

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218730Orig1s000

OTHER REVIEW(S)

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	December 18, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 218730
Product Name, Dosage Form, and Strength:	Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor) tablets, 4 mg/20 mg/50 mg per tablet and 10 mg/50 mg/125 mg per tablet
Applicant Name:	Vertex Pharmaceuticals Incorporated (Vertex)
FDA Received Date:	December 12, 2024, December 16, 2024, and December 17, 2024
TTT ID #:	2024-9379-2
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

Vertex Pharmaceuticals Incorporated submitted revised carton labeling, Prescribing Information (PI), and Medication Guide (MG), received on December 12, 2024, December 16, 2024, and December 17, 2024, for Alyftrek. The proposed Medication Guide and associated PI and carton labeling revisions are in response to the Division of Pulmonology, Allergy, and Critical Care's (DPACC) Information Request (IR) issued on December 6, 2024, requesting submission of a Medication Guide that reflects safety information consistent with the revised PI, specifically regarding the concern of drug-induced liver injury (DILI) that may be associated with use of Alyftrek.^a The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised carton labeling, MG, and PI for Alyftrek (Appendix A) to determine if they are acceptable from a medication error perspective.

2 CONCLUSION

We find Vertex's proposals acceptable and we have no additional recommendations at this time.

^a Lee J. Advice/Information Request for Alyftrek (NDA 218730). Silver Spring (MD): FDA, CDER, OND, DPACC (US); 2024 DEC 6. Available from: <https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80787433>.

APPENDIX A. IMAGES OF LABELING RECEIVED ON DECEMBER 17, 2024

Prescribing Information (PI): \\CDSESUB1\EVSPROD\nda218730\0036\m1\us\draft-annot-labeling-text-uspi.pdf

Medication Guide (MG): \\CDSESUB1\EVSPROD\nda218730\0036\m1\us\draft-labeling-text-medication-guide-tracked.pdf

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

LISSA C PRINGLE-OWENS
12/18/2024 12:56:22 PM

DAMON A BIRKEMEIER
12/19/2024 02:29:27 PM

Drug Induced Liver Injury Team Consult Memorandum

**Division of Hepatology and Nutrition (DHN)
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration**

NDA	NDA 218730 (IND 142001)
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	vanzacaftor/tezacaftor/deutivacaftor (VNZ/TZA/D-IVA)
Indication	Cystic fibrosis with F508del and other <i>CFTR</i> mutations
Applicant	Vertex Pharmaceuticals, Incorporated
Requesting Division	Division of Pulmonary Allergy and Critical Care (DPACC)
Primary Reviewer	Eileen Navarro, MD DILI Team Lead, OND/DHN
Pharmacology & Non-clinical Reviewer	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Clinical Data Scientist Reviewer	Aaron Waddell, PhD, Clinical Data Specialist, OND/CDER
Reviewer National Center for Toxicological Research (NCTR)	Minjun Chen, PhD, Senior Staff Fellow, Division of Bioinformatics and Biostatistics, NCTR
Reviewer Office of Pharmacoepidemiology	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Paul H. Hayashi, MD, MPH Associate Director for DILI, OND/DHN
Assessment Date	Dec 17, 2024

- I. Executive Summary
- II. Background
- III. Significant Review Findings
- IV. Assessment
- V. Recommendations:

Appendix: Additional tables and figures

Attachments: DILI Team consult for Trikafta®, IND 132547; NCTR report on VANZA

I. Executive Summary

We conclude that vanzacaftor/tezacaftor/deutivacaftor (VANZA) can cause clinically significant hepatocellular drug induced liver injury (DILI), but the DILI risk should not hold up approval if efficacy is adequate in the opinion of the Division of Pulmonary Allergy and Critical Care (DPACC). There were no cases meeting Hy's law, but three subjects suffered probable VANZA hepatotoxicity

with ALT levels as high as 15 to 28 times upper limit of normal. The number exposed to VANZA is small at < 500 in the two pivotal trials, so more severe cases may occur in a larger post-market population. Moreover, VANZA is related to another cystic fibrosis transmembrane conductance regulator (CFTR) modulator, Trikafta® (TRK), that has caused fatal hepatocellular DILI post-market. DPACC is pursuing updates to the TRK label that include addition of a box warning and increased liver blood test monitoring. Because of overlapping indications, overlapping component agents, similar mechanisms of action, and lack of firm evidence that VANZA has a lower risk of severe DILI, we support VANZA labeling that reflects the TRK updated label, including the added box warning.

II. Background

Vanzacaftor/tezacaftor/deutivacaftor (VANZA) is an oral, fixed dose, triple drug combination for the treatment of patients with cystic fibrosis (CF) due to the F508 del and other disease producing mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. Like Trikafta® (TRK), the first approved triple drug therapy for CF, VANZA is a CFTR modulator that enhances CFTR function, stability, and delivery to the cell membrane. VANZA contains vanzacaftor (VNZ) while TRK has elexacaftor (ELX). However, they share tezacaftor (TZC), and VANZA has a deuterated form of ivacaftor (deutivacaftor, or D-IVA) while TRK has non-deuterated ivacaftor (**Figure 1**).

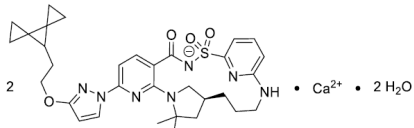
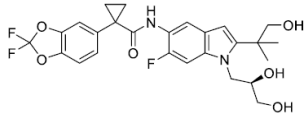
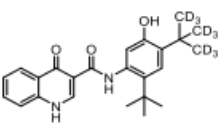
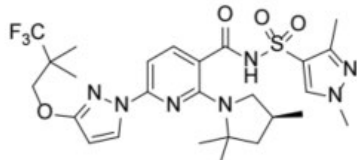
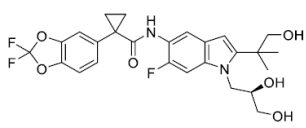
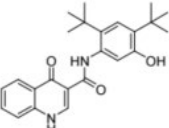
VANZACAFITOR (VANZA)		
Vanzacaftor (VNZ-C)	Tezacaftor (TZC)	Deutivacaftor (D-IVA)
		
TRIKAFTA® (TRK)		
Elexacaftor (ELX)	Tezacaftor (TZC)	Ivacaftor (IVA)
		

Figure 1: Chemical structures of VANZA components: Vanzacaftor (VZA-c) and Deutivacaftor (D-IVA) are distinct from the components of Trikafta® Elexacaftor (ELX) and Ivacaftor (IVA), respectively¹ whereas Tezacaftor is identical in both products.

TRK was approved in 2019 with hepatotoxicity in the label's warning and precautions as well as recommended liver blood test monitoring. By 2021, cases of severe hepatocellular DILI leading to fatalities in patients with underlying hepatic impairment occurred leading to additional labeling that TRK "should not

¹ [IND132547 \(132547 - 0735 - \(723\) - 2024-05-31 - ORIG-1 /Protocol/Investigator\) - Introduction](#)

be used” in patients with severe hepatic impairment and “is not recommended” in those with moderate impairment. By 2024, patients *without* underlying hepatic disease had developed severe DILI leading to fatalities, and a box warning with additional monitoring are to be added. While the increased TRK DILI concern was evolving through 2024, the NDA for VANZA was submitted by the same Sponsor that developed TRK. With the similarities between TRK and VANZA, the Division of Division of Pulmonary Allergy and Critical Care (DPACC) requested the DHN DILI Team assess liver injury cases for attribution to VANZA and assistance with labeling in the context of TRK labeling changes. The DILI Team had already been consulted regarding the emerging TRK hepatotoxicity risk as well as a newly identified safety signals (NISS) assessment for single and dual CFTR modulators on the market.

III. Significant Review Findings

For review of the target disease and VANZA mechanism of action, please see the DILI Team’s consult regarding TRK attached.

A. ADME data pertinent to DILI: Our key findings for absorption, distribution, metabolism, and elimination are in **Table 1**. VANZA is metabolized in the liver primarily by CYP 3A4/5. In humans, there were no major circulating metabolites from VNZ while TEZ has three and D-IVA two. However, there was evidence for tissue accumulation of two VNZ metabolites. D-IVA exhibited more metabolic stability than IVA, but both have qualitatively similar metabolism. Excretion of VNZ and D-IVA were primarily via feces with negligible amounts leaving in urine. The half-lives of the three drugs are relatively long at 17 to 54 hours.

Table 1: ADME summary data pertinent to DILI risk.²

Item	Finding
Absorption	Rapid for TZC and D-IVA, slow for VNZ
Distribution	High plasma protein binding
Metabolism	CYP3A4/5
Elimination	Route: mainly feces and T _{1/2} estimates: 54 hours for VNZ, 25.1 for TEZ, and 17.3 hours for D-IVA

B. Non-clinical Data pertinent to DILI:

1). *In vitro and animal data:* Our key findings for non-clinical data regarding hepatotoxicity are in **Table 2**. In rats, there were enzyme and total bilirubin (TB) elevations and liver histopathology including necrosis that tended to arise or be more prominent in the longer-term studies. There was also IVA accumulation in tissues. Dogs were more tolerant with no substantial changes in liver blood tests or liver histology.

² Table made by DILI Team.

Table 2: Summary of non-clinical data regarding DILI risk.

Item	Finding
In Vitro Studies	
Major CYPs or UGTs	CYP3A4/5
Reactive metabolites (i.e., glutathione trapping)	Minor from TZC
Mitochondria studies/inhibition	Not assessed
Time dependent inhibition	Negative
LogP (lipophilicity) values >3 associated with increased DILI risk	VNZ:4.7, ELE: 4.5; D-IVA: 5.0
Covalent binding	Not assessed
Transporter inhibition (BSEP or MRP2 inhibition may increase risk of DILI)	TEZ and its metabolite inhibited BSEP at IC50: 45.7 and 33.7 uM
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	Increase in ALT, ALP, and total bilirubin in rats
Liver histopathology findings (animal species)	centrilobular vacuolar degeneration, multifocal hepatocellular necrosis, and minimal bile duct hyperplasia in rats.

2). *National Center for Toxicological Research (NCTR) data:* For our TRK consult, we had consulted Minjun Chen, PhD and his group at NCTR to evaluate hepatotoxicity risk of TRK (and later VANZA) using the Rule of 2 (Ro2) and DILIScore.^{3,4} For details on NCTR methodology please see our TRK consult note attached. Briefly, the NCTR developed the Ro2 and DILIScore using multivariate modeling to predict post-market hepatotoxicity based on drug labels. Ro2 identified higher daily dose (>50 mg/d) and higher drug lipophilicity (logP >3.0) as independently associated with increased labeling for hepatotoxicity (e.g., box warnings, warnings and precautions) and post-market actions (e.g., removal for DILI); having both higher dose and lipophilicity garners a “positive” Ro2. The DILIScore was similarly modeled and added reactive metabolite formation based on in vitro studies (when available). The DILIScore outputs a continuous numeric score with greater than six being associated with high DILI risk and less than three a low risk. We provide the main NCTR findings for TRK and VANZA in **Table 3**. All five drugs used in TRK and VANZA have DILIScores over six if reactive metabolites are formed. The Sponsor indicates that glutathione trapping studies were negative for these drugs, but time dependent inhibition (also an indicator for reactive metabolites) was not ruled out for IVA. Thus, IVA is the only drug that is positive on Ro2 and may have a DILIScore over six.

Overall, NCTR data do not suggest a clear difference in risk between VANZA and TRK, although VNZ has the lowest daily dose (<50 mg/d) which has been associated with lower DILI risk by other investigators.⁵

³ Chen M, et al. High Lipophilicity and High Daily Dose of Oral Medications Are Associated with Significant Risk for Drug-Induced Liver Injury. *Hepatology*. 2013; 58:388-396

⁴ Chen M, et al. A Model to Predict Severity of Drug-Induced Liver Injury in Humans. *Hepatology*. 2016; 63:931-940.

⁵ Lammert C, et al. Relationship Between Daily Dose of Oral Medications and Idiosyncratic Drug-Induced Liver Injury: Search for Signals. *Hepatology*. 2008; 47:2003-9

Table 3: Rule of 2 (Ro2) and DILIScores for (a) TRK and (b) VANZA.⁶

(a) TRK (Trikafta®)

	Elexacaftor (ELX)	Ivacaftor (IVA)	Tezacaftor (TEZ)
Daily dose (mg/day)	200	300	100
logP [^]	4.46 (calculated)	5.0 (calculated)	2.98 (calculated)
Reactive metabolite (RM) formation	TBD	Positive (TDI positive) *	TBD
Ro2 test	Positive	Positive	Negative
DILIScore	7.07 (if RM =YES) 4.23 (if RM = NO)	7.44	6.31 (if RM=YES) 3.48 (if RM=NO)

(b) VANZA

	Vanzacaftor (VNZ)	Deuterated-ivacaftor (D-IVA)	Tezacaftor (TEZ)
Daily dose (mg/day)	20	250	100
logP	5.05 (calculated)	5.0 (calculated)	2.98 (calculated)
Reactive metabolite (RM) formation	TBD (TDI negative)*	TBD (TDI negative) *	TBD
Ro2 test	Negative	Positive	Negative
DILIScore	5.80 (if RM =YES) 2.97 (if RM = NO)	7.33 (if RM =YES) 4.49 (if RM = NO)	6.31 (if RM=YES) 3.48 (if RM=NO)

TBD: to be determined.

*TDI: Time dependent inhibition, which is highly suggestive of reactive metabolite formation.

[^] <3 = low DILI risk, >6 = high DILI risk

C. Clinical findings:

1). *In class or near class marketed drugs:* TRK and several other CFTR modulators have been marketed since 2012, IVA as a single agent being the first. All are labeled for hepatotoxicity. For details on their labeling and LiverTox® DILI risk category, see our TRK consult attached.

2). *Study level data:* With our Clinical Data Scientist (CDS) colleague, Aaron Waddell (AW), PhD, we focused on the two phase 3 studies with comparator arms, Studies 102 and 103 (**Table 4**). Study designs for these two studies were identical, treating for 52 weeks during the randomized parts of the studies (**Appendix, Figures A**). However, unbiased comparisons between arms in these two studies is hindered because all subjects received TRK for a 28-day run-in period just prior to randomization to VANZA or TRK. The latency for TRK liver injury is variable from days to months.

⁶ Taken from DILI Team consult note for Trikafta® IND 132547 and NCTR full report (see attachments)

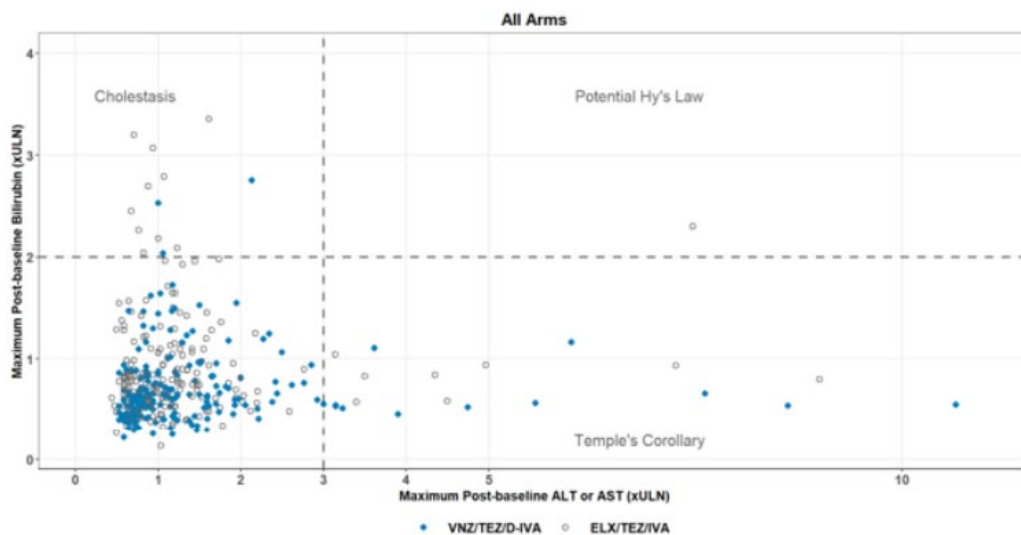
Table 4: Three phase studies assessed by CDS and DILI Team.⁷

Trial Identifier	Trial Population	Trial Design	Treatment Duration	Number of Safety subjects	Study Completion Date
VX20-121-102	Subjects with Cystic Fibrosis	Phase 3, randomized in 1:1 manner, DB, MC	52 weeks	VNZ/TEZ/D-IVA: N=196 ELX/TEZ/IVA: N=202	2023-11-21
VX20-121-103	Subjects with Cystic Fibrosis	Phase 3, randomized in 1:1 manner, DB, MC	52 weeks	VNZ/TEZ/D-IVA: N=284 ELX/TEZ/IVA: N=289	2023-11-30
VX21-121-105	Subjects with Cystic Fibrosis	Phase 3, open-label, multiple study cohorts, MC	22 days (Cohort A1) 24 weeks (Cohort B1)	VNZ/TEZ/D-IVA: A1: N=17 B1: N=78	2023-11-27

- DB: double-blind
- MC: multi-center
- VNZ/TEZ/D-IVA: vanzacaftor 20mg qd, tezacaftor 100mg qd, deutevacaftor 250mg qd
- ELX/TEZ/IVA: elxacaftor 200mg qd, tezacaftor 100mg qd, ivacaftor 150mg q12h

i. Hepatocellular DILI screening plots (eDISH):

For study 102, there were no subjects on VANZA plotting to the Potential Hy's law quadrant, but there were proportionately more subjects on VANZA in Temple's Corollary quadrant (6.1% versus 4%) (**Figure 2**). Study 103 had a similar eDISH plot (**Appendix, Figure B**) with similar imbalance in Temple's. Subject ^{(b) (6)} was on VANZA in study 103 and plotted to the Potential Hy's law quadrant. However, this subject did not have DILI and had Gilbert's explaining the hyperbilirubinemia.



Source: adlib.xpt; Software: R

⁷ From CDS DILI Planning Meeting with AW, Aug 14, 2024

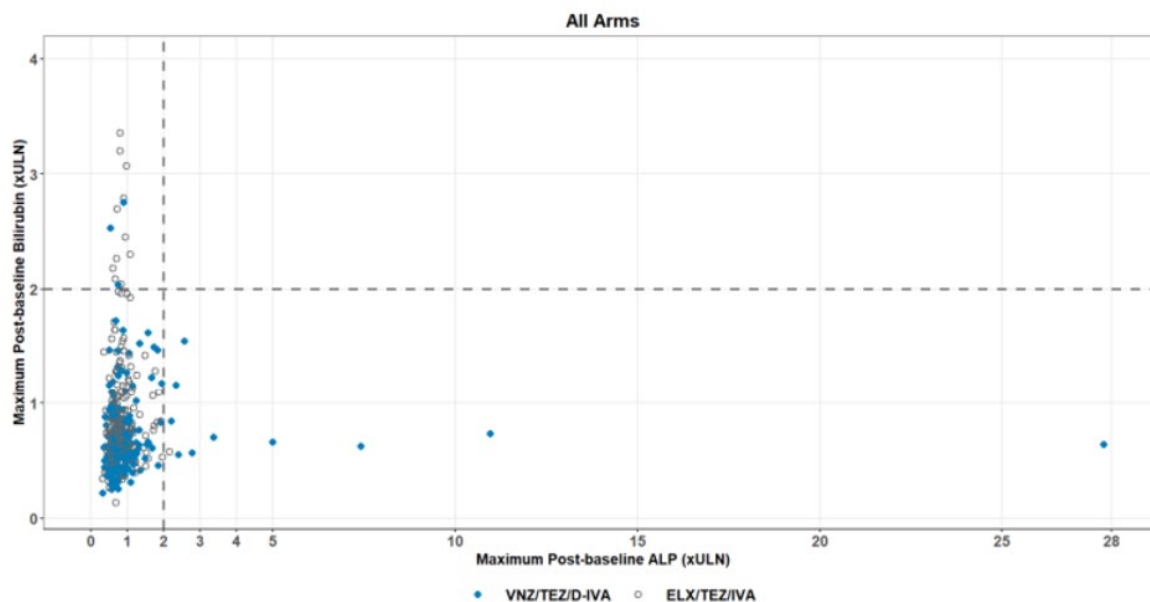
Quadrant	VNZ/TEZ/D-IVA N=196	ELX/TEZ/IVA N=202
Potential Hy's Law (right upper)	0/196 (0)	1/202 (0.5)
Cholestasis (left upper)	3/196 (1.5)	10/202 (5)
Temple's corollary (right lower)	12/196 (6.1)	8/202 (4)
Total	15/196 (7.7)	19/202 (9.4)

Source: adlib.xpt; Software: R

Figure 2: eDISH plot for Study 102.⁸

ii. *Cholestatic DILI screening plots:*

Many subjects particularly in the ELX/TEZ/IVA group plot to the cholestasis quadrant on eDISH suggesting potential for cholestatic liver injury. However, none shifted to the right upper quadrant on cholestatic plotting meaning the jaundice in these subjects was not associated with substantial AT or ALP elevations, making DILI unlikely (**Figure 3**). The reasons for TRK subjects to have this jaundice without enzyme elevations is unclear. There were substantially more subjects on VANZA in the right lower quadrant (10, 5.1% vs. 1, 0.5%). The cholestatic DILI screening plot for Study 103, showed more TRK subjects in the right lower quadrant overall, but more VANZA subjects with ALP >5x ULN (**Appendix, Figure C**). The clinical significance of these difference is unclear particularly for a target disease that can cause chronic cholestasis with ALP elevations. We did not pursue case level analyses for these subjects with ALP elevation and no jaundice, nor the subjects with jaundice and no substantial enzyme elevations (left upper quadrant on both cholestatic and eDISH plots).



⁸ Plot and table made by CDS (AW)

Quadrant	VNZ/TEZ/D-IVA N=196	ELX/TEZ/IVA N=202
>=2X ULN Bilirubin and >=2X ULN ALP (right upper)	0/196 (0)	0/202 (0)
>=2X ULN Bilirubin and <2X ULN ALP (left upper)	3/196 (1.5)	11/202 (5.4)
<2X ULN Bilirubin and >=2X ULN ALP (right lower)	10/196 (5.1)	1/202 (0.5)
Total	13/196 (6.6)	12/202 (5.9)

Source: adlb.xpt; Software: R

Figure 3: Cholestatic DILI screening plot for Study 102.⁹

iii. *Shift table analyses for ALT and AST:*

There were more subjects on VANZA with ALT elevations compared to TRK in Study 103, but similar numbers and proportions between groups in Study 102 (**Table 5**). AST elevations were more frequent on VANZA in both studies.

Table 5: Elevations in aminotransferases (ALT and AST) between study arms for (a) Study 102 and (b) Study 103.¹⁰

(a) Study 102

Laboratory Abnormality	VNZ/TEZ/D-IVA N=196 n (%)	ELX/TEZ/IVA N=202 n (%)	Risk Difference (%) (95% CI)
ALT			
>=1X ULN	67/196 (34.2)	61/202 (30.2)	4.0 (-5.2, 13.1)
>=3X ULN	6/196 (3.1)	7/202 (3.5)	-0.4 (-4.3, 3.5)
>=5X ULN	2/196 (1.0)	2/202 (1.0)	0.0 (-2.6, 2.8)
>=10X ULN	0/196 (0)	0/202 (0)	0.0 (-1.9, 1.9)
>=20X ULN	0/196 (0)	0/202 (0)	0.0 (-1.9, 1.9)
AST			
>=1X ULN	90/196 (45.9)	96/202 (47.5)	-1.6 (-11.4, 8.2)
>=3X ULN	10/196 (5.1)	4/202 (2.0)	3.1 (-0.6, 7.4)
>=5X ULN	4/196 (2.0)	2/202 (1.0)	1.1 (-1.7, 4.3)
>=10X ULN	1/196 (0.5)	0/202 (0)	0.5 (-1.4, 2.8)
>=20X ULN	0/196 (0)	0/202 (0)	0.0 (-1.9, 1.9)

(b) Study 103

Laboratory Abnormality	VNZ/TEZ/D-IVA N=284 n (%)	ELX/TEZ/IVA N=289 n (%)	Risk Difference (%) (95% CI)
ALT			
>=1X ULN	104/284 (36.6)	94/289 (32.5)	4.1 (-3.7, 11.8)
>=3X ULN	14/284 (4.9)	5/289 (1.7)	3.2 (0.3, 6.6) *
>=5X ULN	5/284 (1.8)	1/289 (0.3)	1.4 (-0.4, 3.8)
>=10X ULN	1/284 (0.4)	0/289 (0)	0.4 (-1.0, 2.0)
>=20X ULN	0/284 (0)	0/289 (0)	0.0 (-1.3, 1.3)
AST			
>=1X ULN	131/284 (46.1)	120/289 (41.5)	4.6 (-3.5, 12.7)
>=3X ULN	11/284 (3.9)	5/289 (1.7)	2.1 (-0.6, 5.3)
>=5X ULN	6/284 (2.1)	3/289 (1.0)	1.1 (-1.2, 3.6)
>=10X ULN	2/284 (0.7)	0/289 (0)	0.7 (-0.6, 2.5)
>=20X ULN	1/284 (0.4)	0/289 (0)	0.4 (-1.0, 2.0)

⁹ Plot and table made by CDS (AW)

¹⁰ Made by CDS (AW).

iv. *Liver related adverse events (AE) leading to treatment discontinuation:*

Study 102 had no differences in subject discontinuing treatment for hepatic AE's, whereas Study 3 had more VANZA subjects discontinuing for hepatic AEs compared to TRK (**Table x**).

Table 6: Treatment discontinuations and rates for liver related AEs by treatment group for (a) Study 102 and (b) study 103.¹¹

(a) Study 102			
	VNZ/TEZ/D-IVA	ELX/TEZ/IVA	
	N=196	N=202	
Criteria	n (%)	n (%)	Risk Difference (%) (95% CI)
Completed follow-up but discontinued IP prematurely with one or more of the following:	1 (0.5)	1 (0.5)	0.0 (-2.3, 2.4)
Reason for discontinuation: AEs in Hepatic Failure or Hepatic Injury FMQs	1 (0.5)	1 (0.5)	0.0 (-2.3, 2.4)
(b) Study 103			
	VNZ/TEZ/D-IVA	ELX/TEZ/IVA	
	N=284	N=289	
Criteria	n (%)	n (%)	Risk Difference (%) (95% CI)
Completed follow-up but discontinued IP prematurely with one or more of the following:	6 (2.1)	2 (0.7)	1.4 (-0.6, 3.9)
Reason for discontinuation: AEs in Hepatic Failure or Hepatic Injury FMQs	6 (2.1)	2 (0.7)	1.4 (-0.6, 3.9)

3). *Case level data:* We assessed 45 cases across the development program, identified by DPACC and the Sponsor as having potential DILI. All cases were assessed using the US Drug Induced Liver Injury Network likelihood categories (**Table 7**).¹²

Table 7: US Drug Induced Liver Injury Network (DILIN) causality assessment scoring.

Score	Label	Descriptor
1	Definite	>95%% likelihood of DILI due to investigational product
2	Highly likely	75% to 95% likelihood of DILI due to investigational product
3	Probable	50% to 74% likelihood of DILI due to investigational product
4	Possible	25% to 49% likelihood of DILI due to investigational product
5	Unlikely	<25% likelihood of DILI due to investigational product
6	Indeterminant	Insufficient data

Of the 45, we assessed 35 as unlikely DILI due to study drug and one indeterminate because of inadequate data. The most common alternate diagnosis was myopathy followed by gallstone disease and infections (**Appendix, Table A**). CF liver disease was the alternate diagnosis in just one case. Of the remaining nine cases, we assessed one as highly likely DILI due to

¹¹ Made by CDS (AW)

¹² Fontana RJ, et al. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. *Drug Saf.* 2009; 32:5-68.

TRK because there were positive rechallenges, four as probable DILI due to study drug (one TRK, three VANZA) and four possible DILIs (two each attributed to TRK and VANZA) (**Table 8**). Only one case met Hy's law, and he was on TRK. However, Subject (b) (6) was on VANZA and lacked complete liver enzymes and TB dechallenge data. TB was still rising slowly at last follow-up, so excluding Hy's Law for this case was not possible. For the probable DILI cases, the injuries were all hepatocellular with R-values >5. Latencies ranged from 19 to 258 days. For the three VANZA cases, the latencies were 19, 115 and 258 days.

Table 8: Cases of (a) at least possible and (b) at least probable DILI due to study drug.¹³
(a) At least possible DILI due to study drug.

#	ID	Causality Score**	Alternate diagnosis	Study	Therapy	Age (y)	Sex	Race	Hy's Law	Latency from start drug (d)	Latency from stop drug (d)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak^
1	(b) (6)	2	NA	VX20-121-102	ELX/TEZ/IVA	46	M	White	No	117	[13]	495	232	151	0.96	10.03
4		3	NA	VX20-121-103	ELX/TEZ/IVA	33	M	White	Yes	28	[2]	388	143	216	2.89	5.49
2		3	NA	VX23-121-012	VNZ/TEZ/D-IVA	40	M	White	No	19	5	537	219	198	0.6	8.30
3		3	NA	VX20-121-102	VNZ/TEZ/D-IVA	48	M	White	No	258	1	830	400	123	3.56	20.64
5		3	NA	VX20-121-103	VNZ/TEZ/D-IVA	40	M	White	?	115	[5]	615	328	104	NA	18.09
7		4	HEV	VX20-121-103	ELX/TEZ/IVA	51	F	White	No	40	[351]	341	176	104	0.97	10.03
8		4	Infection	VX20-121-103	ELX/TEZ/IVA	37	M	White	No	112	0	231	124	216	1.71	3.2712
6		4	APAP	VX20-121-104	VNZ/TEZ/D-IVA	48	F	White	No	389	[88]	277	165	465	0.3	1.82
9		4	Unknown	VX20-121-105	VNZ/TEZ/D-IVA	10	F	White	No	161	[18]	107	61	264	0.51	1.24

(b) At least probable DILI due to study drug with descriptive statistics.

#	ID	Causality Score**	Alternate diagnosis	Study	Therapy	Age (y)	Sex	Race	Hy's Law	Latency from start drug (d)	Latency from stop drug (d)~	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak^
1	(b) (6)	2	NA	VX20-121-102	ELX/TEZ/IVA	46	M	White	No	117	[13]	495	232	151	0.96	10.03
2		3	NA	VX20-121-103	ELX/TEZ/IVA	33	M	White	Yes	28	[2]	388	143	216	2.89	5.49
3		3	NA	VX23-121-012	VNZ/TEZ/D-IVA	40	M	White	No	19	5	537	219	198	0.6	8.30
4		3	NA	VX20-121-102	VNZ/TEZ/D-IVA	48	M	White	No	258	1	830	400	123	3.56	20.64
5		3	NA	VX20-121-103	VNZ/TEZ/D-IVA	40	M	White	?	115	[5]	615	328	104	NA	18.09
						Average	41.4			107	[3]	573	264	158	2.0	12.5
						Std Dev	5.3			86	6	148	90	43	1.3	5.8
						Median	40			115	[2]	537	232	151	1.9	10.0
						Min	33			19	[13]	388	143	104	0.6	5.5
						Max	48			258	5	830	400	216	3.6	20.6

*Gilbert's

**1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did not rise above the ULN

~Bracketed [] day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

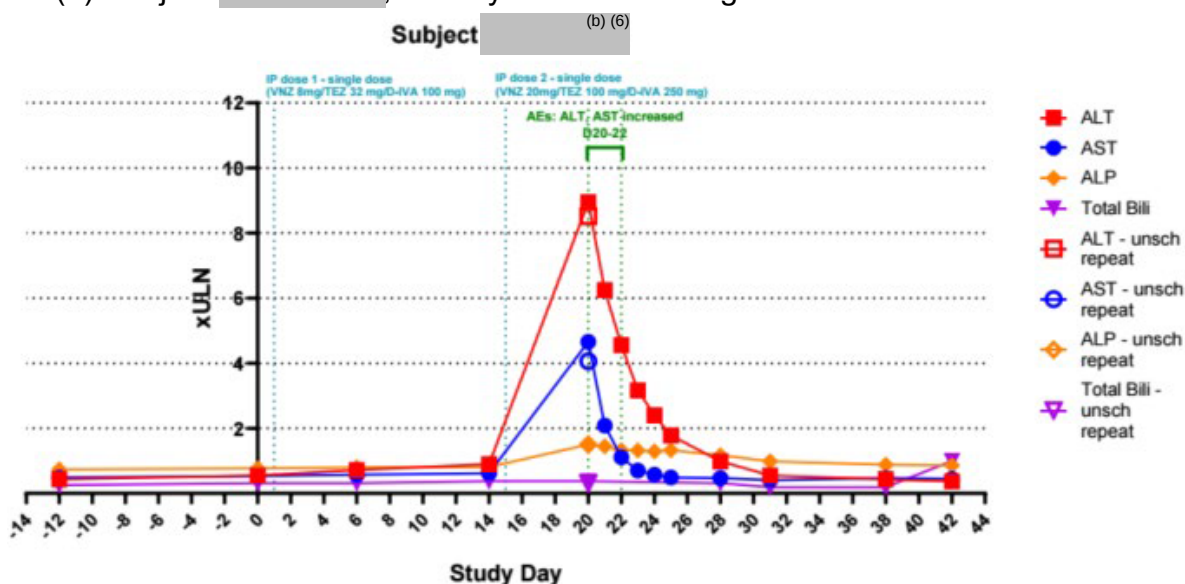
ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

NA = not available or not applicable

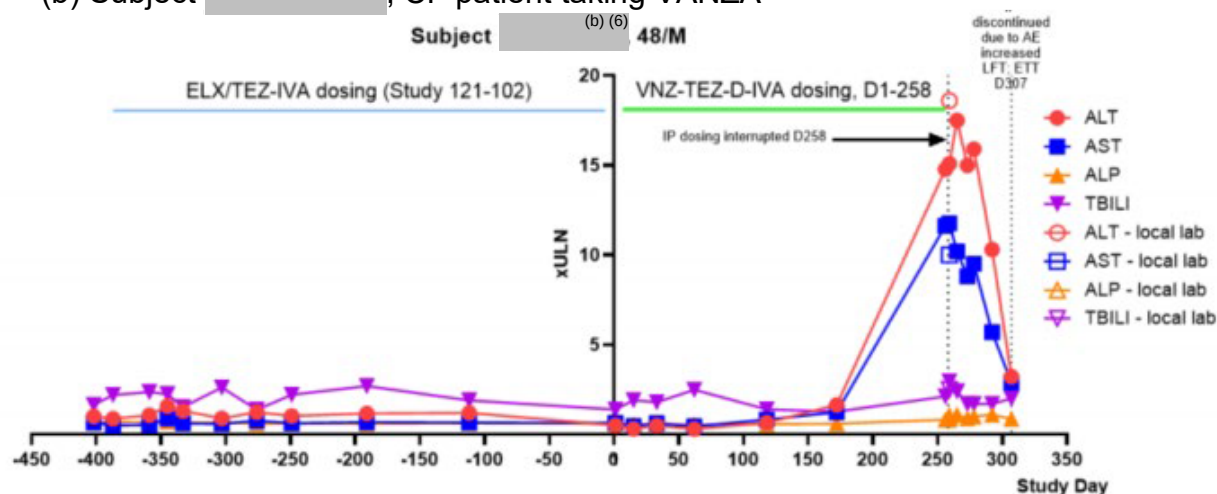
For the three cases with probable DILI due to VANZA, evaluation testing for other liver injury causes was adequate. Subject (b) (6) was a healthy volunteer. Timing of injury onset and pattern were consistent with DILI due to VANZA exposure (**Figure 4**).

¹³ Made by DILI team

(a) Subject (b) (6), healthy volunteer taking VANZA.¹⁴



(b) Subject (b) (6), CF patient taking VANZA.¹⁵



(c) Subject (b) (6) CF patient taking VANZA.¹⁶

¹⁴ [NDA218730 \(218730 - 0028 - \(28\) - 2024-09-23 - ORIG-1 /Clinical/Response To Information Request\) - Response to Clinical Information Request dated September 16, 2024 \(#4\)](#)

¹⁵ [NDA218730 \(218730 - 0015 - \(16\) - 2024-08-02 - ORIG-1 /Clinical/Response To Information Request\) - Response to Clinical Information Request dated 16 July 2024 \(#198\)](#)

¹⁶ [NDA218730 \(218730 - 0028 - \(28\) - 2024-09-23 - ORIG-1 /Clinical/Response To Information Request\) - Response to Clinical Information Request dated September 16, 2024 \(#4\)](#)

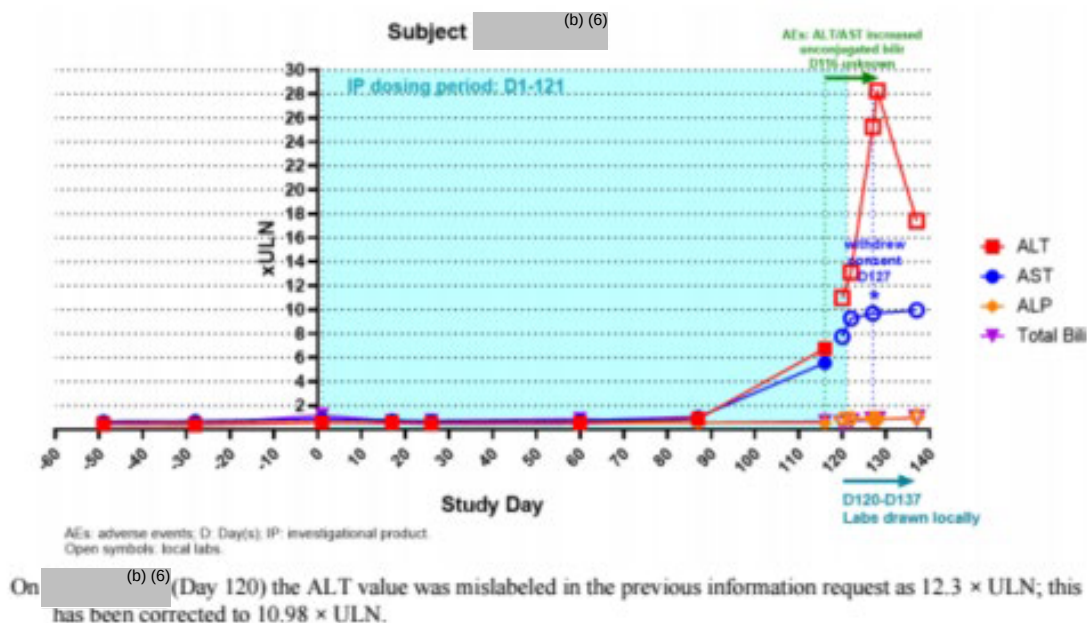


Figure 4: Liver blood test line graphs by study day for three subjects with probable DILI due to VANZA.

IV. Assessment

Vanzacaftor/tezacaftor/deutivacaftor (VANZA) is an oral, fixed dose, triple drug combination for the treatment of patients with cystic fibrosis (CF) due to the F508 del and other disease producing mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. It is similar to another triple combination, Trikafta® (TRK), which was approved in 2019 for CF. The same Sponsor developed VANZA and TRK. VANZA has vanzacaftor (VNZ) and TRK has elxacaftor (ELX), but the other two component drugs are the same or similar for both agents. Both VANZA and TRK have tezacaftor (TZC) and both use ivacaftor (IVA), though VANZA uses the deuterated form of IVA (D-IVA):

Triple agent component drugs

VANZA → VNZ TZC D-IVA

TRK: → ELX TZC IVA

Both agents share the same mechanism of action with IVA or D-IVA enhancing CFTR function while TEZ plus VNZ or ELX increase CFTR stability and deliver to the cell membrane.

All the CFTR modulators whether marketed as single agents or in combination are labeled for hepatotoxicity risk. However, several cases of severe TRK related hepatotoxicity resulting in fatalities have occurred post market and in an IND that aims to expand TRK's indication within the CF population. The severe DILI cases have occurred in CF patients with or without underlying liver disease. DPACC is in the process of adding a box warning and increased liver blood test

monitoring recommendations to the TRK label. For details on these TRK related DILI cases and the DILI Team's assessment of TRK risk, please see our consult for IND 132547.

Not surprisingly, the data from the VANZA NDA also confirm a risk for hepatocellular liver injury. While there were no VANZA liver injury cases meeting Hy's Law, the number exposed to VANZA in the two pivotal trials remains relatively low at less than 500. Imbalances between treatment groups in Temple's Corollary and aminotransferase shift tables are difficult to interpret due to the pivotal trials' study design. The comparator arm was TRK, but all subjects received TRK during a 28-day run-in prior to randomization. There was no washout period between the run-in and starting randomized treatment. TRK latency for liver injury can be short so attributing early elevations in liver enzymes to VANZA may be confounded. Any dropouts during the 28-day run may also create bias. Ultimately, the aggregated study level data (e.g., eDISH, shift tables) did not confirm a lower risk of severe DILI for VANZA compared to TRK. Case level data confirmed three cases of probable hepatocellular DILI due VANZA with substantial ALT increases (15-28 xULN). One subject was a healthy volunteer from a phase 1 study. The two others had liver injuries long enough after the run-in to exonerate TRK.

Overall, the NDA data on DILI risk should not threaten VANZA approvability assuming there was adequate efficacy. However, we suggest labeling VANZA similarly to TRK. The two drug products have similar components, target disease populations, and mechanisms of action. Moreover, the VANZA NDA data do not provide firm evidence that VANZA carries a lower DILI risk than TRK.

V. Recommendations

1. Do not hold up approval for VANZA due to DILI risk if efficacy is adequate.
2. Label VANZA similarly to TRK including the box warning.
3. Consultation with OSE and DPV regarding post market surveillance severe DILI.

Eileen E. Navarro
Almario -S

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Navarro Almario -S
Date: 2024.12.19 09:03:57 -05'00'

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Abbreviations:

ALP or AP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
CDS: Clinical Data Scientist
CF: cystic fibrosis
CFTR: cystic fibrosis transmembrane conductance regulator
D-IVA: deutivacaftor
DB: direct bilirubin
DILI: drug-induced liver injury
eDISH: evaluation for Drug Induced Serious Hepatotoxicity
ELX: elexacaftor
GB: gallbladder
GGT: gamma-glutamyl transferase
ID: identification
INR: international normalized ratio
IP: investigational product
IVA: ivacaftor
LDH: lactate dehydrogenase
NCRT: National Center for Toxicological Research
TB: total bilirubin
TRK: Trikafta® (elexacaftor/tezacaftor/ivacaftor)
TZC: tezacaftor
ULN: upper limit of normal
VANZA: vanzacaftor/tezacaftor/deutivacaftor
VNZ: vanzacaftor

Appendix: Additional Tables and Figures.

Table A: Thirty-six cases assessed as unlikely DILI due to study drug.¹⁷

#	ID	Causality Score*	Alternate diagnosis	Study
	(b) (6)			
1		5	Alcohol	VX20-121-104
2		5	Alcohol	VX20-121-103
3		5	Biliary disease	VX20-121-103
5		5	Cancer pancreas	VX20-121-104
6		5	Cancer pancreas	VX20-121-103
7		5	CF liver disease	VX20-121-104
4		5	Gallstone disease	VX22-121-106
8		5	Gallstone disease	VX20-121-102
9		5	Gallstone disease	VX20-121-102
10		5	Gallstone disease	VX20-121-104
11		5	Infection	VX20-121-102
12		5	Infection	VX20-121-104
13		5	Infection	VX20-121-103
14		5	Infection Antibiotic	VX20-121-102
15		5	Myopathy	VX21-121-006
16		5	Myopathy	VX20-121-104
17		5	Myopathy	VX20-121-102
18		5	Myopathy	VX20-121-104
19		5	Myopathy	VX20-121-104
20		5	Myopathy	VX20-121-104
21		5	Myopathy	VX20-121-104
22		5	Myopathy	VX20-121-103
23		5	Myopathy	VX20-121-104
24		5	Myopathy	VX20-121-103
25		5	Myopathy	VX20-121-103
26		5	Myopathy	VX20-121-103
27		5	Unknown	VX18-561-101
28		5	Unknown	VX20-121-102
29		5	Unknown	VX20-121-102
30		5	Unknown	VX20-121-102
31		5	Unknown	VX20-121-102
32		5	Unknown	VX20-121-103
33		5	Unknown	VX20-121-103
34		5	Unknown	VX20-121-103
35		5	Unknown.	VX20-121-103
36		6	Unknown	VX20-121-104

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

¹⁷ Made by DILI Team.

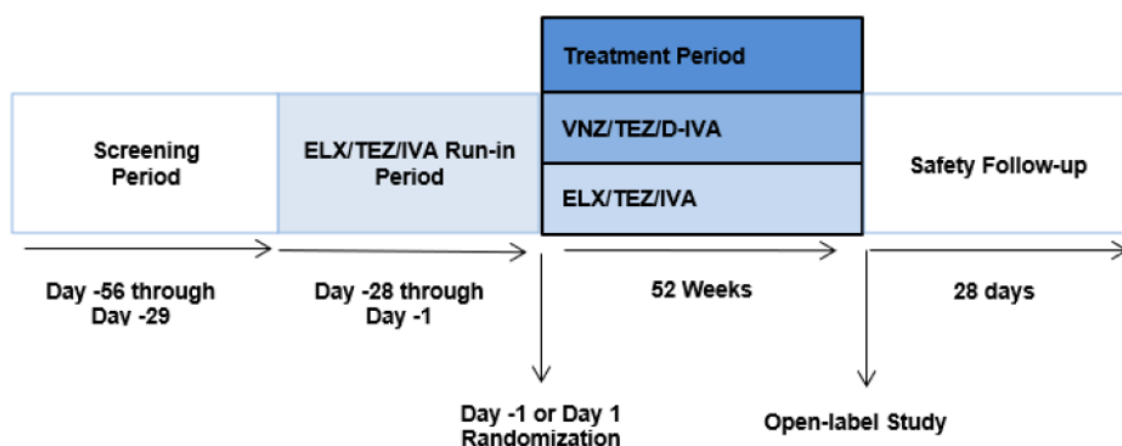
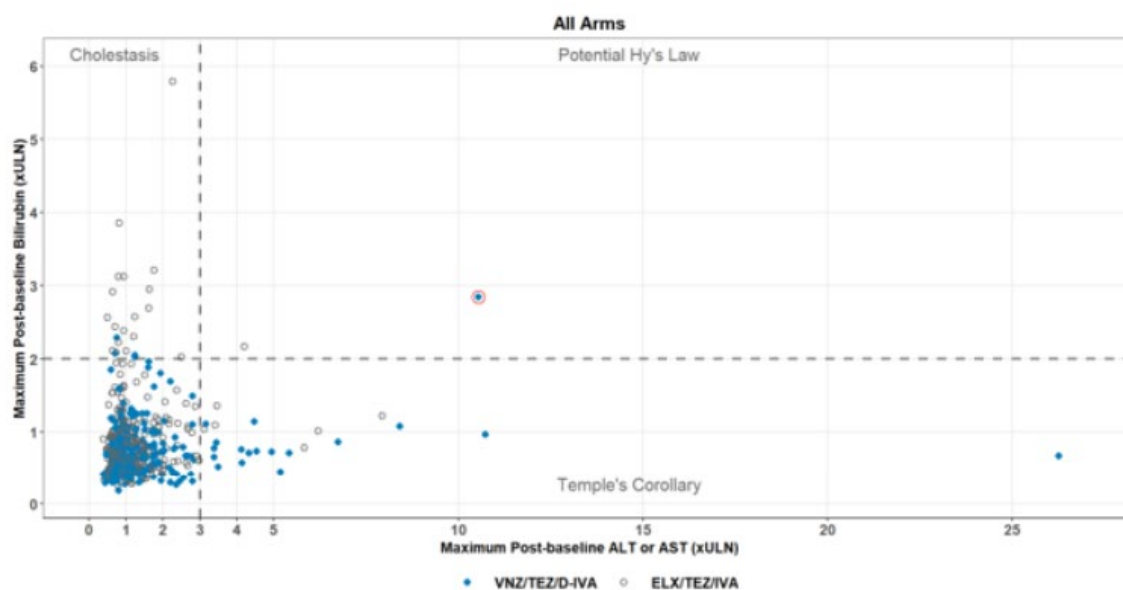


Figure A: Study schematic for Studies 102 and 103.¹⁸



Source: adlb.xpt; Software: R

Quadrant	VNZ/TEZ/D-IVA N=284	ELX/TEZ/IVA N=289
Potential Hy's Law (right upper)	1/284 (0.4)	1/289 (0.3)
Cholestasis (left upper)	4/284 (1.4)	18/289 (6.2)
Temple's corollary (right lower)	17/284 (6)	6/289 (2.1)
Total	22/284 (7.7)	25/289 (8.7)

Source: adlb.xpt; Software: R

Figure B: Hepatocellular DILI screening plot (eDISH) for Study 103.¹⁹ The subject plotting to the potential Hy's law quadrant was on VANZA (red circle), had Gilbert's explaining the hyperbilirubinemia, and TA elevations were not attributable to DILI.

¹⁸ From CDS DILI Planning Meeting, Aug 14, 2024

¹⁹ Made by CDS (AW)

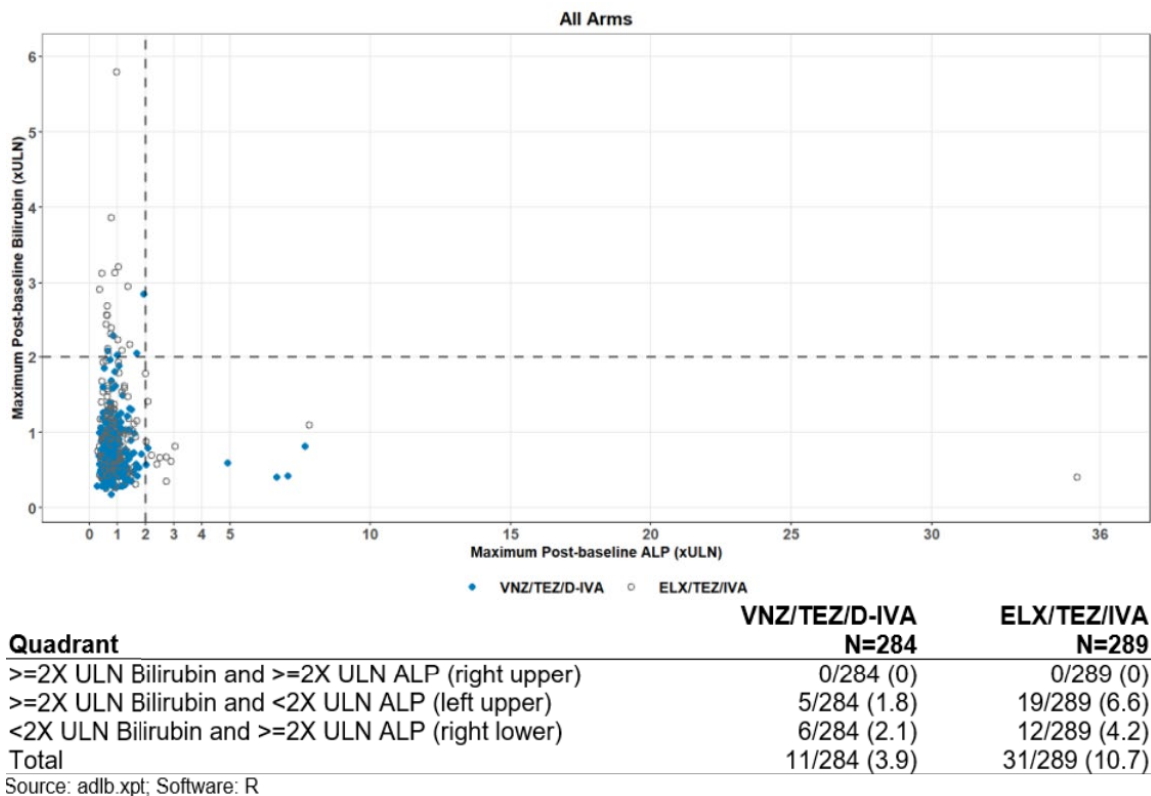


Figure C: Cholestatic DILI screening plot (eDISH) for Study 103.²⁰

²⁰ Made by CDS (AW)

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/s/

EILEEN E NAVARRO ALMARIO
12/19/2024 09:48:05 AM

The Clinical Inspection Summary

Date	December 19, 2024
From	Suyoung Tina Chang, M.D., Medical Officer Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Alison Lennox, M.D., Clinical Reviewer, DPACC Elisabeth Boulos, M.D., Team Leader, DPACC Julianne Lee, PharmD, Regulatory Project Manager, DPACC Division of Pulmonology, Allergy, and Critical Care (DPACC)
NDA #	218730
Applicant	Vertex Pharmaceuticals Inc.
Drug	Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor)
NME (Yes/No)	Yes
Proposed Indication(s)	Cystic fibrosis
Consultation Request Date	June 7, 2024
Summary Goal Date	December 20, 2024
Action Goal Date	December 20, 2024
PDUFA Date	January 2, 2025

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Drs. Brown, Dimango, Keating, Escobar, and Hoppe and the Sponsor Vertex Pharmaceuticals were inspected in support of NDA 218730, covering three Studies: VX20-121-102, VX20-121-103, and VX21-121-105. Based on the inspection results, these studies appear to have been conducted adequately, and the data generated by the clinical investigator sites and submitted by the sponsor appear acceptable in support of this NDA.

II. BACKGROUND

According to the sponsor, Alyftrek (vanzacaftor [VNZ]/ tezacaftor [TEZ]/ deutivacaftor [D-IVA]) is a triple combination therapy comprised of vanzacaftor, a new molecular entity, which acts as a cystic fibrosis transmembrane conductance regulator gene modulator (CFTRm), tezacaftor, which is a previously approved CFTRm, and deutivacaftor, which is a deuterated isotopologue of the previously approved CFTRm ivacaftor. The brand name for tezacaftor is Symdeko, which consists of (TEZ/IVA) and Trikafta (ELX/TEZ/IVA), and the brand name for ivacaftor is Kalydeco. The Sponsor has submitted an application for vanzacaftor (VNZ)/ tezacaftor (TEZ)/ deutivacaftor (D-IVA) triple combination (TC) therapy for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one *F508del* mutation or another responsive mutation in the CFTR gene. The sponsor's clinical development program

consists of three Phase 3 studies: VX20-121-102, VX20-121-103, and VX21-121-105. Five BIMO-Review-Based clinical investigator inspections and a sponsor inspection were requested. The following describes the three studies:

Protocol VX20-121-102: “A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VNZ Combination Therapy in Subjects with Cystic Fibrosis Who Are Heterozygous for *F508del* and a Minimal Function Mutation (F/MF).”

Protocol 102 was a Phase 3 randomized, double-blind, ELX/TEZ/IVA-controlled, parallel group, multi-center study to evaluate the efficacy of vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) in cystic fibrosis (CF) subjects who are heterozygous for *F508del* and a minimal function mutation (F/MF subjects).

Sites: Subjects were randomized at 126 sites in the United States, Europe, Israel, Australia, and New Zealand.

Subjects: A total of 405 subjects were randomized (i.e., 200 subjects received VNZ/TEZ/D-IVA, 205 subjects received ELX/TEZ/IVA), and 367 subjects completed the Treatment Period (i.e., 196 subjects who received VNZ/TEZ/D-IVA, 202 subjects who received ELX/TEZ/IVA).

Study initiation and completion dates: September 14, 2021 (date first eligible subject signed the informed consent form); November 21, 2023 (date last subject completed the last visit)

Database lock date; study unblinding date: December 14, 2023; January 18, 2024

The total study duration was approximately 64 weeks (4 weeks for the Screening Period, 4 weeks for the Run-in Period, 52 weeks for the Treatment Period, and 4 weeks for the Safety Follow-up Period). During the Run-in Period, from Day -28 to Day -1, all subjects received elexacaftor (ELX) 200 mg once daily, tezacaftor (TEZ) 100 mg once daily, and ivacaftor (IVA) 150 mg every 12 hours. Following completion of the Run-in Period, subjects were randomized 1:1 to VNZ (10 mg) /TEZ (50 mg) /D-IVA (125 mg) group or ELX 100 mg/TEZ (50 mg)/IVA (150 mg) group for 52 weeks. Spirometry assessments were conducted in the clinic at Baseline, Day 15, Week 4, Week 8, Week 16, and Week 24.

Key inclusion criteria: Male or female subjects 12 years of age and older and heterozygous for *F508del* and minimal function mutation (F/MF) genotypes and a confirmed diagnosis of cystic fibrosis. Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) through Week 24.

Protocol VX20-121-103: “A Phase 3, Randomized, Double-blind, Controlled Study Evaluating the Efficacy and Safety of VNZ Combination Therapy in Subjects with Cystic Fibrosis Who Are Homozygous for *F508del*, Heterozygous for *F508del* and a Gating Mutation (F/G), or Residual Function (F/RF) Mutation, or Have At Least 1 Other Triple Combination Responsive CFTR Mutation and No *F508del* Mutation.”

Protocol 103 was a Phase 3 randomized, double-blind, ELX/TEZ/IVA-controlled, parallel group, multi-center study to evaluate the efficacy of vanzacaftor/tezacaftor/deutivacaftor (VNZ/TEZ/D-IVA) in subjects with cystic fibrosis (CF) subjects who are homozygous for *F508del*, heterozygous for *F508del* and a gating (F/G) or residual function (F/RF) mutation, or have at least 1 other triple combination responsive (TCR, defined as responsive to elexacaftor/tezacaftor/ivacaftor [ELX/TEZ/IVA]) CFTR mutation and no *F508del* mutation (TCR/non-F).

Sites: Subjects were randomized at 157 sites in the United States, Europe, Israel, Australia, and New Zealand.

Subjects: A total of 574 subjects were randomized (i.e., 285 subjects who received VNZ/TEZ/D-IVA, 289 subjects who received ELX/TEZ/IVA), and 532 subjects completed the Treatment Period (i.e., 259 subjects who received who received VNZ/TEZ/D-IVA, 273 who received ELX/TEZ/IVA).

Study initiation and completion dates: October 27, 2021 (date first eligible subject signed the informed consent form); November 30, 2023 (date last subject completed the last visit)

Database lock date; study unblinding date: December 15, 2023; January 18, 2024

Both Protocols 102 and 103 had similar study designs, except for the genotype of the subject population. Protocol 102 included CF subjects heterozygous for *F508del* and a minimal function mutation (F/MF) genotype, while Protocol 103 included a broader population of mutations: CF subjects homozygous for *F508del*-CFTR mutation (F/F), heterozygous for *F508del* and a minimal function mutation (F/G), heterozygous for the *F508del*-CFTR mutation and a residual function mutation (F/RF), or triple combination responsive (TCR)/non-F genotypes.

Key inclusion criteria: Male or female subjects 12 years of age and older and homozygous for *F508del*, heterozygous for *F508del* and either a gating mutation (F/G) or residual function (F/RF) mutation, or who have at least 1 other triple combination responsive (TCR) mutation identified as responsive to ELX/TEZ/IVA and no *F508del* mutation (TCR/non-F). Please see protocol for full details pertaining to eligibility criteria.

Primary efficacy endpoint: Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) through Week 24.

Protocol VX21-121-105: “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.”

Protocol 105 was an open-label study to evaluate the pharmacokinetic (PK) of VX-121, tezacaftor (TEZ), deutivacaftor (D-IVA), and relevant metabolites when dosed in triple combination (TC) and to evaluate the safety and tolerability of VX-121/TEZ/DIVA.

Sites: Subjects were enrolled at 32 sites in North America, Europe, and Australia.

Subjects: A total of 405 subjects were randomized (i.e., 200 subjects who received VNZ/TEZ/D-IVA, 205 subjects who received ELX/TEZ/IVA), and 367 subjects completed the Treatment Period (i.e., 196 who received VNZ/TEZ/D-IVA, 202 subjects who received ELX/TEZ/IVA).

Study initiation and completion dates: June 21, 2022 (date first eligible subject signed the informed consent form); November 27, 2023 (date last subject, last visit)

Database lock date; study unblinding date: December 15, 2023; January 18, 2024

This was a multicohort study evaluating the PK, safety, tolerability, and efficacy of VNZ/TEZ/D-IVA therapy in CF subjects aged 1 through 11 with at least 1 triple combination responsive mutation in the CFTR gene.

This was a two-part study that included Parts A and B divided into 3 cohorts each based on age. Cohort 1 included subjects 6 through 11 years of age. Cohort 2 included subjects 2 through 5 years of age, and Cohort 3 included subjects 1 to less than 2 years of age. In general, a small number of subjects, between 12 and 20 subjects, were enrolled in Part A and administered VX-121/TEZ/D-IVA for 22 days. Once the results were reviewed for Part A, then a larger number of subjects, approximately 65 subjects, were planned for enrollment in Part B and received VX-121/TEZ/D-IVA for least 24 weeks. The review division is mostly interested in Cohort B1, which evaluated subjects 6 through 11 years of age. Doses were dependent on weight of the subject. If the subject weighed <40 kg, then the subject received VX-121 12 mg daily, TEZ 60 mg daily, and D-IVA 150 mg daily. If the subject weighed ≥40 kg, then the subject received VX-121 20 mg daily, TEZ 100 mg daily, and D-IVA 150 mg daily. Subjects had a safety follow-up visit 28 days after the last dose.

Key inclusion criteria for Cohort B1: Male or female subjects with CF aged 6 through 11 years with at least one triple combination responsive mutation (defined as responsive to ELX/TEZ/IVA). Please see protocol for full details pertaining to eligibility criteria.

Key secondary efficacy endpoint: Absolute change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV1) through Week 24.

III. RESULTS (by site):

1. Dr. Cynthia Brown

Site #41 (Protocols VX20-121-102 and VX20-121-103)

1120 W. Michigan Street

Indianapolis, IN 46202

PDUFA Inspection Dates: July 8-11, 2024

For Protocol VX20-121-102, 5 subjects were screened, 4 subjects were randomized, and all 4

subjects completed the study. For Protocol VX20-121-103, 6 subjects were screened, and all 6 subjects were enrolled, randomized and completed the study.

An audit of the study records was conducted for all 5 randomized subjects for Protocol VX20-121-102 and for all 6 randomized subjects for Protocol VX20-121-103. Records reviewed included, but were not limited to, protocol versions, protocol adherence, eligibility records, informed consent forms, sponsor and IRB communications, FDA 1572s, financial disclosures, monitoring procedures, investigational product accountability, training, electronic case report forms, adverse event reporting, and spirometry reports. Source records for subjects were in paper format.

The Day 1 and Week 24 forced expiratory volume in 1 second (FEV1) values were verified by comparing the data in the line listings submitted by the Sponsor with the site's source documents. No discrepancies were noted. There was no evidence of underreporting of adverse events.

2. Dr. Emily Dimango

Site #51 (Protocol VX20-121-102)
Columbia University Medical Center
622 West 168th Street
New York, NY 10032

PDUFA Inspection Dates: August 5-13, 2024

For Protocol VX20-121-102, 8 subjects were screened, 8 subjects were enrolled and randomized, and 7 subjects completed the treatment period. According to the source documents and the sponsor's data line listings, one subject was lost to follow-up.

An audit of the study records was conducted for all 8 randomized subjects. Records reviewed included, but were not limited to, protocol versions, IRB approval letters and correspondence, subject medical records, financial disclosure reports, FDA1572s, drug accountability records, monitoring reports, informed consent forms, site signature and responsibility logs, site training documentation, test article accountability, dosing, eligibility records, adverse event reports, and spirometry reports. Source records for subjects were in paper format.

The Day 1 and Week 24 FEV1 values were verified by comparing the data in the line listings submitted by the Sponsor with the site's source documents. No discrepancies were noted. There was no evidence of underreporting of adverse events.

3. Dr. Claire Keating

Site #51 (Protocol VX20-121-103)
Columbia University Medical Center
622 West 168th Street
New York, NY 10032

PDUFA Inspection Dates: August 13-16, 2024

For Protocol VX20-121-103, 6 subjects were screened, enrolled, randomized, and completed

the study.

An audit of the study records was conducted for all 6 randomized subjects. Records reviewed included, but were not limited to, protocol versions, IRB approval letters and correspondence, eligibility records, financial disclosure reports, FDA1572s, drug accountability records, monitoring reports, informed consent forms, site training documentation, test article accountability, adverse event reports, and spirometry reports. Source records for subjects were in paper format.

The Day 1 and Week 24 FEV1 values were verified by comparing the data in the line listings submitted by the Sponsor with the site's source documents. No discrepancies were noted. There was no evidence of underreporting of adverse events.

4. Dr. Hugo Escobar

Site #21 (VX21-121-105, Cohort B1)
2401 Gillham Road.
Kansas City, MO 64108

PDUFA Inspection Dates: August 13-15, 2024

For Protocol VX21-121-105 (Cohort B1), 4 subjects were screened, and all 4 subjects were enrolled, randomized and completed the study.

An audit of the study records was conducted for all 4 randomized subjects. Records reviewed included, but were not limited to, protocol versions, IRB approval letters and correspondence, subject medical records, financial disclosure reports, FDA1572s, drug accountability records, monitoring reports, informed consent form, site signature and responsibility logs, site training documentation, investigational product accountability, dosing, eligibility records, concomitant medications, adverse event reports, and spirometry reports. Source records for subjects were in paper and electronic format.

The Day 1 and Week 24 FEV1 values were verified by comparing the data in the line listings submitted by the Sponsor with the site's source documents. No discrepancies were noted. There was no evidence of underreporting of adverse events.

5. Dr. Jordanna Hoppe

Site #74 (Protocol VX121-105, Cohort B1)
13123 East 16th Avenue, 8395
Aurora, CO 80045

PDUFA Inspection Dates: July 18-22, 2024

For Protocol VX121-105 (Cohort B1), 6 subjects were screened, and all 6 subjects were enrolled, randomized and completed the study.

An audit of the study records was conducted for all 6 randomized subjects. Records reviewed included, but were not limited to, protocol versions, IRB approval letters and correspondence, subject medical records, financial disclosure reports, FDA1572s, drug accountability records,

monitoring reports, informed consent form, site signature and responsibility logs, site training documentation, test article accountability, dosing, eligibility records, adverse event reports, and spirometry reports. Source records for subjects were in paper and electronic format.

The Day 1 and Week 24 FEV1 values were verified by comparing the data in the line listings submitted by the Sponsor with the site's source documents. No discrepancies were noted. There was no evidence of underreporting of adverse events.

6. Vertex Pharmaceuticals Inc.

50 Northern Avenue
Boston, MA 02210-1862

PDUFA Inspection Dates: July 18-August 1, 2024

Documents reviewed included, but were not limited to, organizational charts, financial disclosure forms, Independent Data Monitoring Committee Charter and meeting minutes, study protocol, safety reporting, safety data review meeting minutes, training records, monitor selection processes, CVs, and site monitoring records for 5 clinical investigator sites (sites #041 and #051 for Studies -102 and -103, and sites #074 and #021 for Study -105).

The inspection found the site monitoring and general oversight by the sponsor to be adequate. The sponsor did not identify any serious noncompliance at any of the active clinical investigator sites, and none of the sites were terminated. In general, the sponsor appeared to be in compliance with Good Clinical Practice and FDA regulations. No significant concerns regarding the conduct or oversight of studies were identified.

{See appended electronic signature page}

Suyoung Tina Chang, M.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Jenn Sellers, M.D., Ph.D.
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Office of Scientific Investigations

CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: December 17, 2024

To: Julianne Lee, PharmD
Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care (DPACC)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Mary Carroll, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Quynh-Nhu Capasso, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): ALYFTREK (vanzacaftor, texacaftor, and deutevacaftor tablets)

Dosage Form and Route: for oral use

Application Type/Number: NDA 218730

Applicant: Vertex Pharmaceuticals Incorporated

1 INTRODUCTION

On May 3, 2024, Vertex Pharmaceuticals Incorporated submitted for the Agency's review an original New Drug Application (NDA) 218730 for ALYFTREK (vanzacaftor, texacaftor, deutivacaftor) tablets, for oral use. The proposed indication for ALYFTREK (vanzacaftor, texacaftor, deutivacaftor) is for the treatment of cystic fibrosis (CF) in patients aged 6 years and older who have at least one F508del mutation or another responsive mutation in the CFTR gene.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Critical Care (DPACC) on May 10, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for ALYFTREK (vanzacaftor, texacaftor, and deutivacaftor tablets) for oral use.

2 MATERIAL REVIEWED

- Draft ALYFTREK (vanzacaftor, texacaftor, and deutivacaftor) PPI received on May 3, 2024, and received by DMPP and OPDP on December 5, 2024.
- Draft ALYFTREK (vanzacaftor, texacaftor, and deutivacaftor) Prescribing Information (PI) received on May 3, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on December 5, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language

- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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MARCIA B WILLIAMS
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LASHAWN M GRIFFITHS
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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: December 12, 2024

To: Julianne Lee, Regulatory Project Manager
Division of Pulmonology and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for ALYFTREK® (vanzacaftor, tezacaftor, and deutivacaftor tablets), for oral use

NDA: 218730

Background:

In response to DPACC's consult request dated May 9, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), and carton and container labeling for the original NDA submission for ALYFTREK® (vanzacaftor, tezacaftor, and deutivacaftor tablets), for oral use (Alyftrek).

PI/PPI:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on December 5, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed PPI (will now be a Medication Guide due to addition of Boxed Warning), and comments will be sent under separate cover.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on December 9, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov

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/s/

QUYNH-NHU D CAPASSO
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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	December 9, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 218730
Product Name, Dosage Form, and Strength:	Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor) tablets, 4 mg/20 mg/50 mg per tablet and 10 mg/50 mg/125 mg per tablet
Applicant Name:	Vertex Pharmaceuticals Incorporated (Vertex)
FDA Received Date:	November 18, 2024
TTT ID #:	2024-9379-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

Vertex Pharmaceuticals Incorporated submitted revised container labels and carton labeling received on November 18, 2024 for Alyftrek. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for Alyftrek (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

We previously recommended Vertex “Remove the dosage statements: “Take Three Tablets Once a Day” and Take Two Tablets Once a Day.” However, Vertex added a clarification to the dosage statement to allow for alternative dosing scenarios, i.e., “Take three tablets once a day or as directed by your healthcare provider” and “Take two tablets once a day or as directed by your healthcare provider.” Vertex provided the rationale that the recommended dosing is substantially different than prior modulator products and requested to keep the proposed language (in addition to the clarification statement) to reduce the likelihood of a patient inadvertently taking Alyftrek more than once daily.

We further recommended “Remove the Day 1, Day 2, etc., the (b) (4) and the circles that are used to group sets of two or three tablets.” Vertex removed the (b) (4) to allow for alternative dosing scenarios and kept the ‘Day 1, Day 2’ and the circles around the group.

Additionally, to inform our review, we searched FAERS to determine if we have received reports of medication errors associated with wrong dose in relation to special dosing populations/ available packaging presentations with the Vertex product Trikafta (NDA 212273) which has similar packaging presentations and dosing considerations. We did not identify medication error cases relevant to this review. Therefore, we find Vertex’s proposals acceptable at this time.

We note that Vertex Pharmaceuticals Incorporated implemented all of our other recommendations and we have no additional recommendations at this time.

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^a Owens, L. Label and Labeling Review for Alyftrek (NDA 218730). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 OCT 02. TTT ID: 2024-9379.

Appendix B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

On December 6, 2024, we searched FAERS using the criteria in the table below and identified 55 cases. We individually reviewed the cases and limited our analysis to cases that described errors possibly associated with wrong dose in relation to special dosing populations. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.^b We did not identify cases with errors related to special dosing populations.

Table 3. Criteria Used to Search FAERS	
Initial FDA Receive Dates:	Cumulative – December 6, 2024
Product Name:	Trikafta
Product Active Ingredient (PAI):	elexacaftor, tezacaftor, and ivacaftor; ivacaftor
Event:	SMQ <i>Medication errors</i> (Narrow)
Country (Derived):	USA

B.2 Results

Our search identified 55 cases, of which none described errors relevant for this review.

B.3 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at: <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

^b The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

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DAMON A BIRKEMEIER
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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	October 2, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 218730
Product Name, Dosage Form, and Strength:	Alyftrek (vanzacaftor, tezacaftor, and deutevacaftor) tablets, 4 mg/20 mg/50 mg per tablet and 10 mg/50 mg/125 mg per tablet
Product Type:	Multiple Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant Name:	Vertex Pharmaceuticals Incorporated (Vertex)
FDA Received Date:	May 2, 2024
TTT ID #:	2024-9379
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 INTRODUCTION

As part of the approval process for Alyftrek (vanzacaftor, tezacaftor, and deutivacaftor) tablets, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Alyftrek Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 218730.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B

3 CONCLUSION

The proposed Alyftrek Prescribing Information (PI), Patient Package Insert (PPI), container labels, and carton labeling may be improved to promote safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error for the Division of Pulmonology, Allergy, and Critical Care (DPACC) in Section 4 and for Vertex Pharmaceuticals Incorporated in Section 5.

4 RECOMMENDATIONS FOR THE DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

Table 2. Identified Issues and Recommendations for the Division of Pulmonology, Allergy, and Critical Care (DPACC)		
IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues		
As currently presented, the proprietary name is denoted by the placeholder “tradenam”.	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our July 24, 2024, proprietary name request conditionally acceptable letter informing you that the proprietary name, Alyftrek, was found conditionally acceptable. We recommend replacing the placeholder “tradenam” with the conditionally acceptable proprietary name, Alyftrek, and use the intend-to-market presentation of the

Table 2. Identified Issues and Recommendations for the Division of Pulmonology, Allergy, and Critical Care (DPACC)		
IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
Highlights of Prescribing Information		
As currently presented, the Dosage and Administration table contain the symbols “≥ and <”.	Error prone symbols may lead to misinterpretation and medication error.	We recommend replacing the symbols with their intended meanings.
Full Prescribing Information – Section 2 Dosage and Administration		
As currently presented, the Dosage and Administration tables contains the symbols “≥ and <”.	Error prone symbols may lead to misinterpretation and medication error.	We recommend replacing the symbols with their intended meanings.
Patient Package Insert (PPI)		
Under the header “How should I take...” the dosage statements: (b) (4) (b) (4) are listed.	These statements do not encompass all potential dosing scenarios (i.e., dosage modifications for patients taking CYP3A inhibitors) and therefore may lead to confusion and wrong dose errors for some patients.	Remove the dosage statements: (b) (4)

5 RECOMMENDATIONS FOR VERTEX PHARMACEUTICALS INCORPORATED

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	As currently presented, the proprietary name is denoted by the placeholder “tradenam”.	We are unable to assess the prominence and readability of the intended presentation of the proprietary name.	We reference our July 24, 2024, proprietary name request conditionally acceptable letter informing you that the proprietary name, Alyftrek, was found conditionally acceptable. We recommend replacing the placeholder “tradenam” with the conditionally acceptable proprietary name, Alyftrek, and use the intend-to-market presentation of the proprietary name (font, color, etc.) so that we may adequately evaluate your labels and labeling.
2.	It is not immediately clear that the designated strength (i.e., 4 mg/20 mg/50 mg and 10 mg/50 mg/125 mg) is per tablet.	Failure to clearly express the product strength in 4 mg/20 mg/50 mg and 10 mg/50 mg/125 mg per single unit tablet may lead to wrong dose errors.	We recommend revising the strength statements “4 mg/20 mg/50 mg” and “10 mg/50 mg/125 mg” to state “4 mg/20 mg/50 mg per tablet” and “10 mg/50 mg/125 mg per tablet” to make it clear that the designated strength is per tablet so there is no confusion as to how much product is contained in a single tablet as compared to the total contents of the entire blister card. See Guidance for Industry: <i>Safety Considerations for Container Labels and Carton</i>

Table 3. Identified Issues and Recommendations for Vertex Pharmaceuticals Incorporated (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			<i>Labeling Design to Minimize Medication Errors (May 2022).</i> ^a
3.	The container labels and carton labeling contain the dosage statements: “Take Three Tablets Once A Day” and “Take Two Tablets Once a Day”.	These statements do not encompass all potential dosing scenarios (i.e., dosage modifications for patients taking CYP3A Inhibitors) and therefore may lead to confusion and wrong dose errors for some patients.	Remove the dosage statements: “Take Three Tablets Once A Day” and “Take Two Tablets Once a Day”.
Container Labels			
1.	The container labels include the words “Day 1, Day 2, etc.”, (b) (4), and circles to group sets of two or three tablets.	This format does not encompass all potential dosing scenarios (i.e., dosage modifications for patients taking CYP3A Inhibitors) and therefore may lead to confusion and wrong dose errors for some patients.	Remove the Day 1, Day 2, etc., the (b) (4) and the circles that are used to group sets of two or three tablets.
Carton Labeling			
1.	As currently presented, the large orange graphic containing the net quantity competes with the prominence of the proprietary name, established name, and strength on the Principal Display Panel (PDP).	The proprietary name and established name along with the product strength, route of administration, and warnings or cautionary statements should be the most prominent information on the PDP.	Decrease the prominence of your orange graphic containing the net quantity relative to the prominence of the proprietary name, established name, and strength on the PDP needed for proper identification and use of your proposed product in accordance with 21 CFR 201.15(a)(6).

^a Guidance for Industry: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. 2022. Available from: <https://www.fda.gov/media/158522/download>.

APPENDICES: METHODS AND RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Alyftrek received on May 2, 2024 from Vertex Pharmaceuticals Incorporated.

Table 4. Relevant Product Information for Alyftrek																
Initial Approval Date	N/A															
Active Ingredient	vanzacaftor, tezacaftor, and deutivacaftor															
Indication	treatment of cystic fibrosis (CF) in people with CF aged 6 years and older who have at least one F508del mutation or another responsive mutation in the CFTR gene															
Dosage Form	tablets															
Strength	4 mg/20 mg/50 mg per tablet and 10 mg/50 mg/125 mg per tablet															
Route of Administration	oral															
Dose and Frequency	(b) (4) Dosage Modification for People with CF Taking Drugs that are CYP3A Inhibitors <table><tr><th colspan="4">Table 2: Dosing Schedule for Concomitant Use of [TRADENAME] with Moderate or Strong CYP3A Inhibitors</th></tr><tr><th>Age</th><th>Weight</th><th>Moderate CYP3A Inhibitors</th><th>Strong CYP3A Inhibitors</th></tr><tr><td colspan="4"> (b) (4) </td></tr></table>				Table 2: Dosing Schedule for Concomitant Use of [TRADENAME] with Moderate or Strong CYP3A Inhibitors				Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors	(b) (4)			
Table 2: Dosing Schedule for Concomitant Use of [TRADENAME] with Moderate or Strong CYP3A Inhibitors																
Age	Weight	Moderate CYP3A Inhibitors	Strong CYP3A Inhibitors													
(b) (4)																
How Supplied	blister pack sealed into a printed wallet, containing vanzacaftor, tezacaftor, deutivacaftor fixed-dose combination tablets. Four such wallets are placed in a printed outer carton. <u>4 mg/20 mg/50 mg</u> : carton containing 84 tablets (4 wallets each containing 21 tablets) <u>10 mg/50 mg/125 mg</u> : carton containing 56 tablets (4 wallets each containing 14 tablets)															
Storage	20°C - 25°C (68°F - 77°F); excursions permitted to 15°C - 30°C (59°F - 86°F) [see USP Controlled Room Temperature]															

Table 4. Relevant Product Information for Alyftrek		
Container Closure	(b) (4)	

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Alyftrek labels and labeling submitted by Vertex Pharmaceuticals Incorporated.

- Prescribing Information received on May 2, 2024, available from <\\CDSESUB1\EVSPROD\nda218730\0001\m1\us\draft-annot-labeling-text-uspi.pdf>
- Patient Package Insert received on May 2, 2024, available from <\\CDSESUB1\EVSPROD\nda218730\0001\m1\us\draft-labeling-text-ppi-clean.pdf>
- Container labels received on May 2, 2024
- Carton labeling received on May 2, 2024

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^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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Interdisciplinary Review Team for Cardiac Safety Studies

QT Study Review

Submission	NDA 218730
Submission Number	1
Submission Date	5/2/2024
Date Consult Received	5/14/2024
Drug Name	vanzacaftor/tezacaftor/deutivacaftor
Indication	Treatment of Cystic Fibrosis
Therapeutic Dose	20 mg vanzacaftor in combination with tezacaftor and deutivacaftor.
Clinical Division	DPACC
Protocol Review	Protocol Review ; Revised protocol review

Note: Any text in the review with a light background should be considered to be copied from the applicant's document.

This review responds to your consult dated 5/14/2024 regarding the applicant's QT evaluation. We reviewed the following materials:

- Previous IRT review dated [02/16/2021](#); [05/10/2023](#); [09/11/2023](#) in DARRTS;
- Clinical study report #VX22-121-013 (NDA218730 / eCTD0001; [link](#));
- Cardiac safety report #VX22-121-013 (NDA218730 / eCTD0001; [link](#));
- Applicant's proposed vanzacaftor drug label (NDA218730 / eCTD0001; [link](#));
- [SYMDEKO® \(tezacaftor/ivacaftor\) drug label](#);
- [Ivacaftor drug label](#); and
- Highlights of clinical pharmacology and cardiac safety (NDA218370 / eCTD0003; [link](#)).

1 SUMMARY

Vanzacaftor (VNZ) monotherapy did not prolong the QTcF interval in this TQT study—see Table 1 for overall results.

The clinical study VX22-121-013 was a double-blind, randomized, placebo- and positive-controlled, parallel with nested crossover, multiple-dose, single-center electrocardiogram (ECG) study investigating the effect of vanzacaftor (hereafter referred to as VNZ) monotherapy on the QT/QTc interval in healthy male and female subjects aged 18 to 45 years, inclusive. Subjects were randomized 2:1:1 to 1 of 3 groups (Groups 1, 2A, or 2B). The highest dose of 60 mg provided 1.3-fold high clinical exposure. Data were analyzed using exposure-response analysis as the primary analysis, which did not suggest that VNZ is associated with significant QTc prolonging effect at both therapeutic (20 mg QD in triple combination with TEZ/D-IVA) and supratherapeutic (60 mg QD) doses (refer to section 4.5). The findings of the primary analysis are further supported by the lack of

QTc prolongation in by-time (refer to section 4.3) and categorical analysis (refer to section 4.4).

Table 1: Summary of findings

Table 1: Summary of findings

QT assessment pathway	☒ Thorough QT study ☐ Substitute for thorough QT study (5.1) ☐ Alternative QT study when a thorough QT study is not feasible (6.1)				
Clinical QT study findings	- The high clinical exposure scenario for VNZ is co-administration with TEZ/D-IVA in the presence of a strong CYP3A4 inhibitor. The steady-state Cmax of VNZ in the high clinical exposure scenario is 3.89 µg/mL in Cystic fibrosis (CF) patients based on PK simulations using the Study 007 results. (Section 3.1) - The highest dose of 60 mg of exposure of VNZ in the TQT study, covers the maximum anticipated high exposure (Cmax), when administered in the presence of strong CYP3A4 inhibitor subjects by 1.3-fold in clinical QT study.				
	ECG parameter	Treatment	Concentration	ΔΔQTcF (msec)	90% CI (msec)
	ΔΔQTcF	20 mg QD	812 ng/mL	0.3	(-2.2 to 2.8)
	ΔΔQTcF	High clinical exposure	3890 ng/mL	0.2	(-2.3 to 2.7)
	ΔΔQTcF	60 mg QD	4920 ng/mL	0.2	(-2.6 to 2.9)
In vitro and In vivo findings	Integrated nonclinical risk assessment was not performed.				

1.1 RESPONSES TO QUESTIONS POSED BY APPLICANT

Not applicable.

1.2 COMMENTS TO THE REVIEW DIVISION

Not applicable.

2 RECOMMENDATIONS

2.1 ADDITIONAL STUDIES

No additional QTc evaluation is needed for this product.

2.2 PROPOSED LABEL

Below are proposed edits to the label submitted to eCTD 0001 ([link](#)) from the CS-IRT.

Our changes are highlighted ([addition](#), ~~deletion~~). Each section is followed by a rationale for the changes made. Please note that this is a suggestion only and that we defer final labeling decisions to the Division.

12.2 Pharmacodynamics

Cardiac Electrophysiology

At ^{(b) (4)} times the maximum recommended dose of vanzacaftor, clinically significant QTc interval prolongation was not observed. Similarly, in separate studies of tezacaftor and ivacaftor evaluating up to 3 times the respective maximum recommended doses, clinically significant QTc interval prolongation was not observed.

(b) (4)

Reviewer's comment: We propose to describe the exposure coverage in terms of dose to be consistent for all three products in the combination.

3 APPLICANT'S SUBMISSION

3.1 OVERVIEW

Vertex Pharmaceuticals Inc. is developing a triple combination containing VNZ (VX-121; VRT-1725010), tezacaftor, and deutivacaftor for the treatment of cystic fibrosis in patients with at least one F508del allele. The proposed therapeutic dose is triple combination of ^{(b) (4)}

We previously agreed that additional characterization of the effects on the QTc interval for tezacaftor and deutivacaftor was not necessary as the exposure was covered by already approved products and we are not aware of any examples of deuterated products having changes in direct ion channel interaction compared to their non-deuterated counterparts. (DARRTS [02/16/2021](#); [09/05/2023](#))

The applicant previously proposed to use data from VX17-121-001 as a substitute for a TQT study to characterize the effects for VNZ (DARRTS [02/16/2021](#)). The applicant subsequently proposed a parallel, nested cross-over TQT study because the previous data would not provide sufficient exposure coverage. We agreed with the proposed TQT study design but recommended using an average baseline for the parallel group. (DARRTS [05/10/2023](#)) The applicant revised the statistical analysis plan incorporating our recommendation. (DARRTS [09/11/2023](#))

The protocol and SAP have not been changed following our previous review.

3.1.1 Clinical pharmacology

See highlights of clinical pharmacology and cardiac safety ([link](#)).

Highest proposed clinical dose is VNZ (Form D) 20 mg once daily (QD) in triple combination (TC) with tezacaftor (TEZ) 100 mg QD and deuterivacaftor (D-IVA) 250 mg QD. The highest dose of VNZ evaluated is 60 mg QD as monotherapy.

The median T_{max} of VNZ was approximately 7.8 hours following both doses and mean VNZ t_{1/2} is 54.0 hours.

VNZ exposure was generally dose proportional between doses of 10 and 60 mg QD.

Following the supratherapeutic dose of VNZ, C_{max} values reached a mean value of 4.92 µg/mL, with the highest observed individual concentration at 9.11 µg/mL.

Age, gender, race, moderate hepatic impairment, and moderate and mild renal impairment has no to minimal effect on the VNZ exposures based on PopPK analysis.

The high clinical exposure scenario for VNZ is co-administration with TEZ/D-IVA in the presence of a strong CYP3A inhibitor. The steady-state C_{max} of VNZ in the high clinical exposure scenario is 3.89 µg/mL in CF patients based on PK simulations.

Table 2: Summary of dose and exposure assessment

		Mean C _{max}
Highest therapeutic or clinical trial dosing regimen	20 mg QD in TC with TEZ/D-IVA, oral tablets (form D)	812 ng/mL (C _{max,ss})
Applicant's High clinical exposure scenario	4.8-fold increase with strong CYP3A4 inhibition	3890 ng/mL
Highest dose in QT assessment	60 mg QD, oral tablets (form A)*	4920 ng/mL
C_{max} Ratio	~ 1.3	

*Clinical data showed VNZ (Form D) 20 mg yields similar exposures to VNZ (Form A) 10 mg.

3.1.2 Nonclinical Safety Pharmacology Assessments

hERG: The applicant evaluated the effects of VNZ on hERG current in the study report (170627.WFJ, [link](#)). The hERG current was assessed at near physiological temperature (33 to 35°C) using manual patch clamp assay.

The reduction in hERG current at the highest concentration 0.9 µM tested was 57.5%. This concentration provides 14-fold (MW: 617.76 g/mol; PB: >99.9%) the high clinical exposure scenario (see Table 2). The hERG IC₅₀ was 0.7 uM (h=1.5), which corresponds to a hERG safety margin of 11-fold using the high clinical exposure scenario (see Table 2), when using a protein binding of 99%.

In vivo: The in vivo QT study (863-495, [link](#)) assessed the effects of VNZ on ECG parameters following single oral doses to conscious telemetrized male dogs (n=4). The free concentration of the highest dose (4 mg/kg) at 6 h post-dose in the study is (total: 7133 ng/mL; PB > 99.9%), which corresponds to 1.8-fold the free C_{max} of the high clinical exposure scenario. No changes in QTc, HR, PR, or QRS were observed at the highest dose.

Reviewer's comment: When the free fraction is <1%, we set it to 1% to account for uncertainties in the assessment (ICH E14/S7B Q&A 1.2). The protein binding of VNZ was extremely high (>99.9%) in human plasma as well as in other species. If the lower bound of the protein binding measured is used, the hERG safety margin is 10x larger, which is more consistent with the clinical data and lack of a QTc prolongation observed in the in vivo dog study.

3.2 APPLICANT'S RESULTS

3.2.1 By-Time Analysis

The primary analysis for VNZ was based on exposure-response analysis, please see section 3.2.3 for additional details.

In the applicant's by-time analysis, the upper bound of the 2-sided 90% CI for QTcF remained below 10 ms at all time points for both VNZ therapeutic (10 mg) and supratherapeutic doses (60 mg). VNZ at the studied doses did not have a clinically relevant effect on heart rate, PR and QRS intervals.

Reviewer's comment: MMRM method for by-time analysis was used by both applicant and reviewer. Results from FDA reviewer's analysis are similar to applicant's results, where the upper bound of the 2-sided 90% CI for QTcF remained below 10 ms at all time points for both VNZ therapeutic (10 mg) and supratherapeutic doses (60 mg). Please see section 4.3 for additional details.

3.2.1.1 Assay Sensitivity

The results of the applicant's analysis show that the predicted QTc effect (6.93 ms [90% CI: 5.47 to 8.39]) was above 5 ms at the geometric mean peak moxifloxacin concentration (1514.98 ng/mL).

Reviewer's comment: The results of the reviewer's analysis are similar to the applicant's conclusion on the assay sensitivity. Please see section 4.5.1.1 for additional details.

3.2.1.1.1 QT Bias Assessment

No QT bias assessment was conducted by the applicant.

3.2.2 Categorical Analysis

There were no significant outliers per the applicant's analysis for QTc (i.e., >500 msec or >60 msec over baseline), HR (>100 beats/min), PR (>200 msec and 25% over baseline), and QRS (>120 msec and 25% over baseline) in the VNZ treatment groups.

Reviewer's comment: Reviewer's analysis results are similar to applicant's analysis results. There were no significant outliers in terms of QTcF, HR, PR and QRS analysis. Please see section 4.4 for details.

3.2.3 Exposure-Response Analysis

The applicant used the model recommended in the white paper. The results of the applicant's analysis show an absence of significant QTc prolongation. The effect on $\Delta\Delta\text{QTcF}$ was predicted to be 0.27 ms (90% CI: -2.24 to 2.78) for 10 mg (677.09 ng/mL)

and 0.17 ms (90% CI: -2.52 to 2.86) for 60 mg (4718.25 ng/mL), respectively. Based on this concentration-QTc analysis, a QTcF effect ($\Delta\Delta\text{QTcF}$) exceeding 10 ms can be excluded within the full range of observed VNZ plasma concentrations up to ~9110 ng/mL

Reviewer's comment: Both applicant and Reviewer used the model recommended in the white paper. The overall results of the reviewer analysis on QTcF at the geometric mean C_{max} after VNZ doses of 10 mg and 60 mg are similar to the applicant predicted values, where the upper bound of 90% CI of $\Delta\Delta\text{QTcF}$ is below 10 msec at C_{max} for both 10 and 60 mg doses.

3.2.4 Safety Analysis

There were no deaths or serious adverse events in the study. One participant discontinued treatment in the VNZ group due to an adverse event of rash maculopapular. None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e., seizure, significant ventricular arrhythmias, or sudden cardiac death) occurred in this study.

4 REVIEWERS' ASSESSMENT

4.1 EVALUATION OF THE QT/RR CORRECTION METHOD

The applicant used QTcF for the primary analysis. This is acceptable, as no large increases or decreases in heart rate (i.e., $|\text{mean}| > 10$ beats/min) were observed (see section 4.3.2).

4.2 ECG ASSESSMENTS

4.2.1 Overall

Digital ECG waveforms were submitted for review. The ECGs were read semi-automatically by a central reader blinded to treatment, visit, day, time point and subject information. Compared to the ECG warehouse algorithm, we did not observe significant bias in QT measurements, the ECG acquisition and interpretation for this study is therefore acceptable.

4.3 BY-TIME ANALYSIS

The analysis population used for by-time analysis included all subjects with a baseline and at least one post-dose ECG.

The statistical reviewer used a linear mixed model to analyze the drug effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The default model includes treatment, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and average baseline as a covariate. The default model also includes an unstructured covariance matrix to explain the associations among repeated measures within the treatment.

The statistical reviewer also used a linear mixed model to analyze the moxifloxacin effect by-time for each biomarker (e.g., ΔQTcF , ΔHR) independently. The default model includes treatment, sequence, period, time (as a categorical variable), and treatment-by-time interaction as fixed effects, and average baseline as a covariate. The default model

also includes subject as a random effect and an unstructured covariance matrix to explain the associations among repeated measures within the period.

4.3.1 QTc

Figure 1 displays the time profile of $\Delta\Delta\text{QTcF}$ for different treatment groups. The maximum $\Delta\Delta\text{QTcF}$ values by treatment are shown in Table 3. The largest upper bound of 90% CI of LS mean $\Delta\Delta\text{QTcF}$ for VNZ was below 10 msec.

Figure 1: Mean and 90% CI of $\Delta\Delta\text{QTcF}$ Time-course (unadjusted CIs).

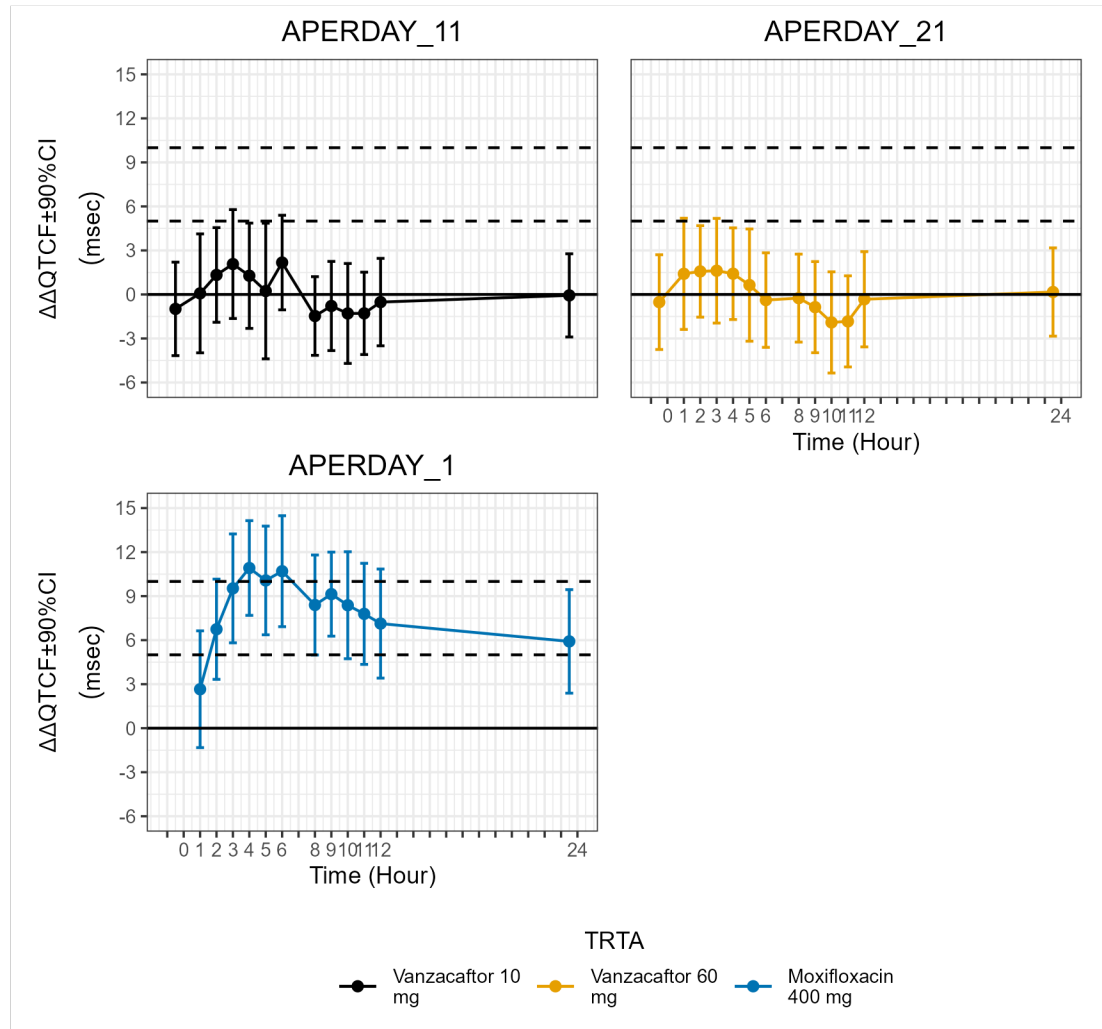


Table 3: Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for $\Delta\Delta\text{QTcF}$

Actual Treatment	Analysis Nominal Period Day (C)	Nact / Npbo	Time (Hour)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Vanzacaftor 10 mg	11	27 / 28	3.0	2.1	(-1.6 to 5.8)
Vanzacaftor 60 mg	21	27 / 28	1.0	1.4	(-2.4 to 5.2)

4.3.1.1 Assay Sensitivity

The primary method for establishing assay sensitivity for this study was based on exposure-response analysis—see section 4.5.1.1 for details.

The assay sensitivity was supported by by-time analysis as shown in Figure 1 and Table 4.

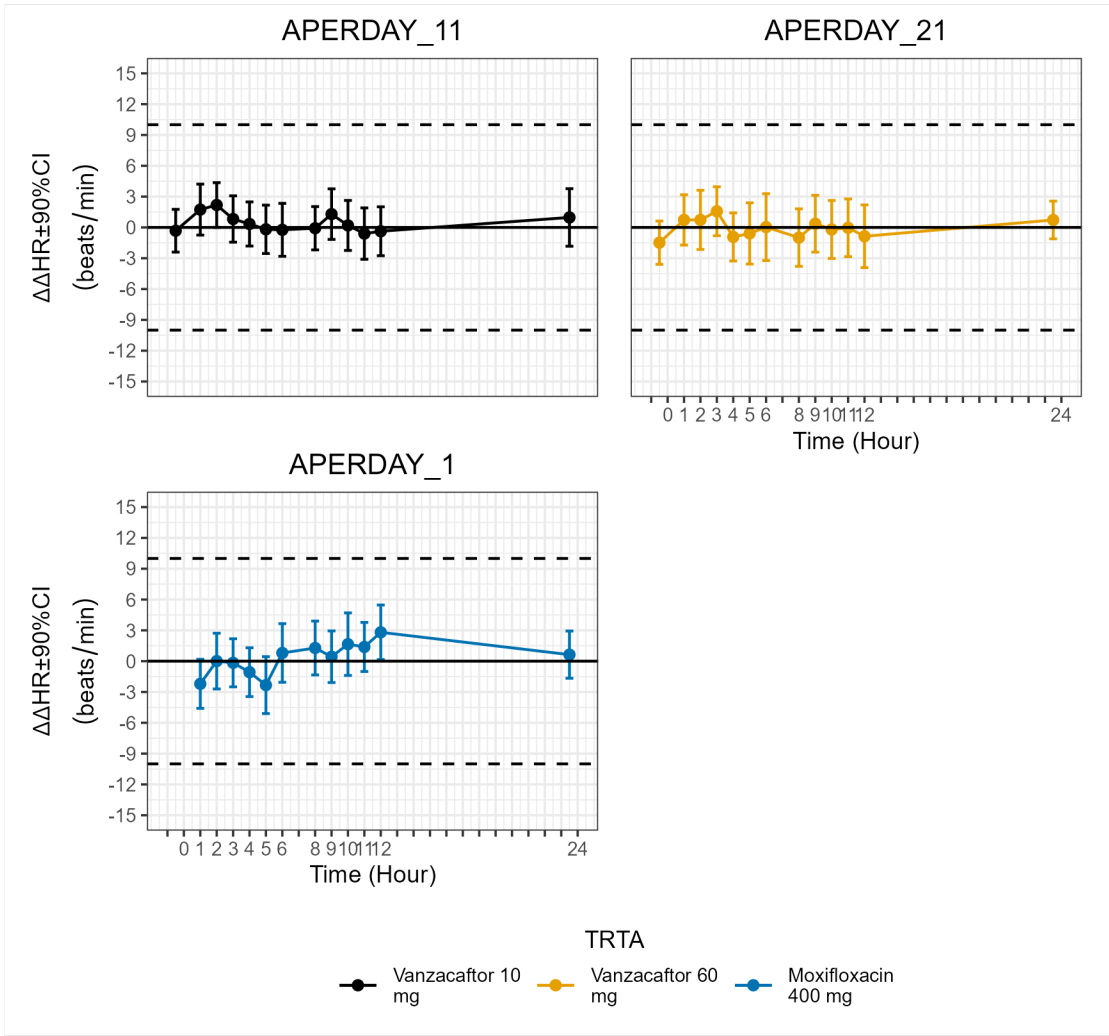
Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Lower Bounds for $\Delta\Delta QTCF$

Actual Treatment	Nact / Npbo	Time (Hour)	$\Delta\Delta QTCF$ (msec)	90.0% CI (msec)	97.5% CI (msec)
Moxifloxacin 400 mg	28 / 28	4.0	10.9	(7.7 to 14.1)	(6.5 to 15.4)

4.3.2 HR

Figure 2 displays the time profile of $\Delta\Delta HR$ for different treatment groups.

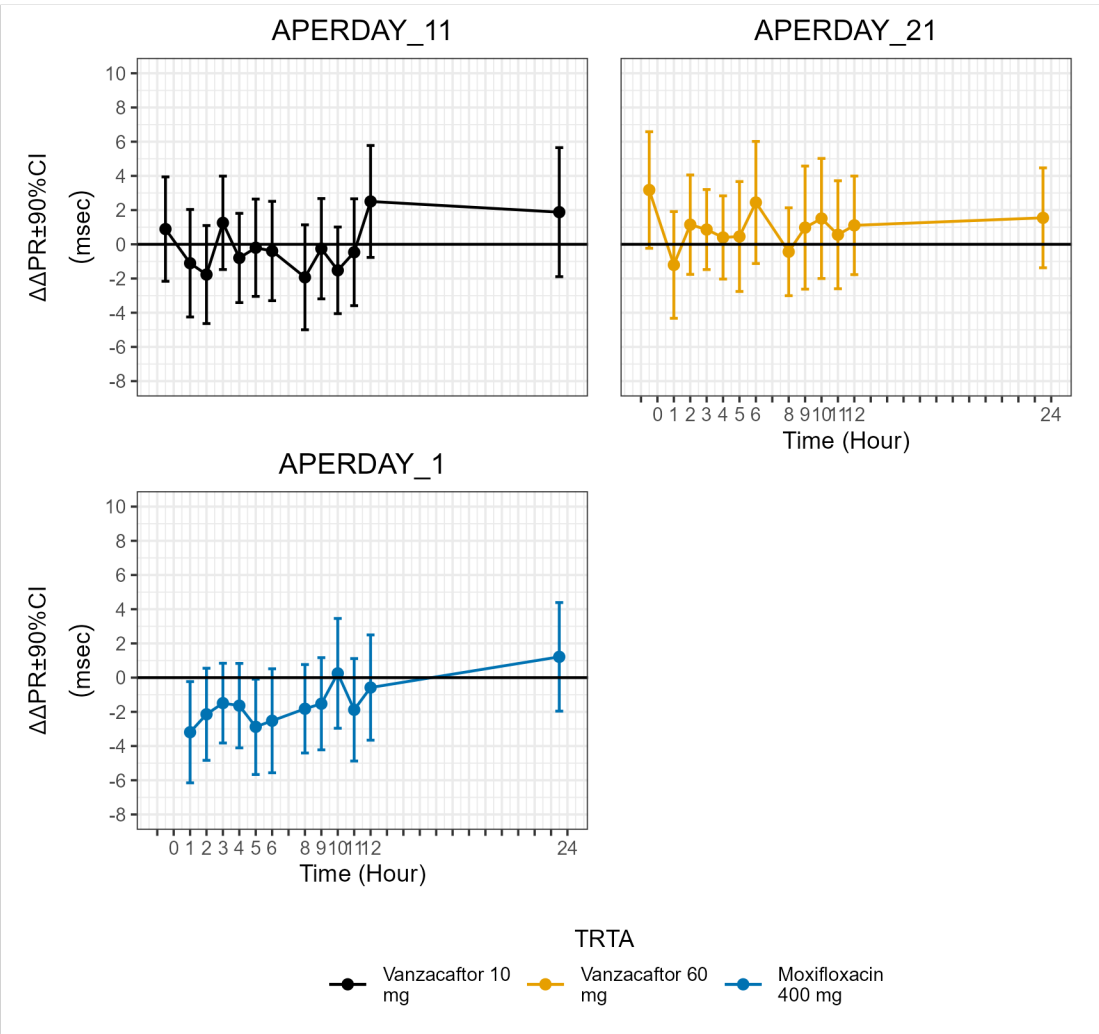
Figure 2: Mean and 90% CI of $\Delta\Delta HR$ Time-course



4.3.3 PR

Figure 3 displays the time profile of $\Delta\Delta\text{PR}$ for different treatment groups.

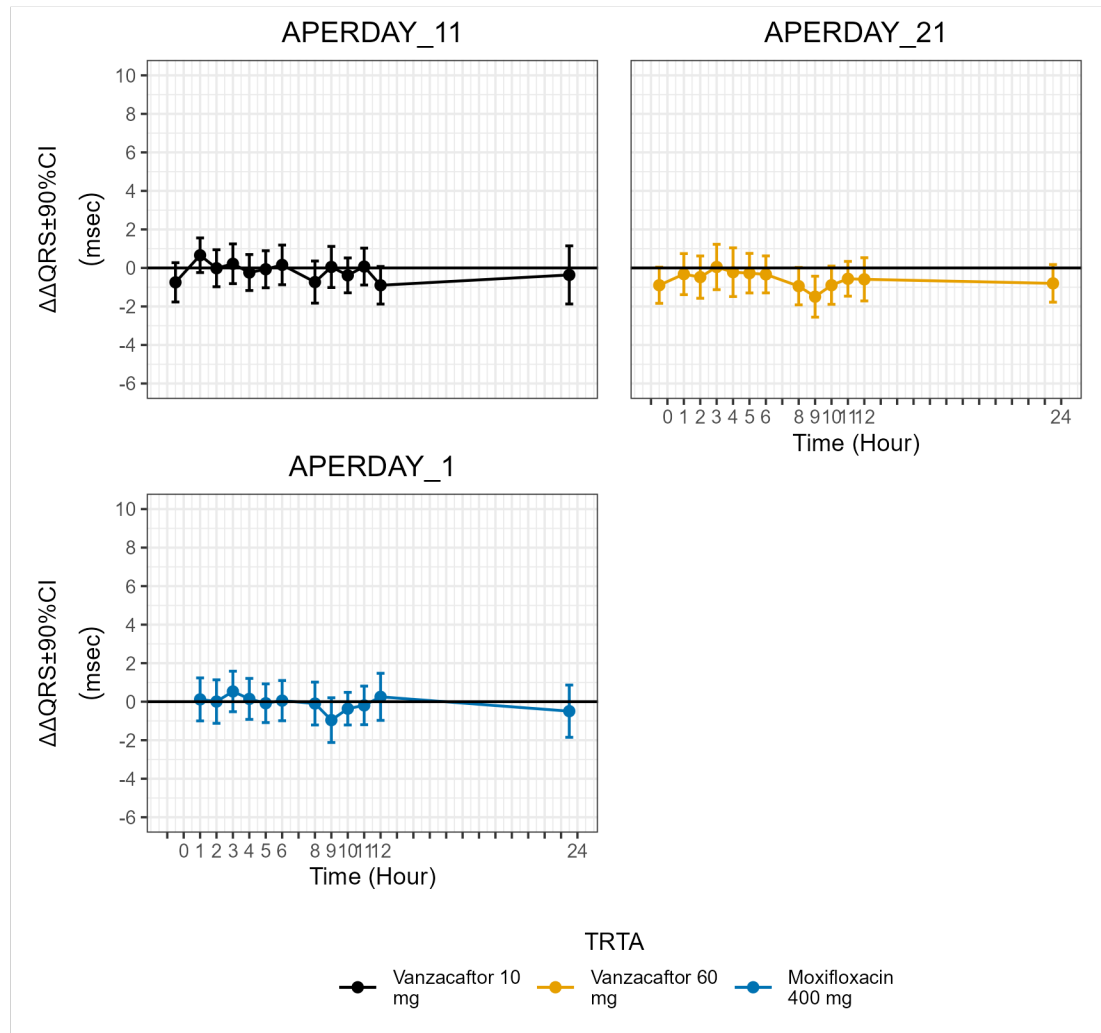
Figure 3: Mean and 90% CI of $\Delta\Delta\text{PR}$ Time-course



4.3.4 QRS

Figure 4 displays the time profile of $\Delta\Delta\text{QRS}$ for different treatment groups.

Figure 4: Mean and 90% CI of $\Delta\Delta$ QRS Time-course



4.4 CATEGORICAL ANALYSIS

Categorical analysis was performed for different ECG measurements, either using absolute values, change from baseline, or a combination of both. The analysis was conducted using the safety population, which includes both scheduled and unscheduled ECGs.

4.4.1 QTc

There were no subjects who had observed QTcF above 450 msec or change from baseline above 60 msec in any of the treatment groups.

4.4.2 HR

There were no subjects having observed HR above 100 beats/min in the VNZ treatment groups.

4.4.3 PR

None of the subjects experienced PR >220 msec in any of the treatment groups.

4.4.4 QRS

None of the subjects experienced QRS >120 msec and 25% increase over baseline in any of the treatment groups.

4.5 EXPOSURE-RESPONSE ANALYSIS

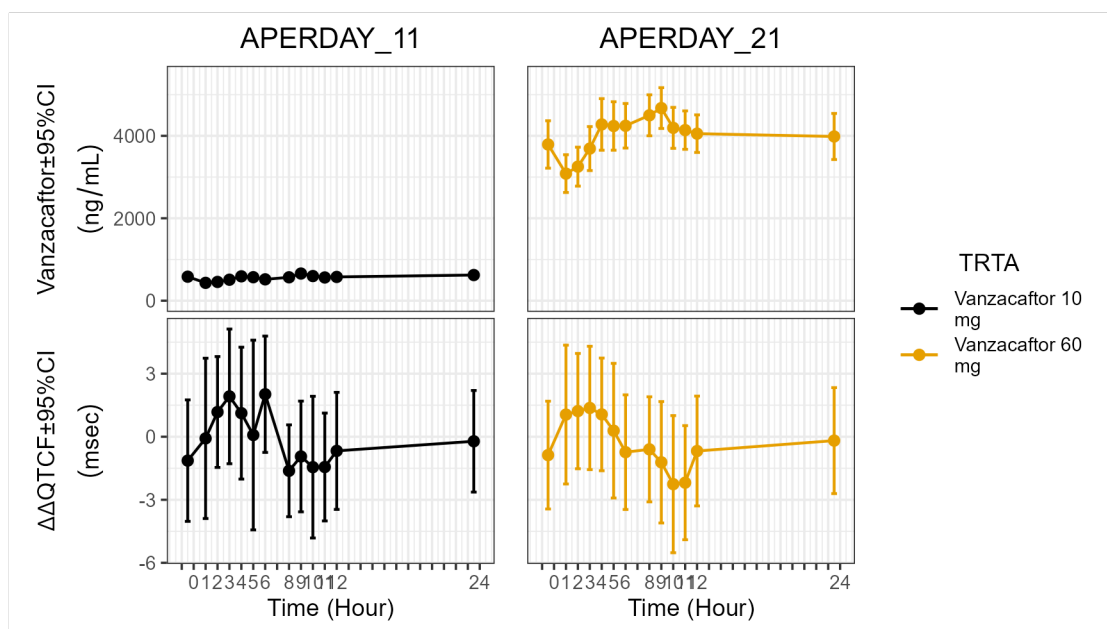
Exposure-response analysis was conducted using all subjects with baseline and at a least one post-baseline ECG, with time-matched PK. A total of twenty-eight (28) subjects in each dose group had ECG and PK data.

4.5.1 QTc

Prior to evaluating the relationship between drug concentration and QTcF using a linear model, the three key assumptions of the model were evaluated using exploratory analysis: 1) absence of significant changes in heart rate (more than a 10 beats/min increase or decrease in mean HR); 2) absence of delay between plasma concentration and $\Delta\Delta\text{QTcF}$; and 3) absence of a nonlinear relationship.

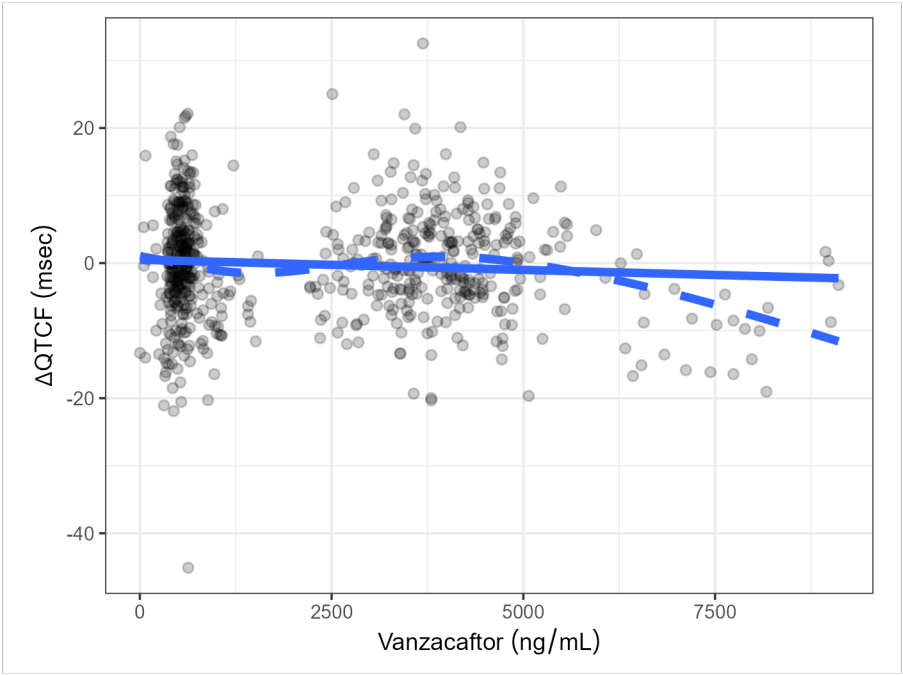
Figure 2 shows the time-course of $\Delta\Delta\text{HR}$, with an absence of significant $\Delta\Delta\text{HR}$ changes. Figure 5 offers an evaluation of the relationship between time-course of drug concentration and $\Delta\Delta\text{QTcF}$, with no appearance of significant hysteresis. Figure 6 shows the relationship between drug concentration and ΔQTcF and supports the use of a linear model.

Figure 5: Time-course of Drug Concentration (top) and QTcF (bottom)¹



¹ $\Delta\Delta\text{QTcF}$ shown were obtained via descriptive statistics and might differ from Figure 1

Figure 6: Assessment of Linearity of the Concentration-QTcF Relationship



Finally, the linear model was applied to the data, and the goodness-of-fit plot is shown in Figure 7. Predictions from the concentration-QTcF model are provided in Table 5.

Figure 7: Goodness-of-fit Plot for QTcF

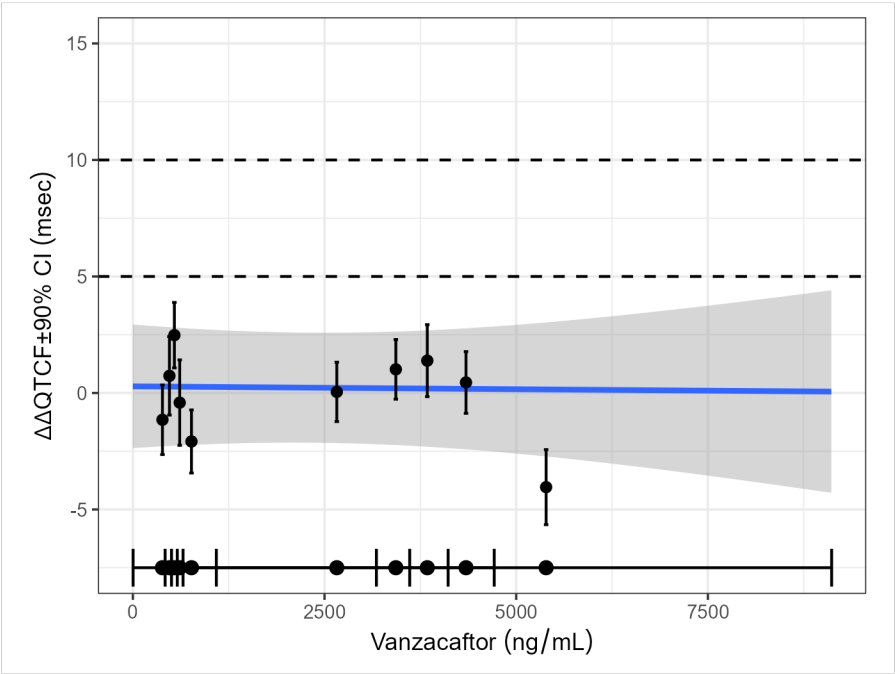


Table 5: Predictions from Concentration-QTcF Model

Actual Treatment	Analysis Nominal Period Day (C)	Vanzacaftor (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Vanzacaftor 10 mg	11	677.1	0.3	(-2.2 to 2.8)
Therapeutic dose 20 mg QD	28	812.0	0.3	(-2.2 to 2.8)
High clinical exposure		3890.0	0.2	(-2.3 to 2.7)
Highest dose 60 mg QD	10	4920.0	0.2	(-2.6 to 2.9)

The overall results of the reviewer analysis were comparable with the applicant predicted values for both doses of 10 and 60 mg.

4.5.1.1 Assay Sensitivity

The time course of moxifloxacin concentration and $\Delta\Delta\text{QTcF}$ is shown in Figure 8. When the same linear mixed effect model is applied, the goodness-of-fit plot for moxifloxacin is shown in Figure 9, and the predicted QTcF at the geometric mean C_{max} is listed in Table 6.

Figure 8: Time-course of Moxifloxacin Concentration (top) and QTcF (bottom)

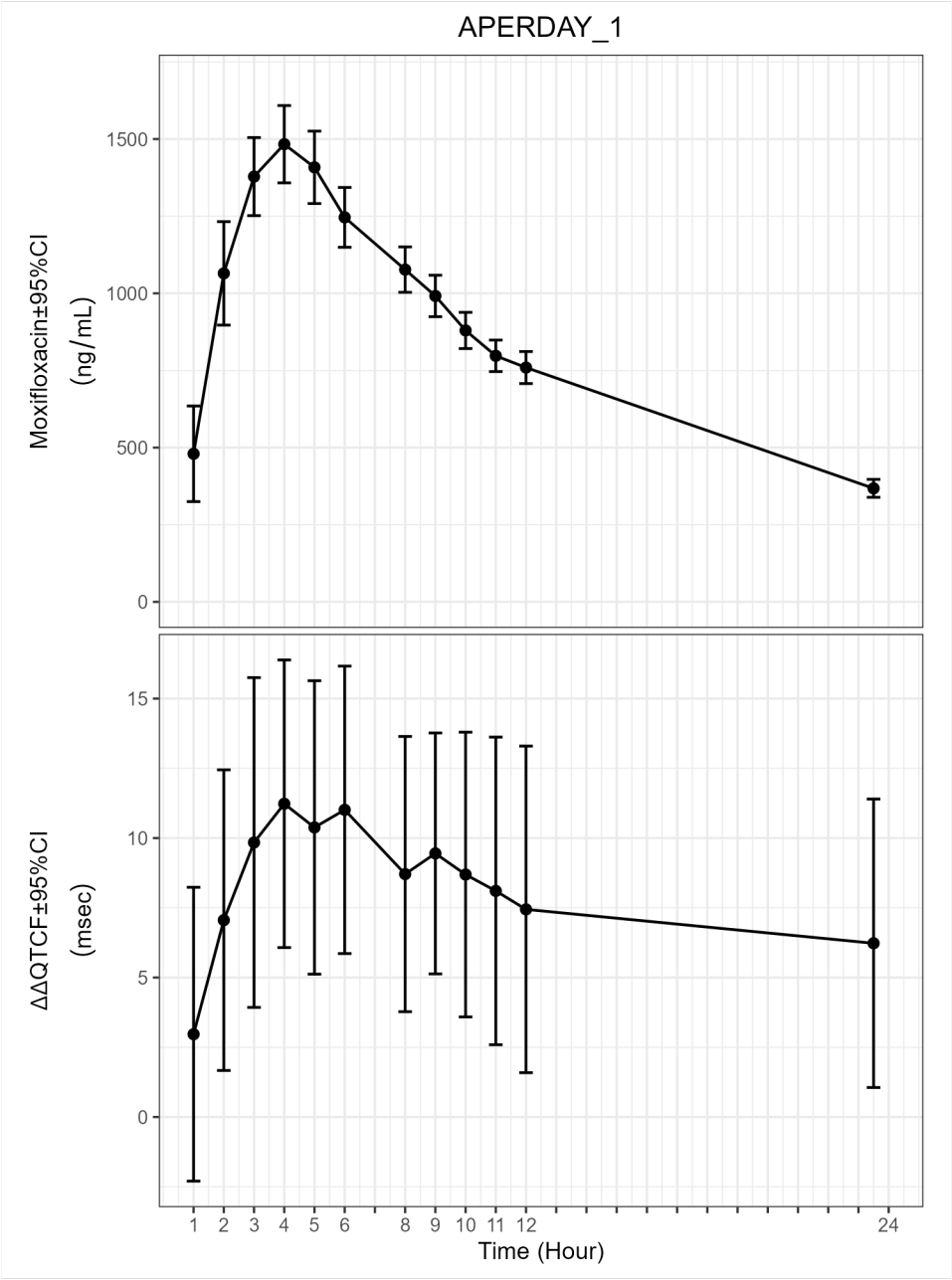


Figure 9: Goodness-of-fit plot of $\Delta\Delta\text{QTcF}$ for Moxifloxacin

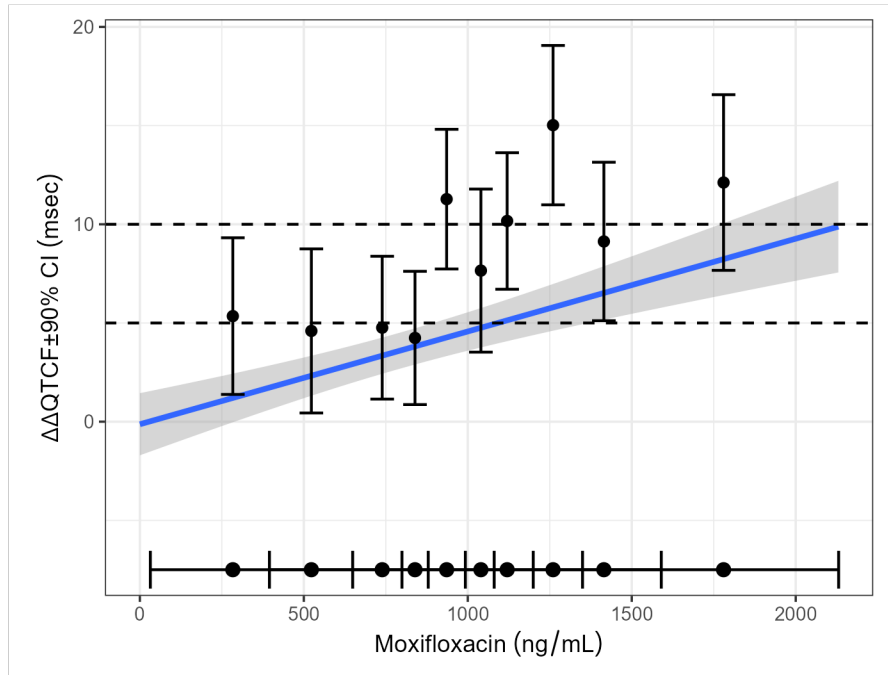


Table 6: Predictions from Concentration-QTcF Model for Moxifloxacin

Actual Treatment	Analysis Nominal Period Day (C)	Moxifloxacin (ng/mL)	$\Delta\Delta\text{QTcF}$ (msec)	90.0% CI (msec)
Moxifloxacin 400 mg	1	1,515	7	(5.5 to 8.5)

4.6 SAFETY ASSESSMENTS

See section 3.2.4. No additional safety analyses were conducted.

5 APPENDIX

5.1 EVALUATION OF THE APPLICANT'S CLINICAL QT STUDIES

Protocol previously reviewed. (DARRTS [05/10/2023](#); [09/11/2023](#))

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/s/

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DEVI KOZELI on behalf of LARS JOHANNESSEN
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Signing on behalf of Lars as he is OOO

CHRISTINE E GARNETT
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