (32.9)	22.0 (65.4)	22.2 (64.9)	8.23 (36.2)	17.5 (20.8)
	Separate tablets	20	4.00 (4.00, 6.00)	0.965 (26.5)	19.8 (46.6)	20.0 (46.0)	8.61 (33.7)	17.9 (15.8)

Source: Table 11-1 CSR VX19-121-003

Note: Dosages, Separate tablets were VX-121 [VNZ] 20 mg [Form A], TEZ 100 mg, and D-IVA 150 mg; FDC tablet was VX-121 [VNZ] 20 mg [Form D] /TEZ 100 mg/D-IVA 150 mg.

^a t_{max} presented as median (minimum, maximum).

^b N=19 for AUC_{0-∞}, CL/F, and t_{1/2} because 1 profile with AUC % extrapolation higher than 20% was excluded from the descriptive statistics.

Abbreviation: AUC, area under the concentration-time curve; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{0-last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; FDC, fixed-dose combination; h, hour; N, number of subjects in treatment group; PK, pharmacokinetic; TEZ, tezacaftor; t_{1/2}, half-life; t_{max}, time to maximum concentration; VX-121 [VNZ], vanzacaftor

The relative BA of VNZ [Form A and Form D], TEZ, and D-IVA after single-dose administration as an FDC tablet or as separate tablets was statistically evaluated. The geometric least squares mean (GLSM) ratios and their associated 90% CIs are provided for AUC_{0-∞}, AUC_{0-last}, and C_{max} in [Table 83](#). The exposure (area under the concentration-time curve [AUC] and C_{max}) of VNZ following Form A was approximately 50% of the exposure following FDC tablet, which contained VNZ Form D.

Table 83. Relative BA Assessment of VNZ, TEZ, and D-IVA Exposures After Administration as an FDC Tablet or as Separate Tablets

Analyte	PK Parameter (Unit)	GLSM Ratio (FDC Tablet/Separate Tablets)	90% CI (Lower, Upper)
VX-121	AUC _{0-∞} (h*µg/mL)	0.495	0.461, 0.532
	AUC _{0-tlast} (h*µg/mL)	0.498	0.462, 0.536
	C _{max} (µg/mL)	0.452	0.412, 0.497
TEZ	AUC _{0-∞} (h*µg/mL)	0.948	0.915, 0.982
	AUC _{0-tlast} (h*µg/mL)	0.950	0.915, 0.986
	C _{max} (µg/mL)	0.991	0.925, 1.06
D-IVA	AUC _{0-∞} (h*µg/mL)	1.06	0.971, 1.17
	AUC _{0-tlast} (h*µg/mL)	1.07	0.972, 1.17
	C _{max} (µg/mL)	1.06	0.972, 1.15

Source: Table 11-2 CSR VX19-121-003

Notes: Reference separate tablets were VX-121 [VNZ] 20 mg Form A, TEZ 100 mg, and D-IVA 150 mg; test FDC tablet was VX-121 [VNZ] 20 mg Form D/TEZ 100 mg/D-IVA 150 mg.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{tlast}, area under the concentration-time curve to the last measurable concentration; BA, bioavailability; CI, confidence interval; C_{max}, maximum plasma concentration; D-IVA, deutivacaftor; FDC, fixed-dose combination; GLSM, geometric least squares mean; PK, pharmacokinetic; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor**Conclusions**

VNZ Form D exposures were approximately 50% to 55% lower than VNZ Form A exposures. Exposures of TEZ and D-IVA were unchanged when study drug was given as the FDC tablet (test) relative to when it was given as the separate tablets (Section 6.1).

14.2.2.3. Study VX21-121-005 (Study 005)**Title**

A Phase 1, Randomized, Open-label Crossover Study to Evaluate the Relative Bioavailability and Food Effect of a Fixed-dose Combination Tablet of VX-121 [VNZ], Tezacaftor, and Deutivacaftor in Healthy Adult Subjects

Study Period

July 15, 2021 to November 24, 2021

Objective**Primary Objectives**

- **Part A:** To evaluate the relative BA of a FDC tablet of VNZ [Form D] /TEZ/D-IVA compared to VNZ [Form A], TEZ, and D-IVA coadministered as separate tablets
- **Part B:** To evaluate the effect of food on the relative BA of VNZ/TEZ/D-IVA administered as an FDC tablet

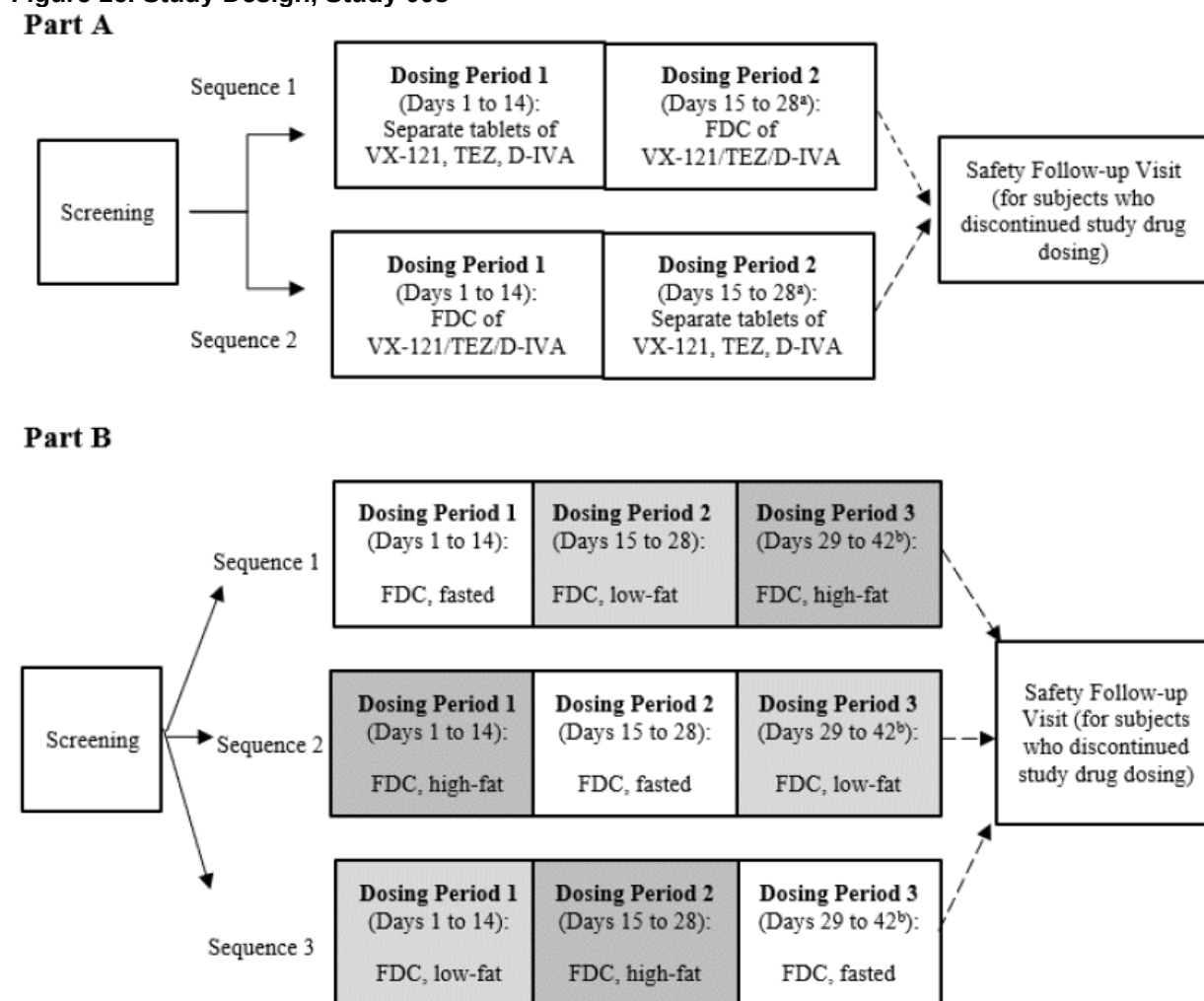
Secondary Objective

- Parts A and B: To assess the safety and tolerability of VNZ, TEZ, and D-IVA

Study Design

This was a phase 1, randomized, open-label, crossover study with two parts: Part A had a 2-period, 2-sequence design to evaluate the relative BA of an FDC tablet of VNZ [Form D]/TEZ/D-IVA compared to VNZ [Form A], TEZ, and D-IVA coadministered as separate tablets; and Part B had a 3-period, 3-sequence design to evaluate the effect of food on the relative BA of the VNZ/TEZ/D-IVA FDC tablet ([Figure 16](#)).

Figure 16. Study Design, Study 005



Source: Figure 2-1 CSR VX21-121-005

Note: Study drug was administered on the first day of each dosing period; there was a 14-day washout period between each dosing occasion.

^a Day 28 was the Safety Follow-up Visit for subjects who completed the Treatment Period in Part A.

^b Day 42 was the Safety Follow-up Visit for subjects who completed the Treatment Period in Part B.

Abbreviations: D-IVA, deutivacaftor; FDC, fixed-dose combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Test Drug

VNZ 20 mg [Form D]/TEZ 100 mg/D-IVA 250 mg was supplied as FDC film-coated tablets, and VNZ [Form A] 10 mg, TEZ 100 mg, and D-IVA 250 mg were supplied as separate tablets ([Table 84](#))

Table 84. Study Drug, Study 005

Drug Name	Dosage Form/ Route	How Supplied	Batch Numbers
VX-121/TEZ/D-IVA	Tablet ^a / oral	Supplied as 10-mg VX-121/50-mg TEZ/125-mg D-IVA FDC tablets	3199049R
VX-121	Tablet ^b / oral	Supplied as 5-mg tablets	2018028
TEZ	Tablet/ oral	Supplied as 50-mg tablets	2017015
D-IVA	Tablet/ oral	Supplied as 50-mg tablets	2018034

Source: Table 9-1 CSR VX21-121-005

^a The VX-121 [VNZ] drug substance in the FDC tablet was provided as Calcium Salt Form D.

^b The VX-121 [VNZ] drug substance in the VX-121 [VNZ] tablet was provided as Calcium Salt Form A.

Abbreviations: D-IVA, deutivacaftor; FDC, fixed-dose combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Samples

Part A and Part B

Blood samples for plasma PK analysis of VNZ, TEZ, D-IVA and their relevant metabolites were collected on Days 1 and 15 at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 96, 144, 192, 240, 288 hours postdose.

Results

Part A

The PK analysis dataset included data from 18 subjects who received both VNZ/TEZ/D-IVA as the FDC tablets and as separate tablets. For the summary statistics, PK analysis, and statistical comparisons, two subjects presented carryover for VNZ in the FDC tablets treatment group; therefore, these subjects were excluded from that period.

[Table 85](#) summarizes the PK parameters of VNZ, TEZ, and D-IVA after a single oral dose of VNZ/TEZ/D-IVA as FDC or separate tablets.

Table 85. Mean (CV%) of VNZ, TEZ, and D-IVA PK Parameters After Administration of VNZ/TEZ/D-IVA as FDC Tablets or Separate Tablets, Study 005 (Part A)

Analyte	Treatment	N	t _{max} ^a (h)	C _{max} (µg/mL)	AUC _{0-<i>t</i>last} (h*µg/mL)	AUC _{0-∞} (h*µg/mL)	t _{1/2} (h)	CL/F (L/h)
VX-121	FDC tablets	16	24.00 (8.05, 48.00)	0.185 (31.3)	18.0 (28.9)	18.7 (28.3)	54.0 (18.7)	1.18 (38.6)
	Separate tablets	18	24.08 (6.00, 48.05)	0.198 (18.7)	18.3 (21.0)	19.1 (21.6)	57.0 (20.4)	0.543 (19.3)
TEZ	FDC tablets	18	3.50 (1.12, 5.38)	5.29 (19.3)	109 (24.0)	115 (24.5)	92.4 (25.0)	0.937 (36.0)
	Separate tablets	18	4.00 (2.00, 6.00)	5.44 (13.4)	107 (20.4)	114 (21.6)	93.2 (19.9)	0.921 (22.8)
D-IVA	FDC tablets	18	5.08 (4.00, 12.00)	1.74 (21.6)	42.6 (30.0)	42.8 (29.9)	17.3 (15.4)	6.52 (42.5)
	Separate tablets	18	5.22 (3.98, 8.12)	1.81 (16.2)	41.5 (23.6)	41.7 (23.5)	17.8 (18.8)	6.34 (24.5)

Source: Table 11-1 CSR VX21-121-005

Note: Dose was VX-121 [VNZ] 20 mg [Form D]/TEZ 100 mg/ D-IVA 250 mg for the FDC tablets and VX-121 [VNZ] 10 mg [Form A], TEZ 100 mg, and D-IVA 250 mg for the separate tablets.

^a t_{max} presented as median (minimum, maximum)Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{tlast}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; FDC, fixed-dose combination; N, number of subjects in treatment group; PK, pharmacokinetic; t_{1/2}, half-life; TEZ, tezacaftor; t_{max}, time to maximum concentration; VX-121 [VNZ], vanzacaftor

The relative BA of VNZ, TEZ, and D-IVA after single-dose administration as FDC tablets or as separate tablets was statistically evaluated. The resultant GLSM ratios and their associated 90% CIs are provided for AUC_{0-∞}, AUC_{0-tlast}, and C_{max} in [Table 86](#).

Table 86. Relative Bioavailability Assessment of VNZ, TEZ, and D-IVA Exposures After Administration of VNZ/TEZ/D-IVA as FDC Tablets Compared to Coadministration of Separate Tablets, Study 005 (Part A)

Analyte	PK Parameter (Unit)	GLSM Ratio (FDC Tablets/Separate Tablets) (%)	90% CI (Lower, Upper) (%)
VX-121	AUC _{0-∞} (h*µg/mL)	97.5	(86.9, 109)
	AUC _{0-tlast} (h*µg/mL)	97.6	(86.9, 110)
	C _{max} (µg/mL)	91.6	(82.6, 102)
TEZ	AUC _{0-∞} (h*µg/mL)	99.8	(91.8, 109)
	AUC _{0-tlast} (h*µg/mL)	99.8	(91.5, 109)
	C _{max} (µg/mL)	96.9	(88.6, 106)
D-IVA	AUC _{0-∞} (h*µg/mL)	102	(91.4, 114)
	AUC _{0-tlast} (h*µg/mL)	102	(91.4, 114)
	C _{max} (µg/mL)	97.1	(87.7, 107)

Source: Table 11-2 CSR VX21-121-005

Note: Dose was 20 mg VX-121 [VNZ] [Form D]/ 100 mg TEZ/250 mg D-IVA for the FDC tablets and VX-121 [VNZ] 10 mg [Form A], TEZ 100 mg, and D-IVA 250 mg for the separate tablets.

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{tlast}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; D-IVA, deutivacaftor; FDC, fixed-dose combination; GLSM, geometric least squares mean; PK, pharmacokinetic; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Part B

The PK analysis dataset included data from 17 subjects who received VNZ/TEZ/D-IVA FDC tablets in the three dosing periods (FDC Fasted, FDC Low-fat, and FDC High-fat). One subject (Sequence 1) received a high-fat meal in Dosing Period 2 instead of the assigned low-fat meal.

Three subjects (two subjects in the FDC Fasted group and one subject in the FDC High-Fat group) presented carryover for VNZ. Therefore, these subjects (three due to carry-over, one due to meal type) were excluded from that period.

[Table 87](#) summarizes the PK parameters of VNZ, TEZ, and D-IVA after administration of FDC tablets under fasted and fed (high-fat and low-fat) conditions. Exposures of VNZ and D-IVA were significantly higher while exposure of TEZ was generally similar after administration of the FDC tablet under fed (high-fat and low-fat) conditions compared to fasted conditions.

Table 87. Mean (CV%) of VNZ, TEZ, and D-IVA PK Parameters After Administration of VNZ/TEZ/D-IVA FDC Tablets Under Fasted and Fed (High-Fat and Low-Fat) Conditions, Study 005 (Part B)

Analyte	Treatment	N	t _{max} ^a (h)	C _{max} (µg/mL)	AUC _{0-tlast} (h*µg/mL)	AUC _{0-∞} (h*µg/mL)	t _{1/2} (h)	CL/F (L/h)
VX-121	FDC Fasted	15	24.03 (10.00, 48.02)	0.0342 (42.3)	3.62 (48.7)	3.90 (48.5)	52.9 (30.1)	6.32 (47.6)
	FDC High-Fat	16	23.98 (8.00, 24.18)	0.219 (32.9)	21.5 (36.2)	22.7 (37.8)	58.2 (26.8)	1.04 (45.4)
	FDC Low-Fat	16	23.97 (8.00, 24.12)	0.145 (44.5)	14.7 (45.1)	15.7 (46.0)	61.9 (29.9)	2.03 (132.7)
TEZ	FDC Fasted	17	2.00 (1.00, 8.03)	4.41 (43.0)	78.7 (31.4)	83.5 (30.5)	93.6 (26.3)	1.37 (49.9)
	FDC High-Fat	17	3.02 (1.98, 6.02)	4.52 (29.0)	93.9 (29.2)	99.9 (29.0)	102 (22.5)	1.10 (33.4)
	FDC Low-Fat	16	3.02 (2.00, 6.00)	5.11 (31.7)	91.9 (34.2)	96.9 (34.4)	86.8 (28.6)	1.56 (136.8)
D-IVA	FDC Fasted	17	4.07 (3.00, 12.00)	0.379 (68.5)	9.63 (58.1)	9.66 (58.0)	18.8 (28.0)	33.9 (60.8)
	FDC High-Fat	17	5.05 (3.00, 8.05)	1.72 (40.7)	38.1 (35.5)	38.1 (35.5)	18.2 (20.2)	7.64 (45.0)
	FDC Low-Fat	16	5.00 (3.97, 6.00)	1.45 (45.1)	32.0 (45.6)	32.1 (45.6)	18.6 (25.5)	12.4 (131.1)

Source: Table 11-3 CSR VX21-121-005

Note: Dose was 20 mg VX-121 [VNZ] [Form D]/ 100 mg TEZ/250 mg D-IVA FDC tablet.

^a t_{max} presented as median (minimum, maximum)

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{0-tlast}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; FDC, fixed-dose combination; N, number of subjects in treatment group; PK, pharmacokinetic; t_{1/2}, half-life; TEZ, tezacaftor; t_{max}, time to maximum concentration; VX-121 [VNZ], vanzacaftor

The effect of food (high-fat and low-fat) on VNZ, TEZ, and D-IVA PK after a single oral dose of the FDC tablet (20 mg VNZ [Form D]/100 mg TEZ/250 mg D-IVA) under fed conditions compared to fasted conditions was statistically evaluated. The resultant GLSM ratios and their associated 90% CIs are provided for AUC_{0-∞}, AUC_{0-tlast}, and C_{max} in [Table 88](#). Administration of a single oral dose of the FDC tablet following a high-fat meal increased VNZ AUC_{0-∞}, AUC_{0-tlast}, and C_{max} by approximately 6-fold compared to fasted state. A low-fat meal increased VNZ AUC_{0-∞}, AUC_{0-tlast}, and C_{max} by approximately 4-fold compared to fasted state. Food had no large impact on TEZ exposures overall. Administration of a single oral dose of the FDC tablet following a high-fat meal increased D-IVA AUC_{0-∞}, AUC_{0-tlast}, and C_{max} by approximately 4-fold, 4-fold, and 5-fold, respectively, compared to fasted state. A low-fat meal increased D-IVA AUC_{0-∞}, AUC_{0-tlast}, and C_{max} by approximately 3-fold, 3-fold, and 4-fold, respectively, compared to fasted state.

Table 88. Food Effect Assessment on VNZ, TEZ, and D-IVA Exposures After Administration of VNZ/TEZ/D-IVA FDC Tablet Under Fed (High-Fat and Low-Fat) Compared to Fasted Conditions

Analyte	Test Treatment	PK Parameter (Unit)	GLSM Ratio (FDC Fed/FDC Fasted)	90% CI (Lower, Upper)
			(%)	(%)
VX-121	FDC High-Fat	AUC _{0-∞} (h*µg/mL)	576	(427, 778)
		AUC _{0-tlast} (h*µg/mL)	597	(439, 810)
		C _{max} (µg/mL)	634	(480, 836)
	FDC Low-Fat	AUC _{0-∞} (h*µg/mL)	374	(277, 505)
		AUC _{0-tlast} (h*µg/mL)	381	(281, 518)
		C _{max} (µg/mL)	390	(296, 515)
TEZ	FDC High-Fat	AUC _{0-∞} (h*µg/mL)	121	(105, 140)
		AUC _{0-tlast} (h*µg/mL)	121	(105, 140)
		C _{max} (µg/mL)	108	(89.6, 130)
	FDC Low-Fat	AUC _{0-∞} (h*µg/mL)	112	(96.4, 129)
		AUC _{0-tlast} (h*µg/mL)	113	(97.3, 130)
		C _{max} (µg/mL)	116	(96.4, 141)
D-IVA	FDC High-Fat	AUC _{0-∞} (h*µg/mL)	419	(325, 540)
		AUC _{0-tlast} (h*µg/mL)	420	(326, 542)
		C _{max} (µg/mL)	537	(395, 731)
	FDC Low-Fat	AUC _{0-∞} (h*µg/mL)	332	(256, 429)
		AUC _{0-tlast} (h*µg/mL)	332	(256, 431)
		C _{max} (µg/mL)	432	(316, 591)

Source: Table 11-4 CSR VX21-121-005

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{tlast}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; D-IVA, deutivacaftor; FDC, fixed-dose combination; GLSM, geometric least squares mean; PK, pharmacokinetic; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Conclusions

Exposures of VNZ 20 mg [Form D], TEZ 100 mg, and D-IVA 250 mg were similar when study drug was given as FDC tablets relative to when it was given as separate tablets as VNZ 10 mg [Form A], TEZ 100 mg, and D-IVA 250 mg (Part A).

Administration of VNZ/TEZ/D-IVA as FDC tablets under fed (high- and low-fat) conditions resulted in increased exposure to VNZ (up to ~6-fold for AUC_{0-∞} and C_{max}) and D-IVA (up to ~4-fold and ~5-fold for AUC_{0-∞} and C_{max}, respectively) compared to fasted conditions. Exposure to TEZ under fed conditions remained comparable to fasted conditions.

14.2.2.4. Study VX22-121-009 (Study 009)

Title

A Phase 1, Randomized, Open-label, Crossover Study to Evaluate the Relative Bioavailability of a Fixed-dose Combination Tablet of VX-121 [VNZ], Tezacaftor, and Deutivacaftor in Healthy Adult Subjects

Study Period

September 15, 2022 to November 9, 2022

Objective

Primary Objective

To evaluate the relative BA of a test FDC tablet of VNZ [Form D] /tezacaftor (TEZ)/deutivacaftor (D-IVA) compared to a reference FDC tablet of VNZ/TEZ/D-IVA

Secondary Objective

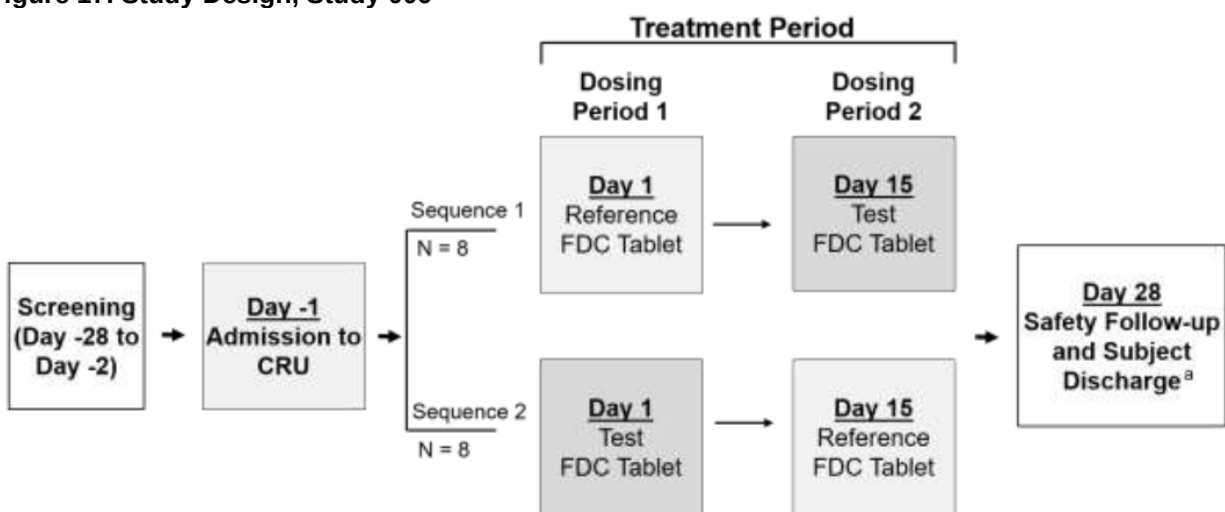
To assess the safety and tolerability of VNZ/TEZ/D-IVA administered as FDC tablets

Study Design

This was a phase 1, randomized, open-label, 2-period, 2-sequence, crossover study to evaluate the relative BA of a test FDC tablet of VNZ/TEZ/D-IVA compared to a reference FDC tablet of VNZ/TEZ/D-IVA. The study design is presented in [Figure 17](#).

In each dosing period, healthy subjects received a single dose of VNZ 20 mg/TEZ 100 mg/ D-IVA 250 mg orally, either as test FDC tablets (supplied as five tablets of VNZ [Form D] 4 mg/TEZ 20 mg/D-IVA 50 mg) or as reference FDC tablets (supplied as two tablets of VNZ [Form D] 10 mg/TEZ 50 mg/D-IVA 125 mg). The Washout Period between doses was 14 days.

Figure 17. Study Design, Study 009



Source: Figure 9-1 Study VX22-121-009

^a Subjects who prematurely discontinued study drug dosing for any reason (except withdrawal of consent) completed a Safety Follow-up Visit 12 to 16 days after their last dose of study drug.

Abbreviations: CRU, clinical research unit; FDC, fixed-dose combination; N, number of subjects in treatment group

Test Drug

Study drug details are presented in [Table 89](#).

Table 89. Study Drug, Study 009

Drug Name	Identifier	Dosing Form/ Route	Formulation Strength	How Supplied	Batch Number
VX-121/TEZ/D-IVA	Test tablet	Tablet/ oral	VX-121 4 mg/TEZ 20 mg/ D-IVA 50 mg	Supplied as FDC tablets	3209516R
VX-121/TEZ/D-IVA	Reference tablet	Tablet/ oral	VX-121 10 mg/TEZ 50 mg/ D-IVA 125 mg	Supplied as FDC tablets	3199049R

Source: Table 9-1 Study VX22-121-009

Abbreviations: D-IVA, deutivacaftor; FDC, fixed-dose combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Samples

Blood samples for plasma PK analysis of VNZ, TEZ, D-IVA and their relevant metabolites were collected on Days 1 and 15 at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 48, 96, 144, 192, 240, 288 hours postdose.

Results

[Table 90](#) summarizes the PK parameters of VNZ, TEZ, and D-IVA after a single oral dose of VNZ/TEZ/D-IVA as test FDC tablets or reference FDC tablets. Exposures of VNZ, TEZ, and D-IVA were generally similar after administration of the test FDC tablets relative to reference FDC tablets.

The relative BA of VNZ, TEZ, and D-IVA after single-dose administration as test FDC tablets or as reference FDC tablets was statistically evaluated. The resultant GLSM ratios and their associated 90% CIs are provided for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} in [Table 91](#).

Table 90. Mean (CV%) of VNZ, TEZ, and D-IVA PK Parameters After Administration of VNZ/TEZ/D-IVA as Test FDC Tablets or Reference FDC Tablets

Analyte	Treatment	N	t _{max} ^a (h)	C _{max} (µg/mL)	AUC _{0-tlast} (h*µg/mL)	AUC _{0-∞} (h*µg/mL)	t _{1/2} (h)	CL/F (L/h)
VX-121	Test	14	10.00 (6.00, 24.00)	0.323 (34.0)	26.0 (31.3)	27.6 (33.0)	59.2 (34.6)	0.830 (43.6)
	Reference	13	12.00 (6.00, 24.00)	0.322 (34.8)	27.7 (43.4)	29.2 (45.9)	57.0 (29.0)	0.812 (45.1)
TEZ	Test	16	5.03 (2.00, 8.02)	4.36 (26.1)	111 (29.1)	118 (30.7)	89.6 (13.1)	0.915 (26.1)
	Reference	14	6.00 (3.00, 10.00)	4.49 (26.5)	114 (32.4)	120 (32.4)	88.8 (27.4)	0.936 (40.1)
D-IVA	Test	16	6.00 (4.00, 10.00)	2.31 (35.8)	52.3 (43.1)	52.4 (42.9)	17.1 (30.0)	5.56 (40.1)
	Reference	14	6.00 (4.00, 12.00)	2.29 (37.2)	53.3 (48.8)	53.6 (48.6)	20.6 (64.7)	5.94 (60.6)

Source: Table 9-1 Study VX22-121-009

Note: A single dose was given as VX-121 [VNZ] 20 mg/ TEZ 100 mg/D-IVA 250 mg orally, either as test FDC tablets (supplied as 5 tablets of VC-121 4 mg/TEZ 20 mg/D-IVA 50 mg), or as reference FDC tablets (supplied as two tablets of VX-121 [VNZ] 10 mg/TEZ 50 mg/D-IVA 125 mg).

^a t_{max} presented as median (minimum, maximum)

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{tlast}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; FDC, fixed-dose combination; h, hour; GLSM, geometric least squares mean; h, hour; N, number of subjects in treatment group; PK, pharmacokinetic; t_{1/2}, half-life; TEZ, tezacaftor; t_{max}, time to maximum concentration; VX-121 [VNZ], vanzacaftor

Table 91. Relative Bioavailability Assessment of VNZ, TEZ, and D-IVA Exposures After Administration of VNZ/TEZ/D-IVA as Test FDC Tablets Compared to Reference FDC Tablets

Analyte	PK Parameter	GLSM Ratio (Test FDC Tablets/Reference FDC Tablets)	90% CI (Lower, Upper)
		(%)	(%)
VX-121	AUC _{0-∞}	98.8	(84.1, 116)
	AUC _{0-tlast}	97.7	(82.4, 116)
	C _{max}	105	(96.1, 115)
TEZ	AUC _{0-∞}	98.7	(92.5, 105)
	AUC _{0-tlast}	98.8	(92.5, 106)
	C _{max}	96.6	(83.4, 112)
D-IVA	AUC _{0-∞}	102	(89.5, 116)
	AUC _{0-tlast}	102	(89.6, 116)
	C _{max}	102	(90.9, 115)

Source: Table 11-2 Study VX22-121-009

Note: A single dose was given as VX-121 [VNZ] 20 mg/ TEZ 100 mg/D-IVA 250 mg orally, either as test FDC tablets (supplied as 5 tablets of VX-121 [VNZ] 4 mg/TEZ 20 mg/D-IVA 50 mg) or as reference FDC tablets (supplied as two tablets of VX-121 [VNZ] 10 mg/TEZ 50 mg/D-IVA 125 mg).

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{tlast}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; D-IVA, deutivacaftor; FDC, fixed-dose combination; GLSM, geometric least squares mean; N, number of subjects in treatment group; PK, pharmacokinetic; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Conclusions

VNZ, TEZ, and D-IVA exposures were comparable following single oral dose of VNZ/TEZ/D-IVA as test FDC tablets (supplied as five tablets of VNZ 4 mg/TEZ 20 mg/D-IVA 50 mg) to the

NDA 218730

ALYFTREK (vanzacافتor/tezacافتor/deutivacافتor) Tablets

single dose of reference FDC tablets (supplied as two tablets of VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg in adults.

14.2.3. Drug Interaction Studies

14.2.3.1. Study VX21-121-006 (Study 006)

Title

A Phase 1, Open-label Study to Evaluate the Pharmacokinetic Effects Between VX-121 [VNZ], Tezacافتor, and Deutivacافتor in Healthy Subjects

Study Period

September 10, 2021 to December 7, 2021

Objective

Primary Objectives

- To assess the effect of TEZ and D-IVA on the PK of VNZ
- To assess the effect of VNZ and TEZ on the PK of D-IVA
- To assess the effect of VNZ and D-IVA on the PK of TEZ

Secondary Objective

- To assess the safety and tolerability of VNZ, TEZ, and D-IVA when administered separately and together

Study Design

A phase 1, open-label, 2-cohort crossover study to evaluate the PK of VNZ, TEZ, and D-IVA when administered separately and together ([Figure 18](#)). During Cohort 1, healthy adult subjects received VNZ monotherapy in Dosing Period 1 and VNZ in combination with TEZ and D-IVA in Dosing Period 2. During Cohort 2, healthy adult subjects received D-IVA monotherapy in Dosing Period 1, TEZ monotherapy in Dosing Period 2, and VNZ in combination with TEZ and D-IVA in Dosing Period 3. VNZ, TEZ, and D-IVA (as monotherapy and in combination) were administered orally in the fed state.

Figure 18. Study Design, Study 006

Cohort 1

Screening	Dosing Period 1 (Days 1 to 14): VX-121 10 mg qd	Washout Period (Days 15 to 28)	Dosing Period 2 (Days 29 to 42): VX-121 10 mg qd/ TEZ 100 mg qd/ D-IVA 250 mg qd Day 43: Discharge	Safety Follow-up Visit (12 to 16 days after last dose of study drug)

Cohort 2

Screening	Dosing Period 1 (Days 1 to 6): D-IVA 250 mg qd	Washout Period (Days 7 to 14)	Dosing Period 2 (Days 15 to 24): TEZ 100 mg qd	Washout Period (Days 25 to 34)	Dosing Period 3 (Days 35 to 48): VX-121 10 mg qd/ TEZ 100 mg qd/ D-IVA 250 mg qd Day 49: Discharge	Safety Follow-up Visit (12 to 16 days after last dose of study drug)

Source: Figure 9-1 CSR VX21-121-006

Note: In Cohort 1, Day 43 was the last day of Dosing Period 2. In Cohort 2, Day 49 was the last day of Dosing Period 3.

Abbreviations: D-IVA, deutivacaftor; qd, once daily; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Test Drug

Study drug details are presented in [Table 92](#). Of note, the vanzacaftor used in Study VX21-121-006 is Form A whereas the vanzacaftor in to-be-marketed FDC is Form D.

Table 92. Study Drug, Study 006

Drug Name	Dosing Form/ Route	Dosage	How Supplied	Lot Number
VX-121	Tablet ^a / oral	VX-121 10 mg	Supplied as 5-mg tablets	2018028
TEZ	Tablet/ oral	TEZ 100 mg	Supplied as 50-mg tablets	2017015
D-IVA	Tablet/ oral	D-IVA 250 mg	Supplied as 50-mg tablets	2018034

Source: Table 9-1 CSR VX21-121-006

^a The VX-121 [VNZ] tablet formulation was Calcium salt Form A.

Abbreviations: D-IVA, deutivacaftor; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Samples

Cohort 1

- Days 1, 2, 5, 10, 12, 13, 29, 30, 33, 38, 40, and 41: Predose.
- Days 14 and 42: Predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose.

Cohort 2

- Days 1, 2, 5, 15, 16, 23, 35, 36, 39, 44, 46, and 47: Predose.
- Days 6, 24, and 48: Predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours postdose

Results

[Table 93](#) summarizes the PK metrics of VNZ, TEZ, and D-IVA after multiple dose administration as monotherapy or in TC. Generally, exposures ($C_{max,ss}$ and AUC) of VNZ, TEZ, and D-IVA increased when administered in TC compared to monotherapy. Time to maximum concentration was similar between treatments for all analytes except VNZ, which reached median t_{max} earlier (5 hours) following administration in TC as compared to monotherapy (median t_{max} of 10 hours).

The exposures ($C_{max,ss}$ and AUC) of active major metabolites (M1-TEZ and M1-D-IVA) were increased following administration of TEZ and D-IVA in TC (with VNZ) compared to monotherapy ([Table 94](#)).

Table 93. Summary of PK Metrics of VNZ, TEZ, and D-IVA Following Multiple Dosing as Monotherapy or in TC

				PK Parameter				
				C _{max,ss} (μg/mL)	T _{max} (h)	AUC _{tau,ss} (μg·h/mL)	AUC _{last} (μg·h/mL)	C _{trough} (μg/mL)
Cohort	Analyte	Treatment	N	Statistic				
1	VX-121	VX-121	18	0.758 (24.3%)	10.0 (0.00, 24.0)	15.0 (26.9%)	15.0 (26.9%)	0.679 (28.8%)
		VX-121/TEZ/D-IVA	17	1.25 (59.6%)	5.00 (0.00, 24.0)	25.4 (58.9%)	25.4 (58.9%)	1.07 (54.2%)
1	TEZ	VX-121/TEZ/D-IVA	17	9.53 (29.8%)	4.00 (2.00, 6.05)	141 (39.6%)	142 (39.6%)	4.09 (59.9%)
1	D-IVA	VX-121/TEZ/D-IVA	17	3.32 (58.0%)	5.00 (3.00, 6.00)	55.5 (70.5%)	54.8 (72.3%)	1.73 (72.4%)
2	VX-121	VX-121/TEZ/D-IVA	20	1.00 (49.3%)	18.0 (0.00, 24.0)	19.5 (54.6%)	19.5 (54.6%)	0.812 (55.2%)
2	TEZ	TEZ	20	6.39 (24.9%)	4.50 (2.00, 6.05)	82.4 (25.7%)	82.4 (25.7%)	1.88 (27.0%)
		VX-121/TEZ/D-IVA	20	8.43 (38.7%)	4.98 (1.00, 5.20)	118 (50.9%)	118 (50.9%)	3.53 (63.1%)
2	D-IVA	D-IVA	20	2.02 (48.5%)	5.00 (2.00, 8.00)	31.3 (64.7%)	31.3 (64.7%)	0.820 (81.3%)
		VX-121/TEZ/D-IVA	20	2.51 (64.0%)	5.05 (4.00, 8.00)	41.1 (76.9%)	41.1 (76.9%)	1.13 (102%)

Source: Table 11-1 CSR VX21-121-006

Notes: C_{trough} was determined as predose concentration on the day of analysis (Day 14 time 0 h for Cohort 1 Period 1; Day 42 time 0 h for Cohort 1 Period 2; Day 6 time 0 h for Cohort 2 Period 1; Day 24 time 0 h for Cohort 2 Period 2; Day 48 time 0 h for Cohort 2 Period 3). T_{max} is presented as median [min, max], data for other PK parameters are presented as Mean (CV%).

Abbreviations: $AUC_{tau,ss}$, area under the concentration-time curve during the dosing interval at steady-state; AUC_{last} , area under the concentration-time curve to the last measurable concentration; $C_{max,ss}$, maximum plasma concentration at steady-state;

C_{trough} , lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; h, hour; N, number of subjects in treatment group; PK, pharmacokinetic; TEZ, tezacaftor; t_{max} , time to maximum concentration; VX-121 [VNZ], vanzacaftor

Table 94. Summary of PK Metrics of M1-TEZ and M1-D-IVA Following Multiple Dosing of TEZ and D-IVA as Monotherapy or in TC

				PK Parameter				
				C _{max,ss} (µg/mL)	T _{max} (h)	AUC _{tau,ss} (µg·h/mL)	AUC _{last} (µg·h/mL)	C _{trough} (µg/mL)
Cohort	Analyte	Treatment	N	Statistic				
1	M1-TEZ	VX-121/TEZ/D-IVA	17	9.07 (14.6%)	5.05 (2.00, 10.0)	178 (11.4%)	178 (11.4%)	6.13 (17.5%)
1	M1-D-IVA	VX-121/TEZ/D-IVA	17	3.02 (40.8%)	5.00 (4.00, 6.05)	51.7 (50.4%)	51.7 (50.4%)	1.73 (51.7%)
2	M1-TEZ	TEZ	20	7.28 (20.6%)	6.00 (2.00, 12.0)	149 (21.6%)	149 (21.6%)	4.77 (18.3%)
		VX-121/TEZ/D-IVA	20	8.54 (19.5%)	6.00 (2.02, 8.00)	166 (20.6%)	166 (20.7%)	6.20 (20.8%)
2	M1-D-IVA	D-IVA	20	2.01 (27.5%)	5.00 (4.00, 6.02)	30.1 (36.0%)	30.1 (36.0%)	0.861 (50.2%)
		VX-121/TEZ/D-IVA	20	2.59 (34.5%)	5.03 (4.00, 10.0)	42.6 (43.1%)	42.6 (43.1%)	1.39 (55.1%)

Source: Table 11-2 CSR VX21-121-006

Notes: C_{trough} was determined as predose concentration on the day of analysis (Day 14 time 0 h for Cohort 1 Period 1; Day 42 time 0 h for Cohort 1 Period 2; Day 6 time 0 h for Cohort 2 Period 1, Day 24 time 0 h for Cohort 2 Period 2; Day 48 time 0h for Cohort 2 Period 3). T_{max} is presented as median [min, max], data for other PK parameters are presented as Mean (CV%).

Abbreviations: $AUC_{tau,ss}$, area under the concentration-time curve during the dosing interval at steady-state; AUC_{last} , area under the concentration-time curve to the last measurable concentration; $C_{max,ss}$, maximum plasma concentration at steady-state; C_{trough} , lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; M1-D-IVA, M1 metabolite of D-IVA; M1-TEZ, M1 metabolite of TEZ; M6-D-IVA, M6 metabolite of D-IVA; max, maximum; min, minimum; PK, pharmacokinetic; TC, triple combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

The PK interaction between VNZ, TEZ, and D-IVA administered as monotherapy or TC was assessed statistically on the log transformed $C_{max,ss}$ and AUC (AUC_{last} and AUC_{tau} at steady state). The GLSM ratios and their associated 90% CIs were reported and are presented in [Table 95](#) for VNZ, TEZ, and D-IVA. VNZ $C_{max,ss}$ and AUC increased 48% and 54%, respectively, when VNZ was administered in TC with TEZ/D-IVA compared to VNZ administered alone. The 90% CIs ranged from 1.28 to 1.72 for $C_{max,ss}$ and 1.34 to 1.77 for AUC.

The extents of exposure increase of TEZ and D-IVA administered in TC compared to administered alone were less than that observed in VNZ. TEZ $C_{max,ss}$ and AUC increased 29% and 35%, respectively, and M1-TEZ $C_{max,ss}$ and AUC were increased 17% and 11%, respectively. D-IVA $C_{max,ss}$ and AUC increased 18% and 27%, respectively, M1-D-IVA $C_{max,ss}$ and AUC increased 27% and 39%, respectively.

Table 95. Statistical Summary of Treatment Comparison for VNZ, TEZ, and D-IVA PK Metric

Analyte	PK Parameter	Units	Reference GLSM	Test GLSM	Ratio (TC/Monotherapy)	90% CI (Lower, Upper)
VX-121	AUC _{tau,ss}	h·µg/mL	14.51	22.30	1.54	1.34, 1.77
	C _{max,ss}	µg/mL	0.74	1.09	1.48	1.28, 1.72
	AUC _{last}	h·µg/mL	14.52	22.31	1.54	1.34, 1.77
TEZ	AUC _{tau,ss}	h·µg/mL	80.04	108.42	1.35	1.25, 1.47
	C _{max,ss}	µg/mL	6.19	7.98	1.29	1.20, 1.38
	AUC _{last}	h·µg/mL	80.04	108.45	1.35	1.25, 1.47
D-IVA	AUC _{tau,ss}	h·µg/mL	27.34	34.69	1.27	1.18, 1.37
	C _{max,ss}	µg/mL	1.86	2.20	1.18	1.07, 1.31
	AUC _{last}	h·µg/mL	27.34	34.70	1.27	1.18, 1.37

Source: Table 11-3 CSR VX21-121-006

Notes: Treatment with monotherapy was set as reference and treatment with TC was set as test

Abbreviations: AUC_{tau,ss}, area under the concentration-time curve during the dosing interval at steady-state; AUC_{last}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max,ss}, maximum plasma concentration at steady-state; C_{trough}, lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; GLSM, geometric least squares mean; M1-D-IVA, M1 metabolite of D-IVA; M1-TEZ, M1 metabolite of TEZ; M6-D-IVA, M6 metabolite of D-IVA; max, maximum; min, minimum; PK, pharmacokinetic; TC, triple combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Conclusions

Following 14 days once daily (QD) regimen of VNZ, TEZ, and D-IVA as administered in TC, exposures of VNZ, TEZ, D-IVA and their respective metabolites were all greater compared to 14 days QD treatment of VNZ, TEZ and D-IVA when administered as monotherapy.

- VNZ C_{max,ss} and AUC increased 48% and 54%, respectively.
- TEZ C_{max,ss} and AUC increased 29% and 35%, respectively, and M1-TEZ C_{max,ss} and AUC were increased 17% and 11%, respectively.
- D-IVA C_{max,ss} and AUC increased 18% and 27%, respectively, M1-D-IVA C_{max,ss} and AUC increased 27% and 39%, respectively.

For additional assessment of these results and their potential impact on assessing TC efficacy and safety, refer to Section [6.1](#).

14.2.3.2. Study VX21-121-007 (Study 007)

Title

A Phase 1, Open-label Study to Evaluate the Effect of Itraconazole on VX-121 [VNZ] in Healthy Adult Subjects

Study Period

January 18, 2022 to April 1, 2022

Objective

Primary Objective

To assess the effect of itraconazole on the PK of a single dose of VNZ

Secondary Objective

To assess the safety and tolerability of VNZ when administered with itraconazole

Study Design

A phase 1, open-label, single-sequence DDI study to evaluate the effect of itraconazole on the PK of VNZ ([Figure 19](#)). There was a Washout Period of 14 days from the single dose of VNZ in Dosing Period 1 to the start of itraconazole dosing in Dosing Period 2.

Figure 19. Study Design, Study 007

Screening	Dosing Period 1 (Days 1 through 14): Day 1: VX-121 5 mg	Dosing Period 2 (Days 15 through 38): Days 15-28: itraconazole 200 mg qd Day 18: VX-121 5 mg	Safety Follow-up Visit (7 to 10 days after discharge)

Source: Figure 9-1 CSR Study VX21-121-007
Abbreviations: qd, once daily; VX-121 [VNZ], vanzacaftor

Test Drug

Study drug details are presented in [Table 96](#). Study drug was administered orally in a fed state.

Table 96. Study Drug, Study 007

Drug Name	Dosing Form/ Route	Dosage	How Supplied	Lot Number
VX-121	Tablet ^a / oral	VX-121 5 mg	Supplied as 5-mg tablets	2018028
Itraconazole	Solution/ Oral	Itraconazole 20 mL	Sourced as 10-mg/mL solution	0A212207

Source: Table 9-1 CSR Study VX21-121-007
^a The VX-121 [VNZ] tablet formulation was calcium salt Form A.
Abbreviations: VX-121 [VNZ], vanzacaftor

Samples

Blood samples for plasma PK analysis of VNZ were collected on Days 1 and 18 at predose and 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 96, 120, 144, 192, 240, and 288 hours postdose for Dosing Period 1 and up to 480 hours for Dosing Period 2.

Results

The PK parameters of VNZ with or without coadministered with itraconazole are summarized in [Table 97](#). The mean C_{max} , $AUC_{0-tlast}$, and $AUC_{0-\infty}$ were higher when VNZ was coadministered

with itraconazole compared to when VNZ was administered alone. The mean elimination half-life ($t_{1/2}$) was more than 3-times longer when VNZ was coadministered with itraconazole compared to VNZ administered alone (185 hours versus 57.1 hours).

Table 97. Summary PK Parameters of VNZ Administered Alone or Coadministered With Itraconazole

PK Parameter	VX-121		VX-121 + Itraconazole	
	N	Mean (CV%) ^a	N	Mean (CV%) ^a
C_{max} (µg/mL)	18	0.0730 (30.1%)	17 ^b	0.114 (27.6%)
t_{max} (h)	18	24.00 [12.00, 24.05]	17 ^b	48.00 [48.00, 216.08]
$AUC_{0-tlast}$ (µg·h/mL)	18	6.43 (29.2%)	17 ^b	36.0 (33.5%)
$AUC_{0-\infty}$ (µg·h/mL)	18	6.99 (26.9%)	12 ^{b,c}	43.3 (28.6%)
$t_{1/2}$ (h)	18	57.1 (26.1%)	12 ^{b,c}	185 (36.0%)
CL/F (L/h)	18	0.761 (23.7%)	12 ^{b,c}	0.124 (29.2%)
V_z/F (L)	18	62.2 (31.9%)	12 ^{b,c}	31.8 (39.2%)

Source: Table 11-1 CSR Study VX21-121-007

^a Mean (CV%) are presented for all parameters except t_{max} , where median [min, max]

^b One subject was excluded due to predose concentration >5% of C_{max} (carryover)

^c $AUC_{0-\infty}$, $t_{1/2}$, CL/F, and V_z/F were excluded from descriptive statistics when AUC extrapolated was >30%

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; $AUC_{0-tlast}$, area under the concentration-time curve to the last measurable concentration; C_{max} , maximum plasma concentration; CV, coefficient of variation; h, hour; max, maximum value; min, minimum value; N, number of subjects in treatment group; PK, pharmacokinetic; $t_{1/2}$, half-life; t_{max} , time to maximum concentration; VX-121 [VNZ], vanzacaftor

To evaluate the impact of itraconazole, a strong CYP3A4 inhibitor, on the PK of VNZ the GLSM and 90% CI were calculated from VNZ C_{max} , $AUC_{0-tlast}$, and $AUC_{0-\infty}$ (Table 98). VNZ coadministered with itraconazole increased VNZ C_{max} by 1.55-fold, $AUC_{0-tlast}$ by 5.55-fold, and $AUC_{0-\infty}$ by 6.37-fold compared to VNZ administration alone.

Table 98. Statistical Comparison of VNZ Pharmacokinetic Metric for VNZ Coadministered With Itraconazole Compared to VNZ Administered Alone

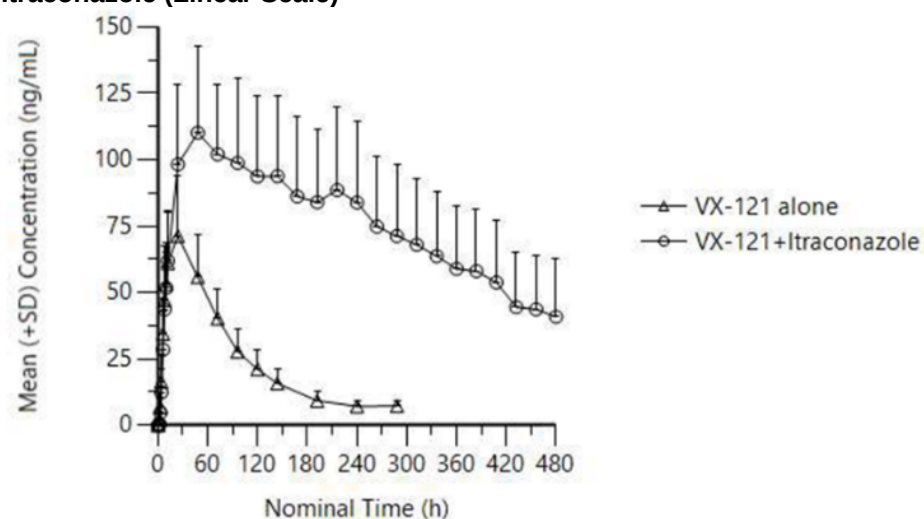
PK Parameter	Units	VX-121 + Itraconazole		GLSM Ratio (Test/Reference)	90% CI (Lower, Upper)
		VX-121 GLSM (Reference)	GLSM (Test)		
C_{max}	µg/mL	0.0703	0.109	1.55	(1.41, 1.70)
$AUC_{0-tlast}$	µg·h/mL	6.20	34.4	5.55	(5.05, 6.09)
$AUC_{0-\infty}$	µg·h/mL	6.77	43.1	6.37	(5.53, 7.35)

Source: Table 11-2 CSR Study VX21-121-007

Note: $AUC_{0-\infty}$ was excluded from inferential statistics when AUC extrapolated >30%

Abbreviations: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; $AUC_{0-tlast}$, area under the concentration-time curve from time 0 to the last measurable concentration; CI, confidence interval; C_{max} , maximum plasma concentration; GLSM, geometric least squares mean; PK, pharmacokinetic; VX-121 [VNZ], vanzacaftor

However, the effect of itraconazole on exposure of VNZ is underestimated in this study as the PK sampling scheme in Period 2 (up to 480 hours) hardly covered three half-lives of VNZ (185 hours ×3) (Figure 20). A physiologically based pharmacokinetic (PBPK) model estimated an increase of AUC_{0-inf} of VNZ by 10.5-fold with sufficient time interval for evaluation. For details, refer to Section 14.5.2.

Figure 20. Mean (+SD) Concentration-Time Profiles of VNZ With or Without Coadministered With Itraconazole (Linear Scale)

Source: Figure 11-1 CSR Study VX21-121-007

Abbreviations: h, hour; SD, standard deviation; VX-121 [VNZ], vanzacaftor

Conclusions

When coadministered with itraconazole, a strong CYP3A4 inhibitor, VNZ C_{max} was increased by 1.55-fold, $AUC_{0-t_{last}}$ increased by 5.55-fold, and $AUC_{0-\infty}$ increased by 6.37-fold. The effect of itraconazole on VNZ AUC values is an underestimate due to the limitation of PK sampling scheme. The PBPK model estimates a 10.5-fold increase of $AUC_{0-\infty}$.

14.2.3.3. Study VX18-445-006 (Study 445-006)**Title**

A Phase 1, Open-label Study to Evaluate the Effect of Itraconazole and Fluconazole on VX-445 [ELX] Triple Combination Therapy in Healthy Adult Subjects

Study Period

May 9, 2018 to July 10, 2018

Objective**Primary Objective**

- To assess the effect of itraconazole on the PK of a single dose of ELX/TEZ/D-IVA and relevant metabolites

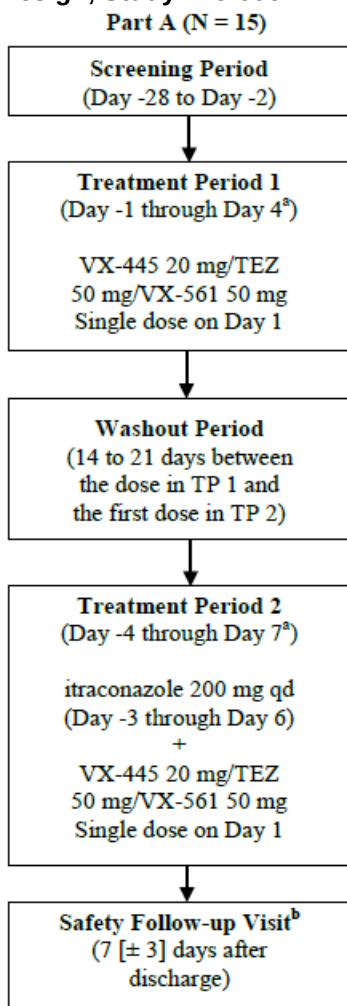
Secondary Objective

- To assess the safety and tolerability of ELX/TEZ/D-IVA when administered with itraconazole

Study Design

A phase 1, 2-part, open-label, drug-drug interaction (DDI) study. Part A was designed to evaluate the effect of itraconazole on the PK of ELX/TEZ/D-IVA administered as separate tablets ([Figure 21](#)). Optional Part B was designed to evaluate the effect of fluconazole on the PK of ELX/TEZ/D-IVA. However, Part B was not conducted based on a review of the PK results from Part A.

Figure 21. Study Design, Study 445-006



Source: Figure 9-1 CSR Study VX18-445-006

Note: Subjects were admitted to the CRU on Day-1 for TP 1 and Day-4 for TP 2 and remained in the CRU for the duration of the treatment periods.

^a Subjects were discharged from the CRU on TP 1 Day 4 to continue in the Washout Period and at the conclusion of the study on TP 2 Day 7 after the final PK assessment.

^b Subjects who prematurely discontinued from the study for any reason (except withdrawal of consent) were asked to return to complete the Safety Follow-up Visit.

Abbreviations: CRU, clinical research unit; N, number of subjects; PK, pharmacokinetic; TEZ, tezacaftor; TP, treatment period; qd, once daily

Test Drug

Study drug details are presented in [Table 99](#). Study drug was administered orally in a fed state.

Table 99. Study Drug, Study 445-006

Drug Name	Dosing Form/ Route	Dosage	How Supplied	Lot Number
VX-445	Tablet/ oral	20 mg VX-445	Supplied as 20-mg tablets	2016062
TEZ	Tablet/ oral	50 mg TEZ	Supplied as 50-mg tablets	2016034
VX-561	Tablet/ oral	50 mg VX-561	Supplied as 50-mg tablets	2017019
itraconazole	Solution/ oral	200 mg itraconazole	Sourced as 10 mg/mL solution	HJB3X01

Source: Table 9-2 Study VX18-445-006
Abbreviations: TEZ, tezacaftor

Samples

Blood samples for plasma PK analysis were collected on at predose, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, 48, and 72 hours postdose in each treatment period.

Results

PK parameters of D-IVA with and without itraconazole are shown in [Table 100](#). The magnitude of the DDI effect of itraconazole on D-IVA, and M1-D-IVA was assessed by computing the GLSM ratios and associated 90% CIs with and without itraconazole ([Table 101](#)). Increases were also observed in D-IVA exposures (approximately 11-fold for $AUC_{0-\infty}$ and 2.0-fold for C_{max}) with itraconazole coadministration relative to administration alone. M1-561 $AUC_{0-\infty}$ increased by approximately 2.0-fold while C_{max} decreased by approximately 73%.

Table 100. PK Parameters (Mean [SD]) of TEZ, D-IVA and Their Active Metabolites After Administration Alone (TP 1) and With Itraconazole (TP 2)

Analyte	TP	N	t_{max}^a (h)	C_{max} (µg/mL)	$AUC_{0-\infty}$ (h·µg/mL)	$t_{1/2}$ (h)
TEZ	1	15	4.00 (3.00, 6.05)	0.476 (0.0786)	11.6 (3.31)	18.3 (4.68)
	2	13	4.03 (3.98, 24.02)	0.499 (0.0789)	32.8 (9.89) ^b	46.4 (14.4)
M1-TEZ	1	15	12.07 (8.00, 36.02)	0.667 (0.136)	65.7 (11.0)	55.9 (18.2)
	2	13	36.10 (35.97, 72.00)	0.181 (0.0540)	40.4 (19.0)	122 (51.9)
D-IVA	1	15	4.00 (3.00, 6.02)	0.286 (0.0870)	5.07 (2.28)	15.5 (3.18)
	2	13	6.00 (6.00, 8.05)	0.539 (0.0816)	52.9 (13.4)	74.4 (12.5)
M1-561	1	15	4.02 (4.00, 6.02)	0.364 (0.0696)	5.65 (1.61)	19.5 (3.22)
	2	13	8.05 (6.00, 48.00)	0.101 (0.0312)	11.3 (2.80)	66.4 (13.0)

Source: Tables 11-1 and 11-2 Study VX18-445-006

Note: TP 1 dose was ELX 20 mg/TEZ 50 mg/D-IVA 50 mg; TP 2 dose was ELX 20 mg/TEZ 50 mg/ D-IVA 50 mg + itraconazole 200 mg qd.

^a presented as Median (min, max); N=13 for $AUC_{0-\infty}$

Abbreviation: $AUC_{0-\infty}$, area under the concentration-time curve estimated to infinity; C_{max} , maximum plasma concentration; D-IVA, deutivacaftor; h, hour; max, maximum; min, minimum; N, number of subjects in treatment group; PK, pharmacokinetic; qd, once daily; SD, standard deviation; $t_{1/2}$, half-life; TEZ, tezacaftor; t_{max} , time to maximum concentration; TP, Treatment Period

Table 101. GLSM Ratios and Associated 90% CIs for D-IVA, and M1-D-IVA With (TP 2) and Without (TP 1) Itraconazole

Analyte	PK Parameter	GLSM Ratio (TP 2:TP 1)	90% CI (Lower, Upper)
TEZ	AUC _{0-∞}	4.51	(3.85, 5.29)
	C _{max}	1.48	(1.33, 1.65)
VX-561	AUC _{0-∞}	11.1	(8.72, 14.1)
	C _{max}	1.96	(1.70, 2.26)
M1-TEZ	AUC _{0-∞}	0.570	(0.452, 0.719)
	C _{max}	0.267	(0.241, 0.296)
M1-561	AUC _{0-∞}	2.02	(1.69, 2.43)
	C _{max}	0.275	(0.236, 0.319)

Source: Table 11-3 Study VX18-445-006

Notes: GLSM ratios and 90% CIs were evaluated with and without the discontinued subjects and were found to be similar. TP 1 dose was ELX 20 mg/TEZ 50 mg/ 50 mg; TP 2 dose was ELX 20 mg/TEZ 50 mg/VX-561 [D-IVA] 50 mg + itraconazole 200 mg QD. Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; D-IVA, deutivacaftor; GLSM, geometric least squares mean; M, metabolite; ND, not determined; PK, pharmacokinetic; QD, once daily; TEZ, tezacaftor; TP, treatment period

Conclusions

When coadministered with itraconazole, a strong CYP3A4 inhibitor, TEZ C_{max} and AUC_{0-inf} increased 1.48 and 4.51-fold, respectively. D-IVA C_{max} and AUC_{0-inf} increased by 1.96-fold, and 11.1-fold, respectively.

14.2.4. Other Clinical Pharmacology Studies

14.2.4.1. Study VX20-121-004 (Study 004)

Title

Phase 1, Open-label, Mass Balance Study to Investigate the Absorption, Distribution, Metabolism, and Excretion of ¹⁴C-VX-121 [VNZ] Following Single Oral Administration in Healthy Subjects

Study Period

January 25, 2021 to February 27, 2021

Objective

Primary Objectives

- To determine the routes and rate of elimination and recovery of total radioactivity (TRA) after a single oral dose of ¹⁴C-VNZ
- To characterize the PK of VNZ and TRA after a single oral dose of ¹⁴C-VNZ

Secondary Objectives

- To profile and identify the metabolites of VNZ, if any, in the urine, plasma, and feces following administration of a single oral dose of ^{14}C -VNZ
- To evaluate the safety and tolerability of a single oral dose of ^{14}C -VNZ

Study Design

A phase 1, nonrandomized, open-label, mass balance study in healthy male subjects ([Figure 22](#)).

Figure 22. Study Design, Study 004

Screening	CRU Admission	Treatment Period		Safety Follow-up Phone Interview
		Study Drug Administration	Discharge from CRU	
Days -28 to -2	Day -1	Day 1	Discharge between Day 14 and Day 28 (after discharge criteria were met) OR Discharge on Day 28 at the latest	7-10 days after discharge

Source: Figure 9-1 CSR Study VX20-121-004
 Abbreviations: CRU, clinical research unit

Test Drug

Study drug details are presented in [Table 102](#). Study drug was administered orally approximately 30 minutes after the start of a standard breakfast.

Table 102. Study Drug, Study 004

Drug Name	Dosing Form/ Route	Dosage	How Supplied	Lot Number
^{14}C -VX-121	Solution/ oral	20 mg/200 μCi ^{14}C -VX-121	Supplied as powder	G189-050-004

Source: Table 9-2 CSR Study VX20-121-004
 Abbreviations: CSR, clinical study report; VX-121 [VNZ], vanzacaftor

Samples

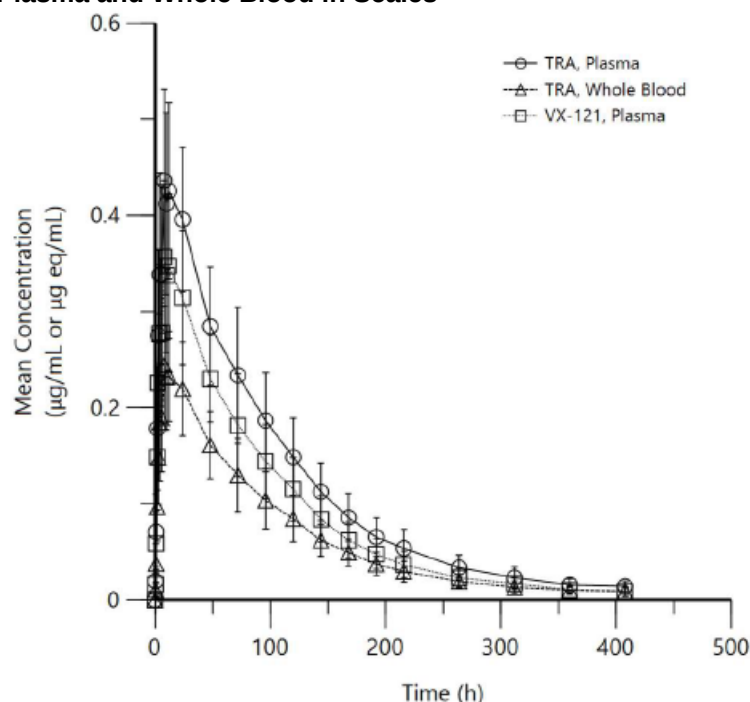
Blood samples for plasma PK analysis of VNZ and its metabolites were collected at predose, 0, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24 hours and on Days 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 13, 15, 17, 19, 21, 23, 25, 27 postdose.

Results

Absorption

The mean concentration-time profiles of unchanged VNZ in plasma and of TRA in plasma and whole blood are presented in [Figure 23](#). Following a single dose of ^{14}C -VNZ 20 mg/200 μCi administered as an oral solution, the unchanged VNZ in plasma and the TRA in plasma and whole blood reached peak concentrations after approximately 8 hours. The mean $t_{1/2}$ was similar for TRA in plasma (68.9 hours) and whole blood (71.8 hours), which was slightly longer than the mean $t_{1/2}$ of unchanged VNZ in plasma (60.8 hours).

Figure 23. Mean (SD) Concentration-Time Profiles of Unchanged VNZ in Plasma and TRA in Plasma and Whole Blood in Scales



Source: Figure 11-1 CSR Study VX20-121-004

Abbreviation: h, hour; SD, standard deviation; TRA, total radioactivity VX-121 [VNZ], vanzacaftor

Distribution

The ratios of VNZ to TRA in plasma and the blood-to-plasma ratio for TRA are presented in [Table 103](#) for both $\text{AUC}_{0-\infty}$ (hereafter referred to as AUC) and C_{max} . As determined by the AUC ratio for VNZ to TRA in plasma, unchanged VNZ accounted for approximately 77% of the TRA in plasma after a single dose of ^{14}C -VNZ 20 mg/200 μCi administered as an oral solution. The TRA in blood was approximately 56% of the TRA in plasma, suggesting that there was no preferential distribution of VNZ into red blood cells.

Table 103. AUC and C_{max} Ratios for Unchanged VNZ to TRA in Plasma and Blood TRA to Plasma TRA After Administration of a Single 20 mg/200 µCi Oral Dose of ¹⁴C-VNZ in Healthy Subjects

	Ratio of AUC		Ratio of C _{max}	
	VX-121/TRA	TRA: Blood/Plasma	VX-121/TRA	TRA: Blood/Plasma
N	6	6	6	6
Mean (CV%)	0.765 (1.55)	0.562 (2.00)	0.813 (1.37)	0.545 (4.52)

Source: Table 11-2 CSR Study VX20-121-004

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; CV, coefficient of variation; N, number of subjects; TRA, total radioactivity; VX-121 [VNZ], vanzacaftor

Metabolism

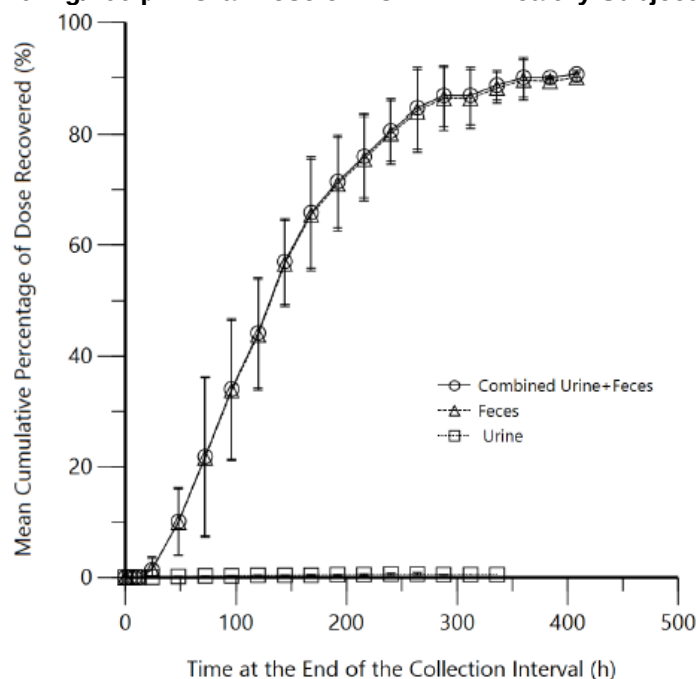
VNZ accounted for the majority of the total circulating radioactivity in plasma (mean =96.2%). M19-VNZ accounted for 3.8% of the total circulating radioactivity, indicating that no major metabolites were observed. VNZ was mainly cleared by metabolism in humans as the mean unchanged parent recovered in excreta accounted for less than 10% of the administered radioactive dose. The most abundant metabolite in feces was M6-VNZ, which accounted for 26.1% of the administered radioactive dose, followed by M55-VNZ, M19-VNZ, M57-VNZ, and M9-VNZ, which accounted for 7.4%, 6.9%, 6.9%, and 6.8% of the administered dose, respectively. Urine metabolites were not profiled because only approximately 0.5% of the radioactive dose was recovered in urine.

Elimination

The TRA in urine and in feces was used for calculation of the A_e of the administered dose. The f_e represents the recovery of TRA. The mean cumulative percentage of TRA recovered in each matrix with respect to time is presented in [Figure 24](#).

The mass balance and overall recovery of TRA are summarized in [Table 104](#). Mean recovery of TRA over 408 hours (17 days) postdose was 0.502% in urine and 91.6% of the radioactive dose recovered in feces, demonstrating that excretion in urine is minimum and elimination in feces accounted for most of the excreted dose. VNZ was mainly cleared by metabolism in humans as the mean unchanged parent recovered in excreta accounted for less than 10% of the administered radioactive dose.

Figure 24. Mean (SD) of Cumulative Percentage of TRA Recovered in Urine and Feces, and Total Recovery at Specified Sample Collection Interval Time Points After Administration of a Single 20 mg/200 μ Ci Oral Dose of ^{14} C-VNZ in Healthy Subjects



Source: Figure 11-2 CSR Study VX20-121-004

Abbreviation: h, hour; SD, standard deviation; TRA, total radioactivity; VX-121 [VNZ], vanzacaftor

Table 104. Mean (CV%) Cumulative Amount and Percentage Fraction of Dose of TRA Excreted in Urine, Feces, and Combined Urine and Feces After Administration of a Single 20 mg/200 μ Ci Oral Dose of ^{14} C-VNZ in Healthy Subjects

Parameter	N	TRA in Urine	TRA in Feces	TRA in Combined Urine and Feces
A_e (μ g eq)	6	94.2 (29.3)	17200 (1.94)	17300 (1.82)
f_e (%)	6	0.502 (29.4)	91.6 (1.84)	92.1 (1.71)

Source: Table 11-3 CSR Study VX20-121-004

Abbreviations: A_e , cumulative amount excreted; CV, coefficient of variation; F_e , fraction of administered dose excreted; N, number of subjects; TRA, total radioactivity; VX-121 [VNZ], vanzacaftor

Conclusions

VNZ was generally safe and well tolerated at the evaluated dose of 20 mg/200 μ Ci in healthy subjects in this study. Unchanged VNZ accounted for most of the total circulating radioactivity in plasma and there were no major circulating metabolites of VNZ. VNZ was mainly cleared by metabolism in humans. VNZ was primarily excreted as metabolites in the feces. Renal excretion of VNZ was negligible.

14.2.4.2. Study VX21-121-008 (Study 008)

Title

A Phase 1, Open-label Study to Assess the Pharmacokinetics and Safety of a Single Dose of VX-121 [VNZ] /Tezacaftor/Deutivacaftor in Subjects With Moderate Hepatic Impairment and in Matched Healthy Subjects

Study Period

July 22, 2022 to March 16, 2023

Objective

Primary Objective

- To evaluate the PK of VNZ, TEZ, D-IVA, and relevant metabolites when administered in subjects with moderate hepatic impairment (MHI) compared to the PK in matched healthy subjects

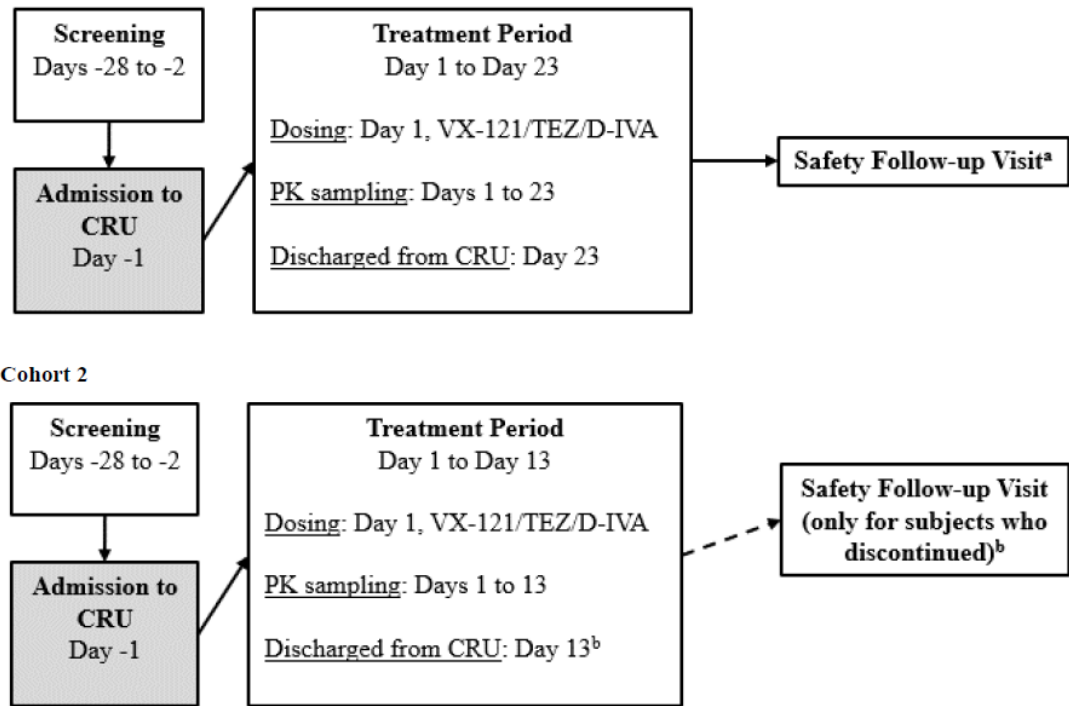
Secondary Objective

- To assess the safety and tolerability of a single dose of VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg FDC tablet in subjects with MHI and in matched healthy subjects

Study Design

This was a phase 1, nonrandomized, open-label study evaluating a single dose of orally administered VNZ/TEZ/D-IVA in subjects with MHI (Cohort 1) and matched healthy subjects (Cohort 2). Subjects in Cohort 1 had to meet the criteria for Child-Pugh Class B: 7 to 9 to be eligible for enrollment. The study design is shown in [Figure 25](#).

Figure 25. Study Design, Study 008
Cohort 1



Source: Figure 9-1 CSR VX21-121-008
Note: Enrollment started with Cohort 1. Once a subject with MHI was enrolled and had completed the treatment period, a matched healthy subject was enrolled in Cohort 2.
Abbreviations: CRU, clinical research unit; D-IVA, deutivacaftor; MHI, moderate hepatic impairment; PK, pharmacokinetic; TEZ, tezacaftor

Test Drug

Study drug details are presented in [Table 105](#). Study drug was administered orally with water under fed condition (standard breakfast).

Table 105. Study Drug, Study 008

Drug Name	Dosing Form/ Route	Dosage	How Supplied	Batch/Lot Number
VX-121/TEZ/D-IVA	FDC Tablet/ oral	VX-121 10 mg TEZ 50 mg D-IVA 125 mg	Supplied as 10 mg VX-121/50 mg TEZ/ 125 mg D-IVA tablets	3202291R

Source: Table 9-1 CSR VX21-121-008
Abbreviations: D-IVA, deutivacaftor; FDC, fixed-dose combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Samples

Blood samples for plasma PK analysis of VNZ, TEZ, D-IVA and their relevant metabolites were collected at predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 hours on Day 1, every 24 hours on Days 2-14, and every 48 hours on Days 15-23 postdose.

Results

[Table 106](#) summarizes the PK metrics of VNZ, TEZ, D-IVA and their active metabolites based on total drug concentrations following a single oral dose of an FDC tablet (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg) in MHI subjects (Cohort 1, n=12) and matched healthy subjects (Cohort 2, n=12). Following oral administration of a single dose of VNZ/TEZ/D-IVA, exposures of VNZ, D-IVA, and M1-D-IVA for MHI subjects in Cohort 1 were lower than for matched healthy subjects in Cohort 2.

Table 106. PK Metrics Summary of VNZ After a Single Oral Dose of VNZ/TEZ/D-IVA in MHI Subjects (Cohort 1, N=12) and Matched Healthy Subjects (Cohort 2, N=12)

Cohort	Mean (%CV)			GLSCM Ratio (CI, %)		
	C _{max} (µg/mL)	AUC _{0-∞} (µg·h/mL)	AUC _{0-last} (µg·h/mL)	C _{max}	AUC _{0-∞}	AUC _{0-last}
VNZ						
MHI	0.0720 (35.1)	7.65 ^a (31.4)	7.17 (32.4)	66.6	70.1	71.7
HS	0.110 (41.5)	10.9 (32.3)	10.1 (34.9)	(55.5, 79.9)	(55.8, 88.1)	(56.2, 91.6)
TEZ						
MHI	2.49 (21.8)	51.6 (28.3)	49.5 (28.8)	98.2	101	103
HS	2.56 (24.6)	51.1 (27.7)	47.8 (26.4)	(79.7, 121)	(82.8, 123)	(84.1, 125)
M1-TEZ						
MHI	0.483 (31.2)	69.6 (32.9)	66.8 (32.9)	96.1	93.6	106
HS	0.501 (29.0)	73.1 (23.4)	61.7 (20.8)	(77.6, 119)	(77.4, 113)	(87.5, 128)
D-IVA						
MHI	0.729 (43.2)	16.0 (49.8)	15.9 (50.1)	81.8	79.8	79.6
HS	0.844 (31.7)	19.3 (36.3)	19.2 (36.3)	(60.5, 111)	(55.9, 114)	(55.6, 114)
M1-D-IVA						
MHI	0.695 (43.9)	14.1 ^a (40.2)	13.3 (45.3)	68.7	71.9 ^a	66.1
HS	0.957 (37.5)	19.3 (35.8)	19.2 (35.9)	(49.1, 96.1)	(53.4, 97.0)	(47.0, 92.9)

Source: Tables 11-1, 11-2, 11-6, 11-7, 11-8, 11-9 CSR VX21-121-008

^an=11; one subject in Cohort 1 had Rsq <0.8 and no λ_z was determined

Abbreviations: AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; GLSM, geometric least squares mean; HS, healthy subjects; M, metabolite; MHI, moderate hepatic impairment; n, number of subjects; PK, pharmacokinetic; VNZ, vanzacaftor

The percentages of unbound VNZ and D-IVA in plasma are summarized for Cohorts 1 and 2 in [Table 107](#). The mean percentage of unbound VNZ was 17.9% higher while the mean percentage of unbound D-IVA was 28% lower in MHI subjects than in matched healthy subjects.

Table 107. Mean (CV%) Percentage of Unbound VNZ and D-IVA in Plasma in Cohorts 1 and 2

Drug	Cohort 1		Cohort 2	Percent Change (%) Relative to Cohort 2
	MHI Subjects (N=12)	Matched Healthy Subjects (N=12)		
VNZ	0.0138% (54.3)	0.0117% (44.8)		17.9
D-IVA	0.00349% (87.6)	0.00484% (84.6)		-28.0

Source: Tables 11-3 and 11-10 CSR VX21-121-008

Abbreviations: CV, coefficient of variation; D-IVA, deutivacaftor; MHI, moderate hepatic impairment; N, number of subjects; VNZ, vanzacaftor

Mean unbound PK metrics for VNZ are summarized in [Table 108](#). Exposures of unbound VNZ and unbound D-IVA for MHI subjects in Cohort 1 were slightly lower than those for matched healthy subjects in Cohort 2. GLSM ratios and associated 90% CIs were calculated to evaluate unbound VNZ and unbound D-IVA exposures in MHI subjects relative to matched healthy

subjects. Unbound VNZ and unbound D-IVA $C_{\max}$ and AUC were 18% to 42% lower for MHI subjects in Cohort 1 than for matched healthy subjects in Cohort 2, and 90% CI ranges included 1. The difference in unbound exposures was not statistically significant.

Table 108. PK Metrics Summary of Unbound VNZ and Unbound D-IVA After a Single Oral Dose of VNZ/TEZ/D-IVA in MHI Subjects (Cohort 1) and Matched Healthy Subjects (Cohort 2)

Drug	Mean (%CV)			GLSM Ratio (CI, %)		
	$C_{\max,u}$ ($\mu\text{g/mL}$)	$\text{AUC}_{0-\infty,u}$ ($\mu\text{g}\cdot\text{h/mL}$)	$\text{AUC}_{0-\text{last},u}$ ($\mu\text{g}\cdot\text{h/mL}$)	$C_{\max,u}$	$\text{AUC}_{0-\infty,u}$	$\text{AUC}_{0-\text{last},u}$
Unbound VNZ						
MHI	0.00932 (46.7)	1.00 ^a (44.8)	0.926 (42.3)	76.3	80.6	82.2
HS	0.0125 (51.6)	1.24 (42.5)	1.15 (44.8)	(58.0, 100)	(58.4, 111)	(59.3, 114)
Unbound D-IVA						
MHI	0.0334 (109)	0.760 (122)	0.757 (122)	70.5	58.1	58.1
HS	0.0428 (96.6)	0.980 (87.8)	0.975 (87.8)	(44.4, 112)	(31.8, 106)	(31.8, 106)

Source: Tables 11-4, 11-5, 11-11, 11-12 CSR VX21-121-008

^an=11; one subject in Cohort 1 had $\text{Rsq} < 0.8$ and no λ_z was determined

Abbreviations: $\text{AUC}_{0-\infty}$, area under the concentration-time curve estimated to infinity; $\text{AUC}_{0-\text{last}}$, area under the concentration-time curve from time 0 to the last measurable concentration; CI, confidence interval; $C_{\max}$, maximum plasma concentration; CV, coefficient of variation; D-IVA, deutivacaftor; GLSM, geometric least-squares mean; MHI, moderate hepatic impairment; N, number of subjects; TEZ, tezacaftor; VNZ, vanzacaftor

Conclusions

While total VNZ exposures in MHI subjects were approximately 30% lower than those in matched healthy subjects, the unbound VNZ exposures in MHI subjects were only 20% lower but the 90% CI included 1.

Total exposures of TEZ and M1-TEZ were comparable between MHI subjects and matched healthy subjects.

Total and unbound D-IVA exposures in MHI subjects were approximately 20% to 40% lower than those in matched healthy subjects, with 90% CI ranges including 1. Total M1-D-IVA in MHI subjects were approximately 30% lower than those in matched healthy subjects.

14.2.4.3. Study VX22-121-013 (Study 013)

Study VX22-121-013 is a thorough QT study which has been reviewed at QT-Interdisciplinary Review Team. Up to 60 mg QD dose of VNZ [Form A] has been investigated in this study. For details, refer to the QT study review dated July 16, 2024.

14.2.5. Dose-Ranging Studies

14.2.5.1. Study VX18-121-101 (Study 101)

Title

A Phase 2, Randomized, Double-blind, Controlled Study to Evaluate the Safety and Efficacy of VX-121 [VNZ] Combination Therapy in Subjects Aged 18 Years and Older With Cystic Fibrosis

Study Period

April 30, 2019 to December 10, 2019

Objective

Primary Objectives

- To evaluate the safety and tolerability of VNZ in TC with TEZ/D-IVA
- To evaluate the efficacy of VNZ in TC with TEZ/D-IVA

Secondary Objectives

- To evaluate the PD effect of VNZ in TC with TEZ/D-IVA
- To evaluate the PK of VNZ when administered in TC with TEZ/D-IVA
- To evaluate the PK of TEZ, D-IVA, and their respective metabolites when administered in TC with VNZ

Study Design

Part 1

Subjects heterozygous for *F508del* and a minimal function variant [F/MF]. Subjects must remain on a stable CF medication (and supplement) regimen (other than protocol-specified changes in medications that affect CFTR processing or function) for their CF from 28 days before the Day 1 Visit (Parts 1) through the Safety Follow-up Visit.

Part 1 had a randomized, double-blind, placebo-controlled, parallel-group design that evaluated VNZ/TEZ/D-IVA (Figure 26). Subjects were randomized in a 2:2:1:1 ratio to the TC-20 mg:TC-10 mg:TC-5 mg:placebo arms.

Figure 26. Study Design, Study 101 (Part 1; F/MF Subjects)

Treatment Period ^a (4 weeks)		Washout Period ^a (18 ± 3 days)		Safety Follow-up Period (4 weeks)
Screening Period (4 weeks)	TC-20 mg (VX-121/TEZ/D-IVA)	TEZ/ D-IVA		
	TC-10 mg (VX-121/TEZ/D-IVA)			
	TC-5 mg (VX-121/TEZ/D-IVA)			
	Triple Placebo	Dual Placebo		

Source: Figure 9-1 CSR VX18-121-101

Note: Randomization was stratified by ppFEV₁ (<70, ≥70).

^a The dosage of TEZ and D-IVA was TEZ 100 mg QD and D-IVA 150 mg QD.

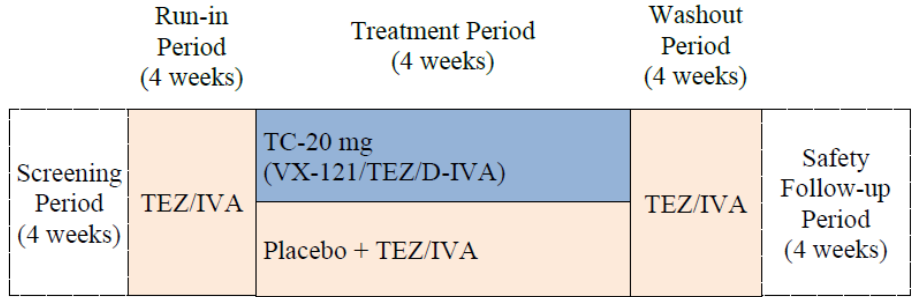
Abbreviations: D-IVA, deutivacaftor; F/MF, heterozygous for *F508del* and a minimal function variant; ppFEV₁, percent predicted forced expiratory volume in 1 second; QD, once daily; TC, triple combination; TC-5 mg, VX-121 [VNZ] 5 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TC-10 mg, VX-121 [VNZ] 10 mg QD/TEZ 100 mg QD/D-IVA 15- mg QD; TC-20 mg, VX-121 [VNZ] 20 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Part 2

Subjects homozygous for *F508del* [F/F]. Subjects must remain on a stable CF medication (and supplement) regimen (other than protocol-specified changes medications that affect CFTR processing or function) for their CF from 28 days before the start of the TEZ/IVA Run-in Period (Part 2) through the Safety Follow-up Visit.

Part 2 had a randomized, double-blind, TEZ/IVA-controlled, parallel-group design that evaluated VNZ/TEZ/D-IVA (Figure 27). Subjects were randomized in a 2:1 ratio to the TC-20 mg:placebo + TEZ/IVA arms.

Figure 27. Study Design, Study 101 (Part 2; F/F Subjects)



Source: Figure 9-2 CSR VX18-121-101
Note: Randomization was stratified by ppFEV₁ (<70, ≥70).
^a The dosage of TEZ/IVA was TEZ 100 mg QD/IVA 150 mg q12h. The dosage of TEZ and D-IVA was TEZ 100 mg QD and D-IVA 150 mg QD.
Abbreviations: D-IVA, deutivacaftor; F/F, homozygous for *F508del*; IVA, ivacaftor; ppFEV₁, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; QD, once daily; TC-20 mg, VX-121 [VNZ] 20 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Test Drug

Study drug details are presented in Table 109. Study drug was administered orally with a fat-containing meal or snack, such as a standard CF meal or snack or a standard meal.

VNZ: Part 1 evaluated 3 dose levels of VNZ (5 mg, 10 mg, and 20 mg QD) in TC with TEZ/D-IVA. Part 2 evaluated VNZ at a dose of 20 mg QD.

TEZ and IVA: The doses of TEZ and IVA were the same as those evaluated in phase 3 studies of TEZ/IVA (TEZ: 100 mg QD; IVA: 150 mg every 12 hours [q12h]).

D-IVA: A D-IVA dose of 150 mg QD was selected for evaluation based on PK, safety, and efficacy results from prior studies of D-IVA administered as monotherapy or in TC with other medications that affect CFTR processing or function. A 150-mg QD dose of D-IVA results in similar exposures as IVA when administered alone at a dose of 150 mg q12h, including AUC_{0-24h} and C_{trough}.

Table 109. Study Drug, Study 101

Drug Name	Strength/Dosing Form/Route	Product Lot
VX-121	5 mg tablet/oral	2018028
VX-121-matching placebo	0 mg tablet/oral	2018029
TEZ	50 mg tablet/oral	2016034
TEZ-matching placebo	0 mg tablet/oral	2016033
D-IVA	50 mg tablet/oral	2018034
D-IVA-matching placebo	0 mg tablet/oral	2018033
TEZ/IVA	100 mg TEZ/150 mg IVA FDC tablet/oral	2017049
TEZ/IVA-matching placebo	0 mg TEZ/0 mg IVA FDC tablet/oral	2016050
IVA	150 mg tablet/oral	3153411R
IVA-matching placebo	0 mg tablet oral	3153408R

Source: Table 9-2 CSR VX18-121-101

Abbreviations: D-IVA, deutivacaftor; FDC, fixed-dose combination; IVA, ivacaftor; TEZ, tezacaftor; VX-121, vanzacaftor

Samples

Blood samples for plasma PK analysis of VNZ, TEZ, D-IVA and their relevant metabolites were collected as below.

Part 1: at predose on Days 2, 8, 15, 29, and 47

Part 2: at predose on Days 8, 15, 29, and 43

Efficacy and Pharmacodynamic Endpoints

Primary Efficacy Endpoint

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV₁) through Day 29

Secondary Efficacy Endpoints

- Absolute change from baseline in sweat chloride (SwCl) concentrations through Day 29
- Absolute change from baseline in cystic fibrosis questionnaire-revised (CFQ-R) respiratory domain (RD) score at Day 29

Results

Pharmacokinetics Results

Part 1

Summary statistics for C_{trough} at Days 2, 8, 15, 29 and 47 are presented in [Table 110](#). VNZ and TEZ appeared to reach steady state by Day 15 while D-IVA appeared to reach steady state by Day 8.

Part 2

Summary statistics for C_{trough} at Days 8, 15, 29, and 43 are presented for analytes in the VNZ/TEZ/D-IVA group in [Table 111](#). VNZ appeared to reach steady state by Day 15 while D-IVA appeared to reach steady state by Day 8.

Table 110. Summary of C_{trough} of Analytes in Plasma, Study 101 (Part 1; F/MF Subjects)

Analyte	Dose (mg)	Day 2		Day 8		Day 15		Day 29		Day 47	
		N	Mean (SD) (CV%)	N	Mean (SD) (CV%)	N	Mean (SD) (CV%)	N	Mean (SD) (CV%)	N	Mean (SD) (CV%)
VX-121 ^a	5	3	69.8 (28.0) 40.2	9	227 (94.7) 41.7	8	317 (119) 37.4	7	366 (130) 35.7	NR	NR
	10	6	107 (60.0) 56.0	17	424 (239) 56.4	18	520 (214) 41.2	14	582 (342) 58.8	NR	NR
	20	6	175 (50.1) 28.6	20	881 (441) 50.0	20	974 (500) 51.3	18	1160 (592) 51.2	13	38.0 (46.6) 123
TEZ	100	15	934 (626) 67.0	46	1770 (1010) 57.4	46	1890 (925) 48.9	46	1920 (994) 51.8	41	2120 (1410) 66.3
M1-TEZ	100	15	1400 (290) 20.7	46	3930 (1090) 27.6	46	4500 (1290) 28.7	46	4640 (1730) 37.3	41	4600 (1650) 35.8
D-IVA	150	15	239 (139) 58.2	46	489 (300) 61.2	46	475 (247) 52.0	46	510 (285) 55.9	40	585 (314) 53.8
M1-D-IVA	150	15	173 (88.9) 51.4	46	328 (179) 54.6	46	311 (141) 45.2	46	336 (173) 51.5	40	397 (202) 51.0

Source: Table 11-1 CSR VX18-121-101

Note: Records that were missing doses were excluded from the concentration-time summary.

^a Since the last dose of VX-121 [VNZ] occurred on Day 29, VX-121 [VNZ] concentrations reported on Day 47 do not have an associated dose.

Abbreviations: C_{trough} , lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; F/MF, heterozygous for *F508del* and a minimal function variant; M, metabolite; number of subjects; NR, not reported since the number of concentrations below the limit of quantitation were greater than 50% of the total number of observations; SD, standard deviation; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Table 111. Summary of C_{trough} of Analytes in the VNZ/TEZ/D-IVA Group in Plasma, Study 101 (Part 2; F/F Subjects)

Analyte	Dose (mg)	Day 8		Day 15		Day 29		Day 43	
		N	Mean (SD) (CV%)	N	Mean (SD) (CV%)	N	Mean (SD) (CV%)	N	Mean (SD) (CV%)
VX-121 ^a	20	18	915 (438) 47.9	17	1050 (414) 39.5	16	1030 (371) 36.0	14	109 (140) 129
TEZ	100	18	2080 (1210) 58.3	17	1870 (675) 36.2	16	2070 (1340) 64.5	16	1920 (915) 47.6
M1-TEZ	100	18	4470 (1630) 36.4	17	4550 (1200) 26.5	16	4440 (1680) 37.8	16	4160 (1670) 40.1
D-IVA	150	18	547 (444) 81.2	17	457 (264) 57.9	16	434 (257) 59.2	NR	
M1-D-IVA	150	18	398 (316) 79.6	17	326 (175) 53.8	16	316 (188) 59.3		

Source: Tables 11-2 and 11-3 CSR VX18-121-101

Note: Records that were missing doses were excluded from the concentration-time summary.

^a Since the last dose of VX-121 [VNZ] occurred on Day 29, VX-121 [VNZ] concentrations reported on Day 43 do not have an associated dose.

Abbreviations: C_{trough} , lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; F/F, homozygous for *F508del*; IVA, ivacaftor; M, metabolite; N, number of subjects; NA, not applicable since subjects resumed TEZ/IVA dosing after Day 29; NR, not reported since the number of concentrations below the limit of quantitation were greater than 50% of the total number of observations; SD, standard deviation; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Spirometry Results

Part 1

The analysis of absolute change from baseline in ppFEV₁ is presented in [Table 112](#) and [Figure 28](#). Treatment with VNZ/TEZ/D-IVA resulted in improvements in ppFEV₁ through Day 29 in each treatment group compared to baseline.

Table 112. Efficacy Results of VNZ Dose Ranging, Study 101

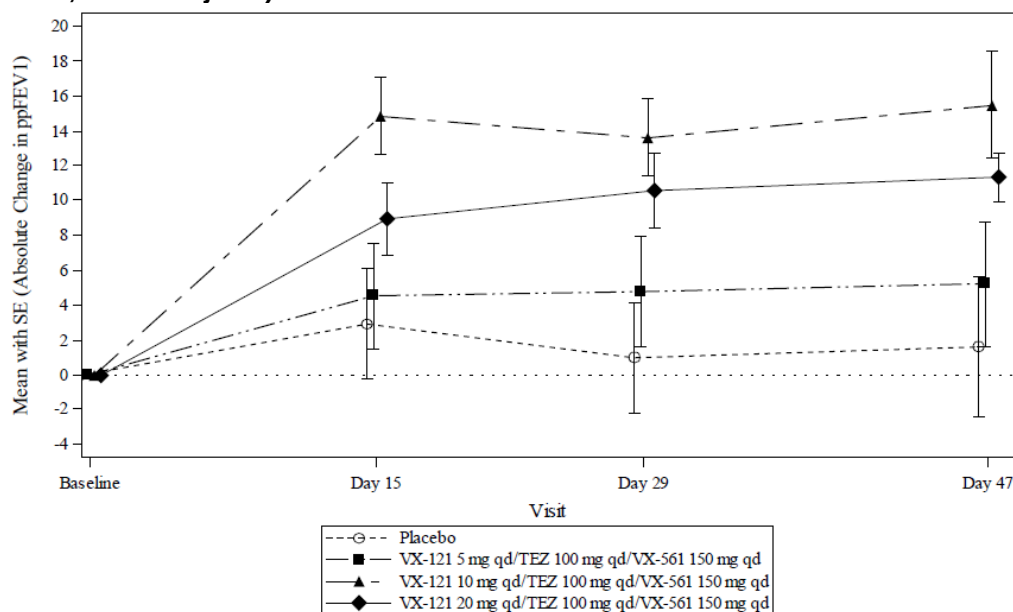
Study Part	Treatment Group	Absolute Change From Baseline in ppFEV ₁ Through Day 29 in percentage points	Absolute Change From Baseline in SwCl Through Day 29 in mmol/L	Absolute Change From Baseline in CFQ-R RD Score At Day 29 in points
Part 1; LS mean (SE)	TC-5 mg	4.6 (3.0)	-42.8 (4.4)	17.6 (7.0)
	TC-10 mg	14.2 (2.1)	-45.8 (3.0)	21.2 (4.7)
	TC-20 mg	9.8 (2.0)	-49.5 (3.2)	29.8 (4.4)
	Placebo	1.9 (3.0)	2.3 (4.6)	3.3 (6.7)
Part 2; LS mean (SE)	TC-20 mg	15.9 (2.3)	-45.5 (2.0)	19.4 (4.3)
	TEZ/IVA	-0.1 (3.0)	-2.6 (2.8)	-5.0 (5.8)

Source: Table 11-10 CSR VX18-121-101

Notes: Within-group LS means (SE) compared to baseline are presented. Baseline in Part 2 was established after a 4-week TEZ/IVA Run-in Period.

Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised respiratory domain; IVA, ivacaftor; LS, least squares; ppFEV₁, percent predicted forced expiratory volume in 1 second; QD, once daily; SE, standard error; SwCl, sweat chloride; TC-5 mg, VNZ 5 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TC-10 mg, VNZ10 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TC-20 mg, VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TEZ, tezacaftor; VNZ, vanzacaftor

Figure 28. Absolute Change From Baseline in ppFEV₁ by Visit in the Treatment Period (Post Day 1 Through Day 29) and Washout Period (Post Day 29 Through Day 47), Full Analysis Set; Study 101 (Part 1; F/MF Subjects)



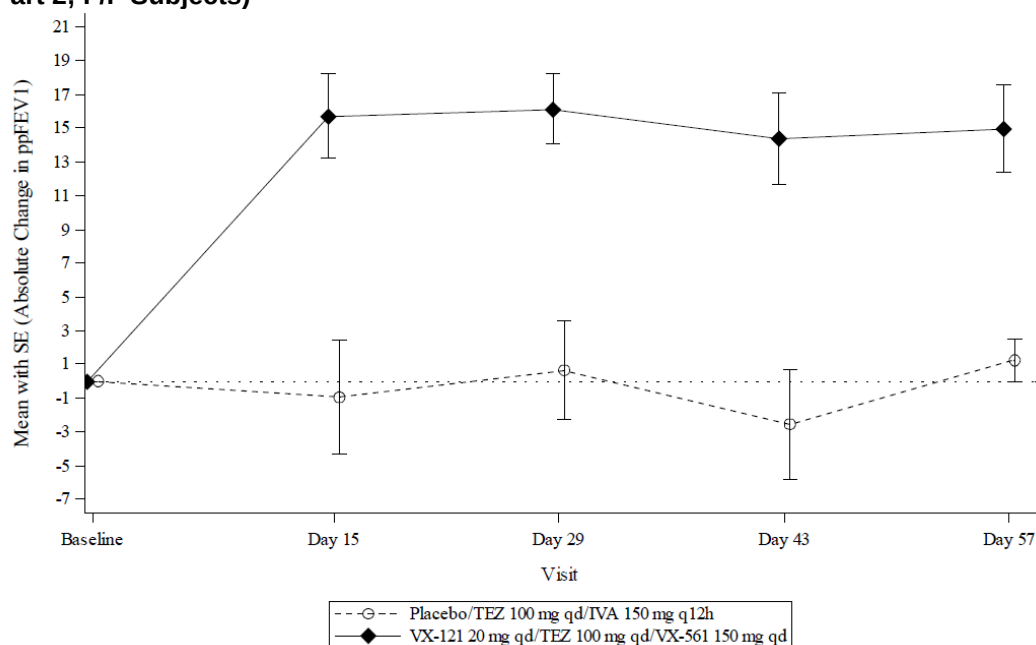
Source: Figure 11-1 CSR VX18-121-101

Abbreviations: D-IVA, deutivacaftor; F/MF, heterozygous for *F508del* and a minimal function variant; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures; ppFEV₁, percent predicted forced expiratory volume in 1 second; QD, once daily; SE, standard error; TC, triple combination; TC-5 mg, VNZ 5 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TC-10 mg, VNZ 10 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TC-20 mg, VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 150 mg QD; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Part 2

The analysis of absolute change from baseline in ppFEV₁ is presented in [Table 112](#) and [Figure 29](#). Treatment with VNZ/TEZ/D-IVA resulted in improvements in ppFEV₁ through Day 29. These improvements were observed relative to baseline established after a 4-week TEZ/IVA Run-in Period.

Figure 29. Absolute Change From Baseline in ppFEV₁ by Visit in the Treatment Period (Post Day 1 Through Day 29) and Washout Period (Post Day 29 Through Day 57), Full Analysis Set; Study 101 (Part 2; F/F Subjects)



Source: Figure 11-2 CSR VX18-121-101

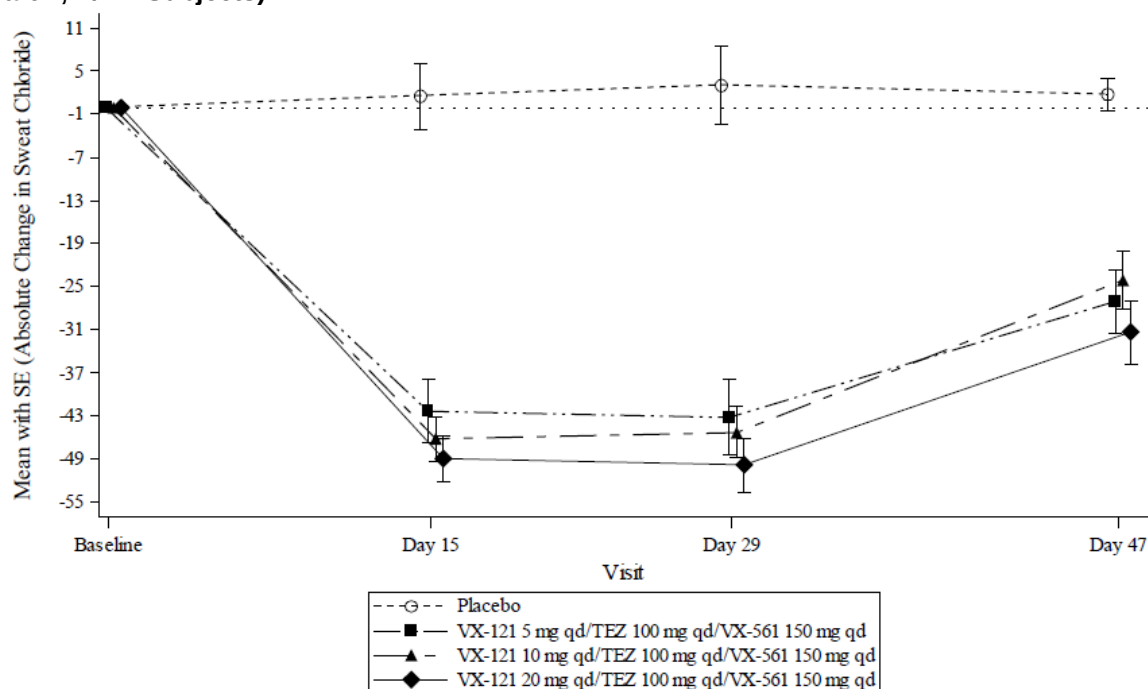
Abbreviations: F/F, homozygous for *F508del*; FAS, full analysis set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; ppFEV₁, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; qd, once daily; SE, standard error; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Sweat Chloride Results

Part 1

The analysis of absolute change from baseline in SwCl is presented in [Table 112](#) and [Figure 30](#). Treatment with VNZ/TEZ/D-IVA resulted in improvements in SwCl through Day 29 in each treatment group compared to baseline.

Figure 30. Absolute Change From Baseline in SwCl by Visit in the Treatment Period (Post Day 1 Through Day 29) and Washout Period (Post Day 29 Through Day 47), Full Analysis Set; Study 101 (Part 1; F/MF Subjects)



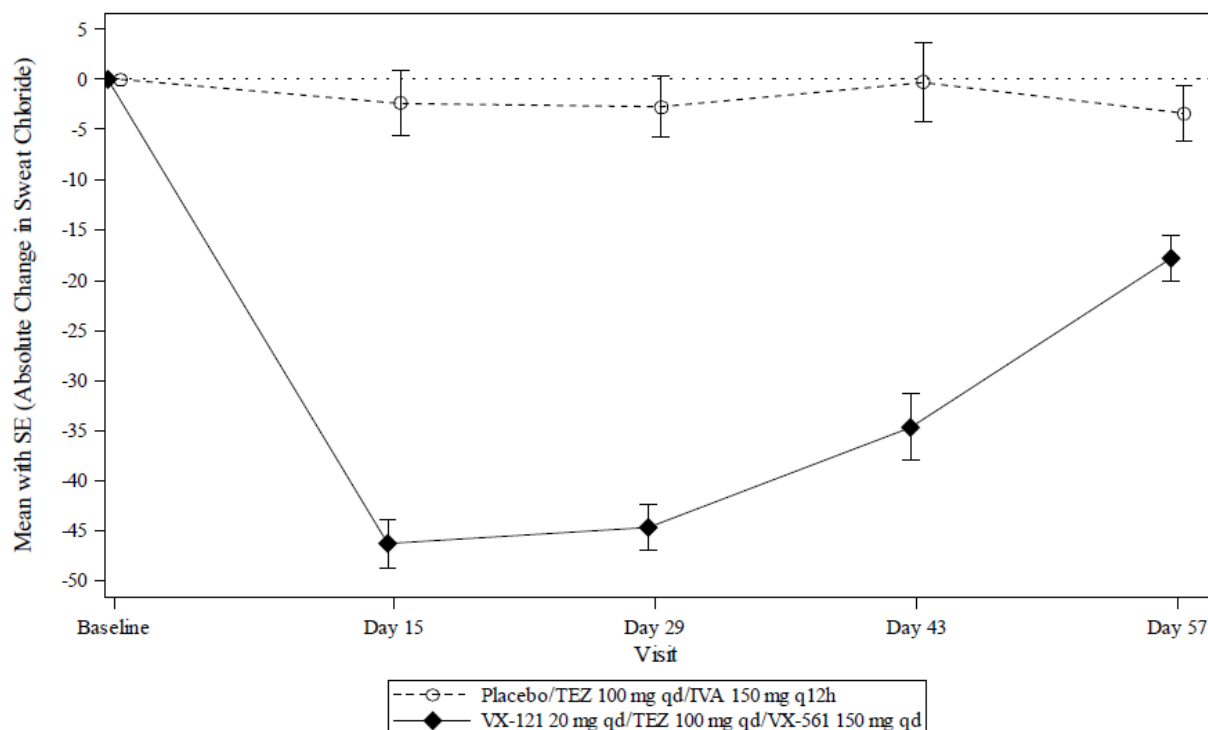
Source: Figure 11-3 CSR VX18-121-101

Abbreviations: D-IVA, deutivacaftor; F/MF, heterozygous for *F508del* and a minimal function variant; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures; ppFEV₁, percent predicted forced expiratory volume in 1 second; qd, once daily; SE, standard error; SwCl, sweat chloride; TC-5 mg, VNZ 5 mg qd/TEZ 100 mg qd/D-IVA 150 mg qd; TC-10 mg, VNZ 10 mg qd/TEZ 100 mg qd/D-IVA 150 mg qd; TC-20 mg, VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 150 mg qd; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Part 2

The analysis of absolute change from baseline in SwCl is presented in [Table 112](#) and [Figure 31](#). Treatment with VNZ/TEZ/D-IVA resulted in improvements in SwCl through Day 29. These improvements were observed relative to baseline established after a 4-week TEZ/IVA Run-in Period.

Figure 31. Absolute Change From Baseline in SwCl by Visit in the Treatment Period (Post Day 1 Through Day 29) and Washout Period (Post Day 29 Through Day 57), Full Analysis Set; Study 101 (Part 2; F/F Subjects)



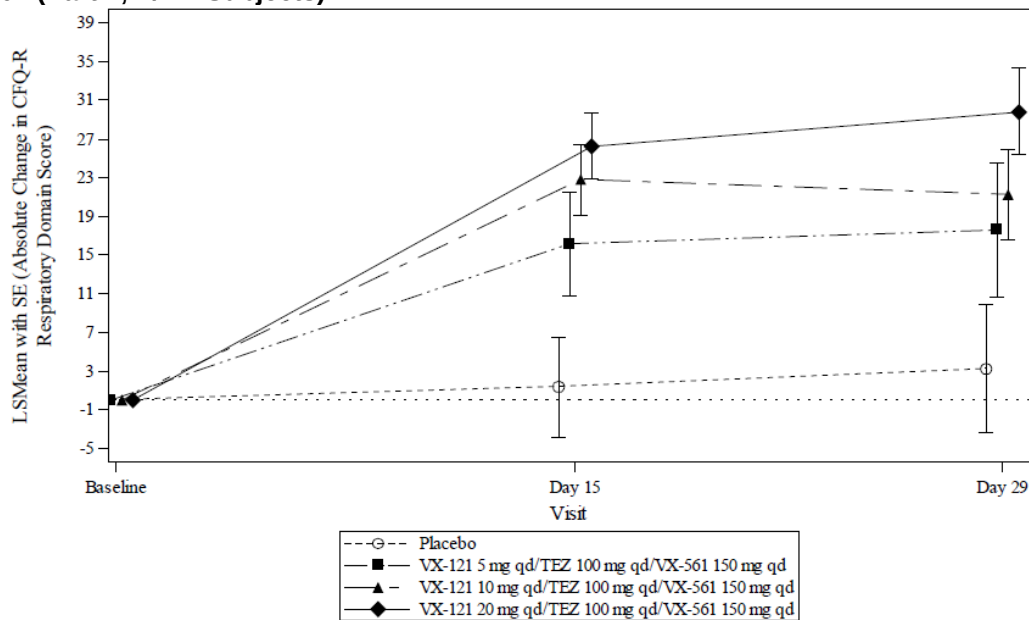
Source: Figure 11-4 CSR VX18-121-101

Abbreviations: F/F, homozygous for *F508del*; FAS, full analysis set; IVA, ivacaftor; LS, least squares; MMRM, mixed-effects model for repeated measures; ppFEV₁, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; qd, once daily; SwCl, sweat chloride; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Cystic Fibrosis Questionnaire – Revised Results

Part 1

The analysis of absolute change from baseline in CFQ-R RD is presented in [Table 112](#) and [Figure 32](#). Treatment with VNZ/TEZ/D-IVA resulted in improvements in CFQ-R RD score at Day 29 in each treatment group compared to baseline that exceeded the minimally clinically important difference (4 points)

Figure 32. Absolute Change From Baseline in CFQ-R RD Score by Visit, Full Analysis Set; Study 101 (Part 1; F/MF Subjects)

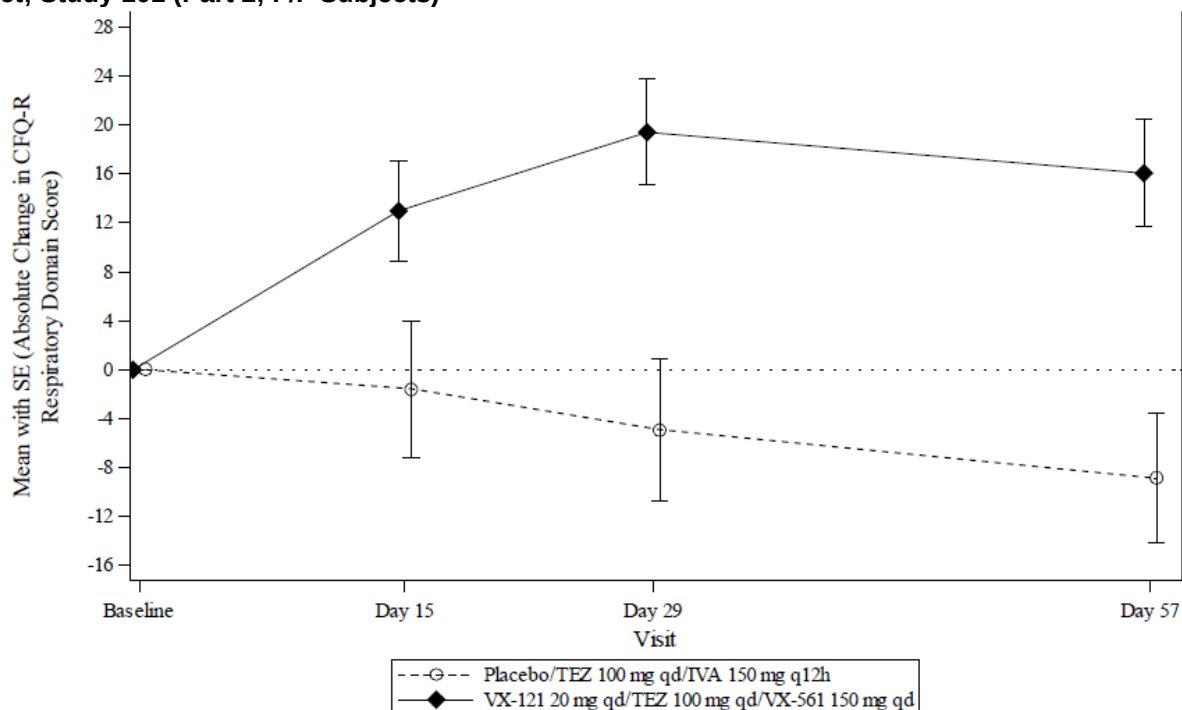
Source: Figure 11-5 CSR VX18-121-101

Abbreviations: CFQ-R, cystic fibrosis questionnaire-revised respiratory domain; F/MF, heterozygous for *F508del* and a minimal function variant; LS, least squares; qd, once daily; SE, standard error; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Part 2

The analysis of absolute change from baseline in CFQ-R RD score is presented in [Figure 33](#). Treatment with VNZ/TEZ/D-IVA resulted in improvements in CFQ-R RD score at Day 29 that exceeded the minimally clinically important difference. These improvements were observed relative to baseline established after a 4-week TEZ/IVA Run-in Period.

Figure 33. Absolute Change From Baseline in CFQ-R RD Score by Visit in the Treatment Period (Post Day 1 Through Day 29) and Washout Period (Post Day 29 Through Day 57), Full Analysis Set; Study 101 (Part 2; F/F Subjects)



Source: Figure 11-6 CSR VX18-121-101

Abbreviations: CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; F/F, homozygous for *F508del*; FAS, full analysis set; IVA, ivacaftor; q12h, every 12 hours; qd, once daily; SE, standard error; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Conclusions

In the context of TC (i.e., in combination with 100 mg TEZ and 150 mg IVA), 10 mg VNZ (in Form A) once daily dose demonstrated a higher ppFEV₁ response (primary efficacy endpoint) compared to 5 mg and 20 mg in CF subjects with F/MF genotype. Although a small numerical dose-response trend was observed for SwCl and CFQ-R RD score (secondary endpoints) from 5 mg to 20 mg, the dose selection of carrying 10 mg VNZ (Form A, which translate into 20 mg in Form D) into phase 3 trials is reasonable.

14.2.5.2. Study VX18-561-101 (Study 561-101)

Title

A Phase 2, Randomized, Double-blind Study to Evaluate the Efficacy and Safety of VX-561 [D-IVA] in Subjects Aged 18 Years and Older With Cystic Fibrosis

Study Period

April 17, 2019 to August 20, 2020

Objective

Primary Objective

- To evaluate the efficacy of D-IVA

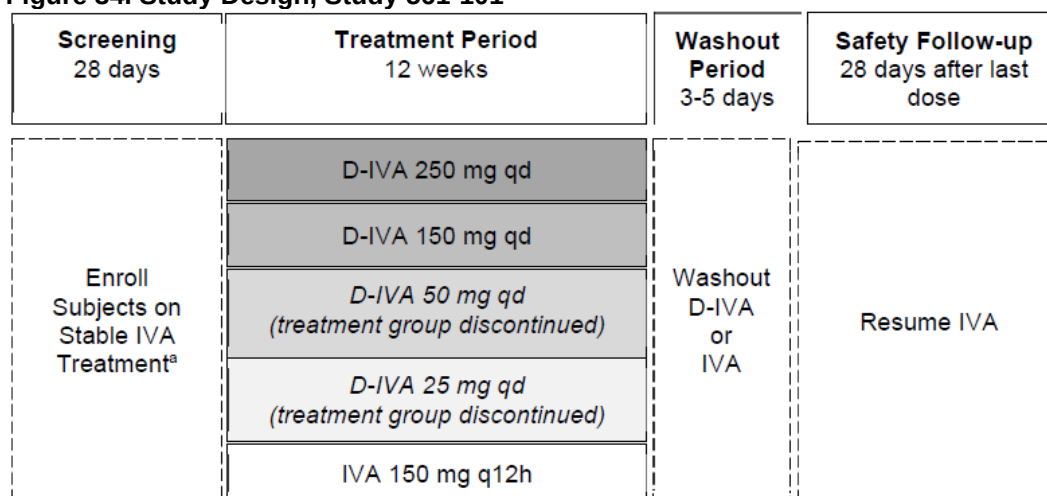
Secondary Objectives

- To evaluate the PD effect of D-IVA
- To evaluate the PK of D-IVA, IVA, and relevant metabolites
- To evaluate the safety and tolerability of D-IVA

Study Design

This was a phase 2, randomized (ratio of 1:2:2:2:1), double-blind, parallel-group, and active-controlled study of D-IVA monotherapy (Figure 34). The study evaluated four dose levels of D-IVA in CF subjects who have a gating (G) variant and were previously taking a stable dose of IVA. Randomization was stratified by ppFEV₁ value at screening (<70 versus ≥70).

Figure 34. Study Design, Study 561-101



Source: Figure 9-1 CSR VX18-561-101

Abbreviations: D-IVA, deutivacaftor; IVA, ivacaftor; q12h, every 12 hours; qd, once daily

Test Drug

Study drug was administered orally twice daily, with a fat-containing meal or snack, consistent with the recommendations for administration of KALYDECO.

D-IVA

Four dose levels of D-IVA (25, 50, 150, and 250 mg) were evaluated to provide a broad range of exposure for exposure-response analyses. The original protocol included 25 mg QD D-IVA and 50 mg QD D-IVA treatment groups; both treatment groups were discontinued at the Applicant's discretion. 44 subjects had been enrolled and randomized to the 5 treatment groups at that point.

A D-IVA dose regimen of 150 mg QD was predicted to provide exposure similar to IVA 150 mg q12h. The 250 mg QD dose of D-IVA was included to provide a range of exposures to enable a more robust exposure-response analysis.

IVA

The IVA dose regimen of 150 mg q12h is the approved regimen for treatment of CF in subjects aged 6 years and older who have one variant in the *CFTR* gene that is responsive to IVA based on clinical and/or in vitro assay data.

Samples

Blood samples for plasma PK analysis of D-IVA, IVA, and their relevant metabolites were collected in all subjects at predose and at 4 hours after dosing on Day 1 following morning dose, at predose on Weeks 2, 4, 8, and 12. In a subset of subjects (up to approximately 20 subjects), additional samples were collected at the Week 4 visit at 1, 2, 4, and 6 hours after morning dose.

Efficacy and Pharmacodynamic Endpoints

Primary Efficacy Endpoint

Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) from baseline at Week 12

Secondary Efficacy Endpoints

Absolute change from baseline in SwCl concentrations at Week 12

Results

Pharmacokinetics Results

The mean observed trough concentrations across visits of D-IVA, IVA and their respective metabolites are presented in [Table 113](#). Based on the observed C_{trough} values, steady state exposures of D-IVA and M1-D-IVA were achieved by Day 15. Based on a comparison of mean C_{trough} values, exposures of D-IVA at the 250 mg QD dose were similar to IVA 150 mg q12h, while exposures of M1-D-IVA were lower than the exposures of M1-IVA.

Table 113. Summary of Observed C_{trough} of Analytes in CF Subjects (PK Set)

Analyte	Dose ^a (mg)	C_{trough} (ng/mL)							
		Day 15		Week 4		Week 8		Week 12	
		N	Mean (CV%)	N	Mean (CV%)	N	Mean (CV%)	N	Mean (CV%)
D-IVA	25	6	28.8 (103)	4	26.1 (94.9)	3	48.0 (73.5)	0	ND
	50	9	122 (63.3)	7	123 (50.1)	4	223 (123)	1	269
	150	20	541 (53.2)	20	458 (59.6)	17	463 (49.3)	15	436 (46.0)
	250	24	1050 (71.5)	20	1100 (77.7)	20	1180 (82.8)	20	1280 (74.4)
M1-D-IVA	25	6	20.6 (77.5)	4	18.1 (97.3)	3	40.7 (90.1)	0	ND
	50	9	106 (59.2)	7	108 (54.4)	4	241 (136)	1	274
	150	20	481 (57.7)	20	378 (56.4)	17	382 (49.8)	15	386 (49.1)
	250	24	737 (53.7)	20	739 (55.1)	20	731 (52.5)	20	924 (91.1)
IVA	150	11	1010 (61.2)	9	952 (80.5)	9	814 (53.7)	9	956 (62.5)
M1-IVA	150	11	1850 (53.9)	9	1330 (58.4)	9	1710 (64.4)	10	1410 (74.0)

Source: Table 11-1 CSR VX18-561-101

^a IVA, M1-IVA and M6-IVA exposures are following q12h doses of IVAAbbreviations: CF, cystic fibrosis; C_{trough} , lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; IVA, ivacaftor; M, metabolite; N, number of subjects; ND, not determined; PK, pharmacokinetics; q12h, every 12 hours

Efficacy Results

The analysis of the primary (ppFEV₁) and the secondary (SwCl) efficacy endpoints is presented in [Table 114](#). The point estimate showed numerically greater reduction of SwCl from baseline at Week 12 for D-IVA 250 mg QD than D-IVA 150 mg QD. The absolute changes in ppFEV₁ and the absolute changes in SwCl at Week 12 for D-IVA 150 mg QD, D-IVA 250 mg QD, and IVA 150 mg q12h were similar to IVA baseline (95% CIs include 0).

The point estimate for the within-treatment SwCl change at Week 12 for D-IVA 250 mg QD was lower than at IVA baseline, while the point estimate for the within-treatment SwCl change at Week 12 for D-IVA 150 mg QD was higher than at IVA baseline.

Table 114. Efficacy and PD of D-IVA Treatment Relative to IVA Baseline

Treatment Group	Absolute Change in ppFEV ₁ in percentage points at Week 12	Absolute Change in SwCl in mmol/L at Week 12
	(LS mean [95% CI])	(LS mean [95% CI])
D-IVA 250 mg qd	2.7 (-1.0, 6.5)	-6.5 (-14.1, 1.2)
D-IVA 150 mg qd	3.1 (-0.8, 7.0)	3.3 (-4.6, 11.2)
IVA 150 mg q12h	-0.8 (-6.2, 4.7)	0.9 (-9.5, 11.3)

Source: Table 11-4 CSR VX18-561-101

Abbreviations: CI, confidence interval; D-IVA, deutivacaftor; IVA, ivacaftor; LS, least squares; PD, pharmacodynamic; ppFEV₁, percent predicted forced expiratory volume in 1 second; q12h, every 12 hours; qd, once daily; SwCl, sweat chloride

Conclusions

Exposures of D-IVA and M1-D-IVA in CF subjects with gating variants were generally similar to exposures seen in healthy subjects administered the same doses of D-IVA. Mean C_{trough} of D-IVA following 250 mg QD regimen was similar to mean C_{trough} of IVA following 150 mg q12h dose in CF subjects with gating variants. Exposures of IVA and its metabolites were consistent with historical exposures.

There was no meaningful difference regarding ppFEV₁ changes from baseline (primary efficacy endpoint) between 150 mg QD and 250 mg QD D-IVA dosing groups when compared to IVA 150 mg Q12h group. However, 250 mg D-IVA group demonstrated a numerically greater reduction of SwCl from baseline (secondary endpoint) than 150 mg D-IVA group. Therefore, the dose selection of carrying 250 mg D-IVA QD into phase 3 studies is reasonable.

14.2.6. Pediatric Pharmacokinetics and Safety Trial

14.2.6.1. Trial VX21-121-105 (Trial 105)

Title

A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of Vanzacaftor/Tezacaftor/Deutivacaftor Triple Combination Therapy in Cystic Fibrosis Subjects 1 Through 11 Years of Age

Trial Period

June 21, 2022 to November 27, 2023

Objective

Part A

Primary Objectives

- To evaluate the PK of VNZ, TEZ, D-IVA, and relevant metabolites when dosed in TC
- To evaluate the safety and tolerability of VNZ/TEZ/D-IVA

Part B

Primary Objective

- To evaluate the safety and tolerability of VNZ/TEZ/D-IVA through Week 24

Secondary Objectives

- To evaluate the efficacy of VNZ/TEZ/D-IVA through Week 24
- To evaluate the PK of VNZ, TEZ, D-IVA, and relevant metabolites

Trial Design

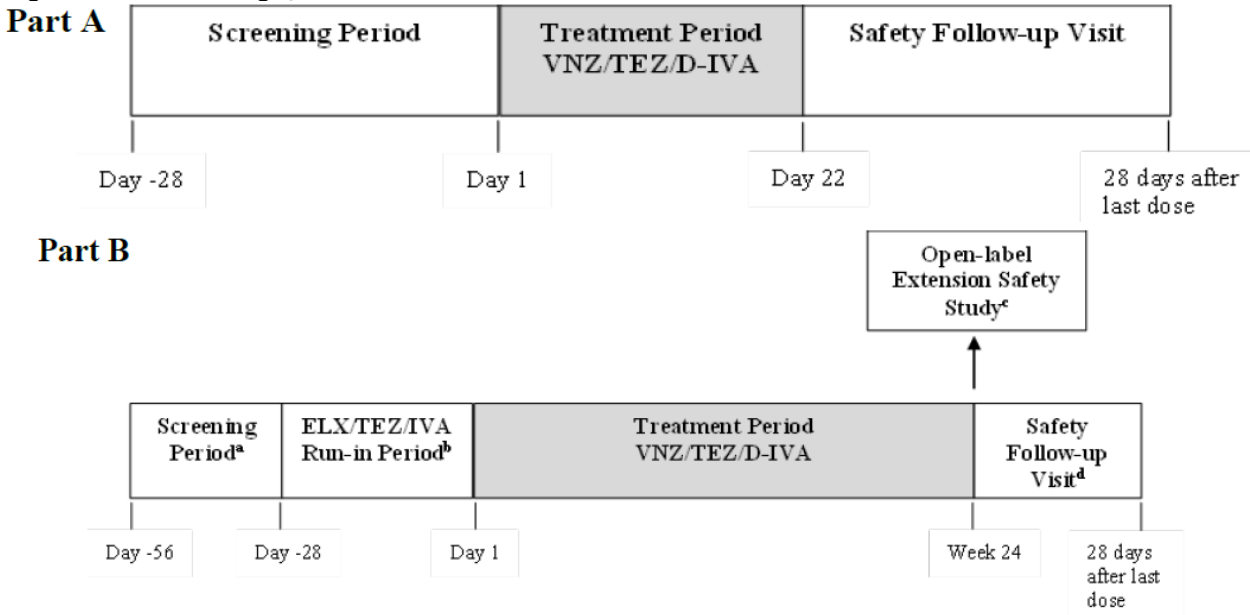
This is a 2-part (Parts A and B), multicohort, multicenter trial evaluating the PK, safety, tolerability, and efficacy of VNZ/TEZ/D-IVA TC therapy in CF subjects 1 through 11 years of age (inclusive) with at least one triple combination responsive (TCR) variant in the *CFTR* gene. This interim analysis report includes final data from subjects 6 through 11 years of age enrolled in Cohorts A1 and B1. Cohorts A2 and B2 will evaluate subjects 2 through 5 years of age (inclusive). Cohorts A3 and B3 will evaluate subjects 1 to less than 2 years of age.

[Figure 35](#) shows the trial design of Trial VX21-121-105. All subjects in Cohort A1 received the same dose (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg QD) without body weight adjustment for 22 days. Subjects who participated in Cohort A1 were permitted to participate in Cohort B1 (if they met eligibility criteria). A review of safety, tolerability, and available PK data was completed by an internal team after Cohort A1 completed treatment to determine the doses and weight cutoffs for Cohort B1. The dose studied in Cohort B1 was adjusted by body weight (i.e., 30 kg was used as a cutoff, see [Table 115](#)).

In Part B, subjects who were receiving stable ELX/TEZ/IVA treatment had the Run-in Period waived and entered the Treatment Period within 28 days following the Screening Visit. Subjects who were not on stable ELX/TEZ/IVA treatment entered the 4-week Run-in Period and received ELX/TEZ/IVA.

Subjects who were eligible were offered the opportunity to enroll in an optional open-label extension safety trial evaluating VNZ/TEZ/D-IVA.

Figure 35. Trial Design, Trial 105



Source: Figures 9-1 and 9-2 CSR VX21-121-105

^a subjects who were receiving stable ELX/TEZ/IVA treatment had the Run-in Period waived and entered the Treatment Period within 28 days following the Screening Visit.

^b Subjects who were not on stable ELX/TEZ/IVA treatment entered the 4-week Run-in Period and received ELX/TEZ/IVA.

^c Subjects who were eligible were offered the opportunity to enroll in an optional open-label extension safety trial evaluating VNZ/TEZ/D-IVA

^d The Safety Follow-up Visit was scheduled to occur 4 weeks (±7 days) after the last dose of trial drug. This visit was not required for subjects who enrolled in an optional open-label extension safety study within 28 days of the last dose.

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

Test Drug

Trial drug details are presented in [Table 115](#). Trial drug was administered with a fat-containing snack or meal, such as a standard “CF” meal or snack.

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Table 115. Trial Drug, Trial 105

Applicable Subjects Study Drug Name	Dosing Form, Route	Tablet Strength	Batch Number
Cohort A1, all subjects VNZ/TEZ/D-IVA	FDC tablet, oral	VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg	3202291R
Cohort B1 Run-in Period, subjects <30 kg at Day -28 ELX/TEZ/IVA	FDC tablet, oral	ELX 50 mg/TEZ 25 mg/IVA 37.5 mg	237.10346.01
IVA	Tablet, oral	75 mg	237.10262.00
Cohort B1 Run-in Period, subjects ≥30 kg at Day -28 ELX/TEZ/IVA	FDC tablet, oral	ELX 100 mg/TEZ 50 mg/IVA 75 mg	2021020
IVA	Tablet, oral	150 mg	3196578
Cohort B1 Treatment Period, subjects <40 kg at Day 1 VNZ/TEZ/D-IVA	FDC tablet, oral	VNZ 4 mg/TEZ 20 mg/D-IVA 50 mg	3209516R, 3213216R, 3213814R
Cohort B1 Treatment Period, subjects ≥40 kg at Day 1 VNZ/TEZ/D-IVA	FDC tablet, oral	VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg	3210851R

Source: Table 9-3 CSR VX21-121-105

Abbreviation: D-IVA, deutivacaftor; ELX, elexacaftor; FDC, fixed-dose combination; IVA, ivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

Samples

Blood samples for plasma PK analysis of VNZ, TEZ, D-IVA and their relevant metabolites were collected as below.

Part A Cohort A1

- Days 1, 8, and 15: predose and 2 h postdose (Day 1 only)
- Day 22: predose, 2.5, 3.5, 6.5, 8 h postdose

Part B Cohort B1

- All subjects: at predose (Days 1, 15, Weeks 4, 12, 16) and 2 h postdose (Day 1 only), at predose, 2.5 and 3.5 h postdose at Week 8.
- For a minimum of 12 subjects who weigh ≥17 kg: at Screening, additional 6.5 and 8 h postdose samples will be collected.

Results

Cohort A1

In Cohort A1, 17 subjects received at least one dose of trial drug, all of whom completed trial drug treatment and the trial. All subjects were White. The mean (SD) age was 9.5 (1.3) years at

Day 1. Overall, nine (52.9%) subjects had the F/F genotype, three (17.6%) subjects had an F/MF genotype, and the rest of the five (29.4%) subjects had another eligible genotype.

The mean observed trough concentrations of VNZ, TEZ, M1-TEZ, D-IVA, and M1-D-IVA, in CF subjects 6 through 11 years of age on Day 22 in Cohort A1 ([Table 116](#)) were at the lower end of the range for each of the analytes (except for M1-TEZ which is similar) observed in CF subjects ≥ 12 years of age from pivotal phase 3 Trials 102 and 103 ([Table 117](#)).

Table 116. Mean (%CV; SD) C_{trough} Observed in CF Subjects 6 Through 11 Years of Age on Day 22, Trial 105 (Cohort A1, N=17)

Parameter	Analytes				
	VNZ	TEZ	M1-TEZ	D-IVA	M1-D-IVA
C_{trough} ($\mu\text{g/mL}$)	0.428 (44.1; 0.189)	1.55 (65.2; 1.01)	5.14 (36.7; 1.89)	0.631 (69.6; 0.439)	0.700 (63.1; 0.442)

Source: Table 11-1 CSR VX21-121-105

Notes: Trial drug dose was VNZ 10 mg qd/TEZ 50 mg qd/D-IVA 125 mg qd.

Abbreviations: CF, cystic fibrosis; C_{trough} , lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; M, metabolite; N, number of subjects; qd, once daily; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

Table 117. Mean (%CV; SD) C_{trough} ($\mu\text{g/mL}$) of VNZ/TEZ/D-IVA Observed in CF Subjects ≥ 12 Years Old

Dosing Group	Dose	VNZ	TEZ	M1-TEZ	D-IVA	M1-D-IVA
12-17 years (N=58)	VNZ 20 mg/ TEZ 100 mg/ D-IVA 250 mg qd	0.58 (0.34)	2.32 (1.61)	5.5 (2.17)	0.87 (0.74)	0.81 (0.62)
≥ 18 years (N=394)		0.77 (0.44)	2.26 (1.29)	4.86 (1.64)	1.12 (0.86)	0.85 (0.63)

Source: Week 8 mean C_{trough} results observed in adults and adolescents from Trials VX20-121-102 and VX20-121-103.

Abbreviations: CF, cystic fibrosis; C_{trough} , lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; M, metabolite; N, number of subjects; qd, once daily; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

Cohort B1

In Cohort B1, 78 subjects enrolled and were on stable ELX/TEZ/IVA treatment for at least 4 weeks prior to receiving VNZ/TEZ/D-IVA on Day 1. Overall, 78 subjects received at least one dose of trial drug in the Treatment Period, 77 (98.7%) subjects completed trial drug treatment, and 78 (100%) subjects completed the trial. Most of subjects (91.0%) were White. A total of 44 (56.4%) subjects were male, and the mean (SD) age was 9.1 (1.7) years at Day 1. Overall, 37 (47.4%) subjects had the F/F genotype, 24 (30.8%) subjects had the F/MF genotype, and the rest of the 17 (21.8%) subjects had another eligible genotype.

Trough concentrations for VNZ, TEZ, D-IVA, and relevant metabolites were consistent across visits. The mean observed trough concentrations of VNZ, TEZ, M1-TEZ, D-IVA, M1-D-IVA, and M6-D-IVA in CF subjects 6 through 11 years of age in Cohort B1 ([Table 118](#)) were similar to the values observed in CF subjects ≥ 12 years of age ([Table 117](#)).

Table 118. Mean (%CV; SD) C_{trough} Observed in CF Subjects 6 Through 11 Years of Age, Trial 105 (Cohort B1)

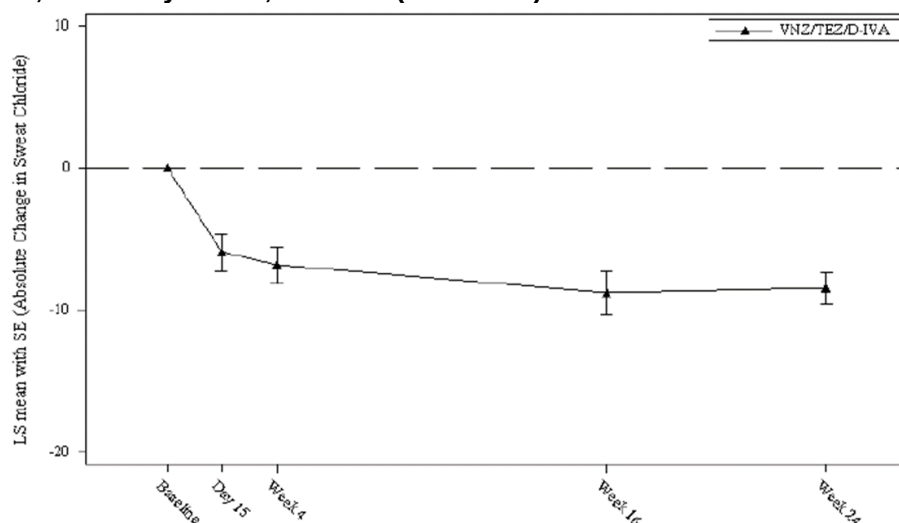
Group and Analyte	C _{trough} (µg/mL) Mean (%CV; SD)				
	Day 15	Week 4	Week 8	Week 12	Week 16
Subjects <40 kg					
VNZ	N = 65 0.476 (49.1; 0.234)	N = 70 0.493 (51.6; 0.255)	N = 67 0.464 (46.4; 0.215)	N = 64 0.507 (60.2; 0.305)	N = 65 0.500 (52.8; 0.264)
TEZ	N = 65 1.47 (66.3; 0.971)	N = 70 1.40 (58.7; 0.821)	N = 67 1.50 (54.6; 0.821)	N = 64 1.40 (55.8; 0.778)	N = 65 1.42 (58.7; 0.835)
M1-TEZ	N=65 6.18 (31.6; 1.95)	N= 70 5.81 (34.9; 2.03)	N = 67 5.91 (35.5; 2.09)	N = 64 5.66 (31.3; 1.77)	N = 65 5.93 (36.6; 2.17)
D-IVA	N = 65 0.565 (77.9; 0.440)	N = 69 0.612 (89.3; 0.547)	N = 67 0.646 (72.6; 0.469)	N = 64 0.590 (86.2; 0.508)	N = 65 0.566 (82.5; 0.467)
M1-D-IVA	N = 65 0.660 (65.2; 0.430)	N = 69 0.685 (68.3; 0.468)	N = 67 0.721 (62.5; 0.451)	N = 64 0.687 (74.4; 0.511)	N = 65 0.666 (69.3; 0.462)
Subject ≥40 kg					
VNZ	N = 8 0.797 (58.0; 0.462)	N = 8 0.591 (53.9; 0.319)	N = 7 0.677 (47.8; 0.323)	N = 7 0.808 (71.3; 0.576)	N = 7 0.807 (59.6; 0.481)
TEZ	N = 8 2.26 (55.5; 1.26)	N = 8 1.82 (60.2; 1.10)	N = 7 2.86 (55.5; 1.59)	N = 7 2.38 (65.5; 1.56)	N = 7 2.69 (50.2; 1.35)
M1-TEZ	N = 8 6.47 (34.4; 2.23)	N = 8 5.12 (49.8; 2.55)	N = 7 6.32 (43.2; 2.73)	N = 7 4.91 (50.7; 2.49)	N = 7 6.23 (29.0; 1.81)
D-IVA	N = 8 1.13 (58.3; 0.659)	N = 8 0.888 (66.0; 0.586)	N = 7 1.59 (72.1; 1.15)	N = 7 1.32 (66.9; 0.881)	N = 7 1.44 (71.3; 1.03)
M1-D-IVA	N = 8 1.12 (44.7; 0.499)	N = 8 0.853 (64.9; 0.554)	N = 7 1.17 (30.7; 0.358)	N = 7 1.14 (55.9; 0.637)	N = 7 1.22 (49.3; 0.600)

Source: Table 11-2 CSR VX21-121-105

Notes: Trial drug dose was VNZ 12 mg qd/TEZ 60 mg qd/D-IVA 150 mg qd for subjects <40 kg and was VNZ 20 mg qd/TEZ 100 mg qd/D-IVA 250 mg qd for subjects ≥40 kg.

Abbreviations: CF, cystic fibrosis; C_{trough}, lowest plasma concentration at steady-state; CV, coefficient of variation; D-IVA, deutivacaftor; M, metabolite; N, number of subjects; qd, once daily; SD, standard deviation; TEZ, tezacaftor; VNZ, vanzacaftor

Treatment with VNZ/TEZ/D-IVA resulted in reductions in SwCl, with a within-group least squares mean absolute change from baseline (Day 1 predose, which was after 28 days ELX/TEZ/IVA run-in period) through Week 24 (estimated by averaging Weeks 16 and 24) of -8.6mmol/L (95% CI: -11.0, -6.3). The time profile of SwCl change from baseline was depicted in [Figure 36](#).

Figure 36. MMRM Analysis of Absolute Change From Baseline in SwCl at Each Visit up to Week 24, Full Analysis Set; Trial 105 (Cohort B1)

Source: Figure 11-1 on page 53 from VX21-121-105-clinical study report.pdf.

Abbreviations: D-IVA, deutivacaftor; FAS, full analysis set; LS, least squares; MMRM, mixed-effects model for repeated measures; SE, standard error; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

Conclusions

Following the proposed pediatric dose in Cohort B1 in children 6 through 11 years of age weighing ≥ 40 kg (VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg QD), the mean observed trough concentrations of VNZ, TEZ, M1-TEZ, D-IVA, and M1-D-IVA were comparable to the values observed in CF subjects ≥ 12 years of age from pivotal phase 3 Trials 102 and 103. Following the recommended pediatric dose in Cohort B1 in CF pediatric subjects 6 through 11 years of age weighing < 40 kg (VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg QD), the mean observed trough concentrations of VNZ, TEZ, M1-TEZ, D-IVA, and M1-D-IVA were at the lower end of the range for each of the analytes (except for M1-TEZ which is similar) observed in CF subjects ≥ 12 years of age from pivotal phase 3 Trials 102 and 103.

There was a small numerical reduction of SwCl (~ 8 nmol/L) from baseline (defined as at the end of ELX/TEZ/IVA run-in treatment period) throughout 24-week treatment following the proposed pediatric doses in children 6 through 11 years of age.

14.3. Bioanalytical Method Validation and Performance

Validation reports for D-IVA (L114), TEZ (L179 and O162), ELX (O068) were previously reviewed and found adequate in the original application for NDA 210491 SYMDEKO and NDA 212273 TRIKAFTA. The summary of bioanalytical method used for the clinical pharmacology trials is listed in [Table 119](#). Method validation for VNZ in plasma (P145, O403), unbound VNZ in plasma (S440), VNZ in urine (R240), VNZ and TEZ in plasma (T008), D-IVA in plasma (O085, O248, N104), and unbound D-IVA in plasma (S438) are adequate.

Table 119. Summary of Method Validation Report for VNZ, TEZ, D-IVA, IVA, ELX and Their Relevant Metabolites and Bioanalysis Report of Each Clinical Trials

Study Number	Validation Report	In-Study Analysis Report
VX16-770-018	L114 (IVA), N104 (D-IVA)	N241 (D-IVA), N242 (IVA)
VX17-121-001	O403 (VNZ), P145 (VNZ), L179 (TEZ), L114 (IVA)	P179 (VNZ), P016 (TEZ), P017 (IVA)
VX18-561-101	O085 (D-IVA), L114 (IVA)	Q214 (D-IVA), Q215 (IVA)
VX18-121-101	P145 (VNZ), L179 (TEZ), O085 (D-IVA)	Q043 (VNZ), Q031 (TEZ), Q030 (D-IVA)
VX18-445-006	O085 (D-IVA)	O224 (D-IVA)
VX18-561-001	O248 (D-IVA)	P046 (D-IVA)
VX19-121-003	P145 (VNZ), L179 (TEZ), O085 (D-IVA)	R073 (VNZ), R034 (TEZ), R035 (D-IVA)
VX20-121-004	P145 (VNZ), R240 (VNZ urine)	R171 (VNZ), R172 (VNZ urine)
VX21-121-005	P145 (VNZ), L179 (TEZ), O085 (D-IVA)	S110 (VNZ), S036 (TEZ), S035 (D-IVA)
VX21-121-006	P145 (VNZ), L179 (TEZ), O085 (D-IVA)	S102 (VNZ), S038 (TEZ), S037 (D-IVA)
VX21-121-007	P145 (VNZ)	S304 (VNZ)
VX21-121-008	T008 (VNZ, TEZ), O085 (D-IVA), S440 (free VNZ), S438 (free D-IVA)	T227 (VNZ, TEZ), T203 (D-IVA), T204 (free IVA), T205 (free VNZ)
VX20-121-102	T008 (VNZ, TEZ), O162 (TEZ, IVA), O085 (D-IVA), O068 (ELX), L114 (IVA)	S039 (IVA), S040 (D-IVA), T481 (ELX), U038 (VNZ, TEZ)
VX20-121-103	T008 (VNZ, TEZ), O162 (TEZ, IVA), O085 (D-IVA), O068 (ELX), L114 (IVA)	S041 (IVA), S042 (D-IVA), T482 (ELX), U039 (VNZ, TEZ)
VX21-121-105	T008 (VNZ, TEZ), O085 (D-IVA)	T486 (VNZ, TEZ), T487 (D-IVA)
VX22-121-009	T008 (VNZ, TEZ), O085 (D-IVA)	T030 (VNZ, TEZ), T035 (D-IVA)
VX22-121-013	P145 (VNZ)	T407 (VNZ), T375 (moxifloxacin)

Source: Reviewer's analysis

Abbreviations: D-IVA, deutivacaftor; ELX, elxacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

Analytical Method for VNZ in Plasma: Report # P145 (Low Range Method)

An analytical method was developed and validated for the determination of VNZ in dipotassium-ethylenediaminetetraacetic acid (K_2 -EDTA) human plasma samples via liquid chromatography–mass spectrometry (LC-MS/MS) Detection and was used in multiple phase 1 studies and phase 2 dose-ranging study (Study 101). The method was precise, accurate, sensitive, and selective with a calibration range of 5.00 to 5000 ng/mL for VNZ. The analytes were stable under laboratory analysis conditions. The long-term stability was 428 days (at -20°C and -70°C) for VNZ.

Analytical Method for VNZ in Plasma: Report # O403

An analytical method was developed and validated for the determination of VNZ in K_2 -EDTA human plasma samples via LC-MS/MS Detection and was used in Study 001. The method was precise, accurate, sensitive, and selective with a calibration range of 50.0 to 50000 ng/mL for VNZ. The analytes were stable under laboratory analysis conditions. The long-term stability was 204 days (-20°C and -70°C) for VNZ.

Analytical Method for VNZ, TEZ, and M1-TEZ in Plasma: Report # T008

An analytical method was developed and validated for the determination of VNZ, TEZ, and M1-TEZ in K_2 -EDTA human plasma samples via LC-MS/MS Detection and was used in many phase

1 studies, pivotal phase 3 trials (Trials 102 and 103), and a pediatric PK and safety trial (Trial 105). The method was precise, accurate, sensitive, and selective with a calibration range of 5.00 to 5000 ng/mL for VNZ and 10.0 to 10000 ng/mL for TEZ and M1-TEZ. The analytes were stable under laboratory analysis conditions. The long-term stability was 275 days (-at -70°C) for VNZ and TEZ/M1-TEZ.

Analytical Method for VNZ in Urine: Report # R240

An analytical method was developed and validated for the determination of VNZ in human stabilized urine via LC-MS/MS Detection and was used in mass-balance Study 004. The method was precise, accurate, sensitive, and selective with a calibration range of 1.0 to 1000 ng/mL for VNZ. The analytes were stable under laboratory analysis conditions. The long-term stability was 96 days (at -20°C and -70°C) for VNZ.

Analytical Method for Unbound VNZ in Plasma: Report # S440

An analytical method was developed and validated for the determination of unbound VNZ in human plasma/phosphate-buffered saline (PBS) (1:1, v/v) samples via LC-MS/MS Detection and was used in dedicated hepatic impairment Study 008. The method was precise, accurate, sensitive, and selective with a calibration range of 0.1 to 100 ng/mL for VNZ. The analytes were stable under laboratory analysis conditions. The long-term stability in human plasma/PBS (1:1, v/v) was 21 days (-80°C) for VNZ.

Analytical Method for D-IVA and M1-D-IVA in Plasma: Report #O085

An analytical method was developed and validated for the determination of D-IVA and M1-D-IVA in K₂-EDTA human plasma samples via LC-MS/MS Detection and was used in all clinical trials that analyzed D-IVA concentrations except one phase 1 study (Study 561-001). The method was precise, accurate, sensitive, and selective with a calibration range of 2.00 to 2000 ng/mL for D-IVA and M1-D-IVA. The analytes were stable under laboratory analysis conditions. The long-term stability was 342 days (at -80°C) for D-IVA and M1-D-IVA.

Analytical Method for D-IVA and M1-D-IVA in Plasma: Report #O248

An analytical method was developed and validated for the determination of D-IVA and M1-D-IVA in K₂-EDTA human plasma samples via LC-MS/MS Detection and was used in a phase 1 study (Study 561-001). The method was precise, accurate, sensitive, and selective with a calibration range of 2.00 to 2000 ng/mL for D-IVA and M1-D-IVA. The analytes were stable under laboratory analysis conditions. The long-term stability was 33 days (at -20°C and -80°C) for D-IVA and M1-D-IVA.

Analytical Method for Unbound D-IVA and Unbound M1-D-IVA in Plasma: Report # S438

An analytical method was developed and validated for the determination of unbound D-IVA and unbound M1-D-IVA in human plasma/PBS (1:1, v/v) samples via LC-MS/MS Detection and was used in dedicated hepatic impairment Study 008. The method was precise, accurate, sensitive, and selective with a calibration range of 5.00 to 5000 pg/mL for D-IVA and M1-D-

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ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

IVA. The analytes were stable under laboratory analysis conditions. The long-term stability in human plasma/PBS (1:1, v/v) was 24 days (at -80°C) for D-IVA and M1-D-IVA.

Analytical Method for D-IVA and M1-D-IVA in Plasma: Report #N104

An analytical method was developed and validated for the determination of D-IVA and M1-D-IVA in K₂-EDTA human plasma samples via LC-MS/MS Detection and was used in a phase 1 study (Study VX16-770-018). The method was precise, accurate, sensitive, and selective with a calibration range of 2.00 to 2000 ng/mL for D-IVA and M1-D-IVA. The analytes were stable under laboratory analysis conditions. The long-term stability was 255 days (at -80°C) for D-IVA and M1-D-IVA.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Population Pharmacokinetic and Exposure Response Assessment

14.5.1.1. VNZ Population PK Analysis (Report T270)

Executive Summary

The FDA's Assessment

In general, the Applicant's population PK analyses are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the clinical pharmacology reviewer, with no significant discordance identified.

Population Pharmacokinetic Assessment Summary

Table 120. Data Structure of VNZ Population PK Analysis, Report T270

General Information	Details
Objectives of PPK analysis	• Characterize the PK disposition of VNZ in subjects 6 years and older using population methodology. • Quantify sources of variability. • Evaluate if a 40 kg weight cutoff for all studied ages resulted in similar exposures to adults. – Simulate VNZ exposure for a VNZ/TEZ/D-IVA TC dosing regimen with a 40 kg weight cutoff in children 6 through 11 years with CF. – Simulate VNZ exposure for a VNZ/TEZ/D-IVA TC dosing regimen with a 40 kg weight cutoff in adolescents 12 through 17 years with CF below the studied 6 through 11 years weight cutoff of 40 kg. • Summarize the predicted VNZ area under the concentration-time curve at steady state from 0 to 24 hours ($AUC_{0-24, ss}$). • Simulate exposures of VNZ for different dosing regimens to inform dosing and/or weight bounds for weight cutoffs other than 40 kg for children 6 through 11 years with CF in Part B1 of Trial VX21-121-105. • Simulate exposures of VNZ for different dosing regimens to inform dosing for adults ≥ 18y with CF with moderate hepatic impairment (MHI). • Simulate exposures of VNZ for different dosing regimens to inform dosing for children 6 through 11 years with CF coadministered a strong or moderate cytochrome P4503A4 (CYP3A4) inhibitor.
Study included	VX17-121-001, VX18-121-101, VX20-121-102, VX20-121-103, VX21-121-105
VNZ dose(s) included	5 mg, 10 mg, 12 mg, 20 mg, 40 mg, 60 mg QD (Table 1, Report T270)
Population included	Healthy, CF (F/MF, F/F, F/G, F/RF, TCR, and F/other genotypes)
<i>Population characteristics (Tables 2 and 3, Report T270)</i>	
General	• Age: 28.9 yr (range: 6.17 – 71.2, 0.28% subj ≥ 65 yr) • Weight: 64.0 kg (range: 19.3 – 130) – N=433 (61.2%) male – N=664 (93.8%) Caucasian or white – N=44 (6.2%) non- Caucasian or non-white
Organ Impairment	• Hepatic (Child-Pugh, NCI, etc): not reported Renal (CrCL, etc.): – N=580 (81.9%) normal (≥ 90 mL/min/1.73 m²) – N=126 (17.8%) mild impairment (60 to <90 mL/min/1.73 m²) – N=2 (0.3%) moderate impairment (30 to <60 mL/min/1.73 m²)
Pediatrics (Part B1)	• Age 9.30 (6.17 – 12.0, 11.0% of subjects ≤ 12 yr) • Weight 28.9 kg (19.3 – 54.0)
No. of patients, PK samples, and BLQ	708 subjects, 6850 PK samples, 304 (4.2%) post-first dose BLQ PK samples (Table S1, Report T270)

General Information	Details
<i>Sampling schedule</i>	
Rich sampling	• Study VX17-121-001: – Part A: Day 1: predose, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dosing. – Part B: Days 1 and 5: predose, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours after dosing. Days 7, 8, and 9: predose. Day 10: predose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours after dosing. – Part C: Days 1 and 7: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. Days 2, 3, 4, 5, 8, 10, and 12: predose. Day 14: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dosing. – Part D: Day 1: predose, 1, 2, 4, and 6 hours after dosing. Days 8 and 29: predose. Day 15: predose, 1, 2, 4, 6, and 8 hours after dosing. • Study VX18-121-101: – Day 1: predose, 1, 2, 4, 6, 8, and 24 hours after dosing. – Days 8, 15, and 29: predose. – Day 47: predose.
In ITT population	• Trial VX20-121-102: – Day 1: Predose and 2 hours post dose. – Weeks 4, 16, and 24: predose. – Week 8: Predose and 4 hours postdose for all subjects <18 years of age. Predose, 4, 5, 6, and 7 hours postdose for up to approximately 40 subjects ≥18 years of age. Predose and 2 hours postdose for all other subjects ≥18 years of age. • Trial VX20-121-103: – Day 1: Predose and 2 hours post dose. – Day 15: Predose. – Weeks 4, 8, 16 and 24: Predose. • Trial VX21-121-105: – Part A1: Day 1: predose and 2 hours postdose. Days 8 and 15: predose. Day 22: predose, 2.5, 3.5, 6.5, 8 h postdose. – Part B1: Day 1: predose and 2 hours postdose. Day 15 and Week 4: predose. Week 8: predose, 2.5 and 3.5 hours postdose for all subjects; for a minimum of 12 subjects who weigh ≥17 kg at screening additional 6.5 and 8 hours postdose samples were collected. Weeks 12 and 16: predose.
<i>Covariates evaluated</i>	
Static	Baseline age, baseline weight, sex, race, genotype, ALT, renal function (eGFR), formulation, disease status (healthy vs. CF patient), monotherapy vs. TC (Section 4.2, Report T270)
Time-varying	NA

Source: Reviewer's summary

Abbreviations: AUC_{0-24,ss}, area under the concentration-time curve from time 0 to 24 hours at steady-state; ALT, alanine transferase; BLQ, below the limit of quantification; CF, cystic fibrosis; CrCL, creatinine clearance; CYP, cytochrome P450; D-IVA, deutivacaftor; F, *F508del* variant; G, gating CFTR variant; eGFR, estimated glomerular filtration rate; h, hour; MF, minimal function CFTR variant; MHI, moderate hepatic impairment; N, total number of subjects; NA, not applicable; NCI, National Cancer Institute; No., number; PK, pharmacokinetic; PPK, population-pharmacokinetic; QD, once daily; RF, residual function CFTR variant; subj, subject; TC, triple combination; TCR, triple combination responsive CFTR variant; TEZ, tezacaftor; vs., versus; VNZ, vanzacaftor; y, year; yr, year

Table 121. Model Evaluation of VNZ Population PK Analysis

Final Model	Summary	Acceptability (FDA's Comments)
Software and Version	NONMEM®, Version 7.5.1	Acceptable
Estimation Algorithm	Monte Carlo importance sampling (IMP)	Acceptable
Model Structure	A linear, 1-compartment popPK model with 6 transit compartments and first-order absorption	Acceptable
Model Parameter Estimates	Fixed effect parameter estimates: Table 5, Report T270 Random effect parameter estimates: Table 6, Report T270	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Except for the additive residual variance, all RSE's (fixed and random effects) were <30%; shrinkage for IIV on CL and V was <30%.	Acceptable
BLQ for Parameter Accuracy	BLQ observations (4.2%) were excluded. No impact of BLQ on PK objectives given the low percentage of BLQ observations	Acceptable
GOF, VPC	Section 6.2.4, Report T270: - Population and individual predictions of VNZ concentration appeared evenly distributed around the identity line (Figures S44 to S50). Examination of the NPDEs, CWRES, or IIV random effects versus covariates generally showed no strong obvious trends in covariate effects remained (Figures S51 to S77) Section 6.3, Report T270: - Prediction-corrected (pc) VPC's showed that simulated VNZ concentrations were similar to observed concentrations at the 5th, 50th, and 95th percentiles across most of the concentration-time profiles, both overall (Figure 6) or when stratified by clinically important patient factors, such as age, weight, and genotype (Figures 7 to 9).	Acceptable
Significant Covariates and Clinical Relevance	Weight was the only covariate that had a clinically significant impact on VNZ disposition in CF patients.	Acceptable
Analysis Based on Simulation (optional)	- Simulations based on the final population PK model for VNZ supported the justification of candidate weight-based dosing regimens of VNZ/TEZ/D-IVA TC in CF patients ≥6 years of age with a 40 kg weight cutoff (Tables 8 and S15; and Figures 10, 11, S100, S111, Report T270). - Additional weight cutoffs were also evaluated: 35 kg: Tables S9, S13; and Figures S93, S113, Report T270. 30 kg: Table S14; and Figures S96, S115, Report T270. - Simulations based on the final population PK model for VNZ in patients with MHI with	Acceptable

Final Model	Summary	Acceptability (FDA's Comments)
	no VNZ dose adjustment showed exposures in the same range as subjects without MHI (Figure S117, Report T270). This result supports that, based on PK, no VNZ dose adjustment was needed for patients with CF with MHI. Simulations based on the final population PK model for VNZ supported the justification of VNZ/TEZ/D-IVA TC dose adjustment regimens for children 6 through 11 years with CF in the presence of coadministered CYP3A4 inhibitors (Figures S119, S122, S125 and S200, Report T270).	

Source: Clinical pharmacology reviewer

Abbreviations: BLQ, below the limit of quantification; CF, cystic fibrosis; CL, clearance; CYP, cytochrome P450; D-IVA, deutivacaftor; GOF, goodness-of-fit; MHI, moderate hepatic impairment; PK, pharmacokinetic; RSE, relative standard error; TC, triple combination; TEZ, tezacaftor; V, volume of distribution; VNZ, vanzacaftor; VPC, visual predictive check; y, year

Table 122. Labeling Statements Supported by VNZ Population PK Analysis

Labeling Language	Description	Acceptability (FDA's Comments)
12.3 PK	(b) (4)	Acceptable

Source: Clinical pharmacology reviewer

Abbreviations: CF, cystic fibrosis; eGFR, estimated glomerular filtration rate; N, number of subjects; PK, pharmacokinetic

Report T270/Tables

Table 123. Summary of Continuous Covariates for Subjects Receiving Vanzacaftor; Stratified by Study

Variable	n	Mean	Median	SD	Min / Max
Study: 001					
Age (years)	88	32.0	28.0	11.6	18.0 / 57.0
Body Weight (kg)	88	78.6	77.8	12.3	51.0 / 108
Baseline eGFR (mL/min/1.73m ²)	88	110	108	21.4	68.0 / 200
ALT (U/L)	88	27.2	24.0	10.9	11.0 / 56.0
Study: 101					
Age (years)	66	32.2	31.0	10.2	18.0 / 64.0
Body Weight (kg)	66	65.5	63.0	13.0	45.4 / 104
Baseline eGFR (mL/min/1.73m ²)	66	112	110	21.3	74.3 / 163
ALT (U/L)	66	22.2	19.0	15.8	7.00 / 96.0
Study: 102					
Age (years)	196	30.8	30.3	10.5	12.4 / 61.7
Body Weight (kg)	196	65.1	63.0	13.3	33.0 / 130
Baseline eGFR (mL/min/1.73m ²)	196	112	109	26.8	62.0 / 199
ALT (U/L)	196	32.0	26.0	22.6	9.00 / 208
Study: 103					
Age (years)	284	33.3	32.6	12.6	12.2 / 71.2
Body Weight (kg)	284	66.5	65.0	13.9	34.0 / 122
Baseline eGFR (mL/min/1.73m ²)	284	110	108	25.3	51.0 / 228
ALT (U/L)	284	33.7	26.0	30.0	7.00 / 388
Study: 105, Part A1					
Age (years)	17	9.55	9.59	1.27	6.41 / 11.0
Body Weight (kg)	17	32.8	34.0	6.32	18.6 / 43.7
Baseline eGFR (mL/min/1.73m ²)	17	136	137	24.1	90.0 / 173
ALT (U/L)	17	22.4	24.0	7.95	10.0 / 35.0
Study: 105, Part B1					
Age (years)	78	9.05	9.30	1.74	6.17 / 12.0
Body Weight (kg)	78	30.2	28.9	7.48	19.3 / 54.0
Baseline eGFR (mL/min/1.73m ²)	78	141	138	23.7	103 / 195
ALT (U/L)	78	23.2	20.5	11.8	8.00 / 74.0
All data					
Age (years)	708	29.5	28.9	13.2	6.17 / 71.2
Body Weight (kg)	708	63.4	64.0	18.0	19.3 / 130
Baseline eGFR (mL/min/1.73m ²)	708	114	112	26.5	51.0 / 228
ALT (U/L)	708	30.3	24.0	23.9	7.00 / 388

Source: Table2, t270 report.

Note: 21 subjects crossed over to different studies or parts of a study and contributed only to the number of records for the overall summary after their cross over in the tabular subject count data

Abbreviations: ALT, alanine aminotransferase; eGFR, estimated glomerular filtration rate; max, maximum; min, minimum; n, number of records summarized; SD, standard deviation; Study 001, VX17-121-001; Study 101, VX18-121-101; Study 102, VX20-121-102; Study 102, VX20-121-103; Study 105, VX21-121-105

Table 124. Final Model Fixed Effect Parameter Estimates

			Estimate	RSE(%)	95% CI
Structural model parameters					
CL/F (L/hr)	$\exp(\theta_1)$	Apparent VNZ clearance	1.23	3.47	1.15, 1.32
V/F (L)	$\exp(\theta_2)$	Apparent central VNZ volume	122	7.75	105, 142
k_a (hr ⁻¹)	$\exp(\theta_3)$	First order absorption rate constant	0.280	6.13	0.248, 0.315
KTR (hr ⁻¹)	$\exp(\theta_4)$	First order transit rate constant	5.66	5.16	5.12, 6.26
Covariate effect parameters					
F _{MONO}	θ_5	Monotherapy effect on F	0.650	-	FIXED
F _{FORM}	θ_6	Formulation effect on F	2.02	-	FIXED
CL/F _{WT,CF}	θ_7	Saturation weight effect on CL/F for CF	37.7	1.12	36.9, 38.6
V/F _{WT,HS}	θ_8	Weight effect on V/F for CF	0.340	25.8	0.168, 0.512
KTR _{HS}	$\exp(\theta_9)$	HS effect on KTR	0.509	6.21	0.450, 0.574
F _{HS}	θ_{10}	HS effect on F	1.76	22.1	0.998, 2.52

Source: Table 5, t270 report.

RSE (%) = SE/estimate × 100

Confidence intervals = estimate ± 1.96 × SE

Parameters estimated in the log-domain were back-transformed for clarity

Abbreviations: CF, cystic fibrosis patients; CI, confidence intervals; F, *F508del* variant; FORM, formulation; HS, healthy subjects; MONO, monotherapy; RSE, relative standard error; SE, standard error; VNZ, vanzacaftor

Table 125. Final Model Random Effect Parameter Estimates

		Estimate	RSE(%)	95% CI	Shrinkage (%)
Interindividual variance parameters					
IIV-CL/F	$\Omega_{(1,1)}$	0.234 [CV%=51.4]	8.56	0.195, 0.274	2.30
IIV-V/F	$\Omega_{(2,2)}$	0.129 [CV%=37.2]	23.7	0.0693, 0.190	26.7
IIV-KTR	$\Omega_{(3,3)}$	0.129 [CV%=37.1]	14.5	0.0922, 0.165	46.2
IIV-k _a	$\Omega_{(4,4)}$	0.382 [CV%=68.3]	17.6	0.250, 0.515	33.0
Interindividual covariance parameters					
CL/F-V/F	$\Omega_{(2,1)}$	0.106 [Corr=0.607]	-	0.0782, 0.133	-
KTR-k _a	$\Omega_{(4,3)}$	-0.0201 [Corr=-0.0908]	-	-0.0796, 0.0393	-
Residual variance					
Proportional	$\Sigma_{(1,1)}$	0.0575 [CV%=24.0]	5.22	0.0516, 0.0634	10.7
Additive (ng/mL) ²	$\Sigma_{(2,2)}$	3.43 [SD=1.85]	46.2	0.321, 6.54	10.7

Source: Table 6, t270 report.

RSE (%) = SE/estimate × 100

CV% of sigma = sqrt(estimate) × 100

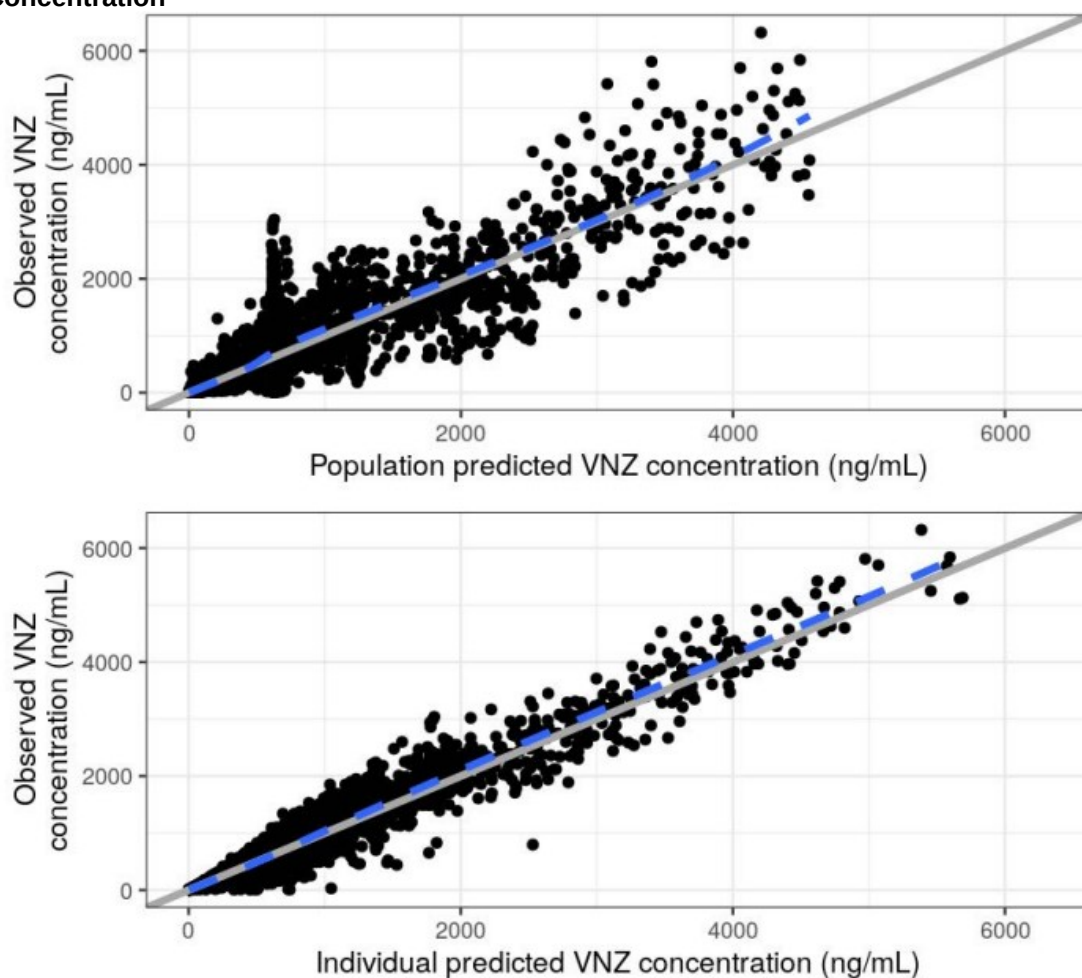
CV% of log-normal omegas = sqrt(exp(estimate) - 1) × 100

Confidence intervals = estimate ± 1.96 × SE

Parameters estimated in the log-domain were back-transformed for clarity

Abbreviations: CI, confidence intervals; CV, coefficient of variation; IIV, interindividual variability; RSE, relative standard error; SD, standard deviation; SE, standard error

Figure 37. Final Model: Observations Versus Population and Individual Predictions of Vanzacaftor Concentration

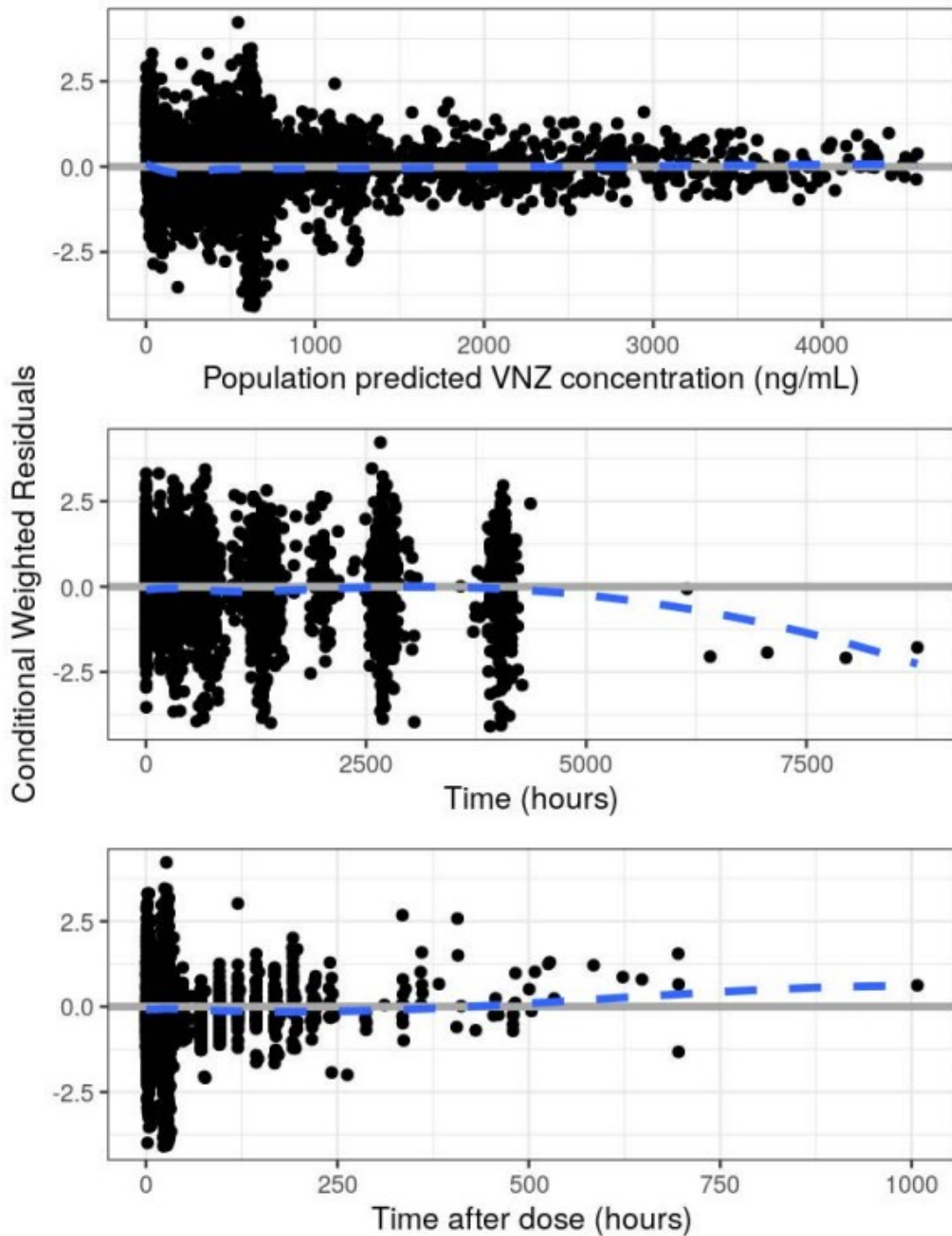


Source: Figure S44, t270 report.

Note: Observed values are indicated by solid black circles. The line of identity (solid grey) is included as a reference ($x=y$). The dashed blue line represents a LOESS smooth through the data.

Abbreviations: LOESS, locally weighted scatterplot smoothing; VNZ, vanzacaftor

Figure 38. Final Model: CWRES Versus Population Predictions, Time, and Time After Dose

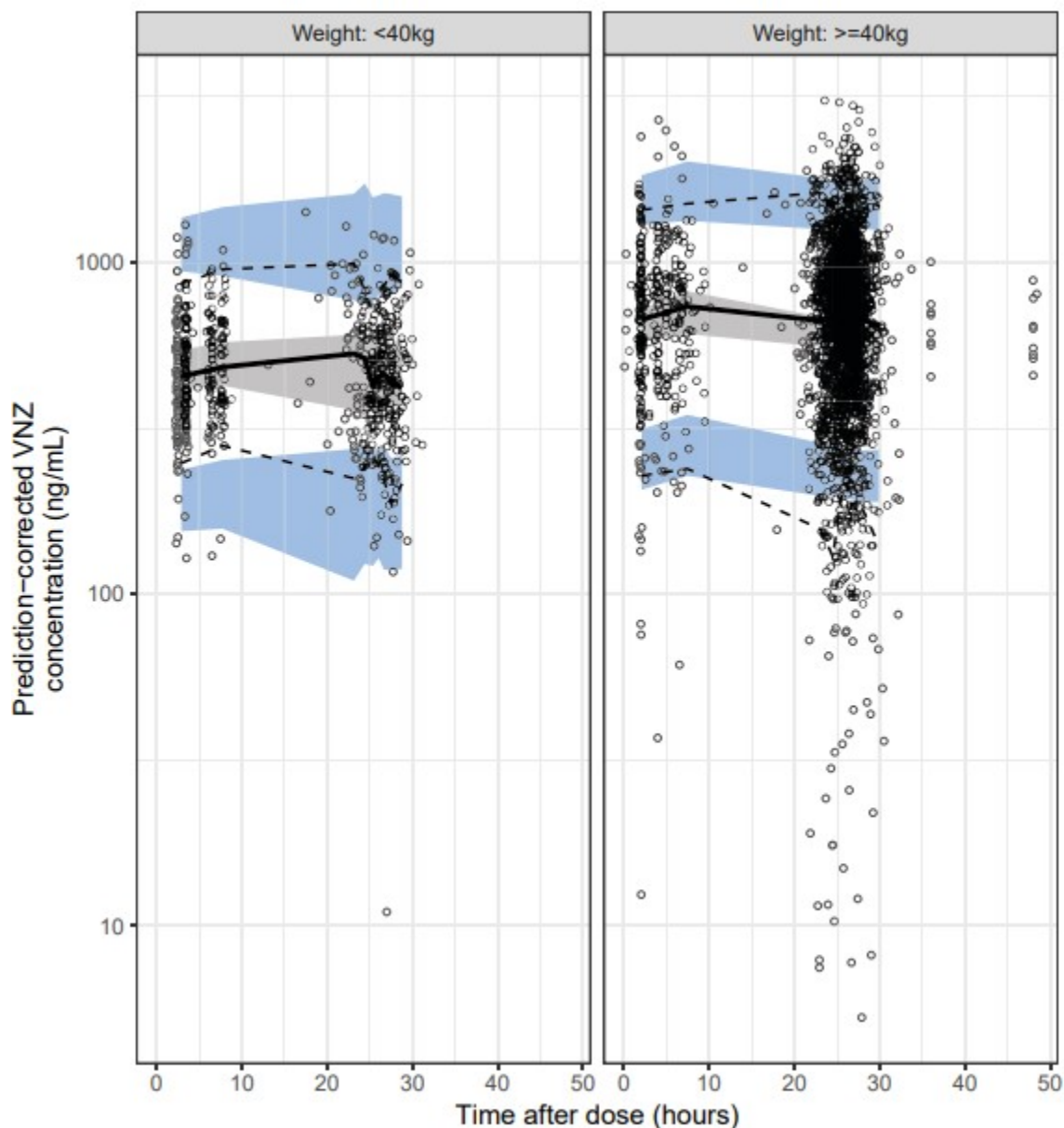


Source: Figure S55, t270 report.

Note: Solid black circles represent the individual CWRES values associated with each observation record. The solid horizontal grey line (residuals = 0) was included for reference. The dashed blue line represents a LOESS smooth through the data.

Abbreviations: CWRES, conditional weighted residuals; LOESS, locally weighted scatterplot smoothing; VNZ, vanzacaftor

Figure 39. Final Model: Prediction-Corrected VPC of Vanzacaftor Concentration Versus Time After Dose at Steady-State; Stratified by Weight Brackets

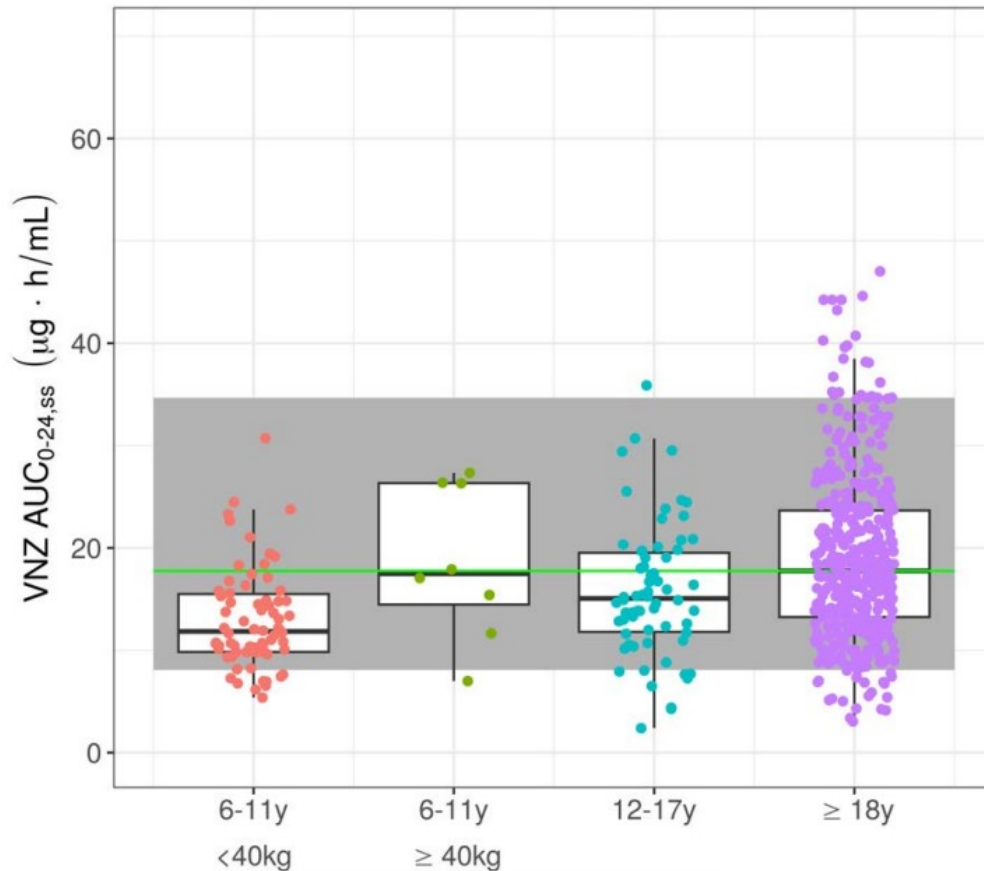


Source: Figure 8, t270 report.

Note: The black lines represent the median (solid) or 5th/95th (dashed) percentiles of the observed data. The shaded areas represent the 95% prediction intervals for median (gray) or 5th/95th percentiles (blue) for simulated data. The black circles indicate the observed data. Data were truncated to (1) greater than after 420 hours (5 half-lives) from the first dose and (2) < 50 hours from time after dose.

Abbreviations: VNZ, vanzacaftor; VPC, visual predictive check

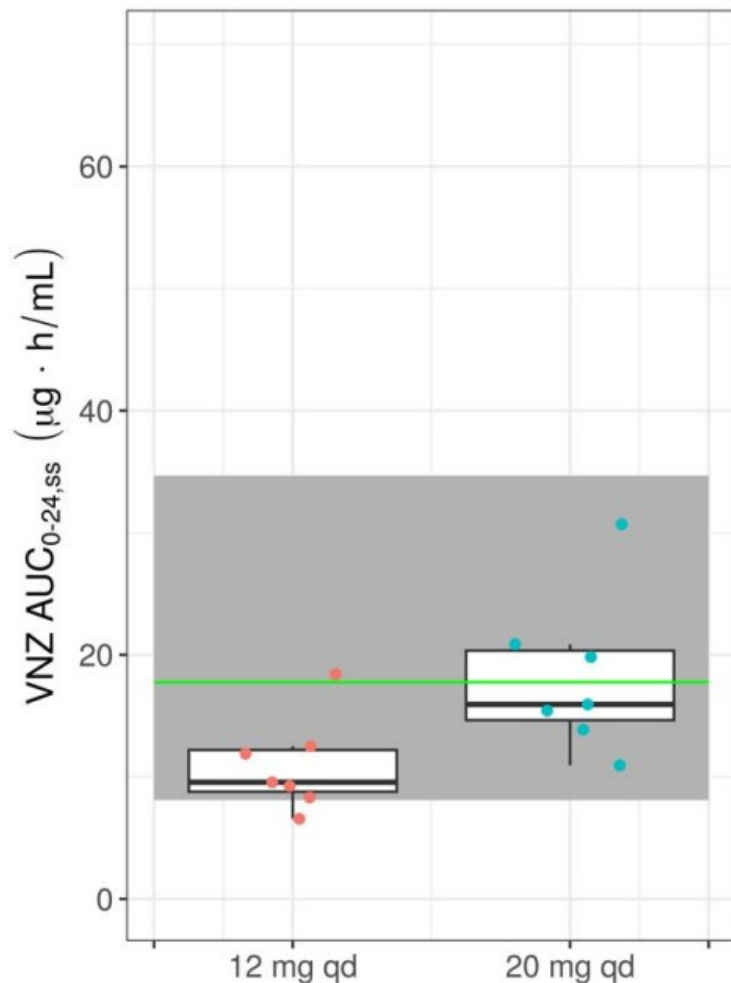
Figure 40. Population Simulated $AUC_{0-24,ss}$ Versus Age Group in Cystic Fibrosis Subjects Administered Different Vanzacaftor Doses; Stratified Weight Groups for Children 6 Through 11 Years of Age With Cystic Fibrosis With Weight Cutoff at 40 kg



Source: Figure 10, t270 report.

Note: The green horizontal line represents the median of individual predicted adult exposures and the corresponding gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from adults who received VNZ 20 mg qd in Studies VX20-121-102 and VX20-121-103. Individual predictions (data points) were made using EBEs from the final population PK model and final administered vanzacaftor dose. Boxes indicate the IQR with whiskers extending to $1.5 \times IQR$ and median values are designated by a solid line in the center of the box. Individual predictions were made using EBEs from the final population PK model and exposure estimates for CF children 6 through 11 years <40 kg were based on 12 mg qd and ≥ 40 kg were based on 20 mg qd. The exposure estimates for other patients were based on actual dosing.

Abbreviations: $AUC_{0-24,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 24 hours at steady-state; CF, cystic fibrosis; EBE, empirical Bayes estimates; IQR, interquartile range; PK, pharmacokinetic; qd, once daily; VNZ, vanzacaftor; y, year(s)

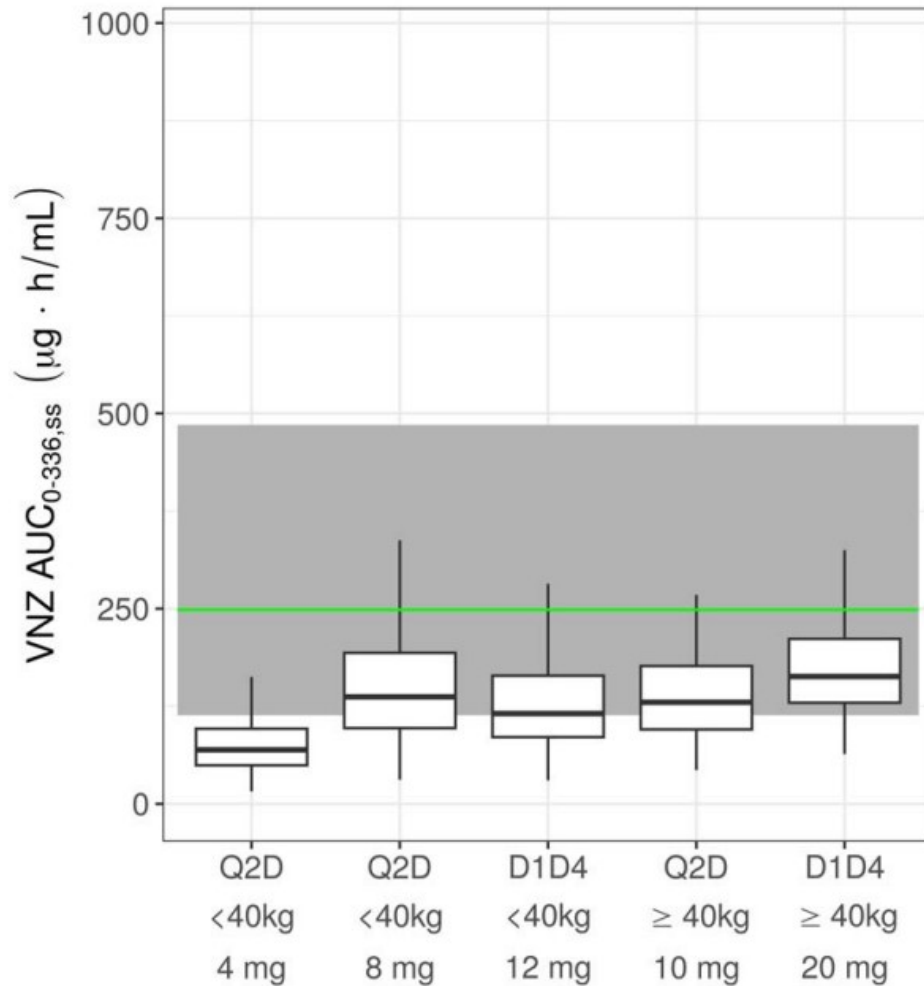
Figure 41. Population Simulated $AUC_{0-24,ss}$ in Cystic Fibrosis Subjects ≥ 12 Years of Age and < 40 kg Administered Different Vanzacaftor Doses

Source: Figure S100, t270 report.

Note: The green horizontal line represents the median of individual predicted adult exposures and the corresponding gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from adults who received VNZ 20 mg qd in Studies VX20-121-102 and VX20-121-103. Individual predictions were made using EBE from the final population PK model and exposure estimates were based on vanzacaftor dose indicated.

Abbreviations: $AUC_{0-24,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 24 hours at steady-state; EBE, empirical Bayes estimates; PK, pharmacokinetic; qd, once daily; VNZ, vanzacaftor; y, year(s)

Figure 42. Population Simulated $AUC_{0-336,ss}$ in Children 6 Through 11 Years of Age With Cystic Fibrosis Administered Different Vanzacaftor Doses With Fluconazole (Moderate CYP3A4 Inhibitor) With a Weight Cut of 40 kg

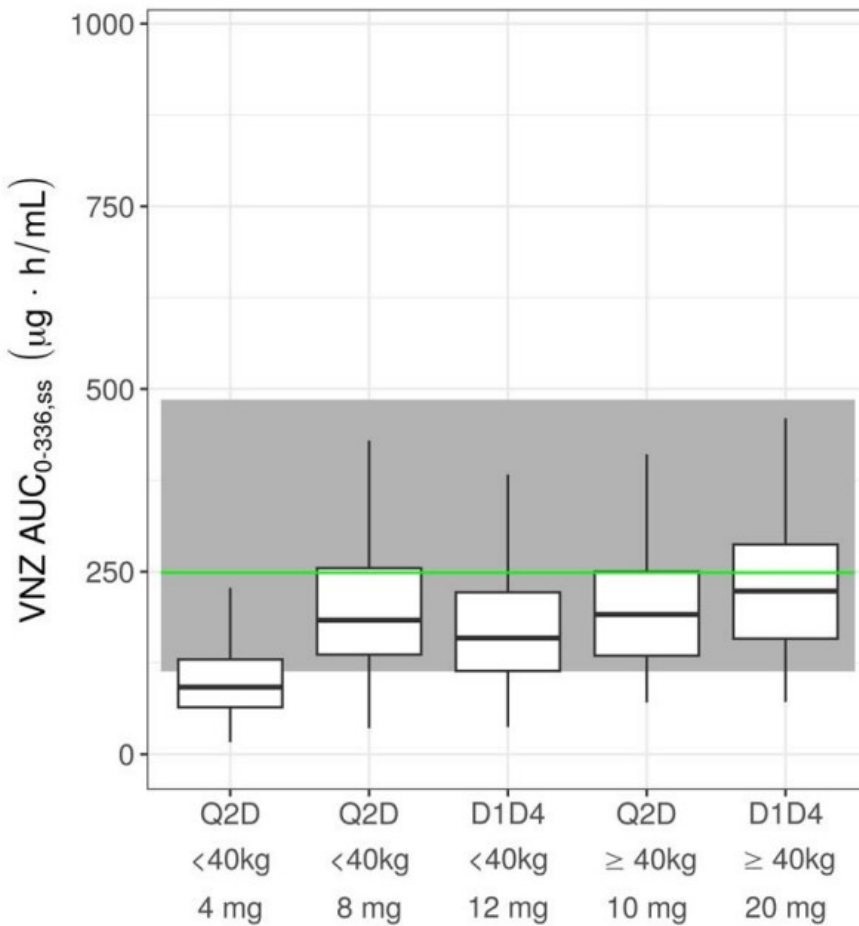


Source: Figure S119, t270 report.

Note: The green horizontal line represents the median of individual predicted adult exposures and the corresponding gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from adults who received VNZ 20 mg qd in Studies VX20-121-102 and VX20-121-103. Boxes indicate the IQR with whiskers extending to 1.5*IQR.

Abbreviations: $AUC_{0-336,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; D1D4, Day 1 and 4 weekly; IQR, interquartile range; Q2D, every other day; qd, once daily; VNZ, vanzacaftor; y, year(s)

Figure 43. Population Simulated $AUC_{0-336,ss}$ in Children 6 Through 11 Years of Age With Cystic Fibrosis Administered Different Vanzacaftor Doses With Erythromycin (Moderate CYP3A4 Inhibitor) With a Weight Cut of 40 kg

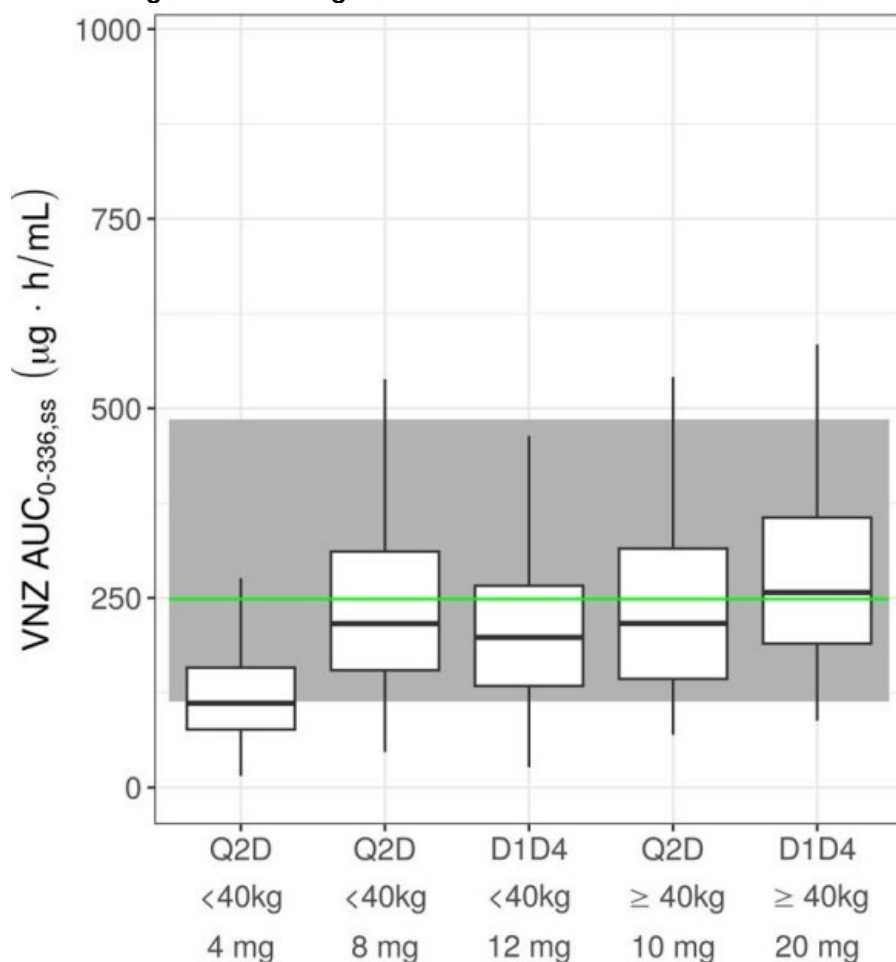


Source: Figure S122, t270 report.

Notes: The green horizontal line represents the median of individual predicted adult exposures and the corresponding gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from adults who received VNZ 20 mg qd in Studies VX20-121-102 and VX20-121-103. Boxes indicate the IQR with whiskers extending to $1.5 \times IQR$.

Abbreviations: $AUC_{0-336,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; D1D4, Day 1 and 4 weekly; IQR, interquartile range; Q2D, every other day; qd, once daily; VNZ, vanzacaftor; y, year(s)

Figure 44. Population Simulated $AUC_{0-336,ss}$ in Children 6 Through 11 Years of Age With Cystic Fibrosis Administered Different Vanzacaftor Doses With Verapamil (Moderate CYP3A4 Inhibitor) With a Weight Cut of 40 kg

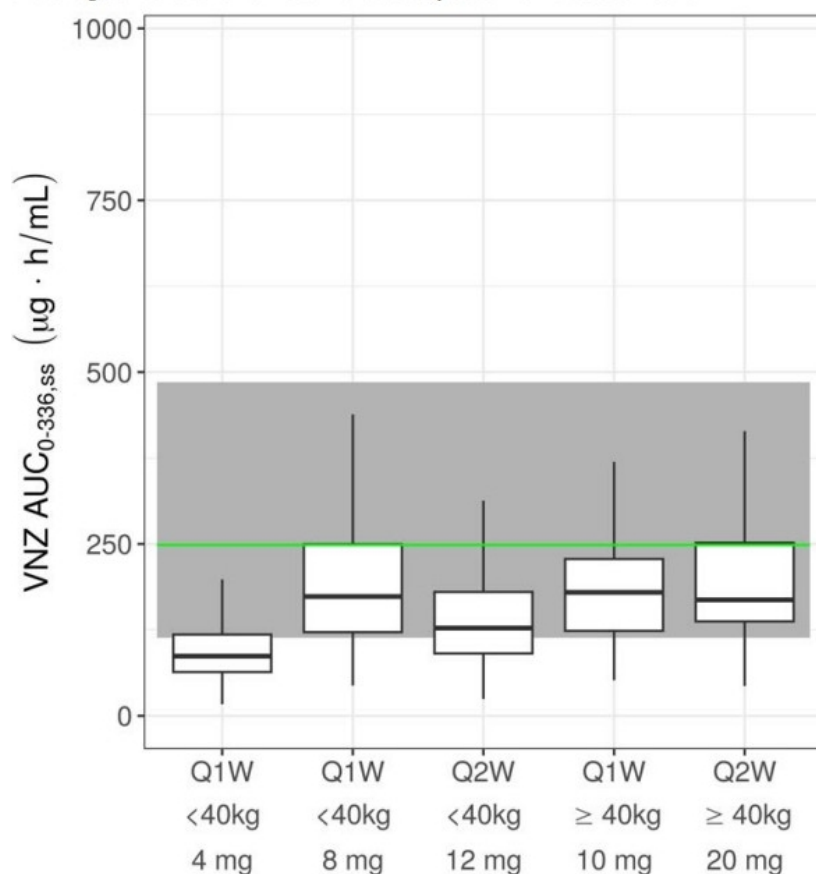


Source: Figure S125, t270 report.

The green horizontal line represents the median of individual predicted adult exposures and the corresponding gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from adults who received VNZ 20 mg qd in Studies VX20-121-102 and VX20-121-103. Boxes indicate the IQR with whiskers extending to $1.5 \times \text{IQR}$.

Abbreviations: $AUC_{0-336,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; CYP, cytochrome P450; D1D4, Day 1 and 4 weekly; IQR, interquartile range; Q2D, every other day; qd, once daily; VNZ, vanzacaftor; y, year(s)

Figure 45. Population Simulated $AUC_{0-336,ss}$ in Children 6 Through 11 Years of Age With Cystic Fibrosis With Weight Cutoff at 40 kg Administered Different Vanzacaftor Doses With Itraconazole (Strong CYP3A4 Inhibitor)



Source: Figure S200, t270 report.

The green horizontal line represents the median of individual predicted adult exposures and the corresponding gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from adults who received VNZ 20 mg qd in Studies VX20-121-102 and VX20-121-103. Boxes indicate the IQR with whiskers extending to 1.5*IQR.

Abbreviations: $AUC_{0-336,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; CYP, cytochrome P450; D1D4, Day 1 and 4 weekly; IQR, interquartile range; Q1W, every week; Q2W, every other week; qd, once daily; VNZ, vanzacaftor; y, year(s)

The FDA's Assessment

The Applicant's population PK analysis is considered acceptable for the purpose of supporting the analyses objectives.

14.5.1.2. TEZ Population PK Analysis (Report T271)

Executive Summary

The FDA's Assessment

In general, the Applicant's population PK analyses are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Population Pharmacokinetic Assessment Summary

Table 126. Data Structure of TEZ Population PK Analysis, Report T271

General Information	Details
Objectives of PPK analysis	• Characterize the PK disposition of TEZ in subjects 6 years of age and older using population methodology; • Quantify the effects of covariates, including body weight and <i>CFTR</i> genotype, as sources of PK variability in TEZ; • Summarize predicted $AUC_{0-24,ss}$ for TEZ from the studied dosing regimen for phase 3 subjects due to sparse PK sampling; • Evaluate if a 40 kg weight cutoff for all studied ages resulted in similar exposures to adults; – Simulate TEZ exposures for a VNZ/TEZ/D-IVA dosing regimen with a 40 kg weight cutoff in children 6 through 11 years with CF; – Simulate TEZ exposures for a VNZ/TEZ/D-IVA dosing regimen with a 40 kg weight cutoff in adolescents 12- 17y with CF; • Simulate exposures of TEZ to inform dosing and/or weight bounds for weight cutoffs other than 40 kg for subjects ≥ 6 years of age; • Simulate exposures of TEZ for different dosing regimens to inform dosing for adults with CF with moderate hepatic impairment (MHI); and • Simulate exposures of TEZ for different dosing regimens to inform dosing for children 6 through 11 years coadministered a strong or moderate CYP3A4 inhibitor.
Study included	VX17-121-001, VX18-121-101, VX20-121-102, VX20-121-103, VX21-121-105
TEZ dose(s) included	50 mg, 60 mg, 100 mg qd (Table 1, Report T271)
Population included	Healthy, CF (F/MF, F/F, F/G, F/RF, TCR, and F/other genotypes)
<i>Population characteristics (Tables 2 and 3, Report T271)</i>	
General	• Age: 28.9 yr (range: 6.17 – 71.2, 0.28% subj ≥ 65 yr) • Weight: 62.0 kg (range: 19.3 – 130) • N=357 (56.8%) male
Organ impairment	• Hepatic (Child-Pugh, NCI, etc.): not reported • Renal (CrCL, etc.): not reported
Pediatrics (if any)	• Age 9.30 (range: 6.17 – 12.0, 12.4 % subj ≤ 12 yr) • Weight 28.9 kg (range: 19.3 – 54.0)
No. of subjects, PK samples, and BLQ	629 subjects, 4971 PK samples, 65 (1.29%) post-first dose BLQ PK samples (Table S1, Report T271)

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

General Information	Details
<u>Sampling schedule</u>	
Rich sampling	• Study VX17-121-001: – Part A: Day 1: predose, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dosing. – Part B: Days 1 and 5: predose, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours after dosing. Days 7, 8, and 9: predose. Day 10: pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours after dosing. – Part C: Days 1 and 7: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. Days 2, 3, 4, 5, 8, 10, and 12: predose. Day 14: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dosing. – Part D: Day 1: predose, 1, 2, 4, and 6 hours after dosing. Days 8 and 29: predose. Day 15: predose, 1, 2, 4, 6, and 8 hours after dosing. • Study VX18-121-101: – Day 1: predose, 1, 2, 4, 6, 8, and 24 hours after dosing. – Days 8, 15, and 29: predose. – Day 47: predose.
In ITT population	• Trial VX20-121-102: – Day 1: Predose and 2 hours post dose. – Weeks 4, 16, and 24: predose. – Week 8: Predose and 4 hours postdose for all subjects <18 years of age. Predose, 4, 5, 6, and 7 hours postdose for up to approximately 40 subjects ≥18 years of age. Predose and 2 hours postdose for all other subjects ≥18 years of age. • Trial VX20-121-103: – Day 1: Predose and 2 hours post dose. – Day 15: Predose. – Weeks 4, 8, 16 and 24: Predose. • Trial VX21-121-105: – <u>Part A1</u>: Day 1: predose and 2 hours postdose. Days 8 and 15: predose. Day 22: predose, 2.5, 3.5, 6.5, 8 h postdose. – <u>Part B1</u>: Day 1: predose and 2 hours postdose. Day 15 and Week 4: predose. Week 8: predose, 2.5 and 3.5 hours postdose for all subjects; for a minimum of 12 subjects who weigh ≥17 kg at screening additional 6.5 and 8 hours postdose samples were collected. Weeks 12 and 16: predose.

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

General Information	Details
<i>Covariates evaluated</i>	
Static	Baseline age, baseline weight, sex, and genotype (Section 4.2, Report T271)
Time-varying	NA

Source: Reviewer's summary

Abbreviations: AUC_{0-24,ss}, area under the concentration-time curve at steady state from time 0-24 hours; BLQ, below the limit of quantification; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CrCL, creatinine clearance; CYP, cytochrome P450; D-IVA, deutivacaftor; F, 508del *CFTR* variant; G, gating *CFTR* variant; ITT, intent-to-treat; MF, minimal function *CFTR* variant; N, total number of subjects; NCI, National Cancer Institute; NA, not applicable; No., number; PK, pharmacokinetic; subj, subject; RF, residual function *CFTR* variant; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor; VNZ, vanzacaftor; y, year(s); yr, years(s)

Table 127. Model Evaluation of TEZ Population PK Analysis

Final Model	Summary	Acceptability (FDA's Comments)
Software and version	NONMEM®, Version 7.5.1	Acceptable
Estimation algorithm	First-order conditional estimation with η - ϵ interaction	Acceptable
Model structure	2-compartment model with first-order absorption and an absorption lag time	Acceptable
Model parameter estimates	Table 7, Report T271	Acceptable
Uncertainty and variability (RSE, IIV, shrinkage, bootstrap)	Except for Vp, IIV on Vp, and the additive residual variances, all RSE's (fixed and random effects) were <30%; shrinkage for IIV on CL was <10%.	Acceptable
BLQ for parameter accuracy	BLQ observations (1.29%) were excluded. No impact of BLQ on PK objectives given the low percentage of BLQ observations	Acceptable
GOF, VPC	Section 6.3, Report T271: - Diagnostic plots (Figures S5 to S36) indicated that the final model adequately described all the data with no discernible systematic bias, including that for the 6 through 11 years age group. Section 6.4, Report T271: - VPC (Figures S49 to S52) and pcVPC (Figures 10 to 13) results showed simulated TEZ concentrations were similar to observed concentrations at the 5th, 50th, and 95th percentiles across most of the concentration-time profile, both overall or when stratified by relevant covariates such as age, weight, and genotype.	Acceptable
Significant covariates and clinical relevance	Body weight was the only covariate that had a clinically meaningful impact on TEZ disposition.	

Final Model	Summary	Acceptability (FDA's Comments)
Analysis based on simulation (optional)	- Simulations based on the final population PK model for TEZ supported the justification of candidate weight-based dosing regimens of VNZ/TEZ/D-IVA TC in CF patients ≥ 6 years of age with a 40 kg weight cutoff (Table 8; and Figures 14, 15, S66, S71, Report T271). - Additional weight cutoffs were also evaluated: 35 kg: Table S3; and Figures S60 and S72, Report T271 30 kg: Table S6; and Figures S63 and S73, Report T271. - Simulations based on the final population PK models showed exposures of TEZ and M1-TEZ in adult CF subjects with MHI and no TEZ dose adjustment were in the same range as subjects without MHI (Figure S74, Report T271). This result supports that, based on PK, no TEZ dose adjustment was needed for adult CF subjects with MHI. - Simulations based on the final population PK models for TEZ and M1-TEZ supported the justification of VNZ/TEZ/D-IVA dose adjustment regimens with reduced daily dose and/or dosing frequency for children 6 through 11 years with CF in the presence of coadministered CYP3A4 inhibitors (Figure S76 and S88, Report T271).	Acceptable

Source: Reviewer's summary

Abbreviations: BLQ, below the limit of quantification; CF, cystic fibrosis; CL, clearance; CYP, cytochrome P450; D-IVA, deutivacaftor; GOF, goodness-of-fit; IIV, interindividual variability; IVA, ivacaftor; M, metabolite; MHI, moderate hepatic impairment; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic; RSE, relative standard error; TC, triple combination; TEZ, tezacaftor; V, volume of distribution; VNZ, vanzacaftor; VPC, visual predictive check; y, year

Table 128. Labeling Statements Supported by TEZ Population PK Analysis

Labeling Language	Description	Acceptability (FDA's Comments)
12.3 PK	(b) (4)	Acceptable

Source: Reviewer's summary

Abbreviations: CF, cystic fibrosis; PK, pharmacokinetic

Report T271/Tables

Table 129. TEZ: Baseline Categorical Covariate Summary After All Data Exclusions

Study	n	Genotype					Sex	
		F/MF	F/F	F/G	F/RF and F/other	TCR/any	female	male
121-001	9	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	8 (88.9)
121-101	66	48 (72.7)	18 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)	23 (34.8)	43 (65.2)
121-102	196	196 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	80 (40.8)	116 (59.2)
121-103	284	0 (0.0)	222 (78.2)	19 (6.7)	23 (8.1)	20 (7.0)	135 (47.5)	149 (52.5)
121-105, Part A1	17	3 (17.6)	9 (52.9)	0 (0.0)	0 (0.0)	5 (29.4)	7 (41.2)	10 (58.8)
121-105, Part B1	78	25 (32.1)	37 (47.4)	3 (3.8)	3 (3.8)	10 (12.8)	34 (43.6)	44 (56.4)
All data	629	271 (43.1)	278 (44.2)	22 (3.5)	26 (4.1)	32 (5.1)	272 (43.2)	357 (56.8)

Source: Table 2, T271 report.

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; F, *F508del* CFTR variant; G, gating CFTR variant; MF, minimal function CFTR variant; RF, residual function CFTR variant; TCR, triple combination responsive CFTR variant; TEZ, tezacaftor

Table 130. TEZ: Baseline Continuous Covariate Summary After All Data Exclusions

Study	n	Mean	Median	SD	Min	Q25	Q75	Max
Age (years)								
121-001	9	34.4	34.0	12.9	21.0	22.0	41.0	57.0
121-101	66	32.2	31.0	10.2	18.0	24.0	38.0	64.0
121-102	196	30.8	30.3	10.5	12.4	22.8	37.4	61.7
121-103	284	33.3	32.6	12.6	12.2	24.3	41.5	71.2
121-105, Part A1	17	9.55	9.59	1.27	6.41	9.14	10.6	11.0
121-105, Part B1	78	9.05	9.30	1.74	6.17	7.61	10.4	12.0
All data	629	29.2	28.9	13.4	6.17	18.8	38.8	71.2
Weight (kg)								
121-001	9	67.3	73.0	11.7	51.0	60.0	74.0	86.0
121-101	66	65.5	63.0	13.0	45.4	56.0	73.5	104
121-102	196	65.1	63.0	13.3	33.0	56.2	73.0	130
121-103	284	66.6	65.0	13.9	34.0	56.0	75.0	122
121-105, Part A1	17	32.8	34.0	6.32	18.6	29.0	37.8	43.7
121-105, Part B1	78	30.2	28.9	7.48	19.3	24.0	35.2	54.0
All data	629	61.4	62.0	17.6	19.3	52.0	73.0	130

Source: Table 3, T271 report.

Abbreviations: max, maximum; min, minimum; n, number of subjects; Q25, first quartile; Q75, third quartile; SD, standard deviation; TEZ, tezacaftor

Table 131. TEZ: Final Model: PK Parameter Estimates

				Estimate	%RSE	95% CI	SHK (%)
Structural model parameters							
CL/F (L/hr)	θ_1	Apparent clearance		1.22	3.40	1.14, 1.30	-
Vc/F (L)	θ_2	Apparent central volume		20.1	5.09	18.1, 22.1	-
Vp/F (L)	θ_3	Apparent peripheral volume		57.1	85.1	-38.2, 152	-
Q/F (L/hr)	θ_4	Apparent intercompartmental clearance		1.05	28.2	0.471, 1.63	-
k_a (hr ⁻¹)	θ_5	First order absorption rate constant		3.24	26.3	1.57, 4.91	-
ALAG (hr)	θ_6	Absorption lag time		0.548	15.4	0.383, 0.713	-
Covariate effect parameters							
CL _{WT}	θ_7	Weight effect on CL/F		0.341	11.5	0.264, 0.417	-
Vc _{WT}	θ_8	Weight effect on Vc/F		0.543	6.55	0.474, 0.613	-
Vp _{WT}	θ_9	Weight effect on Vp/F		1.00	-	FIXED	-
Q _{WT}	θ_{10}	Weight effect on Q/F		0.750	-	FIXED	-
CL _{GTN}	θ_{11}	Combined genotype effect (F/G, TCR/any) on CL/F		0.885	3.93	0.817, 0.953	-
Interindividual variance parameters							
IIV-CL/F	$\Omega_{(1,1)}$	Variance of CL/F		0.0922 [CV%=31.1]	8.28	0.0772, 0.107	3.55
IIV-Vc/F	$\Omega_{(2,2)}$	Variance of Vc/F		0.00256 [CV%=5.06]	183	-0.00663, 0.0118	81.8
Interindividual covariance parameters							
CL/F-Vc/F	$\Omega_{(2,1)}$	Covariance of CL/F-Vc/F		0.00191 [Corr=0.124]	-	-0.00881, 0.0126	-
Residual variance							
Proportional (Phase 1/2 studies)	$\Sigma_{(1,1)}$	Variance		0.113 [CV%=33.6]	11.2	0.0880, 0.138	-
Additive (Phase 1/2 studies)	$\Sigma_{(2,2)}$	Variance		1.01e+03 [SD=31.8]	760	-1.41e+04, 1.61e+04	-
Proportional (Phase 3 studies)	$\Sigma_{(3,3)}$	Variance		0.0857 [CV%=29.3]	6.09	0.0754, 0.0959	-
Additive (Phase 3 studies)	$\Sigma_{(4,4)}$	Variance		1.99e+04 [SD=141]	45.6	2.13e+03, 3.76e+04	-

Source: Table 7, T271 report.

Typical estimates of the structural model PK parameters are presented for the reference covariates: weight = 70 kg; genotype = F/MF, F/F, or F/RF and F/other.

Confidence intervals = estimate $\pm$ 1.96 * SE

CV% of log-normal omegas = $\sqrt{\exp(\text{estimate}) - 1} * 100$

CV% of sigma = $\sqrt{\text{estimate}} * 100$

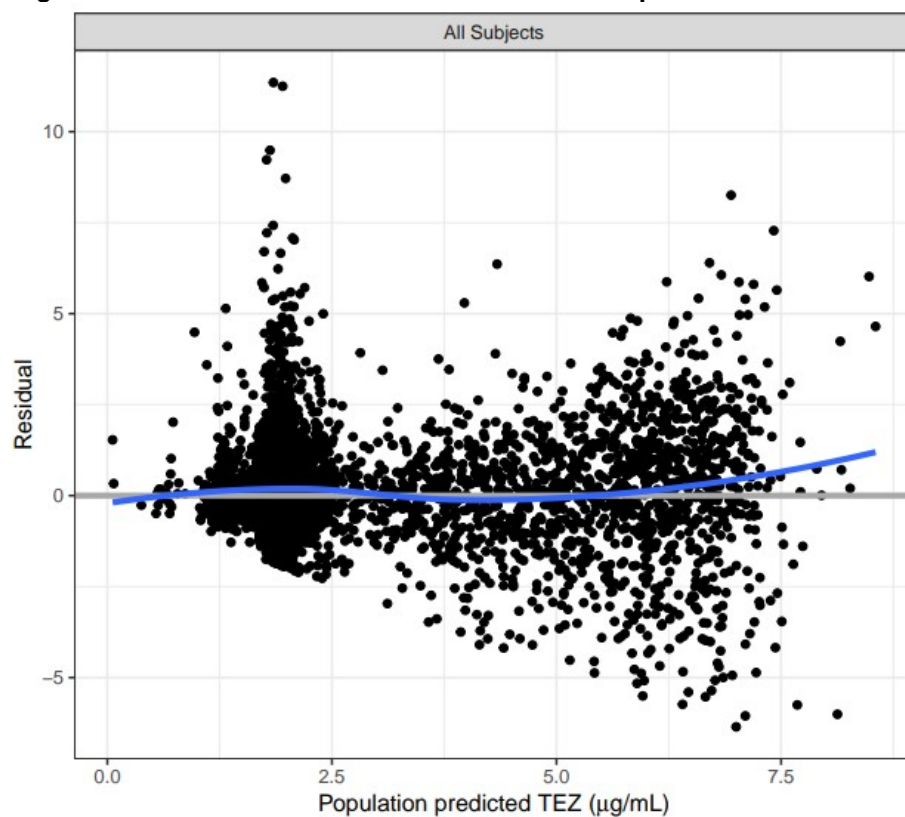
Source code: tez-parenter-table.R

Remaining parameters defined in the text

Abbreviations: CI, confidence interval; CFTR, cystic fibrosis transmembrane conductance regulator; Corr, correlation coefficient; CV, coefficient of variation; F, *F508del CFTR* variant; MF, minimal function *CFTR* variant; PK, pharmacokinetic; RF, residual function *CFTR* variant; %RSE, percent relative standard error; SD, standard deviation; SE, standard error; SHK, shrinkage

Report T271/Figures

Figure 46. TEZ: Final Model: Residuals Versus Population Predicted Concentration: All Subjects

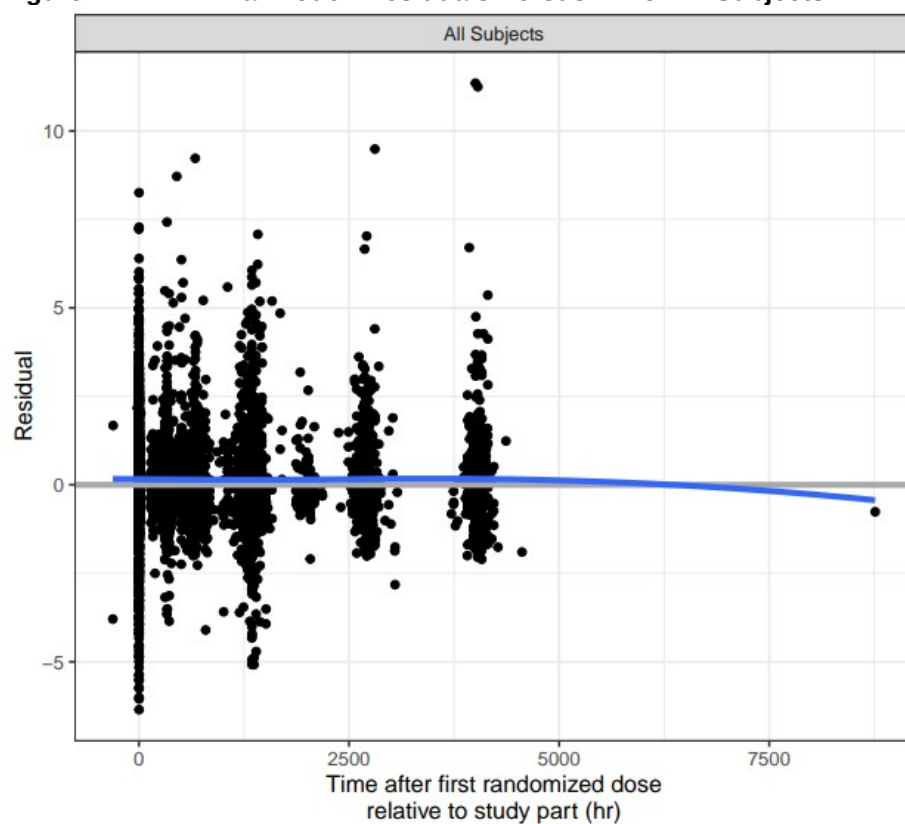


Source: Figure S13, T271 report.

Note: Residuals are plotted vs. population predictions. Values are indicated by black circles with a LOESS smooth trend line (solid blue) through the data. A solid gray line at $y = 0$ is included as a reference

Abbreviations: LOESS, locally weighted scatterplot smoothing; TEZ, tezacaftor

Figure 47. TEZ: Final Model: Residuals Versus Time: All Subjects

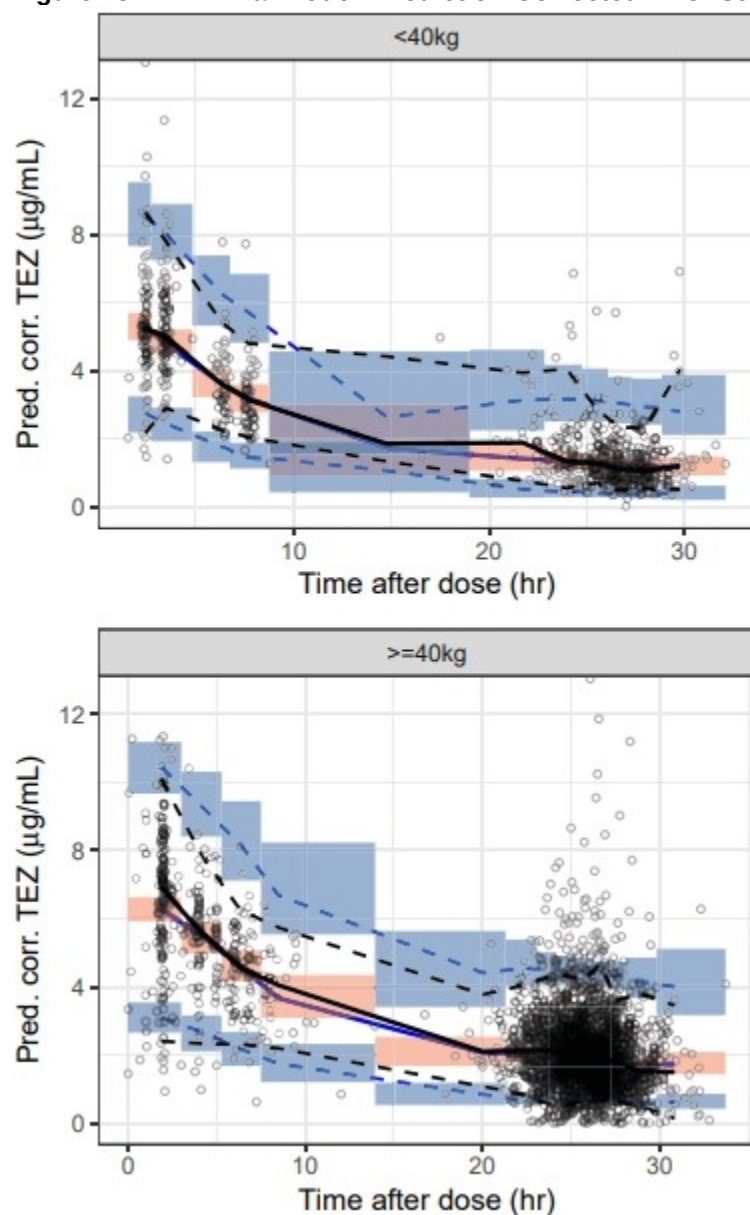


Source: Figure S17, T271 report.

Note: Residuals are plotted vs. time. Values are indicated by black circles with a LOESS smooth trend line (solid blue) through the data. A solid gray line at $y = 0$ is included as a reference.

Abbreviations: hr, hour; LOESS, locally weighted scatterplot smoothing; TEZ, tezacaftor

Figure 48. TEZ: Final Model: Prediction-Corrected VPC: Stratified by Weight Group

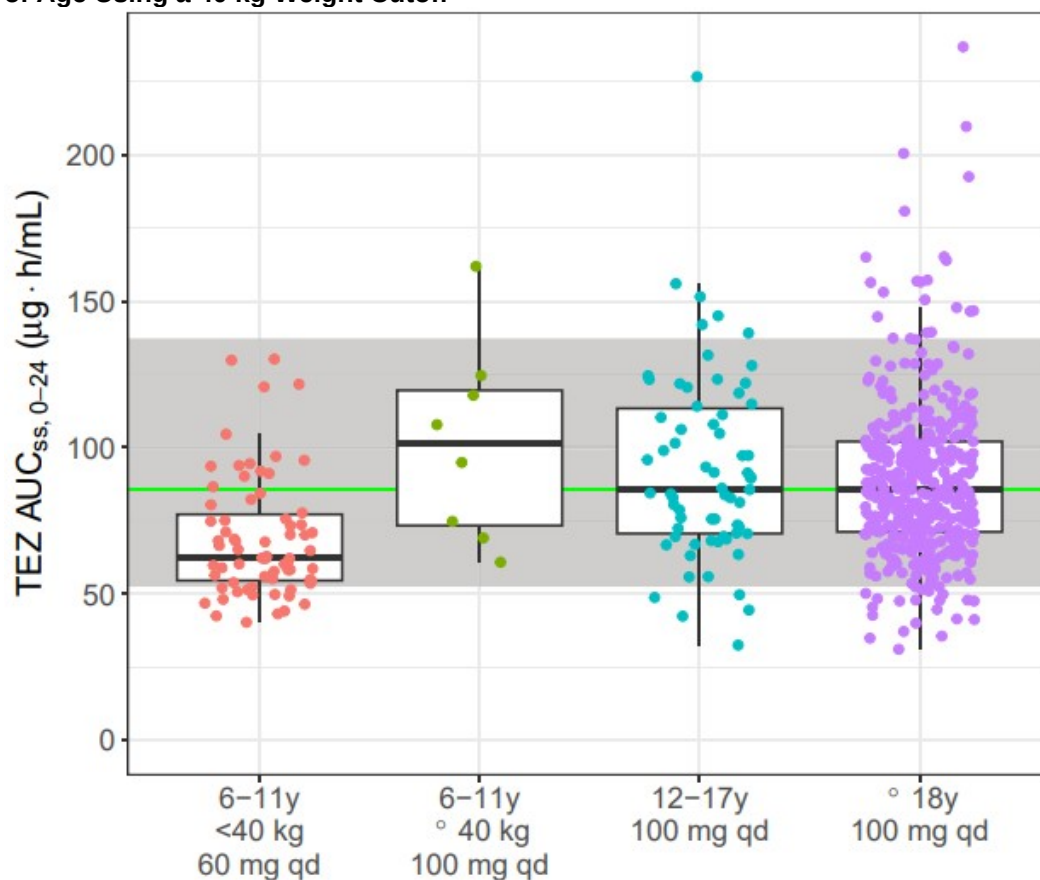


Source: Figure 12, T271 report.

Note: 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)

Abbreviations: hr, hour; Pred. corr., prediction-corrected; TEZ, tezacaftor; VPC, visual predictive check

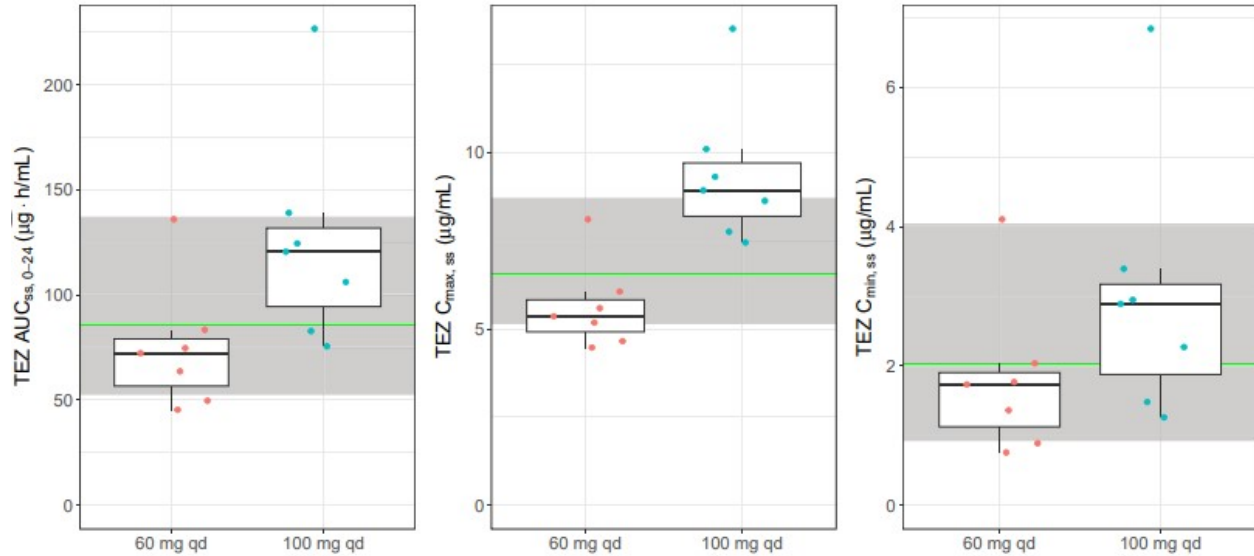
Figure 49. TEZ: Individual Predicted AUC_{ss} Versus Age Group: TEZ Dosed in 6 Through 11 Years of Age Using a 40 kg Weight Cutoff



Source: Figure 14, T271 report.

Note: The points represent individual predicted exposures under different dosing regimens: TEZ 100 mg qd for adults, adolescents (12-17y), and 6 through 11 years subjects weighing $\geq$ 40 kg; TEZ 60 mg qd for 6 through 11 years subjects weighing <40 kg. The predictions were made using EBEs from the final population PK model. The individual points are summarized 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 $1.5 \times \text{IQR}$. The green horizontal line represents the median of the adult values, and the gray shaded area indicates the 5th and 95th percentiles. The adult reference exposures were derived from subjects in Studies 121-102 and 121-103. Subjects in the 12-17y age group are from Studies 121-102 and 121-103, and the 6 through 11 years subjects are from Part B1 of Study 121-105. Abbreviations: AUC_{ss} , area under the plasma drug concentration-time curve at steady state; $AUC_{0-24,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 24 hours; EBE, empirical Bayes estimates; IQR, interquartile range; PK, pharmacokinetic; qd, once daily; TEZ, tezacaftor; y, year

Figure 50. TEZ: Individual Predicted Exposures in Subjects ≥ 12 Years of Age and < 40 kg Administered Different TEZ Doses

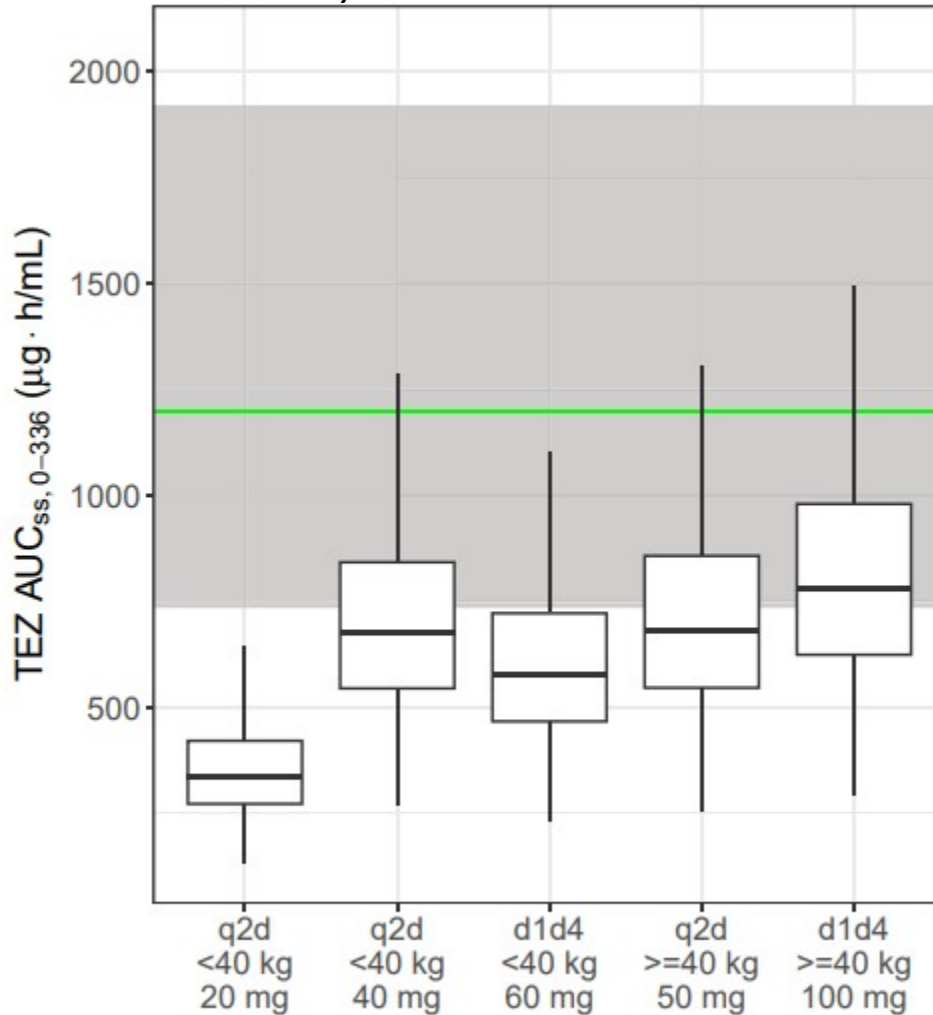


Source: Figure S66, T271 report.

Note: The points represent individual predicted exposures under different TEZ dosing regimens for subjects ≥ 12 y and < 40 kg. The individual points are summarized 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 $1.5 \times \text{IQR}$. The green horizontal line represents the median of individual predicted adult values and the gray shaded area indicates the 5th and 95th percentiles. Individual predictions were made using EBEs from the final population PK model. The adult reference exposures were derived from subjects in Studies 121-102 and 121-103.

Abbreviations: AUC_{0-24,ss}, area under the plasma drug concentration-time curve at steady state from 0 to 24 hours; C_{max,ss}, maximum plasma concentration at steady-state; C_{min,ss}, minimum plasma concentration at steady-state; EBE, empirical Bayes estimates; IQR, interquartile range; PK, pharmacokinetic; qd, once daily; TEZ, tezacaftor; y, year.

Figure 51. TEZ: Population Simulated AUC_{ss} in Children 6 Through 11 Years of Age Following Different TEZ Dosing Regimens With a 40 kg Cutoff and Coadministered With Fluconazole (Moderate CYP3A4 Inhibitor)

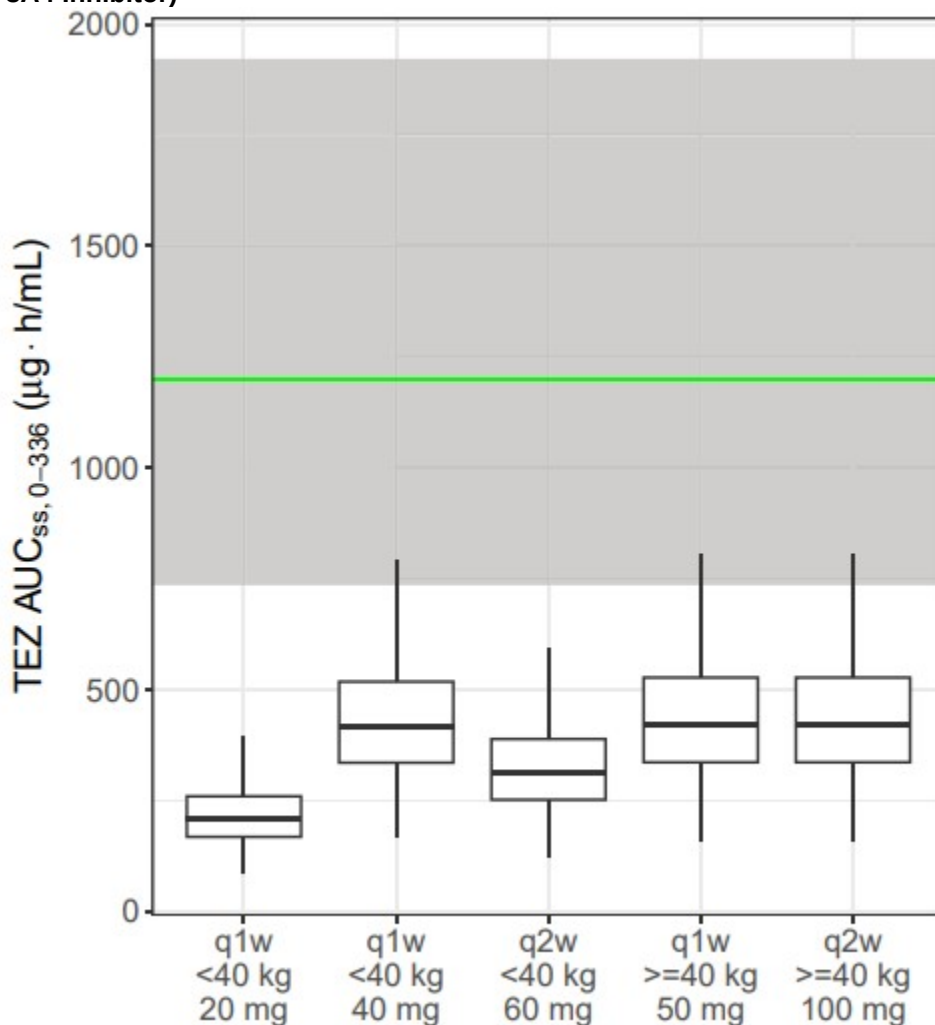


Source: Figure S76, T271 report.

Note: The following TEZ regimens were evaluated in the population simulations. For subjects weighing <40 kg: 20 mg q2d, 40 mg q2d, or 60 mg d1d4. For subjects weighing ≥40 kg: 50 mg q2d or 100 mg d1d4. The population simulated exposures are summarized 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×IQR. The green horizontal line represents the median of individual predicted adult exposures and the gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from subjects in Studies 121-102 and 121-103.

Abbreviations: AUC_{ss} , area under the plasma drug concentration-time curve at steady state; $AUC_{0-336,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; CYP, cytochrome P450; d1d4, Day 1 and 4 weekly; IQR, interquartile range; Q1W, every week; q2d, every other day; Q2W, every other week; qd, once daily; TEZ, tezacaftor; y, year(s)

Figure 52. TEZ: Population Simulated AUC_{ss} in Children 6 Through 11 Years of Age Following Different TEZ Dosing Regimens With a 40 kg Cutoff and Coadministered With Itraconazole (Strong CYP3A4 Inhibitor)



Source: Figure S88, T271 report.

The following TEZ regimens were evaluated in the population simulations. For subjects weighing <40 kg: 20 mg q1w, 40 mg q1w, or 60 mg q2w. For subjects weighing ≥40 kg: 50 mg q1w or 100 mg q2w. The population simulated exposures are summarized 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×IQR. The green horizontal line represents the median of individual predicted adult exposures and the gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from subjects in Studies 121-102 and 121-103. Abbreviations: AUC_{ss} , area under the plasma drug concentration-time curve at steady state; $AUC_{0-336,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; CYP, cytochrome P450; hr., hour; IQR, interquartile range; Q1W, every week; Q2W, every other week; TEZ, tezacaftor; y, year

The FDA's Assessment

The Applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives.

14.5.1.3. M1-TEZ Population PK Analysis (Report T271)

Executive Summary

The FDA's Assessment

In general, the Applicant's population PK analyses are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the clinical pharmacology reviewer, with no significant discordance identified.

Population Pharmacokinetic Assessment Summary

Table 132. Data Structure of M1-TEZ Population PK Analysis, Report T271

General Information	Details
Objectives of PPK analysis	• Characterize the PK disposition of M1-TEZ in subjects 6 years of age and older using population methodology; • Quantify the effects of covariates, including body weight and CFTR genotype, as sources of PK variability in TEZ and M1-TEZ; • Summarize AUC_{ss}, 0–24 for M1-TEZ from the studied dosing regimen for phase 3 subjects due to sparse PK sampling; • Evaluate if a 40 kg weight cutoff for all studied ages resulted in similar exposures to adults; – Simulate M1-TEZ exposures for a VNZ/TEZ/D-IVA dosing regimen with a 40 kg weight cutoff in children 6 through 11 years with CF; – Simulate M1-TEZ exposures for a VNZ/TEZ/D-IVA dosing regimen with a 40 kg weight cutoff in adolescents 12 through 17 years with CF; • Simulate exposures of M1-TEZ to inform dosing and/or weight bounds for weight cutoffs other than 40 kg for subjects ≥6 years of age; • Simulate exposures of M1-TEZ for different dosing regimens to inform dosing for adults with CF with moderate hepatic impairment (MHI); and • Simulate exposures of M1-TEZ for different dosing regimens to inform dosing for children 6 through 11 years coadministered a strong or moderate CYP3A4 inhibitor.
Study included	VX17-121-001, VX18-121-101, VX20-121-102, VX20-121-103, VX21-121-105
TEZ Dose(s) included	50 mg, 60 mg, 100 mg qd (Table 1, Report T271)
Population included	Healthy, CF (F/MF, F/F, F/G, F/RF, TCR, and F/other genotypes)
<i>Population characteristics (Tables 2 and 3, Report T271)</i>	
General	• Age: 28.9 yr (range: 6.17 – 71.2, 0.28% subj ≥65 yr) • Weight: 62.0 kg (range: 19.3 – 130) • N=357 (56.8%) male
Organ impairment	• Hepatic (Child-Pugh, NCI, etc.): not reported • Renal (CrCL, etc.): not reported
Pediatrics (if any)	• Age 9.30 (range: 6.17 – 12.0, 11.4% subj ≤12 yr)

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

General Information	Details
	Weight 28.9 kg (range: 19.3 – 54.0)
No. of subjects, PK samples, and BLQ	629 subjects, 4970 PK samples, 66 (1.31%) postdose BLQ post-first dose BLQ PK samples (Table S13, Report T270)
<i>Sampling schedule</i>	
Rich sampling	- Study VX17-121-001: - Part A: Day 1: predose, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dosing. - Part B: Days 1 and 5: predose, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours after dosing. Days 7, 8, and 9: predose. Day 10: pre-dose, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, and 96 hours after dosing. - Part C: Days 1 and 7: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours after dosing. Days 2, 3, 4, 5, 8, 10, and 12: predose. Day 14: predose, 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24, 36, 48, 72, and 96 hours after dosing. - Part D: Day 1: predose, 1, 2, 4, and 6 hours after dosing. Days 8 and 29: predose. Day 15: predose, 1, 2, 4, 6, and 8 hours after dosing. - Study VX18-121-101: - Day 1: predose, 1, 2, 4, 6, 8, and 24 hours after dosing. Days 8, 15, and 29: predose. Day 47: predose.
In ITT population	- Trial VX20-121-102: - Day 1: Predose and 2 hours post dose. - Weeks 4, 16, and 24: predose. - Week 8: Predose and 4 hours postdose for all subjects <18 years of age. Predose, 4, 5, 6, and 7 hours postdose for up to approximately 40 subjects ≥18 years of age. Predose and 2 hours postdose for all other subjects ≥18 years of age. - Trial VX20-121-103: - Day 1: Predose and 2 hours post dose. - Day 15: Predose. - Weeks 4, 8, 16 and 24: Predose. - Trial VX21-121-105: - Part A1: Day 1: predose and 2 hours postdose. Days 8 and 15: predose. Day 22: predose, 2.5, 3.5, 6.5, 8 h postdose. - Part B1: Day 1: predose and 2 hours postdose. Day 15 and Week 4: predose. Week 8: predose, 2.5 and 3.5 hours postdose for all subjects; for a minimum of 12 subjects who weigh ≥17 kg at screening additional 6.5 and 8 hours postdose samples were collected. Weeks 12 and 16: predose.
<i>Covariates evaluated</i>	
Static	Baseline age, baseline weight, and genotype (Section 4.2, Report T271)
Time-varying	NA

Source: Reviewer's summary

Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state; BLQ, below the limit of quantification; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CYP, cytochrome P450; D-IVA, deutivacaftor; F, *F508del* CFTR variant; G, gating CFTR variant; M, metabolite; MF, minimal function CFTR variant; NA, not applicable; PK, pharmacokinetic; qd, once daily; subj, subject; RF, residual function CFTR variant; TCR, triple combination responsive CFTR variant; TEZ, tezacaftor; VNZ, vanzacaftor; yr, year

Table 133. Model Evaluation of M1-TEZ Population PK Analysis

Final Model	Summary	Acceptability (FDA's Comments)
Software and Version	NONMEM®, Version 7.5.1	Acceptable
Estimation Algorithm	First-order conditional estimation with η - ϵ interaction (FOCEI)	Acceptable
Model Structure	2-compartment model (sequentially developed using the empirical Bayes estimates from the TEZ model)	Acceptable
Model Parameter Estimates	Table 16, Report T271	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Except for the residual variances for phase 1/2 studies, all RSE's (fixed and random effects) were <30%; shrinkage for IIV on CL was <10%.	Acceptable
BLQ for Parameter Accuracy	BLQ observations (1.31%) were excluded. No impact of BLQ on PK objectives given the low percentage of BLQ observations	Acceptable
GOF, VPC	Section 7.3, Report T271: - Overall, diagnostic plots (Figures S106 to S137) indicated that the final model adequately described all the data with no marked systematic bias, including that for the 6 through 11 years age group. Section 7.4, Report T271: - VPC (Figures S150 to S153) and pcVPC (Figures 19 to 22) results showed simulated M1-TEZ concentrations were similar to observed concentrations at the 5th, 50th, and 95th percentiles across most of the concentration-time profile both overall or when stratified by relevant covariates such as age, weight, and genotype.	Acceptable
Significant Covariates and Clinical Relevance	Body weight was the only covariate that had a clinically meaningful impact on M1-TEZ disposition	Acceptable

Final Model	Summary	Acceptability (FDA's Comments)
Analysis Based on Simulation (optional)	• Simulations based on the final population PK model for TEZ supported the justification of candidate weight-based dosing regimens of VNZ/TEZ/D-IVA TC in CF patients ≥ 6 years of age with a 40 kg weight cutoff (Table 17; and Figures 23, 24, S167, and S172, Report T271). • Additional weight cutoffs were also evaluated: – 35 kg: Table S15; and Figures S161 and S173, Report T271 – 30 kg: Table S18; and Figures S164 and S174, Report T271. • Simulations based on the final population PK models showed exposures of TEZ and M1-TEZ in adult CF subjects with MHI and no TEZ dose adjustment were in the same range as subjects without MHI (Figure S175, Report T271). This result supports that, based on PK, no TEZ dose adjustment was needed for adult CF subjects with MHI. • Simulations based on the final population PK models for TEZ and M1-TEZ supported the justification of VNZ/TEZ/D-IVA dose adjustment regimens with reduced daily dose and/or dosing frequency for children 6 through 11 years with CF in the presence of coadministered CYP3A4 inhibitors (Figure S177 and S189, Report T271).	Acceptable

Source:

Abbreviations: BLQ, below the limit of quantification; CF, cystic fibrosis; CL, clearance; CYP, cytochrome P450; D-IVA, deutivacaftor; IIV, interindividual variability; M, metabolite; MHI, moderate hepatic impairment; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic; RSE, relative standard error; TC, triple combination; TEZ, tezacaftor; VNZ, vanzacaftor; y(s), year(s)

Table 134. Labeling Statements Supported by M1-TEZ Population PK Analysis

Labeling Language	Description	Acceptability (FDA's Comments)
12.3 PK	NA	NA

Source: Reviewer's summary

Abbreviations: NA, not applicable; PK, pharmacokinetic

Report T271/Tables

Table 135. M1-TEZ: Baseline Categorical Covariate Summary After All Data Exclusions

Study	n	Genotype					Sex	
		F/MF	F/F	F/G	F/RF and F/other	TCR/any	female	male
121-001	9	9 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (11.1)	8 (88.9)
121-101	66	48 (72.7)	18 (27.3)	0 (0.0)	0 (0.0)	0 (0.0)	23 (34.8)	43 (65.2)
121-102	196	196 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	80 (40.8)	116 (59.2)
121-103	284	0 (0.0)	222 (78.2)	19 (6.7)	23 (8.1)	20 (7.0)	135 (47.5)	149 (52.5)
121-105, Part A1	17	3 (17.6)	9 (52.9)	0 (0.0)	0 (0.0)	5 (29.4)	7 (41.2)	10 (58.8)
121-105, Part B1	78	25 (32.1)	37 (47.4)	3 (3.8)	3 (3.8)	10 (12.8)	34 (43.6)	44 (56.4)
All data	629	271 (43.1)	278 (44.2)	22 (3.5)	26 (4.1)	32 (5.1)	272 (43.2)	357 (56.8)

Source: Table 11, T271 report

Note: Summary is count (percent), n: number of records summarized

Note: 21 subjects crossed over to different studies or parts of a study and contributed to the number of records for the overall summary (i.e., "All data" row) only after their cross over in the tabular subject count data.

Abbreviations: F, *F508del CFTR* variant; G, *gating CFTR* variant; M, metabolite; MF, minimal function *CFTR* variant; n, number of subjects; RF, residual function *CFTR* variant; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor

Table 136. M1-TEZ: Baseline Continuous Covariate Summary After All Data Exclusions

Study	n	Mean	Median	SD	Min	Q25	Q75	Max
Age (years)								
121-001	9	34.4	34.0	12.9	21.0	22.0	41.0	57.0
121-101	66	32.2	31.0	10.2	18.0	24.0	38.0	64.0
121-102	196	30.8	30.3	10.5	12.4	22.8	37.4	61.7
121-103	284	33.3	32.6	12.6	12.2	24.3	41.5	71.2
121-105, Part A1	17	9.55	9.59	1.27	6.41	9.14	10.6	11.0
121-105, Part B1	78	9.05	9.30	1.74	6.17	7.61	10.4	12.0
<i>All data</i>	629	29.2	28.9	13.4	6.17	18.8	38.8	71.2
Weight (kg)								
121-001	9	67.3	73.0	11.7	51.0	60.0	74.0	86.0
121-101	66	65.5	63.0	13.0	45.4	56.0	73.5	104
121-102	196	65.1	63.0	13.3	33.0	56.2	73.0	130
121-103	284	66.6	65.0	13.9	34.0	56.0	75.0	122
121-105, Part A1	17	32.8	34.0	6.32	18.6	29.0	37.8	43.7
121-105, Part B1	78	30.2	28.9	7.48	19.3	24.0	35.2	54.0
<i>All data</i>	629	61.4	62.0	17.6	19.3	52.0	73.0	130

Source: Table 12, T271 report

Note: 21 subjects crossed over to different studies or parts of a study and contributed to the number of records for the overall summary (i.e., "All data" row) only after their cross over in the tabular subject count data.

Abbreviations: M, metabolite; max, maximum; min, minimum; n, number of subjects; Q25, first quartile; Q75, third quartile; SD, standard deviation; TEZ, tezacaftor

Table 137. M1-TEZ: Final Model: PK Parameter Estimates

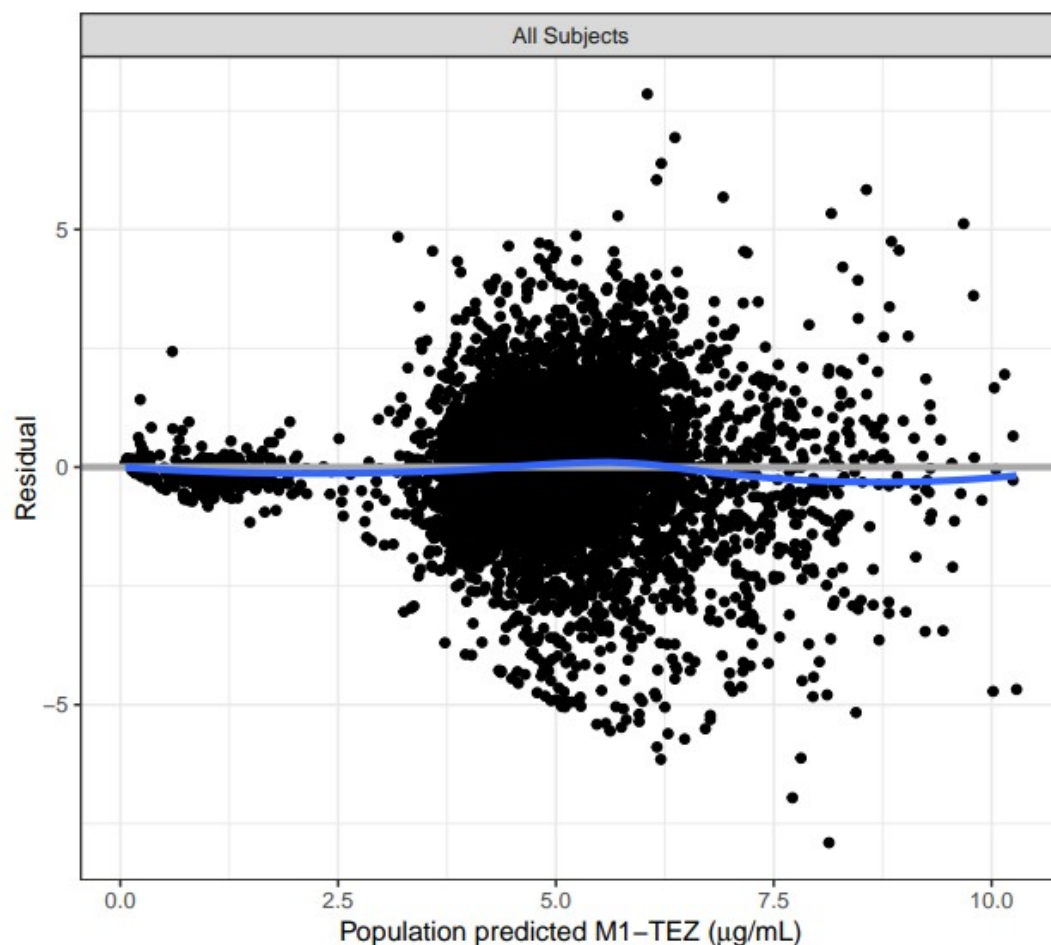
			Estimate	%RSE	95% CI	SHK (%)
Structural model parameters						
CL/F (L/hr)	θ_1	Apparent clearance	0.410	1.24	0.400, 0.420	-
Vc/F (L)	θ_2	Apparent central volume	3.70	15.3	2.59, 4.81	-
Q/F (L/hr)	θ_3	Apparent intercompartmental clearance	4.96	11.0	3.89, 6.02	-
Vp/F (L)	θ_4	Apparent peripheral volume	15.1	5.27	13.5, 16.7	-
FM1	-	Fraction of TEZ converted to M1-TEZ	0.8	-	FIXED	-
Covariate effect parameters						
CLWTCUT (kg)	θ_5	Weight cut point for CL/F effect	37.6	0.146	37.5, 37.7	-
CL _{WT} [WT≤CLWTCUT]	θ_6	Weight effect on CL/F for WT≤CLWTCUT	1.02	6.93	0.882, 1.16	-
CL _{WT} [WT>CLWTCUT]	θ_7	Weight effect on CL/F for WT>CLWTCUT	0.750	-	FIXED	-
Vc _{WT}	θ_8	Weight effect on Vc/F	1.00	-	FIXED	-
Q _{WT}	θ_9	Weight effect on Q/F	0.750	-	FIXED	-
Vp _{WT}	θ_{10}	Weight effect on Vp/F	1.00	-	FIXED	-
CL _{GTN}	θ_{11}	Combined genotype (F/G, F/RF, F/other, and TCR/any) effect on CL/F	0.884	2.28	0.844, 0.923	-
Interindividual variance parameters						
BC for IIV-CL/F	θ_{12}	Box-Cox transformation factor	1.23	18.6	0.784, 1.69	-
IIV-BC-CL/F	$\Omega_{(1,1)}$	Variance of Box-Cox transformed CL/F	0.0594	8.39	0.0496, 0.0692	4.84

Source: Table 16, T271 report

Abbreviations: CI, confidence interval; Corr, Correlation coefficient; CV, coefficient of variation; F, *F508del CFTR* variant; G, gating *CFTR* variant; IIV, interindividual variability; M, metabolite; PK, pharmacokinetic; %RSE, percent relative standard error; RF, residual function *CFTR* variant; SD, standard deviation; SE, standard error; SHK, shrinkage; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor; WT, weight

Report T271/Figures

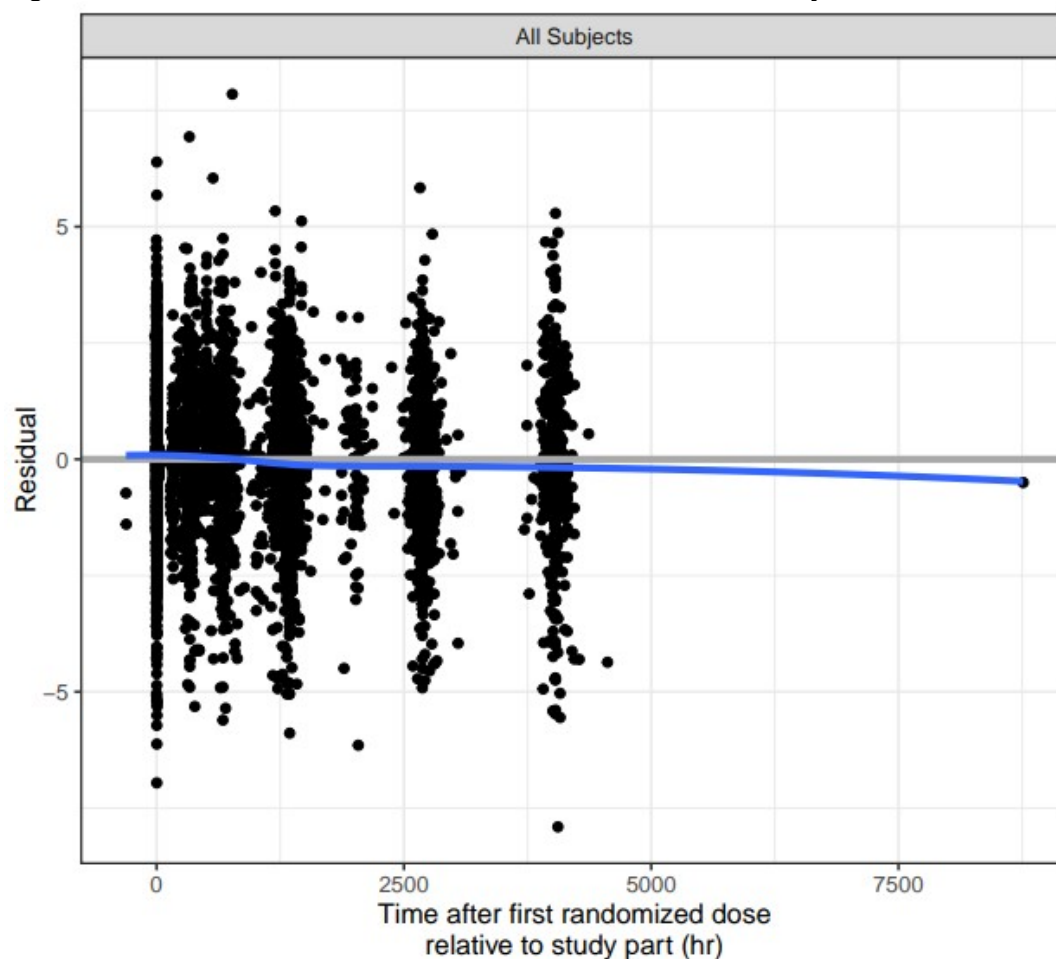
Figure 53. M1-TEZ: Final Model: Residuals Versus Population Predicted Concentration: All Subjects



Source: Figure S114, T271 report

Note: Residuals are plotted vs. population predictions. Values are indicated by black circles with a LOESS smooth trend line (solid blue) through the data. A solid gray line at $y = 0$ is included as a reference.

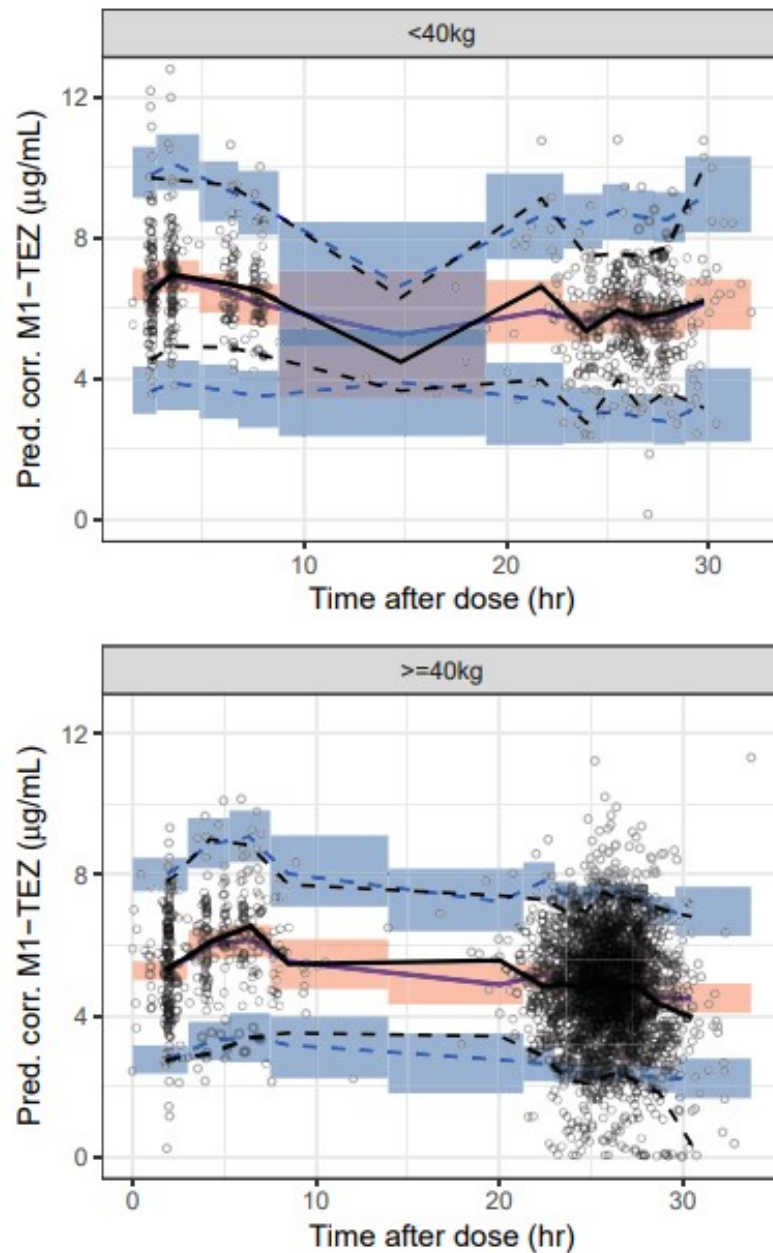
Abbreviations: LOESS, locally weighted scatterplot smoothing; M, metabolite; TEZ, tezacaftor

Figure 54. M1-TEZ: Final Model: Residuals Versus Time: All Subjects

Source: Figure S118, T271 report

Note: Residuals are plotted vs. time. Values are indicated by black circles with a LOESS smooth trend line (solid blue) through the data. A solid gray line at $y = 0$ is included as a reference.

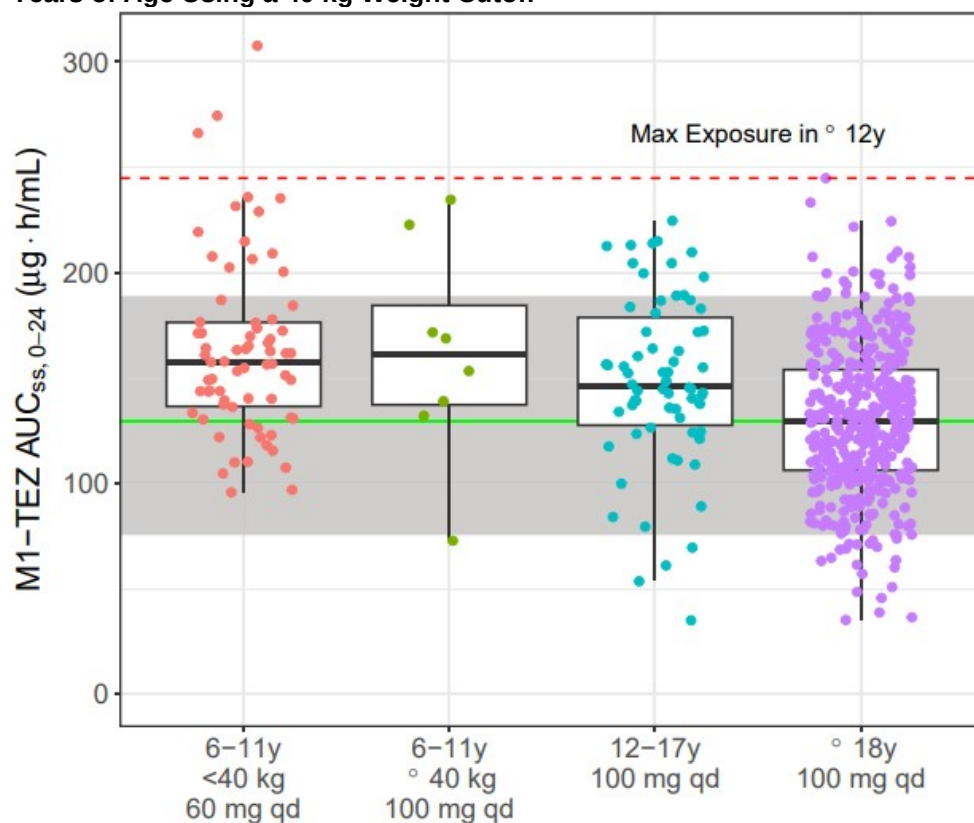
Abbreviations: hr, hour; LOESS, locally weighted scatterplot smoothing; M, metabolite; TEZ, tezacaftor

Figure 55. M1-TEZ: Final Model: Prediction-Corrected VPC: Stratified by Weight Group

Source: Figure 21, T271 report

Note: 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).

Abbreviations: hr, hour; M, metabolite; Pred. corr., prediction-corrected; TEZ, tezacaftor; VPC, visual predictive check

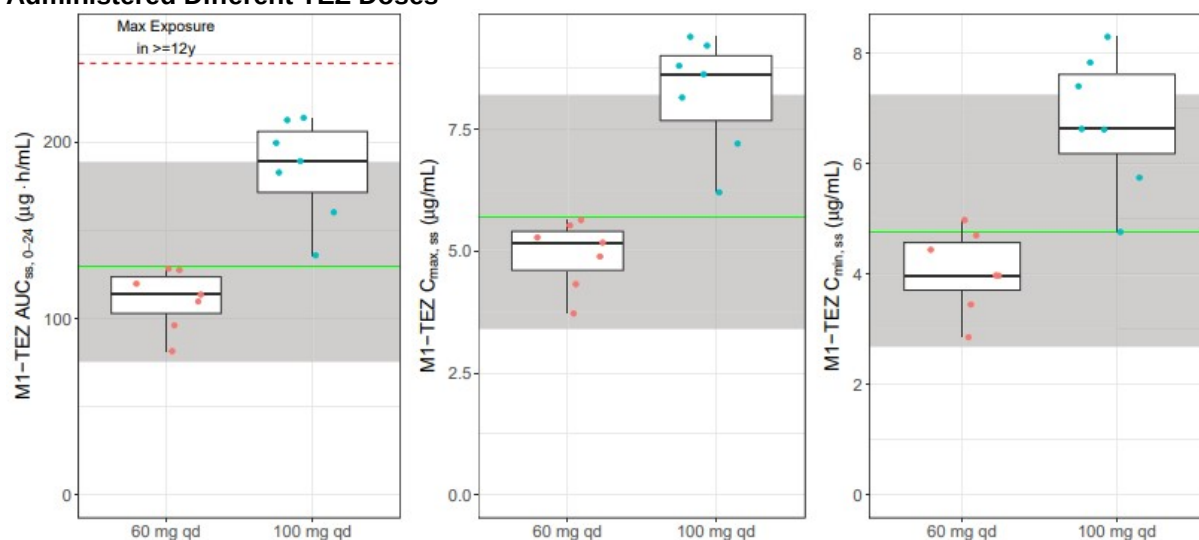
Figure 56. M1-TEZ: Individual Predicted AUC_{ss} Versus Age Group: TEZ Dosed in 6 Through 11 Years of Age Using a 40 kg Weight Cutoff

Source: Figure 23, T271 report

Note: The points represent individual predicted exposures under different dosing regimens: TEZ 100 mg qd for adults, adolescents (12-17y), and 6 through 11 years subjects weighing ≥ 40 kg; TEZ 60 mg qd for 6 through 11 years subjects weighing < 40 kg. The predictions were made using EBEs from the final population PK model. The individual points are summarized 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 $1.5 \times \text{IQR}$. The green horizontal line represents the median of the adult values, and the gray shaded area indicates the 5th and 95th percentiles. The adult reference exposures were derived from subjects in Studies 121-102 and 121-103. Subjects in the 12-17y age group are from Studies 121-102 and 121-103, and the 6 through 11 years subjects are from Part B1 of Study 121-105. The dashed red line indicates the maximum EBE simulated exposure in subjects ≥ 12 y from Studies 121-102 and 121-103.

Abbreviations: AUC_{ss}, area under the plasma drug concentration-time curve at steady state; AUC_{0-24,ss}, area under the plasma drug concentration-time curve at steady state from 0 to 24 hours; EBE, empirical Bayes estimates; IQR, interquartile range; M, metabolite; max, maximum; PK, pharmacokinetic; qd, once daily; TEZ, tezacaftor; y, year

Figure 57. M1-TEZ: Individual Predicted Exposures in Subjects ≥ 12 Years of Age and < 40 kg Administered Different TEZ Doses

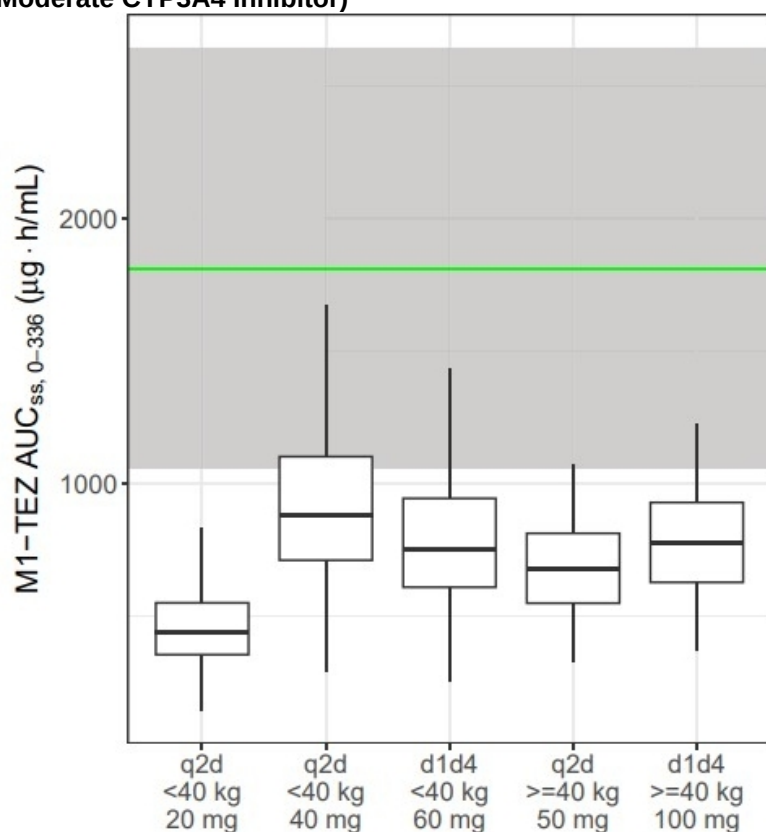


Source: Figure S167, T271 report.

Note: The points represent individual predicted exposures under different TEZ dosing regimens for subjects ≥ 12 y and < 40 kg. The individual points are summarized 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 $1.5 \times \text{IQR}$. The green horizontal line represents the median of individual predicted adult values and the gray shaded area indicates the 5th and 95th percentiles. Individual predictions were made using EBEs from the final population PK model. The adult reference exposures were derived from subjects in Studies 121-102 and 121-103. The dashed red line indicates the maximum EBE simulated exposure in subjects ≥ 12 y from Studies 121-102 and 121-103.

Abbreviations: AUC_{0-24,ss}, area under the plasma drug concentration-time curve at steady state from 0 to 24 hours; C_{max,ss}, maximum plasma concentration at steady state; C_{min,ss}, minimum plasma concentration at steady state; EBE, empirical Bayes estimates; IQR, interquartile range; M, metabolite; max, maximum; PK, pharmacokinetic; qd, once daily; TEZ, tezacaftor; y, year

Figure 58. M1-TEZ: Population Simulated AUC_{ss} in Children 6 Through 11 Years of Age Following Different TEZ Dosing Regimens With a 40 kg Cutoff and Coadministered With Fluconazole (Moderate CYP3A4 Inhibitor)

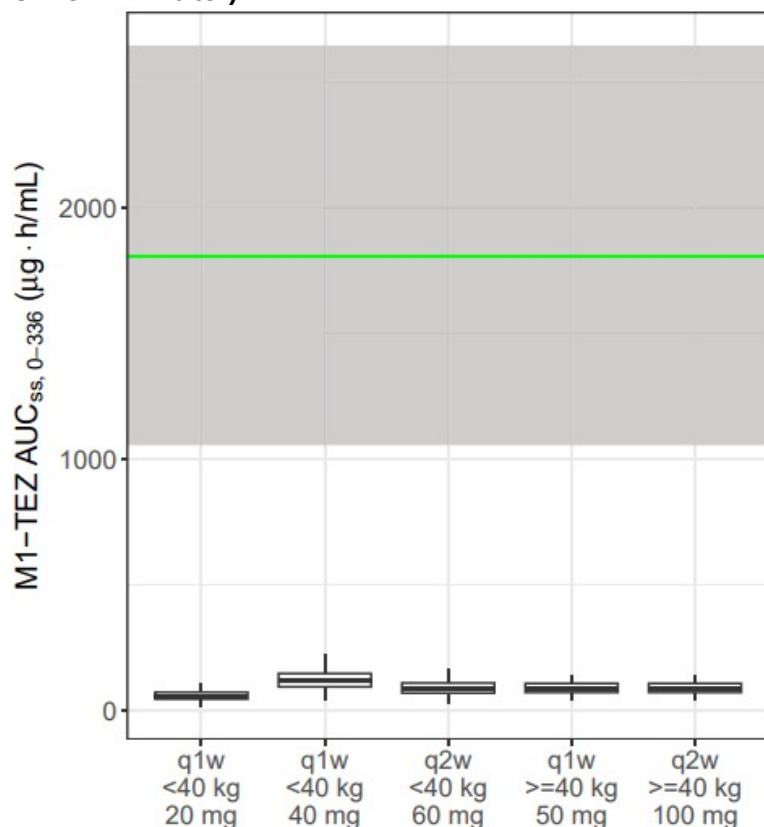


Source: Figure S177, T271 report

Note: The following TEZ regimens were evaluated in the population simulations. For subjects weighing <40 kg: 20 mg q2d, 40 mg q2d, or 60 mg d1d4. For subjects weighing $\geq$ 40 kg: 50 mg q2d or 100 mg d1d4. The population simulated exposures are summarized 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 $1.5 \times \text{IQR}$. The green horizontal line represents the median of individual predicted adult exposures and the gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from subjects in Studies 121-102 and 121-103.

Abbreviations: AUC_{ss} , area under the plasma drug concentration-time curve at steady state; $AUC_{0-336,ss}$, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; CYP, cytochrome P450; d1d4, Day 1 and 4 weekly; IQR, interquartile range; M, metabolite; q2d, every other day; TEZ, tezacaftor

Figure 59. M1-TEZ: Population Simulated AUC_{ss} in Children 6 Through 11 Years of Age Following Different TEZ Dosing Regimens With a 40 kg Cutoff and Coadministered With Itraconazole (Strong CYP3A4 Inhibitor)



Source: Figure S189, T271 report.

Note: The following TEZ regimens were evaluated in the population simulations. For subjects weighing <40 kg: 20 mg q1w, 40 mg q1w, or 60 mg q2w. For subjects weighing ≥40 kg: 50 mg q1w or 100 mg q2w. The population simulated exposures are summarized 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×IQR. The green horizontal line represents the median of individual predicted adult exposures and the gray shaded area indicates the 5th and 95th percentiles. Adult reference exposures were derived from subjects in Studies 121-102 and 121-103. Abbreviations: AUC_{ss}, area under the plasma drug concentration-time curve at steady state; AUC_{0-336,ss}, area under the plasma drug concentration-time curve at steady state from 0 to 336 hours; CYP, cytochrome P450; QR, interquartile range; M, metabolite; q1w, every week; q2w, every other week; TEZ, tezacaftor

The FDA's Assessment

The Applicant's population PK analysis is considered acceptable for the purpose of supporting analyses objectives.

14.5.1.4. D-IVA Population PK Analysis (Report T406)

Executive Summary

The FDA's Assessment

In general, the Applicant's population PK analyses are considered acceptable for the purpose of supporting analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Population Pharmacokinetic Assessment Summary

Table 138. Data Structure of D-IVA Population PK Analysis, Report T406

General Information	Details
Objectives of PPK analysis	• To characterize the PK disposition of D-IVA in subjects 6 years and older using population methodology; • To quantify the sources of variability; • To summarize predicted area under the curve (AUC) exposures for D-IVA at steady state from the time of dosing (0 h) to 24h post dose (AUC_{0-24h}) from the studied dosing regimen for phase 3 subjects due to sparse PK sampling; • To evaluate if a 40 kg weight cutoff for all studied ages resulted in similar exposures to adults; – To simulate D-IVA and its metabolites exposures for a VNZ/TEZ/D-IVA TC dosing regimen with a 40 kg weight cutoff in children 6 through 11 years with CF; – To simulate D-IVA and its metabolites exposures for a VNZ/TEZ/D-IVA TC dosing regimen with a 40 kg weight cutoff in adolescents 12 through 17 years with CF; • To simulate exposures of D-IVA and its metabolites to inform dosing and/or weight bounds for weight cutoffs other than 40 kg for subjects ≥ 6 years of age; • To simulate exposures of D-IVA for different dosing regimens to inform dosing for CF subjects with moderate hepatic impairment (MHI); • To simulate exposures of D-IVA for different dosing regimens to inform dosing for children 6 through 11 years with CF coadministered a strong or moderate cytochrome P4503A4 (CYP3A4) inhibitor
Study included	VX18-121-101, VX20-121-102, VX20-121-103, VX21-121-105, VX17-561-001, VX18-561-101, VX16-770-018
D-IVA dose(s) included	25 mg, 50 mg, 100 mg, 125 mg, 150 mg, 250 mg QD (Table 5.4, Report T406)
Population included	Healthy, CF (F/MF, F/F, F/G, F/RF, TCR, and F/other genotypes)
<i>Population characteristics (Table 7.1, Report T406)</i>	
General	• Age: 29.8 yr (range: 6.17 – 71.2, 0.28% subj ≥ 65 yr) • Weight: 63 kg (range: 19.3 – 130) • N=408 (57.4%) male • N=670 (94.2%) White • N=24 (3.3%) Non-white • N=17 (2.4%) Not reported (imputed as White)
Organ impairment	• Hepatic (Child-Pugh, NCI, etc.): not reported Renal (CrCL, etc.): • N=577 (81.2%) normal (≥ 90 mL/min/1.73 m²) • N=132 (18.6%) mild impairment (60 to <90 mL/min/1.73 m²) • N=2 (0.3%) moderate impairment (30 to <60 mL/min/1.73 m²)
Pediatrics (if any)	• Age 9.30 (range: 6.17 – 12.0, 12.4% subj ≤ 12 yr) • Weight 28.9 kg (range: 19.3 – 54.0)
No. of subjects, PK samples, and BLQ	711 subjects, 5811 PK samples, 236 (3.9%) post-first dose BLQ PK samples (Section 7.1.1, Report T406)

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General Information	Details
<u>Sampling schedule</u>	
Rich sampling	• Study VX18-121-101: – Day 1: predose, 1, 2, 4, 6, 8, and 24 hours after dosing. – Days 8, 15, and 29: predose. – Day 47: predose. • Study VX17-561-001: – Days 1, 6, 11: predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours (Days 2, 7, 12) postdose; – Days 3, 4, 8, 9, 13, 14: predose; – Days 5, 10: predose and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose; – Day 15: predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 16), 36, 48 (Day 17), and 72 hours (Day 18) postdose • Study VX18-561-101: – Day 1: Predose, 4 hours postdose; – Day 15, Weeks 4, 8, and 12: Predose; In a subset of subjects (up to approximately 20 subjects), additional samples will be collected at the Week 4 visit at 1, 2, 4, and 6 hours postdose • Study VX16-770-018: – Days 1, 8, and 15: Predose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose
In ITT population	• Trial VX20-121-102: – Day 1: Predose and 2 hours post dose. – Weeks 4, 16, and 24: predose. – Week 8: Predose and 4 hours postdose for all subjects <18 years of age. Predose, 4, 5, 6, and 7 hours postdose for up to approximately 40 subjects ≥18 years of age. Predose and 2 hours postdose for all other subjects ≥18 years of age. • Trial VX20-121-103: – Day 1: Predose and 2 hours post dose. – Day 15: Predose. – Weeks 4, 8, 16 and 24: Predose. • Trial VX21-121-105: – <u>Part A1</u>: Day 1: predose and 2 hours postdose. Days 8 and 15: predose. Day 22: predose, 2.5, 3.5, 6.5, 8 h postdose. – <u>Part B1</u>: Day 1: predose and 2 hours postdose. Day 15 and Week 4: predose. Week 8: predose, 2.5 and 3.5 hours postdose for all subjects; for a minimum of 12 subjects who weigh ≥17 kg at screening additional 6.5 and 8 hours postdose samples were collected. Weeks 12 and 16: predose.

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General Information	Details
<i>Covariates evaluated</i>	
Static	Baseline age, baseline weight, race, sex, genotype, ALT, eGFR, formulation (Section 6.3.5.3, Report T406)
Time-varying	NA

Source: Reviewer's summary

Abbreviations: ALT, alanine aminotransferase; AUC, area under the plasma drug concentration-time curve; AUC₀₋₂₄, area under the plasma drug concentration-time curve from 0 to 24 hours; BLQ, below the limit of quantification; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; eGFR, estimated glomerular filtration rate; F, *F508del CFTR* variant; G, gating *CFTR* variant; ITT, intent-to-treat; MF, minimal function *CFTR* variant; NA, not applicable; No., number; PK, pharmacokinetic; PPK, population pharmacokinetic; RF, residual function *CFTR* variant; Subj., subject; TC, triple combination; TCR, triple combination responsive *CFTR* variant; yr, year

Table 139. Model Evaluation of D-IVA Population PK Analysis

Final Model	Summary	Acceptability (FDA's Comments)
Software and Version	NONMEM®, Version 7.4.4	Acceptable
Estimation Algorithm	First-order conditional estimation with η - ϵ interaction (FOCE-I)	Acceptable
Model Structure	Linear, 1-compartment popPK model with 7 transit compartments and first-order absorption	Acceptable
Model Parameter Estimates	Table 7.3, Report T406	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Except for the TCR genotype and additive residual variances, all RSE's (fixed and random effects) were <30%; shrinkage for IIV on CL was <10%.	
BLQ for Parameter Accuracy	BLQ observations (3.9%) were excluded. No impact of BLQ on PK objectives given the low percentage of BLQ observations	Acceptable
GOF, VPC	Section 7.1.6, Report T406: - Diagnostics plots (Figures 11.33 to 11.52) indicated that the final model adequately described all the data with no discernible systematic bias, including that for the 6 through 11 years age group. Section 7.1.7, Report T406: - pcVPCs indicated that the final model captured the observed data reasonably well overall (Figure 7.6). The pcVPCs stratified by age group (Figure 7.7), weight group (Figure 7.8), and genotype (Figure 7.9) showed that the model adequately captured both the central tendency and the variability of the steady-state data.	There are missing data points in Figure 11.36. The Applicant provided clarification and/or correction to 11.36 in IR dated Aug 25, 2024. The update figures are acceptable.
Significant Covariates and Clinical Relevance	Body weight was the only covariate that had a clinically meaningful impact on D- IVA disposition.	Acceptable

Final Model	Summary	Acceptability (FDA's Comments)
Analysis Based on Simulation (optional)	• Simulations based on the final population PK model for D-IVA supported the justification of candidate weight-based dosing regimens of VNZ/TEZ/D-IVA TC in CF patients ≥ 6 years of age with a 40 kg weight cutoff (Table 11.7; and Figures 11.136, 11.139, 11.148, 11.165, Report T406). • Additional weight cutoffs were also evaluated: – 35 kg: Table 11.11; and Figures 11.142 and 11.168, Report T406 – 30 kg: Table 11.12; and Figures 11.145 and 11.171, Report T406. • Simulations based on the final population PK models showed exposures of D-IVA in adult CF subjects with MHI and no TEZ dose adjustment were in the same range as subjects without MHI (Figure 11.174, Report T406). This result supports that, based on PK, no D-IVA dose adjustment was needed for adult CF subjects with MHI. • Simulations based on the final population PK models for D- supported the justification of VNZ/TEZ/D-IVA dose adjustment regimens with reduced daily dose and/or dosing frequency for children 6 through 11 years with CF in the presence of coadministered CYP3A4 inhibitors (Figures 11.177, 11.181, 11.185 and 11.189, Report T406).	Acceptable

Source: Reviewer's summary

Abbreviations: BLQ, below the limit of quantification; CF, cystic fibrosis; CYP, cytochrome P450; D-IVA, deutivacaftor; GOF, goodness-of-fit; IIV, interindividual variability; MHI, moderate hepatic impairment; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic; popPK, population pharmacokinetic; RSE, relative standard error; TC, triple combination; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor; VNZ, vanzacaftor; VPC, visual predictive check

Table 140. Labeling Statements Supported by D-IVA Population PK Analysis

Labeling Language	Description	Acceptability (FDA's Comments)
12.3 PK	• [REDACTED] • [REDACTED] • [REDACTED] • [REDACTED]	(b) (4) Acceptable

Source: Reviewer's summary

Abbreviations: CF, cystic fibrosis; eGFR, estimated glomerular filtration rate; N, number of subjects; PK, pharmacokinetic

Report T406/Tables

Table 141. Summary of Covariates in the D-IVA PK Analysis Dataset

Study	770-018 Part D	561-001	561-101	121-101	121-102	121-103	121-105 Part A1	121-105 Part B1	Overall
N	17	9	64	66	195	283	17	78	711
Male (%)	7 (41.2)	9 (100)	42 (65.6)	43 (65.2)	115 (59)	148 (52.3)	10 (58.8)	44 (56.4)	408 (57.4)
Female (%)	10 (58.8)	0 (0)	22 (34.4)	23 (34.8)	80 (41)	135 (47.7)	7 (41.2)	34 (43.6)	303 (42.6)
Healthy (%)	17 (100)	9 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	26 (3.7)
CF, F/MF (%)	0 (0)	0 (0)	0 (0)	48 (72.7)	195 (100)	0 (0)	3 (17.6)	25 (32.1)	265 (37.3)
CF, F/F (%)	0 (0)	0 (0)	0 (0)	18 (27.3)	0 (0)	221 (78.1)	9 (52.9)	37 (47.4)	277 (39)
CF, F/G (%)	0 (0)	0 (0)	64 (100)	0 (0)	0 (0)	19 (6.7)	0 (0)	3 (3.8)	85 (12)
CF, F/RF and F/other (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	23 (8.1)	0 (0)	3 (3.8)	26 (3.7)
CF,TCR/any (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	20 (7.1)	5 (29.4)	10 (12.8)	32 (4.5)
D-IVA Monotherapy (%)	17 (100)	9 (100)	64 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	89 (12.5)
VX-121/TEZ/D-IVA (%)	0 (0)	0 (0)	0 (0)	66 (100)	195 (100)	283 (100)	17 (100)	78 (100)	622 (87.5)
White (%)	9 (52.9)	5 (55.6)	64 (100)	63 (95.5)	190 (97.4)	269 (95.1)	17 (100)	71 (91)	670 (94.2)
Black or African American (%)	8 (47.1)	4 (44.4)	0 (0)	1 (1.5)	4 (2.1)	0 (0)	0 (0)	1 (1.3)	18 (2.5)
Asian (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)	1 (0.4)	0 (0)	0 (0)	2 (0.3)
Multiple (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.7)	0 (0)	1 (1.3)	3 (0.4)
Other (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)	0 (0)	1 (0.1)
Not reported (%)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)	10 (3.5)	0 (0)	5 (6.4)	17 (2.4)
Age, year (median [min, max])	34 [20, 51]	39 [27, 52]	32 [18, 67]	31 [18, 64]	30.7 [12.4, 61.7]	32.6 [12.2, 71.2]	9.59 [6.41, 11]	9.3 [6.17, 12]	29.8 [6.17, 71.2]
Age, year (mean [SD])	33.8 [9.27]	39.6 [8.34]	33 [10.3]	32.2 [10.2]	30.8 [10.5]	33.3 [12.6]	9.55 [1.27]	9.05 [1.74]	29.8 [13.1]
Body weight, kg (median [min, max])	74.4 [57, 95.8]	93.4 [73.4, 113]	74 [50, 116]	63 [45.4, 104]	63 [33, 130]	65 [34, 122]	34 [18.6, 43.7]	28.9 [19.3, 54]	63 [19.3, 130]
Body weight, kg (mean [SD])	74 [10.4]	91.2 [12.9]	75.6 [14.4]	65.5 [13]	65.1 [13.3]	66.5 [13.9]	32.8 [6.32]	30.2 [7.48]	63.2 [18]
eGFR, mL/min/1.73m2 (median [min, max])	107 [90.9, 134]	80.4 [65, 103]	107 [63.8, 179]	110 [74.3, 163]	109 [62, 199]	108 [51, 228]	137 [90, 173]	138 [103, 195]	111 [51, 228]
eGFR, mL/min/1.73m2 (mean [SD])	107 [12.3]	83.4 [11.1]	109 [23.1]	112 [21.3]	112 [26.8]	110 [25.3]	136 [24.1]	141 [23.7]	114 [26.6]
eGFR, Normal (%)	17 (100)	2 (22.2)	49 (76.6)	55 (83.3)	155 (79.5)	221 (78.1)	17 (100)	78 (100)	577 (81.2)
eGFR, Mild renal impairment (%)	0 (0)	7 (77.8)	15 (23.4)	11 (16.7)	40 (20.5)	60 (21.2)	0 (0)	0 (0)	132 (18.6)
eGFR, Moderate renal impairment (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (0.7)	0 (0)	0 (0)	2 (0.3)
ALT, U/L (median [min, max])	14 [9, 32]	20 [11, 29]	24.5 [7, 189]	19 [7, 96]	26 [9, 208]	26 [7, 388]	24 [10, 35]	20.5 [8, 74]	24 [7, 388]
ALT, U/L (mean [SD])	17.9 [6.98]	19.9 [6.17]	35.5 [33.1]	22.2 [15.8]	32.1 [22.6]	33.8 [30.1]	22.4 [7.95]	23.2 [11.8]	30.7 [25.7]
AST, U/L (median [min, max])	21 [16, 32]	21 [16, 25]	23 [9, 482]	19.5 [11, 77]	23 [11, 231]	24 [12, 143]	28 [21, 37]	28 [18, 64]	24 [9, 482]
AST, U/L (mean [SD])	21.1 [4.5]	20.2 [2.68]	35.5 [60.4]	22.5 [11.8]	28 [19.2]	27.2 [14.1]	27.3 [4.77]	29.3 [7.65]	27.8 [23.1]

Source: Table 7.1, T406 report.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate transaminase; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; eGFR, estimated glomerular filtration rate; F, *F508del CFTR* variant; G, gating *CFTR* variant; max, maximum; min, minimum; PK, pharmacokinetic; RF, residual function *CFTR* variant; SD, standard deviation; TCR, triple combination responsive *CFTR* variant; VX-121 [VNZ], vanzacaftor

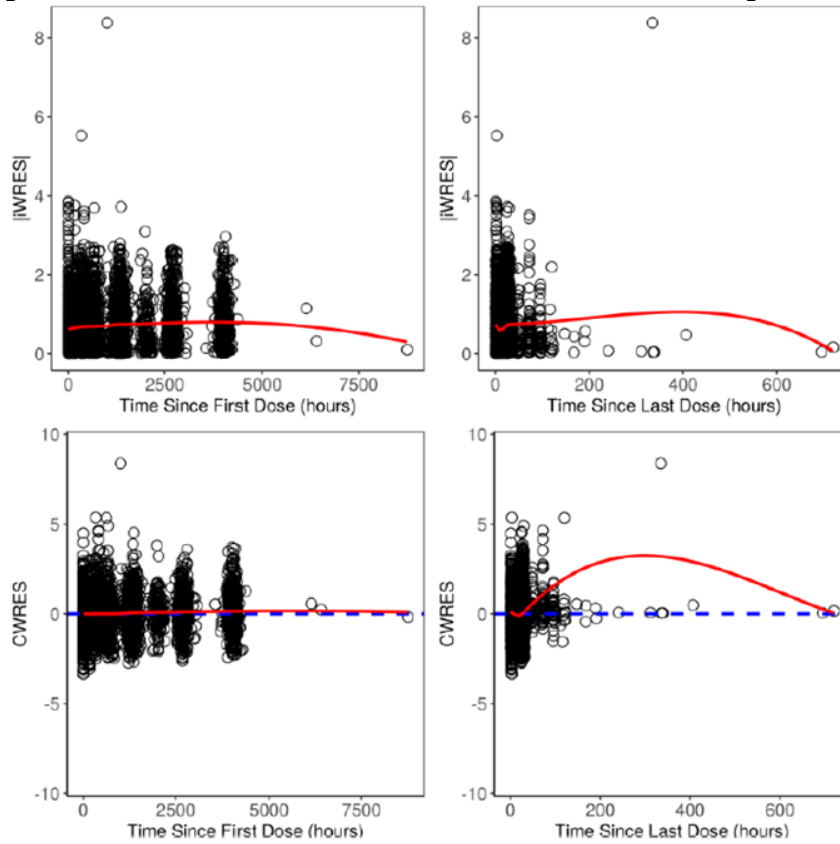
Table 142. D-IVA Population Pharmacokinetic Final Model Parameter Estimates (Model 517)

Parameter (unit)	Typical Estimate (%RSE)	95% Confidence Interval
Structural model parameters		
CL/F, Central clearance (L/h)	7.03 (1.05)	[6.75,7.31]
V/F, Central volume (L)	183 (0.679)	[170,196]
KA, Absorption rate (1/h)	1.64 (23.9)	[1.3,2.06]
KTR, Transit rate (1/h)	4.98 (2.84)	[4.56,5.45]
F1, Bioavailability (fixed)	1	
Covariate effect parameters		
Weight exponent on CL/F	0.75	
Weight saturation on CL/F (kg)	38.2 (0.391)	[37.9,38.5]
Weight exponent on V/F (fixed)	1	
Weight saturation on V/F (kg)	50 (0.0734)	[49.9,50.1]
Effect of monotherapy on F1 (fixed)	0.787	
Effect of TCR genotype on CL/F	0.84 (32.8)	[0.752,0.94]
Effect of non-white race on CL/F	1.25 (29.8)	[1.1,1.43]
Effect of low-load drug tablet on F1	1.33 (13.8)	[1.23,1.44]
Effect of female gender on V/F	0.797 (15.2)	[0.745,0.853]
Interindividual variance parameters		
IIV CL/F [%CV]	0.144 [38] (7.64)	[0.123,0.166]
IIV V/F [%CV]	0.066 [25.7] (21)	[0.0388,0.0932]
IIV KTR [%CV]	0.211 [45.9] (12.8)	[0.158,0.264]
Residual variance parameters		
Proportional error CF [%CV]	0.139 [37.3] (5.03)	[0.125,0.153]
Additive error CF [SD] (ng/mL)	2810 [53] (57.7)	[-366,5990]
Proportional error HV [%CV]	0.0647 [25.4] (8.41)	[0.0541,0.0754]
Additive error HV [SD] (ng/mL)	9.36 [3.06] (41)	[1.85,16.9]

Source: Table 7.3, T406 report.

Abbreviations: %RSE, percent relative standard error; CF, cystic fibrosis; D-IVA, deutivacaftor; F, *F508del CFTR* variant; G, gating *CFTR* variant; IIV, interindividual variability; MF, minimal function *CFTR* variant; RF, residual function *CFTR* variant; SD, standard deviation; TCR, triple combination responsive *CFTR* variant

Figure 60. D-IVA Final Model: Individual and Conditional Weighted Residuals Versus Time



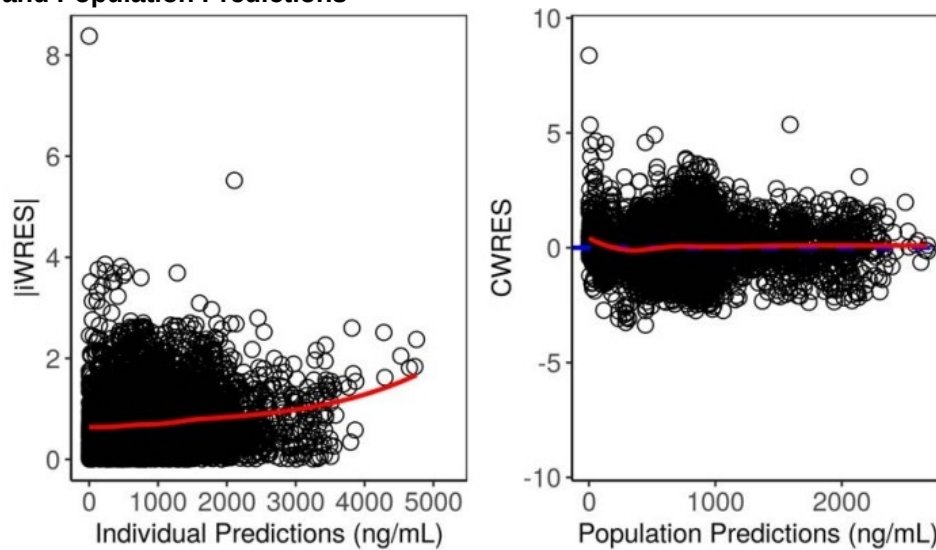
Source: data on file (corresponds to Figure 11.36 of Report T406)

D-IVA: deutivacaftor

Source: Figure 1, IR response dated Aug 23, 2024

Abbreviations: CWRES, conditional weighted residuals; IWRES individual weighted residuals

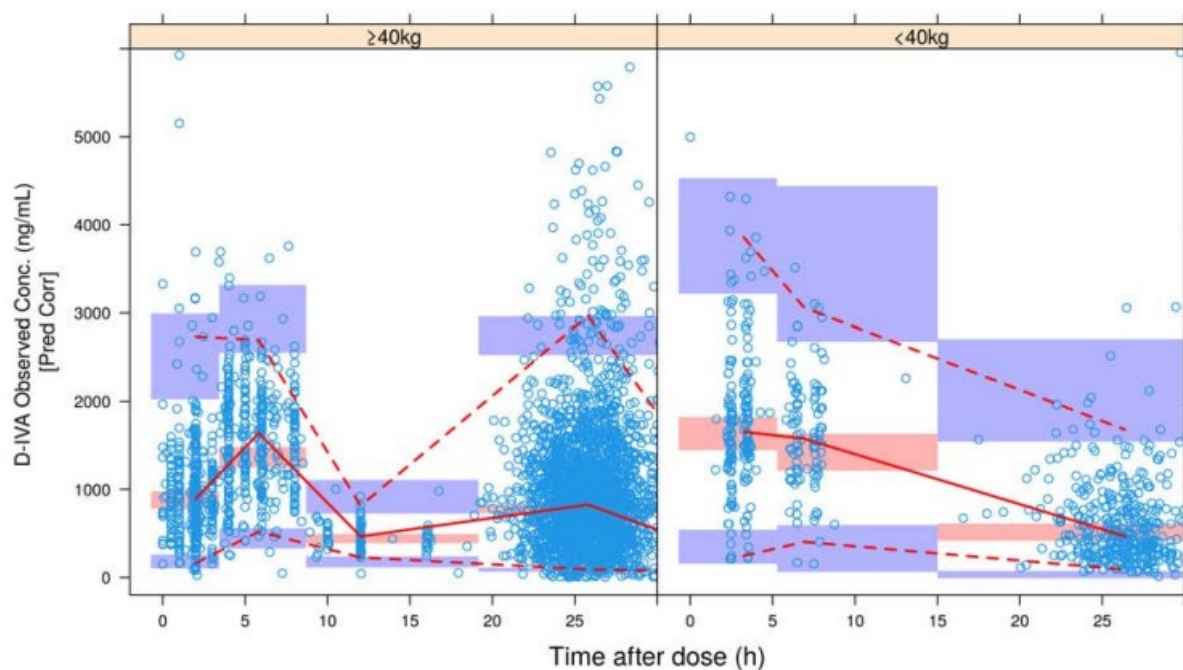
Figure 61. D-IVA Final Model: Individual and Conditional Weighted Residuals Versus Individual and Population Predictions



Source: Figure 11.39, T406 report

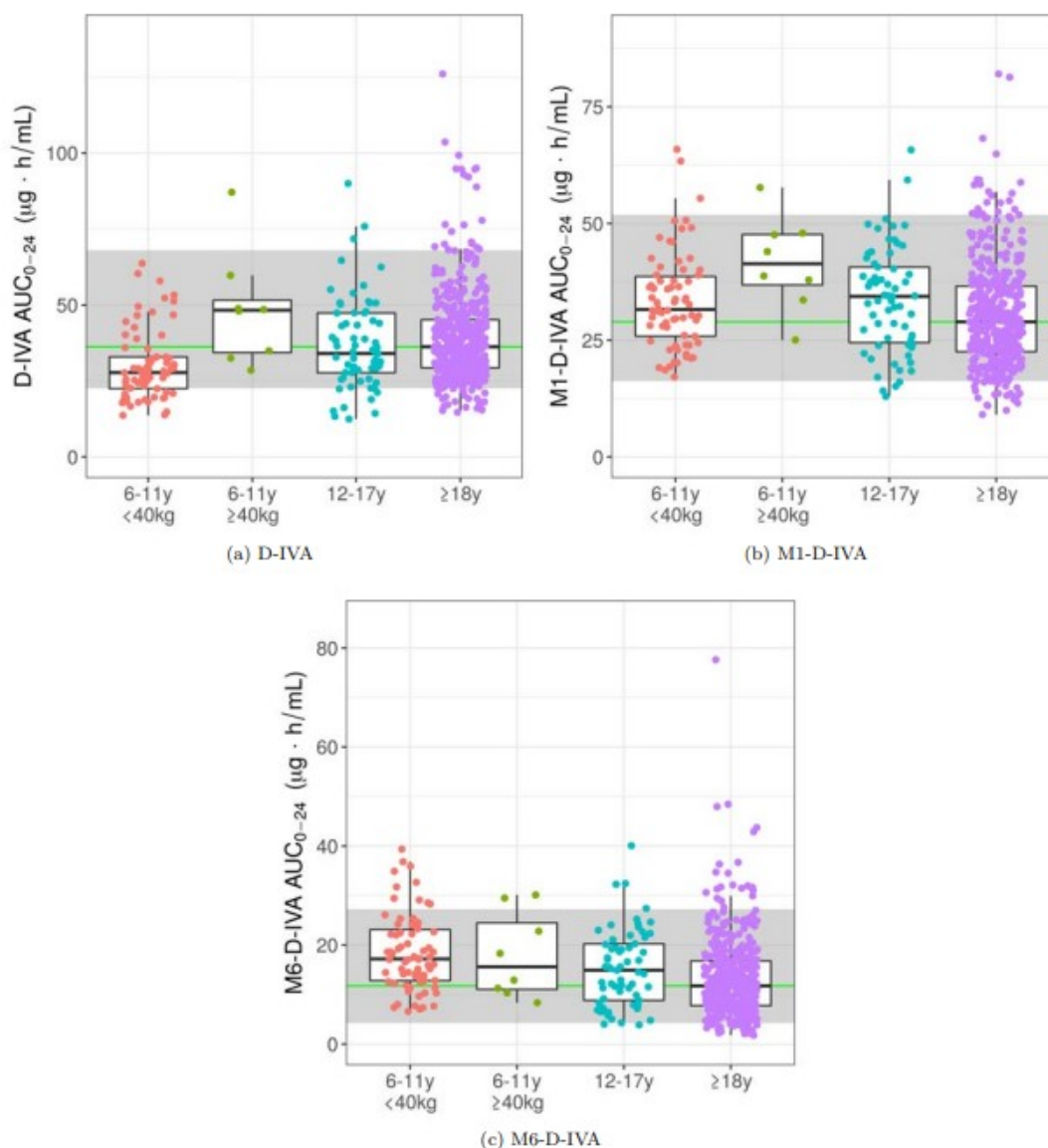
Abbreviations: CWRES, conditional weighted residuals; D-IVA, deutivacaftor; IWRES individual weighted residuals

Figure 62. Steady-State VPCs of the D-IVA Final Population PK Model: Stratified by Weight Group
pcVPC by Weight Group



Source: Figure 7.8, T406 report

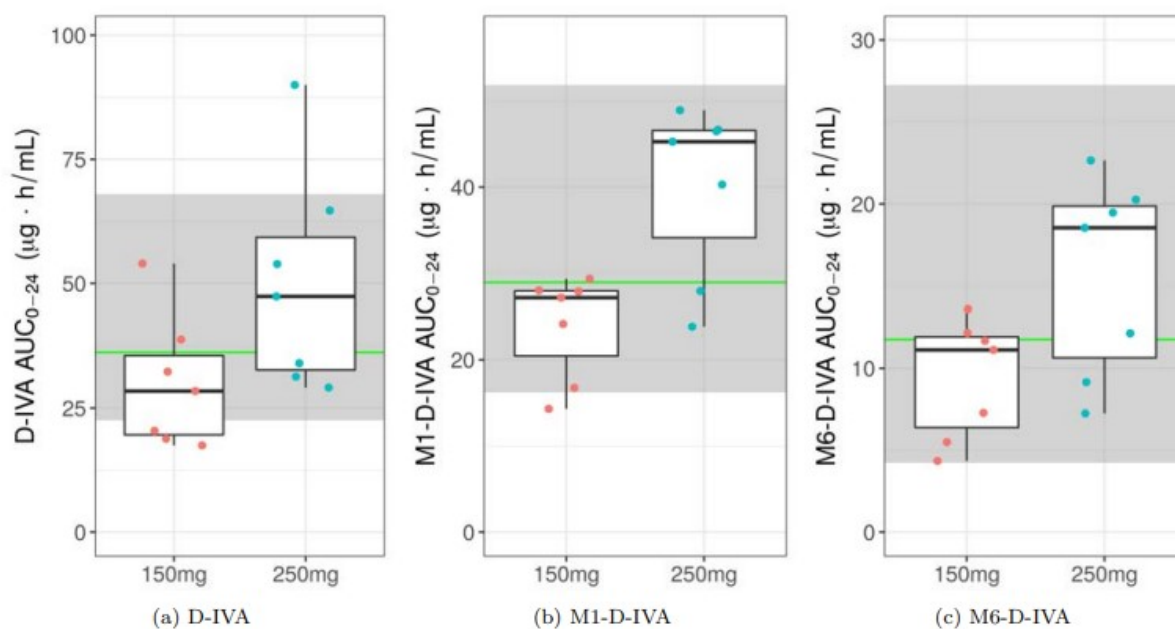
Abbreviations: D-IVA, deutivacaftor; h, hour; pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetic; VPC, visual predictive check

Figure 63. D-IVA, M1-D-IVA, and M6-D-IVA AUC_{0-24h} Simulations by Age and Weight Group

Source: Figure 11.136, T406 report

Abbreviations: AUC_{0-24h} , area under the plasma drug concentration-time curve 0 to 24 hours; D-IVA, deutivacaftor; y, year(s)

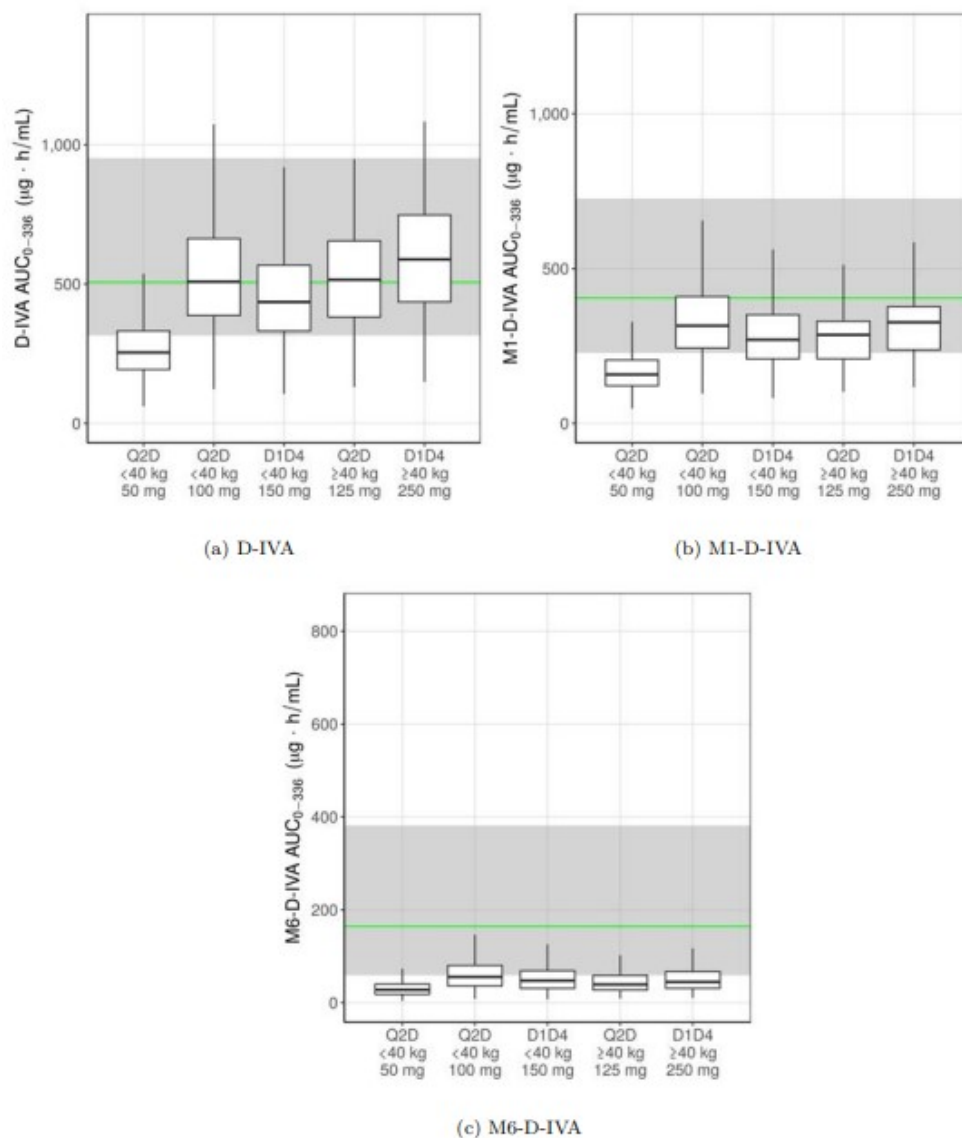
Figure 64. AUC_{0-24h} Simulations for Subjects ≥ 12 Years of Age and < 40 kg Administered D-IVA 150 mg Versus 250 mg QD



Source: Figure 11.148, T406 report

Abbreviations: AUC_{0-24h} , area under the plasma drug concentration-time curve 0 to 24 hours; D-IVA, deutivacaftor; qd, once daily

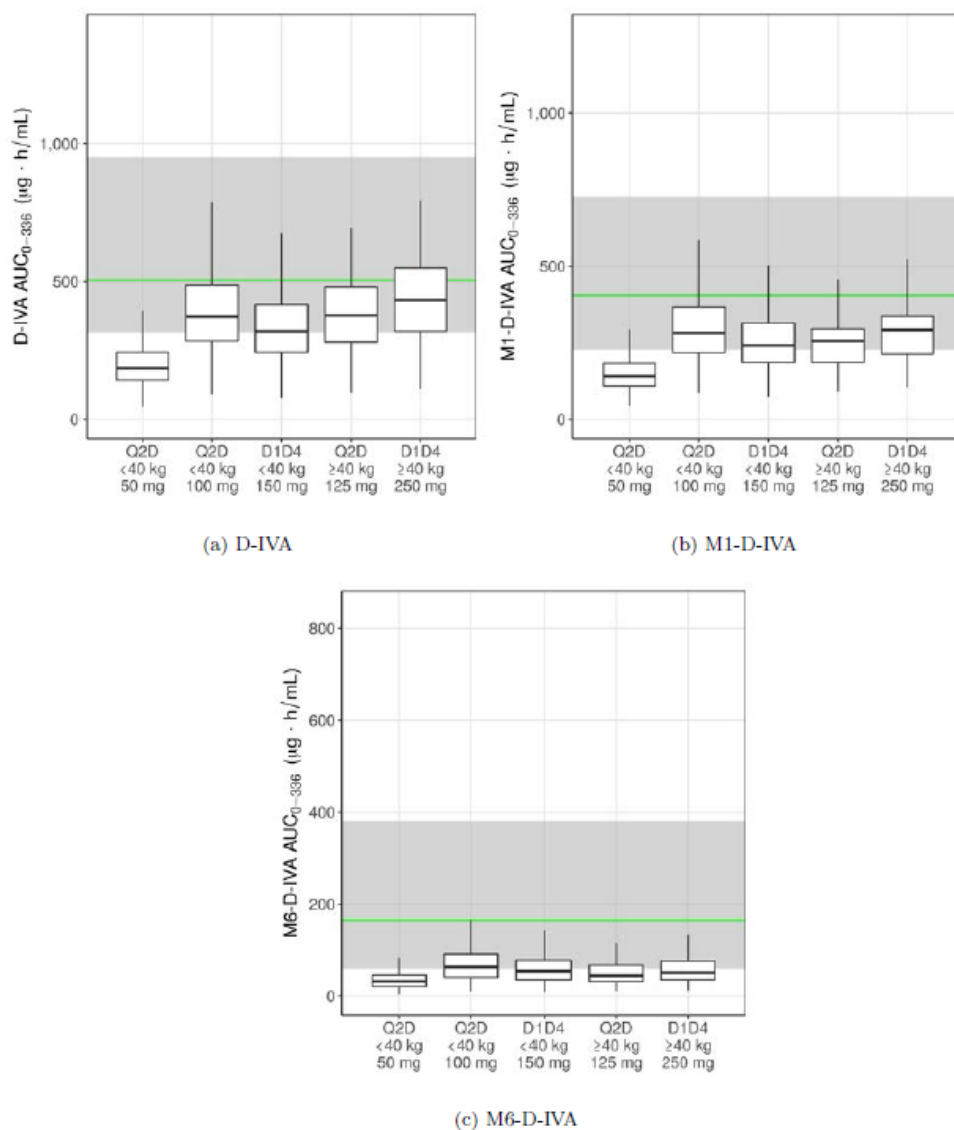
Figure 65. D-IVA, M1-D-IVA, and M6-D-IVA, AUC_{0-336h} Stochastic Simulations With Erythromycin (Moderate CYP3A Inhibitor) Coadministration for 6 Through 11 Years of Age by Age and Weight Group



Source: Figure 11.177, T406 report

Abbreviations: AUC_{0-336h} ; area under the plasma drug concentration-time curve from 0 to 336 hours; D1D4, Day 1 and 4 weekly; D-IVA, deutivacaftor; Q2D, every other day

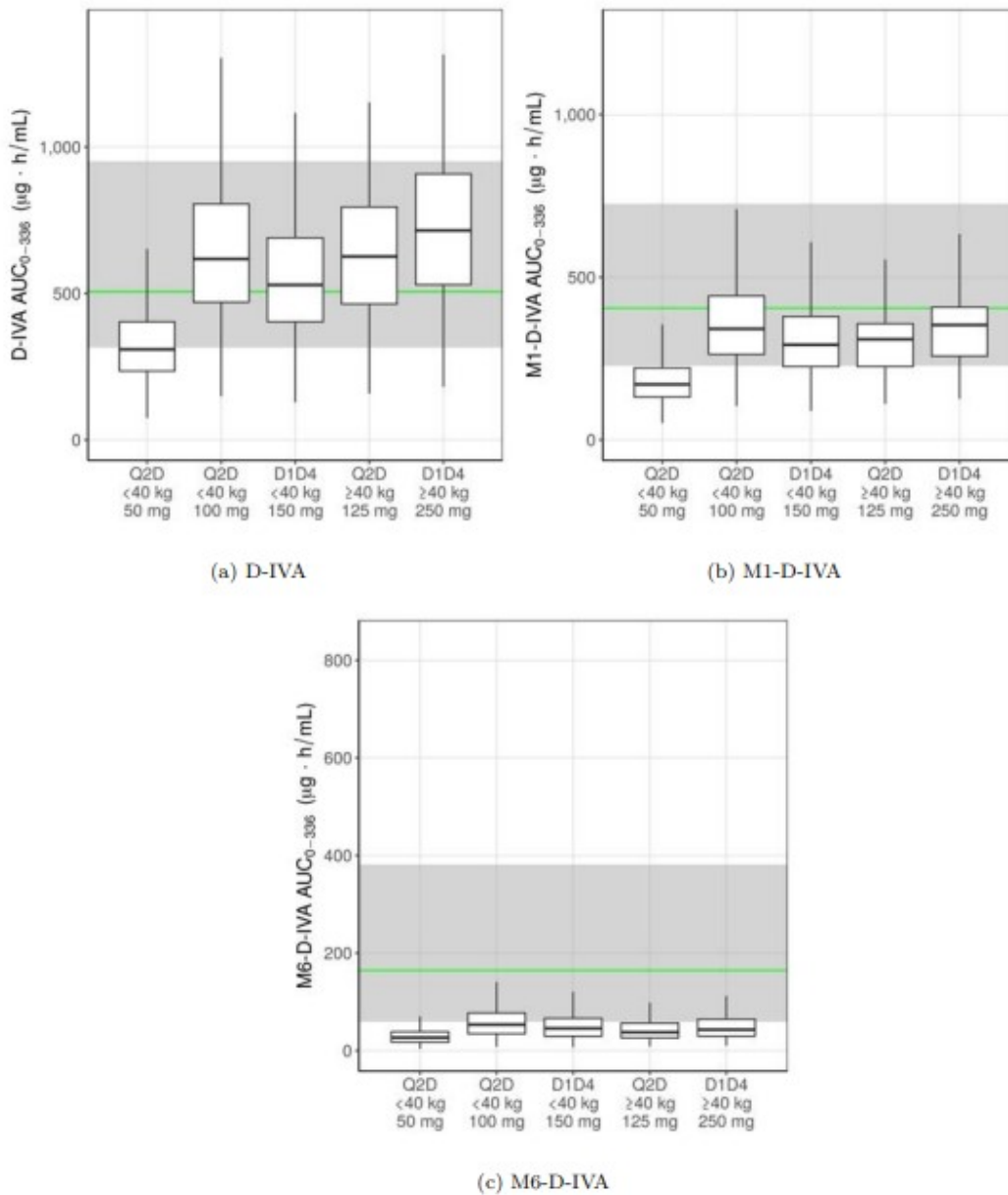
Figure 66. D-IVA, M1-D-IVA, and M6-D-IVA, AUC_{0-336h} Stochastic Simulations With Fluconazole (Moderate CYP3A Inhibitor) Coadministration for 6 Through 11 Years of Age by Age and Weight Group



Source: Figure 11.181 T406 report

Abbreviations: AUC_{0-336h} , area under the plasma drug concentration-time curve from 0 to 336 hours; D1D4, Day 1 and 4 weekly; D-IVA, deutivacaftor; Q2D, every other day

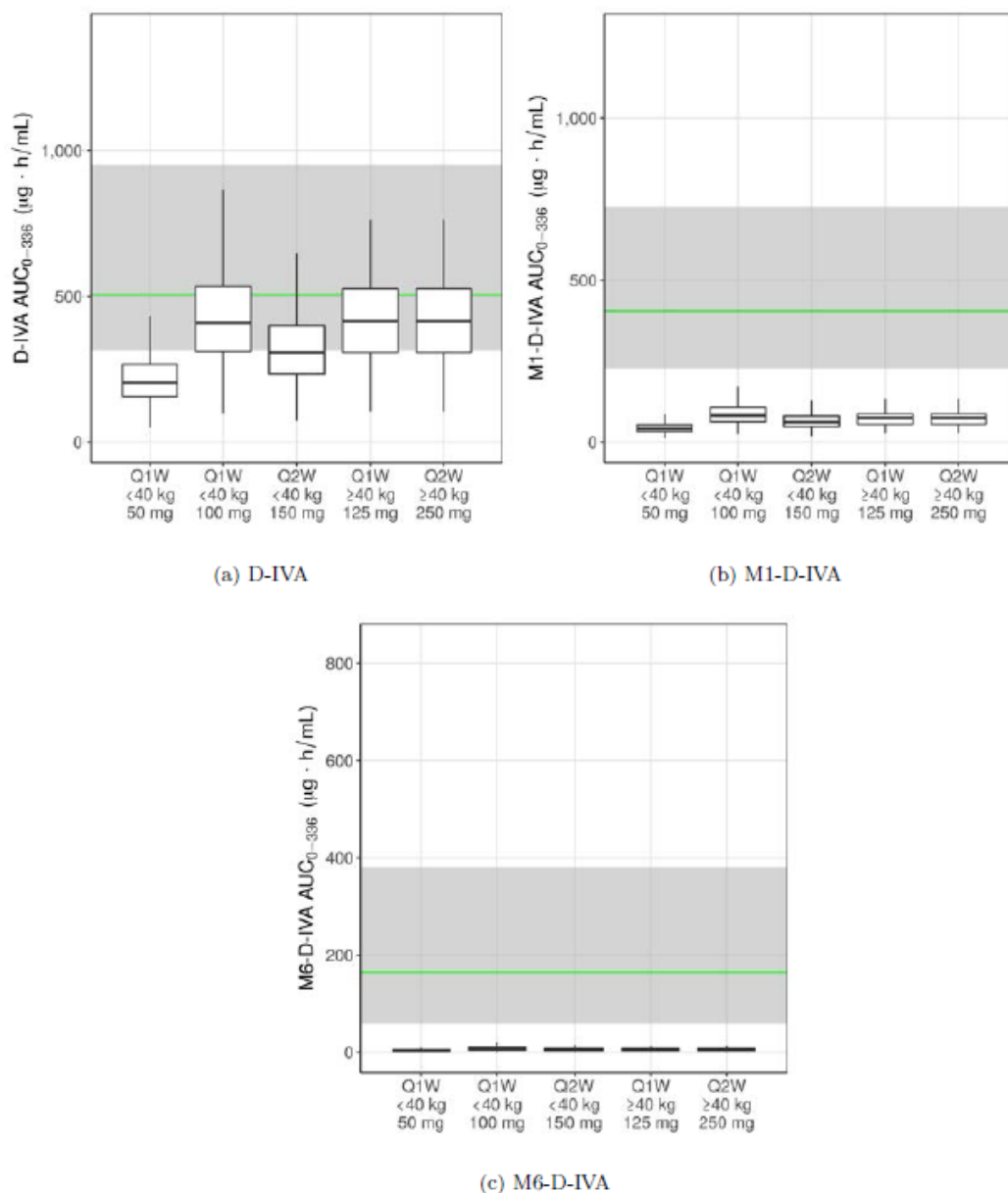
Figure 67. D-IVA, M1-D-IVA, and M6-D-IVA, AUC_{0-336h} Stochastic Simulations With Verapamil (Moderate CYP3A Inhibitor) Coadministration for 6 Through 11 Years of Age by Age and Weight Group



Source: Figure 11.185, T406 report

Abbreviations: AUC_{0-336h} , area under the plasma drug concentration-time curve from 0 to 336 hours; CYP, cytochrome P450; D1D4, Day 1 and 4 weekly; D-IVA, deutivacaftor; Q2D, every other day

Figure 68. D-IVA, M1-D-IVA, and M6-D-IVA, AUC_{0-336h} Stochastic Simulations With Strong CYP3A Inhibitors Coadministration for 6 Through 11 Years of Age by Age and Weight Group



Source: Figure 11.189, T406 report

Abbreviations: AUC_{0-336h} , area under the plasma drug concentration-time curve from 0 to 336 hours; CYP, cytochrome P450; D-IVA, deutivacaftor; Q1W, every week; Q2W, every other week

The FDA's Assessment

The Applicant's population PK analysis is considered acceptable for the purpose of supporting the analyses objectives.

14.5.1.5. M1-D-IVA and M6-D-IVA Population PK Analysis (Report T406)

Executive Summary

The FDA's Assessment

In general, the Applicant's population PK analyses are considered acceptable for the purpose of supporting the analyses objectives. The Applicant's analyses were verified by the clinical pharmacology reviewer, with no significant discordance identified.

Population Pharmacokinetic Assessment Summary

Table 143. Data Structure of M1-D-IVA and M6-D-IVA Population PK Analysis, Report T406

General Information	Details
Objectives of PPK analysis	• To characterize the PK disposition of M1-D-IVA and M6-D-IVA (D-IVA metabolites) in subjects 6 years and older using population methodology; • To quantify the sources of variability; • To summarize predicted AUC_{0-24h} from the studied dosing regimen for phase 3 subjects due to sparse PK sampling; • To evaluate if a 40 kg weight cutoff for all studied ages resulted in similar exposures to adults; – To simulate D-IVA and its metabolites exposures for a VNZ/TEZ/D-IVA TC dosing regimen with a 40 kg weight cutoff in children 6 through 11 years with CF; – To simulate D-IVA and its metabolites exposures for a VNZ/TEZ/D-IVA TC dosing regimen with a 40 kg weight cutoff in adolescents 12 through 17 years with CF; • To simulate exposures of D-IVA and its metabolites to inform dosing and/or weight bounds for weight cutoffs other than 40 kg for subjects ≥6 years of age; • To simulate exposures of D-IVA for different dosing regimens to inform dosing for CF subjects with MHI; • To simulate exposures of D-IVA for different dosing regimens to inform dosing for children 6 through 11 years with CF coadministered a strong or moderate cytochrome P4503A4 (CYP3A4) inhibitor
Study included	VX18-121-101, VX20-121-102, VX20-121-103, VX21-121-105, VX17-561-001, VX18-561-101, VX16-770-018
D-IVA Dose(s) included	25 mg, 50 mg, 100 mg, 125 mg, 150 mg, 250 mg QD (Table 5.4, Report T406)
Population included	Healthy, CF (F/MF, F/F, F/G, F/RF, TCR, and F/other genotypes)

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

General Information	Details
<i>Population characteristics (Table 7.1)</i>	
General	• Age: 29.8 yr (range: 6.17 – 71.2, 0.28% subj ≥65 yr) • Weight: 63 kg (range: 19.3 – 130) • N=408 (57.4%) male • N=670 (94.2%) White • N=24 (3.3%) Non-white • N=17 (2.4%) Not reported (imputed as White)
Organ impairment	• Hepatic (Child-Pugh, NCI, etc.): not reported Renal (CrCL, etc.): • N=577 (81.2%) normal (≥90 mL/min/1.73 m²) • N=132 (18.6%) mild impairment (60 to <90 mL/min/1.73 m²) • N=2 (0.3%) moderate impairment (30 to <60 mL/min/1.73 m²)
Pediatrics (if any)	• Age 9.30 (range: 6.17 – 12.0, 12.4% subj ≤12 yr) • Weight 28.9 kg (range: 19.3 – 54.0)
No. of subjects, PK samples, and BLQ	• M1-D-IVA: 711 subjects, 5800 PK samples, 247 (4.1%) post-first dose BLQ PK samples • M6-D-IVA: 711 subjects, 5639 PK samples, 408 (6.7%) post-first dose BLQ PK samples (Section 7.2.1, Report T406)
<i>Sampling schedule</i>	
Rich sampling	• Study VX18-121-101: – Day 1: predose, 1, 2, 4, 6, 8, and 24 hours after dosing. – Days 8, 15, and 29: predose. – Day 47: predose. • Study VX17-561-001: – Days 1, 6, 11: predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, and 24 hours (Days 2, 7, 12) postdose; – Days 3, 4, 8, 9, 13, 14: predose; – Days 5, 10: predose and 0.5, 1, 2, 3, 4, 5, 6, 8, and 12 hours postdose; – Day 15: predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 24 (Day 16), 36, 48 (Day 17), and 72 hours (Day 18) postdose • Study VX18-561-101: – Day 1: Predose, 4 hours postdose; – Day 15, Weeks 4, 8, and 12: Predose; In a subset of subjects (up to approximately 20 subjects), additional samples will be collected at the Week 4 visit at 1, 2, 4, and 6 hours postdose • Study VX16-770-018: – Days 1, 8, and 15: Predose and at 1, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48, 72, and 96 hours postdose

General Information	Details
In ITT population	• Trial VX20-121-102: – Day 1: Predose and 2 hours post dose. – Weeks 4, 16, and 24: predose. – Week 8: Predose and 4 hours postdose for all subjects <18 years of age. Predose, 4, 5, 6, and 7 hours postdose for up to approximately 40 subjects ≥18 years of age. Predose and 2 hours postdose for all other subjects ≥18 years of age. • Trial VX20-121-103: – Day 1: Predose and 2 hours post dose. – Day 15: Predose. – Weeks 4, 8, 16 and 24: Predose. • Trial VX21-121-105: – Part A1: Day 1: predose and 2 hours postdose. Days 8 and 15: predose. Day 22: predose, 2.5, 3.5, 6.5, 8 h postdose. – Part B1: Day 1: predose and 2 hours postdose. Day 15 and Week 4: predose. Week 8: predose, 2.5 and 3.5 hours postdose for all subjects; for a minimum of 12 subjects who weigh ≥17 kg at screening additional 6.5 and 8 hours postdose samples were collected. Weeks 12 and 16: predose.
<i>Covariates evaluated</i>	
Static	Baseline age, baseline weight, race, sex, genotype, ALT, eGFR, formulation (Section 6.3.5.3, Report T406)
Time-varying	NA

Source: Reviewer's summary

Abbreviations: ALT, alanine aminotransferase; AUC_{0-24h}, area under the plasma drug concentration-time curve from 0 to 24 hours; BLQ, below the limit of quantification; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CrCL, creatinine clearance; CYP, cytochrome P450; D-IVA, deutivacaftor; eGFR, estimated glomerular filtration rate; F, *F508del* CFTR variant; G, gating CFTR variant; ITT, intent-to-treat; MF, minimal function CFTR variant; MHI, moderate hepatic impairment; NA, not applicable; NCI, National Cancer Institute; PK, pharmacokinetic; PPK, population pharmacokinetic; RF, residual function CFTR variant; TC, triple combination; TCR, triple combination responsive CFTR variant

Table 144. Model Evaluation of M1-D-IVA and M6-D-IVA Population PK Analysis

Final Model	Summary	Acceptability (FDA's Comments)
Software and Version	NONMEM®, Version 7.4.4	Acceptable
Estimation Algorithm	First-order conditional estimation with η - ϵ interaction (FOCE-I)	Acceptable
Model Structure	Linear, one-compartment M1-D-IVA, and 2-compartment M6-D-IVA popPK model with sequential conversion of D- IVA to M1-D-IVA, and M1-D-IVA to M6-D-IVA	Acceptable
Model Parameter Estimates	Table 7.5, Report T406	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Except for the weight exponent on V/F of M1 and IIV on V/F of M1, and additive residual variances, all RSE's (fixed and random effects) were <30%; shrinkage for IIV on CL was <10%.	
BLQ for Parameter Accuracy	BLQ observations (4.1% for M1 and 6.7% for M6) were excluded. No impact of BLQ on PK objectives	Acceptable

Final Model	Summary	Acceptability (FDA's Comments)
GOF, VPC	Section 7.2.6, Report T406: - Diagnostics plots indicated that the final model provided an adequate description of the D-IVA metabolite concentration data, as judged by visual inspection of the observed versus the population and the individual predictions, respectively (Figures 11.103 to 11.133). Section 7.2.7, Report T406: - pcVPCs indicated that the final model captured the observed data reasonably well overall (Figure 7.20). The pcVPCs stratified by age group (Figure 7.21), weight group (Figure 7.22), and genotype (Figure 7.23) showed that the model adequately captured both the central tendency and the variability of the steady-state data.	There are missing data points in Figure 11.109. The Applicant provided clarification and/or correction to 11.109 in IR dated Aug 30, 2024. There are missing data points in Figure 11.110. The Applicant provided clarification and/or correction to 11.110 in IR dated Aug 25, 2024. The updated figures are acceptable.
Significant Covariates and Clinical Relevance	Figure 7.17, Report T406 (Forest plot) Body weight was the only covariate that had a clinically significant impact on D-IVA disposition requiring dose adjustment to align exposures in CF subjects <40 kg.	Acceptable

Final Model	Summary	Acceptability (FDA's Comments)
Analysis Based on Simulation (optional)	- Simulations based on the final population PK model for D-IVA supported the justification of candidate weight-based dosing regimens of VNZ/TEZ/D-IVA TC in CF patients ≥ 6 years of age with a 40 kg weight cutoff (Table 11.7; and Figures 11.136, 11.139, 11.148, 11.165, Report T406). - Additional weight cutoffs were also evaluated: 35 kg: Table 11.11; and Figures 11.142 and 11.168, Report T406 30 kg: Table 11.12; and Figures 11.145 and 11.171, Report T406. - Simulations based on the final population PK models showed exposures of D-IVA in adult CF subjects with MHI and no TEZ dose adjustment were in the same range as subjects without MHI (Figure 11.174, Report T406). This result supports that, based on PK, no D-IVA dose adjustment was needed for adult CF subjects with MHI. - Simulations based on the final population PK models for D- supported the justification of VNZ/TEZ/D-IVA dose adjustment regimens with reduced daily dose and/or dosing frequency for children 6 through 11 years with CF in the presence of coadministered CYP3A4 inhibitors (Figures 11.177, 11.181, 11.185 and 11.189, Report T406).	Acceptable

Source: Reviewer's summary

Abbreviations: BLQ, below the limit of quantification; CF, cystic fibrosis; D-IVA, deutivacaftor; GOF, goodness-of-fit; IIV, interindividual variability; MHI, moderate hepatic impairment; PK, pharmacokinetic; popPK, population pharmacokinetic; RSE, relative standard error; TC, triple combination; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor; VNZ, vanzacaftor; VPC, visual performance check

Table 145. Labeling Statements Supported by M1-D-IVA and M6-D-IVA Population PK Analysis

Labeling Language	Description	Acceptability (FDA's Comments)
12.3 PK	NA	NA

Source: Reviewer's summary

Abbreviations: NA, not applicable; PK, pharmacokinetic

Report T406/Tables

Table 146. D-IVA Metabolite Population Pharmacokinetic Final Model Parameter Estimates (Model 626)

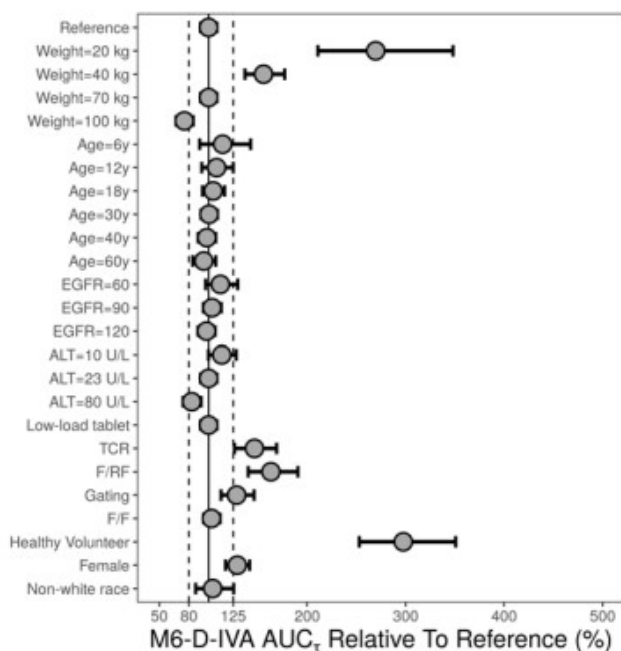
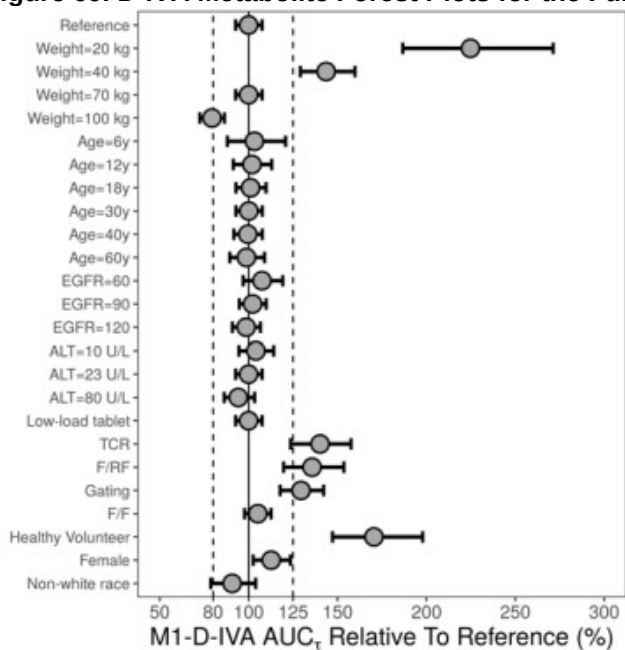
Parameter (unit)	Typical Estimate (%RSE)	95% Confidence Interval
Structural model parameters		
CL/F M1, Central clearance (L/h)	9.57 (0.833)	[9.23,9.93]
V/F M1, Central volume (L)	3.33 (2.97)	[3.1,3.57]
CL/F M6, Central clearance (L/h)	23.4 (0.959)	[22.1,24.8]
V/F M6, Central volume (L)	66.7 (1.19)	[60.5,73.5]
Q/F M6, Peripheral clearance (L/h)	1.63 (21)	[1.33,1.99]
VP/F M6, Peripheral volume (L)	78.6 (11.7)	[28.8,214]
Covariate effect parameters		
Weight exponent on CL/F M1	0.676 (5.89)	[0.598,0.754]
Weight exponent on V/F M1	0.216 (38.4)	[0.0533,0.379]
Weight exponent on CL/F and Q/F M6	0.929 (6.46)	[0.811,1.05]
Weight exponent on V/F and VP/F M6	0.795 (10.6)	[0.63,0.96]
Effect of healthy volunteers on CL/F M1	0.597 (11.7)	[0.53,0.672]
Effect of gating genotype on CL/F M1	0.778 (18.3)	[0.711,0.851]
Effect of F/RF genotype on CL/F M1	0.713 (18.4)	[0.631,0.805]
Effect of TCR genotype on CL/F M1	0.726 (19.6)	[0.642,0.821]
Effect of healthy volunteers on CL/F M6	0.302 (6.54)	[0.259,0.352]
Effect of gating genotype on CL/F M6	0.783 (29)	[0.681,0.9]
Effect of F/RF genotype on CL/F M6	0.558 (13.4)	[0.479,0.65]
Effect of TCR genotype on CL/F M6	0.671 (19.3)	[0.577,0.78]
Effect of female gender on CL/F M6	0.878 (21.8)	[0.83,0.928]
Effect of healthy volunteers on V/F M6	0.365 (10.2)	[0.299,0.447]
Interindividual variance parameters		
IIV on CL/F M1 [%CV]	0.118 [34.4] (10.5)	[0.0941,0.143]
IIV on CL/F M6 [%CV]	0.284 [53.3] (9.25)	[0.232,0.335]
IIV on V/F M1 [%CV]	0.194 [44.1] (33.8)	[0.0655,0.323]
IIV on V/F M6 [%CV]	0.198 [44.5] (19.5)	[0.122,0.273]
CL/F M1 - CL/F M6	0.157 (10.8)	[0.124,0.19]
Residual variance parameters		
M1 Proportional error CF [%CV]	0.122 [35] (4.64)	[0.111,0.134]
M1 Additive error CF [SD] (ng/mL)	1050 [32.4] (56.5)	[-113,2220]
M1 Proportional error HV [%CV]	0.122 [35] (8.76)	[0.101,0.143]
M1 Additive error HV [SD] (ng/mL)	103 [10.2] (30.9)	[40.7,166]
M6 Proportional error CF [%CV]	0.143 [37.8] (4.24)	[0.131,0.155]
M6 Additive error CF [SD] (ng/mL)	105 [10.2] (64.2)	[-27,237]
M6 Proportional error HV [%CV]	0.0902 [30] (21.7)	[0.0519,0.129]
M6 Additive error HV [SD] (ng/mL)	9.86 [3.14] (170)	[-23,42.7]

Source: Table 7.5, T406 report

Abbreviations: %RSE, percent relative standard error; CF, cystic fibrosis; D-IVA, deutivacaftor; F, *F508del CFTR* variant; G, gating *CFTR* variant; IIV, interindividual variability; MF, minimal function *CFTR* variant; RF, residual function *CFTR* variant; SD, standard deviation TCR, triple combination responsive *CFTR* variant

Report T406/Figures

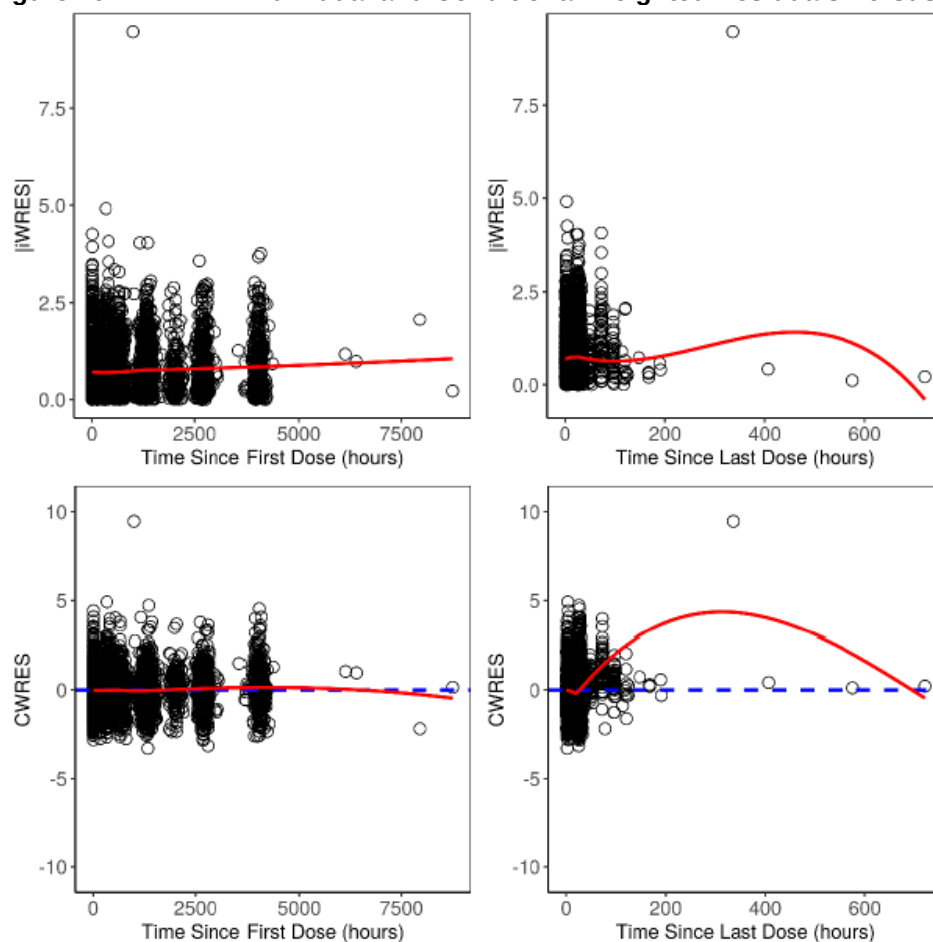
Figure 69. D-IVA Metabolite Forest Plots for the Full Model (614)



Source: Figure 7.17, T406 report

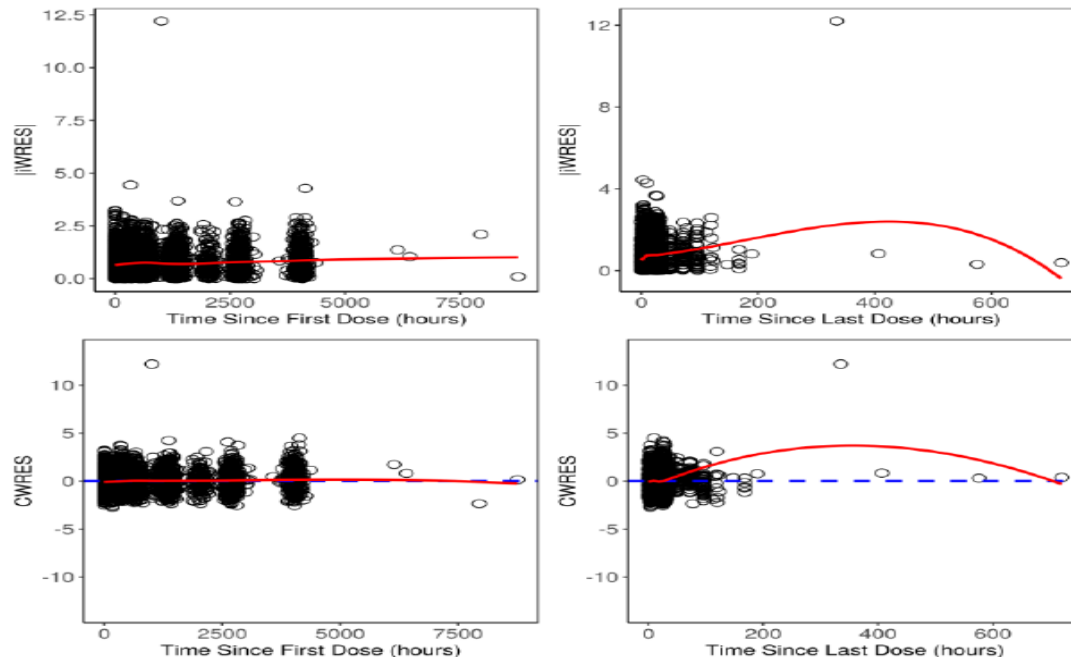
Abbreviations: ALT, alanine aminotransferase; AUC, area under the concentration-time curve; D-IVA, deutivacaftor; EGFR, estimated glomerular filtration rate; F, *F508del* *CFTR* variant; G, gating *CFTR* variant; MF, minimal function *CFTR* variant; RF, residual function *CFTR* variant; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor

Figure 70. M1-D-IVA Individual and Conditional Weighted Residuals Versus Time



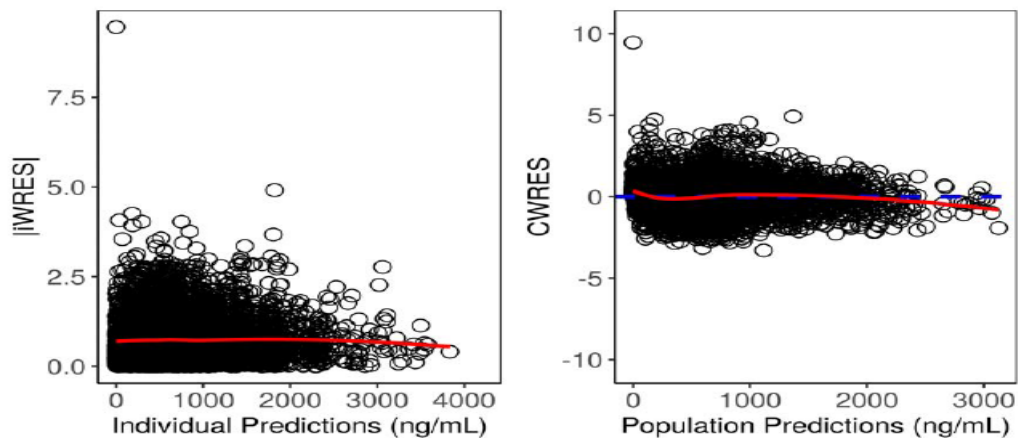
Source: Figure 1, IR response dated Aug 30, 2024

Abbreviations: CWRES, conditional weighted residuals; D-IVA, deutivacaftor; IWRES individual weighted residuals

Figure 71. D-IVA Metabolite Final Model: M6-D-IVA Individual and Conditional Weighted Residuals Versus Time

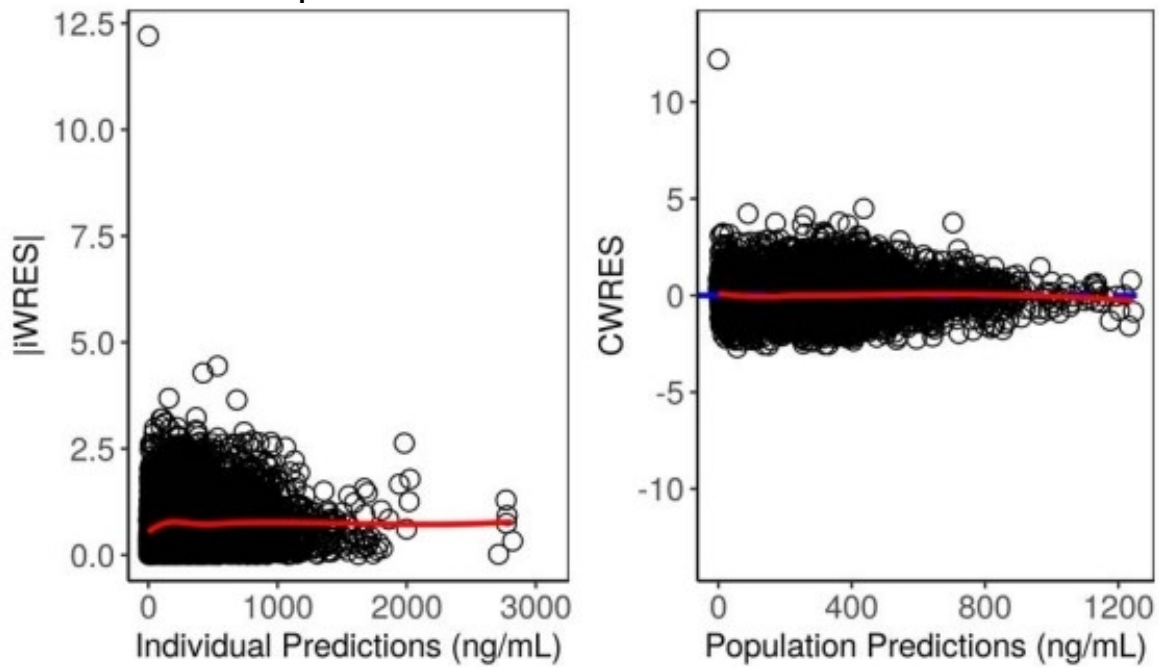
Source: Figure 2, IR response dated Aug 25, 2024

Abbreviations: CWRES, conditional weighted residuals; D-IVA, deutivacaftor; IWRES individual weighted residuals

Figure 72. D-IVA Metabolite Final Model: M1-D-IVA Individual and Conditional Weighted Residuals Versus Individual and Population Predictions

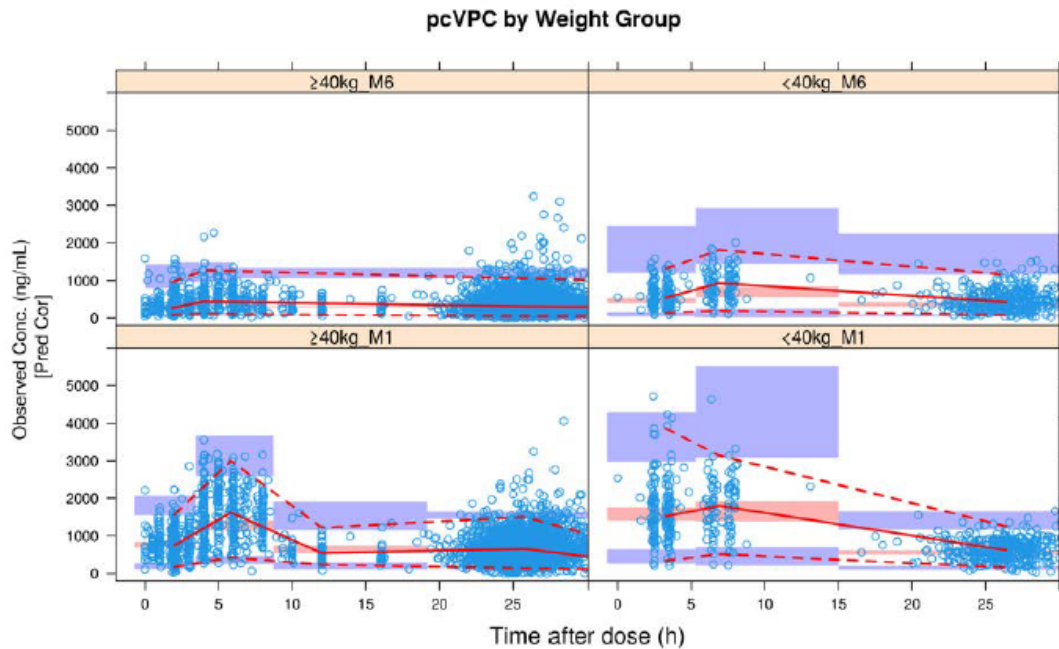
Source: Figure 11.115, T406 report

Abbreviations: CWRES, conditional weighted residuals; D-IVA, deutivacaftor; IWRES individual weighted residuals

Figure 73. D-IVA Metabolite Final Model: M6-D-IVA Individual and Conditional Weighted Residuals Versus Individual and Population Predictions

Source: 11.116, T406 report

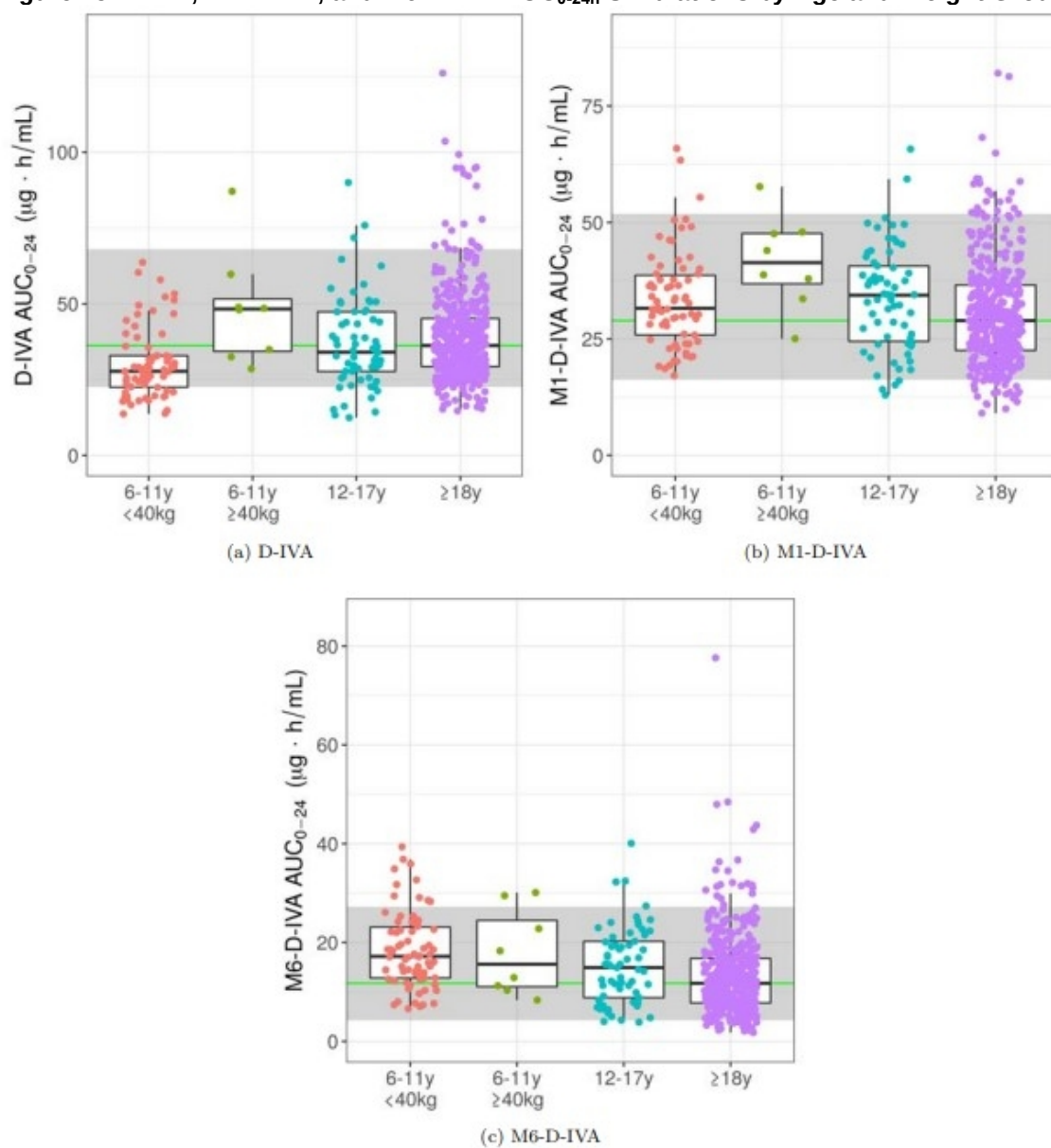
Abbreviations: CWRES, conditional weighted residuals; D-IVA, deutivacaftor; iWRES individual weighted residuals

Figure 74. pcVPCs of the D-IVA Metabolite Final Population PK Model: Stratified by Weight Group

Source: Figure 7.2, T406 report

Abbreviations: pcVPC, prediction-corrected visual predictive check; PK, pharmacokinetics

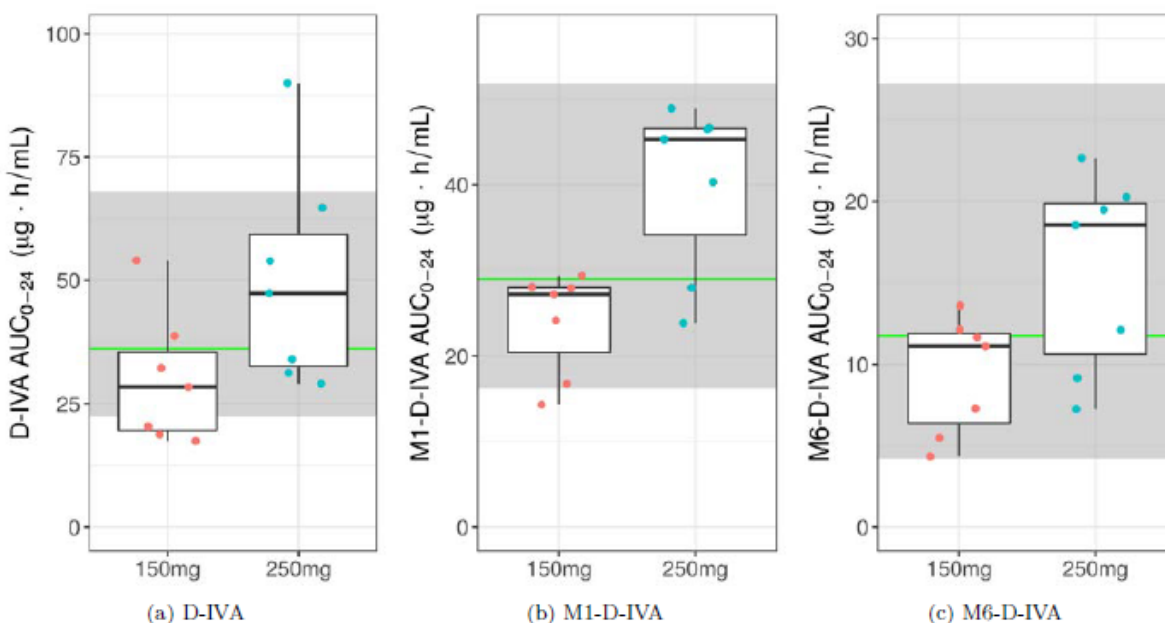
Figure 75. D-IVA, M1-D-IVA, and M6-D-IVA AUC_{0-24h} Simulations by Age and Weight Group



Source: Figure 11.136, T406 report

Abbreviations: AUC_{0-24h} , area under the plasma drug concentration-time curve from 0 to 24 hours; D-IVA, deutivacaftor

Figure 76. AUC_{0-24h} Simulations for Subjects ≥ 12 Years of Age and <40 kg Administered D-IVA 150 mg Versus 250 mg QD



Source: Figure 11.148, T406 report

Abbreviations: AUC_{0-24h} , area under the plasma drug concentration-time curve from 0 to 24 hours; D-IVA, deutivacaftor; qd, once daily

The FDA's Assessment

The Applicant's population PK analysis is considered acceptable for the purpose of supporting the analyses objectives.

14.5.1.6. ppFEV₁ Population PK/PD Analysis (Report T299)

Executive Summary

The FDA's Assessment

In general, the Applicant's population PK/PD analyses are considered acceptable for the purpose of supporting the analyses objectives. The Applicant's analyses were verified by the reviewer, with no significant discordance identified.

Population Pharmacokinetic Assessment Summary

Table 147. Data Structure of VNZ PK-ppFEV₁ Analysis, Report T299

General Information	Details
Objectives of PPK analysis	• Characterize the PK/PD relationship of vanzacaftor in VNZ/TEZ/D-IVA for the longitudinal clinical endpoint percent-predicted forced expiratory volume in 1 second (ppFEV₁) • Simulate the dose-response relationship for vanzacaftor in VNZ/TEZ/D-IVA to support the phase 3 dose justification • Evaluate graphically the impact of steady-state exposures of TEZ and D-IVA on vanzacaftor E_{max}
Study included	VX18-121-101, VX20-121-102, VX20-121-103, VX21-121-105
Dose(s) included	• VNZ 5 mg/TEZ 100 mg/D-IVA 150 mg QD • VNZ 10 mg/TEZ 100 mg/D-IVA 150 mg QD • VNZ 20 mg/TEZ 100 mg/D-IVA 150 mg QD • VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg QD • VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg QD (Table 1, Report T299)
Population included	CF (F/MF, F/F, F/G, F/RF, TCR, and F/other genotypes)
<i>Population characteristics (Tables S5 and S6, Report T299)</i>	
General	• Age: 30.8 yr (range: 6.17 – 71.2, 0.28% subj ≥65 yr) • ppFEV₁: 68.0 p.p. (range: 28.0 – 146) • N=620 (55.7%) male
Organ impairment	• Hepatic (Child-Pugh, NCI, etc.): not reported • Renal (CrCL, etc.): not captured in the dataset
Pediatrics	• Age 9.16 (6.17 – 12.0, 6.9% subj ≤12 yr) • ppFEV₁: 101 p.p. (range: 29.3 – 146)
No. of patients and samples	1113 subjects, 8194 ppFEV ₁ measurements (Section 6.1.1; Table S2, Report T299)
<i>Sampling schedule</i>	
Rich sampling	• Study VX18-121-101: – Screening visit. Days 1, 2, 8, 15, and 29. Day 47 for F/MF genotype. Days 43 and 56 for F/F genotype. Follow-up 28 days after last dose of study drug.
In ITT population	• Trial VX20-121-102: – Screening visit. Run-in. Days 1 and 15. Weeks 4, 8, 16, 24, 36, 52. Follow-up 28 days after last dose of study drug. • Trial VX20-121-103: – Screening visit. Run-in. Days 1 and 15. Weeks 4, 8, 16, 24, 36, 52. Follow-up 28 days after last dose of study drug. • Trial VX21-121-105: – Part A1: Screening visit. Days 1, 2, 8, 15, and 22. Follow-up 28 days after last dose of study drug. – Part B1: Screening visit. Days 1 and 15. Weeks 4, 8, 12, 16, and 24. Follow-up 28 days after last dose of study drug.

General Information	Details
<i>Covariates evaluated</i>	
Static	- Baseline age on baseline response, vanzacaftor E_{max}, elexacaftor effect, and additive residual error - Sex on baseline response - Genotype on vanzacaftor E_{max}, standard of care (tezacaftor and ivacaftor) (SOC) effect, elexacaftor effect - Baseline ppFEV₁ on vanzacaftor E_{max} (Section 4.2, Report T299)
Time-varying	NA

Source: Reviewer's summary

Abbreviations: ALT, alanine aminotransferase; BLQ, below the limit of quantification; CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CrCL, creatinine clearance; D-IVA, deutivacaftor; eGFR, estimated glomerular filtration rate; E_{max} , maximum effort; F, *F508del CFTR* variant; G, gating *CFTR* variant; ITT, intent-to-treat; MF, minimal function *CFTR* variant; NA, not applicable; PK, pharmacokinetic; PPK, population pharmacokinetic; QD, once daily; RF, residual function *CFTR* variant; SOC, system organ class; TC, triple combination; TCR, triple combination responsive *CFTR* variant

Table 148. Model Evaluation of VNZ PK-ppFEV1 Analysis

Final Model	Summary	Acceptability (FDA's Comments)
Software and Version	NONMEM®, Version 7.5.0	Acceptable
Estimation Algorithm	First-order conditional estimation with η - ϵ interaction (FOCE-I)	Acceptable
Model Structure	Indirect response model with E_{max} using C_{avg} as the PK metric for the exposure- response model (Section 5.3.1)	Acceptable
Model Parameter Estimates	- Fixed effect parameter estimates: Table 3, Report T299 - Random effect parameter estimates: Table 4, Report T299	Acceptable
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Fixed and random effects parameters were generally estimated with reasonable precision as judged by the width of the asymptotic CIs; shrinkage for IIV on PP0 was <30% (Section 6.1.2.3, Report T299).	Acceptable
GOF, VPC	Section 6.1.2.3, Report T299: - The final model provided a reasonable description of the data, as judged by visual inspection of model diagnostic plots (Figures S49 to S69) Section 6.1.3, Report T299: - VPCs demonstrated that model- predicted ppFEV₁ change from baseline from the final model were similar to the observed change from baseline at the 5th, 50th, and 95th percentiles, both overall or stratified by treatment group, study phase, age group, and genotypes (Figures S70 to S76).	Acceptable

Final Model	Summary	Acceptability (FDA's Comments)
Analysis Based on Simulation (optional)	The PK/PD model for ppFEV ₁ showed a flat response across VNZ exposure at the phase 3 dose of 20 mg, indicating that this dose is on the plateau region of the E-R relationship for VNZ (Figures A1 and A3, Table S10, Report T299)	Acceptable

Source: Reviewer's summary

Abbreviations: BLQ, below the limit of quantification; CF, cystic fibrosis; D-IVA, deutivacaftor; E_{max}, maximum effort; GOF, goodness-of-fit; IIV, interindividual variability; MHI, moderate hepatic impairment; PK, pharmacokinetic; popPK, population pharmacokinetic; RSE, relative standard error; TC, triple combination; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor; VNZ, vanzacaftor; VPC, visual performance check

Table 149. Labeling Statements Supported by VNZ PK-ppFEV₁ Analysis

Labeling Language	Description	Acceptability (FDA's Comments)
12.3 PK	NA	NA

Source: Reviewer's summary

Abbreviations: NA, not applicable; PK, pharmacokinetic

Report T299/Tables

Table 150. ppFEV₁ Data: Baseline Categorical Covariate Summary Stratified by Study

	Study				Summary n = 1113
	101 n = 86	102 n = 389	103 n = 561	105 n = 77	
Sex					
Male	59 (68.6)	232 (59.6)	285 (50.8)	44 (57.1)	620 (55.7)
Female	27 (31.4)	157 (40.4)	276 (49.2)	33 (42.9)	493 (44.3)
Genotype					
F/MF	58 (67.4)	389 (100.0)	0 (0.0)	25 (32.5)	472 (42.4)
F/F	28 (32.6)	0 (0.0)	437 (77.9)	37 (48.1)	502 (45.1)
F/G	0 (0.0)	0 (0.0)	37 (6.6)	3 (3.9)	40 (3.6)
F/RF or F/other	0 (0.0)	0 (0.0)	46 (8.2)	3 (3.9)	49 (4.4)
TCR	0 (0.0)	0 (0.0)	41 (7.3)	9 (11.7)	50 (4.5)
Age Group					
6-11 years	0 (0.0)	0 (0.0)	0 (0.0)	77 (100.0)	77 (6.9)
12-17 years	0 (0.0)	54 (13.9)	77 (13.7)	0 (0.0)	131 (11.8)
Adults	86 (100.0)	335 (86.1)	484 (86.3)	0 (0.0)	905 (81.3)

Source: S5, t299 report

Abbreviations: F, *F508del* *CFTR* variant; G, gating *CFTR* variant; MF, minimal function *CFTR* variant; ppFEV₁, percent-predicted forced expiratory volume in 1 second; RF, residual function *CFTR* variant; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor

Table 151. ppFEV₁ Data: Baseline Continuous Covariate Summary Stratified by Study

Study	n	Mean	Median	SD	Min / Max
Baseline Age (years)					
101	86	32.0	30.5	9.53	18.0 / 64.0
102	389	30.7	30.8	10.9	12.2 / 71.6
103	561	33.7	33.1	12.5	12.2 / 71.2
105	77	9.04	9.16	1.75	6.17 / 12.0
<i>All data</i>	1113	30.8	30.8	12.8	6.17 / 71.6
Baseline ppFEV₁ (p.p.)					
101	86	58.9	59.3	13.8	28.4 / 89.9
102	389	67.1	67.9	15.0	28.0 / 109
103	561	66.8	66.9	14.7	36.4 / 112
105	77	99.7	101	15.1	29.3 / 146
<i>All data</i>	1113	68.6	68.0	17.2	28.0 / 146

Source: S6, t299 report

Abbreviations: max, maximum; min, minimum; n, total number of subjects; ppFEV₁, percent-predicted forced expiratory volume in 1 second; SD, standard deviation

Table 152. ppFEV₁ Final Model: Summary of ppFEV₁ Fixed Effects Parameter Estimates

			Estimate	95% CI	RSE (%)
Structural model parameters					
PP0 (age ≥ 12)	$\exp(\theta_1)$	Untreated baseline ppFEV ₁ when age ≥ 12 years (reference age: 32 years)	52.3	51.4, 53.2	0.872
PP0 (age < 12)	$\exp(\theta_7)$	Untreated baseline ppFEV ₁ when age < 12 years	85.1	82.3, 88.1	1.75
EC50 (ng/mL)	$\exp(\theta_2)$	VNZ concentration achieving half of the maximum effect	69.6	13.3, 365	102
E _{max}	$\exp(\theta_3)$	VNZ maximum effect	135	65.2, 278	38.3
t _{1/2} VNZ (days)	$\exp(\theta_5)$	Half-life of VNZ effect	7.18	5.82, 8.86	10.8
EELX	θ_6	ELX effect	10.4	FIXED	-
Covariate effect parameters					
PP0 (age ≥ 12) ~ Age	θ_8	Effect of age on PP0 (age ≥ 12)	-0.289	-0.328, -0.251	6.81
PP0 ~ F/RF or F/other	θ_{11}	Effect of F/RF or F/other genotypes on PP0	9.39	5.63, 13.1	20.4
PP0 ~ TCR	θ_{12}	Effect of TCR genotype on PP0	3.68	-0.0525, 7.42	51.7
SIGA ~ AGEslope	$\exp(\theta_9)$	Slope of age effect on SIGA (prior to age cut-off)	0.248	0.166, 0.370	20.7
SIGA ~ AGE _{max}	$\exp(\theta_{10})$	Age (years) cut-off for effect of age on SIGA	19.5	18.4, 20.6	2.87

Source: Table 3, t299 report

Model run 217: Parameters estimated in the log-domain were back-transformed for clarity

Confidence intervals = estimate ± 1.96 times SE

RSE (%) of thetas = (SE/abs(estimate)) times 100

RSE (%) of log-transformed thetas = sqrt(exp(SE²) - 1) times 100

Abbreviations: abs, absolute value; CI, confidence intervals; ELX, elxacaftor; F, *F508del* CFTR variant; G, gating CFTR variant; MF, minimal function CFTR variant; ppFEV₁, residual standard error; RF, residual function CFTR variant; TCR, triple combination responsive CFTR variant; VNZ, vanzacaftor

Table 153. ppFEV₁ Final Model: Summary of ppFEV₁ Random Effects Parameter Estimates

		Estimate	95% CI	Shrinkage (%)	RSE (%)
Interindividual variance parameters					
IIV-PP0	$\Omega_{(1,1)}$	123 [SD=11.1]	103, 143	17.3	8.28
IIV-PPMAX	$\Omega_{(2,2)}$	61.0 [SD=7.81]	39.1, 83.0	40.4	18.4
Residual variance					
Additive SD	$\exp(\theta_4)$	3.24	3.08, 3.41	-	2.62

Source: Table 4, t299 report

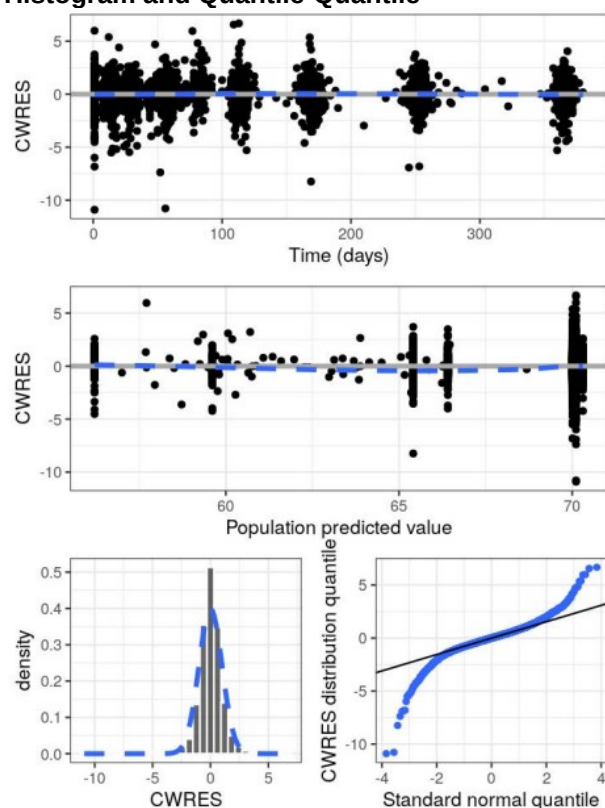
Model run 217: Parameters estimated in the log-domain were back-transformed for clarity

Confidence intervals = estimate $\pm$ 1.96 times SE

RSE (%) of diagonal omegas = (SE/abs(estimate)) times 100

Abbreviations: abs, absolute value; CI, confidence intervals; IIV, interindividual variability; PP0, untreated baseline ppFEV₁; PPMAX, ppFEV₁ maximum effect; ppFEV₁, percent-predicted forced expiratory volume in 1 second; RSE, residual standard error; SD, standard deviation; SE, standard error

Report T299/Figures

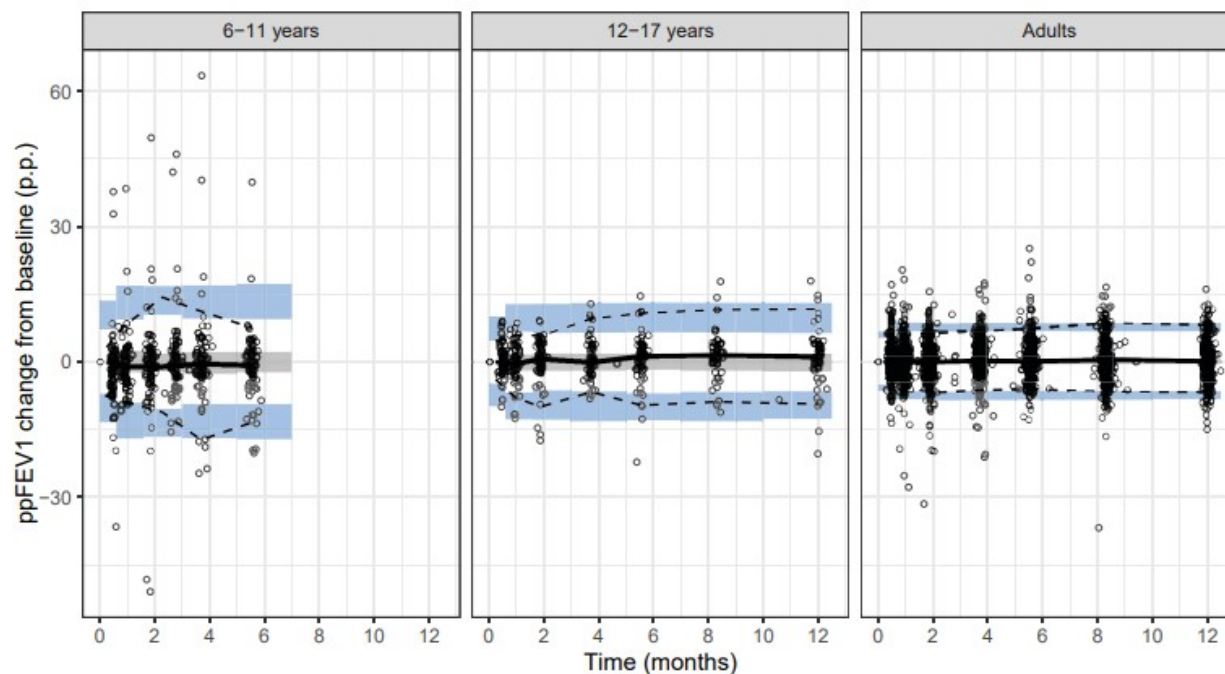
Figure 77. ppFEV₁ Base Model: CWRES Versus Time and Population Predictions, CWRES Density Histogram and Quantile-Quantile

Source: Figure S36, t299 report

Scatter plots: Solid black circles represent the individual CWRES values associated with each observation record. The solid horizontal gray line (residuals = 0) was included for reference. The dashed blue line represents a LOESS smooth through the data. Density plot: density frequency (count) of the CWRES. Q-Q plot: solid blue circles represent the conditional weighted residual values associated with each observation record.

The solid black line (y=x) is included for reference.

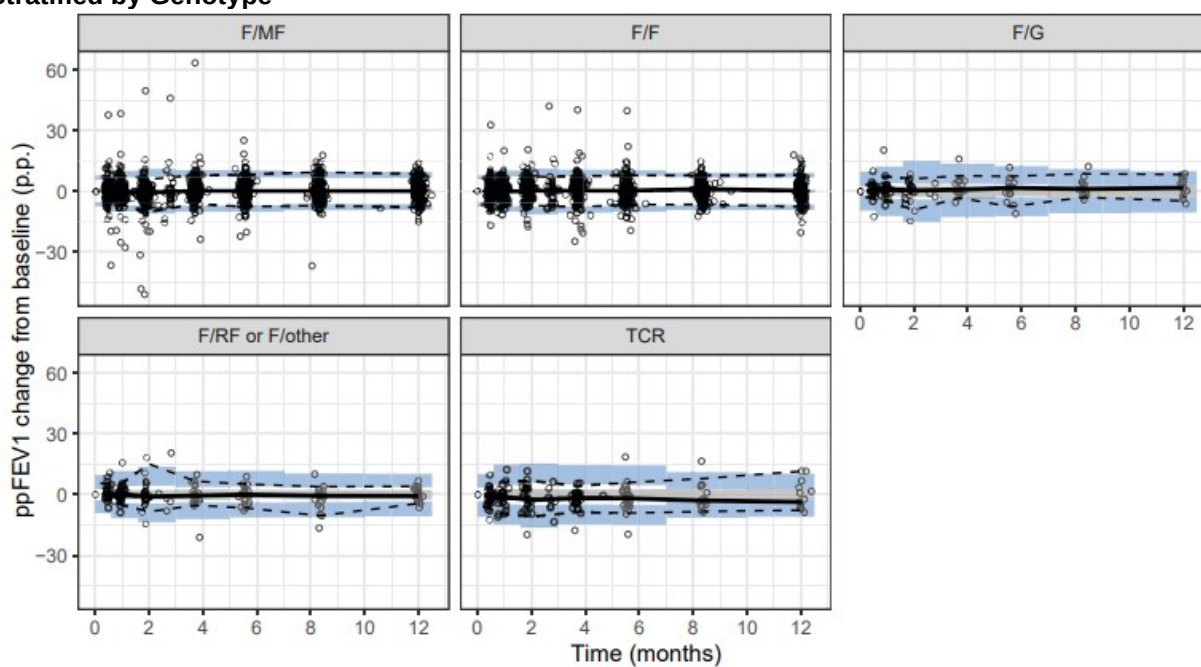
Abbreviations: CWRES, conditional weighted residuals; LOESS, locally weighted scatterplot smoothing; ppFEV₁, percent-predicted forced expiratory volume in 1 second

Figure 78. ppFEV₁ Final Model: VPC of the ppFEV₁ Change From Baseline Versus Time in Phase 3 Stratified by Age Group

Source: Figure S73, t299 report

The black lines represent the median (solid) or 5th/95th (dashed) percentiles of the observed data. The shaded areas represent 95% prediction intervals for median (gray) or 5th/95th percentiles (blue) for simulated data.

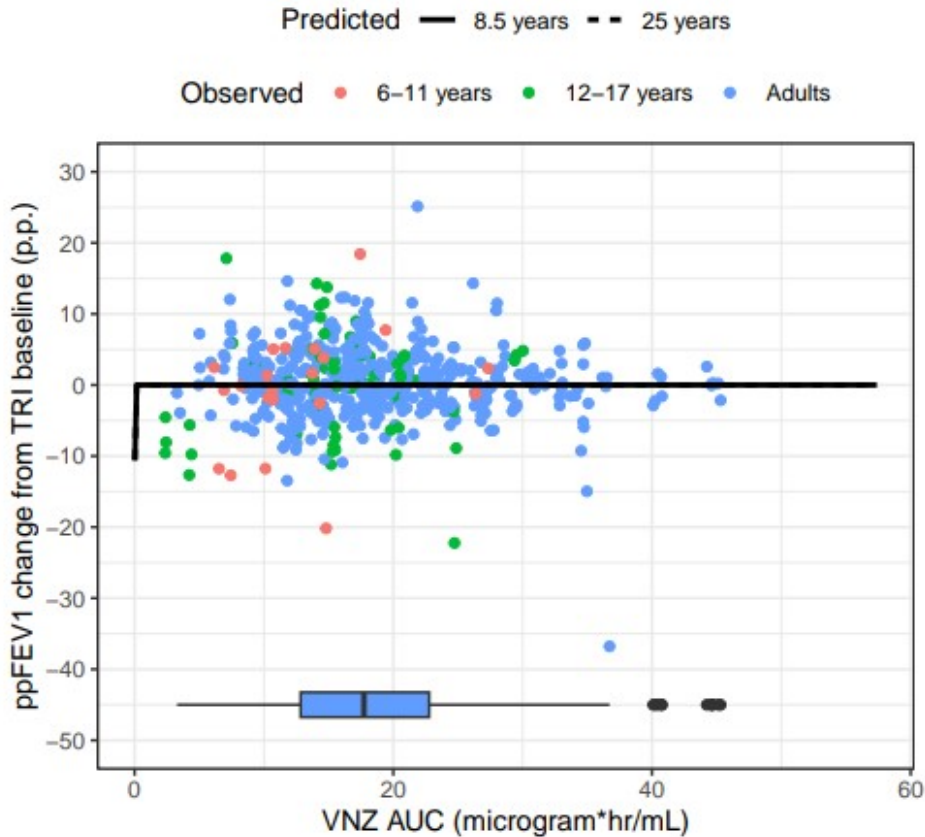
Abbreviations: ppFEV₁, percent-predicted forced expiratory volume in 1 second; VPC, visual predictive check

Figure 79. ppFEV₁ Final Model: VPC of the ppFEV₁ Change From Baseline Versus Time in Phase 3 Stratified by Genotype

Source: Figure S75, t299 report

The black lines represent the median (solid) or 5th/95th (dashed) percentiles of the observed data. The shaded areas represent 95% prediction intervals for median (gray) or 5th/95th percentiles (blue) for simulated data.

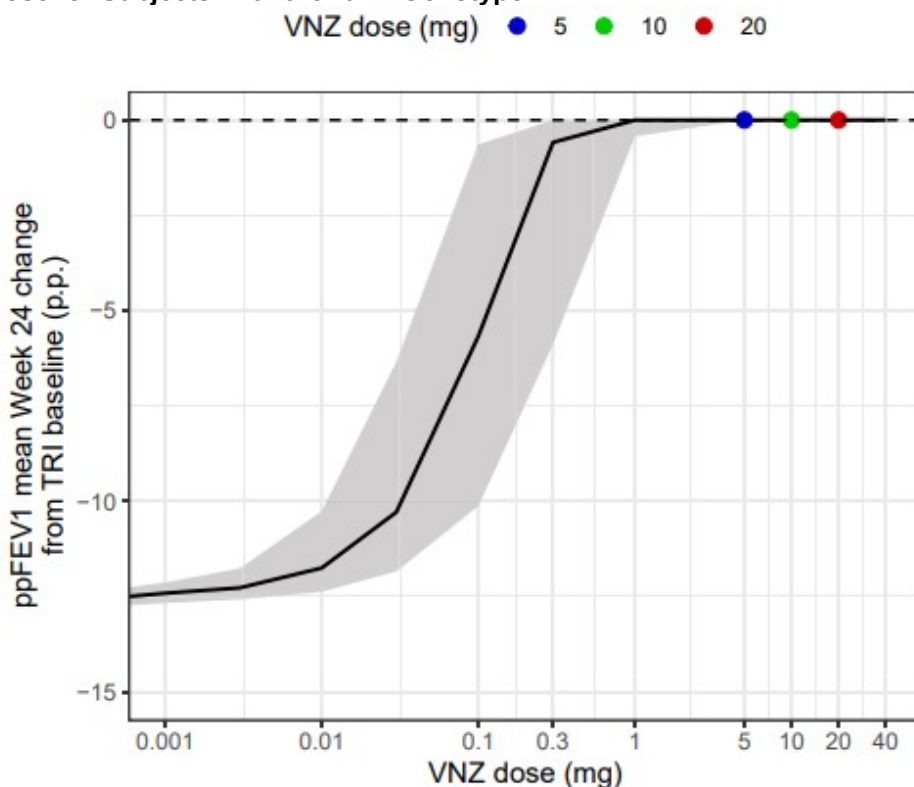
Abbreviations: F, *F508del CFTR* variant; G, gating *CFTR* variant; MF, minimal function *CFTR* variant; ppFEV₁, percent-predicted forced expiratory volume in 1 second; RF, residual function *CFTR* variant; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor; VPC, visual predictive check

Figure 80. ppFEV₁ Simulation: ppFEV₁ Change From Baseline Versus Vanzacaftor AUC for Subjects With the F/MF Genotype

Source: Figure A1, t299 report

The points represent observed ppFEV₁ change from baseline in patients from phase 3 studies, measured 24 or more weeks after randomization to VNZ/TEZ/D-IVA following ELX/TEZ/IVA run-in. The black lines are population predictions from the final ppFEV₁ model for an 8.5 (solid) and 25 (dashed) year old patient. All data, observed and simulated, reflect ppFEV₁ under treatment with TEZ/D-IVA in addition to VNZ. The boxplot summarizes observed vanzacaftor AUC in adult patients with the F/MF genotype administered 20 mg vanzacaftor (in combination with TEZ/D-IVA). Median AUC values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to 1.5*IQR. F/MF: heterozygous for *F508del* variant and a minimal function *CFTR* variant.

Abbreviations: AUC, area under the concentration-time curve; F, *F508del* *CFTR* variant; IQR, interquartile range; MF, minimal function *CFTR* variant; ppFEV₁, percent-predicted forced expiratory volume in 1 second; VNZ, vanzacaftor;

Figure 81. ppFEV₁ Simulation: ppFEV₁ Change From Baseline at 24 Weeks Versus Vanzacaftor Dose for Subjects With the F/MF Genotype

Source: Figure A3, t299 report

The shaded area marks the 95% confidence interval for the mean ppFEV₁ change from ELX/TEZ/IVA baseline dose-response curve across 1000 simulation replicates and the solid line marks the median. The dashed horizontal line indicates zero change from baseline. The blue, green, and red points mark the median prediction for the 5, 10, and 20 VNZ dose groups, respectively. Simulations reflect ppFEV₁ change from baseline under treatment with TEZ/D-IVA in addition to VNZ. F/MF: heterozygous for *F508del* variant and a minimal function *CFTR* variant.

Abbreviations: AUC, area under the concentration-time curve; F, *F508del CFTR* variant; MF, minimal function *CFTR* variant; ppFEV₁, percent-predicted forced expiratory volume in 1 second; VNZ, vanzacaftor

The FDA's Assessment

The Applicant's population PK/PD analysis is considered acceptable for the purpose of supporting the analyses objectives.

14.5.1.7. SwCI Population PK / PD Analysis (Report T299)

Executive Summary

The FDA's Assessment

In general, the Applicant's population PK/PD analyses are considered acceptable for the purpose of supporting the analyses objectives. The Applicant's analyses were verified by the clinical pharmacology reviewer, with no significant discordance identified.

Population Pharmacokinetic Assessment Summary

Table 154. Data Structure of VNZ PK-SwCl Analysis, Report T299

General Information	Details
Objectives of PPK analysis	• Characterize the population PK/PD relationship of vanzacaftor in VNZ/TEZ/D-IVA for the longitudinal pharmacodynamic endpoint SwCl • Simulate the dose-response relationship for vanzacaftor in VNZ/TEZ/D-IVA to support the phase 3 dose justification • Evaluate graphically the impact of steady-state exposures of TEZ and D-IVA on vanzacaftor $E_{\max}$
Study included	VX18-121-101, VX20-121-102, VX20-121-103, VX21-121-105
Dose(s) included	• VNZ 5 mg/TEZ 100 mg/D-IVA 150 mg QD • VNZ 10 mg/TEZ 100 mg/D-IVA 150 mg QD • VNZ 20 mg/TEZ 100 mg/D-IVA 150 mg QD • VNZ 20 mg/TEZ 100 mg/D-IVA 250 mg QD • VNZ 12 mg/TEZ 60 mg/D-IVA 150 mg QD (Table 1, Report T299)
Population included	CF (F/MF, F/F, F/G, F/RF, TCR, and F/other genotypes)
<i>Population characteristics (Tables S5 and S6, Report T299)</i>	
General	• Age: 30.8 yr (range: 6.17 – 71.2, 0.28% subj ≥65 yr) • SwCl: 48.5mmol/L (range: 10.0 – 115) N=620 (55.7%) male
Organ impairment	• Hepatic (Child-Pugh, NCI, etc.): not reported • Renal (CrCL, etc.): not captured in the dataset
Pediatrics	• Age 9.16 (6.17 – 12.0, 6.9% subj ≤12 yr) • SwCl: 39mmol/L (range: 11.0 – 110)
No. of patients and samples	1113 subjects, 7883 SwCl measurements (Section 6.2.1; Table S11, Report T299)
<i>Sampling schedule</i>	
Rich sampling	• Study VX18-121-101: – Screening visit. Days 1, 15, and 29. Day 47 for F/MF genotype. Days 43 and 56 for F/F genotype. Follow-up 28 days after last dose of study drug for F/MF genotype.
In ITT population	• Trial VX20-121-102: – Screening visit. Run-in. Days 1 and 15. Weeks 4, 24, 36, 52. • Trial VX20-121-103: – Screening visit. Run-in. Days 1 and 15. Weeks 4, 16, 24, 36, 52. • Trial VX21-121-105: – Part A1: Screening visit. Days 1 and 22. – Part B1: Screening visit. Days 1 and 15. Weeks 4, 16, and 24.

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ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

General Information	Details
<i>Covariates evaluated</i>	
Static	- Baseline age on baseline response, vanzacaftor $E_{\max}$, elexacaftor effect, additive residual error - Sex on baseline response - Genotype on vanzacaftor $E_{\max}$, standard of care (tezacaftor and ivacaftor) (SOC) effect, elexacaftor effect - Baseline SwCl on vanzacaftor $E_{\max}$ (Section 4.2, Report T299)
Time-varying	NA

Source: Reviewer's summary
Abbreviations: CF, cystic fibrosis; CFTR, cystic fibrosis transmembrane conductance regulator; CrCL, creatinine clearance; D-IVA, deutivacaftor; $E_{\max}$, maximum effect; F, *F508del CFTR* variant; ITT, intent-to-treat; MF, minimal function *CFTR* variant; NCI, National Cancer Institute; PK/PD, pharmacokinetic-pharmacodynamic; QD, once daily; SOC, system organ class; SwCl, sweat chloride; TEZ, tezacaftor; vs., versus; VNZ, vanzacaftor; yr, year

Table 155. Model Evaluation of VNZ PK - SwCl Analysis

Final Model	Summary	Acceptability (FDA's Comments)
Software and Version	NONMEM®, Version 7.5.0	
Estimation Algorithm	SAEM estimation	
Model Structure	Indirect response model with $E_{\max}$ using C_{avg} as the PK metric for the Exposure- Response model (Section 5.3.1, Report T299)	
Model Parameter Estimates	Fixed effect parameter estimates: Table 6, Report T299 Random effect parameter estimates: Table 7, Report T299	
Uncertainty and Variability (RSE, IIV, Shrinkage, Bootstrap)	Based on the widths of the asymptotic CIs and RSEs, the fixed and random effects parameters were generally estimated with reasonable precision. All shrinkages were <30% (Section 6.1.2.3, Report T299).	
GOF, VPC	Section 6.2.2.3, Report T299: - The final model provided a reasonable description of the data, as judged by visual inspection of the model diagnostic plots (Figures S131 to S152). Section 6.2.3, Report T299: - VPCs demonstrated the final model-predicted SwCl changes from baseline were generally similar to the observed changes from baseline at the 5th, 50th, and 95th percentiles across age and genotype in phase 3 data (Figures S153 to S159).	

Final Model	Summary	Acceptability (FDA's Comments)
Analysis Based on Simulation (optional)	Results of the SwCl PK/PD analyses indicated that VNZ exposure at the phase 3 dose of 20 mg is on the plateau region of the E-R curve for CFTR correction when dosed in TC (Figures A4 and A6, Table S20, Report T299). After accounting for the influence of VNZ exposures (the primary exposure driver for the SwCl response), the E_{max} for the SwCl response trended towards larger response with higher D-IVA exposures. This trend was consistent with the results of the SwCl E-R analyses for the phase 2 dose-ranging Study 561-101 (Report Q116).	

Source: Reviewer's summary

Abbreviations: C_{avg} , average concentration at steady-state; CI, confidence interval; CFTR, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; E_{max} , maximum effect; E-R, exposure response; GOF, goodness-of-fit; IIV, interindividual variability; IVA, ivacaftor; PK, pharmacokinetic; PK/PD, pharmacokinetic-pharmacodynamic; RSE, relative standard error; SAEM, stochastic approximation expectation maximization; SwCl, sweat chloride; TC, triple combination; VNZ, vanzacaftor; VPC, visual predictive check; yr, year

Table 156. Labeling Statements Supported by VNZ PK - SwCl Analysis

Labeling Language	Description	Acceptability (FDA's Comments)
12.3 PK	NA	

Source: Reviewer's summary

Abbreviations: NA, not applicable; PK, pharmacokinetic

Report T299/Tables

Table 157. SwCl Data: Baseline Categorical Covariate Summary Stratified by Study

	Study				Summary n = 1113
	101 n = 86	102 n = 390	103 n = 560	105 n = 77	
Sex					
Male	59 (68.6)	233 (59.7)	285 (50.9)	43 (55.8)	620 (55.7)
Female	27 (31.4)	157 (40.3)	275 (49.1)	34 (44.2)	493 (44.3)
Genotype					
F/MF	58 (67.4)	390 (100.0)	0 (0.0)	24 (31.2)	472 (42.4)
F/F	28 (32.6)	0 (0.0)	436 (77.9)	37 (48.1)	501 (45.0)
F/G	0 (0.0)	0 (0.0)	39 (7.0)	3 (3.9)	42 (3.8)
F/RF or F/other	0 (0.0)	0 (0.0)	46 (8.2)	3 (3.9)	49 (4.4)
TCR	0 (0.0)	0 (0.0)	39 (7.0)	10 (13.0)	49 (4.4)
Age Group					
6-11 years	0 (0.0)	0 (0.0)	0 (0.0)	77 (100.0)	77 (6.9)
12-17 years	0 (0.0)	55 (14.1)	76 (13.6)	0 (0.0)	131 (11.8)
Adults	86 (100.0)	335 (85.9)	484 (86.4)	0 (0.0)	905 (81.3)

Source: Table S16, t299 report

Abbreviations: F, *F508del* *CFTR* variant; G, gating *CFTR* variant; MF, minimal function *CFTR* variant; RF, residual function *CFTR* variant; SwCl, sweat chloride; TCR, triple combination responsive *CFTR* variant; TEZ, tezacaftor

Table 158. SwCl Data: Baseline Continuous Covariate Summary Stratified by Study

Study	n	Mean	Median	SD	Min / Max
Baseline Age (years)					
101	86	32.0	30.5	9.53	18.0 / 64.0
102	390	30.7	30.8	10.9	12.2 / 71.6
103	560	33.7	33.2	12.4	12.2 / 71.2
105	77	9.03	9.16	1.74	6.17 / 12.0
<i>All data</i>	1113	30.8	30.8	12.8	6.17 / 71.6
Baseline SwCl (mmol/L)					
101	86	96.5	97.5	10.3	63.5 / 115
102	390	54.0	53.9	17.6	10.0 / 114
103	560	42.8	42.4	18.2	10.0 / 113
105	77	40.4	39.0	20.9	11.0 / 110
<i>All data</i>	1113	50.7	48.5	22.8	10.0 / 115

Source: Table S17, t299 report
 Abbreviations: SD, standard deviation; SwCl, sweat chloride

Table 159. SwCl Final Model: Summary of SwCl Fixed Effects Parameter Estimates

			Estimate	95% CI	RSE (%)
Structural model parameters					
EC50 (ng/mL)	$\exp(\theta_1)$	VNZ concentration achieving half of the maximum effect	17.7	11.4, 27.3	22.5
$t_{1/2}$ VNZ (days)	$\exp(\theta_4)$	Half-life of VNZ effect	2.60	2.21, 3.05	8.32
$t_{1/2}$ ELX (hours)	θ_5	Half-life of ELX effect	27.4	FIXED	-
Genotype effects					
EELX ~ F/MF (mmol/L)	θ_6	ELX effect for F/MF genotype	-41.6	-43.3, -40.0	2.00
EELX ~ F/F (mmol/L)	θ_8	ELX effect for F/F genotype	-45.1	-46.8, -43.4	1.93
EELX ~ F/G (mmol/L)	θ_9	ELX effect for F/G genotype	-22.4	-27.1, -17.7	10.6
EELX ~ F/RF (mmol/L)	θ_{10}	ELX effect for F/RF genotype	-19.1	-23.8, -14.3	12.7
EELX ~ TCR (mmol/L)	θ_{11}	ELX effect for TCR genotype	-32.7	-43.7, -21.6	17.3
E _{max} ~ F/MF	θ_2	VNZ E _{max} for F/MF genotype	-50.2	-52.2, -48.3	1.97
E _{max} ~ F/F	θ_{12}	VNZ E _{max} for F/F genotype	-51.9	-53.9, -50.0	1.89
E _{max} ~ F/G	θ_{13}	VNZ E _{max} for F/G genotype	-22.1	-28.3, -15.8	14.4
E _{max} ~ F/RF	θ_{14}	VNZ E _{max} for F/RF genotype	-21.6	-26.8, -16.4	12.3
E _{max} ~ TCR	θ_{15}	VNZ E _{max} for TCR genotype	-39.7	-49.5, -29.9	12.6
Covariate effect parameters					
SwCl0 ~ Female	θ_{16}	Female effect on untreated baseline SwCl	-0.0511	-0.0685, -0.0336	17.4
E _{max} ~ AGE	θ_{18}	Age < 12 effect on E _{max}	-4.46	-7.04, -1.88	29.5

Source: Table 6, t299 report
 Model run 3005: Parameters estimated in the log-domain were back-transformed for clarity
 Confidence intervals = estimate $\pm$ 1.96 x SE
 RSE (%) of thetas = (SE/abs(estimate)) x 100; RSE (%) of log-transformed thetas = $\sqrt{\exp(\text{SE}^2) - 1} \times 100$
 Abbreviations: abs, absolute value; CI, confidence intervals; ELX, elxacaftor; EELX, elxacaftor effect; E_{max}, VNZ maximum effect; F, *F508del CFTR* variant; G, gating *CFTR* variant; MF, minimal function *CFTR* variant; RF, residual function *CFTR* variant; RSE, residual standard error; SE, standard error; SwCl, sweat chloride TCR, non-*F508del* triple combination responsive genotype; VNZ, vanzacaftor

Table 160. SwCl Final Model: Summary of SwCl Random Effects Parameter Estimates

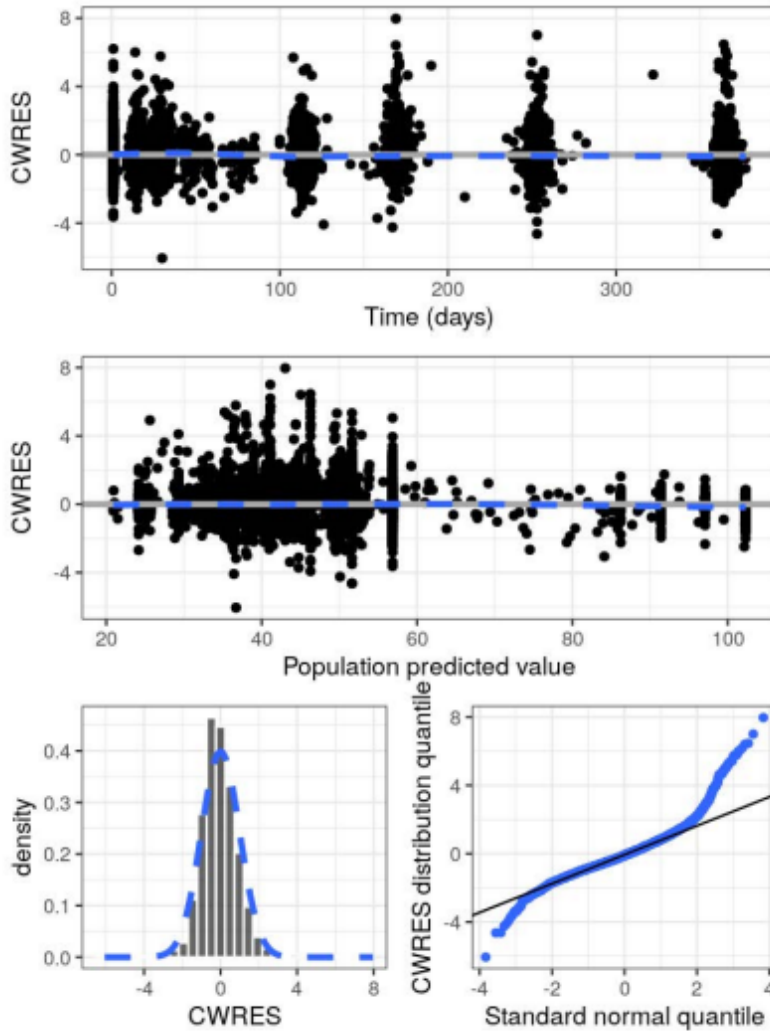
		Estimate	95% CI	Shrinkage (%)	pRSE
Interindividual variance parameters					
IIV-SwCl0	$\Omega_{(1,1)}$	45.9 [SD=6.78]	9.36, 82.5	28.0	40.6
IIV-Emax	$\Omega_{(2,2)}$	151 [SD=12.3]	101, 200	15.0	16.7
IIV-EELX	$\Omega_{(3,3)}$	136 [SD=11.7]	83.0, 189	11.2	19.9
Interindividual covariance parameters					
SwCl0-Emax	$\Omega_{(2,1)}$	28.2 [Corr=0.338]	-0.282, 56.6	-	-
SwCl0-EELX	$\Omega_{(3,1)}$	33.5 [Corr=0.424]	12.2, 54.8	-	-
Emax-EELX	$\Omega_{(3,2)}$	136 [Corr=0.950]	92.9, 179	-	-
Residual variance					
Additive	$\exp(\theta_7)$	83.2 [SD=9.12]	75.3, 92.0	-	5.12

Source: Table 7, t299 report

Abbreviations: CI, confidence interval; EELX, elexacaftor effect; $E_{\max}$, maximum effect; IIV, interindividual variability; pRSE, percent relative standard error; SD, standard deviation; SwCl, sweat chloride

Report T299/Figures

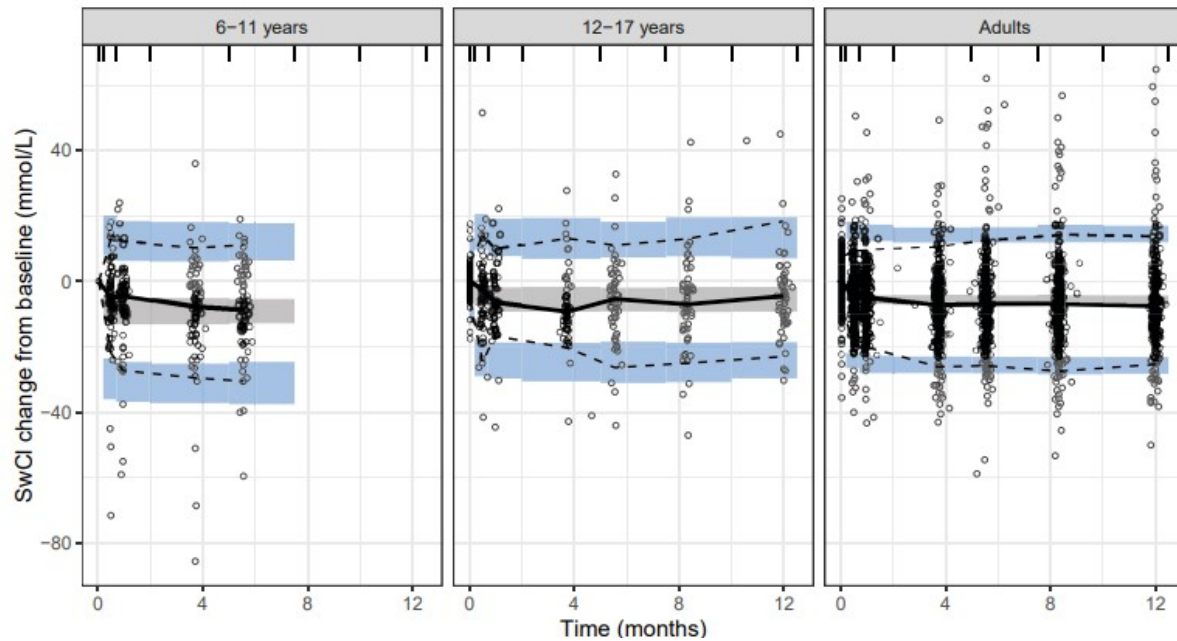
Figure 82. SwCI Final Model: CWRES Versus Time and Population Predictions, CWRES Density Histogram and Quantile-Quantile



Source: Figure S139, t299 report

Note: Scatter plots: Solid black circles represent the individual CWRES values associated with each observation record. The solid horizontal gray line (residuals = 0) was included for reference. The dashed blue line represents a LOESS smooth through the data. Density plot: density frequency (count) of the CWRES. Q-Q plot: solid blue circles represent the conditional weighted residual values associated with each observation record. The solid black line (y=x) is included for reference.

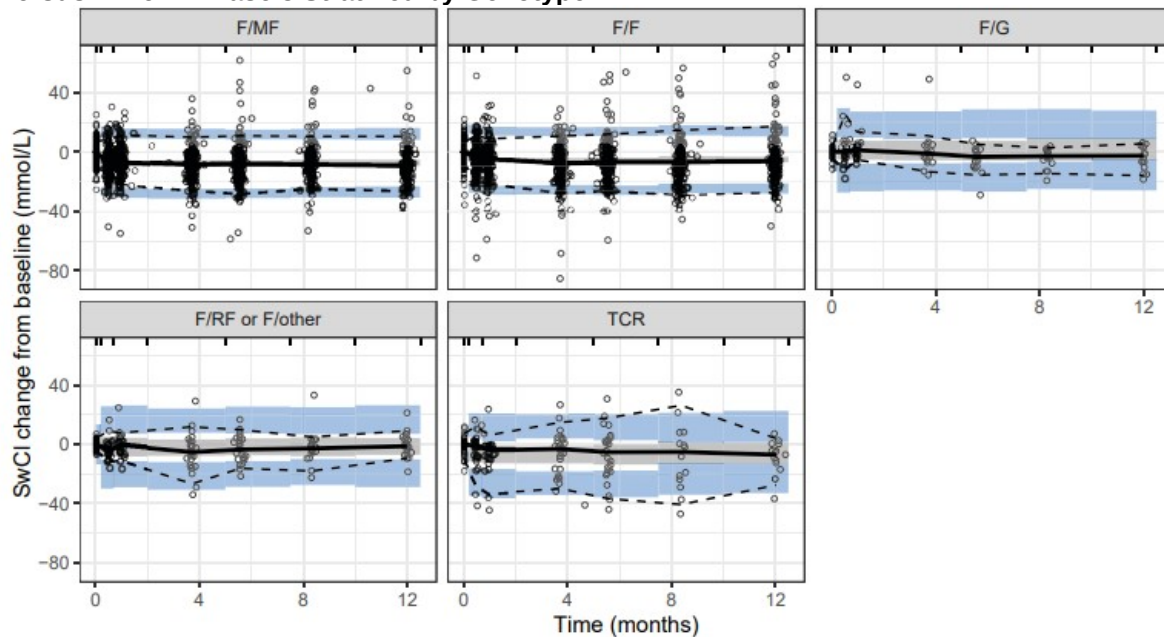
Abbreviations: CWRES, conditional weighted residual; LOESS, locally weighted scatterplot smoothing

Figure 83. SwCl Final Model: VPC of the Sweat Chloride Concentration Change From Baseline Versus Time in Phase 3 Stratified by Age Group

Source: S156, t299 report

The black lines represent the median (solid) or 5th/95th (dashed) percentiles of the observed data. The shaded areas represent 95% prediction intervals for median (gray) or 5th/95th percentiles (blue) for simulated data.

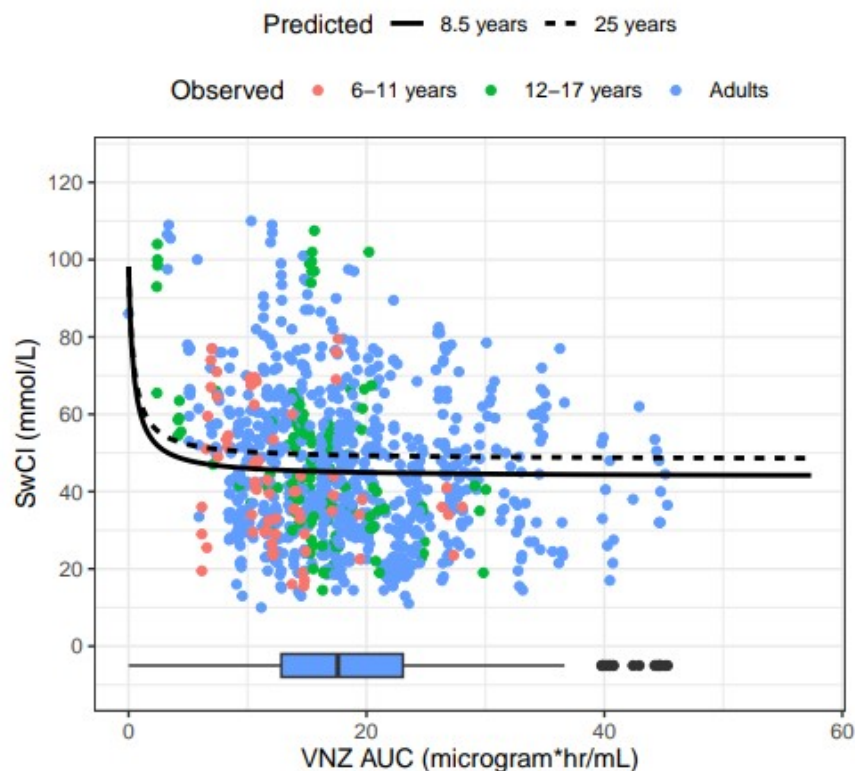
Abbreviations: SwCl, sweat chloride; VPC, visual predictive check

Figure 84. SwCl Final Model: VPC of the Sweat Chloride Concentration Change From Baseline Versus Time in Phase 3 Stratified by Genotype

Source: Figure S158, t299 report

The black lines represent the median (solid) or 5th/95th (dashed) percentiles of the observed data. The shaded areas represent 95% prediction intervals for median (gray) or 5th/95th percentiles (blue) for simulated data.

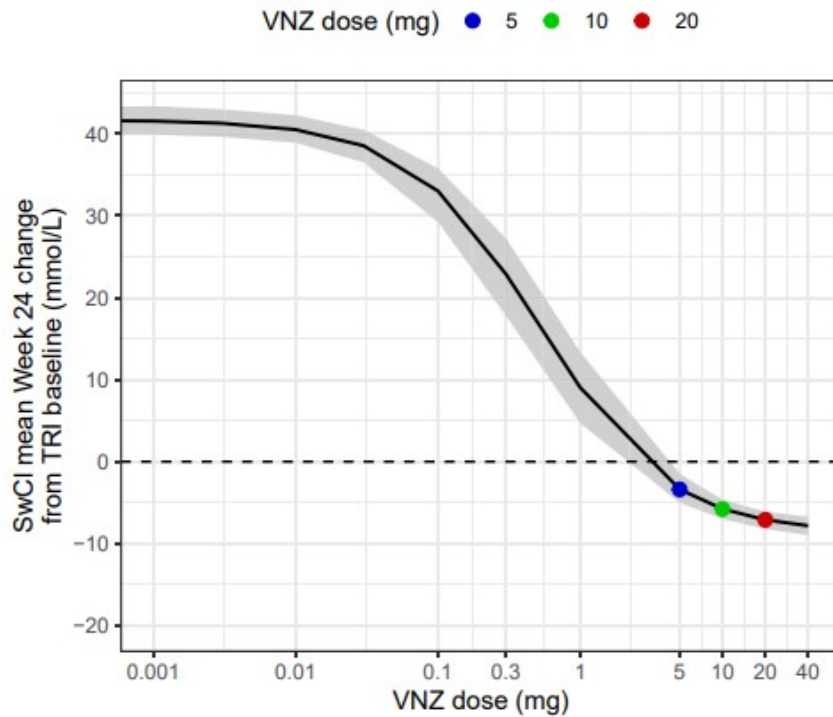
Abbreviations: F, *F508del* *CFTR* variant; G, gating *CFTR* variant; MF, minimal function *CFTR* variant; SwCl, sweat chloride; RF, residual function *CFTR* variant; TCR, non-*F508del* triple combination responsive genotype; VNZ, vanzacaftor; VPC, visual predictive check

Figure 85. SwCl Simulation: Sweat Chloride Concentration Versus Vanzacaftor AUC for Subjects With the F/MF Genotype

Source: Figure A4, t299 report

The points represent observed SwCl in patients from phase 3 studies, measured 4 or more weeks after randomization to VNZ/TEZ/D-IVA following ELX/TEZ/IVA run-in. The black lines are population predictions from the final SwCl model for an 8.5 (solid) and 25 (dashed) year old patient. All data, observed and simulated, reflect SwCl under treatment with TEZ/D-IVA in addition to VNZ. The boxplot summarizes observed vanzacaftor AUC in adult patients with the F/MF genotype administered 20 mg vanzacaftor (in combination with TEZ/D-IVA). Median AUC values are designated by a solid line in the center of the box. Boxes indicate the IQR with whiskers extending to 1.5*IQR.

Abbreviations: AUC, area under the concentration-time curve; F, *F508del CFTR* variant; G, gating *CFTR* variant; IQR, interquartile range; MF, minimal function *CFTR* variant; SwCl, sweat chloride; TCR, non-*F508del* triple combination responsive genotype; VNZ, vanzacaftor; VPC, visual predictive check

Figure 86. SwCl Simulation: Sweat Chloride Concentration Change From ELX/TEZ/IVA Baseline at 24 Weeks Versus Vanzacaftor Dose for Subjects With the F/MF Genotype

Source: Figure A6, t299 report

The shaded area marks the 95% confidence interval for the mean SwCl change from ELX/TEZ/IVA baseline dose-response curve across 1000 simulation replicates and the solid line marks the median. The dashed horizontal line indicates zero change from baseline. The blue, green, and red points mark the median prediction for the 5, 10, and 20 VNZ dose groups, respectively.

Simulations reflect SwCl change from baseline under treatment with TEZ/D-IVA in addition to VNZ.

Abbreviations: ELX, elexacaftor; TEZ, tezacaftor; VNZ, vanzacaftor; VPC, visual predictive check

The FDA's Assessment

The Applicant's population PK/PD analysis is considered acceptable for the purpose of supporting analyses objectives.

14.5.2. Physiologically Based Pharmacokinetic Modeling Review

Executive Summary

The objective of this review is to evaluate the adequacy of the Applicant's PBPK modeling analyses to predict the following:

- (1) The DDI effect of moderate CYP3A4 inhibitors (fluconazole, erythromycin, and verapamil) on the PK of single and multiple doses of VNZ and D-IVA in adults.
- (2) The DDI effect of strong and moderate CYP3A4 inducers on the PK of multiple doses of VNZ and D-IVA in adults.
- (3) The DDI effect of strong and moderate CYP3A4 inhibitors on the PK of multiple doses of VNZ and D-IVA in children aged 6 through 11 years.
- (4) To determine dose adjustment regimens when using the to-be marketed FDC tablet (VNZ Form D 10 mg /TEZ 50 mg/D-IVA 125 mg) in the presence of moderate or strong CYP3A inhibitors in adults.
- (5) The DDI effect of VNZ and D-IVA on CYP2C9 substrates.

The Divisions of Inflammation and Immune Pharmacology and Pharmacometrics have reviewed the PBPK submission (Reports T183, T322, T333, response to Information Requests, August 23, 2024, and September 6, 2024, SDN 0019 and 0022, Module 1.11.3) to conclude the following:

- Simulations predicted 2.4- to 3.9-fold increase in the AUC of VNZ when single or multiple doses of VNZ was coadministered with multiple doses of a moderate CYP3A inhibitor.
- Simulations predicted 2.9- to 4.8-fold increase in area under the concentration-time estimated to infinity (AUC_{inf}) and 3.1- to 5.1-fold increase in $AUC_{0-24,ss}$ of D-IVA when a single dose or multiple doses of D-IVA was coadministered, respectively, with a moderate CYP3A inhibitor.
- Simulations predicted 82% and 90% reduction in VNZ and D-IVA exposure, respectively, when coadministered with rifampin, a strong CYP3A inducer. Efavirenz, a moderate CYP3A inducer, was predicted to decrease the exposure to VNZ and D-IVA by 69% and 73%, respectively.
- Simulation predicted increase in VNZ $C_{max,ss}$ and $AUC_{0-24,ss}$ by approximately 10- and 11-fold in children 6 through 11 years weighing ≥ 40 kg, and 10- and 9.5-fold in children 6 through 11 years weighing < 40 kg, respectively, when multiple doses of VNZ were coadministered with itraconazole, a strong CYP3A inhibitor. Similarly, D-IVA $C_{max,ss}$ and $AUC_{0-24,ss}$ is predicted to increase by 7.4- and 14-fold in children 6 through 11 years weighing ≥ 40 kg, and 6.8- and 14-fold in children 6 through 11 years weighing < 40 kg, respectively, when D-IVA was coadministered with itraconazole.
- Simulation predicted increase in VNZ $C_{max,ss}$ and $AUC_{0-24,ss}$ by 2.5- and 2.6-fold in children 6 through 11 years weighing ≥ 40 kg, and 2.5- and 2.6-fold in children 6 through 11 years

weighing <40 kg when multiple doses of VNZ were coadministered with fluconazole, a moderate CYP3A inhibitor. The increase in D-IVA $C_{max,ss}$ and $AUC_{0-24,ss}$ when coadministered with fluconazole was predicted to be 2.1- and 3.2-fold, respectively, in children 6 through 11 years weighing ≥ 40 kg or <40 kg.

- The predicted increases in AUC and C_{max} with CYP3A inhibitors were similar between children aged 6 through 11 years and adults at the proposed therapeutic doses of VNZ and D-IVA, assuming the exposure levels of CYP3A inhibitors are similar between adults and pediatrics.
- PBPK simulations in adults support reduction in the therapeutic dose of VNZ/TEZ/D-IVA when coadministered with CYP3A4 inhibitors as follows:
 - When coadministered with a strong CYP3A inhibitor reduce dose from two FDC tablets of (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg) daily to one FDC tablet once weekly (b) (4)
 - When coadministered with a moderate CYP3A inhibitor reduce dose from two FDC tablets of (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg) daily to one FDC tablet every other day (b) (4).
- PBPK simulations did not rule out the DDI risk for clinical inhibition of D-IVA with a sensitive CYP2C9 substrate (e.g., warfarin and tolbutamide)

PBPK Model for Tezacaftor

The PBPK model for TEZ was reviewed under the original NDA 210491. The analysis was considered adequate to predict the extent of the interaction effect with a moderate CYP3A inhibitors under multiple-dose TEZ. Tezacaftor steady-state AUC and C_{max} were predicted to increase 2.1-fold and 1.7-fold, respectively, when the moderate CYP3A4 inhibitor fluconazole is coadministered (NDA 210491, Clinical Pharmacology and Biopharmaceutics Review(s), Section 4). In a clinical DDI study with TEZ and the strong CYP3A4 inhibitor itraconazole, the observed increase in AUC in the presence of itraconazole was 4-fold. The Applicant has prioritized matching VNZ and D-IVA exposures over matching TEZ exposure for dose adjustments to ensure exposures remain within the range of the therapeutic regimen. The reason for this approach is that VNZ and D-IVA exposures were substantially increased by CYP3A inhibitors as compared to TEZ. Therefore, dose adjustment of VNZ/TEZ/D-IVA will be by the same percentage. This rationale was considered acceptable by the review team.

PBPK Model for Vanzacaftor

Background

VNZ, TEZ, and D-IVA are mainly metabolized by CYP3A4/5. In recombinant human CYPs system, the remaining percentages of VNZ in CYP3A4 and CYP3A5 incubates were 43% and 81%, respectively, suggesting CYP3A4 and CYP3A5 may be the CYP isozymes involved in VNZ metabolism (Study N295).

VNZ showed inhibition of CYP2B6 ($IC_{50}=14.2$ μ M), CYP2C8 ($IC_{50}=18.1$ μ M), and CYP2C9 ($IC_{50}=18.4$ μ M) in vitro (Study N189). At clinically relevant exposures, VNZ, TEZ, and D-IVA

and their major metabolites showed low potential for CYP induction in human hepatocyte in vitro assessments using mRNA as endpoint (Study 661-006 and Study CNCT-1005)

The Madin-Darby canine kidney and Caco-2 cells permeability results indicated VNZ is a low permeable compound (Reports 280 and 327) and D-IVA exhibited moderate permeability in wild-type Madin-Darby canine kidney II cells (Report CTP-656 DM-090). In vitro, VNZ was not a substrate of efflux or hepatic uptake transporters, and it showed low potential to inhibit organic anion transporter (OAT)P1B1 ($IC_{50}=45.1 \mu M$, $R=1.008$), and OATP1B3 ($IC_{50}=61.7 \mu M$, $R=1.006$), but it may inhibit breast cancer resistance protein (BCRP) ($IC_{50}=0.252 \mu M$, $R=532$), P-glycoprotein (P-gp) ($IC_{50}=3.8$, $R=35$), and OAT1 ($IC_{50}=0.42 \mu M$, $R=0.8$) (see Section 8.2). The plasma protein binding, mainly to albumin, for VNZ and D-IVA is >99% (Reports N355, M108, and T235).

Human mass balance data of VNZ (Study 004) showed that mean $AUC_{0-\infty}$ value for unchanged VNZ in plasma was approximately 77% of circulating TRA as determined by the AUC ratio after a single dose of ^{14}C -VNZ 20 mg/200 μCi administered as an oral solution. Mean recovery of TRA was 0.502% in urine and 91.6% of the radioactive dose recovered in feces, demonstrating minimal renal excretion and major fecal excretion. VNZ accounted for most of the total circulating radioactivity in plasma (mean =96.2%) without major circulating metabolites. VNZ is mainly cleared by metabolism in humans with unchanged VNZ recovered in excreta accounted for less than 10% of the administered radioactive dose. The most abundant metabolite in feces was M6-VNZ, which accounted for 26.1% of the administered radioactive dose followed by M55-VNZ, M19-VNZ, M57-VNZ, and M9-VNZ, which accounted for 7.4%, 6.9%, 6.9%, and 6.8% of the administered dose, respectively. The mean $t_{1/2}$, clearance (CL)/F and V_z/F of VNZ in plasma were 60.8 hr, 0.596 L/hr and 50.6 L, respectively. The distribution to blood was 56%.

Methods

Software

Simcyp® Version 21 (Simcyp Ltd, A Certara Company) was used for PBPK analyses by the Applicant and the review team.

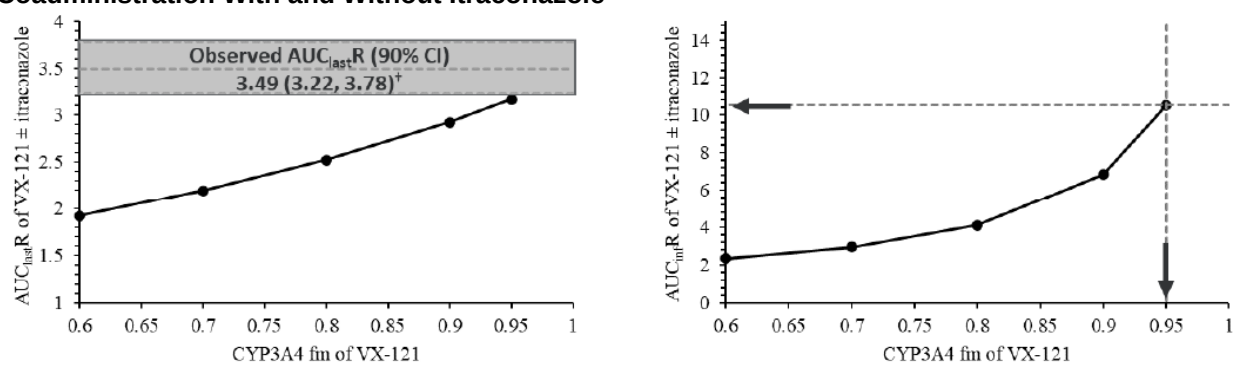
Model Development

The VNZ base model was constructed using the available in vitro ADME data and clinical data (Study 007; itraconazole DDI study). The fraction of VNZ escaping gut extraction (F_g) and fraction of VNZ dose absorbed (F_a) were predicted to be 0.98 and 0.90, respectively, by the first-order absorption model, and bioavailability (F) was estimated to be 0.88. The absorption rate constant (K_a) for VNZ was optimized to $0.91 h^{-1}$.

The central volume of distribution and CL were estimated using the full PBPK model and PK data from Study 007 in which a single dose of 5 mg VNZ Form A was administered alone or in the presence of itraconazole. The fraction of VNZ metabolized by CYP3A4 (f_m CYP3A4) was optimized to 0.95 based on in vitro human CYP reaction phenotyping studies (Study N295, % of VNZ remaining in CYP3A4 occupant was 43%) and the clinical itraconazole DDI data (Study 007, $f_m=0.71$).

In response to FDA's request for information (dated August 23, 2024), the Applicant conducted sensitivity analysis of CYP3A4 f_m values in the range of 60% to 95% to evaluate the impact of uncertainty of the CYP3A4 f_m value on the DDI effect of CYP3A4 inhibitors (Figure 87). Using a CYP3A4 f_m value of 0.95, the predicted $AUC_{last}R$ value was 3.2 following VNZ administration with and without itraconazole for 14 days, which is at the lower limit of the observed $AUC_{last}R$ (90%CI) of 3.49 (3.22, 3.78). Moreover, CYP3A4 f_m of 0.95 predicted a $AUC_{inf}R$ of 10.5 following VNZ administration with and without itraconazole for 65 days. On the other hand, the AUC ratios of VNZ were relatively insensitive to the CYP3A4 f_m values in the range of 60% to 95% for moderate CYP3A4 inhibitors (e.g., fluconazole). For example, the range of the $AUC_{inf}R$ for VNZ over the considered f_m values was approximately 1.6 (Figure 88).

Figure 87. Parameter Sensitivity Analysis for the Fractional Contribution of CYP3A4 to Total Clearance of VNZ on the Ratio of its Predicted AUC_{last} (Left) or AUC_{inf} (Right) Upon Coadministration With and Without Itraconazole



Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Figure 4

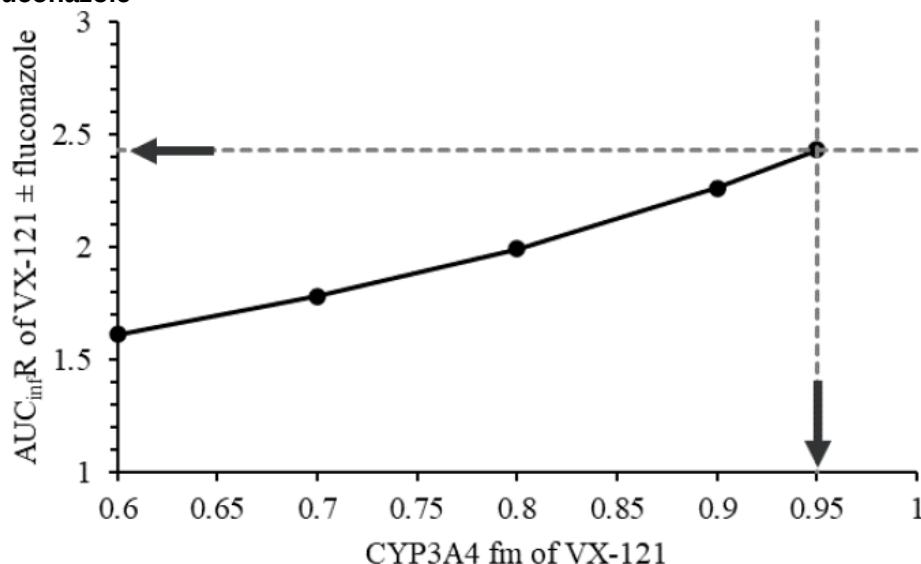
Notes: Left panel: AUC_{last} corresponds to AUC_{0-264h} calculated based on individual plasma concentration-time profiles of VX-121 [VNZ] in the presence of itraconazole for 264 hours. The VX-121 [VNZ] f_m value was calibrated using $AUC_{last}R$ because itraconazole dosing did not fully cover the VX-121 [VNZ] elimination phase in Study 007 due to the long half-life of VX-121 [VNZ].

Right panel: Arrows indicate the optimized f_m CYP3A4 from the point estimate of AUC ratio based on the itraconazole DDI study (Study 007) and in vitro human CYP reaction phenotyping studies (Report N295).

At each CYP3A4 f_m , CL_{int} was calculated using the reverse transitional tool then simulation was conducted to predict the increase in AUC of VX-121 [VNZ] following the administration of itraconazole 200 mg once daily for 14 days and 65 days.

Abbreviations: AUC, area under the concentration-time curve; AUC_{inf} , area under the concentration-time curve estimated to infinity; AUC_{last} , area under the concentration-time curve to the last measurable concentration; AUC_{0-264h} , area under the concentration-time curve from time 0 to 264 hours; CI, confidence interval; CYP, cytochrome P450; D-IVA, deutivacaftor; DDI, drug-drug interaction; f_m , fraction metabolized; IVA, ivacaftor; PK, pharmacokinetic; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Figure 88. Parameter Sensitivity Analysis for the Fractional Contribution of CYP3A4 to Total Clearance of VNZ on the Ratio of its Predicted AUC_{inf} Upon Coadministration With and Without Fluconazole



Source: Applicant's response to IR submitted Aug 23, 2024, SDN 0019, Module 1.11.3, Figure 5

Note: Arrows indicate the optimal f_m CYP3A4 from the point estimate of AUC ratio.

At each CYP3A4 f_m , CL_{int} was calculated using the reverse transitional tool then simulation was conducted to predict the increase in AUC of VX-121 [VNZ] following the administration of fluconazole 200 mg once daily for a total of 19 doses.

Abbreviations: AUC_{inf}, area under the concentration-time curve estimated to infinity; CYP, cytochrome P450; f_m , fraction metabolized; VX-121 [VNZ], vanzacaftor

CYP3A4-mediated intrinsic clearance, CL_{int} , was calculated using the retrograde method, an $f_m=0.95$ and estimated hepatic clearance CL_{iv} of 0.52 L/h. [Table 161](#) summarizes model input parameters for VNZ.

The predicted V_{ss} was 0.605 (L/kg) using Method 2 and a full PBPK model which is comparable to the measured $V_{ss}=50.6$ L from the mass balance Study 004 (0.583 L/kg for subjects weighting 86.8 kg) and to population pharmacokinetic (PopPK) predicted volume of distribution/ $F=59.2$ L for Study 007. The mean CL/F of unchanged VNZ obtained from the mass balance Study 004 was 0.596 L/h. The apparent clearance ($CL/F=0.78$ L/h) obtained from the PBPK predicted VNZ PK profiles when administered alone is comparable to the $CL/F=0.761$ obtained from Study 007. The PBPK predicted oral CL (Dose/AUC_{inf}) of VNZ PK profile when administered with itraconazole was 0.13 L/h, while the observed CL/F in Study 007 was 0.124 L/h. The blood to plasma ratio of 0.588 is comparable to the distribution to blood of 56% obtained from the mass balance Study 004.

Table 161. Model Input Parameters for VNZ PBPK Model

Parameter	Value	Reference
Physical-Chemical Properties		
Mol Weight (g/mol)	617.76	VV-NC-005208
$\log P_{o:w}$	5.41	VV-NC-005208
Compound Type	Weak Acid	VV-NC-005208
pK_a	4.65	VV-NC-005208
Blood to plasma ratio	0.588	Report N309
f_{up}	0.000137	Report N355
Plasma binding components	HSA	Assumed

Parameter	Value	Reference
Absorption (First Order Model)		
Fraction available for absorption (F_a)	1	Assumption
Absorption Rate constant (K_a) (1/h)	0.19	Optimized in Simcyp
F_u (gut)	0.007 (PSA)	Optimized in Simcyp
Q_{gut} (L/h)	14.491	Optimized in Simcyp, predicted value =6.49 L/h
Disposition (Full PBPK)		
V_{ss} (L/kg)	0.605	Predicted with Method 2
CL_{iv} (L/hr)	0.5155	Optimized in Simcyp
K_p scalar	11.0	Optimized in Simcyp
Elimination		
f_m CYP3A4	95%	Optimized in SimCyp
rCYP3A4 CL_{int} (μ L/min/pmol of isoform)	8.21	Optimized in Simcyp
Other HLM (μ L/min/mg protein)	52.8	Optimized in Simcyp

Source: Report T183, Table 10-1

Abbreviations: CYP, cytochrome P450; HAS, human serum albumin; PBPK, population-based pharmacokinetic; VNZ, vanzacaftor

Based on in vitro studies, VNZ is not a substrate of P-gp, BCRP, OATP1B1, or OATP1B3. VNZ may have the potential to inhibit BCRP (IC_{50} =0.252 μ M, R =532), P-gp (IC_{50} =3.8 μ M, R =35) and OAT1 (IC_{50} =0.42 μ M, R =0.8). The VNZ inhibition parameters towards CYP2C9 (IC_{50} =18.4 μ M) determined in vitro (Study N189) was used in the model for DDI risk assessment on CYP2C9 substrates (e.g., warfarin and tolbutamide).

Model Validation

Clinical PK and DDI studies used to support VNZ model development, and validation are listed in [Table 162](#).

Vanzacaftor was provided in two forms in the clinical program, Form A and Form D. Form D has had 50% bioavailability of Form A based on relative bioavailability results. To simulate the PK profiles of VNZ Form D that was used in phase 3 studies in FDC, half the clinical dose was used during simulations (i.e., if the clinical dose of VNZ is 20 mg, simulations were conducted with 10 mg dose to capture the PK profile of 20 mg).

In response to FDA's request for information (dated August 23, 2024), the Applicant conducted additional validation of the predictive performance of the PBPK models of VNZ and D-IVA (and its metabolites) for multiple-dose PK in subjects with cystic fibrosis using FDC tablet from Studies 102 and 103 ([Table 162](#)). Additional validation for VNZ PBPK model was performed by the review team using PK data obtained following the administration of single or multiple doses of VNZ Form A or Form D.

All simulation were conducted in adult healthy population with VNZ administered in fed state. The fixed-dose combination drug is recommended to be taken with food. In DDI simulations with itraconazole, VNZ was administered at the same time in fed stated. Simulations conducted with VNZ administered in fed state 1 hour following the administration of itraconazole in fasted state showed similar PK parameters compared to when VNZ and itraconazole were administered at the same time.

Table 162. Clinical Studies Used in VNZ PBPK Model Development and Validation

Study No.	Study Description	Roles in PBPK Analyses	Model Objective
<i>Studies Used by the Applicant</i>			
007	- Clinical DDI between VNZ (Form A, 5 mg) with itraconazole (200 mg QD) in healthy adult subjects. - VNZ was given on Day 1 and 18 as a separate tablet under fed conditions. - Itraconazole was given on Days 15 through 28 under fasting state.	- To estimate disposition parameters and CYP3A4 f_m - To validate model performance in predicting single dose PK (using data from control group)	Development and validation
102 103	- Subjects with cystic fibrosis received VNZ (20 mg, Form D)/TEZ (100 mg)/D-IVA (250 mg) QD over 52 weeks treatment period. - Subjects in Trials 102 and 103 were different in the genetic variants responsible for CF - PK samples collected predose on Week 4, 16, and 24. On Week 8: pr-dose and 2, 4, 5, 6, and 7 hours postdose	To validate model performance in predicting multiple dose PK	Validation
<i>Studies Used by the Reviewer</i>			
003	Healthy adult subjects received a single dose of VNZ 20 mg, TEZ 100 mg, and D-IVA 150 mg orally in the fed state, either as an FDC [Form D] or as separate tablets [Form A]	To validate model performance in predicting single dose PK	Validation
005	To evaluate relative BA of a FDC tablet of VNZ 20 mg [Form]/TEZ 100 mg/D-IVA 250 mg compared to VNZ 10 mg [Form A], TEZ 100 mg, and D-IVA 250 mg coadministered as separate tablets	To validate model performance in predicting single dose PK	Validation
006	To evaluate the PK of VNZ (10 mg, Form A), TEZ (100 mg), and D-IVA (250 mg) when administered separately and together for 14 days in healthy subjects	To validate model performance in predicting multiple dose PK	Validation

Source: Reviewer's summary

Abbreviations: BA, bioavailability; CF, cystic fibrosis; CYP, cytochrome P450; D-IVA, deutivacaftor; DDI, drug-drug interaction; No., number; PBPK, population-based pharmacokinetic; FDC, fixed-dose combination PK, pharmacokinetic; QD, once daily; TEZ, tezacaftor; IVA, ivacaftor; VNZ, vanzacaftor

Clinical PK data from Study 006 suggested that VNZ C_{max} and AUC increased by 48% and 54% in the presence TEZ/D-IVA. This study PK data was used in verification of predictive PK performance of VNZ. Further, the target VNZ exposure for DDI dose adjustment was based on

the exposure following administration of the FDC tablet. Of note, these VNZ exposure increases were not considered to be clinically meaningful as dose-selection for the two phase 3 trials was based on triple combination (TC) therapy instead of monotherapy. Therefore, it is acceptable that the PBPK model of VNZ and analyses did not incorporate TEZ/D-IVA.

Perpetrator Models

The software's default PBPK models of the strong CYP3A inhibitor itraconazole (fasted solution) and moderate CYP3A inhibitors fluconazole, erythromycin, and verapamil, were used to predict the CYP3A inhibition effects on VNZ PK.

Model Application

- To simulate the effect of the strong CYP3A4 inhibitor itraconazole on the PK of VNZ at steady state in adults and children aged 6 through 11 years.
- To simulate the effect of moderate CYP3A4 inhibitors (fluconazole, erythromycin, and verapamil) on the PK of VNZ following single-dose and at steady state, in adults and children aged 6 through 11 years.
- To determine dose adjustment regimens when using the FDC tablet (VNZ Form D 10 mg /TEZ 50 mg/D-IVA 125 mg) in the presence of strong and moderate CYP3A inhibitors in adults and children 6 through 11 years of age.

Results

Model Validation

Evaluation of the Predictive Performance for PK Under Different Dosing Scenario

The VNZ PBPK model adequately described the VNZ plasma concentration-time profiles ([Figure 89](#)) and PK parameters (AUC_{last} and C_{max}) following a single dose of 5 mg [Form A] administered under fed condition with predicted/observed ratios within 0.8 to 1.25 ([Table 163](#)). Further, the model adequately predicted the PK of VNZ in the presence of itraconazole up to 264 hours post VNZ coadministration ([Figure 89](#)), and the AUC_{last} and C_{max} ratio for the DDI with itraconazole ([Table 164](#)).

Of note, in the clinical DDI study (Study 007), itraconazole (solution) was taken in the fasted condition approximately 1 hour before VNZ dosing in the fed state on the day of coadministration. Although the Applicant's PBPK analyses allowed dosing of VNZ under fed state and itraconazole under fasted state, the 1-hour staggering in drugs dosing was not applied. The review team conducted simulations between VNZ and itraconazole with 1-hour staggering between the two drugs, and the simulated PK profiles and DDI effects were similar to dosing VNZ and itraconazole at the same time. Moreover, this reviewer conducted the simulation with itraconazole administered on Day 15 and VNZ administered on Day 18 (after 72 hours) and the results were comparable to same day administration.

Additional model validation was conducted using PK of VNZ administered as 10 mg (Form A, separate tablet, Study 005) and 20 mg (Form A separate tablet, Study 003), which showed

predicted/observed ratios for AUC_{last} and C_{max} within 0.8 to 1.25 ([Table 163](#), [Figure 90](#)).

Moreover, the review team conducted model validation using multiple dose PK data in healthy subjects of VNZ from two cohorts in Study 006. The predicted/observed ratios for AUC_{last} and C_{max} were within 0.8 to 1.25 for one cohort in Study 006 ([Table 163](#)).

It appears that the performance of VNZ PBPK model to predict the PK data obtained from healthy subjects (e.g., Studies 007, 005, and 006) is different to certain extent from the predictability of PK data from subjects with CF (e.g., Studies 102 and 103). Of note, VNZ model prediction of PK data from subjects with CF is around unity, compared to a wide prediction performance (e.g., predicted/observed ratios range from 0.8 to 1.32) using PK data from healthy subjects.

Table 163. Summary of Observed and Predicted Mean AUC_{last} and C_{max} of VNZ Used in Model Development and Validation

Study		C_{max} (µg/mL)	AUC_{last} (h·µg/mL)
Study 007 VNZ 5 mg Form A alone	Observed	0.073	6.63
	Predicted	0.82	7.18
	P/O	1.12	1.08
Study 007 VNZ 5 mg Form A + itraconazole	Observed	0.113	23.5
	Predicted	0.103	22.4
	P/O	0.904	0.953
Trial 102 ^a VNZ 20 mg Form D, FDC	Observed	0.805	18.4
	Predicted	0.816	18.8 ^c
	P/O	1.01	1.02
Trial 103 ^a VNZ 20 mg Form D, FDC	Observed	0.817	18.7
	Predicted	0.816	18.8 ^c
	P/O	0.99	1
Study 003 [#] VNZ 20 mg [Form A] separate tablet	Observed	0.368	34.6
	Predicted	0.33	29.31
	P/O	0.89	0.84
Study 003 ^{#\$} VNZ 20 mg [Form D] FDC tablet	Observed	0.168	17.9
	Predicted	0.16	14.65
	P/O	0.95	0.81
Study 005 [#] VNZ 10 mg [Form A] separate tablet	Observed	0.198	18.3
	Predicted	0.16	14.65
	P/O	0.8	0.8
Study 005 ^{#\$} VNZ 20 mg [Form D] FDC tablet	Observed	0.185	18
	Predicted	0.16	14.65
	P/O	0.86	0.81

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Study		C_{max} ($\mu\text{g/mL}$)	AUC_{last} (h· $\mu\text{g/mL}$)
Study 006 ^b VNZ 10 mg [Form A] FDC tablet	Observed	1.25/1	25.4/19.5
	Predicted	0.835	19.01
	P/O	0.688/0.835	1.32/1.01

Source: Report N183, Table 7-1; Study 003, Table 11-1; Study 005, Table 11-1; Study 006, Table 11-1, Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Table 1; and Reviewer's analysis.

* AUC_{last} corresponds to AUC_{0-264h} calculated based on individual plasma concentration – time profiles. VNZ PK were collected in presence of itraconazole for 264 hr postdose.

[§] Half the dose of VNZ Form D was used in the PBPK model to predict the exposure.

[#] Studies used by the reviewer for model verification.

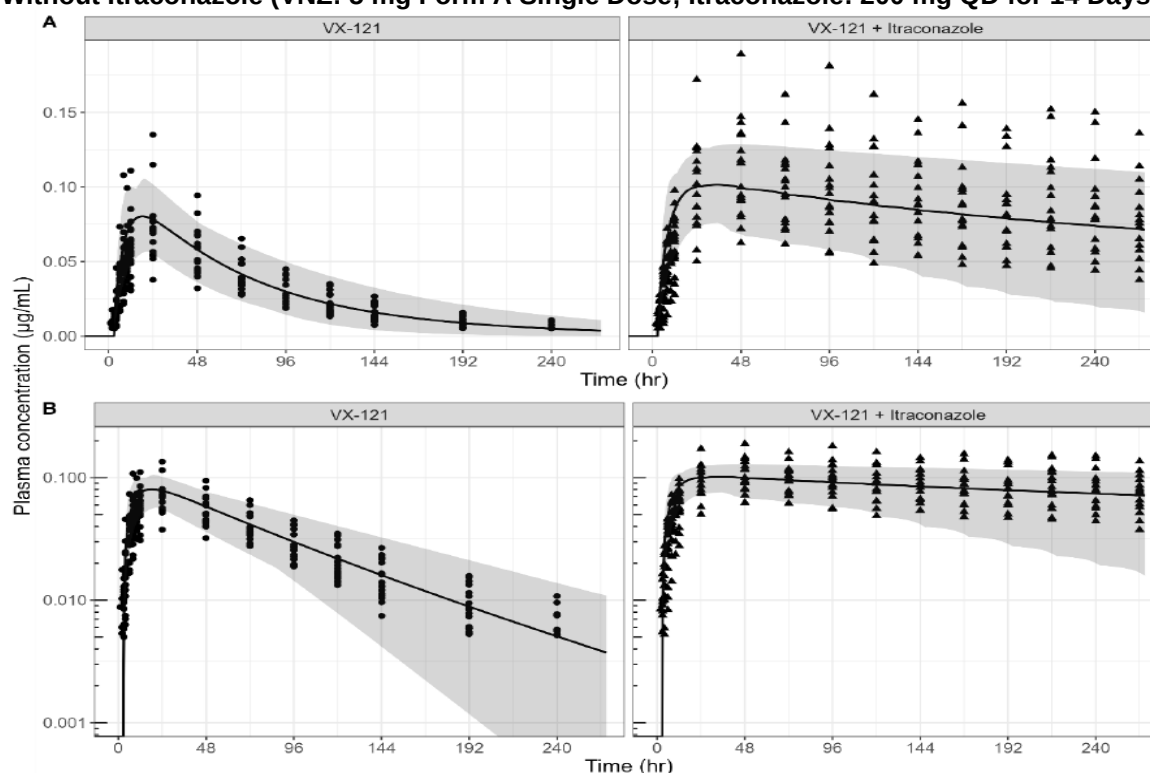
^a The observed C_{max} and AUC_{last} were estimated by popPK (Report T270, Table 7). PopPK estimated C_{min} in studies 102, 103 and 006 were 0.717, 0.727, and 1.07/0.812 $\mu\text{g/mL}$, respectively. The PBPK predicted C_{min} is 0.722 $\mu\text{g/mL}$.

^b VNZ concentrations were measured from two cohorts following the administration of FDC tablet.

^c AUC calculated at steady state from 624 to 648 hours post-last dose

Abbreviations: AUC_{0-264h} , area under the concentration-time curve from time 0 to 264hr; AUC_{last} , area under the concentration-time curve to the last measurable concentration; C_{max} , maximum plasma concentration; C_{min} , minimum plasma concentration; FDC, fixed-dose combination; P/O, predicted/observed; PBPK, population-based pharmacokinetic; popPK, population pharmacokinetic; QD, once daily; VNZ, vanzacaftor; VNZ, vanzacaftor

Figure 89. Observed and Predicted VNZ Individual Plasma Concentration-Time Profiles With and Without Itraconazole (VNZ: 5 mg Form A Single Dose; Itraconazole: 200 mg QD for 14 Days)



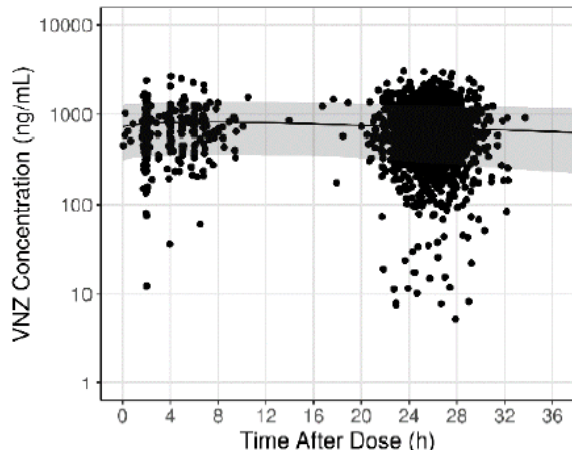
Source: Report N183, Figure 10-1

A) Linear plot of VX-121 [VNZ] total plasma concentration vs. time profiles from 0-264 hours post VX-121 [VNZ] dose; alone (left) and in the presence of itraconazole (right).

B) Semi-log plot for the total VX-121 [VNZ] plasma concentration vs. time profiles from 0-264 hours post VX-121 [VNZ] dose; alone (left) and in the presence of itraconazole (right). Individual observed data from Study VX21-121-007 CSR are presented as filled symbols. Simulated data from VX-121 [VNZ] PBPK model is the solid line while the shaded region denotes the simulated 5th and 95th percentiles.

Abbreviations: hr, hour; PBPK, population-based pharmacokinetic; QD, once daily; vs., versus; VX-121 [VNZ], vanzacaftor

Figure 90. Observed and Predicted VNZ Individual Plasma Concentration-Time Profiles in CF Subjects, Trials 102 and 103



Source: Applicant’s response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Figure 1A
Semi-log plot individual observed VX-121 [VNZ] plasma concentrations from studies 102 and 103 are presented as filled symbols. Simulated data from the VX-121 [VNZ] PBPK model is the solid line while the shaded region denotes the simulated 5th and 95th percentiles.
Abbreviations: CF, cystic fibrosis; h, hour; PBPK, population-based pharmacokinetics; VNZ, vanzacaftor; VX-121 [VNZ], vanzacaftor

Table 164. Summary of Observed and Predicted Geometric Mean Ratio (90%CI) for AUC_{last} and C_{max} of VNZ With and Without Itraconazole

	AUC _{last} Ratio [#]	C _{max} Ratio [#]
Observed	3.49 (3.22, 3.78)	1.55 (1.43, 1.69)
Predicted	3.16 (2.92, 3.43)	1.26 (1.22, 1.31)
P/O	0.905	0.81

Source: Report N183, Table 7-2
VNZ + Itraconazole/VNZ alone
*AUC_{last} corresponds to AUC_{0-264h} calculated based on individual plasma concentration – time profiles of VNZ in the presence of itraconazole (200 mg QD) for 264 hours.
Abbreviations: AUC_{0-264h}, area under the concentration-time curve from time 0 to 264hr; AUC_{last}, area under the concentration-time curve to the last measurable concentration; CI, confidence interval; C_{max}, maximum plasma concentration; P/O, predicted/observed; QD, once daily; VNZ, vanzacaftor

Model Application

Predict DDI With Single Dose and The proposed Therapeutic Dose of VNZ With CYP3A Inhibitors and Inducers

VNZ PBPK model was used to simulate the effect of multiple doses of strong and moderate CYP3A4 inhibitors on the PK of single and multiple doses of VNZ. Simulation results predicted 10.5-fold increase in the AUC_{inf}, and a small change was predicted in C_{max} (1.2-fold) of VNZ following the administration of 5 mg single dose with multiple doses of itraconazole (Table 165). Further, AUC_{inf} of VNZ was predicted to increase by approximately 2.4- to 3.9-fold with minimal change in C_{max} (1.2-fold) when VNZ is coadministered as a single dose with multiple doses of a moderate CYP3A inhibitor (Table 165).

The Applicant proposed to use the predicted exposure change after single dose administration of VNZ to determine the DDI dose adjustment with CYP3A inhibitors. In response to FDA’s request for information (dated August 23, 2024), the Applicant conducted PBPK simulations to predict AUC_{0-24h,ss} and C_{max,ss} ratios for the proposed therapeutic doses of VNZ (20 mg, Form D,

once daily for 40 weeks) at steady state in the presence of strong and moderate CYP3A inhibitors. Due to VNZ concentration accumulation after multiple doses, the predicted ratios of $C_{max,ss}$ at steady state were higher than the ratios of C_{max} after a single dose. The predicted ratios of $AUC_{0-24h,ss}$ at steady state for VNZ with and without multiple doses of CYP3A inhibitors were similar to those from the single dose simulations based on AUC_{inf} . Based on these results, the performance of VNZ PBPK model to predict DDI appears compatible when VNZ was administered as a single dose and at the proposed therapeutic doses. Therefore, the predicted AUC ratios after single dose administration of VNZ can be used to determine dose adjustment regimens when using the FDC tablet (VNZ Form D 10 mg /TEZ 50 mg/D-IVA 125 mg) in the presence of strong and moderate CYP3A inhibitors.

Table 165. Summary of Predicted Geometric Mean Ratios of AUC and C_{max} for Single and Multiple Doses VNZ When Coadministered With Strong and Moderate CYP3A Inhibitors Compared to Administered Alone

CYP3A Inhibitor	Inhibitor Dose	Classification ^a	Geometric Mean Ratio ^b (90% CI) of VNZ Exposure Parameters			
			Single Dose		Multiple Dose (qd)	
			AUC_{inf}	C_{max}	$AUC_{0-24h,ss}$	$C_{max,ss}$
Itraconazole	200 mg qd	Strong	10.5 (9.61 – 11.4)	1.22 (1.21 – 1.24)	10.8 (9.96 - 11.8)	10.4 (9.54 – 11.3)
Fluconazole	200 mg qd	Moderate	2.43 (2.38 – 2.48)	1.13 (1.12 – 1.13)	2.55 (2.50 - 2.61)	2.48 (2.43 – 2.53)
Erythromycin	500 mg qid	Moderate	3.23 (3.00 – 3.49)	1.14 (1.13 – 1.15)	3.29 (3.05 - 3.56)	3.19 (2.95 – 3.45)
Verapamil	80 mg tid	Moderate	3.85 (3.56 – 4.17)	1.16 (1.15 – 1.17)	3.93 (3.63 - 4.25)	3.80 (3.51 – 4.11)

Source: Report N183, Table 7-3; and Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Table 2.

^a Simcyp classification

^b VNZ + CYP3A inhibitor/VNZ alone

Note: For VNZ 5 mg single dose, DDI simulations were conducted with itraconazole 200 mg administered once daily for 65 days, erythromycin 500 mg administered 4 times a day for 29 days, fluconazole 200 mg once daily 19 days, and verapamil 80 mg 3 times daily for 29 days.

For VNZ 20 mg administered once daily for 40 weeks, DDI simulations were conducted with itraconazole 200 mg administered once daily for 40 weeks, erythromycin 500 mg administered 4 times a day for 40 weeks, fluconazole 200 mg once daily for 40 weeks, and verapamil 80 mg 3 times daily for 40 weeks.

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-24h,ss}$, area under the concentration-time curve from time 0 to 24hr at steady-state; AUC_{inf} , area under the concentration-time curve estimated to infinity; CI, confidence interval; C_{max} , maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady-state; CYP, cytochrome P450; DDI, drug-drug interaction; qd, once daily; qid, 4 times daily; tid, 3 times daily; VNZ, vanzacaftor

Comparison of Predicted DDI Ratios With CYP3A4 Inhibitors Between Adult and Pediatric (6 through 11 years) Populations at the Proposed Therapeutic Doses of VNZ

The exposure changes of VNZ when coadministered with strong or moderate CYP3A inhibitors in adults were used to determine the DDI dose adjustment in children 6 through 11 years of age. This approach assumes the effect of these CYP3A inhibitors on the PK of VNZ in this pediatric age group are comparable to those in adults. To support this assumption, the pediatric population model should be able to describe the PK of VNZ in children and the predicted DDI ratios with CYP3A inhibitors in adults and pediatrics should be similar.

In response to FDA's request for information (dated August 23, 2024), the Applicant used the PK data of VNZ from Trial 105 to demonstrate the predictive PK performance of the pediatric

PBPK model for children 6 through 11 years of age, categorized by body weight (<40 kg or ≥40 kg). Pediatric subjects with cystic fibrosis in Cohort B1 from Trial 105 received a weight-based dosing of the triple combination (TC) as follows:

- For pediatric <40 kg, the TC was given as VNZ 12 mg [Form D] /TEZ 60 mg/D-IVA 150 mg administered once daily for 24 weeks.
- For pediatric ≥40 kg, the TC was given as VNZ 20 mg [Form D] /TEZ 100 mg/D-IVA 250 mg administered once daily for 24 weeks.

The pediatric model adequately described VNZ plasma concentration-time profiles from Trial 105 ([Figure 91](#)) and PK parameters ($AUC_{0-24,ss}$ and $C_{max,ss}$) with predicted/observed ratios marginally at acceptable limit of 0.8 to 1.25 for pediatrics ≥40 kg, while the ratios for pediatrics <40 kg were considerably above the acceptable limit ([Table 166](#)). Although the observed PK data from Trial 105 were overpredicted by the PBPK model in pediatric subjects <40 kg, most of the observed data is contained between the 5th and 95th percentile of the simulated PK profile of VNZ in pediatric 6 through 11 years weighing <40 kg ([Figure 91](#)). Overall, the comparison of the observed and predicted pediatric steady-state PK parameters of VNZ appears reasonable due to the limited PK data of VNZ in pediatric subjects at the time of NDA submission in addition to the high variability observed in the PK data from Trial 105.

Table 166. Summary of Observed and Predicted Steady-State PK Parameters of VNZ [Form D] in CF Subjects 6 Through 11 Years of Age Weighing <40 kg or ≥40 kg, Trial 105 (Cohort B1)

Subjects 6 Through 11 Years Weighing <40 kg			
Parameter	$AUC_{0-24,ss}$ (h.µg/mL) ^a	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
Observed	13	0.576	0.497
Predicted [#]	19.7	0.881	0.723
P/O	1.5	1.5	1.45
Subjects 6 Through 11 Years Weighing ≥40 kg			
Parameter	$AUC_{0-24,ss}$ (h.µg/mL) ^a	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
Observed	18.6	0.826	0.71
Predicted [#]	23.6	1.04	0.885
P/O	1.26	1.25	1.24

Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Tables 6 and 7

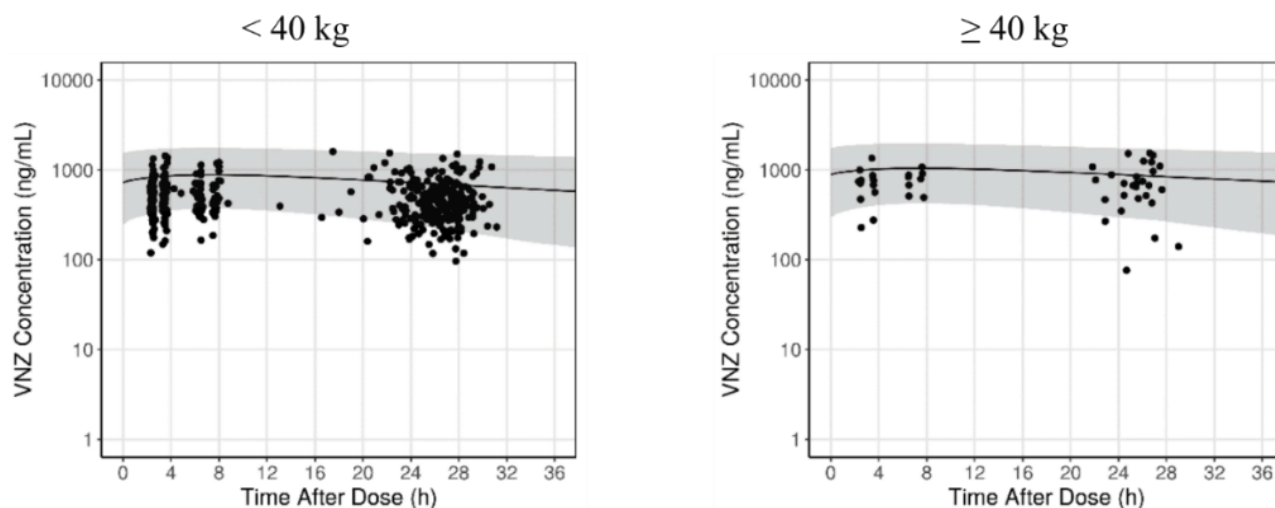
The observed C_{max} and AUC_{last} were estimated by popPK (Report T270, Table 8).

^a AUC calculated at steady state from 624 to 648 hours postdose

[#] Simulations were conducted with VNZ administered once daily in fed state for 27 days.

Abbreviations: $AUC_{0-24,ss}$, area under the concentration-time curve from time 0 to 24hr at steady-state; AUC_{last} , area under the concentration-time curve to the last measurable concentration; $C_{max,ss}$, maximum plasma concentration at steady-state; $C_{min,ss}$, minimum plasma concentration at steady-state; CF, cystic fibrosis; P/O, predicted/observed; PK, pharmacokinetic; popPK, population pharmacokinetic; QD, once daily; VNZ, vanzacaftor; VNZ, vanzacaftor

Figure 91. Observed and Predicted Steady-State PK Plasma Concentration-Time Profiles of VNZ [Form D] in CF Subjects 6 Through 11 Years of Age Weighing <40 kg or ≥40 kg, Trial 105 (Cohort B1)



Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Figures 2 and 3

Note: Individual observed data from Trial 105 Cohort B1 are presented as filled circles. For the simulated data, the solid line denotes the mean, and the shaded region denotes the 5th to 95th percentiles. 6 through 11 years, <40 kg and ≥40 kg populations: Fixed trial design (100 subjects) provided in this submission

Abbreviations: CF, cystic fibrosis; h, hour; PK, pharmacokinetic; VNZ, vanzacaftor

Afterward, the Applicant used the pediatric PBPK model to predict the effects of coadministration of strong and moderate CYP3A inhibitors on the PK of VNZ in children aged 6 through 11 years. A comparison of the predicted ratios of $AUC_{0-24,ss}$ and $C_{max,ss}$ for VNZ after multiple daily doses when coadministered with the strong CYP3A inhibitor itraconazole and the moderate CYP3A inhibitor fluconazole in this pediatric group and in adults is provided in [Table 167](#). Note that the doses of the CYP3A inhibitors were reduced in the pediatric group to match the exposure levels observed in healthy adult subjects at steady state. Overall, the fold changes in AUC and C_{max} with CYP3A inhibitors were similar between pediatric 6 through 11 years and adult populations at the proposed therapeutic doses of VNZ, assuming the exposure levels of the CYP3A inhibitor are similar between adult and pediatric populations.

Table 167. Comparison of Predicted Geometric Mean Ratios of $AUC_{0-24h,ss}$ and $C_{max,ss}$ for VNZ at Steady State After Multiple Daily Doses When Coadministered With a Strong CYP3A Inhibitor (Itraconazole) or Moderate CYP3A Inhibitor (Fluconazole) to Those When Administered Alone in Healthy Adult Subjects and Pediatrics 6 Through 11 Years of Age

Populations	VNZ Dose (single dose, Form D	Inhibitor Dose ^a	Geometric Mean Ratio ^b (90% CI) of VNZ Exposure Parameters	
			C _{max,ss}	AUC _{0-24h,ss}
DDI Simulation with Itraconazole (strong CYP3A inhibitor)				
Healthy adults ^c	20 mg qd	200 mg qd	10.4 (9.54 - 11.3)	10.8 (9.96 - 11.8)
6-11 y, ≥40 kg ^d	20 mg qd	155 mg qd	10.3 (9.32 - 11.4)	10.9 (9.84 – 12.0)
6-11 y, <40 kg ^e	12 mg qd	105 mg qd	9.48 (8.44 - 10.7)	10.1 (8.96 - 11.3)
DDI Simulation with Fluconazole (moderate CYP3A inhibitor)				
Healthy adults	20 mg qd	200 mg qd	2.48 (2.43 - 2.53)	2.55 (2.50 - 2.61)
6-11 y, ≥40 kg	20 mg qd	135 mg qd	2.54 (2.49 - 2.59)	2.64 (2.59 - 2.69)
6-11 y, <40 kg	12 mg qd	100 mg qd	2.49 (2.43 - 2.54)	2.60 (2.55 - 2.66)

Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Table 4.

^a Inhibitor's dose in 6 through 11-yr-old children is adjusted to match the exposure of inhibitor in healthy adult subjects.

^b VNZ + CYP3A inhibitor/VNZ alone

^c 10 trials, 10 subjects in each trial, gender ratio – 0.5, age range – 20-50-yr-old

^{d,e} Fixed trial design (101 subjects); Modified Upreti ontogeny profile for CYP3A4

Note: $AUC_{0-24,ss}$ was calculated from 6696 to 9720 hours postdose.

Abbreviations: $AUC_{0-24,ss}$, area under the concentration-time curve from time 0 to 24hr at steady-state; $C_{max,ss}$, maximum plasma concentration at steady-state; CI, confidence interval; CYP, cytochrome P450; DDI, drug-drug interaction; D-IVA, deutivacaftor; QD, once daily; VNZ, vanzacaftor; VNZ, vanzacaftor; yr, year(s)

PBPK Model for D-IVA and Metabolites

Method

Software

Simcyp® Version 21 (Simcyp Ltd, A Certara Company) was used for PBPK analyses by the Applicant and the review team.

Model Development

D-IVA

The D-IVA PBPK model consists of a first-order absorption model constructed using available in vitro ADME data and drug interaction with itraconazole (Study VX18-445-006, NDA 212273). The absorption of D-IVA was assumed to be complete ($F_a=1$), and the absorption rate constant for D-IVA was assumed to be similar to ivacaftor ($K_a=0.546$ h⁻¹). (See NDA 203188, Clinical Pharmacology and Biopharmaceutics Review(s), Appendix 1). The F_g of D-IVA was predicted to be 0.76.

D-IVA PK was described by a one-compartment popPK model with seven transit compartments, first-order absorption, and linear elimination (Report t406). A minimal PBPK model and single adjusting compartment were used to estimate $V_{ss}=0.85$ L/kg for D-IVA with K_{in} and K_{out} of 0.1 and 0.14 h⁻¹, respectively.

Ivacaftor has a large V_z/F , suggesting extensive tissue distribution. The mean V_z/F of ivacaftor after a single dose of 275 mg of ivacaftor in healthy subjects and subjects with CF in fed state

was 203 to 206 L and after multiple-dose administration of ivacaftor 250 mg q12h was 206 L in healthy subjects in the fed state. Similarly, D-IVA showed large V_z/F . Values of 106 L and 250 L were reported when coadministered with and without itraconazole, respectively (Study VX18-445-006), and a $V_z/F = 183$ L was estimated by popPK analysis (Report t406). The geometric mean predicted V_{ss} for D-IVA when administered alone was 228 L calculated from CL and λ_z , which is comparable to the observed value in Study VX18-445-006. The predicted geometric mean CL of D-IVA when coadministered with and without itraconazole was 11.83 L/h and 1.53 L/h, respectively, which is comparable to the observed CL values of 11.9 L/h and 1.01 L/h, respectively, from Study VX18-445-006.

The fraction of D-IVA metabolized by CYP3A4 was optimized to 0.95 based on in vitro human CYP reaction phenotyping studies (Report S286, % of D-IVA remaining in CYP3A4 occupant was 6%) and the clinical itraconazole DDI data (Study VX18-445-006, $f_m = 0.9$). Sensitivity analysis of CYP3A4 f_m showed that there is a narrow range of CYP3A4 f_m values that is required to describe the clinical DDI data with itraconazole for D-IVA. For example, using CYP3A4 f_m of 0.95 predicted an $AUC_{infR} = 12.4$ following D-IVA administration with and without itraconazole that was contained within the observed 90%CI of AUC_{infR} (8.72 – 14.1) (Figure 92). The AUC_{infR} for D-IVA was relatively insensitive to CYP3A4 f_m values in the range of 60% to 95% for fluconazole. For example, the range of AUC_{infR} for D-IVA over the considered f_m values was approximately 1.8 to 2.9 for the moderate CYP3A inhibitor fluconazole (Figure 92).

The CL_{int} of 24.2 $\mu\text{L}/\text{min}/\text{pmol}$ for D-IVA by CYP3A was calculated using the retrograde method based on estimated $CL_{iv} = 7.1$ L/h and $f_m = 0.95$. The additional clearance by human liver microsomes was estimated to be 155.7 $\mu\text{L}/\text{min}/\text{mg}$ protein. The PBPK model input parameters for D-IVA are listed in Table 168.

Table 168. Modeling Input Parameters of D-IVA

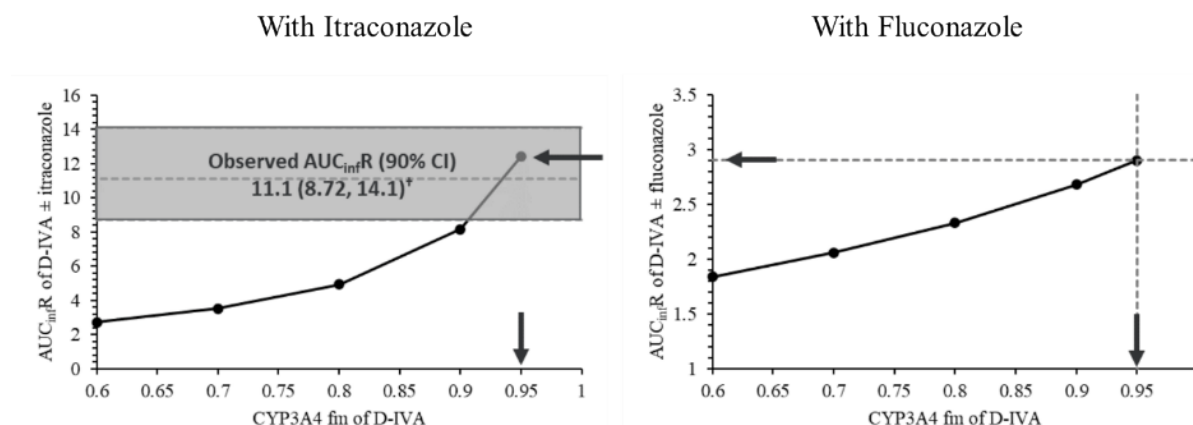
Parameter	Value	Reference
Physical-Chemical Properties		
Mol Weight (g/mol)	401.55	AR-44389
$\log P_{o:w}$	5.203	AR-44389
Compound Type	Diprotic Acid	AR-44389
pKa	9.45, 11.28	AR-44389
Blood to plasma ratio	0.55	VX06-770-003, assumed to be similar to IVA
f_{up}	0.000733	Report T235
Absorption (First Order Model)		
Fraction available for absorption (F_a)	1	Assumed
Absorption Rate constant (K_a) (1/h)	0.546	Optimized in Simcyp
$f_u(\text{gut})$	0.05	Optimized in Simcyp
Q_{gut} (L/h)	15.67	Optimized in Simcyp
Distribution (Minimal PBPK)		
K_{in} (1/h)	0.100	Optimized in Simcyp
K_{out} (1/h)	0.140	Optimized in Simcyp
V_{sac} (L/kg)	1E-05	Optimized in Simcyp
V_{ss} (L/kg)	0.85	Optimized in Simcyp
Elimination		
CL_{iv} (L/h)	7.1	Optimized in Simcyp
rCYP3A4 CL_{int} ($\mu\text{L}/\text{min}/\text{pmol}$ of isoform)	24.217	Optimized in Simcyp; f_m optimized to be 0.95 based on VX18-445-006
Other HLM ($\mu\text{L}/\text{min}/\text{mg}$ protein)	155.76	Optimized in Simcyp

Parameter	Value	Reference
Interaction		
CYP2C8 Ki (μM)	9.5	Report DM-058 ⁷ , fu _{mic} =1
CYP2C9 Ki (μM)	15.6	Report DM-058, fu _{mic} =1
CYP3A4 Ki (μM)	21	Report DM-058, fu _{mic} =1

Source: Report T322, Table 11-1

Abbreviations: CYP, cytochrome P450; D-IVA, deutivacaftor; IVA, ivacaftor; PBPK, population-based pharmacokinetics

Figure 92. Parameter Sensitivity Analysis for the Fractional Contribution of CYP3A4 to Total Clearance of D-IVA on the Ratio of its Predicted AUC_{inf} Upon Coadministration With and Without Itraconazole or Fluconazole



Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Figures 6 and 7.

At each CYP3A4 f_m , CL_{int} was calculated using the reverse transitional tool then simulation was conducted to predict the increase in AUC of D-IVA following the administration of itraconazole or fluconazole 200 mg once daily for 10 days. D-IVA was administered as single dose of 50 mg in fed state on Day 4 and 1 hours staggering following the administration of itraconazole or fluconazole.

Abbreviations: AUC, area under the concentration-time curve; AUC_{inf}, area under the concentration-time curve estimated to infinity; CI, confidence interval; CYP, cytochrome P450; D-IVA, deutivacaftor; f_m , fraction metabolized

The D-IVA inhibitory potential of CYP enzymes were included in the model. This is because in vitro data showed that D-IVA inhibited CYP2C8 (IC₅₀=9.5 μM), CYP2C9 (IC₅₀=15.6 μM), and CYP3A4 (IC₅₀=15.7 μM, testosterone as a probe substrate) with R-value above the defined criteria (Reports D-IVA DM-058, CPT-656-DM-085). Clinically, IVA did not significantly affect the PK of rosiglitazone, a CYP2C8 substrate, and IVA and TEZ/IVA had no clinically significant effect on midazolam exposures, CYP3A substrate (Study 770-010, NDA 203188 and Study 661-006, NDA 210491). Based on in vitro inhibition parameters and the above clinical DDI data, it is expected that D-IVA and its metabolites have low potential to mediate CYP enzymes inhibition at clinically relevant concentrations, except that D-IVA may inhibit CYP2C9.

There is no mass balance Study available for D-IVA. In mass balance Study 003 for ivacaftor (NDA 203188), mean total recovery was 94.6%, of which 87.8% (mean) was excreted in feces and 6.6% was excreted in urine. The amount of unchanged drug excreted in feces was only 2.52%, suggesting that most of the drug was excreted as metabolites.

Based on in vitro studies, D-IVA and M1-D-IVA are substrates of P-gp and BCRP. The model did not include intestinal efflux transport-mediated disposition for D-IVA based on the assumption of high oral absorption (as reported with ivacaftor) and approximately linear PK after single dose. D-IVA and M1-D-IVA are P-gp inhibitors with IC₅₀ of 3.83 and 9.86 μM,

respectively (see Section 8.2). However, when TEZ/IVA was coadministered with digoxin, Study 661-006 (NDA 210491), a sensitive P-gp substrate, digoxin exposure increased by 1.3-fold, indicating weak inhibition of P-gp by IVA ($IC_{50}=10.6 \mu M$) which has similar P-gp inhibition potency as D-IVA. Therefore, the DDI risk of D-IVA is predicted to be similar to IVA. Moreover, D-IVA and M1-D-IVA are BCRP inhibitors with IC_{50} of 1.19 and 9.15 μM , respectively (see Section 8.2).

Model Validation

Clinical PK and DDI studies used to support the model development and validation are listed in Table 169. The PBPK models for D-IVA and its metabolites were developed and validated using the PK data obtained from DDI with itraconazole (Study VX18-445-006, NDA 212273).

Study VX18-445-006 evaluated the effect of itraconazole on the PK of a single dose of elexacaftor (ELX) 20 mg/TEZ 50 mg/D-IVA 50 mg and relevant metabolites administered as separate tablets. In period 1, ELX, TEZ, and D-IVA, were administered on Day 1 in fed state followed by 14 to 21 washout period. In Period 2 (Day -4 to 7), itraconazole 200 mg was administered in fasted from Day -3 to Day 6, followed by breakfast and administration of ELX/TEZ/D-IVA on Day 1 (i.e., Day 4 of itraconazole administration).

All PBPK simulation were conducted in fed state with ELX/TEZ/D-IVA administered on Day 4 of itraconazole administration with 1 hours staggering where itraconazole was administered in the fasted state.

Table 169. Clinical Studies Used in D-IVA PBPK Model Development and Validation

Study/Trial No.	Study Description	Roles in PBPK Analyses	Model Objective
<i>Studies used by the Applicant</i>			
VX18-445-006	- Clinical DDI between single dose of elexacaftor (ELX) 20 mg/TEZ 50 mg/D-IVA 50 mg and itraconazole (200 mg QD) in healthy adult subjects. - D-IVA was given as a separate tablet under fed conditions on Day 1 and Day 4 following the administration of itraconazole.	- To estimate disposition parameters and CYP3A4 f_m - To validate model performance in predicting single dose PK (using data f_m from control group)	Development and validation
102 103	- Subjects with cystic fibrosis received VNZ 20 mg [Form D]/TEZ (100 mg)/D-IVA (250 mg) QD over 52 weeks treatment period. - Subjects in Trials 102 and 103 were different in the genetic variants responsible for CF - PK samples collected predose on Week 4, 16, and 24. On Week 8: predose and 2, 4, 5, 6, and 7 hours postdose	To validate model performance in predicting multiple dose PK	Validation

Study/Trial No.	Study Description	Roles in PBPK Analyses	Model Objective
<i>Studies used by the reviewer</i>			
003	Healthy adult subjects received a single dose of VNZ 20 mg, TEZ 100 mg, and D-IVA 150 mg orally in the fed state, either as an FDC or as separate tablets	To validate model performance in predicting single dose PK	Validation
005	To evaluate relative BA of a FDC tablet of VNZ 20 mg [Form D]/TEZ 100 mg/D-IVA 250 mg compared to VNZ 10 mg [Form A], TEZ 100 mg, and D-IVA 250 mg coadministered as separate tablets	To validate model performance in predicting single dose PK	Validation
006	To evaluate the PK of VNZ (10 mg, Form A), TEZ (100 mg), and D-IVA (250 mg) when administered separately and together once daily for 14 days in healthy subjects	To validate model performance in predicting multiple dose PK	Validation

Source: Reviewer's summary

Abbreviations: BA, bioavailability; CF, cystic fibrosis; C_{max} , maximum plasma concentration; D-IVA, deutivacaftor; DDI, drug-drug interaction; FDC, fixed-daily dose; No., number; PBPK, population-based pharmacokinetics; PK, pharmacokinetic; QD, once daily; TEZ, tezacaftor; VNZ, vanzacaftor

Perpetrator Models

The software's default PBPK models of the strong CYP3A inhibitor itraconazole (fasted solution) and moderate CYP3A inhibitors fluconazole, erythromycin, and verapamil were used to predict the CYP3A inhibition effects on the PK of D-IVA.

Model Application

- To simulate the effect of moderate CYP3A4 inhibitors (fluconazole, erythromycin, and verapamil) on the PK of D-IVA in adults and children aged 6 through 11 years.
- To determine dose adjustment regimens when using the FDC tablet (VNZ Form D 10 mg /TEZ 50 mg/D-IVA 125 mg) in the presence of strong and moderate CYP3A inhibitors in adults and children aged 6 through 11 years.

Results

Model Validation

Evaluation of the Predictive Performance for PK Under Different Dosing Scenario

The PBPK model for D-IVA adequately described the plasma concentration-time profiles of D-IVA when D-IVA was administered with and without itraconazole in Study VX18-445-006 ([Figure 93](#)). In addition, the model adequately predicted the mean values for PK parameters (AUC_{inf} and C_{max}) when a single 50 mg dose of D-IVA was administered alone and in the presence of itraconazole with predicted/observed ratios marginally deviating from 0.8 to 1.25

(Table 170). Further, the model adequately predicted the AUC_{inf} and C_{max} ratios for the DDI with itraconazole (Study VX18-445-006) (Table 171).

Table 170. Summary of Observed and PBPK Predicted Mean AUC_{inf} and C_{max} Used in Model Development and Validation, Study 006

Parameter	D-IVA Alone		D-IVA + Itraconazole	
	AUC_{inf} (h.µg/mL)	C_{max} (µg/mL)	AUC_{inf} (h.µg/mL)	C_{max} (µg/mL)
Observed	5.07	0.286	52.9	0.539
Predicted	4.71	0.287	69.2	0.545
P/O ^a	0.93	1	1.31	1.01

Source: Report T322, Table 8-1

^a P/O: predicted/observed

Note: PBPK simulation were based on administration instructions in Study 006.

Abbreviations: AUC_{inf} , area under the concentration-time curve estimated to infinity; C_{max} , maximum plasma concentration; D-IVA, deutivacaftor; P/O, predicted/observed; PBPK, population-based pharmacokinetics

Table 171. Summary of Observed and Predicted Geometric Mean Ratio (90% CI) for AUC_{inf} and C_{max} of D-IVA When D-IVA Coadministered With Itraconazole Compared to When Administered Alone

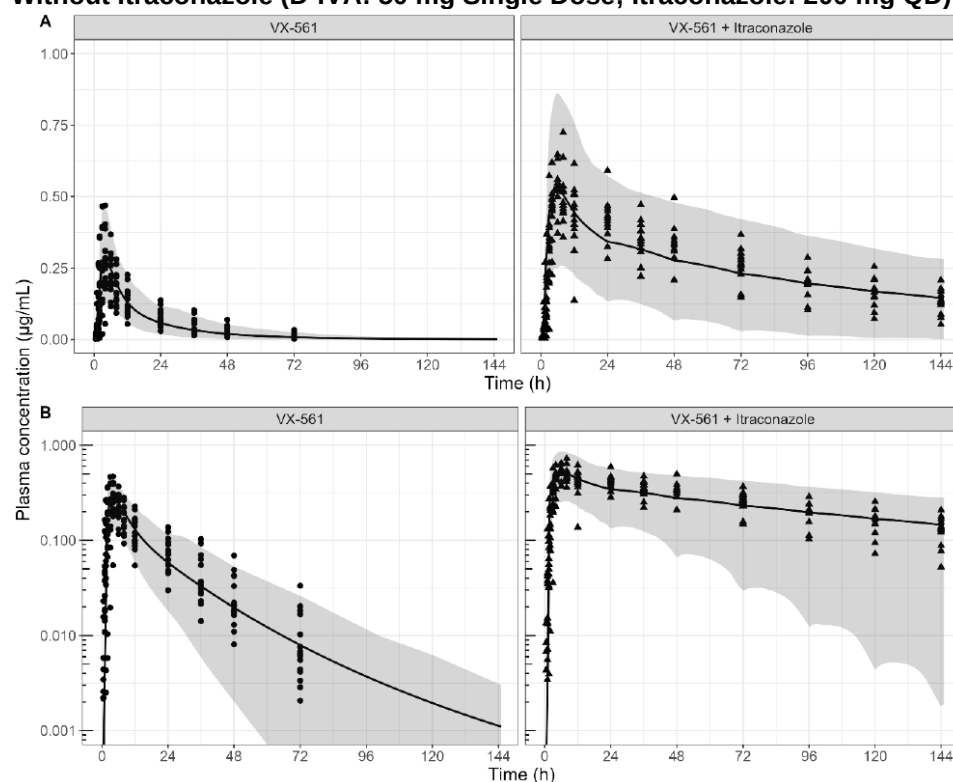
Parameter	D-IVA	
	AUC_{inf} Ratio	C_{max} Ratio
Observed	11.1 (8.72, 14.1)	1.96 (1.70, 2.26)
Predicted	12.4 (11.4, 13.5)	1.90 (1.85, 1.95)
P/O ^a	1.11	0.968

Source: Report T322, Table 8-2

^a P/O: predicted/observed

Note: PBPK simulation were based on administration instructions in Study 006. To calculate AUC_{inf} and C_{max} ratios, D-IVA + CYP3A inhibitor/D-IVA alone

Abbreviations: AUC_{inf} , area under the concentration-time curve estimated to infinity; C_{max} , maximum plasma concentration; D-IVA, deutivacaftor; FDC, fixed-daily dose; P/O, predicted/observed; PBPK, population-based pharmacokinetics

Figure 93. Observed and Predicted D-IVA Total Plasma Concentration-time Profiles With and Without Itraconazole (D-IVA: 50 mg Single Dose; Itraconazole: 200 mg QD)

Source: Report T322, Figure 11-1

A) Linear plot of the total D-IVA plasma concentration vs. time profiles from 0-144 h post D-IVA dose.

B) Semi-log plot for the total D-IVA plasma concentration vs. time profiles from 0-144 h post D-IVA dose. Individual observed data from Study VX18-445-006 presented as filled symbols. Simulated data is the solid line while the shaded region denotes the 5th and 95th percentiles.

Abbreviations: D-IVA, deutivacaftor; h, hour; QD, once daily vs., versus; VX-561 [D-IVA], deutivacaftor

In response to FDA's request for information (dated August 23, 2024), the Applicant conducted additional validation of D-IVA PBPK model by comparing predicted versus observed steady-state PK parameters of D-IVA, M1-D-IVA, and M6-D-IVA in CF subjects from studies 102 and 103 when D-IVA was administered as FDC tablet (TEZ 100 mg/VNZ 20 mg Form D/D-IVA 250 mg) once daily in fed state ([Table 172](#) and [Figure 94](#)). It appears that D-IVA model tends to under predict the popPK estimates of AUC_{last} from studies 102 and 103 following the administration of 250 mg once daily. Similarly, the additional model validation, conducted by the reviewer, showed that D-IVA model under predicted the observed AUC_{last} from Study 006. This bias for under prediction noted in the D-IVA model could be justified by the high variability in observed and predicted PK data.

The review team acknowledges this limitation in the D-IVA PBPK model. We note, however, this model limitation is not expected to have a significant impact on the overall application to inform dose reduction when D-IVA is coadministered with CYP3A4 inhibitors, when considering the constraints of DDI dose adjustment strategy (i.e., use of FDC formulation, reducing number of tablets and/or dosing frequency).

Further, this review did not focus on evaluating the adequacy of the PBPK models for the metabolites M1-D-IVA and M6-D-IVA because their exposure changes in the presence of a CYP3A inhibitor were not considered in the DDI dose adjustments strategy.

Table 172. Summary of Observed and Predicted Mean AUC₀₋₂₄ and C_{max} of D-IVA Used in Model Development and Validation

Study/Trial			AUC ₀₋₂₄ (h·µg/mL) ^c	C _{max} (µg/mL)
Trial 102 ^a D-IVA 250 mg daily, FDC	D-IVA	Observed	38.1	2.29
		Predicted	25.2	1.89
		P/O	0.66	0.82
Trial 103 ^a D-IVA 250 mg daily, FDC	D-IVA	Observed	39.7	2.36
		Predicted	25.2	1.89
		P/O	0.63	0.8
Study 003 D-IVA 150 mg FDC tablet, single dose	D-IVA	Observed	19.8	0.965
		Predicted	14.3	0.8
		P/O	0.72	0.83
Study 005 D-IVA 250 mg FDC tablet, single dose	D-IVA	Observed	42.6	1.74
		Predicted	23.74	1.34
		P/O	0.56	0.77
Study 006 D-IVA 250 mg daily, FDC tablet for 14 days in healthy subjects ^b	D-IVA	Observed	55.5/41.1	3.32/2.5
		Predicted	23.8	1.76
		P/O	0.72/0.58	0.53/0.7

Source: Applicant's response to IR submitted Aug 23, 2024, SDN 0019, Module 1.11.3, Table 1; Study 006 Report, Table 11-1 and 11-2; Study 005 Report, Tables 14.4.1.1.10; Study 006 Report, Table 14.4.1.1; and Reviewer's Analysis

^a The observed C_{max} and AUC_{last} were estimated by popPK (Report T406, Table 11.6).

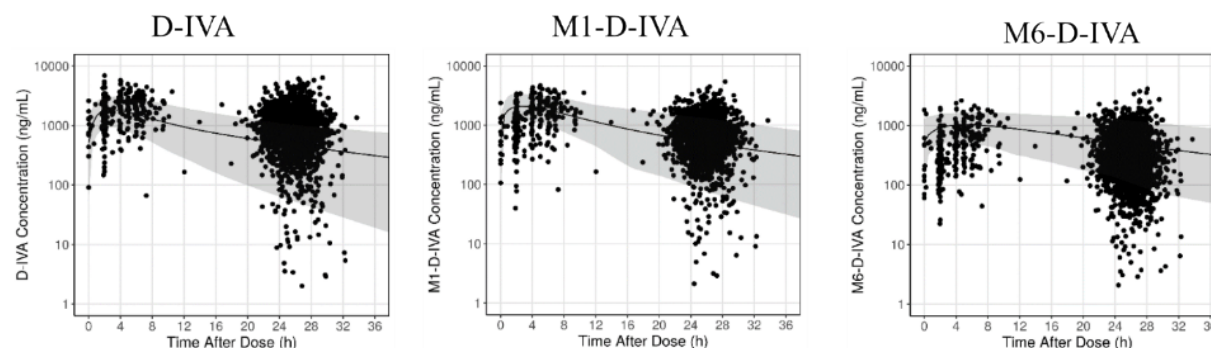
^b D-IVA concentrations were measured from two cohorts following the administration of FDC tablet.

^c AUC calculated at steady state from 624 to 648 hours post-last dose

Note: Simulations were conducted with D-IVA 250 mg administered once daily in fed state for 27 days.

Abbreviations: AUC, area under the concentration-time curve; AUC₀₋₂₄, area under the concentration-time curve from time 0 to 24hr; AUC_{last}, area under the concentration-time curve to the last measurable concentration; C_{max}, maximum plasma concentration; D-IVA, deutivacaftor; FDC, fixed-daily dose; P/O, predicted/observed

Figure 94. Observed and Predicted D-IVA, M1-D-IVA and M6-D-IVA Individual Plasma Concentration-Time Profiles in CF Subjects, Trials 102 and 103



Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Figures 1B, 1C, and 1D.

Semi-log plot individual observed D-IVA, M1-D-IVA and M6-D-IVA plasma concentrations from studies 102 and 103 are presented as filled symbols. Simulated data from the qualified PBPK model is the solid line while the shaded region denotes the simulated 5th and 95th percentiles.

Abbreviations: CF, cystic fibrosis; D-IVA, deutivacaftor; M, metabolite; PBPK, population-based pharmacokinetics

Model Application

Predict DDI With Single Dose and the Proposed Therapeutic Dose of D-IVA With CYP3A Inhibitors and Inducers

The D-IVA model was used to simulate the effect of multiple doses of strong and moderate CYP3A4 inhibitors on the PK of single (50 mg) and multiple doses (250 mg once daily for 12 weeks) of D-IVA. Simulation results predicted 12.4-fold increase in the AUC_{inf} , and 1.9-fold increase in C_{max} of D-IVA following the administration of a single 50 mg dose of D-IVA with itraconazole. Further, simulations predicted 2.9- to 4.78-fold increase in AUC_{inf} of D-IVA when D-IVA was coadministered as a single dose with moderate CYP3A inhibitors (Table 173).

PBPK simulations to predict $AUC_{0-24h,ss}$ ratios for the proposed therapeutic doses of D-IVA (250 mg once daily) at steady state in the presence of strong or moderate CYP3A inhibitors showed similar increase in $AUC_{0-24h,ss}$ of D-IVA when compared to DDI ratios of single dose D-IVA. Due to D-IVA concentration accumulation after multiple doses, the predicted ratios of $C_{max,ss}$ at steady state were higher than the ratios of C_{max} after a single dose (Table 173). The predicted ratios of $AUC_{0-24h,ss}$ at steady state for D-IVA with and without multiple doses of CYP3A inhibitor were similar to those from the single dose simulations based on AUC_{inf} .

Table 173. Summary of Predicted Geometric Mean Ratios of AUC and C_{max} for Single and Multiple Doses D-IVA When Coadministered With Strong and Moderate CYP3A Inhibitors Compared to Administered Alone

Analyte	CYP3A Inhibitor	Classification ^a	Geometric Mean Ratio ^b (90% CI) of D-IVA, M1-D-IVA, and M6-D-IVA Exposure Parameters			
			Single Dose		Multiple Dose (qd)	
			AUC_{inf}	C_{max}	$AUC_{0-24h,ss}$	$C_{max,ss}$
D-IVA	itraconazole	Strong	12.4 (11.4 - 13.5)	1.90 (1.85 - 1.95)	14.0 (12.9 - 15.3)	8.01 (7.36 - 8.73)
	fluconazole	Moderate	2.90 (2.83 - 2.96)	1.50 (1.47 - 1.53)	3.13 (3.05 - 3.21)	2.27 (2.21 - 2.32)
	erythromycin	Moderate	3.93 (3.61 - 4.28)	1.59 (1.55 - 1.64)	4.13 (3.80 - 4.50)	2.89 (2.69 - 3.10)
	verapamil	Moderate	4.78 (4.35 - 5.26)	1.70 (1.65 - 1.75)	5.11 (4.64 - 5.62)	3.43 (3.16 - 3.73)

Source: Report T322, Table 8-7; and Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Table 3.

^a Simcyp classification

^b D-IVA+ CYP3A inhibitor/D-IVA alone

Note: DDI simulations were conducted with D-IVA 50 mg single dose administered in fed state on Day 4 of 1 hour after the administration of perpetrator drugs including itraconazole 200 mg administered once daily for 10 days, erythromycin 500 mg administered 4 times a day for 6 days, fluconazole 200 mg once daily 10 days, and verapamil 80 mg 3 times daily for 9 days. For D-IVA 250 mg administered once daily for 12 weeks, DDI simulations were conducted with itraconazole 200 mg administered once daily for 12 weeks, erythromycin 500 mg administered 4 times a day for 12 weeks, fluconazole 200 mg once daily for 12 weeks, and verapamil 80 mg 3 times daily for 12 weeks.

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-24h,ss}$, area under the concentration-time curve from time 0 to 24h at steady-state; CI, confidence interval; C_{max} , maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady-state; C_{min} , minimum plasma concentration; CYP, cytochrome P450; D-IVA, deutivacaftor; DDI, drug-drug interaction; M, metabolite

Comparison of Predicted DDI Ratios With CYP3A4 Inhibitors Between Adult and Pediatric (6 Through 11 Years) Populations at the Proposed Therapeutic Doses of D-IVA

Similar to analysis conducted for VNZ, the Applicant used the PK data of D-IVA from Trial 105 to demonstrate the predictive PK performance of the pediatric PBPK model for children 6 through 11 years of age, categorized by body weight (<40 kg or ≥40 kg).

The predicted PK parameters ($AUC_{0-24,ss}$ and $C_{max,ss}$) for D-IVA and its metabolites were within a ~2-fold range of the observed PK data from Trial 105 Cohort B1 due to the high variability in PK data (Table 174). Generally, the observed data is contained between the 5th and 95th percentile of the simulated PK profile of D-IVA in pediatric 6 through 11 years weighing <40 kg; however, the model under predicted the PK profiles of D-IVA in pediatric 6 through 11 years weighing ≥40 kg (Figure 95). Overall, the comparison of the observed and predicted pediatric steady-state PK parameters of D-IVA appears reasonable due to the limited PK data of D-IVA in pediatric subjects at the time of NDA submission and the limitation noted in D-IVA PBPK model, as previously discussed.

Table 174. Summary of Observed and Predicted Steady-State PK Parameters of VNZ [Form D] in CF Subjects 6 Through 11 Years of Age Weighing <40 kg or ≥40 kg, Trial 105 (Cohort B1)

Subjects 6 Through 11 Years Weighing <40 kg				
Drug	Parameter	$AUC_{0-24,ss}$ (h.µg/mL) ^a	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
D-IVA	Observed	30.2	2.06	0.642
	Predicted [#]	27	2.51	0.391
	P/O	0.89	1.22	0.61
Subjects 6 Through 11 Years Weighing ≥40 kg				
Drug	Parameter	$AUC_{0-24,ss}$ (h.µg/mL) ^a	$C_{max,ss}$ (µg/mL)	$C_{min,ss}$ (µg/mL)
D-IVA	Observed	48.5	2.97	1.25
	Predicted [#]	31.9	2.69	0.539
	P/O	0.66	0.91	0.43

Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Table 6 and 7; P/O was calculated by the reviewer.

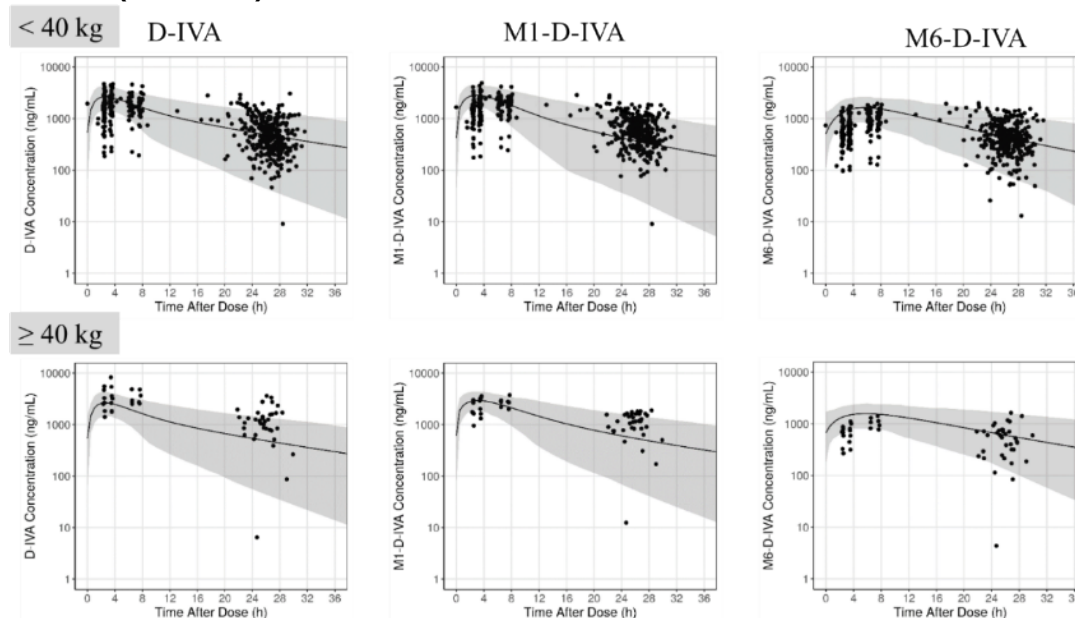
The observed C_{max} , C_{min} , and AUC_{last} were estimated by popPK (Report T270, Table 8).

^a AUC calculated at steady state from 624 to 648 hours postdose

[#] Simulations were conducted with D-IVA administered once daily in fed state for 27 days.

Abbreviations: $AUC_{0-24h,ss}$, area under the concentration-time curve from time 0 to 24h at steady-state; AUC_{last} , area under the concentration-time curve to the last measurable concentration; CF, cystic fibrosis; CI, confidence interval; C_{max} , maximum plasma concentration; $C_{max,ss}$, maximum plasma concentration at steady-state; C_{min} , minimum plasma concentration; $C_{min,ss}$, minimum plasma concentration at steady-state; CYP, cytochrome P450; D-IVA, deutivacaftor; DDI, drug-drug interaction; P/O, predicted/observed; PK, pharmacokinetic; popPK, population pharmacokinetic; yr, year

Figure 95. Observed and Predicted Steady-State PK Plasma Concentration-Time Profiles of D-IVA, M1-D-IVA, and M6-D-IVA in CF Subjects 6 Through 11 Years of Age Weighing <40 kg or ≥40 kg, Trial 105 (Cohort B1)



Source: Applicant's response to IR submitted Aug 23, 2024, SDN 0019, Module 1.11.3, Figure 2 and 3

Notes: Individual observed data from Trial 105 Cohort B1 are presented as filled circles. For the simulated data, the solid line denotes the mean, and the shaded region denotes the 5th to 95th percentiles. 6 through 11 years, <40 kg and ≥40 kg populations: Fixed trial design (100 subjects) provided in this submission.

Abbreviations: CF, cystic fibrosis; D-IVA, deutivacaftor; h, hour; M, metabolite; PK, pharmacokinetic; y, year(s)

The Applicant has used the pediatric PBPK model to predict the effects of coadministration of strong and moderate CYP3A inhibitors on the PK of D-IVA in children aged 6 through 11 years. A comparison of predicted ratios of $AUC_{0-24h,ss}$ and $C_{max,ss}$ for D-IVA and its metabolites at steady state after multiple daily doses when coadministered with a strong or a moderate CYP3A inhibitor to those when administered alone in this pediatric group and adults is provided in [Table 175](#). Note the doses of the CYP3A inhibitors were reduced in the pediatric group to match the exposure levels observed in healthy adult subjects at steady state. Overall, the fold changes in AUC and C_{max} with CYP3A inhibitors were similar between pediatric 6 through 11 years and adult populations at the proposed therapeutic dose of D-IVA, assuming the exposure levels of the CYP3A inhibitor are similar between adults and pediatrics.

Table 175. Comparison of Predicted Geometric Mean Ratios of $AUC_{0-24h,ss}$ and $C_{max,ss}$ for D-IVA at Steady State After Multiple Daily Doses When Coadministered With a Strong CYP3A Inhibitor (Itraconazole) or Moderate CYP3A Inhibitor (Fluconazole) to Those When Administered Alone in Healthy Adult Subjects and Pediatrics 6 Through 11 Years of Age

				Geometric Mean Ratio ^b (90% CI) of D-IVA, Exposure Parameters	
Analyte	Populations	D-IVA Dose	Inhibitor Dose ^a	C _{max,ss}	AUC _{0-24h,ss}
DDI Simulation with Itraconazole (strong CYP3A inhibitor)					
D-IVA	Healthy adults ^c	250 mg QD	200 mg QD	8.01 (7.36 - 8.73)	14.0 (12.9 - 15.3)
	6-11y, ≥40 kg ^d	250 mg QD	155 mg QD	7.36 (6.72 - 8.07)	14.3 (13.2 - 15.6)
	6-11y, <40 kg ^e	150 mg QD	105 mg QD	6.76 (6.13 - 7.45)	14.0 (12.8 - 15.4)

Analyte	Populations	D-IVA Dose	Inhibitor Dose ^a	Geometric Mean Ratio ^b (90% CI) of D-IVA, Exposure Parameters	
				C _{max,ss}	AUC _{0-24h,ss}
DDI Simulation with Fluconazole (moderate CYP3A inhibitor)					
D-IVA	Healthy adults	250 mg QD	200 mg QD	2.27 (2.21 - 2.32)	3.13 (3.05 - 3.21)
	6-11y, ≥40 kg	250 mg QD	135 mg QD	2.17 (2.12 - 2.22)	3.17 (3.10 - 3.24)
	6-11y, <40 kg	150 mg OD	100 mg OD	2.10 (2.05 - 2.15)	3.17 (3.09 - 3.25)

Source: Applicant's response to IR submitted on Aug 23, 2024, SDN 0019, Module 1.11.3, Table 5.

Note: AUC_{0-24,ss} was calculated from 1992 to 2016 hours postdose.

^a Inhibitor's dose in 6-11-yr-old children is adjusted to match the exposure of inhibitor in healthy adult subjects.

^b Analyte + CYP3A inhibitor/Analyte alone

^c 10 trials, 10 subjects in each trial, gender ratio – 0.5, age range – 20-50-yr-old

^{d,e} Fixed trial design (101 subjects); Modified Upreti ontogeny profile for CYP3A4

Abbreviations: AUC_{0-24h,ss}, area under the concentration-time curve from time 0 to 24h at steady-state; CI, confidence interval; CYP, cytochrome P450; C_{max,ss}, maximum plasma concentration at steady-state; D-IVA, deutivacaftor; DDI, drug-drug interaction; QD, once daily; yr, year

PBPK Modeling to Support Dose Adjustment of VNZ and D-IVA

Coadministration of TC therapy with CYP3A4 inhibitors resulted in a substantial decrease in CL/F which in return increased the overall exposure of VNZ and D-IVA compared to subjects taking TC therapy without coadministration of CYP3A4 inhibitors. PBPK simulations were performed to evaluate two different dose adjustment regimens of VNZ and D-IVA when the FDC tablet (VNZ Form D 10 mg /TEZ 50 mg/D-IVA 125 mg) is coadministered with strong or moderate CYP3A inhibitors in adults. Given that the predicted increase exposures in the presence of CYP3A inhibitors were higher for VNZ and D-IVA compared to TEZ, and the constraints of using a FDC tablet, the Applicant has prioritized matching VNZ and D-IVA exposures over matching TEZ exposure for DDI dose adjustments to ensure exposures remain within the range of the therapeutic regimen. Therefore, dose adjustment of VNZ/TEZ/D-IVA will be by the same percentage.

Strong CYP3A Inhibitors

The Applicant has evaluated two dose adjustments, one FDC tablet once weekly and two FDC tablets every other week, against the exposures at the therapeutic dose in the absence of CYP3A inhibitors, two FDC tablets once daily. The simulated plasma concentration-time profiles of VNZ and D-IVA are shown in [Figure 96](#). The geometric fold change of simulated steady-state VNZ and D-IVA exposures for the dose adjustment regimens in the presence of a strong CYP3A inhibitor (itraconazole) relative to two FDC tablets once daily in the absence of a CYP3A inhibitor are presented in [Table 176](#). Alternative dosing regimens of VNZ (one FDC Q1W and two FDC Q2W) coadministered with strong CYP3A4 inhibitors has maintained exposure within or below the 5th and 95th percentiles determined from therapeutic dosing regimen of TC (two FDC QD) in the absence of strong CYP3A3 inhibitors. The exposure to VNZ and D-IVA from the two dose adjustment regimes in the presence of strong CYP3A4 inhibitors is within 1.5-fold of VNZ and D-IVA exposures from the therapeutic dosing regimen in the absence of strong CYP3A4 inhibitors ([Table 176](#)).

Moderate CYP3A4 Inhibitors

Two dose adjustments, one FDC tablet every other day and two FDC tablets on Day 1 and two FDC tablets on Day 4 weekly, against the exposures at the therapeutic dose in the absence of

CYP3A inhibitors, two FDC tablets once daily. The simulated plasma concentration-time profiles of VNZ and D-IVA are shown in [Figure 97](#) and [Figure 98](#), and the geometric fold change of simulated steady-state VNZ and D-IVA exposures for the dose adjustment regimens in the presence of moderate CYP3A inhibitors (fluconazole, erythromycin, and verapamil) relative to two FDC tablets once daily in the absence of a CYP3A inhibitor are presented in [Table 176](#). Alternative dosing regimens of VNZ and D-IVA coadministered with moderate CYP3A4 inhibitors has maintained exposure within or below the 5th and 95th percentiles determined from therapeutic dosing regimen in the absence of moderate CYP3A3 inhibitors. The exposure to VNZ and D-IVA from the two dose adjustment regimens (1FDC Q2D and 4 FDC D1D4) in the presence of moderate CYP3A4 inhibitors is within 1.5-fold of VNZ or D-IVA exposure from the therapeutic dosing regimen 2FDC QD in the absence of moderate CYP3A4 inhibitors.

Table 176. Geometric Mean Ratio (90% CI) of Steady-State VNZ and D-IVA Exposure for the Dose Adjustment Regimens in the Presence of Strong and Moderate CYP3A Inhibitors Relative to Two FDC Tablets Once Daily in the Absence of CYP3A Inhibitors

Dose Adjustment Regimen		AUC ^a	C _{max}	C _{min}
<i>Strong CYP3A4 Inhibitors</i>				
VNZ				
Itraconazole	1FDC Q1W	0.748 (0.687, 0.813)	0.796 (0.744, 0.853)	0.696 (0.619, 0.782)
	2FDC Q2W	0.748 (0.687, 0.814)	0.899 (0.850, 0.950)	0.574 (0.485, 0.679)
D-IVA				
Itraconazole	1FDC Q1W	1.00 (0.926, 1.08)	1.15 (1.09, 1.21)	0.748 (0.547, 1.02)
	2FDC Q2W	1.00 (0.926, 1.08)	1.83 (1.73, 1.93)	0.174 (0.0916, 0.332)
<i>Moderate CYP3A4 Inhibitor</i>				
VNZ				
Fluconazole	1FDC Q2D	0.640 (0.619, 0.662)	0.650 (0.630, 0.671)	0.632 (0.609, 0.657)
	4FDC D1D4	0.721 (0.704, 0.738)	0.810 (0.793, 0.828)	0.613 (0.593, 0.634)
Erythromycin	1FDC Q2D	0.819 (0.761, 0.882)	0.825 (0.769, 0.885)	0.758 (0.89)
	4FDC D1D4	0.937 (0.87, 1.01)	1.03 (0.97, 1.1)	0.819 (0.742, 0.903)
Verapamil	1FDC Q2D	0.981 (0.903, 1.07)	0.98 (0.905, 1.06)	0.997 (0.911, 1.09)
	4FDC D1D4	1.12 (1.032, 1.22)	1.21 (1.13, 1.3)	1.014 (0.911, 1.13)

NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Dose Adjustment Regimen		AUC ^a	C _{max}	C _{min}
D-IVA				
Fluconazole	1FDC Q2D	0.785 (0.765, 0.805)	0.822 (0.794, 0.852)	0.822 (0.758, 0.890)
	4FDC D1D4	0.897 (0.874, 0.921)	1.42 (1.36, 1.48)	0.323 (0.276, 0.376)
Erythromycin	1FDC Q2D	1.02 (0.942, 1.10)	0.977 (0.923, 1.03)	1.25 (1.08, 1.44)
	4FDC D1D4	1.17 (1.08, 1.26)	1.62 (1.54, 1.70)	0.576 (0.455, 0.728)
Verapamil	1FDC Q2D	1.26 (1.15, 1.38)	1.15 (1.08, 1.23)	1.65 (1.41, 1.93)
	4FDC D1D4	1.44 (1.32, 1.58)	1.87 (1.76, 1.98)	0.826 (0.641, 1.06)

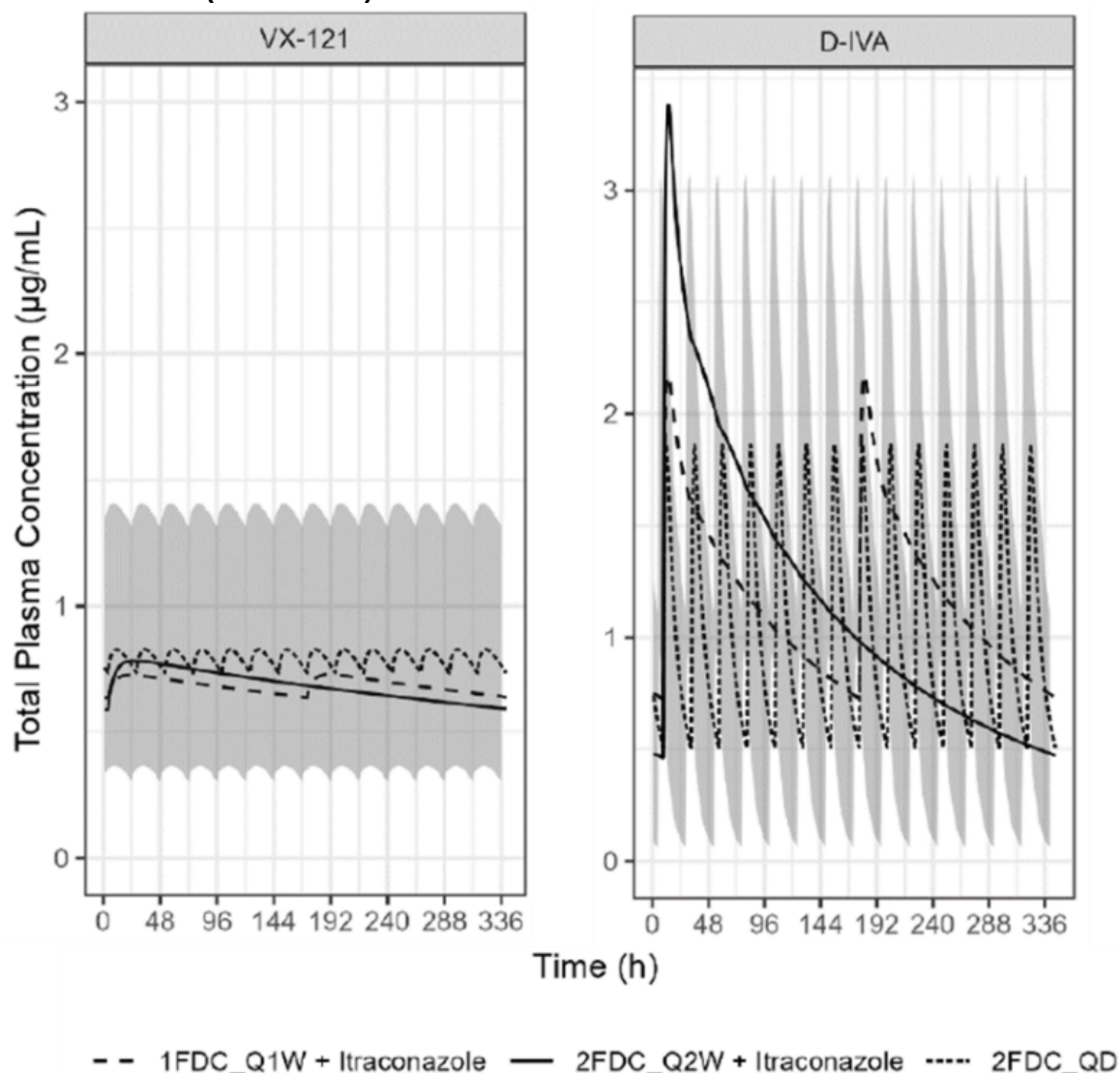
Source: Report T333, Table 7-2, 7-3, and 7-5 and Reviewer's analysis

FDC tablet: VNZ Form D 10 mg /TEZ 50 mg/D-IVA 125 mg; Q1W: once weekly; Q2W every other week; 1FDC_Q2D: One FDC tablet every other day; 4FDC_D1D4: two FDC tablets on Day 1 and two FDC tablets on Day 4 weekly; CI: Confidence interval; Ratio (itraconazole): dose adjustment regimen in the presence of CYP3A inhibitor/2FDC_QD in the absence of CYP3A inhibitor.

^a Steady state AUC over 336 hours (2 weeks)

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum plasma concentration; C_{min}, minimum plasma concentration; CYP, cytochrome P450; D1D4, doses on day 1 and day 4; D-IVA, deutivacaftor; FDC, fixed-daily dose; h, hour; Q2D, every other day; Q1W, every week; Q2W, every other week; TC, triple combination; TEZ, tezacaftor; VNZ, vanzacaftor

Figure 96. Steady-State VNZ and D-IVA Concentration-Time Profiles for Two FDC Tablets Daily in the Absence of a CYP3A Inhibitor and the Dose Adjustment Regimens in the Presence of Strong CYP3A Inhibitor (Itraconazole)



Source: Report T333, Figure 7-4

Notes: Dotted lines represent simulated mean plasma concentration-time profile of the TC two FDC tablets once daily (VX-121 [VNZ] Form D 20 mg /TEZ 100 mg/D-IVA 250 mg) and shaded areas represent the 5th and 95th percentile of the total virtual population.

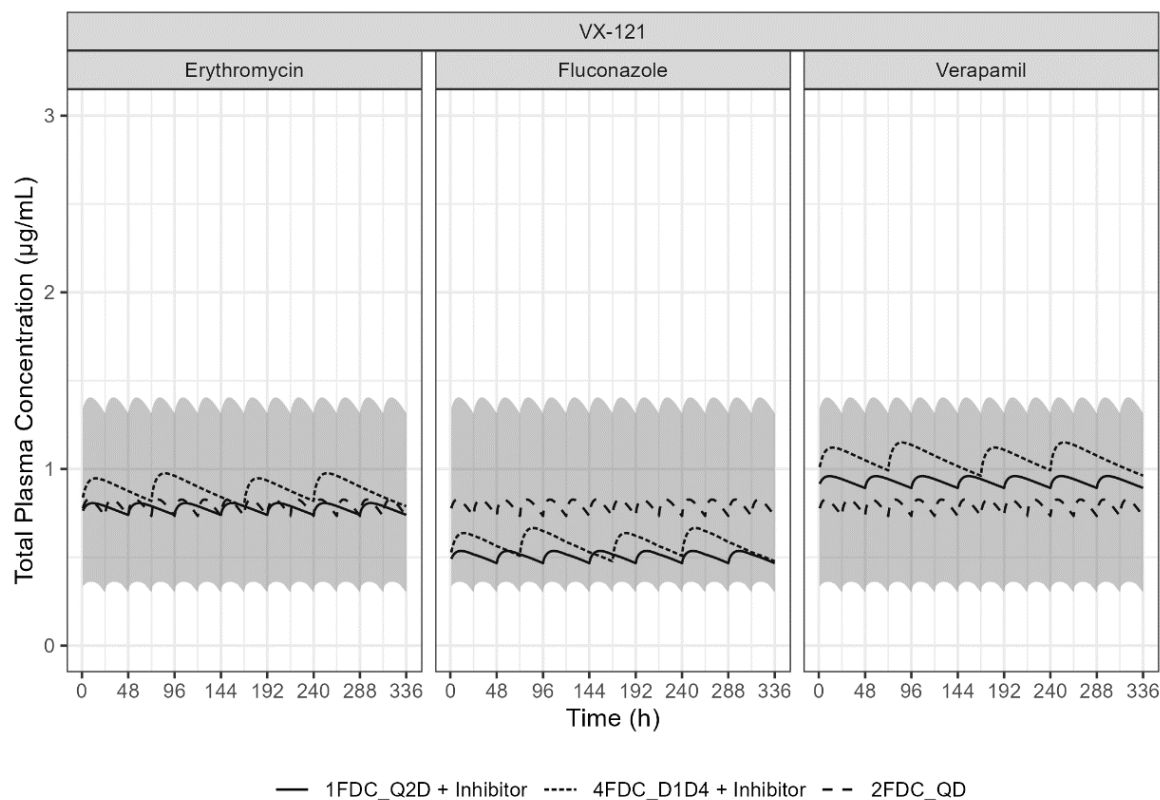
Dashed lines represent simulated mean plasma concentration-time profile after 1FDC_Q1W (one FDC tablet once weekly) dose adjustment and the solid lines represent simulated mean plasma concentration-time profile after 2FDC_Q2W (two FDC tablets every other week) dose adjustment in the presence of strong CYP3A inhibitor (itraconazole).

For VX-121 [VNZ], simulations with 1FDC_Q1W and 2FDC_Q2W regimens were performed with TC tablets administered for 40 weeks and itraconazole 200 mg was administered once daily starting on Day 43 for 34 weeks following starting the administration of TC.

For D-IVA, simulations with 1FDC_Q1W and 2FDC_Q2W regimens were performed with TC tablets administered for 12 weeks and itraconazole 200 mg was administered once daily starting on Day 8 for 11 weeks following starting the administration of TC. Simulation presented from 0 to 336 hours (2 weeks) at steady state. The time frame of 336 hours was selected because all considered regimens (Q1W, Q2W, D1D4 weekly, or Q2D) had a common multiple of 2 weeks (336 hours).

Abbreviations: CYP, cytochrome P450; D1D4, doses on day 1 and day 4; D-IVA, deutivacaftor; FDC, fixed-daily dose; h, hour; Q2D, every other day; Q1W, every week; Q2W, every other week; TC, triple combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Figure 97. Steady-State VNZ Concentration-Time Profiles for Two FDC Tablets Daily in the Absence of a CYP3A Inhibitor and the Dose Adjustment Regimens in the Presence of Moderate CYP3A Inhibitors



Source: Report T333, Figure 7-4

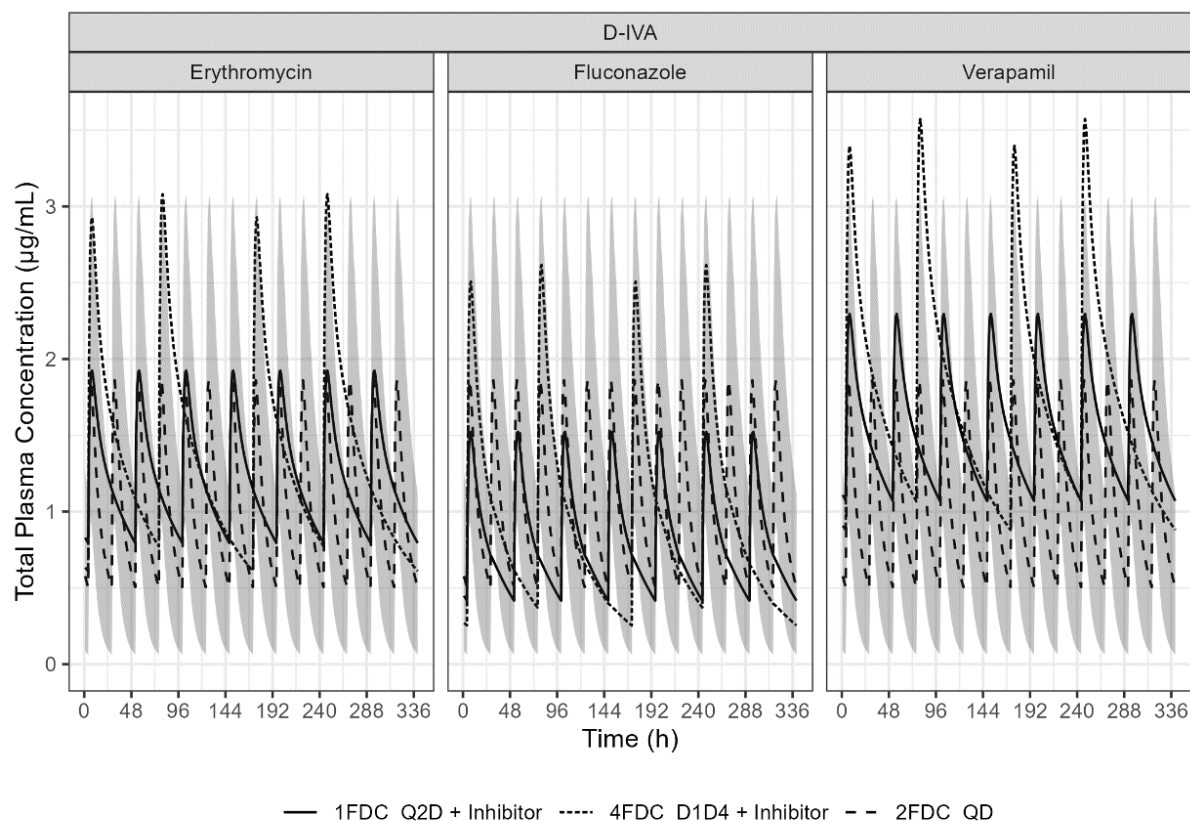
Notes: Dashed lines represent simulated mean plasma concentration-time profile of VX-121 [VNZ] at 2FDC tablets once daily (VX-121 [VNZ] Form D 20 mg / TEZ 100 mg/D-IVA 250 mg) and shaded areas represent the 5th and 95th percentile of the total virtual population.

Solid lines represent simulated mean plasma concentration-time profile after 1FDC_Q2D (one FDC tablet every other day) dose adjustment and the dotted lines represent simulated mean plasma concentration-time profiles after 4FDC_D1D4 (two FDC tablets on Day 1 and two FDC tablets on Day 4 weekly) dose adjustment in the presence of moderate CYP3A inhibitors.

Simulations with 1FDC_Q2D and 2FDC_D1D4 regimens were performed with TC tablets administered for 40 weeks. Fluconazole 200 once daily, erythromycin 500 mg four times daily, and verapamil 200 mg three times daily were administered starting on Day 43 for 34 weeks following starting the administration of TC. Simulation presented from 0 to 336 hours (2 weeks) at steady state. The time frame of 336 hours was selected because all considered regimens (Q1W, Q2W, D1D4 weekly, or Q2D) had a common multiple of 2 weeks (336 hours).

Abbreviations: CYP, cytochrome P450; D1D4, doses on day 1 and day 4; D-IVA, deutivacaftor; FDC, fixed-daily dose; h, hour; Q2D, every other day; Q1W, every week; Q2W, every other week; TC, triple combination; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Figure 98. Steady-State D-IVA Concentration-Time Profiles for Two FDC Tablets Daily in the Absence of a CYP3A Inhibitor and the Dose Adjustment Regimens in the Presence of Moderate CYP3A Inhibitors



Source: Report T333, Figure 7-7

Notes: Dashed lines represent simulated mean plasma concentration-time profile of D-IVA at 2FDC tablets once daily (VNZ Form D 20 mg /TEZ 100 mg/D-IVA 250 mg) and shaded areas represent the 5th and 95th percentile of the total virtual population. Solid lines represent simulated mean plasma concentration-time profile of D-IVA after 1FDC_Q2D (one FDC tablet every other day) dose adjustment and the dotted lines represent simulated mean plasma-time profile of D-IVA after 4FDC_D1D4 (two FDC tablets on Day 1 and two FDC tablets on Day 4 weekly) dose adjustment in the presence of moderate CYP3A inhibitors. Simulations with 1FDC_Q2D and 2FDC_D1D4 regimens were performed with TC tablets administered for 12 weeks. Fluconazole 200 once daily, erythromycin 500 mg 4 times daily, and verapamil 200 mg three times daily were administered starting on Day 8 for 11 weeks following starting the administration of TC.

Simulation presented from 0 to 336 hours (2 weeks) at steady state. The time frame of 336 hours was selected because all considered regimens (weekly (Q1W), every other week (Q2W), doses on Day 1 and Day 4 (D1D4) weekly, or every other day (Q2D) had a common multiple of 2 weeks (336 hours).

Abbreviations: CYP, cytochrome P450; D1D4, doses on day 1 and day 4; D-IVA, deutivacaftor; FDC, fixed-daily dose; h, hour; Q2D, every other day; Q1W, every week; Q2W, every other week; TC, triple combination; TEZ, tezacaftor; VNZ, vanzacaftor

PopPK model-based simulations were performed to inform dose adjustments for adults and children aged 6 through 11 years with CF that were coadministered CYP3A4 inhibitors. For these simulations, clearance values were adjusted for subjects receiving strong or moderate CYP3A4 inhibitor based on changes in AUC predicted by the PBPK simulations ([Table 165](#) and [Table 173](#)). The potential dose adjustments for children aged 6 to 11 years coadministered VNZ and D-IVA with CYP3A4 inhibitors aimed to provide exposures that are similar to VNZ and D-IVA exposures without CYP3A4 inhibitors in adults with CF. Review of this model-based analysis and final recommendations of DDI dose adjustment for pediatrics are presented in [Section 14.5.1](#) of the review.

Prediction of DDI Potential of VNZ and D-IVA as Victims for Moderate and Strong CYP3A4 Inducers

In response to FDA's information request (dated September 6, 2024), the Applicant provided PBPK simulations to support the DDI management strategy of VNZ/D-IVA with moderate and strong CYP3A inducers in the proposed label. Simulation showed that the exposure to VNZ and D-IVA decreased significantly by 82% and 90%, respectively, when coadministered with rifampin, a strong CYP3A inducer. Moreover, carbamazepine, a strong CYP3A inducer, significantly decreased VNZ and D-IVA exposures by 57% and 76%, respectively ([Table 177](#)).

Simulation showed that the exposure to VNZ and D-IVA decreased by 69% and 73%, respectively, when coadministered with efavirenz, a moderate CYP3A inducer.

In summary, moderate or strong CYP3A4 inducers significantly decreased the exposure to VNZ and D-IVA, which may impact the efficacy of TC therapy in CF patients. Therefore, coadministration of TC therapy with moderate or strong CYP3A4 inducers is not recommended.

Table 177. PBPK Simulations Predicted Changes in Steady-State PK Parameters of VNZ When Coadministered With a Strong or Moderate CYP3A Inducer or Administered Alone

Analyte	CYP3A Inducer	Geometric Mean Ratio ^a (90% CI) of Exposure Parameters		
		AUC _{0-24h,ss}	C _{max,ss}	C _{min,ss}
VNZ	Rifampin	0.180	0.218	0.119
	600 mg QD	(0.169 - 0.191)	(0.207 - 0.230)	(0.108 - 0.130)
	Carbamazepine	0.435	0.457	0.394
	400 mg bid	(0.418 - 0.453)	(0.439 - 0.476)	(0.377 - 0.411)
	Efavirenz	0.313	0.347	0.251
D-IVA	600 mg QD	(0.294 - 0.333)	(0.328 - 0.367)	(0.231 - 0.271)
	Rifampin	0.0987	0.199	0.0234
	600 mg QD	(0.0891 - 0.109)	(0.182 - 0.218)	(0.02 - 0.0273)
	Carbamazepine	0.237	0.324	0.127
	400 mg bid	(0.220 - 0.255)	(0.303 - 0.346)	(0.115 - 0.139)
	Efavirenz	0.271	0.445	0.0952
	600 mg QD	(0.250 - 0.293)	(0.420 - 0.471)	(0.0829 - 0.109)

Source: Applicant's response to IR submitted on Sep 6, 2024, SDN 0022, Module 1.11.3, Table 1 and 2.

Note: VNZ was dosed for 29 days at 20 mg Form D QD and D-IVA was dosed for 29 days at 250 mg QD on Day 6, Day 8, or Day 10 after dosing rifampin 600 mg QD for 34 days, carbamazepine 400 mg bid for 36 days, or efavirenz 600 mg QD for 38 days, respectively.

^a analyte + CYP3A4 Inducer/analyte alone

Abbreviations: AUC_{0-24,ss}, area under the concentration-time curve from time 0 to 24 hour at steady-state; bid, twice daily; C_{max,ss}, maximum plasma concentration at steady-state; C_{min,ss}, minimum plasma concentration at steady-state; CYP, cytochrome P450; D-IVA, deutivacافتor; PBPK, population-based pharmacokinetics QD, once daily; VNZ, vanzacافتor; VNZ, vanzacافتor

Prediction of DDI Potential of VNZ and D-IVA as Inhibitors on CYP2C9 Substrates

In vitro data showed that D-IVA inhibited CYP2C8 (IC₅₀=9.5 μM, R-value =1.05), CYP2C9 (IC₅₀=15.6 μM, R-value =1.03), and CYP3A4 (IC₅₀=15.7 μM, testosterone as a probe substrate, R-value =1.03) with R-value above the defined criteria (Reports D-IVA DM-058, CPT-656-DM-085). Clinically, IVA did not significantly affect the PK of rosiglitazone, a CYP2C8 substrate (Study 770-010, NDA 203188) or midazolam, CYP3A substrate, (Study 661-006, NDA 210491)). Moreover, in vitro data showed that M1-D-IVA inhibited CYP2C9 (IC₅₀=4.6 μM, R-value =1.09). Therefore, D-IVA and its metabolites have low potential to mediate CYP enzymes inhibition at clinically relevant concentrations, except that D-IVA and M1-D-IVA may inhibit

CYP2C9. VNZ may have weak inhibition CYP2C9 ($IC_{50}=18.4 \mu M$) (Study N189) with R-value below the defined criteria.

In response to FDA's information request (dated September 6, 2024), The Applicant provided PBPK simulations for DDI of multiple-doses of VNZ and D-IVA as perpetrators (i.e., CYP2C9 inhibitors) with a CYP2C9 substrate (e.g., warfarin and tolbutamide). Using in vitro determined IC_{50} values, the inhibition of CYP2C9 by VNZ or D-IVA had no notable impact on the exposure to warfarin and tolbutamide (Table 178). However, applying a minimal uncertainty factor of 3-fold lower IC_{50} value for D-IVA, the risk for a clinical interaction could not be excluded (e.g., the predicted AUC R values of tolbutamide reached the threshold of 1.25). Therefore, the PBPK analysis supports the Applicant's proposed DDI management strategy of cautionary use or monitoring when D-IVA is coadministered with CYP2C9 substrates, such as warfarin.

Table 178. PBPK Simulations Predicted Changes in Steady-State PK Parameters of Warfarin and Tolbutamide (CYP2C9 Substrates) When Coadministered With VNZ or D-IVA Compared to When Administered Alone

Analyte	CYP2C9 Perpetrator	Geometric Mean Ratio ^b (range with +/- 3-fold CYP2C9 IC_{50}) of Exposure Parameters		
		AUC _{0-24h,ss} Ratio	C _{max,ss} Ratio	C _{min,ss} Ratio
Warfarin	VNZ	1.00	1.00	1.01
		(1.00 - 1.01)	(1.00 - 1.01)	(1.00 - 1.01)
	D-IVA ^a	1.08	1.06	1.11
		(1.03 - 1.22)	(1.02 - 1.16)	(1.04 - 1.31)
Tolbutamide	VNZ	1.00	1.00	1.01
		(1.00 - 1.01)	(1.00 - 1.01)	(1.00 - 1.02)
	D-IVA ^a	1.09	1.06	1.19
		(1.03 - 1.25)	(1.02 - 1.15)	(1.06 - 1.58)

Source: Table 3 from clin-info-amend-resp-rcvd-03sep2024.pdf

Notes: VNZ is dosed at 20 mg Form D QD; D-IVA is dosed at 250 mg QD; warfarin is dosed at 2 mg QD after 29 days of VNZ or D-IVA dosing; tolbutamide is dosed at 1000 mg QD after 29 days of VNZ or D-IVA dosing; Ratios of 1.00 indicate no interaction between CYP2C9 substrate and perpetrator.

The PBPK model for VNZ included the inhibition potential CYP1A2 ($IC_{50}=36.4 \mu M$), CYP2B6 ($IC_{50}=14.2 \mu M$), CYP2C8 ($IC_{50}=18.1 \mu M$), CYP2C9 ($IC_{50}=18.4 \mu M$), CYP2C19 ($IC_{50}=51 \mu M$), CYP2D6 ($IC_{50}=30.9 \mu M$), and CYP3A4 ($IC_{50}=33 \mu M$) and unbound fraction in the microsomes ($f_{u,mic}$) of 0.00709 (Report N189). The PBPK model for D-IVA included the inhibition potential CYP2C8 ($IC_{50}=9.5 \mu M$), CYP2C9 ($IC_{50}=15.6 \mu M$), and CYP3A4 ($IC_{50}=15.7 \mu M$) and unbound fraction in the microsomes ($f_{u,mic}$) of 0.0196 (Report D-IVA DM-058). The PBPK model for M1-D-IVA included the inhibition potential CYP2B6 ($IC_{50}=23.2 \mu M$), CYP2C8 ($IC_{50}=4.8 \mu M$), CYP2C9 ($IC_{50}=4.6 \mu M$), CYP2C19 ($IC_{50}=46 \mu M$), CYP2D6 ($IC_{50}=55.9 \mu M$), and CYP3A4 ($IC_{50}=14.9 \mu M$, midazolam as probe substrate) and unbound fraction in the microsomes ($f_{u,mic}$) of 0.167 (Report CTP-656 DM-085).

The in vitro CYP2C9 IC_{50} values for VNZ, D-IVA, and M1-D-IVA measured in human liver microsomes were corrected for nonspecific binding in the assay to obtain free IC_{50} values (Reports DM-058, CTP-656 DM-085, S016, R015, and S079). The free IC_{50} values were varied 3-fold from the measured value in both directions to incorporate the impact of any experimental uncertainty in measurements.

^a The PBPK model included D-IVA and M1-D-IVA but not M6-D-IVA since Simcyp software limitations only allow parent and a single metabolite to be included as an inhibitor. However, M6-D-IVA does not inhibit CYP2C9 in vitro and its absence in the model has no impact on the outcome (Report CTP-656 DM-085).

^b CYP2C9 Substrate + CYP2C9 perpetrator/CYP2C9 Substrate. Source: Applicant's response to IR submitted on Sep 6, 2024, SDN 0022, Module 1.11.3, Table 3.

Abbreviations: AUC_{0-24h,ss}, area under the concentration-time curve from time 0 to 24 hour at steady-state; C_{max,ss}, maximum plasma concentration at steady-state; C_{min,ss}, minimum plasma concentration at steady-state; CYP, cytochrome P450; D-IVA, deutivacaftor; IC_{50} , half maximal inhibitory concentration; M, metabolite; PBPK, population-based pharmacokinetics QD, once daily; VNZ, vanzacaftor

Conclusions

VNZ AUC was predicted to increase by approximately 2.4- to 3.9-fold when single or multiple doses of VNZ was coadministered with multiple doses of a moderate CYP3A inhibitor.

Coadministration of a moderate CYP3A inhibitor with single dose VNZ increased VNZ C_{max} by 1.2-fold, whereas VNZ $C_{max,ss}$ increased by 2.5- to 3.8-fold due to accumulation.

Simulations predicted 2.9- to 4.5-fold increase in AUC_{inf} and 3.1- to 5.1-fold increase in D-IVA $AUC_{0-24,ss}$ when D-IVA was coadministered as a single dose or multiple doses, respectively, with a moderate CYP3A inhibitor. Coadministration of a moderate CYP3A inhibitor with single dose D-IVA increased D-IVA C_{max} by 1.7-fold, whereas D-IVA $C_{max,ss}$ increased by 2.3 to 3.4-fold due to accumulation.

Simulation predicted increase in VNZ $C_{max,ss}$ and $AUC_{0-24,ss}$ by approximately 10- and 11-fold in children 6 through 11 years weighing ≥ 40 kg, and 10- and 9.5-fold in children 6 through 11 years weighing < 40 kg, respectively, when multiple doses of VNZ were coadministered with a strong CYP3A inhibitor. D-IVA geometric mean ratio of $C_{max,ss}$ and $AUC_{0-24,ss}$ by 7.36 and 14.3 (in children 6 through 11 years weighing ≥ 40 kg) and 6.76 and 14 (in children 6 through 11 years weighing < 40 kg), respectively, when D-IVA was coadministered with itraconazole

Simulation predicted increase in VNZ geometric mean ratio of $C_{max,ss}$ and $AUC_{0-24,ss}$ by 2.54 and 2.64 (in children 6 through 11 years weighing ≥ 40 kg) and 2.49 and 2.6 (in children 6 through 11 years weighing < 40 kg) when multiple doses of VNZ were coadministered with fluconazole, a strong CYP3A4. The increase in D-IVA geometric mean ratio of $C_{max,ss}$ and $AUC_{0-24,ss}$ when coadministered with fluconazole was predicted to be 2.1 and 3.17, respectively, in children 6 through 11 years weighing ≥ 40 kg or < 40 kg.

PBPK simulations in adults support reduction in the therapeutic dose of VNZ/TEZ/D-IVA when coadministered with CYP3A4 inhibitors as follows:

- When coadministered with a strong CYP3A inhibitor: reduce dose from two FDC tablets of (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg) daily to one FDC tablet once weekly (b) (4)
- When coadministered with a moderate CYP3A inhibitor: reduce dose from two FDC tablets of (VNZ 10 mg/TEZ 50 mg/D-IVA 125 mg) daily to one FDC tablet every other day (b) (4)

Simulations predicted 82% and 90% reduction in VNZ and D-IVA exposure, respectively, when coadministered with rifampin, a strong CYP3A inducer. In addition, simulations predicted 57% and 76%, reduction in VNZ and D-IVA exposure, respectively, when coadministered with carbamazepine, a strong CYP3A inducer. Efavirenz, a moderate CYP3A inducer, was predicted to decrease the exposure to VNZ and D-IVA by 69% and 73%, respectively. Therefore, simulations support that coadministration of TC therapy with moderate or strong CYP3A4 inducers is not recommended.

The DDI potential of D-IVA as inhibitor of CYP2C9 substrates (e.g., warfarin and tolbutamide) cannot be ruled out.

14.6. Pharmacogenetics

Not applicable.

15. Study / Trial Design

15.1. Phase 3 Trials, Trials 102 and 103

Overview and Objectives

Trials VX20-121-102 (Trial 102) and VX20-121-103 (Trial 103) were phase 3, multicenter, randomized, double-blind, parallel-group, controlled, noninferiority trials evaluating the safety and efficacy of VNZ/TEZ/D-IVA in subjects with CF 12 years of age and older.

Trial 102 Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VX-121 [VNZ] Combination Therapy [VNZ/TEZ/D-IVA] in Subjects with Cystic Fibrosis who are Heterozygous for *F508del* and a Minimal Function Mutation (F/MF)

- Trial dates: September 14, 2021 to November 21, 2023
- Trial report date: April 5, 2024

Trial 103 Title: A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VNZ Combination Therapy [VNZ/TEZ/D-IVA] in Subjects with Cystic Fibrosis Who Are Homozygous for *F508del*, Heterozygous for *F508del* and a (F/G) or (F/ RF) Mutation, or Have At Least 1 Other Triple Combination Responsive *CFTR* Mutation and No *F508del* Mutation

- Trial dates: October 27, 2021 to November 30, 2023
- Trial report date: April 5, 2024

Overall, the two phase 3 trials were similar in design and were adequate and well controlled. The general trial designs will be reviewed together with relevant differences noted.

Primary Objective

- To evaluate the efficacy of VNZ/TEZ/D-IVA in CF subjects

Secondary Objectives

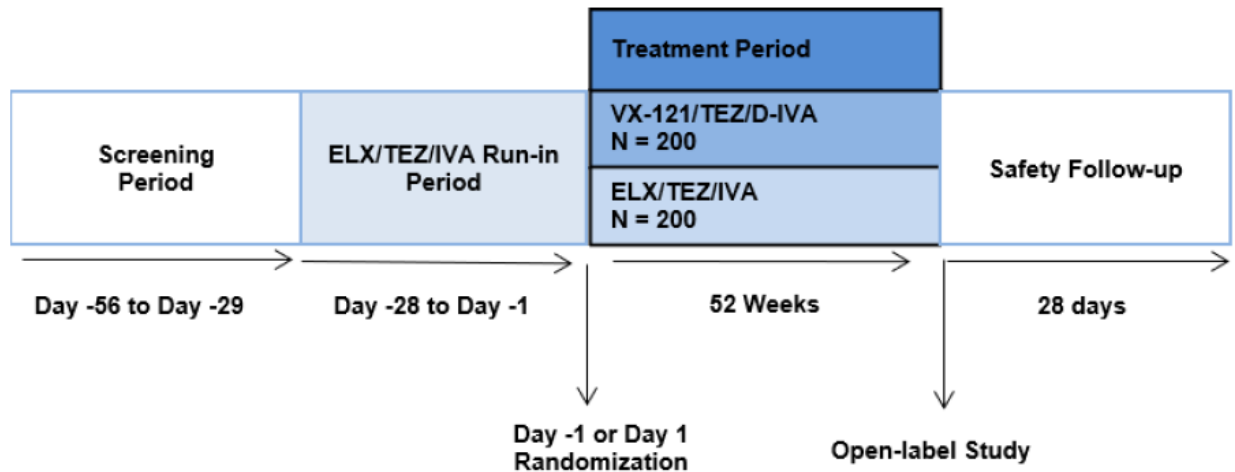
- To evaluate the safety of VNZ/TEZ/D-IVA
- To evaluate the pharmacokinetics (PK) of VNZ/TEZ/D-IVA

Trial Design

The phase 3 trials included a 4-week (28 day) screening period followed by a 4-week (28 day) run-in period during which all subjects received ELX 200 mg QD/TEZ 100 mg QD/IVA 150 mg q12h (the commercially approved dose) to establish a reliable on-treatment (ELX/TEZ/IVA) baseline for the treatment period. Spirometry and SwCl assessments obtained during the run-in period (Day -14) were obtained and used for stratification and randomization. Following completion of the run-in period, the subjects were randomized 1:1 to the VNZ/TEZ/D-IVA

(treatment) arm or the ELX/TEZ/IVA (control) arm for a 52-week treatment period that included in-person clinic visits on Day 14, Weeks 4, 8, 12, 16, 24, 36, and 52 with intermittent telephone contact in between scheduled visits. A follow-up safety visit occurred for any subject who prematurely discontinued trial drug (28±7 days after the last dose of trial drug). Safety follow-up visits were not required for subjects who completed the treatment period and transitioned within 28 days to one of the following: an open-label trial, another qualified trial run by the Applicant, or a commercially available or managed access program-supplied program for another medication from the Applicant. The trial schematic is shown below in [Figure 99](#).

Figure 99. Pivotal Phase 3 Trial Schematic, Trial 102



Source: Applicant provided (Protocol VX20-121-102, Version 3.0. Figure 2-1).
Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; N, number of subjects, TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Subjects were permitted to be rescreened once during which all screening assessments were repeated with the exception of *CFTR*-genotyping and, if applicable, follicle-stimulating hormone level and ophthalmologic examinations. Subjects were stratified by age at screening visit (<18 years versus ≥18 years of age), ppFEV₁ determined during the Run-in Period (<70% versus ≥70%), SwCl determined during the Run-in Period (<30mmol/L versus ≥30mmol/L), and prior use of a medication that affects *CFTR* processing or function (e.g., ELX/TEZ/IVA) use (yes versus no).

Subjects who completed the 52-day treatment period were able to enroll in the open-label extension study (Trial VX20-121-104), if eligible.

Trial Population

The trials enrolled adults and adolescents (12 years and older) with stable CF per the following enrollment criteria and eligible *CFTR* genotypes as outlined in [Table 179](#).

Table 179. CFTR Genotypes Eligible for Enrollment

Trial Number	CFTR Genotypes Eligible for Enrollment
Trial 102	Heterozygous for <i>F508del</i> and a MF variant (defined as a variant that either results in no translated CFTR protein or that is nonresponsive to TEZ, IVA, or TEZ/IVA based on in vitro testing)
Trial 103	One of the following: • Homozygous for <i>F508del</i> (F/F) • Heterozygous for <i>F508del</i> and a gating variant (F/G) • Heterozygous for <i>F508del</i> and a residual function variant (F/RF) • At least one other triple combination-responsive CFTR variant identified as responsive to ELX/TEZ/IVA and no <i>F508del</i> (TCR/non-F)

Source: Clinical reviewer

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; ELX, elxacaftor; F, *F508del* CFTR variant; G, gating CFTR variant; IVA, ivacaftor; MF, minimal function CFTR variant; RF, residual function CFTR variant; TCR, triple combination responsive CFTR variant; TEZ, tezacaftor

The Applicant included a list of example gating and residual function variants that is outlined in [Table 180](#). Investigators were to contact the medical monitor to review additional potential qualifying gating or residual function variants.

Table 180. Examples of Gating and Residual Function CFTR Variants Eligible for Trial 103

<i>711+3A<G</i>	<i>D110H</i>	<i>A455E</i>	<i>S977F</i>	<i>D1152H</i>
<i>2789+5G>A</i>	<i>R117C</i>	<i>S549N</i>	<i>F1052V</i>	<i>G1244E</i>
<i>3272+26A>G</i>	<i>R117H</i>	<i>S549R</i>	<i>K1060T</i>	<i>S1251N</i>
<i>3849+10kbC>T</i>	<i>G178R</i>	<i>G551D</i>	<i>A1067T</i>	<i>S1255P</i>
<i>E56K</i>	<i>E193K</i>	<i>G551S</i>	<i>G1069R</i>	<i>D1270N</i>
<i>P67L</i>	<i>L206W</i>	<i>D579G</i>	<i>R1070Q</i>	<i>G1349D</i>
<i>R74W</i>	<i>R347H</i>	<i>E831X</i>	<i>R1070W</i>	
<i>D110E</i>	<i>R352Q</i>	<i>S945L</i>	<i>F1074L</i>	

Source: Clinical reviewer, Applicant provided data

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator

The additional key eligibility criteria are listed below:

Key Inclusion Criteria

- Ages 12 years or older
- Confirmed diagnosis of CF as determined by the investigator
- CFTR genotype as reviewed in [Table 179](#)
- Percent predicted forced expiratory volume in one second {Quanjer, 2012 #12}:
 - Subjects receiving ELX/TEZ/IVA at screening: $\geq 40\%$ and $\leq 90\%$
 - Subjects not receiving ELX/TEZ/IVA at screening: $\geq 40\%$ and $\leq 80\%$
- Stable CF disease as judged by the investigator

Key Exclusion Criteria

- History of comorbidity that might confound the results in the opinion of the investigator. Including, but not limited to:
 - Hepatic cirrhosis with portal hypertension, moderate hepatic impairment (Child Pugh Score 7 to 9), severe hepatic impairment (Child Pugh Score 10 to 15)
 - Solid organ or hematological transplantation
 - Alcohol or drug abuse in the past year
 - Cancer except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ
- History of intolerance to trial drug that would pose additional risk to the subject in the opinion of the investigator (e.g., subjects with a history of liver function test (LFT) elevations requiring treatment interruption or discontinuation, allergy or hypersensitivity to the trial drug)
- Any of the following abnormal labs at screening:
 - Hemoglobin <10 g/dL
 - Total bilirubin ≥ 2 x upper limit of normal (ULN)
 - Aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase, or alkaline phosphatase (ALP) ≥ 3 x ULN
 - Abnormal renal function defined as glomerular filtrate rate ≤ 50 mL/min/1.73 m² (Modification of Diet in Renal Disease Study Equation ([Levey et al. 1999](#); [Levey et al. 2006](#))) for subjects ≥ 18 years and ≤ 45 mL/min/1.73 m² (Counahan-Barratt equation ([Counahan et al. 1976](#))) for subjects 12-17 years
- An acute upper or lower respiratory tract infection, infectious pulmonary exacerbation (PE_x) of CF, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before the first dose of ELX/TEZ/IVA in the run-in period
- 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*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
 - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent
 - The subject has at least two respiratory tract cultures negative for these organisms within the 12 months before the day of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent

- An acute illness not related CF (e.g., gastroenteritis) within 14 days before the first dose of ELZ/TEZ/IVA in the run-in period
- Ongoing or prior participation in a study of an investigational treatment other than the Applicant's medications that affect CFTR processing or function
- Use of prohibited medications
- Pregnant or breast-feeding females

The overall population for the phase 3 trials was reasonable and consistent with other similar clinical development programs in the CF population. Note that subjects unable to tolerate ELX/TEZ/IVA were excluded. This is a limitation of the trial design and may affect both the overall generalizability and ability to assess the safety of VNZ/TEZ/D-IVA in patients unable to tolerate ELX/TEZ/IVA, an area of unmet need in the CF population, as reviewed in Section [7.7.1](#).

Trial Drug Interruption and Stopping Rules

Liver Function Tests

The protocol stated that the central laboratory would notify the medical monitor of ALT or AST $>3 \times \text{ULN}$ and total bilirubin $>2 \times \text{ULN}$. Subjects with new treatment-emergent ALT or AST elevations of $>3 \times \text{ULN}$, with or without total bilirubin $>2 \times \text{ULN}$ were followed closely with confirmatory testing within 28 to 72 hours of the initial finding.

Trial drug administration was interrupted immediately (prior to confirmatory testing) if any of the following criteria were met:

- ALT or AST $>8 \times \text{ULN}$
- ALT or AST $>5 \times \text{ULN}$ for more than 2 weeks
- ALT or AST $>3 \times \text{ULN}$ in association with total bilirubin $>2 \times \text{ULN}$ and/or clinical jaundice

A thorough investigation of potential causes was conducted, and the subject was monitored closely for clinical progression.

Trial drug administration was discontinued if subsequent ALT or AST values confirmed the initial evaluation that satisfied the interruption rule and no convincing alternative etiology (e.g., acetaminophen use, viral hepatitis, alcohol ingestion) was identified, regardless of whether the transaminase levels improved. All subjects for whom treatment was discontinued for elevated transaminases and bilirubin, had levels monitored closely until normalization or return to baseline. If an alternative, reversible cause of transaminase elevation, with or without increased bilirubin or clinical jaundice, was identified, trial drug administration was resumed once the transaminases returned to baseline or were $\leq 2 \times \text{ULN}$, whichever was higher. Upon resumption, transaminases and bilirubin were assessed weekly for 4 weeks. Trial drug was permanently discontinued if a protocol-defined transaminase interruption threshold recurred within 4 weeks of the rechallenge of the trial drug.

Rash

Trial drug dosing was interrupted for subjects who developed a generalized rash Grade 3 or higher or a rash that was considered a serious adverse event (SAE). The investigators were advised to consider additional evaluations and were able to reconsider resumption of trial drug if considered clinically appropriate.

Other

In addition, subjects were discontinued from trial drug treatment if they met any of the following criteria:

- Had a screening *CFTR* genotype that does not confirm trial eligibility if a previous *CFTR* genotype laboratory report was used to establish eligibility.
- Became pregnant
- Met any trial drug discontinuation criteria (reviewed above)

Subjects who withdrew before the first does of trial drug prior to Day 1 of the Treatment Period were able to be replaced.

The stopping criteria outlined in the protocol's was acceptable.

Dose and Duration of Treatment

The dosages evaluated in the phase 3 trials were as follows:

- Active control: ELX 200 mg QD/TEZ 100 mg QD/IVA 150 mg q12h
- Treatment: VNZ 20 mg QD/TEZ 100 mg QD/D-IVA 250 mg QD

The trial drug was administered orally with a fat-containing meal or snack. It was recommended that the dose be taken within 30 mins of the start of the meal or snack.

If six hours or fewer had passed since the missed morning or evening dose, the subject was to take the missed dose as soon as possible and continue on the original schedule. If more than 6 hours had passed since the missed morning dose, the subject was to take the missed dose as soon as possible and not take the evening dose. If more than six hours had passed since the missed evening dose, the subject should not take the missed doses. The next scheduled morning dose was to be taken at the usual time. The morning and evening doses were not to have been taken at the same time.

All subjects (and their parents/caregivers/companions), site personnel (including investigators, site monitor, and trial team), and members of the Applicant's trial team were blinded to the treatment group. The Applicant's trial team did not have access to the spirometry or SwCl results after the first dose of the trial drug on Day 1 of the treatment period, with the exception of spirometry related adverse event reporting. Individual SwCl results were also not disclosed to the trial sites with the exception of the screening visit and Day -14 values. Subjects and their

parents/caregivers/companions were not to be informed of trial-related spirometry results until the Applicant determined that the trial had completed.

Subjects remained on their stable standard-of-care CF regimen with the exception of any alternative medications that affect CFTR processing or function, approved or investigational. The key prohibited and acceptable concomitant medications, reviewed below, were acceptable and consistent with prior phase 3 trials in the CF population.

Key Prohibited Medications

- Moderate and strong CYP3A inducers (within 14 days before the first dose of ELX/TEZ/IVA through the completion of trial participation)
- Moderate and strong CYP3A inhibitors except ciprofloxacin (within 14 days before the first dose of ELX/TEZ/IVA through the completion of trial participation)
- Non-Vertex medications that affect CFTR processing or function, investigational or approved (none allowed within 28 days or 5 terminal half-lives before screening through completion of trial participation)
- Vertex medications that affect CFTR processing or function, investigational or approved (none allowed from the first dose of ELX/TEZ/IVA on Day -28 until after the last dose of trial drug)

Prior and Concomitant Medications

- Subjects were to remain on stable treatment regimen for CF from 28 days before the Run-in through completion of trial participation. Guidelines for stable CF treatment regimens included:
 - Subjects on inhaled tobramycin or other chronically inhaled antibiotics should remain on that regimen throughout the trial.
 - Subjects on cycle on and off inhaled antibiotics should continue on their prior schedule. The timing of the first dose of ELX/TEZ/IVA in the Run-in Period should be synchronized as closely as possible (e.g., not more than ± 3 days).
 - Subjects who alternate between two different inhaled antibiotics should remain on the same cycling schedule during the trial. The timing of the first dose of ELX/TEZ/IVA in the Run-in Period should be synchronized as closely as possible (e.g., not more than ± 3 days) to the first day in the cycle onto one of the inhaled antibiotics.
- Subjects may receive doses of prednisone or prednisolone of up to 10 mg/day chronically. Subjects could not receive prednisone or prednisolone at doses of >60 mg daily for longer than a 5-day period.
- Caution and appropriate monitoring should be used when coadministration of trial drugs with medicinal products that are substrates of OATP1B1/1B3, such as statins, glyburide, nateglinide, and repaglinide.

- Digoxin and other substrates of P-glycoprotein with a narrow therapeutic index, such as cyclosporine, everolimus, sirolimus, and tacrolimus, should be used with caution and appropriate monitoring.
- During coadministration with warfarin, additional monitoring of the international normalized ratio is recommended. Other medicinal products that are CYP2C9 substrates for which exposure may be increased include glimepiride and glipizide; these should be used with caution.

Trial Endpoints

Primary Endpoint

- Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV₁) through Week 24

Key Secondary Endpoints

- Absolute change from baseline in SwCl through Week 24
- Proportion of subjects with SwCl <60mmol/L through Week 24 (pooled with data from Trials 102 and 103)
- Proportion of subjects with SwCl <30mmol/L through Week 24 (pooled with data from Trials 102 and 103)

Other Secondary Endpoints

- Number of PEx through Week 48
- Absolute change from baseline in CFQ-R RD score through Week 24
- Absolute change from baseline in ppFEV₁ through Week 48
- Absolute change from baseline in SwCl through Week 48
- Proportion of subjects with SwCl <60mmol/L through Week 24
- Proportion of subjects with SwCl <30mmol/L through Week 24
- Safety and tolerability assessments based on adverse events (AEs), clinical laboratory values, ECGs, vital signs, and pulse oximetry

Other Endpoints

- Proportion of subjects with SwCl <60mmol/L through Week 48
- Proportion of subjects with SwCl <30mmol/L through Week 48
- Absolute change from baseline in body mass index (BMI) at Week 48
- Absolute change from baseline in BMI z-score at Week 48
- Absolute change from baseline in weight at Week 48
- Absolute change from baseline in CFQ-R RD score through Week 48
- PK parameters of VNZ, TEZ, and D-IVA

Overall, the trial endpoints are acceptable and consistent with other similar phase 3 trials in this population. They evaluate a number of factors considered to be clinically meaningful to patients with CF including ppFEV₁, CFQ-R RD, BMI, SwCl, weight, and CF PExs, although these endpoints were outside of the statistical hierarchy. Further discussions regarding the use of SwCl-based key secondary endpoints are included in Section [6.3.3](#).

Efficacy Assessments

Spirometry

Spirometry was performed according to the American Thoracic Society/European Respiratory Society guidelines ([Graham et al. 2019](#)). Pre-bronchodilator was defined as spirometry performed for subjects who withheld short-acting bronchodilators for ≥ 4 hours, long-acting bronchodilator for ≥ 12 hours, and once-daily long-acting bronchodilator ≥ 24 hours prior to the spirometry assessment.

During the Screening period, spirometry assessments were able to be performed pre- or post-bronchodilator. At all other visits, spirometry assessments were performed pre-bronchodilator and, during the treatment period, before trial drug dosing at approximately the same time each visit.

Measured spirometry values were converted to percent predicted values using standard equations of the Global Lung Institute ([Quanjer et al. 2012](#)). Note these trials were conducted prior to the recent American Thoracic Society statement on the use race-neutral approaches to pulmonary function test (PFT) interpretation ([Bhakta et al. 2023](#)).

All spirometry data was transmitted to a centralized spirometry service for quality review. The investigator's assessments of spirometry results were used for the screening assessment and determination of eligibility.

Sweat Chloride

SwCl is a pharmacodynamic measure of CFTR function. A SwCl concentration of ≥ 60 mmol/L is diagnostic of CF and ≤ 30 mmol/L is the normal range ([Farrell et al. 2017](#)). The trials completed the SwCl test (quantitative pilocarpine iontophoresis) using an approved collection device. The

protocol required collection before trial drug dosing. At each time point, two samples were collected (one from each arm). Samples were sent to a central laboratory for testing and interpretation.

CF Pulmonary Exacerbation Definition

A CF pulmonary exacerbation was defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for four or more of the following signs or symptoms:

- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C (approximately 100.4°F)
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10%
- Radiographic change indicative of pulmonary infection.

Overall, the definition of CF pulmonary exacerbations used is acceptable and consistent with similar pivotal trials in this population. It was recommended that the trial drug not be interrupted during an exacerbation unless it was determined to be in the best interest of the subject, as determined by the investigator.

Cystic Fibrosis Questionnaire-Revised

The CFQ-R is a disease-specific health-related quality of life measure for CF that consists of generic and CF-specific scales grouped into three modules and nine domains. The scales measure quality of life, health perception, and symptoms over a 2-week recall period. It is available in age-appropriate versions: child age 6 through 11 years (interview format), child age 12-13 years (self-reported format), adolescent/adult ages ≥ 14 years (self-reported), and a parent/caregiver proxy format. The RD of the CFQ-R has also been utilized independently to evaluate for respiratory symptoms relevant to patients with CF. In patients with stable respiratory symptoms and chronic *Pseudomonas aeruginosa* infection, a difference of at least four points in the CFQ-R RD score is generally considered the meaningful within patient change ([Quittner et al. 2009](#)).

Subjects were asked to complete the CFQ-R in their native language if validated translations were available. If no validated translation was available in the subject's native language, the subject did not complete the questionnaire. Subjects 12 and 13 years of age at the date of

informed consent were asked to complete the CFQ-R Child version themselves, and their parents/caregivers completed the CFQ-R Parent version, at all visits, regardless of whether the subject subsequently turned 14 years of age during the trial. Subjects 14 years of age and older at the date of informed consent completed the Adolescent/Adult version of the questionnaire themselves at all visits.

Height and Weight

Weight and height were measured with shoes off. Following screening, height was collected only for subjects ≤ 21 years of age on the date of informed consent.

Ophthalmologic Examination

Ophthalmologic examinations were only obtained in subjects < 18 years of age on the date of informed consent. All examinations were conducted by a licensed ophthalmologic or optometrist and included the measurement of best-corrected distance visual acuity of each eye and pharmacologically-dilated examination of the lens with a slit lamp. A screening examination was not required if there was documentation of an examination meeting the protocol requirements within the 3 months before the date of informed consent. No examinations were required in subjects with documentation of bilateral lens removal.

Examinations occurred at screening and within 4 weeks prior to completion of trial participation (in subjects who have completed at least 12 weeks of trial drug treatment).

Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, PExs, and pulse oximetry.

Statistical Analysis Plan

Sample Size and Power

The primary null hypothesis to be tested was that the mean absolute change in ppFEV₁ from baseline through Week 24 for VNZ/TEZ/D-IVA is inferior by > 3 percentage points compared to ELX/TEZ/IVA.

The noninferiority (NI) margin represented a clinically acceptable loss of effectiveness as outlined in *Non-Inferiority Clinical Trials to Establish Effectiveness* ([November 2016](#)) regulatory guidance. Furthermore, a statistical approach using the Rothmann method recommends that the NI margin preserves at least 50% of the treatment effect of the active control (ELX/TEZ/IVA) compared to placebo ([Schumi and Wittes 2011](#)), where the treatment effect is estimated by the lower bound of the 95% CI. In the overall population eligible for Trials 102 and 103, the lower bound of the 95% CI of the treatment effect for ELX/TEZ/IVA was approximately 12 percentage points for ppFEV₁. The selected noninferiority margin of three percentage points was consistent with this statistical method for ppFEV₁ in clinical studies evaluating CF treatments.

For Trial 102, assuming a within-group standard deviation (SD) of 8 and a 10% drop-out rate at Week 24 and a treatment difference of 0 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, a

sample size of 200 subjects in each group for a total of 400 subjects would have more than 90% power to test the primary hypothesis for the primary endpoint, based on a 1-sided, 2-sample t-test at a significance level of 0.025.

For Trial 103, assuming a within-group standard deviation (SD) of 8 and a 10% drop-out rate at Week 24 and a treatment difference of 0 between VNZ/TEZ/D-IVA and ELX/TEZ/IVA, a sample size of 275 subjects in each group for a total of 550 subjects would have more than 95% power to test the primary hypothesis for the primary endpoint, based on a 1-sided, 2-sample t-test at a significance level of 0.025.

Noninferiority Margin for Trial 103

Although placebo-controlled data with ELX/TEZ/IVA in direct comparison with placebo was not available for F/F, F/G, and F/RF subjects, a treatment effect could be estimated using Bucher's Indirect Comparison method by pooling data from Studies 445-103/105 and 661-106 for F/F subjects, Studies 445-104 and 770-102 for F/G subjects, and Studies 445-104 and 661-108 for F/RF subjects (see [Table 181](#)).

Table 181. Indirect Comparison of ppFEV₁ Treatment Effect of ELX/TEZ/IVA vs. Placebo in F/F, F/RF, and F/G Subjects

Mutation Group	Study	Comparison	Treatment Effect (95% CI)
F/F	445-103/105	ELX/TEZ/IVA vs TEZ/IVA	10.7 (9.1, 12.3)
	661-106	TEZ/IVA vs Placebo	3.9 (3.0, 4.8)
	Indirect Comparison	ELX/TEZ/IVA vs Placebo	14.6 (12.8, 16.4)
F/RF	445-104	ELX/TEZ/IVA vs TEZ/IVA	2.0 (0.5, 3.4)
	661-108	TEZ/IVA vs Placebo	6.8 (5.7, 7.8)
	Indirect Comparison	ELX/TEZ/IVA vs Placebo	8.8 (7.0, 10.6)
F/G	445-104	ELX/TEZ/IVA vs IVA	5.8 (3.5, 8.0)
	770-102	IVA vs Placebo	10.6 (8.6, 12.6)
	Indirect Comparison	ELX/TEZ/IVA vs Placebo	16.4 (13.4, 19.4)

Source: Response on FDA's EOP2 Preliminary Comments dated Feb 19, 2021

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; ELX, elxacaftor; F, *F508del* CFTR variant; G, gating CFTR variant; IVA, ivacaftor; ppFEV₁, percent predicted forced expiratory volume in 1 second; RF, residual function CFTR variant; TEZ, tezacaftor; vs, versus

The planned genotype distribution for Study 121-103 was approximately 80% F/F subjects, 10% F/G subjects, and 10% F/RF subjects. By using a weighted average to combine the estimated treatment effects in each of these populations, the overall treatment effect of ELX/TEZ/IVA compared to placebo estimated by the lower bound of 95% confidence interval was 12.3 (see [Table 182](#)), which was consistent with the treatment effect estimated by the lower bound of the 95% confidence interval of ELX/TEZ/IVA compared to placebo for Trial 102 (F/MF subjects) (12.7 percentage points). Using the Rothmann method, the NI margin to preserve 50% of the

treatment effect of ELX/TEZ/IVA versus placebo in Trial 103 was 6.2 percentage points, which was less stringent than the proposed NI margin of three percentage points.

Table 182. ppFEV₁ Treatment Effect of ELX/TEZ/IVA vs. Placebo in Study VX20-121-103 From Bucher's Indirect Comparison

Mutation Group	Planned Enrollment Proportion	Treatment Effect (95% CI) of ELX/TEZ/IVA vs Placebo	Lower bound of 95% CI	Studies for Indirect Comparison
F/F	80%	14.6 (12.8, 16.4)	12.8	445-103/105 and 661-106
F/RF	10%	8.8 (7.0, 10.6)	7.0	445-104 and 661-108
F/G	10%	16.4 (13.4, 19.4)	13.4	445-104 and 770-102
Overall	100%	---	12.3*	---

Source: Response on FDA's EOP2 Preliminary Comments dated Feb 19, 2021

* Weighted average of the lower bounds of three variant groups

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator; CI, confidence interval; ELX, elxacaftor; F, *F508del* CFTR variant; G, gating CFTR variant; IVA, ivacaftor; ppFEV₁, percent predicted forced expiratory volume in 1 second; RF, residual function CFTR variant; TEZ, tezacaftor

Overall, these data supported the proposed NI margin of three percentage points for Trial 103. Additionally, the Applicant agreed to clearly define residual function and gating variants in the clinical trial protocol. An analysis of efficacy for the primary endpoint for the variant subgroups (F/F versus non-F/F) was specified in the statistical analysis plan with a proposal to present the estimated treatment effect along the 95% CI (see [Figure 4](#)).

Primary Estimand

The primary estimand is defined as the following:

- Treatment: VNZ/TEZ/D-IVA versus ELX/TEZ/IVA
- Population: Trial population represented by inclusion and exclusion criteria
- Variable: Absolute change from baseline (after ELX/TEZ/IVA run-in) in ppFEV₁ through Week 24 (estimated by averaging Weeks 16 and 24)
- Handling of intercurrent events:
 - The treatment policy strategy will be used to handle the use of non-trial drug that affects CFTR processing or function for >3 days in either the Run-in Period or the Treatment Period prior to Week 24, which means that observed ppFEV₁ values will be used, if available, after this prohibited medication use.
 - The treatment policy strategy will be used to handle treatment discontinuation prior to Week 24, which means that observed ppFEV₁ values will be used, if available, after treatment discontinuation.
- Population level summary: Difference in variable means between VNZ/TEZ/D-IVA and ELX/TEZ/IVA groups

Primary Analysis

The primary null hypothesis tested was that the mean for the primary efficacy variable for VNZ/TEZ/D-IVA was inferior by >3 percentage points compared to ELX/TEZ/IVA. The primary analysis of the primary estimand was performed using a mixed-effects model for repeated measures (MMRM) with change from baseline at Day 15, Week 4, Week 8, Week 16, and Week 24 as the dependent variable. For Trial 102, the model included fixed categorical effects for treatment, visit, age at screening (<18 versus ≥18 years of age), and treatment-by-visit interaction, with baseline ppFEV₁ and baseline SwCl as continuous covariates. The model estimated using restricted maximum likelihood. Denominator degrees of freedom for the F-test for fixed effects were estimated using the Kenward-Roger approximation. An unstructured covariance structure was used to model the within-subject errors. If the model estimation did not converge, an alternative covariance structure like compound symmetry would have been used. For Trial 103, the model included an additional fixed categorical effect for genotype group (F/F, F/G, F/RF, TCR/non-F). If the model estimation did not converge, genotype group was considered with two levels (F/F and non-F/F) or removed from the model, and if non-convergence persisted, an alternative covariance structure like compound symmetry would have been used.

Conditional on the observed data and covariates, missing data was assumed to be missing at random.

The primary result obtained from the model was the estimated treatment difference through Week 24 (estimated by averaging Weeks 16 and 24). The adjusted mean with a 2-sided 95% CI and the 1-sided P value for noninferiority was provided. The primary null hypothesis was rejected, and noninferiority demonstrated, if the lower bound of the CI is ≥-3.0.

The primary null hypothesis of noninferiority described above was tested based on the full analysis set (FAS).

If noninferiority for the primary endpoint was demonstrated, and if the lower bound of the same 95% CI was greater than 0, then superiority for the primary endpoint was also demonstrated, and the 2-sided P value for superiority would be presented.

Supplementary Analysis

An alternative estimand was defined similarly to the primary estimand with the exception that intercurrent events were addressed using the hypothetical strategy. In the hypothetical strategy, observed values after intercurrent events were set to missing to provide a conservative and robust test of noninferiority for the primary endpoint. Supplementary analysis of this alternative estimand was performed similarly to the primary analysis.

Subgroup Analysis

Subgroup analyses of the primary efficacy endpoint were performed for each of the following subgroups:

- Age at screening (<18; ≥18 years)
- ppFEV₁ at baseline (<70; ≥70 percentage points)
- SwCl at baseline (<30; ≥30mmol/L)
- Sex (male; female)
- Geographic region (North America [including United States and Canada]; Rest of the World [including Europe, Israel, Australia, and New Zealand])

The MMRM used for the primary analysis of the primary estimand was used for the subgroup analyses, where the similar model was applied to each category of the subgroup.

Analysis of Key Secondary Efficacy Variables

Absolute Change From Baseline in SwCl Through Week 24

The analysis of absolute change from baseline in SwCl through Week 24 was based on an MMRM similar to the primary analysis of the primary estimand, with absolute change from baseline in SwCl at Day 15, Week 4, Week 16, and Week 24 as the dependent variable. The estimated treatment difference through Week 24 (estimated by averaging Weeks 16 and 24) was presented along with the 2-sided 95% CI and P value.

Proportion of Subjects With SwCl <60mmol/L Through Week 24 (Pooled With Data From Trials 102 and 103)

The response corresponding to SwCl <60mmol/L at each visit through Week 24 in the pooled FAS was analyzed using a generalized estimating equations model. The model included fixed categorical effects for treatment, age at screening (<18 versus ≥18 years of age), genotype group (F/MF, F/F, F/G, F/RF, TCR/non-F), visit, and treatment-by-visit interaction, with baseline

ppFEV₁ and baseline SwCl as continuous covariates. A logit link function and an unstructured working correlation matrix were used in the generalized estimating equations model. If the model estimation did not converge, genotype group was considered with three levels (F/MF, F/F, and Other) or removed from the model, and if nonconvergence persists, an alternative covariance structure like compound symmetry would have been used. The estimated odds ratio through Week 24 (estimated by averaging Weeks 16 and 24) along with the 2-sided 95% CI and P value was presented. The estimates for each visit through Week 24 were also presented.

Proportion of Subjects With SwCl <30mmol/L Through Week 24 (Pooled With Data From Trials 102 and 103)

The analysis was similar to that for the pooled analysis of proportion of subjects with SwCl <60mmol/L through Week 24.

Multiplicity Adjustment

A hierarchical testing procedure was used to control the overall type I error at an alpha of 0.05. The key secondary endpoints were formally tested at an alpha level of 0.05 only if the primary analysis of absolute change from baseline in ppFEV₁ through Week 24 was statistically significant, i.e., if the null hypothesis of inferiority had been rejected. For a test at any step to be considered statistically significant within the testing hierarchy, it must be statistically significant, and all previous tests (if any) within the hierarchy must be statistically significant at the 0.05 level (one-sided 0.025 level for the primary endpoint). The testing order of the key secondary endpoints was as follows:

- Absolute change from baseline in SwCl through Week 24
- Proportion of subjects with SwCl <60mmol/L through Week 24 (pooled with data from Trials 102 and 103)
- Proportion of subjects with SwCl <30mmol/L through Week 24 (pooled with data from Trials 102 and 103)

Analysis of Other Secondary Efficacy Variables

Pulmonary Exacerbations

The number of PEx through Week 52 was analyzed using a negative binomial model with term for treatment, and the estimated PEx rate (per year, with 48 weeks as 1 year) was presented. The difference in PEx rate and the associated 95% CI was provided.

Absolute Change From Baseline in CFQ-R RD Score Through Week 24

The analysis of absolute change from baseline in CFQ-R RD score through Week 24 was based on an MMRM similar to the primary analysis of the primary estimand, with absolute change from baseline in CFQ-R RD score at Week 8, Week 16, and Week 24 as the dependent variable. The estimated treatment difference through Week 24 (estimated by averaging Weeks 16 and 24) was presented along with the 2-sided 95% CI.

Absolute Change From Baseline in ppFEV₁ Through Week 52

Analysis of this endpoint was based on an MMRM similar to the primary analysis of the primary estimand, with the addition of data from Week 36 and Week 52. The estimated change through Week 52 was based on averaging estimates from Weeks 16, 24, 36 and 52.

Absolute change from baseline in SwCl through Week 52

Analysis of this endpoint was based on an MMRM similar to that for absolute change from baseline in SwCl through Week 24, with the addition of data from Week 36 and Week 52. The estimated change through Week 52 was based on averaging estimates from Weeks 16, 24, 36 and 52.

Analysis Population Definitions

- All subject set: all subjects who were randomized or received at least one dose of trial drug
- FAS: all randomized subjects who carry the intended *CFTR* allele variant(s) and received at least one dose of trial drug during the treatment period
- Safety analysis set: Included all subjects who received at least one dose of trial drug. This was broken down into the Safety Set for the Run-in Period (subjects who received at least one dose of trial drug during the Run-in Period) and the Safety Set for the Treatment Period (subjects who received at least one dose of trial drug during the Treatment Period).
- Per-protocol set: a subset of the FAS that excluded subjects with certain important protocol deviations and other situations

Adverse Events

The Applicant provided accurate definitions of AEs and SAEs consistent with 21 CFR 312.32. Trial assessments including laboratory tests, ECGs, PEXs, and vital signs were assessed and those deemed to have clinically significant worsening from baseline were documented as an AE. All AEs were collected from the time of informed consent until the subject completed the trial participation. Treatment-emergent (TE) time periods were broken down into TE period of the run-in period (from the first dose date of trial drug in the run-in period to the first dose date of the trial drug in the treatment period) and the TE period for the treatment period (from the first dose of trial drug in the treatment period to 28 days after the last dose of the trial drug or to the complete of trial participation, whichever occurs first).

AE severity was graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program toxicity scale or as mild, moderate, severe, life-threatening, or death. Causality was assessed as related, possibly related, unlikely related, and not related. AEs were coded using the MedDRA dictionary version 26.1.

Overall, the Applicant's AE and SAE definitions and use of CTCAE severity scale were acceptable and consistent with other CF development programs.

Adverse Events of Special Interest

Liver function test abnormalities, creatinine kinase elevations, rash, cataracts, hypoglycemic events, and neuropsychiatric events were designated as adverse events of special interest (AESIs). These were considered appropriate given the known safety profile of medications similar to VNZ/TEZ/D-IVA (e.g., ELX/TEZ/IVA) and a review of the safety information from the phase 2 development program.

Protocol Amendments

Trial 102, initially dated April 27, 2021, was amended two times. The key changes in each amendment are noted below:

- Version 2.0 (July 12, 2021) – Clarified eligible MF definition.
- Version 3.0 (August 19, 2021) – Increased sample size and treatment duration (with updates to trial endpoints to reflect this), added designation of AESIs (reviewed above), added that the analysis of the primary and key secondary endpoints through Week 24 will be estimated by averaging Week 16 and 14, and provided rationale for the noninferiority margin for the primary analysis.

Trial 103, also initially dated April 27, 2021, was amended two times. The key changes in each amendment are noted below:

- Version 2.0 (July 12, 2021) – Minor changes.
- Version 3.0 (August 19, 2021) – Expanded trial population to include subjects who have at least one *CFTR* variant identified as ELX/TEZ/IVA responsive based on in vitro data and no *F508del* variant, increased sample size and treatment duration (with updates to trial endpoints to reflect this), added designation of AESIs (reviewed above), included that stratification by genotype was to be based on F/F, F/G, F/RF, and TCR/non-F genotypes, added that the analysis of the primary and key secondary endpoints through Week 24 will be estimated by averaging Week 16 and 14, and provided rationale for the noninferiority margin for the primary analysis.

COVID-19 Impact

The trial protocols include safety measures to provide subjects the opportunity to continue to participate in the trial while ensuring safety and minimizing risk of coronavirus disease of 2019 (COVID-19). The Applicant reports that in general, there the impact of COVID-19 on the trial conduct was minimal.

Protocol Deviations

An important protocol deviation was defined as any protocol deviation that may have significant impact the completeness, accuracy, and/or reliability of key trial data or that may have significantly impacted a subject's rights, safety, or well-being.

In Trial 102, the Applicant reported that 20 (5.0%) of subjects had 21 important protocol deviations (VNZ/TEZ/D-IVA: 11, 5.6%; ELX/TEZ/IVA: 9, 4.5%). The deviation summaries

provided were reviewed and included subject use of prohibited concomitant medications (e.g., commercially available medications that affect CFTR processing or function while an SAE was investigated) and enrollment of subjects who did not meet eligibility criteria (e.g., use of antibiotics or acute respiratory infection during the run-in period).

In Trial 103, the Applicant reported that 27 (4.7%) of subjects had important protocol deviations (VNZ/TEZ/D-IVA: 15, 5.3%; ELX/TEZ/IVA: 12, 4.2%). The deviation summaries provided were reviewed and included enrollment of subjects who did not meet eligibility criteria (e.g., use of antibiotics or acute respiratory infection during the run-in period) and use of prohibited concomitant medications (e.g., commercially available or compassionate-use medications that affect CFTR drug processing or function) when protocol-defined criteria were met (e.g., AST levels >8x ULN). The number of subjects with protocol deviations related specifically to the investigational product (e.g., trial drug dispensation errors, compliance, trial drug kits not being returned, and incorrect trial drug dosing) occurred at higher rates in the VNZ/TEZ/D-IVA treatment arm (11, 3.9%) than the ELX/TEZ/IVA treatment arm (5, 1.7%).

Overall, the rates protocol deviations were small and consistent with other similarly sized trials. The reported protocol deviations are unlikely to affect the overall analysis of the phase 3 pivotal trials.

15.2. Pediatric Cohort (6 Through 11 Years Old), Trial 105

Overview and Objectives

Trial VX21-121-105 (Trial 105) was a phase 3, 2-part (Parts A and B), open-label, multicohort, multicenter trial evaluating the PK, safety, tolerability, and efficacy of VNZ/TEZ/D-IVA triple combination therapy in subjects with CF 1 through 11 years of age. The Applicant submitted the interim analysis report of the final data from subjects 6 through 11 years of age (Cohorts A1 and B1) concurrently with the pivotal phase 3 trials in adults in adolescents.

Trial 105 Title: A Phase 3 Study Evaluating the Pharmacokinetics, Safety, and Tolerability of VX-121 [VNZ] /Tezacaftor/Deutivacaftor Triple Combination Therapy [VNZ/TEZ/D-IVA] in Cystic Fibrosis Subjects 1 Through 11 Years of Age.

- Cohort 1 Trial dates: June 21, 2022 to November 27, 2023
- Cohort 1 Trial report date: April 3, 2024

The design of Cohort 1 and the overall pediatric multicohort trial is consistent with other trials performed to support pediatric indications in this population. The consideration of efficacy extrapolation for the 6- to 11-year-old population from the adult and adolescent population is appropriate given the similarity in the disease process between the populations.

Part A Primary Objectives

- To evaluate the PK of VNZ, TEZ, D-IVA and relative metabolites when dosed in triple combination
- To evaluate the safety and tolerability of VNZ/TEZ/D-IVA

Part B Primary Objective

- To evaluate the safety and tolerability of VNZ/TEZ/D-IVA through Week 24

Part B Secondary Objectives

- To evaluate the efficacy of VNZ/TEZ/D-IVA through Week 24
- To evaluate the PK of VNZ, TEZ, D-IVA, and relevant metabolites

Trial Design

Trial 105 was a phase 3, 2-part (Parts A and B), multicenter, multicohort, open-label trial in CF subjects 1 through 11 years of age (inclusive). The cohorts included in Trial 105 were based on subject age:

- Cohorts A1 and B1: Subjects 6 through 11 years of age
- Cohorts A2 and B2: Subjects 2 through 5 years of age
- Cohorts A3 and B3: Subjects 1 to less than 2 years of age

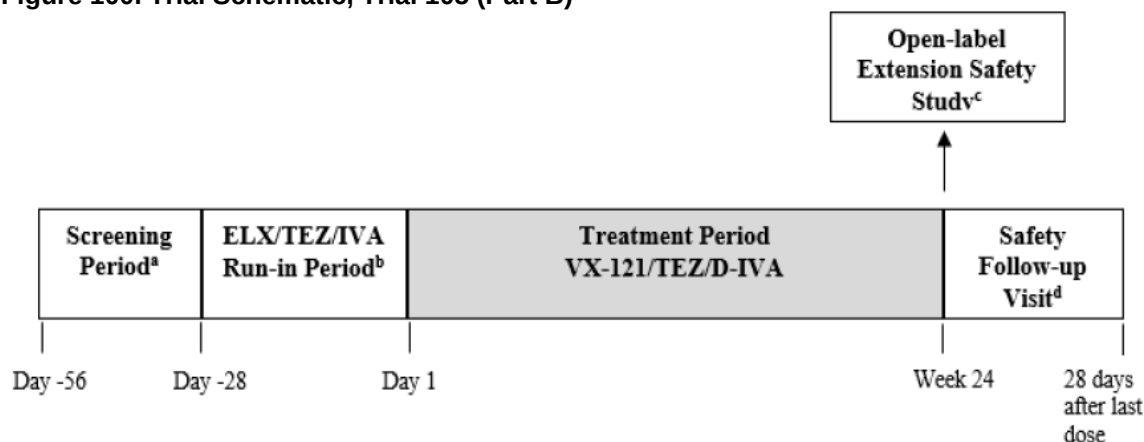
This review will include and refer to Cohorts A1 and B1 only unless otherwise noted. The remainder of the cohorts in Trial 105 are ongoing or have not yet started enrollment at the time of the review.

In Part A, the PK portion, there was a 28-day screening period followed by a 15-day treatment period. PK samples were collected on Days 1, 8, and 15 of the treatment period. A final safety follow-up visit occurred 28 days after the last dose of the trial drug. Trial subjects were eligible to be screened for enrollment in Part B. A review of safety, tolerability, and available PK data was completed by the Applicant's internal team after Cohort A1 completed treatment to determine the doses and weight cutoffs for Cohort B1.

Part B, the primary safety portion, also included a 28-day screening period. Subjects who were not already receiving stable ELX/TEZ/IVA treatment entered the 4-week (28-day) run-in period and received the approved ELX/TEZ/IVA dose. Stable ELX/TEZ/IVA treatment was defined as receiving ELX/TEZ/IVA for at least 28 days prior to the screening visit. This run-in period was waived for subjects already receiving stable ELX/TEZ/IVA. During the treatment period, all subjects received VNZ/TEZ/D-IVA for 24 weeks. Eligible subjects were able to enroll in the optional open-label extension trial (Trial VX22-121-106). A safety follow-up visit occurred at 28 (± 7) days after the last dose of the trial drug but was not required for those who completed the treatment period and transitioned within 28 days of the last dose of trial drug to one of the following: a commercially available Applicant medication that affects CFTR processing or

function regimen, a managed access program-supplied Applicant medication that affects CFTR processing or function regimen, or an open-label study or other qualified Vertex study. The trial schematic for Part B is shown below in [Figure 100](#).

Figure 100. Trial Schematic, Trial 105 (Part B)



Source: Applicant Provided (Protocol VX21-121-105, Version 4.0. Figure 9-1)

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; TEZ, tezacaftor; VX-121 [VNZ], vanzacaftor

Subjects were eligible to be rescreened once. All screening assessments were repeated with the exception of *CFTR* genotyping and ophthalmological examination (if performed within 3 months of the day of informed consent).

Trial Population

Trial 105 enrolled pediatric subjects (ages 6 through 11 years) with stable CF per the enrollment criteria outlined below:

Key Inclusion Criteria

- Ages 6 through 11 years (inclusive), on the date of informed consent
 - Subjects who completed Cohort A1 but were ≥ 12 years of age on the date of informed consent in Cohort B1 are not eligible to enroll in Cohort B1.
- Weight between 5th and 9th percentile (inclusive) for weight-for-age at the Screening Visit based on current CDC growth charts
- Confirmed diagnosis of CF as determined by the investigator
- At least one triple combination responsive variant (including *F508del*) in the *CFTR* gene
- FEV₁ $\geq 60\%$ predicted at screening ([Quanjer et al. 2012](#))
- Stable CF disease as judged by the investigator
- Negative serum pregnancy test at screening for female subjects of childbearing potential

Key Exclusion Criteria

- History of comorbidity that might confound the results in the opinion of the investigator. Including, but not limited to:
 - Hepatic cirrhosis with portal hypertension, moderate hepatic impairment (Child Pugh Score 7 to 9), severe hepatic impairment (Child Pugh Score 10 to 15)
 - Chronic kidney disease (Stage 3 or above)
 - Solid organ or hematological transplantation
 - Alcohol or drug abuse in the past year
 - Cancer
- Any clinically significant laboratory abnormalities at screening that would interfere with the trial assessments or pose an under risk for the subject
- History of intolerance to trial drug that would pose additional risk to the subject in the opinion of the investigator (e.g., subjects with a history of LFT elevations requiring treatment interruption or discontinuation, allergy, or hypersensitivity to the trial drug)
- Any of the following abnormal labs at screening:
 - Hemoglobin <10 g/dL
 - Total bilirubin $\geq 2 \times$ ULN
 - AST, ALT, gamma-glutamyl transferase, or alkaline phosphatase (ALP) $\geq 3 \times$ ULN
 - Abnormal renal function defined as glomerular filtration rate ≤ 45 mL/min/1.73 m² ([Counahan et al. 1976](#))
- An acute upper or lower respiratory tract infection, infectious PEx of CF, or changes in therapy (including antibiotics) for sinopulmonary disease within 28 days before Day 1 (first dose of VNZ/TEZ/D-IVA)
- 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*). For subjects who have had a history of a positive culture, the investigator will apply the following criteria to establish whether the subject is free of infection with such organisms:
 - The subject has not had a respiratory tract culture positive for these organisms within the 12 months before the date of informed consent/assent
 - The subject has at least two respiratory tract cultures negative for these organisms within the 12 months before the day of informed consent, with the first and last of these separated by at least 3 months, and the most recent one within the 6 months before the date of informed consent/assent

- An acute illness not related CF (e.g., gastroenteritis) within 14 days before Day 1 (the first dose of VNZ/TEZ/D-IVA)
- Ongoing or prior participation in a trial of an investigational treatment other than Vertex medications that affect CFTR processing or function

The inclusion and exclusion criteria were reasonable to define the trial population and support the proposed indication. The inclusion and exclusion criteria are similar to that used in the pivotal phase 3 trials reviewed in Section [15.1](#) and for other CF development programs in this age-range.

Trial Drug Interruption and Stopping Rules

The protocol for Trial 105 included trial drug interruption and stopping rules related to liver function testing and rash as in the Trials 102 and 103 (outlined in more detail in Section [15.1](#)).

Dose and Duration of Treatment

A review of safety, tolerability, and available PK data was completed by the Applicant's internal team after Cohort A1 completed treatment to determine the doses and weight cutoffs for Cohort B1. Further discussion of the PK and dosing regimen for Trial 105 appears in Section [14.2.6](#). The doses and weight cutoffs for Trial 105 are summarized below.

Table 183. Doses by Cohort and Treatment Period, Trial 105

Cohort A Treatment Period (VNZ/TEZ/D-IVA)	VNZ	TEZ	D-IVA
All subjects	10 mg QD	50 mg QD	125 mg QD
Cohort B1 Run-In Period (ELX/TEZ/IVA)	ELX	TEZ	IVA
Weight at Day -28			
<30 kg	100 mg QD	50 mg QD	75 mg q12h
≥30 kg	200 mg QD	100 mg QD	150 mg q12h
Cohort B1 Treatment Period (VNZ/TEZ/D-IVA)	VNZ	TEZ	D-IVA
Weight at Day 1			
<40 kg	12 mg QD	60 mg QD	150 mg QD
≥40 kg	20 mg QD	100 mg QD	250 mg QD

Source: Clinical Reviewer based on Applicant Provided data

Abbreviations: D-IVA, deutivacaftor; ELX, elexacaftor; IVA, ivacaftor; q12h, dose every 12 hours; QD, once daily; TEZ, tezacaftor; VNZ, vanzacaftor

The trial drug was administered orally with a fat-containing meal or snack. It was recommended that the dose be taken within 30 mins of the start of the meal or snack. Additional instructions were provided for missed doses were consistent with those outlined in Trials 102 and 103 (Section [15.1](#)).

All subjects (and their parents/caregivers/companions), site personnel (including investigators, site monitor, and trial team), and members of the Applicant's trial team were blinded to the treatment group. The Applicant's trial team did not have access to the spirometry or SwCl results after the first dose of the trial drug on Day 1 of the treatment period, with the exception of spirometry related adverse event reporting. Individual SwCl results were also not disclosed to the trial sites with the exception of the screening visit and Day-14 values. Subjects and their

parents/caregivers/companions were not to be informed of trial -related spirometry results until the Applicant determined that the trial had completed.

Subjects remained on their stable standard-of-care CF regimen with the exception of any alternative medications that affect CFTR processing or function, approved or investigational. Subjects were permitted to remain on approved medications that affect CFTR processing or function (e.g., IVA, TEZ/IVA, or ELZ/TEZ/IVA) during the screening period with the exception of lumacaftor/IVA that was not allowed within the 14 days prior to the first dose of trial drug in Part A or the first dose of trial drug in the run-in period of Part B. The key prohibited and acceptable concomitant medications were acceptable and consistent with prior phase 3 trials in the CF population. Refer to Section [15.1](#) for a complete list of medications.

Trial Endpoints

Part A (Cohort 1)

Primary Endpoints

- PK parameters of VNZ, TEZ, D-IVA, and relevant metabolites
- Safety and tolerability as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

Part B (Cohort 1)

Primary Endpoint

- Safety and tolerability as determined by AEs, clinical laboratory values, standard 12-lead ECGs, vital signs, and pulse oximetry

Secondary Endpoints

- Absolute change in SwCl from baseline through Week 24
- PK parameters of VNZ, TEZ, D-IVA, and relevant metabolites
- Drug acceptability assessment using Modified Facial Hedonic Scale
- Absolute change in ppFEV₁ from baseline through Week 24
- Number of PEx and CF-related hospitalizations through Week 24
- Absolute change in CFQ-R RD score from baseline through Week 24
- Absolute change in BMI and BMI-for-age z-score from baseline at 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
- Proportion of subjects with SwCl <60mmol/L through Week 24
- Proportion of subjects with SwCl <30mmol/L through Week 24

Other Endpoints

- Absolute change in FE-1 levels from baseline at Week 24
- Absolute change in serum levels of immunoreactive trypsinogen from baseline at Week 24
- Absolute change in fecal calprotectin levels from baseline at Week 24
- Absolute change in lung clearance index 2.5 from baseline through Week 24
- Absolute change in fat soluble vitamins from baseline through Week 24
- Number of PEx and CF-related hospitalizations through Week 24

Overall, the endpoints are acceptable and consistent with similar CF trials in this population. In addition, the secondary efficacy endpoints in Part B evaluate a number of factors considered to be clinically meaningful to patients with CF including ppFEV₁, CFQ-R, BMI, SwCl, weight, and CF PExs.

Efficacy Assessments

Efficacy assessments, including pulmonary function testing, SwCl measurements, CFQ-R, definition of CF PEx, and ophthalmological examinations were the same as Trials 102 and 103 and outlined in more detailed in Section [15](#). Height and weight were measured with shoes off prior to trial drug administration on the days of the in-person clinical visits.

Statistical Analysis Plan

The statistical analyses were descriptive. The analysis plan was outlined in Section [6.2.4.3](#).

Adverse Events

The Applicant provided accurate definitions of AEs and SAEs consistent with 21 CFR 312.32. trial assessments including laboratory tests, ECGs, PExs, and vital signs were assessed and those deemed to have clinically significant worsening from baseline were documented as an AE. All AEs were collected from the time of informed consent until the subject completed the trial participation. TE time periods were broken down in to TE period of the run-in period (Part B only, from the first dose date of trial drug in the run-in period to the first dose date of the trial drug in the treatment period) and the TE period for the treatment period (from the first dose of trial drug in the treatment period to 28 days after the last dose of the trial drug or to the complete of trial participation, whichever occurs first).

AE severity was graded using the CTCAE, Version 5.0, Cancer Therapy Evaluation Program toxicity scale or as mild, moderate, severe, life-threatening, or death. Causality was assessed as related, possibly related, unlikely related, and not related. AEs were coded using the MedDRA dictionary version 26.1.

Overall, the Applicant's AE and SAE definitions and use of CTCAE severity scale were acceptable and consistent with Trials 102 and 103 and with other CF development programs in this population.

AESIs were the same as the phase 3 trials in adolescents and adults and are outlined in more detail in Section [15.1](#).

Protocol Amendments

Trial 105, initially dated December 1, 2021, was amended three times. The key changes in each amendment are noted below:

- Version 2.0 (May 12, 2022) – Added VNZ/TEZ/D-IVA doses and weight cut-offs for Cohort B1 based on preliminary population-PK modeling.
- Version 3.0 (July 15, 2022) – Added specifications regarding postdose PK sampling at Week 8 for subjects ≥ 17 kg and removed vitamin and blood biomarker collection in Cohort B1 for < 20 kg. These changes were to reduce the total blood drawn from the subjects, if appropriate.
- Version 4.0 (December 19, 2022) – Updated doses administered and weight cutoffs for Cohort B1 based on emerging PK and safety data from Cohort A1 and other phase 3 studies evaluating VNZ/TEZ/D-IVA.

COVID-19 Impact

The trial protocol included safety measures to provide subjects the opportunity to continue participate in the trial while ensuring safety and minimizing risk of COVID-19. The Applicant reports that in general, the impact of COVID-19 on the trial conduct was minimal.

Protocol Deviations

An important protocol deviation was defined as any protocol deviation that may have significantly impacted the completeness, accuracy, and/or reliability of key trial data or that may have significantly impacted a subject's rights, safety, or well-being.

In Part A, two subjects were reported as having protocol deviations due to enrollment without documented review of screening laboratory analyses and no baseline hemoglobin value confirmed prior to screening. In Part B, an additional two subjects were reported as having important protocol deviations both related to incorrect dispensation of trial drug (both subjects received the incorrect (≥ 40 kg) kit at Day 1 but where dispensed the correct (< 40 kg) kit on Day 15). The rates of protocol deviations were small and unlikely to affect the overall analysis of Trial 105.

16. Efficacy

16.1. Subject Demographics

16.1.1. Trial 102

Trial 102 limited enrollment to subjects who were heterozygous for *F508del* and a MF variant (Section 15.1) and the genotypes of the population included 97 different MF variants. The specific genotypes reported in at least six subjects are listed in Table 184.

Table 184. CFTR Genotype Distribution Occurring in ≥6 Subjects (FAS), Trial 102

CFTR Genotype	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
<i>F508del</i> /G542X	24 (11.9)	29 (14.8)	53 (13.3)
<i>F508del</i> /W1282X	16 (7.9)	13 (6.6)	29 (7.3)
<i>F508del</i> /N1303K	12 (5.9)	15 (7.7)	27 (6.8)
<i>F508del</i> /R553K	11 (5.4)	11 (5.6)	22 (5.5)
<i>F508del</i> /621+1G > T	11 (5.4)	10 (5.1)	21 (5.3)
<i>F508del</i> /1717-1G > A	12 (5.9)	9 (4.6)	21 (5.3)
<i>F508del</i> /CFTRdele2,3	4 (2.0)	9 (4.6)	13 (3.3)
<i>F508del</i> /G85W	4 (2.0)	8 (5.1)	12 (3.0)
<i>F508del</i> /E60X	8 (4.0)	3 (1.5)	11 (2.8)
<i>F508del</i> /394delTT	5 (2.5)	4 (2.0)	9 (2.3)
<i>F508del</i> /2184insA	3 (1.5)	5 (2.6)	8 (2.0)
<i>F508del</i> /3659delC	3 (1.5)	5 (2.6)	8 (2.0)
<i>F508del</i> /2183AA.G	5 (2.5)	2 (1.0)	7 (1.8)
<i>F508del</i> /R1162X	3 (1.5)	4 (2.0)	7 (1.8)
<i>F508del</i> /I507del	3 (1.5)	3 (1.5)	6 (1.5)
<i>F508del</i> /R560T	4 (2.0)	2 (1.0)	6 (1.5)
<i>F508del</i> /R1066C	4 (2.0)	2 (1.0)	6 (1.5)

Source: Clinical reviewer, JMP 15.0, adsl.xpt dataset using the following parameters: FAS(Y), GENOTYPE
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator, D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; N, number of subjects; TEZ, tezacaftor; VNZ, vanzacaftor

The concomitant medications used by ≥20% of subjects in Trial 102 are included in Table 185. The medications listed are reflective of the standard of care guidelines for an adolescent and adult CF population.

Table 185. Concomitant Medications Used by ≥20% of Subjects (FAS), Trial 102

Medication	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
Sodium chloride	145 (71.8)	138 (70.4)	283 (71.1)
Pancreatin	141 (69.8)	139 (70.9)	280 (70.4)
Dornase alfa	139 (68.8)	124 (63.3)	263 (66.1)
Salbutamol	122 (60.4)	126 (63.3)	248 (62.3)
Azithromycin	97 (48.0)	97 (64.3)	194 (48.7)
Colecalciferol	83 (41.1)	77 (49.5)	160 (40.2)
Ibuprofen	74 (36.6)	74 (39.3)	148 (37.2)
Paracetamol	76 (37.6)	71 (37.8)	147 (36.9)
Tobramycin	59 (29.2)	59 (36.2)	118 (29.6)

Medication	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
Ciprofloxacin	60 (29.7)	47 (30.1)	107 (26.9)
Ursodeoxycholic acid	46 (22.8)	58 (29.6)	104 (26.1)
Pancrealipase	49 (24.3)	50 (25.5)	99 (24.9)
Vitamins NOS	41 (20.3)	50 (25.5)	91 (22.9)
Omeprazole	44 (21.8)	46 (23.5)	90 (22.6)

Source: Clinical reviewer, JMP 15.0, adcm.xpt dataset using the following parameters: FAS(Y), ONTRTFL, CMDECOD

Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator, D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; N, number of subjects; NOS, not otherwise specified; TEZ, tezacaftor; VNZ, vanzacaftor

The past medical history conditions reported that occurred in $\geq 10\%$ of subjects in Trial 102 are listed below in [Table 186](#). The conditions reported were generally balanced between treatment arms and consistent with a CF population.

Table 186. Past Medical History by Condition Occurring in $\geq 10\%$ of Subjects (FAS), Trial 102

Past Medical History	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
CF of the lung	193 (95.5)	184 (93.9)	377 (94.7)
Pancreatic failure	190 (94.1)	182 (92.9)	372 (96.5)
CF related diabetes	65 (32.2)	60 (30.6)	125 (31.4)
GERD	66 (32.7)	54 (27.6)	120 (30.2)
Chronic sinusitis	62 (30.7)	51 (26.0)	113 (28.4)
Bacterial disease carrier	52 (25.7)	52 (26.5)	104 (26.1)
Seasonal allergy	40 (19.8)	46 (23.5)	86 (21.6)
Vitamin D deficiency	43 (21.3)	38 (19.4)	81 (20.4)
Asthma	38 (18.8)	39 (19.9)	77 (19.3)
Drug hypersensitivity	36 (17.8)	40 (20.4)	76 (19.1)
CF hepatic disease	31 (15.3)	38 (19.4)	69 (17.3)
Bronchiectasis	27 (13.4)	38 (19.4)	65 (16.3)
Depression	36 (17.8)	28 (14.3)	64 (13.1)
Constipation	30 (14.9)	32 (16.3)	62 (15.6)
Nasal polyps	32 (15.8)	28 (14.3)	60 (15.1)
Osteopenia	26 (12.9)	30 (15.3)	56 (14.1)
Rhinitis allergic	30 (14.9)	24 (12.2)	54 (13.6)
Anxiety	30 (14.9)	21 (10.7)	51 (12.8)
Hemoptysis	24 (11.9)	27 (13.8)	51 (12.8)
Headache	14 (6.9)	27 (13.8)	41 (10.3)
Hypovitaminosis	29 (14.4)	12 (6.1)	41 (10.3)
ABPA	21 (10.4)	19 (9.7)	40 (10.1)

Source: Clinical reviewer, OCS Analysis Studio, dm.xpt and mh.xpt datasets using the following parameters: ACTARMCD, MHDECOD

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; GERD, gastroesophageal reflux disorder; IVA, ivacaftor; N, number of subjects; TEZ, tezacaftor; VNZ, vanzacaftor

Trial drug compliance was measured as: $100 \times [1 - (\text{total number of days of trial drug interruption during the treatment period}) / (\text{duration of trial drug exposures in the days during the treatment period})]$. There were three (0.8%) subjects with a reported compliance of $< 80\%$ for the treatment period. This is consistent with other similar trials in this population.

16.1.2. Trial 103

Trial 103 limited enrollment to subjects who were homozygous for *F508del*, heterozygous for *F508del* with a second variant classified as a gating or residual function variant, or a variant that was responsive to ELX/TEZ/IVA based on in vitro FRT data (Section 15.1). The specific genotypes reported in at least six subjects appear in [Table 187](#).

Table 187. CFTR Genotype Distribution Occurring in ≥6 Subjects (FAS), Trial 103

Genotype	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	Total N=573
<i>F508del/F508del</i>	223 (77.2)	220 (77.5)	443 (77.3)
<i>F508del/G551D</i>	14 (4.8)	14 (4.9)	28 (4.9)
<i>F508del/3849+10kbC > T</i>	8 (2.8)	6 (2.1)	14 (2.4)
<i>F508del/3272-26A > G</i>	4 (1.4)	4 (1.4)	8 (1.4)
<i>F508del/2789+5G > A</i>	2 (0.7)	5 (1.8)	7 (1.2)

Source: Clinical reviewer, JMP 15.0, adsl.xpt dataset using the following parameters: FAS(Y), GENOTYPE
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator, D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; N, number of subjects; TEZ, tezacaftor; VNZ, vanzacaftor

The concomitant medications used by ≥20% of subjects in Trial 103 are included in [Table 188](#) and are reflective of current standard of care guidelines for an adolescent and adult CF population.

Table 188. Concomitant Medications Used by ≥20% of Subjects (FAS), Trial 103

Medication	ELX/TEZ/IVA N=289	VNZ/TEZ/D-IVA N=284	Total N=573
Pancreatin	192 (66.4)	195 (68.7)	387 (67.5)
Dornase alfa	184 (63.7)	184 (64.8)	368 (64.2)
Sodium chloride	189 (65.4)	169 (59.5)	358 (62.5)
Salbutamol	170 (58.8)	164 (57.7)	334 (58.3)
Colecalciferol	123 (42.6)	137 (48.2)	260 (45.4)
Azithromycin	118 (40.8)	128 (45.1)	246 (42.9)
Paracetamol	110 (38.1)	129 (45.4)	239 (41.7)
Ibuprofen	102 (35.3)	82 (28.9)	184 (32.1)
Tobramycin	70 (24.2)	70 (24.6)	140 (24.4)
Pancrealipase	65 (22.5)	55 (19.4)	120 (20.9)
Ursodeoxycholic acid	72 (24.9)	48 (16.9)	120 (20.9)
Omeprazole	57 (19.7)	61 (21.5)	118 (20.6)
Ciprofloxacin	61 (21.1)	56 (19.7)	117 (20.4)

Source: Clinical reviewer, JMP 15.0, adcm.xpt dataset using the following parameters: FAS(Y), ONTRTFL, CMDECOD
Abbreviations: CFTR, cystic fibrosis transmembrane conductance regulator, D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; IVA, ivacaftor; N, number of subjects; TEZ, tezacaftor; VNZ, vanzacaftor

The past medical history by condition occurring in ≥10% of subjects in Trial 103 are listed below in [Table 189](#). The conditions reported were generally balanced between treatment arms, consistent with a CF population, and similar to Trial 102.

Table 189. Past Medical History by Condition Occurring in ≥10% of Subjects (FAS), Trial 103

Past Medical History	ELX/TEZ/IVA N=202	VNZ/TEZ/D-IVA N=196	Total N=398
CF of the lung	278 (96.2)	279 (98.2)	557 (97.2)
Pancreatic failure	251 (86.9)	244 (85.9)	495 (86.4)
GERD	93 (32.2)	96 (33.9)	189 (33.0)
CF related diabetes	99 (34.3)	78 (27.5)	177 (30.9)
Chronic sinusitis	82 (28.4)	77 (27.1)	159 (27.7)
Asthma	56 (19.4)	62 (21.8)	118 (20.6)
Bacterial disease carrier	55 (19.0)	58 (20.4)	113 (19.7)
Vitamin D deficiency	44 (15.2)	61 (21.5)	105 (18.3)
Constipation	47 (16.3)	55 (19.4)	102 (17.8)
Seasonal allergy	48 (16.6)	49 (17.3)	97 (16.9)
Bronchiectasis	54 (18.7)	41 (14.4)	95 (16.6)
Nasal polyps	43 (14.9)	49 (17.3)	92 (16.1)
Osteopenia	44 (15.2)	42 (14.8)	86 (15.0)
Drug hypersensitivity	36 (12.5)	48 (16.9)	84 (14.7)
Depression	45 (15.6)	63 (12.7)	81 (14.1)
Hemoptysis	46 (15.9)	34 (12.0)	80 (14.0)
Rhinitis allergic	40 (13.8)	34 (12.0)	74 (12.9)
Headache	32 (11.1)	39 (13.7)	71 (12.4)
Anxiety	35 (12.1)	33 (11.6)	68 (11.9)
Pneumonia pseudomonal	32 (11.1)	28 (9.9)	60 (10.5)
CF hepatic disease	32 (11.1)	27 (9.5)	59 (10.3)
Hypovitaminosis	31 (10.7)	22 (7.7)	53 (9.2)

Source: Clinical reviewer, Analysis Studio, dm.xpt and mh.xpt datasets using the following parameters: ACTARMCD, MHDECOD
Abbreviations: CF, cystic fibrosis; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; GERD, gastroesophageal reflux disorder; IVA, ivacaftor; N, number of subjects; TEZ, tezacaftor; VNZ, vanzacaftor

Trial drug compliance was measured as: $100 \times [1 - (\text{total number of days of trial drug interruption during the treatment period}) / (\text{duration of trial drug exposures in the days during the treatment period})]$. There were two (0.3%) subjects with a reported compliance of <80% for the treatment period. This is consistent with other similar trials in this population.

16.1.3. Trial 105

Trial 105 enrolled subjects with any *CFTR* variant that was responsive to ELX/TEZ/IVA. The specific genotypes reported in at least two subjects are shown in [Table 190](#).

Table 190. *CFTR* Genotype Distribution Occurring in at Least Two Subjects (FAS), Trial 105 (Cohort B1)

<i>CFTR</i> Genotype	Total N=78
<i>F508del/F508del</i>	37 (47.4)
<i>F508del/G551D</i>	3 (3.8)
<i>F508del/621+1G>T</i>	3 (3.8)
<i>F508del/G542X</i>	2 (2.6)
<i>F508del/R553X</i>	2 (2.6)

Source: Clinical reviewer, JMP 15.0, adsl.xpt dataset using the following parameters: FAS(Y), GENOTYPE
Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator, FAS, full analysis set; N, number of subjects

NDA 218730

ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

A list of ‘triple combination responsive’ *CFTR* variants (i.e., variants responsive to ELX/TEX/IVA on in vitro FRT testing) in enrolled subject who did not also carry a copy of *F508del* is included in [Table 191](#).

Table 191. Triple Combination *CFTR* Variants in Enrolled Subjects Without a Copy of *F508del* (FAS), Trial 105 (Cohort B1)

<i>CFTR</i> variant¹					
<i>G551D</i>	<i>L206W</i>	<i>R347P</i>	<i>R352Q</i>	<i>S549R</i>	<i>S945L</i>

Source: Clinical reviewer, JMP 15.0, adsl.xpt dataset using the following parameters: FAS(Y), GENOTYPE

¹ *CFTR* variant *I502T* was evaluated in Cohort A1 but subject did not enroll in Cohort B1

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; FAS, full analysis set

[Table 192](#) includes a list of concomitant medications used by subjects during the trial. These are consistent with current standard of care guidelines for CF.

Table 192. Concomitant Medications Used by $\geq 20\%$ of Subjects (FAS), Trial 105 (Cohort B1)

Medication	Total N=78
Sodium chloride	64 (82.1)
Salbutamol	53 (67.9)
Dornase alfa	49 (62.8)
Pancreatin	44 (56.4)
Fluticasone propionate	26 (33.3)
Ibuprofen	26 (33.3)
Paracetamol	25 (32.1)
Pancrealipase	23 (29.5)
Cetirizine hydrochloride	18 (23.1)
Macrogol 3350	17 (21.8)
Vitamins NOS	17 (21.8)

Source: Clinical reviewer, JMP 15.0, adcm.xpt dataset using the following parameters: FAS(Y), ONTRTFL, CMDECOD

Abbreviations: FAS, full analysis set; N, number of subjects; NOS, not otherwise specified

The past medical history by condition occurring in $\geq 10\%$ of subjects in Cohort B1 of Trial 105 are listed in [Table 193](#). The conditions reported were consistent with a pediatric CF population.

Table 193. Past Medical History by Condition, Occurring in ≥10% of Subjects (FAS), Trial 105 (Cohort B1)

Past Medical History	Total N=78
CF of the lung	72 (92.3)
Pancreatic failure	69 (88.5)
Constipation	27 (34.6)
Seasonal allergy	19 (24.4)
GERD	16 (20.5)
Asthma	14 (17.9)
Rhinitis allergic	13 (16.7)
Bacterial disease carrier	12 (15.4)
CF gastrointestinal disease	11 (14.1)
CF hepatic disease	11 (14.1)
ADHD	10 (12.8)
Chronic sinusitis	10 (12.8)
Nasal polyps	9 (11.5)
Drug hypersensitivity	8 (10.3)

Source: Clinical reviewer, Analysis Studio, dm.xpt and mh.xpt datasets using the following parameters: MHDECOD
Abbreviations: ADHD, attention deficit hyperactivity disorder; CF, cystic fibrosis; D-IVA, deutivacaftor; ELX, elxacaftor; FAS, full analysis set; GERD, gastroesophageal reflux disorder; IVA, ivacaftor; N, number of subjects in treatment group; TEZ, tezacaftor; VNZ, vanzacaftor

Trial drug compliance was measured as: $100 \times [1 - (\text{total number of days of trial drug interruption during the treatment period}) / (\text{duration of trial drug exposures in the days during the treatment period})]$. There were no subjects with a reported compliance of <80% for the treatment period.

16.2. Efficacy Results

16.2.1. Phase 3 Trials, Trials 102 and 103

All Efficacy Results

A summary of the efficacy results from Trials 102 and 103 is included in [Table 194](#). The secondary endpoints of each trial were supportive of efficacy of VNZ/TEZ/D-IVA in subjects with CF. Note that the ‘other secondary endpoints’ were not included in the formal statistical testing hierarchy and, therefore, not multiplicity controlled.

Table 194. Efficacy Results (FAS), Trials 102 and 103

Parameter/Endpoint	Trial 102	Trial 103
Subjects randomized, N	405	574
Subjects treated, N	398	573
ELX/TEZ/IVA, n	202	289
VNZ/TEZ/D-IVA, n	196	284
VNZ/TEZ/D-IVA vs. ELX/TEZ/IVA		
Primary endpoint	Parameter (95% CI)	
CFB ppFEV ₁ (W24), %	0.2 (-0.7, 1.1)	0.2 (-0.5, 0.9)
Key secondary endpoints		
CFB in SwCl (W24), mmol/L	-8.4 (p<0.0001)	-2.8 (p=0.0034)
Pooled proportion of subjects with SwCl <60 (W24), OR		2.21 (p<0.0001)
Pooled proportion of subjects with SwCl <30 (W24), OR		2.87 (p<0.0001)

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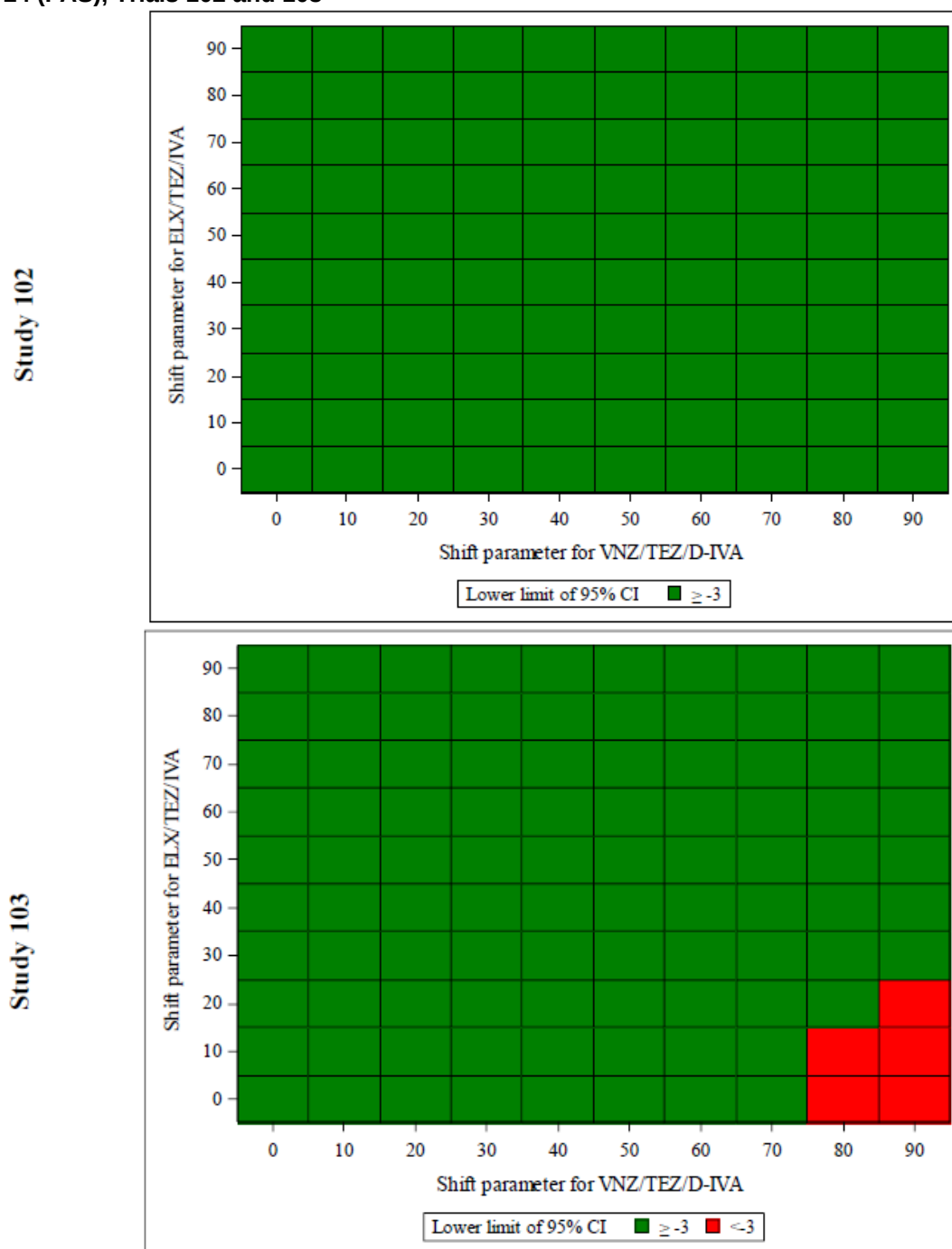
Parameter/Endpoint	Trial 102	Trial 103
Other secondary endpoints	Parameter (95% CI)	
Number of CF PEx (W52), rate diff	-0.10 (-0.24, 0.04)	0.03 (-0.07, 0.13)
CFB CFQ-R RD (W24), points	2.3 (-0.6, 5.2)	-0.1 (-2.3, 2.1)
CFB ppFEV ₁ (W52), %	0.1 (-0.8, 1.0)	0.3 (-0.4, 1.0)
CFB SwCl (W52), mmol/L	-8.0 (-9.9, -6.1)	-2.8 (-4.6, -1.0)
Proportion of subjects with SwCl <60 (W24), OR	4.28 (2.57, 7.11)	1.10 (0.65, 1.87)
Proportion of subjects with SwCl <30 (W24), OR	7.19 (3.54, 14.59)	2.06 (1.33, 3.18)

Source: Statistical analyst using adsl, adsp, adsw, adcfqr, and adce datasets.

Abbreviations: CFB, change from baseline; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; CI, confidence interval; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; LS, least squares; mmol, millimole; N, number of subjects in treatment group; n, number of subjects in subset; OR, odds ratio; ppFEV₁, percent predicted forced expiratory volume in 1 second; SD, standard deviation, SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor; W, week

The robustness of the primary analysis, the change from baseline in ppFEV₁ through 24 weeks, to missing data was supported by tipping point sensitivity analyses. The tipping points of losing significance are denoted as red cells and, as shown in in [Figure 101](#), rarely occurred in the clinically plausible missing data assumptions in both trials.

Figure 101. Tipping Point Analyses for Absolute Change From Baseline in ppFEV₁ Through Week 24 (FAS), Trials 102 and 103



Source: Response to FDA Information Request dated July 2, 2024

Abbreviations: CI, confidence interval; D-IVA, deutivacaftor; ELX, elexacaftor; FAS, full analysis set; IVA, ivacaftor; ppFEV₁, percent predicted forced expiratory volume in 1 second; TEZ, tezacaftor; VNZ, vanzacaftor

ppFEV₁ Through Week 52

The Applicant evaluated the absolute change from baseline of the ppFEV₁ through Week 52, which the Applicant defined as the average of the estimated treatment effects in Weeks 16, 24,

36, and 52. These endpoints supported the primary endpoint. As shown in [Table 194](#), the mean (95% CI) change from baseline in ppFEV₁ through 52 weeks was 0.1% (-0.8%, 1.0%) in Trial 102 and 0.3 (-0.4%, 1.0%) in Trial 103.

SwCl Through Week 52

The Applicant also evaluated the absolute change from baseline of the SwCl through Week 52, which the Applicant defined as the average of the estimated treatment effects in Weeks 16, 24, 36, and 52. VNZ/TEZ/D-IVA treatment led to lower SwCl through 52 weeks compared to ELX/TEZ/IVA. The mean (95% CI) absolute change in SwCl through 52 weeks was -8.0 (-9.9, -6.1) mmol/L and -2.8 (-4.6, -1.0) mmol/L in Trials 102 and 103, respectively. The clinical significance of this unclear and reviewed in more detail in Section [6.3.2](#).

Responder Analysis: Proportion of Subjects With SwCl <60mmol/L Through Week 24

The Applicant presented the odds ratio for the proportion of subjects with a SwCl <60mmol/L for the pooled phase 3 population and by individual trial. Subjects treated with VNZ/TEZ/D-IVA were more likely to have a SwCl <60mmol/L through Week 24 than subjects treated with ELX/TEZ/IVA in the pooled phase 3 population: odds ratio (95% CI): 2.21 (1.55, 3.15), $p < 0.0001$. Similar results were demonstrated when the phase 3 trials were analyzed separately, although in Trial 103, the 95% confidence interval did not exclude the null. These results are supportive of the efficacy of VNZ/TEZ/D-IVA, but the overall clinical significance is unclear, as reviewed in more detail in Section [6.3.2](#).

Responder Analysis: Proportion of Subjects With SwCl <30mmol/L Through Week 24

The Applicant also presented the odds ratio for the proportion of subjects with a SwCl <30mmol/L. Similar to the responder analysis of subjects below the CF diagnostic threshold, subjects treated with VNZ/TEZ/D-IVA were more likely to have a SwCl <30mmol/L through Week 24 than subjects treated with ELX/TEZ/IVA in the pooled phase 3 population: odds ratio (95% CI): 2.87 (2.00, 4.12), $p < 0.0001$. Similar results were demonstrated when the phase 3 trials were analyzed separately, and for this analysis, the 95% confidence intervals excluded the null in both trials. These results are supportive of the efficacy of VNZ/TEZ/D-IVA, but the overall clinical significance is unclear, as reviewed in more detail in Section [6.3.2](#).

16.2.2. Pediatric Cohort (6 Through 11 Years Old), Trial 105

Secondary Efficacy Endpoints

As noted previously, efficacy in the 6- to 11-year-old CF population was extrapolated from adults and adolescents. The Applicant also evaluated a number of exploratory efficacy endpoints in the 6- to 11-year-old population as reviewed in [Table 195](#). The lack of a control arm limits the ability to interpret these data, but, in general, the results support the efficacy of VNZ/TEZ/D-IVA in this age range.

Table 195. Secondary Efficacy Endpoints (FAS), Trial 105 (Cohort B1)

Secondary Endpoints	n	Parameter	VNZ/TEZ/D-IVA N=78
			Result (95% CI)
CFB in SwCl through Week 24 ^a , mmol/L	77	LS mean	-8.6 (-11.0, -6.3)
Absolute CFB in ppFEV ₁ through Week 24 ^a , %	74	LS mean	0.0 (-2.0, 1.9)
CFB in CFQ-R RD ^b score through Week 24 ^a , units	75	LS mean	3.9 (1.5, 6.3)
CFB BMI at Week 24, kg/m ²	78	LS mean	0.22 (0.05, 0.38)
CFB BMI Z-score at Week 24, units	78	LS mean	-0.05 (-0.12, 0.2)
CFB weight at Week 24, kg	78	LS mean	1.67 (1.34, 2.00)
CFB height at Week 24, cm	78	LS mean	2.7 (2.5, 3.0)
Proportion of subjects w/SwCl <60mmol/L through Week 24 ^a , %	78	Average	94.9 (87.4, 98.6)
Proportion of subjects w/SwCl <30mmol/L through Week 24 ^a , %	78	Average	52.6 (40.9, 64.0)

Source: Applicant provided data, VX21-121-105 CSR. Tables 11-3, 11-5, 11-7, 11-8, 11-9, 11-10

^a Through Week 24 estimated by averaging Weeks 16 and 24

^b CFQ-R RD, Child's version

Abbreviations: BMI, body mass index; CFB, change from baseline; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; CI, confidence interval; cm, centimeters; D-IVA, deutivacaftor; FAS, full analysis set; kg, kilogram; L, liter; LS, least squared; N, number of subjects in treatment arm; n, number of subjects included in analysis; ppFEV₁, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride; TEZ, tezacaftor; VNZ, vanzacaftor

Drug Acceptability Assessment at Week 24

The drug acceptability assessment was evaluated using the Modified Hedonic Scale at Week 24. Only 2 out of 74 subjects (2.8%) indicated that they disliked the medication (“disliked it a little” or “disliked it very much”) and 24 (32.4%) subjects responded that they were neutral. The remainder of subjects 48 (64.8%) indicated they liked the medication (“liked it a little” or “disliked it very much”). These results are supportive of VNZ/TEZ/D-IVA in this population.

Number of PEx and CF-Related Hospitalizations Through Week 24

The Applicant recorded the number of PEx including PEx requiring hospitalization or IV antibiotics therapy. Overall, six subjects (7.7%) experienced PExs with one subject (1.3%) hospitalized and requiring IV antibiotic therapy. The lack of comparator arm limits the analysis of these data, but these rates appear to be consistent with published data in CF patients in this age range.

CFQ-R RD Through Week 24

Treatment with VNZ/TEZ/D-IVA lead to an increase in the mean CFQ-R RD score through 24 weeks of 3.9 points. This is supportive of the efficacy of VNZ/TEZ/D-IVA. The magnitude of the absolute mean change from baseline is smaller than the changes observed in the ELX/TEZ/IVA trial in this population but higher than the adult and adolescent population in the phase 3 trials. The significance of this difference is unclear given the lack of control arm.

BMI, Weight, Height, and BMI Z-Scores at Week 24

Treatment with VNZ/TEZ/D-IVA resulted in within subject increases in absolute change from baseline for weight (1.67 kg), height (2.7 cm), and BMI (0.22 kg/m²) at Week 24. BMI z-scores remained similar over this period (-0.05). The assessment of these changes is limited by the absence of a comparator arm, and it is unclear if the observed absolute increases in weight and height reflect normal development or a treatment effect. Based on CDC growth charts for healthy

children, the average weight gain and growth for children between the age of 6 through 11 years is approximately 1-3 kg and 4-6 cm (NCHS 2024). While the observed change in stature is below the CDC growth chart averages in healthy children, the stability of the BMI z-score is reassuring.

Proportion of Subjects With SwCl <60mmol/L or <30mmol/L Through Week 24

The mean SwCl at Week 24 was 40.4mmol/L. The proportion of subjects with a SwCl less than 60mmol/L was 94.9% at Week 24 and 52.6% of subjects had a SwCl less than 30mmol/L at Week 24. The ability to interpret these results is limited by the lack of control arm. In addition, the clinical meaningfulness of these endpoints is unclear, as discussed in further detail in Section 6.3.2.

Other Efficacy Endpoints

The Applicant also evaluated multiple other efficacy endpoints including fecal elastase-1, serum immunoreactive trypsinogen, fecal calprotectin, lung clearance index 2.5, and levels of the fat-soluble vitamins. The evaluation of these results is limited because of the lack of comparator arm and because these are exploratory endpoints.

16.2.3. VNZ / TEZ / D-IVA Indication by CFTR Variant

Table 196 includes the CFTR variants proposed by the Applicant to be included in the indication for VNZ/TEZ/D-IVA, organized by the source of supportive data.

Table 196. Summary of CFTR Variants Included in VNZ/TEZ/D-IVA Indication

Summary of CFTR Variants				
Clinical Data ^a				
F508del	G85E	M1101K	S1251N	V754M
A455E	H1054D	R1066H	S549N	W1098C
D1152H	I336K	R352Q	S549R	W1282R
G1244E	L1077P	R75Q	S945L	Y563N
G551D	L206W	S1159F	V652I	

Summary of CFTR Variants				
In Vitro Data ^b				
1057_1515del9	F1107L	I125T	P499A	R74W;D1270N ^c
2183A>G	F191V	I1269N	P574H	R74W;V201M ^c
3141del9	F200I	(b) (4)	P5L	R74W;V201M; D1270N ^c
3195del6	F311del	I1366N	P67L	R75L
3199del6	F311L	I1389S	P750L	R751L
546insCTA	F508C	I148N	P99L	R792G
A1066E	F508C;S1251N ^c	I148T	Q1100P	R933G
A1067P	F575Y	I175V	Q1291R	S1045Y
A1067T	F587I	I331N	Q1313K	S108F
A107G	G1047R	I502T	Q237E	S1118F
A120T	G1061R	I506L	Q237H	S1159P
A234D	G1069R	I506T	Q359R	S1235R
A309D	G1123R	I556V	Q372H	S1255P
A349V	G1247R	I601F	Q452P	S13F
A46D	G1249R	I618T	Q493R	S341P
A554E	G126D	I807M	Q552P	S364P
A559T	G1349D	I980K	Q98R	S492F
A559V	G149R	K1060T	R1048G	S549I
A561E	G178E	K162E	R1066C	S589N
A613T	G178R	K464E	R1066L	S737F
A62P	G194R	L1011S	R1066M	S912L
A72D	G194V	L102R	R1070Q	S977F
C491R	G27E	L1065P	R1070W	T1036N
D110E	G27R	L1324P	R1162L	T1053I
D110H	G314E	L1335P	R117C	T1086I
D1270N	G424S	L137P	R117C;G576A; R668C ^c	T1246I
D1445N	G463V	L1480P	R117G	T1299I
D192G	G490C	L15P	R117H	T338I
D443Y	G480S	L165S	R117L	T351I
D443Y;G576A; R668C ^c	G551A	L320V	R117P	T604I
D513G	G551S	L333F	R1283M	V1153E
D565G	G576A	L333H	R1283S	V1240G
D579G	G576A;R668C ^c	L346P	R170H	V1293G
D614Y	G622D	L441P	R258G	V201M
D836Y	G628R	L453S	R297Q	V232D
D924N	G91R	L619S	R31C	V392G
D979V	G970D	L967S	R31L	V456A
D993Y	G970S	L997F	R334L	V456F
E116K	H1085P	M1101R	R334Q	V520F
E116Q	H1085R	M1137V	R347H	V603F
E193K	H1375P	M150K	R347L	W361R
E292K	H139R	M152V	R347P	Y1014C
E403D	H199R	M265R	R352W	Y1032C
E474K	H199Y	M952I	R516G	Y109N
(b) (4)	H609R	M952T	R516S	Y161D
E588V	H620P	N1088D	R533Q	Y161S
E60K	H620Q	N1303I	R555G	Y301C
E822K	H393R	N1303K ^d	R560S	Y569C
E92K	H393R;H949L ^c	N186K	R560T	Y913C
F1016S	I1027T	N187K	R668C	

Summary of <i>CFTR</i> Variants				
<i>F1052V</i>	<i>I105N</i>	<i>N418S</i>	<i>R709Q</i>	
<i>F1074L</i>	<i>I1139V</i>	<i>P140S</i>	<i>R74Q</i>	
<i>F1099L</i>	<i>I1234Vdel6aa</i>	<i>P205S</i>	<i>R74W</i>	
Extrapolation^e				
<i>1341G>A</i>	<i>2789+5G>A</i>	<i>3600G>A</i>	<i>3850-3T>G</i>	<i>621+3A>G</i>
<i>1898+3A>G</i>	<i>296+28A>G</i>	<i>3849+10kbC>T</i>	<i>4005+2T>C</i>	<i>711+3A>G</i>
<i>2752-26A>G</i>	<i>3041-15T>G</i>	<i>3849+4A>G</i>	<i>5T;TG12</i>	<i>E831X</i>
<i>2789+2insA</i>	<i>3272-26A>G</i>	<i>3849+40A>G</i>	<i>5T;TG13</i>	

Source: Clinical Reviewer based on Applicant data

^a Clinical data is obtained from Trials 102 and 103. Included variants are also predicted to be responsive based on electrophysiology FRT data.

^b In vitro data based on predicted responsiveness based on electrophysiology data. Variants were tested in an FRT cell model unless otherwise noted.

^c Complex/compound variants where a single allele of the *CFTR* gene has multiple variants; these exist independent of the presence of variants on the other allele.

^d The *N1303K* variant is predicted to be responsive only by electrophysiology data in an HBE cell system.

^e Efficacy is extrapolated to certain noncanonical splice variants because clinical trials in all variants in this subgroup are infeasible and these variants are not amenable to interrogation by FRT or HBE systems.

Abbreviations: *CFTR*, cystic fibrosis transmembrane conductance regulator; D-IVA, deutivacaftor; FRT, ficsher rat thyroid; HBE, human bronchial epithelial; TEZ, tezacaftor; VNZ, vanzacaftor

17. Clinical Safety

17.1. Additional Subgroup Analyses

Safety Analysis in Adolescent Subgroup

Less than 15% of subjects enrolled in Trials 102 and 103 were under 18 years of age. An overview of the AEs occurring in the adolescent subgroup is presented in [Table 197](#).

Table 197. Overview of Adverse Events During the Treatment Period Occuring in Subjects <18 Years of Age (Pooled SAS), Trials 102 and 103

Adverse Events	ELX/TEZ/IVA	VNZ/TEZ/D-IVA
	N=69 n (%)	N=67 n (%)
Number of total AEs	499	350
Subjects with any AE	63 (91.3)	60 (89.6)
Subjects with AE		
Leading to discontinuation	1 (1.4)	2 (3.0)
Leading to drug interruption	4 (5.8)	1 (1.5)
Subjects with Grade 3 or higher AE	9 (13.0)	9 (13.4)
Subjects with related ^a AE	1 (1.4)	0
Subjects with SAE	15 (21.7)	10 (14.9)
Subjects with AE leading to death	0	0

Source: Clinical reviewer; JMP version 15.0 and OCS Analysis Studio, adae.xpt using SAFFL(Y), TRTEMFL(Y), STRAT1V, AREL, ATOXGR, AESER, AEACON, TRT01A

^a relatedness determined by the Investigator

Abbreviations: AE, adverse event; D-IVA, deutivacaftor; ELX, elhexacaftor; IVA, ivacaftor; N, number of subjects in treatment group; n, number of subjects in subset; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor; VNZ, vanzacaftor

Overall, the rates of AEs and SAEs were similar between treatment groups in the adolescent population. There was a numerically higher proportion of subjects in the VNZ/TEZ/D-IVA treatment group who experienced AEs leading to trial drug discontinuation, two (3.0%)

VNZ/TEZ/D-IVA treated subjects compared to one (1.4%) ELX/TEZ/IVA treated subjects. However, there was a numerically higher proportion of subjects in the ELX/TEZ/IVA treatment arm (4, 5.8%) who experienced AEs leading to trial drug interruption compared to the VNZ/TEZ/D-IVA treatment arm (1, 1.5%). The overall rates of trial drug discontinuation or interruption were low, and these minor imbalances in the adolescent subgroup are unlikely to be clinically significant.

The most common AEs and SAEs occurring in the adolescent subgroup were also reviewed (data not shown). Overall, they were similar to the total population, and there were no significant imbalances noted between the treatment groups. No new or age-related specific safety signals that were identified.

A summary of the maximum LFT elevations occurring in the adolescent subgroup is reviewed in [Table 198](#).

Table 198. Maximum Liver Function Test Elevations During the Treatment Period in Subjects <18 Years of Age (Pooled SAS), Trials 102 and 103

	ELX/TEZ/IVA N=69 n (%)	VNZ/TEZ/D-IVA N=67 n (%)
Liver Function Test Elevation		
ALT or AST (U/L)		
>3x to ≤5x ULN	5 (7.2)	6 (9.0)
>5x to ≤8x ULN	1 (1.4)	1 (1.5)
>8x to ≤20x ULN	0	1 (1.5)
>20x ULN	0	0
ALT or AST (U/L) and total bilirubin (μmol/L)		
ALT or AST >3x ULN and total bilirubin >2x ULN	1 (1.4)	1 (1.5)

Source: Clinical reviewer; JMP version 15.0 and OCS Analysis Studio, adae.xpt (SAFFL, ONTRTFL, STRAT4V, PARAMCD, AVALC, MCRIT1, ANL02FL)

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-IVA, d-ivacaftor; ELX, elxacaftor; IVA, ivacaftor; N, number of subjects in treatment group; n, number of subjects in subset; SAE, serious adverse event; TEZ, tezacaftor; ULN, upper limit of normal; VNZ, vanzacaftor

The maximum LFT elevations noted during the treatment period in the adolescent subgroup were similar to that of the overall population. The risk for VNZ/TEZ/D-IVA-induced liver injury is reviewed in more detail in Section [7.7.2](#).

17.2. Overview of Adverse Events Occurring in the Run-In or Follow-Up Periods, Pooled Analysis, Trials 102 and 103

Adverse Events in the Run-In Period

[Table 199](#) provides an overview of the AEs occurring in the run-in period of Trials 102 and 103.

Table 199. Overview of Adverse Events During the Run-in Period (Pooled SAS), Trials 102 and 103

	ELX/TEZ/IVA N=1032 n (%)
Subjects With Adverse Events	
Subjects with any AE	395 (38.3)
Subjects with AE	
Leading to discontinuation	4 (0.4)
Leading to drug interruption	0
Subjects with Grade 3 or higher AE	14 (1.4)
Subjects with related ^a AE	100 (9.7)
Subjects with SAE	11 (1.1)
Subjects with AE leading to death	0

Source: Clinical reviewer; JMP version 15.0 and OCS Analysis Studio, adae.xpt using SAFFL(Y), TRTEMFL (Y), STRAT1V, AREL, ATOXGR, AESER, AEACON

^a relatedness determined by the Investigator

Abbreviations: AE, adverse event; ELX, elexacaftor; IVA, ivacaftor; N, number of subjects in treatment group; n, number of subjects in subset; SAE, serious adverse event; SAS, safety analysis set; TEZ, tezacaftor

Overall, 395 (38.3%) of subjects reported an AE during the run-in period with 11 (1.1%) subjects reporting an SAE. The most common AEs reported were headache, cough, and COVID-19. The most common AE leading to drug discontinuation was infective pulmonary exacerbation of CF.

Overall, the review of the AEs in the run-in period did not reveal any new safety signals.

Adverse Events in the Follow-Up Period

The Applicant reported that 822 (84.6%) subjects from Trials 102 and 103 enrolled in the open-label extension, Trial VX20-121-104 (Trial 104). Of those subjects who did not enroll in Trial 104 and entered the run-in period, the review of AEs and SAEs did not reveal any new safety concerns. The most common AE reported during this time was infective pulmonary exacerbation of CF.

17.3. Adverse Events, Trial 105 (Cohort A1)

AEs occurring in Cohort A1 of Trial 105 were also reviewed. Overall, 12 (70.6%) subjects experienced an AE. All AEs were considered mild to moderate and 3 (17.6%) subjects experienced AEs that were determined to be related by the investigator. There were no deaths and no SAEs reported during Cohort A1. The most common AEs reported in subjects were cough (3, 17.6%), abdominal pain (2, 11.8%), and rash (2, 11.8%). There were no new safety signals identified during the review of the safety data from Cohort A1 of Trial 105.

17.4. Additional Safety Analyses

Electrocardiograms

No clinically significant ECG trends or safety concerns were identified in the phase 3 trials of VNZ/TEZ/D-IVA. We note there was a numerically higher proportion of subjects in the VNZ/TEZ/D-IVA treatment group with a decrease of ≥ 20 beats per minute from baseline compared to the ELX/TEZ/IVA (8.6% versus 6.5%). This finding is unlikely to be clinically significant. AEs related to ECG findings were similar between the treatment groups.

QT Study

VNZ/TEZ/D-IVA did not prolong the QTcF interval in the thorough QT study assessment (Study VX22-121-013). This was reviewed by the Interdisciplinary Review team for Cardiac Safety Studies (review dated July 16, 2024).

Safety Specific Clinical Trials

The Applicant submitted a 90-day safety update that consisted of updates that became available since the safety data cut for the NDA submission and included any deaths, all new SAEs, AEs leading to treatment discontinuation, and pregnancies from February 13, 2024, to May 15, 2024, for ongoing studies in the VNZ/TEZ/D-IVA program.

The safety update included the following trials listed in [Table 200](#):

Table 200. Summary of Clinical Studies Included in the 90-Day Safety Update

Trial Number	Study Title	Planned Duration	Number of Subjects
VX20-121-104 (ongoing)	A phase 3, open-label study evaluating the long-term safety and efficacy of VX-121 [VNZ] combination therapy [VNZ/TEZ/D-IVA] in subjects with CF	<u>Part A</u> : 96 weeks <u>Part B</u> : 48 weeks	822 subjects
VX22-121-106 (ongoing)	A phase 3, open-label study evaluating the long-term safety and efficacy of VNZ/TEZ/D-IVA triple combination therapy in CF subjects 1 year of age and older	96 weeks	75 subjects
VX23-121-012 (dosing complete)	A phase 1, randomized, open-label, 2-part study to evaluate the relative bioavailability, food effect, and dose proportionality of a granule formulation of VNZ in combination with TEZ and D-IVA in healthy adult subjects	<u>Part A</u> : Single doses on 3 separate occasions <u>Part B</u> : Single doses on 2 separate occasions	<u>Part A</u> : 18 subjects <u>Part B</u> : 16 subjects

Source: Clinical reviewer from Applicant data

Abbreviations: CF, cystic fibrosis; D-IVA, deutivacaftor; TEZ, tezacaftor; VNZ, vanzacaftor

There were no deaths reported in the included trials. Narratives for SAEs and AEs leading to discontinuation were reviewed. There were four (0.5%) subjects in Trial 104 who discontinued the study drug because of pregnancy. In Trial 105, one (0.1%) subject discontinued trial drug due to LFT abnormalities and one (0.1%) subject discontinued trial drug due to elevations in creatine

phosphokinase. Review of the 90-day safety report provided by the Applicant did not reveal any new safety signals or concerns.

18. Clinical Virology

This section is not applicable to the review of VNZ/TEZ/D-IVA tablets.

19. Clinical Microbiology

This section is not applicable to the review of VNZ/TEZ/D-IVA tablets.

20. Mechanism of Action / Drug Resistance

This section is not applicable to the review of VNZ/TEZ/D-IVA tablets.

21. Other Drug Development Considerations

This section is not applicable to the review of VNZ/TEZ/D-IVA tablets.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

An Office of Scientific Investigation consult evaluated 5 trial sites from the phase 3 program based on high enrollment, efficacy outcomes, and safety. The sites chosen are shown in [Table 201](#). Based on discussions with the Office of Scientific Investigation, the studies appear to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the Applicant appear acceptable to support this NDA. The final Clinical Inspection Summary is pending at the time of this review.

Table 201. Office of Scientific Investigation Inspection Sites

Principal Investigator	Address	Trial(s)	Site No.	No. of Subjects
Brown, Cynthia	1120 W. Michigan St Indianapolis, IN 46202	102 and 103	41	10
DiMango, Emily	622 West 168 th St. Ph 8, Room 859 New York, NY 10032	102	51	8
Keating, Claire	622 West 168 th St. Ph 8, Room 859 New York, NY 10032	103	51	6
Escobar, Hugo	2401 Gilham Rd. Kansas City, MO 64108	105 Cohort B1	21	4
Hoppe, Jordana	13123 East 16 th Ave., B395 Aurora, CO 80045	105 Cohort B1	74	6

Principal Investigator	Address	Trial(s)	Site No.	No. of Subjects
Vertex Pharmaceuticals	50 Northern Ave. Boston, MA 02210	102, 103, and 105 Cohort B1	N/a	N/a

Source: Clinical Reviewer
 Abbreviations: No., number

23. Labeling: Key Changes

This Prescribing Information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI ([Table 202](#)). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 202. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
BOXED WARNING	A Boxed Warning for the risk of drug-induced liver injury and liver failure was added.
1 INDICATIONS AND USAGE	The established pharmacological class information was updated.
2 DOSAGE AND ADMINISTRATION	(b) (4) was removed.
4 CONTRAINDICATIONS	
5 WARNINGS AND PRECAUTIONS	- The Warnings and Precautions were updated to include information on the risk for drug-induced liver injury and liver failure with recommendations for monitoring of LFTs. - A warning was added regarding the potential risks and uncertainty in patients who discontinued or interrupted ELX, TEZ, or IVA containing drugs due to adverse reactions (ARs). - A warning was added to include the risk of hypersensitivity reactions, consistent with ELX/TEZ/IVA. - The remaining warnings and precautions include the risk of reduced effectiveness with concomitant use of CYP3A inducers, the risk of ARs with concomitant use with CYP3A inhibitors, and the risk of cataracts. The Warnings and Precautions are similar to those of ELX/TEZ/IVA and medications that contain one or more of its components.
6 ADVERSE REACTIONS	- This section was updated to include potential reactions based on the data from the phase 3 clinical trials. As these were noninferiority trials without a placebo-controlled treatment arm, ARs were defined as events occurring at or above a threshold of 5% and ≥1% higher frequency in the VNZ/TEZ/D-IVA exposed patients compared to ELX/TEZ/IVA exposed patients. - A caveat was added to inform prescribers that there is no data available in patients who could not tolerate ELX/TEZ/IVA. - Additional data on LFTs was added, including a dedicated table.
7 DRUG INTERACTIONS	(b) (4) were removed.

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Nonclinical information was updated to be in proper PLLR format, per the FDA draft guidance for industry <i>Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products—Content and Format</i> (July 2020).
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	
12 CLINICAL PHARMACOLOGY	- Drug-drug interaction content was reorganized by in vitro/in vivo source (b) (4). - The table of indicated mutations was reorganized by data source (e.g., clinical trials, in vitro data).
13 NONCLINICAL TOXICOLOGY	Juvenile toxicology information was removed from this section and added to Section 8.4 to adhere to the PLLR guidance format guidelines (July 2020).
14 CLINICAL STUDIES	(b) (4) - Exploratory endpoints of the mean change from baseline in ppFEV₁ through Week 52, CF pulmonary exacerbations, and the results of the CFQ-R RD questionnaire were included because they provide data clinically meaningful to prescribers. Language was included to convey results were not statistically significant.
17 PATIENT COUNSELING INFORMATION	Updated to include information regarding the risks related to the Boxed Warning and warnings and precautions. Additional updates included edits to ensure the section was directed to patients and not prescribers consistent with the FDA guidance for industry <i>Instructions for Use—Patient Labeling for Human Prescription Drug and Biological Products—Content and Format</i> (July 2022).
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	No significant changes.

Source: Clinical reviewer.

¹ Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.

² For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): CF, cystic fibrosis; CFQ-R RD, cystic fibrosis questionnaire-revised respiratory domain; D-IVA, deutivacaftor; ELX, elexacaftor; LFT, liver function test; PI, prescribing information; PLLR, pregnancy and lactation labeling; ppFEV₁, percent predicted forced expiratory volume in 1 second; SwCl, sweat chloride; TEZ, tezacaftor

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Medication Guide
- Carton/container

24. Postmarketing Requirements and Commitments

The following postmarketing requirements and commitments are being issued at the time of regulatory action.

PMR 4734-1

Conduct a 2-year carcinogenicity study in rats administered vanzacaftor.

Study Completion: 02/2025

Final Report Submission: 04/2025

PMR 4734-2

Conduct a clinical pharmacokinetic trial to assess the effect of multiple doses of VNZ/TEZ/D-IVA on the single-dose pharmacokinetics of a substrate of BCRP, to address the potential for increased drug toxicity and provide appropriate drug interaction management strategies for coadministration of VNZ/TEZ/D-IVA with this substrate. Design and conduct the study in accordance with the FDA guidance for industry *Clinical Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* ([January 2020](#)).

Final Protocol Submission: 06/2025

Trial Completion: 05/2026

Final Report Submission: 11/2026

25. Financial Disclosure

[Table 203](#) summarizes the financial disclosures submitted to the NDA that include Trial 102, 103, and 105. There were several significant payments that included speaker fees, steering committee and advisory board fees, and investigator-initiated grants. No investigator reported that the payments received were related to the clinical study.

The payments were unlikely to have a significant impact upon the conduct of the clinical trials, given that the majority of individual sites enrolled a small number of subjects and the pivotal efficacy trials were randomized, double-blinded, and controlled with objective spirometric, nutritional, and exacerbation related endpoints. In addition, site-based sensitivity analyses were performed on the primary endpoint and the removal of the subjects from any individual site does not affect the evaluation of efficacy or safety evaluation of this NDA.

Table 203. Covered Clinical Studies: Trials 102, 103, and 105

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1147		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 19		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 19 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

26.1. Literature

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26.2. Guidance for Industry

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NDA 218730
ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

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26.4. Prescribing Information

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27. Review Team

Table 204. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Julianne Lee/Brandi Wheeler (Acting CPMS)
Nonclinical reviewer	Wei Sun
Nonclinical team leader	Jessica A. Bonzo
OCP reviewers	Hyewon Kim Junshan Qiu (Pharmacometrics) Youssef Mousa (PBPK) Claudia Alvarez-Baron (DARS)
OCP team leaders	Yunzhao Ren Jingyu Yu (Pharmacometrics) Manuela Grimstein (PBPK) Wendy Wu (DARS)
Clinical reviewer	Alison Lennox
Clinical team leader	Elisabeth Boulos
Biometrics analyst	Spencer Hauptert
Biometrics reviewer	Yongman Kim
Biometrics team leader	Weiya Zhang
Cross-discipline team leader	Elisabeth Boulos
Deputy Division director (pharm/tox)	Carmen Booker
Division director (OCP)	Chandahas Sahajwalla
Supervisory statistician (OB)	Weiya Zhang
Division director (clinical)	Sally Seymour
Office director (or designated signatory authority)	Nikolay Nikolov

Abbreviations: CPMS, Chief Project Management Staff; DARS, Division of Applied Regulatory Science; OB, Office of Biostatistics; PBPK, physiologically-based pharmacokinetic; OCP, Office of Clinical Pharmacology;

Table 205. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Craig Bertha (ATL)/Nina Ni (Unit Supervisor) Ghaled Hamad/Craig Bertha (Drug Product) Sam Bain/Lawrence Perez (Drug Substance) Kalpana Paudel/Tapash Ghosh (Biopharmaceutics) Vicky He/Shu-Wei Yang (Manufacturing and microbiology-OPMA) Emma Gimose (RBPM)
Carcinogenicity	Malick Mbodj (Statistical Reviewer)/Mohammad A. Rahman (Concurring Reviewer)
OSI	Suyoung Tina Chang/Phillip Kronstein
OPDP	Quynh-Nhu Capasso/Adewale Adeleye
OSE/DEPI	Alice Cheng Chen/Mingfeng Zhang
OSE/DPV	Scott Janiczak/Michelle C. Hines
OSE/PLT	Mary Carroll/Marcia Williams
OSE/DRISK	May Chan-Liston/Jacqueline Sheppard/Cynthia Lacivita
OSE/DMEPA	Lissa Pringle-Owens/Sherly Abraham/Damon Birkemeier
SRPM	Cristina Attinello/Ameet Joshi
ADL	Jessica Lee
OND/DHN	Eileen NavarroAlmario/Paul Hayashi
QT-IRT	Jing Sun
CDS	Jun Zhu/Ling Cao

Abbreviations: ADL, Associate Director of Labeling; ATL, Application Technical Lead; CDS, Clinical Data Scientist; DEPI, Division of Epidemiology; DILI, Drug-Induced Liver Injury Team; DMEPA, Division of Medication Error Prevention and Analysis; DPV, Division of Pharmacovigilance; DRISK, Division of Risk Management; LPT, Labeling Policy Team; ONDP, Office of New Drug Policy; OPDP, Office of Prescription Drug Promotion; OPMA, Office of Pharmaceutical Manufacturing Assessment; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations; PLT, Patient Labeling Team; QT-IRT, QT Interdisciplinary Review Team; RBPM, Regulatory Business Process Manager; SRPM, Safety Regulatory Project Manager

27.1. Reviewer Signatures

Table 27-206 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Craig Bertha OPQAII DPQAVIII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Craig Bertha		Digitally signed by Craig Bertha		
		Date: 12/19/2024 2:03 PM EST GUID: 2024121919358		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Jessica Bonzo OII DPTII	Sections: 5.1, 7.1, 13.1, 13.2	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jessica Bonzo		Digitally signed by Jessica Bonzo		
		Date: 12/19/2024 2:04 PM EST GUID: 2024121919457		

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Youssef Mousa OCP DIIP	Sections: 14.5.2.	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Youssef Mousa		Digitally signed by Youssef Mousa Date: 12/19/2024 2:06 PM EST GUID: 2024121919641		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Alison Lennox OII DPACC	Sections: 1,2,3,4,6,7,8.3,8.4,10, 11,15,16,17,22,23,25	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Alison Lennox		Digitally signed by Alison Lennox Date: 12/19/2024 2:17 PM EST GUID: 20241219191726		

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Weiya Zhang OB DBIII	Sections: 6, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Weiya Zhang Digitally signed by Weiya Zhang Date: 12/19/2024 2:35 PM EST GUID: 20241219193522				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non- clinical Discipline Tertiary Reviewer	Carmen Booker OII DPTII	Sections: 5.1, 7, 8.3, 8.4, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Carmen Booker Digitally signed by Carmen Booker Date: 12/19/2024 2:35 PM EST GUID: 20241219193537				

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Hyewon Kim OCP DIIP	Sections: 5.2, 6.1, 6.2, 7.7, 8.1, 8.2, 14.1, 14.2, 14.3	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hyewon Kim Digitally signed by Hyewon Kim Date: 12/19/2024 2:37 PM EST GUID: 20241219193717				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Julianne Lee ORO DROII	Sections: 12. Summary of Regulatory History	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Julianne Lee Digitally signed by Julianne Lee Date: 12/19/2024 2:39 PM EST GUID: 20241219193936				

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Yunzhao Ren OCP DIIP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yunzhao Ren		Digitally signed by Yunzhao Ren Date: 12/19/2024 2:43 PM EST GUID: 20241219194315		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Ladan Jafari ORO DROII	Sections: 12. Summary of Regulatory History	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Ladan Jafari		Digitally signed by Ladan Jafari Date: 12/19/2024 2:43 PM EST GUID: 20241219194339		

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Hyewon Kim OCP DIIP	Sections: 5.2, 6.1, 6.2, 8.1, 8.2, 14.1, 14.2, 14.3	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hyewon Kim Digitally signed by Hyewon Kim Date: 12/19/2024 2:46 PM EST GUID: 2024121919463				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Jingyu Yu OCP DPM	Sections: 14.5.1	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jingyu Yu Digitally signed by Jingyu Yu Date: 12/19/2024 2:47 PM EST GUID: 20241219194759				

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Wendy Wu OCP DARS	Sections: 14.1.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Wendy Wu Digitally signed by Wendy Wu Date: 12/19/2024 2:52 PM EST GUID: 20241219195240				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Claudia Alvarez Baron OCP DARS	Sections: 14.1.2	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Claudia Alvarez Baron Digitally signed by Claudia Alvarez Baron Date: 12/19/2024 2:53 PM EST GUID: 20241219195319				

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Wei Sun OII DPTII	Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Wei Sun				
Digitally signed by Wei Sun Date: 12/19/2024 3:26 PM EST GUID: 2024121920260				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Junshan Qiu OCP DPM	Sections: 14.5.1	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Junshan Qiu				
Digitally signed by Junshan Qiu Date: 12/19/2024 3:29 PM EST GUID: 20241219202944				

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Yongman Kim OB DBIII	Sections: 6, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yongman Kim Digitally signed by Yongman Kim Date: 12/19/2024 3:37 PM EST GUID: 20241219203736				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Chandrabhas Sahajwalla OCP DIIP	Sections: 5, 6, 8, and 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Chandrabhas Sahajwalla Digitally signed by Chandrabhas Sahajwalla Date: 12/19/2024 7:08 PM EST GUID: 202412200821				

NDA 218730
 ALYFTREK (vanzacaftor/tezacaftor/deutivacaftor) Tablets

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Elisabeth Boulos OII DPACC	Sections: 1, 2, 3, 4, 6, 7, 8.3, 8.4, 10, 11, 15, 16, 17, 22, 23, 25	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elisabeth Boulos		Digitally signed by Elisabeth Boulos Date: 12/19/2024 7:15 PM EST GUID: 2024122001516		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Elisabeth Boulos OII DPACC	Sections: 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Elisabeth Boulos		Digitally signed by Elisabeth Boulos Date: 12/19/2024 7:18 PM EST GUID: 2024122001830		

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

/s/

ELISABETH S BOULOS
12/19/2024 07:18:58 PM

SALLY M SEYMOUR
12/19/2024 07:23:48 PM

NIKOLAY P NIKOLOV
12/19/2024 07:53:34 PM