CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218730Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 142001

MEETING MINUTES

Vertex Pharmaceuticals Incorporated
Attention: Christine Pai, PhD
Senior Manager, Global Regulatory Affairs
50 Northern Avenue
Boston, MA 02110

Dear Dr. Pai:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for vanzacaftor/ tezacaftor/ deutivacaftor (VNZ/TEZ/D-IVA).

We also refer to the video conference between representatives of your firm and the FDA on April 5, 2024. The purpose of the meeting was to discuss topics related to the pivotal phase 3 studies and the proposed NDA.

A copy of the official minutes of the video conference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Elaine Sit, PharmD
Senior Regulatory Health Project Manager
Pulmonology, Allergy, and Critical Care
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Friday, April 5, 2024 @ 11:00 AM-11:30 AM ET
Meeting Location:	Video conference
Application Number:	IND 142001
Product Name:	vanzacaftor/ tezacaftor/ deutivacaftor (VNZ/TEZ/D-IVA)
Indication:	cystic fibrosis (CF)
Sponsor Name:	Vertex Pharmaceuticals Incorporated
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Sally Seymour
Meeting Recorder:	Elaine Sit

FDA ATTENDEES

Kathleen Donohue, MD, Acting Deputy Director, Office of Immunology and Inflammation (OII)
Sally Seymour, MD, Director, Division of Pulmonology, Allergy, and Critical Care (DPACC), OII
Banu Karimi Shah, MD, Deputy Director, DPACC, OII
Elisabeth Boulos, MD, Clinical Team Leader, DPACC, OII
Alison Lennox, MD, Clinical Reviewer, DPACC, OII
Jessica Bonzo, PhD, Pharmacology/Toxicology Team Leader, Division of Pharmacology-Toxicology for Immunology and Inflammation (DPT-II), OII
Emma Gimose, PharmD, Regulatory Business Project Manager, Division of Regulatory & Business Process Management II (DRBPMII), Office of Program and Regulatory Operations (OPRO), Office of Pharmaceutical Quality (OPQ)
Yunzhao Ren, MD, PhD, Master Pharmacokineticist, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP)
Hyewon Kim, PhD, Clinical Pharmacology Reviewer, DIIP, OCP
Sarah Dorff, PhD, Master Pharmacokineticist, Division of Translational and Precision Medicine (DTPM), OCP
Joseph (Youssef) Roman, PharmD, PhD, Genomics Reviewer, DTPM, OCP
Wendy Wu, PhD, Electrophysiologist/Chemist, Division of Applied Regulatory Science (DARS), OCP
Claudia AlvarezBaron, MD, PhD, Electrophysiologist/Biologist, DARS, OCP

Damon Birkemeier, PharmD, FISMP, NREMT, Team Leader, Division of Medication Error Prevention and Analysis I (DMEPA-I), Office of Medication Error Prevention and Risk Management (OMEPRM), Office of Surveillance and Epidemiology (OSE)
Lissa Owens, PharmD, Safety Evaluator, DMEPA-I, OMEPRM, OSE
Ameet Joshi, PharmD, Team Leader, Project Management Staff (PMS), OSE
Frances Fahnbulleh, PharmD, Safety Regulatory Health Project Manager, OSE
Elaine Sit, PharmD, Safety Regulatory Health Project Manager, DPACC
Julianne Lee, PharmD, Regulatory Health Project Manager, DPACC

SPONSOR ATTENDEES
Nia Tatsis, PhD, Executive Vice President, Chief Regulatory and Quality Officer
Carmen Bozic, MD, Executive Vice President, Clinical Development
David Waltz, MD, Vice President, Clinical Development
Patrick Sosnay, MD, Executive Medical Director, Clinical Development
Neil Ahluwalia, MD, Senior Medical Director, Global Patient Safety
Fredrick Van Goor, PhD, Vice President, Head of Cystic Fibrosis Research
Ian Hawkins, Vice President, Global Regulatory Strategy
James Witty, PhD, Executive Director, Global Regulatory Strategy
Chayla Freeman, MS, JD, Director, Global Regulatory Strategy
Christine Pai, PhD, Senior Manager, Global Regulatory Strategy

1.0 BACKGROUND

Vertex Pharmaceuticals (Vertex) requested a Type B Pre-NDA meeting in a submission dated February 2, 2024, to discuss the following topics regarding the initial marketing application:

- Submission of a Fischer rat thyroid (FRT) report addendum during the submission
- Potential need for an Advisory Committee meeting
- Covered studies for purpose of financial disclosure
- Timing and content of safety update report

The Division granted the meeting as a video conference in a letter dated February 9, 2024. Vertex submitted the briefing package containing their questions for this meeting in a submission dated, February 2, 2024.

FDA sent Preliminary Comments to Vertex on March 25, 2024.

The questions from this briefing package are printed below in ***bold italics font*** followed by FDA responses and discussion in normal font.

2.0 DISCUSSION

Introductory Comments:

We have reviewed your pre-NDA submission for the fixed dose combination of vanzacaftor (VNZ)/tezacaftor (TEZ)/deutivacaftor (D-IVA) that included a phase 3 program with 2, 52-week, randomized, multicenter, double-blind, non-inferiority trials with an active control of Trikafta (elexacaftor/tezacaftor/ivacaftor).

To ensure the NDA submission is sufficiently organized to support your proposed Priority Review, we strongly recommend your future application clearly outline how your development program has addressed the following review issues.

1. Satisfaction of the 'Combination Rule' for all mutations, whether supported by clinical and/or nonclinical data;

2. Dose justification for D-IVA for all age groups;

3. Adequacy of in vitro data to support the indication for additional *CFTR* mutations;

4. Adequacy of the safety database.

In addition, your application should include:

5. Any clinical or in vitro data, in its entirety (including datasets or raw data), intended to support the proposed indication for all relevant *CFTR* mutations.

6. The Statistical Analysis Plans for the phase 3 trials (Studies 102 and 103).

7. A summary table of all *CFTR* mutation indications, organized by clinically meaningful groupings, that clearly outlines the origin of primary data to support an indication, as well as any complementary data. The current summary in Section 7 of the pre-NDA Meeting Package lacks clarity.

Discussion on Introductory Comments:
Vertex requested to clarify Introductory Comments 1 and 7.

For Introductory Comment 1, Vertex reviewed their proposed outline for the data sources that will be included in the NDA application in support of the 'Combination Rule' for VNZ/TEZ/D-IVA (See Slide 4 in Section 6 Attachments and Handouts). They stated that the organization will be similar to the approach used for the NDA application for Trikafta (elexacaftor/tezacaftor/ivacaftor). The Agency reiterated that the ability of VNZ/TEZ/D-IVA to satisfy the 'Combination Rule' will be a key review issue, but Vertex's proposal appears reasonable at this time.

For Introductory Comment 7, Vertex presented a summary slide (Slide 6 in Section 6) and provided a review of the proposed data sources for the various *CFTR* mutations in the proposed indication of VNZ/TEZ/D-IVA. The Agency appreciated the additional clarity provided and reiterated that the application will need to present data sources for the various *CFTR* mutation populations clearly.

Question 1: ***Vertex is conducting in vitro FRT testing to systematically characterize the pharmacological response to VNZ/TEZ/D-IVA of all missense and in-frame insertion/deletion mutations that have been reported in people with CF (approximately 600 CFTR mutations). This testing will be ongoing at the time of the marketing application. Completed testing that supports 134 responsive mutations will be included in the initial submission. Vertex requests to submit an addendum to the FRT study report to provide data from approximately 100 additional mutations at the time of the 90-day safety update (refer to Question 4). Does the Division agree that these data can be submitted during the procedure and will not extend the review cycle time?***

FDA Response to Question 1:
We do not agree. We expect the NDA application to be complete and include all the data necessary to support registration at the time of submission. The submission of the proposed FRT data during the review period would represent a Major Amendment. We recommend you consider your options regarding the delay in availability of the FRT data for additional mutations. For example, data that is not available at the time of the initial application submission may be submitted as a subsequent labeling supplement after the initial regulatory action.

Discussion on Question 1:
The Agency inquired about Vertex's plans for submission of the ongoing FRT data analyses based on FDA's feedback. (b) (4)

Question 2: ***Does the Division anticipate that a Pulmonary and Allergy Advisory Committee would be convened as part of the NDA review process for VNZ/TEZ/D-IVA?***

FDA Response to Question 2:
Based on our initial evaluation of the clinical summary data provided, we do not anticipate the need for an Advisory Committee meeting. However, the final determination will be a review issue.

Discussion on Question 2:
No further discussion on Question 2.

Question 3: ***Does the Division agree that Studies 101, 561-101, 102, 103, and 105 are considered the covered studies for this NDA under 21 CFR 54 for purposes of Financial Disclosure?***

FDA Response to Question 3:
This proposal appears reasonable and consistent with the recommendations outlined in 21 CFR 54.2(e).

Discussion on Question 3:
No further discussion on Question 3.

Question 4: ***Per 21 CFR 314.50(d)(5)(vi), a safety update report should be provided 4 months after the initial NDA submission. Under Priority Review, Vertex plans to provide the Safety Update Report to the Division 90 days after the initial NDA submission. Does the Division agree with the timing and proposed content of the safety update?***

FDA Response to Question 4:
The proposal for the submission of the Safety Update Report appears reasonable.

Discussion on Question 4:
No further discussion on Question 4.

Other Meeting Discussion Comments:

Sweat chloride
Vertex summarized their overall CF drug development history, including the approved medications targeting *CFTR*, the VNZ/TEZ/D-IVA fixed dose combination that was the subject of this pre-NDA meeting, and mRNA therapy (under the purview of CBER). They expressed interest in a follow-up discussion with the Agency regarding the role of SwCl (b) (4) . Vertex plans to submit a separate meeting request, and the Agency agreed that a separate meeting would be the best forum for further discussion of SwCl.

Safety report clarification
Vertex noted that the safety database for VNZ/TEZ/D-IVA is derived from about 1000 patients enrolled in the clinical development program. They stated that the upcoming NDA submission will include patients who tolerated Trikafta. This will include both patients who were tolerating Trikafta prior to trial initiation and those who initiated Trikafta only during the run-in period. Therefore, the study excluded patients who could not tolerate Trikafta.

Vertex observed that their review of the safety data for VNZ/TEZ/D-IVA appears similar to Trikafta, and some safety events appear even less frequent compared to Trikafta. Vertex explained this may be a result of the exclusion of Trikafta intolerant patients. They are proposing to include summaries of the safety data from the Trikafta clinical development program for reference. Of note, similar data was included in the pre-NDA meeting package. The Agency acknowledged that this approach to data presentation is reasonable.

3.0 OTHER IMPORTANT MEETING COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 9, 2024, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VII. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to

specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[5]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues required further discussion.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Attached are slides which were presented during the meeting.

6 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

[5] https://www.fda.gov/media/85061/download

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/

ELAINE SIT
04/09/2024 02:14:04 PM

IND 142001

MEETING MINUTES

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

Attention: Barbara Balter, PhD
Manager, Global Regulatory Affairs

Dear Dr. Balter:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-121.

We also refer to the telecon between representatives of your firm and the FDA on February 26, 2021. The purpose of the meeting was to discuss the proposed clinical developmental pivotal program for VX-121/TEZ/D-IVA.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-348-1896.

Sincerely,

{See appended electronic signature page}

Ngoc-Linh Do, PharmD
Regulatory Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End-of-Phase 2

Meeting Date and Time: February 26, 2021; 11:00 AM – 12:00 PM
Meeting Location: Teleconference

Application Number: 142001
Product Name: VX-121

Indication: Treatment of cystic fibrosis (CF) in patients 12 years of age and older with at least one *F508del* allele
Sponsor Name: Vertex Pharmaceuticals Incorporated

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Ngoc-Linh Do, PharmD

FDA ATTENDEES

Sally Seymour, MD, Director, Division of Pulmonology, Allergy, and Critical Care (DPACC)
Robert Lim, MD, Clinical Team Leader, DPACC
Sarah Zaidi, MD, Clinical Reviewer, DPACC
Yongman Kim, PhD, Biostatistics Team Leader, Division of Biometrics III (DBIII), Office of Biostatistics (OB)
Mingyu Xi, PhD, Biostatistics Reviewer, DBIII, OB
Timothy Robison, PhD, Pharmacology/Toxicology Team Leader, Division of Pharmacology/Toxicology for Immunology and Inflammation (DPT-II)
Wei Sun, PhD, Pharmacology/Toxicology Reviewer, DPT-II
Yunzhao Ren, PhD, Acting Team Lead, DIIP, Office of Clinical Pharmacology (OCP)
Priya Brunsdon, PharmD, Clinical Pharmacology Reviewer, DIIP, OCP
Wendy Wu, PhD, Chemistry Reviewer, Division of Applied Regulatory Science (DARS), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
James Weaver, PhD, Clinical Pharmacology Review, DARS, OCP, OTS
Girish Bende, PhD, Co-Lead IRT for Cardiac Safety Studies, Office of Clinical Pharmacology, Division of Cardiometabolic and Endocrine Pharmacology
Nichelle Rashid, MS, Team Leader, Office of Surveillance and Epidemiology (OSE) Safety Project Management Staff
Cristina Attinello, MPH, Senior Safety Regulatory Project Manager, (OSE)
Ngoc-Linh Do, PharmD, Regulatory Project Manager, DPACC

SPONSOR ATTENDEES

Nia Tatsis, PhD Executive Vice President, Chief Regulatory and Quality Officer

Carmen Bozic, MD, Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer
Joanne Palmisano, MD, Vice President, Global Regulatory Affairs
James Witty, PhD, Director, Global Regulatory Affairs
Barbara Balter, PhD, Manager, Global Regulatory Affairs
David Waltz, MD, Vice President, Clinical Development
Patrick Sosnay, MD, Medical Director, Clinical Development
Bo Yang, PhD, Vice President, Biometrics
Nitin Nair, PhD, Associate Director, Biostatistics
Henry Seto, MD, Vice President, Global Patient Safety
Simon Tian, MD, Executive Medical Director, Global Patient Safety
Paul Panorchan, PhD, Senior Director, Clinical Pharmacology
Wan Sun, PhD, Director, Clinical Pharmacology
Brenda Cirincione, PhD, Executive Director, Modeling and Simulations
Eric Haseltine, PhD, Senior Director, Modeling and Simulations
John Pettersen, PhD, Senior Director, Toxicology – Preclinical Safety Assessment
(b) (4)

1.0 BACKGROUND

On December 9, 2020, Vertex Pharmaceutical submitted an End-of-Phase 2 meeting request to discuss the proposed nonclinical and clinical program to support the initiation of the Phase 3 study for the treatment of patients with cystic fibrosis (CF) aged 12 years and older with at least one *F508del* allele. The Division sent Preliminary Comments to Vertex on February 19, 2021 and on February 24, 2021 Vertex requested to further discuss questions 2 and 3. The questions from the briefing package, received on January 8, 2021, and FDA responses are listed below in normal font, followed by the meeting minutes in bold.

2.0 DISCUSSION

Question 1
Does the Division agree that the overall nonclinical package is sufficient to support initiation of Phase 3 and an initial NDA for VX-121/TEZ/D-IVA?

FDA Response
Pending review, we agree.

Discussion
Further discussion was not needed.

Question 1a
Does the Division agree with submission of the results of the 104-week carcinogenicity study as a postmarketing requirement?

FDA Response
Yes, we agree.

Question 2
Does the Division agree that the overall clinical pharmacology package is sufficient to support an initial NDA for VX-121/TEZ/D-IVA?

FDA Response
No, we do not agree. Your Study 121-001 showed that the steady state systemic exposure of VX-121 following the 10 mg dose with concomitant TEZ/IVA is more than two-fold higher than VX-121 alone when compared between different treatment arms. Therefore, contribution of each of the three mono-components to efficacy of the combination VX-121/TEZ/D-IVA product may be partly explained by the higher exposure of VX-121 due to the potential PK interaction. We recommend that you conduct a dedicated crossover PK study with four treatment arms (VX-121, TEZ, D-IVA, and VX-121/TEZ/D-IVA) to evaluate the PK interaction potential among the three mono-components prior to embarking on the proposed Phase 3 studies. A final determination of the adequacy of the clinical pharmacology program will depend on the review of the PK interaction study results.

In addition, we have the following comments on your QT assessment plan for each component of the combination product.

1. VX-121: You have proposed to use the concentration-QTc analysis from data collected in study # VX17-121-001 as a substitute for a thorough QT study as per ICH E14 Q&A (R3) 5.1. Study # VX17-121-001 appears adequate to characterize the QTc prolongation potential of your drug and can potentially serve as an alternative to the thorough QT study. Whether these data exclude a 10-msec mean QTc effect at the highest clinically relevant exposure will be a review issue when the final therapeutic dose is determined.

2. Tezacaftor: We agree with your proposal that a standalone thorough QT study is not required if the steady-state exposures (Cmax) of tezacaftor and its relevant metabolites from the to-be marketed product at the highest therapeutic dose are not significantly higher than those for marketed product (Symdeko; NDA-210491) and the QT relevant sections of marketed product can be extended to your product label (ICH E14, section 1.3).

3. Deutivacaftor: We agree that you can use the findings of your thorough QT study if the steady-state exposures (Cmax,ss) of deutivacaftor and its relevant metabolites for the to-be-marketed formulation of your triple combination product are similar to those associated with highest dose studied dose of ivacaftor in the thorough QT study.

Discussion

Vertex opened the discussion referring to their responses submitted to the Division on February 24, 2021, regarding the higher exposure due to a potential PK interaction of VX-121 and the other two components, D-IVA and TEZ. Vertex stated their position that the in vitro and clinical data do not show a clinically relevant interaction between VX-121 and D-IVA. The Sponsor conveyed that they do not believe a dedicated crossover PK study is necessary.

The Division acknowledged the Sponsor's position but stated that based on the observed data from Study 121-001, the potential drug-drug interaction (DDI) between the three components VX-121, TEZ, and D-IVA, cannot be excluded, including for VX-121 at the 10 mg level. The Division reiterated that a dedicated DDI study with crossover design is the best approach to help clarify this issue. The Division reminded the Sponsor that evaluation of the DDI between individual components of a combination product is a required step in order to satisfy the combination rule, as changes in systemic exposure of individual components can influence the efficacy and safety of the combination product.

The Sponsor asked for clarification on the treatment arms of this DDI study. The Division relayed their preference for all three components (a crossover study with four treatment arms: VX-121, TEZ, D-IVA, and VX-121/TEZ/D-IVA), as this provides the most clearly interpretable data. However, a three-treatment-arm (VX-121, TEZ/D-IVA, and VX-121/TEZ/D-IVA) approach may be feasible if sufficient justification of the comparison of TEZ/IVA and TEZ/D-IVA can be provided. The sponsor asked if this DDI study can be conducted in parallel with the Phase 3 studies. The Division commented that a DDI study is typically conducted prior to the Phase 3 studies for a combination product. However, since the completed dose ranging study 121-101 was based on the triple combination product, the sponsor may conduct the DDI study in parallel with the Phase 3 studies. The Division noted that the DDI results will be taken into consideration to justify the contribution of each individual component to the efficacy and safety of the combination product.

The Division also pointed out that if there is potential drug interaction between the components leading to increase in exposures of VX-121, this will impact the substitution request for the thorough QT study. To use the proposed clinical study (Study # VX17-121-001) as a substitute for a thorough QT study as per ICH E14 Q&A (R3) 5.1, Vertex will need to show that the PK and ECG data are collected at a sufficiently high multiples of the clinically relevant exposure (e.g., twice the supratherapeutic exposures) with the combination product in the target population, such that a separate positive control would not be necessary (see ICH E14 Section 2.2.2).

The Division reiterated that based on the information in the meeting package, it was not clear that Vertex had sufficient data to support the contribution of each component in the combination product. In the meeting package, Vertex did not explicitly address their approach to addressing the contribution of the components. To support the contribution of each component, the Division stated that in vitro data alone would not be sufficient and clinical data would also be necessary. Vertex agreed to submit a follow-up meeting request to discuss their approach to address the combination rule before initiating their Phase 3 program.

Question 3
Does the Division agree with the proposed Phase 3 clinical development plan for the initial NDA to support an indication of "treatment of CF in patients 12 years of age and older who have at least one *F508del* mutation"?

FDA Response
Discussion of the specific wording of the indication is premature at this time. In general, indication statements are reflective of the clinical trial population. With regard to the proposed phase 3 trials, see FDA Responses to Questions 3a-3c.

Discussion
Further discussion was not needed.

Question 3a
Does the Division agree with the doses selected for evaluation in Studies A and B?

FDA Response
We have concerns with the proposed dose for D-IVA (250 mg QD). It appears the dose selection of D-IVA is based on Study 561-101 conducted under IND 128544. The clinical study report for Study 561-101 is not provided, limiting our assessment. However, we note that the PK comparison results show that the systemic exposure of D-IVA 150 mg QD matches closer to IVA 150 mg BID as compared to D-IVA 250 mg QD. The systemic exposure of D-IVA 250 mg QD is approximately 50-70% higher than that of the approved dose of IVA 150 mg BID. The higher systemic exposure of D-IVA 250 mg QD compared to both the approved IVA dose and D-IVA 150 mg QD dose may raise exposure related safety concerns. In addition, for change in ppFEV1 values in Study 561-101 results were similar between D-IVA 150 mg QD and D-IVA 250 mg QD. This suggests that, in terms of benefit-risk, the D-IVA 150 mg dose may be more appropriate to carry into phase 3. In addition, D-IVA 150 mg QD was investigated in dose ranging Study 121-101 supporting the dose selection of VX-121. Due to the potential DDI between VX-121 and TEZ/D-IVA, any change of the D-IVA dose may affect the dose selection of VX-121. Therefore, we recommend the D-IVA 150 mg QD dose be used for your proposed triple combination drug in phase 3 trial. The proposed dose for VX-121 (i.e., 20 mg QD, Form D) may be reasonable based on the ppFEV1 results from Study 121-101 showing the 10 mg (Form A) group had the greatest numerical improvement from baseline, pending review of the dedicated crossover PK

interaction study (see FDA Response to Question 2). Similarly, the dose selection of TEZ (100 mg) appears reasonable based on the dose exploration of TEZ in the TEZ/IVA clinical program, pending review of the dedicated crossover PK interaction study (see FDA Response to Question 2). We recommend that you submit results from the recommended dedicated crossover PK interaction study prior to embarking on phase 3 trials (see FDA Response to Question 2).

Additionally, we note that the design of the phase 3 trials implicitly assume that the tezacaftor/ivacaftor dose in the elexacaftor/tezacaftor/ivacaftor combination is equivalent to the tezacaftor/D-IVA dose in the VX-121/tezacaftor/D-IVA combination in terms of clinical effect. You have not provided any clinical data to directly support this implicit assumption. Such data and/or justification will be necessary to support your development program and to facilitate interpretation of your phase 3 trials.

Discussion

Regarding the selection of the 250mg dose of D-IVA, the Sponsor stated that the dose was selected to achieve optimal improvement in efficacy "balanced by safety".

The Division acknowledged that the Sponsor's rationale for the selection of D-IVA 250mg QD is based on the sweat chloride (SwCl) results from the dose-ranging study. The Division stated that ppFEV1 data from the same study show a flat dose-response between the 150mg and 250mg dose, which indicates that both doses may be similarly efficacious. Therefore, the dose selection of 150 mg may have more favorable benefit/risk assessment than the 250 mg dose. In addition, the PK profiles of IVA and D-IVA are very different. Thus, the dose selection of 250 mg D-IVA QD regimen with a higher systemic exposure than the approved 150 mg IVA BID regimen could be a safety issue. If Vertex chooses to proceed with the 250mg dose of D-IVA, more clinical safety data or adequate justification should be provided.

The Division also pointed out that the Sponsor's current safety database for D-IVA is extremely limited, and that safety for D-IVA could not be borrowed from the IVA program. Given that higher doses lead to higher exposures, choosing the 250 mg dose of D-IVA may impact the Division's view of what would be considered an adequate safety database for the NDA submission. Vertex inquired what the Division's expectations would be for the NDA submission. The Division stated that for efficacy, within the context of comments provided, and provided that the DDI study was conducted, the proposal was reasonable. As far as safety, the Division is looking for controlled 52-week safety data in a sufficient number of patients at the time of the NDA submission. See also the discussion under Question 3b.

Question 3b
Does the Division agree with the design, endpoints, proposed non-inferiority margin for ppFEV1, and proposed analysis plan for Study A?

FDA Response
Your proposal appears generally reasonable with regard to design, endpoints and non-inferiority margins. However, to better characterize the safety and efficacy of your combination product, we recommend a 1-year randomized, double-blind, active controlled treatment period. Additionally, the protocol should clearly state how minimal function mutations are defined.

Discussion
The Division stated that with the approval of Trikafta, highly effective therapies are now available for this patient population, which has changed the treatment landscape for CF. Given the current treatment landscape, the Division's assessment of benefit-risk weighs safety even more heavily; more safety data may be necessary then in previous Vertex programs (i.e., longer duration of controlled data in a larger number of patients) to support benefit-risk evaluation. Therefore, given the availability of Trikafta, the relative paucity of clinical data for the components of the new proposed triple combination therapy, and the potentially higher D-IVA exposure; to support safety, the Division strongly recommends a 52-week controlled trial to allow for a more complete evaluation of safety.

Question 3c
Does the Division agree with the design, endpoints, proposed non-inferiority margin for ppFEV1, and proposed analysis plan for Study B?

FDA Response
Your proposal appears generally reasonable with regard to design and endpoints. We note that, at this time, there is no placebo controlled clinical trial data with regard to the ppFEV1 effect of elexacaftor/tezacaftor/ivacaftor for the F/G and F/RF mutations and that there is only active controlled data for the F/F mutation. In that light, additional justification for the NI margin should be provided. In addition, we recommend including pre-specified efficacy analyses of the mutation subgroups (i.e., F/F and non-F/F). We also recommend a longer controlled treatment period (see FDA Response to Question 3b). Additionally, the protocol should clearly state how gating and residual function mutations are defined.

Discussion
The Division noted that the justification for NI margin using a meta analytic approach with indirect comparisons was helpful from a statistical viewpoint, given there is no historical placebo-controlled data on the population with F/G and F/RF mutations. The Division noted limitations with this approach that adds uncertainty to an essentially indirect comparison of the proposed product with

placebo in NI trial. The substitution of D-IVA for IVA adds to the uncertainty of indirect comparisons. To mitigate such limitation, the Division recommended that Vertex provide further biological or clinical justification. The sponsor agreed to provide additional justification in the future submission. The Division re-iterated the relevance of subgroup analyses to support efficacy in each mutation subgroup.

Question 4
Does the Division agree that the overall clinical package is sufficient to support an initial NDA for VX-121/TEZ/D-IVA?

FDA Response
See FDA Responses to Questions 2 and 3. We also have concerns with the adequacy of the proposed long-term safety database. As this combination product includes two novel components (VX-121 and D-IVA) and will likely be administered for a lifetime, the proposed 1-year safety database may be insufficient to adequately characterize the safety profile of your product. To better characterize the safety and to facilitate benefit-risk assessment, at the time of NDA submission, the safety database should consist of 1-year long controlled data in all patients in trials A and B (see Response to Questions 3b and 3c regarding length of controlled treatment period).

Additionally, we note that in this meeting package you have not explicitly outlined your approach to demonstrating that each component of the combination contributes to the clinical effect of the combination. We refer you to the meeting minutes issued on November 6, 2020 regarding the use of clinical and in vitro data to satisfy this requirement.

In vitro data meant to support the contribution of the components to the combination should be based on but expanded from the in vitro studies used to demonstrate the effects of each member of the ivacaftor/tezacaftor/elexacaftor combination. As there are two novel drugs in this combination, the in vitro studies should demonstrate the effect of each new drug alone as well as all possible double combinations and the triple combination.

As D-IVA is proposed to replace ivacaftor, your studies should directly compare the in vitro dose response characteristics between ivacaftor and D-IVA for both Western blot and chloride channel studies. Similarly, as VX-121 is proposed to take the place of elexacaftor, similar parallel dose response studies should be performed with VX-121.

Discussion
Further discussion was not needed.

3.0 ADDITIONAL INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[3]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data.* This guidance describes

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[4] that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application

[4] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[5]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale

[5] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[6] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[7]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical*

[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/media/109533/download

Specifications.[8]

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

(1) Study phase

(2) Statement of whether the study is intended to support marketing and/or labeling changes

(3) Study objectives (e.g., dose finding)

(4) Population

(5) A brief description of the study design (e.g., placebo or active controlled)

(6) Specific concerns for which you anticipate the Division will have comments

(7) For changes to protocols only, also include the following information:

- A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
- Other significant changes
- Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug.

[8] https://www.fda.gov/media/85061/download

Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

Attached are the Sponsor's responses to the Preliminary comments.

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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/

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