

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

219209Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 146185

MEETING MINUTES

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

Attention: Cassidy Kelley
Sr. Manager, Regulatory Strategy

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-548.

We also refer to the video conference between representatives of your firm and the FDA on December 13, 2023. The purpose of the meeting was to discuss with the Division on several procedural topics related to the upcoming NDA submission and adequacy for filing for VX-548.

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, please contact me via email at Jane.Mun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jane Mun, PharmD
Regulatory Project Manager
Anesthesiology, Addiction Medicine, and
Pain Medicine
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Guidance

Meeting Date and Time: December 13, 2023, 3:00-4:00 PM EST
Meeting Location: Videoconference

Application Number: IND 146185
Product Name: VX-548
Indication: Treatment of moderate to severe acute pain.
Applicant Name: Vertex Pharmaceuticals Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Rigoberto Roca, MD, Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of Neuroscience (ON)

Meeting Recorder: Jane Mun, PharmD, Regulatory Project Manager, Division of Regulatory Operations for Neuroscience (DRO-N)

FDA Attendees	Title
Rigoberto Roca, MD	Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of Neuroscience (ON)
Peter Stein, MD	Director, Office of New Drug Center for Drug Evaluation and Research
Mary Thanh Hai, MD	Deputy Director, Office of New Drug Center for Drug Evaluation and Research
Tanya Brescia-Oddo, MD	Clinical Team Leader (Acting), DAAP, ON
Julia Pinto, PhD	Branch IV Chief, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Valerie Amspacher, PharmD	CMC Quality Assessment Lead, ONDP, OPQ
Irene Surh, PhD	Pharmacology/Toxicology Reviewer Division of Pharm/Tox for Neuroscience (DPT-N)
Misol Ahn, PhD	Pharmacology/Toxicology Team Leader, DPT-N

Jay Chang, PhD	Pharmacology/Toxicology Supervisor, DPT-N
Deep Kwatra, PhD	Clinical Pharmacology Team Leader, Division of Neuropsychiatric Pharmacology (DNP), Office of Combination Products (OCP)
Suresh Naraharisetti, PhD	Clinical Pharmacology Reviewer, DNP, OCP
Sue-Jane Wang, PhD	Deputy Director, Division of Biometrics I (DB1), Office of Biostatistics (OB)
Xinyu Tang, PhD	Statistics Secondary Reviewer, Team Lead, DB1/OB
Yunjiang Ge, PhD	Statistics Primary Reviewer, DB1/OB
Sharon Kelly, PhD	API Primary Reviewer, OPQ, ONDP, DNDAPI
Jane Mun, PharmD	Regulatory Project Manager, DRO-N

SPONSOR ATTENDEES:

Sponsor Attendees	Title
Ian Hawkins	Vice President, Global Regulatory Affairs
Ransi Somaratne, MD, FACC	Senior Vice President, Clinical Development
Jim Jones, MD, PharmD, FACEP	Vice President, Global Clinical Development - Pain
Brenda Cirincione, PhD	Vice President, Clinical & Quantitative Pharmacology
Sandra Lechner, PhD	Vice President, Senior Vertex Fellow, North American Pain Research
Meghan Johnston	Executive Director, Chemistry Manufacturing Controls
Xiaopeng Miao, PhD	Director, Biostatistics
Tiffany Healey, MD	Associate Medical Director, Global Patient Safety
Nicole Hurst, PhD, DABT	Senior Research Fellow, Preclinical Safety
Wendy Tian, MS	Senior Director, Global Regulatory Affairs

Zane Craft, MS	Director, Global Regulatory Affairs
Cassidy Kelley	Sr. Manager, Global Regulatory Affairs

BACKGROUND

Vertex Pharmaceuticals Inc. submitted a Type B meeting request on September 22, 2023, to discuss with the Division on several procedural topics related to the upcoming NDA submission and adequacy for filing for VX-548.

There were three topics Vertex wanted to focus on during the industry meeting with the Division (Questions 1, 9, and 11). The three topics included clarification of the integrated summary in the ISE, the role of Study 107 and financial disclosure reporting, and the acceptance of drug product and drug substance stability data packages for NDA filing for VX-548. Vertex did not need any additional clarification on the remaining questions in the meeting background package.

The questions from the October 27, 2023, background package are shown in italic font. The Division responses are shown in bold font, and the meeting discussion is in normal font.

FDA sent Preliminary Comments to Vertex Pharmaceuticals on December 10, 2023. Vertex submitted a Power Point Slide Deck (Appendix 1) as a reference during the industry VCON.

DISCUSSION

Question Related to Clinical Development

Question 1:

Does the Division agree with the proposed structure of the Integrated Summary of Efficacy (ISE) and planned data presentation in the ISE for the assessment of efficacy results across the clinical program?

FDA Response to Question 1

Your plan for the Integrated Summary of Efficacy (ISE) looks reasonable. Based on the example you provided in Section 3, you propose to provide comprehensive assessments of the controlled Phase 3 and Phase 2 studies as follows:

- **Study 104 (Phase 3, bunionectomy) compared to Study 105 (Phase 3, abdominoplasty)**

- **Study 101 (Phase 2, bunionectomy) compared to Study 104 (Phase 3, bunionectomy)**
- **Study 102 (Phase 2, abdominoplasty) compared to Study 105 (Phase 3, abdominoplasty)**

You propose to provide side-by-side tables of the pairs of studies above; however, such tables are not meant to formally compare between studies. Include a description of how you will present the integrated summary in the ISE. If you have already provided these descriptions in your submission, direct us to their location for our review. We may provide further comments once we receive your submission. For additional details on the types of information to include in the ISE, we refer you to point #2 of the Advice Letter issued July 12, 2023.

Discussion:

Regarding Question 1, Vertex asked for clarification if their description of plans for the integrated summary in the ISE as presented was acceptable. The Division responded that the information listed on Slide 6 of the PowerPoint Slide Deck and Section 11.1 of the background package was acceptable. Vertex asked the Division if additional submissions are expected in advance of the NDA submission related to the integrated summary in the ISE. The Division responded that no additional submissions are needed; however, the Division may request additional information when the NDA submission is ready to be filed. Additional Information Requests may be listed in the 74-Day letter and in other correspondences. Vertex acknowledged the Division's comments.

Question 2:

Can the Agency confirm if it is acceptable to submit the CSR for Study 014 (severe or moderate renal impairment subjects) during the NDA review?

FDA Response to Question 2

We recommend that all clinical study reports be submitted at the time of NDA submission. However, the Division will be able to review the CSR for Study 014 if submitted no later than 60 days from the receipt date of the original NDA submission. If the Study 014 CSR is submitted after that time, the Division cannot guarantee that it will be reviewed.

Discussion:

There was no further discussion for this question.

Question 3:

Clinical study data will be placed in the SDTM and ADaM folders according to the eCTD file directory structure for study datasets in accordance with FDA Study Data Technical Conformance Guide, dated June 2023. To facilitate the review:

Question 3a:

Vertex submitted the study data standardization plan (SDSP; provided as an appendix). Does the Division agree with the plan?

FDA Response to Question 3a:

We have no concerns with the submitted study data standardization plan at this time.

Question 3b: Vertex plans to include the following SAS Version 9.4 programs in the submission. Does the Division agree that this plan is acceptable?

- i) Non-executable programs as PDF files for all ADaM datasets.
- ii) Executable programs as SAS files for the tables and figures associated with the analyses for the efficacy endpoints for the 2 controlled Phase 3 Studies 104 and 105 only.

Discussion:

There was no further discussion for this question.

FDA Response to Question 3b

Since Study 107 will provide supportive effectiveness data, we recommend you submit the SAS codes for Study 107 as well. Additionally, we suggest you submit the executable programs for all ADaM datasets for Studies 104, 105, and 107.

Discussion:

There was no further discussion for this question.

Questions Related to Regulatory Pathway

Question 4:

Does the Division agree with the content to be included in the abuse potential and dependence assessment package, which includes chemistry, mechanism, nonclinical, and clinical studies conducted in accordance with the 2017 FDA Abuse Potential Guidance, and location of these information in the proposed CTD sections of the NDA?

FDA Response to Question 4

In principle, the Agency agrees with your proposal to submit the abuse liability data consistent with the 2017 FDA guidance for industry, *Assessment of Abuse Potential of Drugs*. However, further data, or clarification of the data, may be requested upon review of the cumulative data submitted, either during the IND stage or following NDA submission. We also agree that the submission of this information should be organized in the following manner:

- a. Section 1.11.4 of your NDA should contain your proposal and rationale for placing or not placing the drug substance or product into any schedule of the CSA.**
- b. Section 2.7.4 should contain a subsection devoted to details of your abuse potential assessment, including a description of data, interpretation, and discussion of all abuse potential data provided in the NDA under other modules, including any drug accountability discrepancies and an analysis of abuse-related adverse events. Section 2.7.4 should also contain a comprehensive table of contents that provides links to all studies (nonclinical and clinical) and references in the NDA submission related to the assessment of abuse potential.**

Discussion:

There was no further discussion for this question.

Question 5

Vertex will request priority review for the planned VX-548 NDA. Assuming confirmatory safety and efficacy from the Phase 3 data, does the Division agree that the VX-548 NDA meets the criteria for and would be granted Priority Review Designation?

FDA Response to Question 5:

VX-548 appears to meet the qualifying criteria for priority review designation; however, the Division cannot commit in advance of NDA receipt to granting a

priority review designation for VX-548. This determination is done at the time of filing of an NDA submission.

Discussion:

There was no further discussion for this question.

Question 6

Vertex would like to understand the Division's perspective on whether they anticipate the need for an AADPAC for VX-548.

FDA Response to Question 6:

As a first-in-class drug that will likely have a substantial impact on outpatient management of moderate-to-severe acute pain, the Division anticipates that convening an Advisory Committee may be warranted. However, a decision has not been made at this time. Additionally, though not anticipated, it is possible that an issue may be identified during the NDA review which necessitates convening an Advisory Committee.

Discussion:

There was no further discussion for this question.

Question 7

Does the Division agree with Vertex providing the safety update report 90 days after the initial NDA submission, if granted Priority Review?

FDA Response to Question 7:

No, we do not agree. Submission of the safety update report 120 days after the initial NDA submission should permit sufficient time for review no matter the review designation, standard or priority. Moreover, safety data will continue to be generated

(b) (4)

and this safety data will need to be included in the safety update report. Submission of the report 90 days after initial NDA submission risks excluding important safety data needed to determine the benefit: risk profile for VX-548.

Discussion:

There was no further discussion for this question.

Question 8

Can the Division advise if an Application Orientation Presentation Meeting will be needed within 30 days after the NDA submission?

FDA Response to Question 8:

Though an Application Orientation Meeting may not be vital, we agree that this type of meeting within 30 days of submission would be helpful to the review team, facilitating efficient completion of discipline-specific filing and NDA reviews, especially if VX-548 is granted priority review.

Discussion:

There was no further discussion for this question.

Question Related to Regulatory Pathway

Question 9:

Does the Division agree that the Phase 3 studies (Studies 104, 105, and 107) are the studies in this NDA which are under 21 CFR 54 for purposes of Financial Disclosure?

FDA Response to Question 9:

No, we do not agree. Studies 104 and 105 will be relied upon to establish that VX-548 is effective for the treatment of moderate-to-severe acute pain, and therefore, meet the 21 CFR 54.2(e) definition of a covered clinical study. In this instance, only covered clinical studies require financial disclosure. Study 107, while supportive of the positive results of Study 104 and 105, will not be relied upon to establish the efficacy of VX-548, and therefore, does not require a financial disclosure. For additional detail, we refer you to FDA's guidance for Clinical Investigators, Industry, and FDA Staff *Financial Disclosure by Clinical Investigators*.¹

Discussion:

Regarding Question 9, Vertex sought clarification on the role of Study 107 for the NDA for the treatment of moderate to severe acute pain. Vertex stated that they agree with the Division that Study 107 is supportive of the two Phase 3 pivotal studies supporting an indication for the treatment of moderate to severe acute pain in adults. Vertex plans to include a description of Study 107 in the Adverse Reactions Section (Section 6) of the label. Vertex believes Study 107 should qualify as a covered clinical study under

¹ <https://www.fda.gov/media/85293/download>

21CFR54.2(e) which includes "...any study in which a single investigator makes a significant contribution to the demonstration of safety."

The Division responded that Slide 7 of Vertex's Power Point Presentation was helpful to understand the context of Vertex's question. The Division stated that it is their understanding that Study 107 is a multicenter study with nine or more clinical investigators and approximately 250 patients enrolled. Over 1000 patients would be exposed to VX-548 in the Phase 3 program; therefore, Study 107 would account for approximately 25% of the safety data for the Phase 3 program. Although Study 107 is not designed to evaluate a specific safety signal and may not meet the criteria for a covered clinical study (i.e., studies for which financial disclosure is required), Vertex may submit a financial disclosure for Study 107 for completeness of the NDA submission. Vertex acknowledged the Division's statement.

Question Related to Chemistry, Manufacturing, and Controls

Question 10:

Due to anticipated VX-548 production demand and to enhance the robustness of the VX-548 supply chain, Vertex intends to submit comparability protocols at the time of NDA submission to qualify second source suppliers of drug substance, (b) (4) and drug product post approval.

Does the Agency agree to review the post-approval change management protocols (PACMPs) with the initial NDA?

FDA Response to Question 10:

The comparability protocols to qualify a second source of suppliers of VX-548 drug substance and drug product will be reviewed if submitted with the initial NDA.

Discussion:

There was no further discussion for this question.

Question 11:

Vertex intends to submit a stability package aligned with the proposal discussed in the Type D meeting, held on 08 Jun 2023. Vertex aims to provide 6 months of drug substance formal stability (accelerated and long-term) (b) (4) and 12 months of long-term drug product formal stability data (b) (4) (i.e., within (b) (4) days of submission).

Does the Agency agree that additional stability data can be submitted and reviewed during review according to the timelines above?

FDA Response to Question 11:

The proposal discussed in the Type D meeting, held on 08 Jun 2023, conveyed the API recommendation that the NDA submission include 6 months of real-time and accelerated stability data for the primary stability batches. Additional stability data from the 9-month timepoint should be submitted early during the NDA review cycle. This recommendation took into consideration MAPP 5015.13. Your current proposal only provides a maximum of 6 months data for three primary batches within (b) (4) days of submission. We do not agree with your current proposal. After further consideration of the available stability data from Appendix 2, we recommend at least 6 months data for the three primary batches within 30 days of the original NDA submission.

We remind you of the 08 Jun 2023 discussion regarding the commercial retest period for the drug substance, as follows (1) demonstrate the comparability of the supporting batches with the commercial material and (2) any additional stability data should be submitted within 30 days of the NDA submission. The retest period will be a matter of review based on the totality of the data provided. Therefore, we recommend that you update stability data for all batches manufactured by Olon within 30 days of NDA submission.

From the drug product perspective, we expect the stability package to be complete with 12 months of long-term and 6-months of accelerated data at the time of NDA submission. Given the potential for a shorter review clock (if priority review is granted), any additional data must be submitted within 30 days of filing, in order to allow time for adequate review.

Discussion:

Vertex asked for clarification from the Division on the adequacy of drug product and drug substance stability data packages for NDA filing of VX-548. Vertex stated that based on an end-of-May 2024 NDA submission date for the drug substance, 6 months of long-term and accelerated stability data for the three primary lots will be provided in the initial NDA submission. Regarding the drug product, Vertex proposed to provide 9 months of long-term and 6 months of accelerated stability data from three primary batches in all packaging configurations with initial NDA submission and 12 months of long-term stability data within 30 days of the NDA submission. The Division responded that this timeline is acceptable as long as the 12 months stability data is received within 30 days of the NDA submission. The Division stated that it is critical the 12 months data are received within the 30 days of the NDA submission, because if they do not receive this information in this timeline, it will be unclear if there is enough time for the review

team to review the product as the shelf-life of the product may be limited to 9 months. Vertex acknowledged the Division's comments.

Additional Clinical Pharmacology Comments:

- a. You conducted some of the Phase 1 studies and both Phase 2 studies using 10 mg strength tablet. Since your Phase 3 formulation is 50 mg strength tablet, you need to provide sufficient bridging information between 10 mg and 50 mg strength tablets, so the data obtained with 10 mg strength can be extended to 50 mg strength.**
- b. We would like to reiterate that the final to-be-marketed formulation should ideally be used in critical clinical pharmacology and pivotal clinical studies to support your NDA submission. We acknowledge that you may evaluate earlier (pilot) formulation(s) during drug development. To use results from a pilot formulation to support your NDA submission, you will need to provide adequate justification and/or bridging information.**
- c. In the initial NDA submission, summarize bioanalytical methods for each clinical pharmacology study that involved pharmacokinetic concentration evaluation, as outlined in Bioanalytical Methods Templates, Guidance for Industry Technical Specifications Document ²**

Discussion:

There was no further discussion for the additional Clinical Pharmacology comments.

Additional Topics Discussed:

In addition, Vertex presented to the Division a timeline of their NDA submission plan listed on Slide 10 of the Power Point Presentation. In this timeline, Vertex stated that they intend to have a Pre-NDA meeting in April 2024 after data readout of the VX-548 Phase 3 studies. The Division recommended submitting a meeting request as soon as possible to secure a meeting date. Vertex confirmed that a complete NDA submission would occur in May 2024.

The Division also inquired if Vertex considered submitting a rolling review request since VX-548 has been granted Breakthrough Therapy Designation. The Division stated that if Vertex does have complete modules, the submission of these complete modules ahead of time could be helpful. Vertex stated that an early submission for Nonclinical Module 5 could be a possibility, while the other modules would most likely not have a complete submission until the NDA submission date of May 2024. Vertex stated they will have

² <https://www.fda.gov/media/131425/download>

internal discussions around the topic of a rolling review. The Division acknowledged this statement.

Lastly, Vertex confirmed receipt of the 12 December 2023 Study 107 Statistical Analysis Plan Advice Letter and plans to submit the updated final Study 107 SAP to IND 146185 prior to database lock. The Division acknowledged this statement.

Post Meeting Note:

If Vertex plans to submit some portion of the application separately, a request for submission of portions of an application should be sent as an amendment to the IND, along with a proposed schedule for submission of portions, as soon as possible. Also refer to guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics*³ for additional information.

ISSUES REQUIRING FURTHER DISCUSSION

There were no additional issues requiring further discussion.

ACTION ITEMS

There were no action items discussed.

ATTACHMENTS AND HANDOUTS

Appendix 1 (Power Point Slides)

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

³ <https://www.fda.gov/media/86377/download>

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 guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.⁴ 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.⁵

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*.

SUBMISSIONS WITH REAL-WORLD EVIDENCE

CDER strongly encourages sponsors to include information in their submission cover letters that identifies uses or proposed uses of real-world evidence (RWE) to support a regulatory decision regarding product safety and/or effectiveness. For recommendations on specific information to include in submission cover letters, see the guidance for industry *Submitting Documents Using Real-World Data and Real-World Evidence to FDA for Drug and Biological Products*.⁶ For questions or clarification, contact cdermedicalpolicy-realworldevidence@fda.hhs.gov.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used

⁴ <https://www.fda.gov/media/86340/download>

⁵ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁶ <https://www.fda.gov/media/124795/download>

for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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/s/

JANE J MUN
01/08/2024 01:40:26 PM



IND 146185

**MEETING REQUEST-
WRITTEN RESPONSES**

Vertex Pharmaceuticals Incorporated
Attention: Alexander Craft
Regulatory Strategy Associate Director, Regulatory
50 Northern Avenue
Boston, MA 02210

Dear Mr. Craft:¹

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-548.

We also refer to your submission dated September 26, 2022, containing a meeting request. The purpose of the requested meeting was to gain preliminary feedback on Vertex's proposed regulatory starting materials, impurity control strategy, and VX-548 drug substance formal stability data proposal.

Further reference is made to our Meeting Granted letter dated October 7, 2022, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your October 14, 2022 background package.

If you have any questions, contact Anika Lalmansingh, Sr. Regulatory Business Process Manager at (240) 402-0356 or anika.lalmansingh@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Julia Pinto, PhD
Branch Chief
Division of New Drug Products II
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

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>.



WRITTEN RESPONSES

Meeting Type: B
Meeting Category: EOP2

Application Number: IND 146185

Product Name: VX-548
Indication: Treatment of Pain
Sponsor Name: Vertex Pharmaceuticals Incorporated

1.0 BACKGROUND

Vertex Pharmaceuticals Incorporated (Vertex) submitted IND 146185 to the FDA on January 8, 2020 and is developing VX-548 for the treatment of moderate to severe acute pain.

Vertex is currently conducting Phase 3 of clinical trials and received Fast Track designation on March 5, 2020 and Breakthrough Therapy designation on June 30, 2020.

Vertex has previously participated in a multidisciplinary, Type B, EOP2 meeting on July 14, 2022 with the Division of Anesthesia, Addiction Medicine and Pain Medicine.

2.0 QUESTIONS AND RESPONSES

Question 1: *Does the Agency agree with the proposed VX-548 drug substance starting materials?*

FDA Response to Question 1:

Based on the information provided in the briefing package, (b) (4) does not qualify as an acceptable regulatory starting material for the manufacture of the drug substance. The main issues (b) (4)



are provided to justify its selection. Note that a nitrosamine risk assessment for the manufacture of the drug substance is required in your eventual NDA application.

Question 2: *Does the Agency agree with Vertex's drug substance impurity control strategy, including, Vertex's approach to control (b) (4) in VX-548?*

FDA Response to Question 2:

According to the information presented in the meeting package, the impurity control strategy appears reasonable. A final decision will be made during the NDA review when all the information is available for review.

Question 3: *Does the Agency agree that Vertex can submit additional stability data during the review cycle? Specifically: (b) (4) months of stability data on three primary batches of drug substance will be submitted with the initial NDA (b) (4)*

(b) (4) and drug product will be submitted with the initial NDA and 12 months of stability data will be submitted during the review cycle

FDA Response to Question 3:

No, we do not agree. A minimum of 12 months of stability data obtained from the proposed drug substance commercial site should be submitted in the original application. Similarly, 12 months of stability data for the drug product is required at the time of NDA submission. Given our tight internal deadlines, we cannot guarantee to have time to review any additional data submitted after initial submission. Based on ICH Q1A(2R) and Q1E, data for 6-month accelerated stability studies and 12-month long term stability studies should be available at the time of NDA submission. In the event there are less than the required 12 months of data available at time of NDA submission, the proposed shelf life of the drug product will not exceed the shortest period supported by any batch.

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/

JULIA C PINTO
12/01/2022 10:59:21 AM



IND 146185

MEETING MINUTES

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210

Attention: Alexander Craft
Director, Regulatory Affairs

Dear Mr. Craft:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VX-548.

We also refer to the telecon between representatives of your firm and the FDA on July 14, 2022; 2:00 p.m. ET. The purpose of the meeting was to obtain the Division's input on the proposed development plan and Phase 3 clinical studies to support the registration of VX-548 for the indication to treat moderate to severe acute pain.

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, please contact me via email at Jane.Mun@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jane Mun, PharmD
Regulatory Project Manager
Anesthesiology, Addiction Medicine, and
Pain Medicine
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2
Meeting Date and Time: July 14, 2022; 2:00 p.m. ET
Meeting Location: Teleconference
Application Number: IND 146185
Product Name: VX-548
Indication: Treatment of moderate to severe acute pain.
Sponsor Name: Vertex Pharmaceuticals Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair: Rigoberto Roca, MD, Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of Neuroscience (ON)
Meeting Recorder: Jane Mun, PharmD, Regulatory Project Manager, Division of Regulatory Operation for Neuroscience (DRO-N), Office of Regulatory Operations (ORO)

FDA Attendees	Title
Rigoberto Roca, MD	Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of Neuroscience (ON)
Silvana Borges, MD	Deputy Director (Acting), DAAP, ON
Tanya Brescia-Oddo, MD	Clinical Reviewer, DAAP, ON
Misol Ahn, PhD	Pharmacology/Toxicology Team Leader, DPT-N
Daniel Mellon, PhD	Deputy Director, Division of Pharm/Tox for Neuroscience (DPT-N)
Yun Xu, PhD	Clinical Pharmacology Team Leader, Division of Neuropsychiatric Pharmacology, OCP
Suresh Narahariseti, PhD	Clinical Pharmacology Team Leader, Division of Neuropsychiatric Pharmacology, OCP

Jing Han, PhD	Primary Statistical Reviewer, Division of Biometrics I (DB1), Office of Biostatistics (OB)
Sue-Jane Wang, PhD	Deputy Director, DB1/OB
Jane Mun, PharmD	Regulatory Project Manager, Division of Regulatory Operation for Neuroscience, Office of Regulatory Operations

SPONSOR ATTENDEES:

Sponsor Attendees	Title
Reshma Kewalramani, MD FASN	President & Chief Executive Officer
Nia Tatsis, PhD	Executive Vice President and Chief Regulatory and Quality Officer
Carmen Bozic, MD	Executive Vice President and Chief Medical
Ian Hawkins	Vice President, Regulatory Affairs
Wendy Tian	Sr. Director, Regulatory Affairs
Jim Jones, MD, PharmD, FACEP	Vice President, Clinical Development
Simon Tian, MD	Executive Medical Director, Patient Safety
Brenda Cirincione, PhD	Vice President, Clinical and Quantitative Pharmacology
Mazin Derzi, Sr.	Vice President, Preclinical Safety
Nicole Hurst, PhD, DABT	Sr. Fellow, Preclinical Safety
Bo Yang, PhD	Vice President, Biostatistics
Xiaopeng Miao, PhD	Director, Biostatistics
Zane Craft MS, Director	Director, Regulatory Affairs
Cassidy Kelley	Sr. Manager, Regulatory Affairs

BACKGROUND

Vertex Pharmaceuticals Inc. submitted a Type B, End of Phase 2 meeting request on April 4, 2022, requesting the Division's input on the proposed development plan and

Phase 3 clinical studies to support the registration of VX-548 for the indication to treat moderate to severe acute pain. Vertex plans to conduct two pivotal Phase 3 studies to evaluate the efficacy and safety of VX-548 following bunionectomy and abdominoplasty.

A breakthrough designation request was granted in June of 2022 for the treatment of moderate-to-severe acute pain. We acknowledge that the Breakthrough Designation Granted letter dated June 30, 2022, stated that your End-of-Phase 2 meeting will also be used as the initial Breakthrough Therapy meeting. However, in order to provide adequate time to discuss the questions previously submitted in the briefing package, we encourage you to submit a separate type B meeting request.

The questions from the May 25, 2022, background package are shown in *italic font*. The Division responses are shown in **bold font**, and the meeting discussion in regular font.

FDA sent Preliminary Comments to Vertex Pharmaceuticals Inc. on July 12, 2022.

DISCUSSION

Nonclinical

Question 1:

- a. *Does the Division agree that the nonclinical data completed by the end of Phase 2 supports the initiation of Phase 3 clinical studies in moderate to severe acute pain?*
- b. *Does the Division agree that the nonclinical package, upon completion, is adequate to support future registration of VX-548 for the treatment of moderate to severe acute pain?*

FDA Response to Question 1a:

No, we do not agree that the nonclinical data completed by the end of Phase 2 support the initiation of your planned Phase 3 studies. Based on the list of the completed and planned nonclinical studies described in your briefing package, it appears you plan to conduct photo safety studies during Phase 3 and submit those data with your NDA application. Note that an evaluation of the phototoxic potential of your drug product should be completed before exposure of large numbers of subjects (i.e., Phase 3) as recommended in the ICH guidance for industry: *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals*.¹ In addition, all disproportionate major human metabolites, which are those that represent

¹ <https://www.fda.gov/media/71542/download>

greater than 10% of the total drug-related exposure, should be adequately qualified for safety prior to initiating a large-scale clinical studies as recommended in the FDA guidance for industry: *Safety Testing of Drug Metabolites*.² We agree with your plan to complete Segment 1 fertility studies in male and female rats and definitive embryo-fetal development studies in rats and rabbits before the initiation of your planned Phase 3 studies. However, we note that based on your pharmacology data, potencies of VX-548 against Nav1.8 in rats and rabbits are approximately 100-fold lower compared to that in human. Therefore, you need to justify how reproductive toxicity studies in rats and rabbits adequately address on-target effects on relevant reproductive toxicity endpoints.

The adequacy of the nonclinical package to support the initiation of Phase 3 clinical studies in moderate to severe acute pain can only be determined after a full review of the submitted nonclinical data.

Meeting Discussion:

Vertex acknowledged the Division's comments in the preliminary meeting package. Vertex stated that VX-548 is chemically non-photoreactive in a Reactive Oxygen Species (ROS) assay, that a tissue distribution study in pigmented animals suggests that VX-548 does not preferentially distribute into pigmented tissues, and that they will submit a phototoxicity assessment report to the IND following the End of Phase 2 meeting. The Division asked a clarification question whether VX-548 is not photoreactive at the range of natural sunlight of 290-700 nm and the Sponsor confirmed that the data indicate VX-548 is not photoreactive. The Division indicated that the described in vitro and in vivo phototoxicity evaluation appears to be appropriate to submit prior to initiating the planned Phase 3 study; however, the Division noted that the adequacy of data supporting safety of the planned Phase 3 study cannot be determined until the data are submitted and fully reviewed.

Vertex stated that M6-548 is the only major metabolite in humans and is qualified through nonclinical studies in NHP, rat and rabbit. Vertex explained that M6-548 is not a disproportionate human metabolite as it was detected at concentrations at least 4 times greater in all nonclinical species tested compared to humans. The proportion of metabolite to parent is similar in monkey and human with the metabolite detected at 3 times the level of parent. The Division indicated that it is not clear whether a human mass balance study to assess all potential disproportionate human metabolites was conducted and requested that the Sponsor update Pharmacokinetics Written Summary in Module 2 if or when available. The Sponsor indicated that human ADME data would be submitted and updated in Module 2 of the IND prior to Phase 3 initiation. The Division indicated that adequacy of the data to qualify the safety of major human

² <https://www.fda.gov/media/72279/download>

metabolites to support the planned Phase 3 program will be determined after a review of the study reports submitted to the IND.

Vertex also stated that the rat and rabbit studies have demonstrated on-target effects of Nav1.8 inhibition in reproductive studies and are pharmacologically relevant species for the assessment of reproductive and development toxicity of VX-548. They noted that the free concentrations of drug achieved in the preliminary embryo-fetal development studies at the NOAELs were greater than or equal to the species specific IC₅₀ values for Nav1.8 inhibition (rat 1x and rabbit 5x). They also referred to literature that suggested that Nav1.8 knock-out data does not adversely impact embryofetal development. Vertex asked the Division if these nonclinical data address the Division's request for justification. The Division asked how the expected saturation levels of VX-548 in plasma of humans compare to the IC₅₀s obtained in animals. Vertex responded that in clinical studies they are targeting the IC₉₀ level, and they achieved free concentrations in rabbits that were 5 times greater than the IC₅₀ for Nav1.8 inhibition. The Division noted that based on their response it could be that Vertex may not be achieving the levels in rats that are comparable to the targeted receptor saturation expected in the clinical setting, which is less than ideal. The Division asked what the basis of high-dose selection was in the rat studies. Vertex responded that the high dose selection was based on the maximum tolerated dose from dose range-finding studies. The Division also noted the challenges of interpreting knock-out data due to the potential for compensation. The Division indicated that the Division understands the limitations and challenges around pharmacologically relevant species selection and the Division noted that the Sponsor should submit the definitive embryofetal development study reports, including rationale for the study design and all supporting data to the IND. The Division recommended that the Sponsor should also include information regarding any limitations of the study studies in both the investigational brochure and the informed consent. Once this information is submitted, the Division will review and provide any feedback regarding the overall data. Based on the summary data and rationale provided to date, limitations of the studies may not preclude moving into Phase 3; however, the Division will have to review the study reports and supporting data to provide a definitive response. Vertex acknowledged the Division's comments and will submit the appropriate reviews and studies.

FDA Response to Question 1b:

No, we cannot agree that the nonclinical package, upon completion, is adequate to support future registration of VX-548 for the treatment of moderate to severe acute pain. However, overall, your proposed nonclinical package appears to be appropriate for NDA filing of VX-548 for treatment of moderate to severe acute pain. We note that you plan to submit long-term repeat-dose general toxicity studies (i.e., 26-week rat and 39-week monkey studies) with your NDA. While those studies are not needed for an NDA proposing an acute pain indication, it is acceptable for you to submit these studies to the acute pain indication NDA. If you elect to pursue a chronic indication for NDA, carcinogenicity studies should also be completed and carcinogenicity data should be submitted at the time of NDA submission. To determine if carcinogenicity studies are warranted for your program, refer to the ICH guidance for industry *S1A The Need for Long-term Rodent Carcinogenicity Studies of Pharmaceuticals*.³ If warranted, you are strongly encouraged to submit a special protocol assessment to receive agreement from the Executive Carcinogenicity Assessment Committee prior to initiation of this study.

The adequacy of the nonclinical package to support registration of VX-548 in moderate to severe acute pain can only be determined after a full review of the submitted nonclinical data.

Refer to the additional nonclinical comments below to determine if any additional nonclinical studies are warranted for your drug development program.

Meeting Discussion:

Vertex asked if the Division agrees that the nonclinical package is sufficient to proceed to Phase 3. The Division indicated that the Sponsor's approach appears to be appropriate but the Division cannot agree that the supporting studies are adequate to support the planned Phase 3 study until we review the data.

Vertex asked if, provided that Vertex resolves the Division's comments in Question 1a, the Division agrees that the proposed nonclinical package is sufficient to support filing an NDA for the treatment of moderate to severe acute pain. Additionally, Vertex stated that they understand that submission of long-term toxicity data is not required to support an NDA for the treatment of moderate to severe acute pain, therefore, the Sponsor is not planning to submit long-term repeat-dose general toxicity studies, which would include 26-week rat and 39-week monkey studies, with an NDA for the treatment of moderate to severe acute pain. The Division noted that the proposed plan appears

³<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM074911.pdf>

adequate to support filing an NDA for an acute indication. The Division encouraged the Sponsor to submit the chronic studies as soon as they are finalized.

Clinical Pharmacology

Question 2:

- a. *Does the Division agree that the completed/ongoing clinical pharmacology studies listed in Table 12-3 can support the initiation of the proposed VX-548 Phase 3 clinical program while the rest of planned studies can be conducted concurrently with Phase 3 studies?*
- b. *Does the Division agree that all the studies listed in Table 12-3 are sufficient to support the future NDA submission of VX-548 for the treatment of moderate to severe acute pain?*

FDA Response to Question 2a:

We cannot agree at this stage. Some of the clinical pharmacology studies, such as tQT, hepatic impairment, DDI, food effect are not completed. Since some of the results from these studies may be required to be considered for Phase 3 studies' dosing, you will need to provide adequate inclusive/exclusive criteria and monitoring plan to support your proposed Phase 3 studies based on available information.

QT prolongation potential of your product needs to be evaluated before large scale clinical studies such as Phase 3 clinical trials. It is recommended that you adequately evaluate the QT prolongation potential of your product before the proposed Phase 3 study. Without an adequate characterization, an expanded ECG safety evaluation plan will be needed for your proposed protocol. Refer to "E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs".⁴

We note that you have evaluated food effect using 10 mg strength of tablet formulation at a total dose of 40 mg (10 mg x 4 tablets). We note that you have proposed a "Phase 1 confirmatory BA and food effect: relative BA and food effect study using Phase 3 formulation". Note that food effect study needs to be evaluated before initiating the Phase 3 studies for informed dosing in Phase 3 trials. Also, the food effect needs to be evaluated on the highest strength of final to-be-marketed product, using the highest proposed clinical dose, with FDA recommended high fat meals.

⁴ <https://www.fda.gov/media/71372/download>

Based on your in vitro studies, the IC₅₀ values of VX-548 to inhibit certain transporters and CYP enzymes appear to be in low micromolar range. For example, IC₅₀ values of VX-548 for OATP1B1, OATP1B3 and CYP2C19 are 1.7, 3.0 and 5.2 mcM, respectively. You need to determine whether VX-548 at the clinically relevant highest concentrations have the potential to inhibit any enzymes and thereby cause drug-drug interactions. We refer you to the guidance for industry: *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry | FDA*⁵. You need to provide this information before initialing your phase 3 trials.

In the writeup for Question 2a, we note that you proposed, “as a conservative approach, subjects with a history of significant hepatic disease will be excluded from Phase 3 studies, and concomitant medications known to be strong or moderate CYP3A inducers or inhibitors will be prohibited”. However, in the Exclusion criteria of proposed Phase 3 trails’ synopses, there is no language related to the exclusion of subjects taking CYP3A inducers or inhibitors. Update CYP3A inducers or inhibitors language for your Phase 3 protocols.

Based on the information provided in the meeting package, it appears that VX-548 is predominantly eliminated by non-renal routes. For drugs that are predominantly eliminated via nonrenal routes and likely to be used in patients with impaired renal function, a reduced study design can be used to determine the need for dose adjustment. Refer to the Clinical Pharmacology Guidance – *Pharmacokinetics in Patients with Impaired Renal Function*⁶. You should conduct a renal impairment study with a reduced study design.

The final to-be-marketed formulation, and delivery device if applicable, should ideally be used in critical clinical pharmacology and pivotal clinical studies to support your NDA submission. It is possible that you use earlier (pilot) formulation(s) or pilot delivery device(s) during drug development. To use results from a pilot formulation or delivery device to support your NDA submission, you should provide adequate justification and/or bridging information.

Meeting Discussion:

Vertex agreed with the Division’s preliminary comments regarding hepatic impairment, food effect and renal impairment and plans to conduct the following studies: a study in patients with impaired hepatic function, and a study in patients with impaired renal function utilizing a reduced study design concurrently with Phase 3. The Phase 3 study will exclude subjects with severe renal impairment and subjects with a history of

⁵ <https://www.fda.gov/media/134582/download>

⁶ <https://www.fda.gov/media/78573/download>

significant hepatic disease will and transaminase elevations greater than 2.5x ULN. Also, a food effect study with the highest planned commercial dose (100 mg) and a high fat meal per FDA guidance will be submitted prior to Phase 3 studies. Lastly, Vertex plans to clarify in the Phase 3 protocols that moderate and strong CYP3A inducers and inhibitors will be prohibited. Vertex asked the Division if this was sufficient to proceed to Phase 3 studies.

The Division responded to Vertex stating that we encourage these clinical pharmacology studies be conducted before Phase 3 study initiation to inform the specific inclusion/exclusion criteria and dose adjustments. If the information from these studies are not available then Vertex will need to address the missing information in the Phase 3 protocols by providing adequate recommendations such as dosing adjustment, inclusion/exclusion criteria, monitoring plan, etc. as Vertex plans to conduct some studies in parallel with P3 study (i.e., renal, hepatic impairment study) The Division noted that the less information there is available, the more restrictive the Phase 3 study protocol will need to be, as the subject's safety is the Division's priority. The Division stated that based on a quick review, in principle Vertex's plan seems reasonable, but the Division emphasized that at this stage they cannot agree on the specific criteria of the Phase 3 studies as a review of the protocol is needed. The Division can only make this decision at the protocol review stage.

The Division stated some concerns based on the information with several completed clinical pharmacology studies. For example, itrocinonide, a strong 3A4 inhibitor will increase AUC of VX-548 by 4-fold based on the DDI study. If Vertex plans to include mild 3A4 inhibitors in the Phase 3 studies, Vertex needs to provide adequate information or justification to demonstrate that exposure of VX-548 will not have clinically significant changes with mild 3A4 inhibitors. VX-548 is mainly metabolized by liver, so Vertex needs to provide justification to support their exclusion/inclusion criteria regarding hepatic impairment. The Division will provide more comments when the protocol is in. Additionally, the Division mentioned that VX-548 is a 3A4 inducer, but there was no information on whether VX-548 has induction effect on other CYP enzymes. The Division encouraged Vertex to provide induction evaluation for other CYPs in addition to 3A4, such as 1A2, 2B6, 2C9, etc., and provide adequate inclusion/exclusion criteria in the P3 protocol accordingly. The Division noted that we could not find such information in the submission. The DDI guidance in the preliminary guidance for a complete list for DDI evaluation is an available reference.

Regarding the food effect study, the Division stated it appears reasonable at this stage, but if the food study shows significant effect, then food restrictions on the Phase 3 study could be implemented.

FDA Response to Question 2b:

We cannot agree at this stage. Although the studies listed in Table 12.3 appear to be reasonable, depending on some of the requested data/information before initiating your phase 3 trials as well as the results from your planned studies, as we noted in our 2a response, additional studies may be needed for your NDA submission.

Meeting Discussion:

Vertex acknowledged the Division's comments regarding tQT and plans to include expanded ECG safety evaluation in the three Phase 3 protocols per E14: Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs. Vertex highlighted the following information:

- 1) The Concentration QT assessment of data collected in SAD and MAD studies has been completed.
- 2) Preclinical and clinical evaluations of this data to date have not identified a risk of QT prolongation
- 3) Vertex intends to submit to IRT, via the Division, to determine the adequacy of the package to fulfill the QT requirement per the ICH guidelines.

Vertex believes the following studies addressed the Division's request and asked if the Division agrees. The Division responded that in general the approach seems reasonable and recommended Vertex to submit their QT evaluation plan before the start of Phase 3 study. The cover letter should state that they are seeking the Division and QT/IRT input on the QT evaluation plan, so the Division can consult the QT-IRT group. Vertex acknowledged these comments from the Division and stated that they will address these concerns when they submit their Phase 3 protocol.

Question 3:

The proposed Phase 3 study designs are provided in the briefing document, including 2 pivotal studies in bunionectomy and abdominoplasty (Studies 104 and 105) and a single-arm safety and effectiveness study in a broad range of acute pain conditions (Study 107). We seek the Division's agreement on the following key elements of the program.

- a. *Does the Division agree with the study designs of the Phase 3 studies?*
- b. *Does the Division agree with the proposed analyses of the primary endpoint for both pivotal Phase 3 studies?*

- c. *Does the Division agree with the proposed key secondary endpoints and the multiplicity control strategy in the pivotal Phase 3 studies?*

FDA Response to Question 3a:

1. **At a high level, certain proposed study design features listed in the protocol synopses for Studies 104, 105, and 107 appear reasonable. However, in order to avoid replicating possible study design limitations of your Phase 2 studies (101 and 102) we suggest that you consider the following points when finalizing your pivotal Phase 3 protocols.**
 - a. **Why the mid-dose VX-548 treatment arm (60 mg/30 mg q12h) performed worse than any other treatment arm.**
 - b. **Why the opioid comparator arm did not reach statistical significance in either Study 101 or 102 for SPID48 and SPID24. If flaws in study design cannot explain the lack of statistical significance in the opioid comparator arm for SPID48 and SPID24, consider if the opioid dose and/or frequency, while within the labeled dosage, is too low to provide analgesia in bunionectomy and abdominoplasty pain models.**
 - c. **Despite the delayed absorption of VX-548 observed on Day 1 after abdominoplasty in Study 102, we note that the ad hoc analysis performed for endpoints of “time to 1-point reduction in NPRS score” and “time of 2-point reduction in NPRS score” achieved statistical significance in this study. However, despite no delayed absorption on Day 1 after bunionectomy, the ad hoc analysis performed for these same endpoints did not reach statistical significance.**
2. **Additionally, we recommend incorporating the following study design features when finalizing your pivotal Phase 3 protocols.**
 - a. **Blinding: Ensure that the study staff who are administering study medications are different from staff performing efficacy and safety assessments.**
 - b. **Rescue medication: We refer you to the draft guidance for industry, *Development of Non-Opioid Analgesics for Acute Pain*, Section header *Secondary Efficacy Endpoints*⁷ which contains important information for recording data related to rescue medication use so as not to jeopardize the validity of your studies.**

⁷ <https://www.fda.gov/media/156063/download>

- c. Ensure that pain intensity (PI) scores are recorded immediately prior to rescue medication use, and that the PI score is carried forward (i.e., using the last observation carried forward (LOCF) methodology) for the appropriate time period based on your choice of rescue medication.**
- d. Include the following secondary endpoints:**
 - i. Proportion of patients requesting first rescue medication in the first 12 hours.**
 - ii. Median time to first rescue in the first 12 hours.**
 - iii. Proportion of patients using rescue pain medication over time intervals of 0-24 hours and 24-48 hours.**
 - iv. SPID12 and SPID36 to evaluate pain control during the proposed dosing interval.**

We may have additional comments when the final protocols are reviewed.

Meeting Discussion:

The Division emphasized the following points with respect to Question 3a:

- a. If there are overlapping rescue periods, Vertex proposed that the pre-rescue NPRS for the first rescue period will be used for the imputation. Vertex will need to specify how much time the pre-rescue NPRS for the first rescue will be carried over.
- b. Vertex proposed LOCF for subjects that discontinued the study or completed the treatment but with missing data from certain time point to 48 hours, which is not appropriate. For example, discontinuation due to lack of efficacy may suggest the assessments after the discontinuation will get worse and may be different from the observed assessments. An appropriate imputation scheme would be to assume these subjects do not contribute any treatment benefit in the primary analysis, such as multiple imputations of the subject's baseline score.

Vertex acknowledged these statements.

FDA Response to Question 3b:

The protocol synopses in the meeting package do not include discussion of the estimated framework, how intercurrent events, missing data, and use of rescue will be handled. In general, the planned ANCOVA model with terms for treatment, site, and baseline pain NRS is appropriate, but without more detail we cannot give more comments until we review the full protocols.

Meeting Discussion:

There was no discussion on Question 3b during the meeting.

FDA Response to Question 3c:

Your proposed key secondary endpoints to evaluate time to onset of VX-548 as an acute analgesic in lieu of the double stopwatch method are reasonable. However, ensure that the frequency of efficacy assessments is appropriate to accurately capture the onset of analgesia. We may have additional comments when the final protocols are reviewed.

The multiplicity control strategy proposed is to address 4 key secondary endpoints in the order shown below:

- 1) SPID48 compared to placebo.
- 2) SPID48 compared to HB/APAP.
- 3) Time to ≥ 2 -point reduction in NPRS from baseline compared to placebo.
- 4) Time to ≥ 1 -point reduction in NPRS from baseline compared to placebo.

Note that test of SPID48 comparing VX-548 to HB/APAP is not required in the key secondary endpoint testing sequence. This endpoint can be a secondary endpoint, but it would not be considered as a key secondary endpoint as FDA reviews a new drug application for whether the experimental drug is safe and effective and not about its comparative efficacy. We request the analysis of SPID48 comparing HB/APAP and placebo be performed, which we will review; this hypothesis test addresses assay sensitivity for study interpretability and is not subject to multiplicity control.

Meeting Discussion:

The Division acknowledged the key secondary endpoints mentioned in the preliminary meeting comments.

Regulatory

Question 4:

Does the Division agree that the Phase 3 program as proposed (2 controlled studies and 1 single-arm study) will support a VX-548 NDA for the treatment of moderate to severe acute pain?

FDA Response to Question 4:

Overall, we agree with the approach that your Phase 3 program consisting of two adequate and well-controlled trials and a single-arm safety and effectiveness study in a broad range of acute pain conditions will support filing of a VX-548 NDA for treatment of moderate to severe acute pain.

Discussion:

There was no discussion of Question 4 at the meeting.

ADDITIONAL COMMENTS

CONTROLLED SUBSTANCE STAFF

Abuse and Dependence:

- 1. Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry, *Assessment of Abuse Potential of Drugs*.⁸**

⁸ <https://www.fda.gov/media/116739/download>

- a. **The Agency notes that many of the studies referred to in the above guidance may have already been conducted. At this time, the Agency requests that you clarify the activity of the major circulating metabolite, VRT-1875420, at the Orexin 1 receptor and that you continue to monitor for abuse related adverse events as described below.**
- b. **During all Phase 1, 2, and 3 studies, capture adverse events (AEs) that may be indicative of abuse potential (e.g., CNS-related, drug abuse-related) and provide detailed narratives for these AEs. The incidence of these AEs in comparison to placebo in trials should be reported by study, population, and dose and should be displayed in tabular format, including study number and type of study, subject ID number, narratives, case description and details. Tables should be created for higher level MedDRA terms, even if there were few patients or subjects who experienced a particular AE. Also, you should provide a list of terms that will prompt these reports, including AE terms such as euphoria, dissociative effects, impaired cognition and attention, psychomotor effects, inappropriate affect, overdose, misuse, or lost or unaccounted for medication and unjustified dose increases.**
- c. **Narratives describing these events should be provided, including time to onset in relation to drug administration, duration of the event, dose of drug, severity, medical outcome, and disposition of the subject (e.g., if the AE resulted in discontinuation from the study); also, indicate if more than one event was observed simultaneously, and if other drugs were taken by subjects at the time of the event. In addition, if available, provide pharmacokinetic measures for subjects reporting the event to understand if there is a temporal correlation between drug plasma levels and these AEs. Refer to section V.B. of guidance for industry, *Assessment of Abuse Potential of Drugs*.**
- d. **You should conduct studies to assess whether VX-548 produces physical dependence and signs and symptoms of drug withdrawal upon abrupt drug discontinuation or rapid dose reduction. The guidance for industry, *Assessment of Abuse Potential of Drugs*, linked above, contains guidance on the nonclinical and clinical assessment of physical dependence. Specifically, information on the nonclinical assessment is located in section IV(D)(5) and this assessment should be conducted before a clinical assessment. Guidance on how to conduct a clinical assessment is located in section V(E). The Agency requests that you submit protocols for**

review by the Agency with enough time to receive feedback before conducting the study.

NONCLINICAL

2. **New excipients should be adequately qualified for safety as recommended in the guidance for industry, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.⁹ As noted in the guidance, “the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration*.” (emphasis added).**

In addition, note the following:

- a. **Published literature to support the safety of an excipient rarely provides adequate detail of the study design and study results to permit a thorough and independent evaluation of the data. Summary reviews, [e.g., BIBRA Toxicology Advice & Consulting (BIBRA), Cosmetic Ingredient Review (CIR), Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA)], although potentially useful to identify original source material, are not acceptable because the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports should be accompanied by a detailed comparison to modern toxicology study endpoints, discussion of any shortcomings of the study, and justification to support your assertion that these data are adequate to support the safety of your drug product formulation.**
- b. **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can adequately justify the safety of your excipient. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a no-adverse-effect level (NOAEL) for the novel excipient.**

⁹ <https://www.fda.gov/media/72260/download>

- c. Safety justifications for oral drug products based on a compound being reported as generally recognized as safe (GRAS) in foods should be accompanied by appropriate reference to the Code of Federal Regulation, a discussion of any GRAS limitations, and an assessment of exposures typically obtained via food compared to the levels that will be obtained via your drug product when dosed up to the maximum daily dose. Maximum daily doses that exceed levels commonly consumed in foods are not supported by CFSAN GRAS determinations.
3. Any impurity or degradation product that exceeds ICH thresholds should be adequately qualified for safety as recommended in ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:
- a. You should complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.
- b. In addition, you should conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. A study of 14 days should be completed for an acute indication and 90 days for a chronic indication.

Refer to

- Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*¹⁰
- Guidance for industry: *Q3B(R2) Impurities in New Drug Products*¹¹

4. If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, provide a table in your IND submission that compares the impurity profile across batches. Include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.

¹⁰ <https://www.fda.gov/media/71727/download>

¹¹ <https://www.fda.gov/media/71733/download>

5. Your NDA should adequately address the safety of residual solvents as recommended in the ICH guidance document, Q3C(R6): *Residual Solvents*.¹²
6. Your NDA should adequately address the safety of elemental impurities as recommended in the ICH guidance document: *Q3D Elemental Impurities*.¹³ In addition, refer to the FDA guidance, *Elemental Impurities in Drug Products*.¹⁴
7. In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.
8. Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity should be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*¹⁵ for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. As noted in the guidance, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development to mitigate risk.

¹² <https://www.fda.gov/media/71736/download>

¹³ <https://www.fda.gov/media/135956/download>

¹⁴ <https://www.fda.gov/media/98847/download>

¹⁵ <https://www.fda.gov/media/85885/download>

9. Your drug product should be evaluated for the potential presence of nitrosamine impurities and, if present, controlled at acceptable levels. Refer to the guidance for industry, *Control of Nitrosamine Impurities in Human Drugs*.¹⁶
10. All NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, conduct a thorough review and integrated analysis of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm>.
11. We may refuse to file your application if your NDA submission does not contain safety qualification data for any identified impurity, degradant, or residual solvent that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety or if the application lacks extractable leachable safety justification to permit substantive review.

Meeting Discussion:

No additional meeting comments

ACTION ITEMS

1. Vertex will submit the phototoxicity assessment report for VX-548 prior to Phase 3.
Note to Sponsor: These data should be submitted either prior to or at the same time as the final Phase 3 protocol but not after a final protocol is submitted.
2. Vertex will submit the fertility and early embryonic development study in rats and the definitive embryo-fetal development studies in rat and rabbit prior to Phase 3.
Note to Sponsor: These data should be submitted either prior to or at the same time as the final Phase 3 protocol but not after a final protocol is submitted.

¹⁶ <https://www.fda.gov/media/141720/download>

3. Vertex will also submit justification why they believe that the rat and rabbit studies adequately characterize the intended on-target effects of the drug taking into consideration differential binding affinity and expected receptor occupancy across species. This will also be submitted in support of the final Phase 3 protocol.
4. Vertex will submit the food effect study report to support inclusion of food in the final Phase 3 protocol.
5. Vertex will include expanded ECG evaluation in the Phase 3 protocol. Vertex also plans to submit a QT evaluation plan for review. The Division recommended to submit it before the final Phase 3 protocol.

ATTACHMENTS AND HANDOUTS

Appendix 1 (PowerPoint presentation)

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.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk

assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You should include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*.¹⁷

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*.¹⁸ 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.¹⁹

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.²⁰

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

¹⁷ <https://www.fda.gov/media/119658/download>

¹⁸ 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>.

¹⁹ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

²⁰ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page²¹ 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 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

²¹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.²²

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 Resources²³ and the CDER/CBER Position on Use of SI Units for Lab Tests website.²⁴

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support*

²² <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

²³ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

²⁴ <https://www.fda.gov/media/109533/download>

Claims.

APPEARS THIS WAY ON ORIGINAL

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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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CDER Breakthrough Therapy Designation Determination Review Template (BTDDRT)

IND/NDA/BLA #	IND 146185
Request Receipt Date	May 6, 2022
Product	VX-548
Indication	Treatment of moderate-to-severe acute pain
Drug Class/Mechanism of Action	Analgesic / selective inhibitor of voltage-gated sodium channel 1.8 (Nav1.8)
Sponsor	Vertex Pharmaceuticals, Inc.
ODE/Division	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)/Office of Neuroscience (ON)/Office of New Drugs (OND)/Center for Drug Evaluation and Research (CDER)
Breakthrough Therapy Request (BTDR) Goal Date (within 60 days of receipt)	July 5, 2022

*Note: This document must be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.*

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter):

The proposed indication of VX-548 is for the treatment of moderate-to-severe acute pain.

2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold?

YES NO

3. Was the BTDR submitted to a PIND?

YES NO

If "Yes" do not review the BTDR. The sponsor must withdraw the BTDR. BTDR's cannot be submitted to a PIND.

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

4. Consideration of Breakthrough Therapy Criteria:

a. Is the condition serious/life-threatening¹?

YES NO

If 4a is checked "No," please provide the rationale in a brief paragraph below, and send the completed BTDDRT to Miranda Raggio for review so that the BTDR can be denied without MPC review. Once reviewed and cleared by Miranda this BTDR will be removed from the MPC calendar and you can skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?
- YES, the BTDR is adequate and sufficiently complete to permit a substantive review
- Undetermined
- NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore, the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

5. Provide below a brief description of the deficiencies for each box checked above in Section 4b:

If 4b is checked “No”, BTDR can be denied without MPC review. Skip to number 6 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If the division feels MPC review is not required, send the completed BTDDRT to Miranda Raggio for review. Once reviewed, Miranda will notify the MPC Coordinator to remove the BTDR from the MPC calendar. If the BTDR is denied at the Division level without MPC review, the BTDR Denial letter still must be cleared by Miranda Raggio, after division director and office director clearance.

If 4b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

6. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

7. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

- Information regarding the disease and intended population for the proposed indication.
- Disease mechanism (if known) and natural history (if the disease is uncommon).

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

Moderate-to-severe acute pain is a serious clinical condition. When poorly controlled, acute pain may lead to increased morbidity as well as increase the likelihood of developing chronic pain.

VX-548 is an orally bioavailable, highly selective inhibitor of voltage-gated sodium channel 1.8 (Nav1.8). Nav1.8 is one of the nine Nav isoforms expressed in humans and plays a critical role in pain signaling. The Sponsor asserts that because Nav1.8 is preferentially expressed in peripheral pain-sensing neurons (e.g., the dorsal root ganglia [DRG]), Nav1.8 inhibitors are less likely to be associated with the side effects commonly observed with other sodium channel modulators as well as the abuse liability of opioid analgesics. The Sponsor also claims that VX-548 has the potential to address an unmet medical need through comparable analgesic efficacy in moderate-to-severe acute pain without the risks of abuse and addiction associated with opioid analgesics as standard-of-care therapy.

VX-548 was granted Fast Track Designation in March 2020.

8. Information related to endpoints used in the available clinical data:

- a. Describe the endpoints considered by the sponsor as supporting the BTDR and any other endpoints the sponsor plans to use in later trials. Specify if the endpoints are primary or secondary, and if they are surrogates.

To support the efficacy of VX-548, the Sponsor provided preliminary clinical data from two Phase 2 studies in acute pain following bunionectomy and abdominoplasty, Study VX21-548-101 (referred to as Study 101) and Study VX21-548-102 (referred to as Study 102), respectively. The primary endpoint for both studies was the time-weighted sum of the pain intensity difference between 0 and 48 hours after the first dose (SPID48), the results of which are considered supportive of the BTDR by the Sponsor.

Briefly, Study 101 (bunionectomy) and Study 102 (abdominoplasty) were Phase 2, randomized, double-blind, placebo-controlled, multi-dose studies evaluating the efficacy and safety of VX-548 for acute pain in their respective pain models. Subjects were randomized to treatment only after they had moderate to severe pain (≥ 4 out of 10 on the 11-point numerical pain rating scale [NPRS]). Each trial contained treatment arms of two to three dose ranges of VX-548, placebo, and an opioid comparator arm, hydrocodone bitartrate/acetaminophen (HB/APAP), as the standard-of-care treatment for moderate-to-severe acute pain. Patients were treated for 48 hours. VX-548 treatment arms received a loading dose followed by a maintenance dose every 12 hours.

Additionally, the Sponsor submitted a Type B End-of-Phase 2 Meeting Information Package on May 25, 2022 (SDN 57) which contains additional detail of their planned pivotal Phase 3 studies. According to the Sponsor, “Both pivotal Phase 3 studies are randomized, double-blind, and placebo- and active-controlled studies, in 2 different acute nociceptive pain models: pain after bunionectomy as a bony tissue pain model and pain after abdominoplasty as a soft tissue pain model.” The primary endpoint is the SPID48 of VX-548 compared to placebo, and the first secondary endpoint is the SPID48 of VX-548 compared to hydrocodone bitartrate/acetaminophen. Other key secondary endpoints include time to ≥ 2 -point reduction in NPRS from baseline for VX-548 compared to placebo, and time to ≥ 1 -point reduction in NPRS from baseline for VX-548 compared to placebo.

- b. Describe the endpoint(s) that are accepted by the Division as clinically significant (outcome measures) for patients with the disease. Consider the following in your response:
- *A clinical endpoint that directly measures the clinical benefit of a drug (supporting traditional approval).*
 - *A surrogate/established endpoint that is known to predict clinical benefit of a drug (i.e., a validated surrogate endpoint that can be used to support traditional approval).*
 - *An endpoint that is reasonably likely to predict clinical benefit of a drug (supporting accelerated approval), and the endpoint used in a confirmatory trial or trials to verify the predicted clinical benefit.*

The Division accepts SPID over at least 48 to 72 hours as an appropriate primary endpoint that measures clinical benefit of a drug for management of acute pain. SPIDs over 24 hours are often used to preliminarily evaluate efficacy in proof-of-concept studies in acute pain. Secondary endpoints to further evaluate the efficacy of a drug for pain relief include the SPID at different time intervals, time to meaningful pain relief, and the use of rescue medication.

- c. Describe any other biomarkers that the Division would consider likely to predict a clinical benefit for the proposed indication even if not yet a basis for accelerated approval.

The Division is not aware of any biomarkers that are useful in developing pain management products.

9. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

- *If the available therapies were approved under accelerated approval, provide the information for the endpoint used to support accelerated approval and the endpoint used to verify the predicted clinical benefit.*
- *In addition to drugs that have been approved by FDA for the indication, also identify those treatments that may be used off-label for that indication.*

There are several classes of analgesics available for the treatment of pain including acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), anesthetics (such as lidocaine), anticonvulsants, antidepressants, and opioids. These medications are available in multiple formulations and can be administered through a variety of different routes, such as oral, intramuscular injection, intravenous injection, and topical and transdermal systems. However, there are challenges in clinical setting for the treatment of moderate-to-severe acute pain and opioids are commonly prescribed in this setting. There are significant safety concerns associated with opioids including potential for abuse and addiction. There is an urgent need to develop and support alternative treatments for acute pain. VX-548 may provide an alternative option for treatment of moderate-to-severe acute pain.

10. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

The following drug was granted BTDR and is of the same class, mechanism of action, and indication as VX-548, the focus of this BTDR review:

- VX-150, IND (b) (4) is a voltage-gated sodium channel (Nav) blocker prodrug that rapidly converts in vivo to the active form, VRT-1207355, and is highly selective for Nav1.8 relative to other sodium channel subtypes. The indication is the treatment of moderate-to-severe acute pain. VX-150 was granted BTDR on 11/15/2018.

The following two drugs have BTDR for similar indications (acute postsurgical pain/postoperative pain):

- CA-008, IND (b) (4) is a water-soluble prodrug of capsaicin that is rapidly converted to capsaicin via a nonenzymatic process, with the proposed indication of treatment of acute postsurgical pain. CA-008 will be used in the setting of standard of care multimodal analgesia or enhanced recovery programs that includes the use of local anesthetic delivered by a regional block or infiltration into the surgical site (or both). CA-008 was granted BTDR on 09/04/2018.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

- HTX-110 injection (Bupivacaine and Meloxicam), IND 125927, is an extended-release, fixed-ratio combination product. The indication is local administration into the surgical site to reduce postoperative pain and the need for opioid analgesics for 72 hours. HTX-110 was granted BTDR on 06/14/2018.

Lastly, Oliceridine injection (Olinvo), NDA 210730 and IND (b) (4) a small molecule μ -opioid receptor modulator, for the indication of moderate-to-severe acute pain in adult patients for whom an intravenous (IV) opioid is warranted was granted BTDR on 02/19/2016. The Sponsor used a post-surgical pain model; however, when emerging data from two Phase 3, double-blind, placebo- and morphine-controlled studies no longer supported that oliceridine had a safety advantage relative to morphine, BTDR was rescinded on 3/4/2019.

11. Information related to the preliminary clinical evidence:

- Table of clinical trials supporting the BTDR (only include trials which were relevant to the designation determination decision), including study ID, phase, trial design⁴, trial endpoints, treatment group(s), number of subjects enrolled in support of specific breakthrough indication, hazard ratio (if applicable), and trial results.

The Sponsor has completed two Phase 2 clinical trials and references these as supporting the BTDR. Two pain models were utilized, bunionectomy and abdominoplasty, and both studies used the time-weighted sum of the pain intensity difference between 0 and 48 hours after the first dose (SPID48).

Table 1: Clinical Trials Supporting BTDR

Study	VX21-548-101 (Study 101)	VX21-548-102 (Study 102)
Phase	2	2
Design	Randomized, double-blind, placebo-controlled, dose-ranging study in patients undergoing bunionectomy	Randomized, double-blind, placebo-controlled, multi-dose study in patients undergoing abdominoplasty
Endpoint	SPID48	SPID48
Treatment	2:2:1:2:2 Treatment duration: 48 hours -VX-548 100 mg/50 mg q12h -VX-548 60 mg/30 mg q12h -VX-548 20 mg/10 mg q12h -HB/APAP 5mg/325 mg every 6 hours -Placebo	1:1:1:1 Treatment duration: 48 hours -VX-548 100 mg/50 mg q12h -VX-548 60 mg/30 mg q12h -HB/APAP 5mg/325 mg every 6 hours -Placebo
n	274	303

The Sponsor concluded that the primary endpoint (SPID48) was met in both Phase 2 studies, with the high-dose (100 mg/50 mg q12h) VX-548 group reaching statistical significance compared to placebo.

The following is excerpted from the Sponsor's EOP2 meeting package regarding the results of the two Phase 2 trials:

The onset of pain relief was rapid (within 1 hour) and sustained over the 48-hour treatment period. Although Studies 101 and 102 were not designed to provide a direct comparison between VX-548 and the opioid reference group, VX-548 was numerically better than the opioid reference group, hydrocodone

⁴ Trial design information should include whether the trial is single arm or multi-arm, single dose or multi-dose, randomized or non-randomized, crossover, blinded or unblinded, active comparator or placebo, and single center or multicenter.

bitartrate/acetaminophen (HB/APAP), on the SPID48 measure in both studies. Results from the secondary and other endpoints were generally supportive of the primary endpoint results. In addition, the percentage of subjects who discontinued due to lack of efficacy was lower in the VX-548 100 mg/50 mg q12h group than in the placebo and HB/APAP groups in each study, further supporting the efficacy of VX-548.

b. Include any additional relevant information. Consider the following in your response:

- *Explain whether the data provided should be considered preliminary clinical evidence of a substantial improvement over available therapies. In all cases, actual results, in addition to reported significance levels, should be shown. Describe any identified deficiencies in the trial that decrease its persuasiveness.*
- *Identify any other factors regarding the clinical development program that were taken into consideration when evaluating the preliminary clinical evidence, such as trial conduct, troublesome and advantageous aspects of the design, missing data, any relevant nonclinical data, etc.*
- *Safety data: Provide a brief explanation of the drug's safety profile, elaborating if it affects the Division's recommendation.*

Efficacy:

Studies 101 and 102 demonstrated a statistically significant difference in SPID48 for high-dose VX-548 (100 mg/50 mg every 12 hours for 48 hours) compared to placebo after surgery (refer to Tables 2 and 3). Study 102, abdominoplasty, also demonstrated statistical significance compared to placebo on the secondary endpoint, SPID24 ($p = 0.0036$), whereas Study 101, bunionectomy, did not ($p = 0.0823$).

Notably, the opioid comparator arm representing standard-of-care did not reach statistical significance compared to placebo in either trial for SPID48 or SPID24 (secondary endpoint). The Sponsor attributes this to a high placebo response despite using placebo effect mitigation strategies in each study. Interestingly, this reviewer notes that VX-150, referenced above, also a Nav1.8 sodium channel blocker developed by Vertex Pharmaceuticals, and granted BTB, had a similarly designed bunionectomy study for which both VX-150 and the HB/APAP opioid comparator arm (same dose/regimen) reached statistical significance compared to placebo. The reasons for a standard-of-care therapy not reaching statistical significance on a primary endpoint are unclear; however, as compared to other similarly designed studies, reasons could include differences in baseline pain intensity and/or differences in use of rescue medication, among others.

Ibuprofen 400 mg every 6 hours as needed was the rescue analgesic for Studies 101 and 102. In Study 102, there was a statistically significant difference in the proportion of subjects (less) using rescue medication (0 to 48 hours after first dose of study drug) for the high-dose VX-548 treatment group compared to placebo; no other treatment group reached statistical significance for this analysis.

Lastly, the results for the mid-dose (60 mg/30 mg q12h) VX-548 group in Study 101 trended in an unexpected way (Table 2); the LS mean difference from placebo (SE) appeared to perform worse than placebo. While this result cannot be explained at this time, it does not diminish the persuasiveness of the high-dose VX-548 group meeting the primary endpoint.

Study 101 (bunionectomy): Efficacy was evaluated in 274 subjects randomized to five treatment groups.

Table 2 Study 101 Primary Endpoint: SPID48

Statistic	Placebo N = 59	HB/APAP 5/325 mg q6h N = 60	VX-548 Dose (Loading/Maintenance)		
			20 mg/ 10 mg q12h N = 33	60 mg/ 30 mg q12h N = 62	100 mg/ 50 mg q12h N = 60
n	59	60	33	62	60
LS mean (SE)	100.98 (11.60)	115.64 (11.49)	112.92 (15.52)	86.87 (11.33)	137.77 (11.50)
LS mean difference from placebo (SE)	--	14.66 (16.34)	11.94 (19.35)	-14.12 (16.25)	36.79 (16.33)
95% CI of LS mean difference	--	-17.52, 46.84	-26.17, 50.05	-46.12, 17.89	4.63, 68.95
P value versus placebo	--	0.3706	0.5379	0.3859	0.0251

Source: Study 101/Table 14.2.2.2

Source: Sponsor's BTDR submission – Clinical Information Amendment

Study 102 (abdominoplasty): Efficacy was evaluated in 303 subjects randomized four treatment groups.

Table 3 Study 102 Primary Endpoint: SPID48

Statistic	Placebo N = 77	HB/APAP 5/325 mg q6h N = 76	VX-548 Dose (Loading/Maintenance)	
			60 mg/ 30 mg q12h N = 74	100 mg/ 50 mg q12h N = 76
n	77	76	74	76
LS mean (SE)	72.73 (10.23)	85.20 (10.30)	95.11 (10.44)	110.53 (10.30)
LS mean difference from placebo (SE)	--	12.47 (14.53)	22.38 (14.61)	37.80 (14.52)
95% CI of difference	--	-16.13, 41.07	-6.37, 51.14	9.22, 66.38
P value versus placebo	--	0.3914	0.1266	0.0097

Source: Study 102/Table 14.2.2.2

Source: Sponsor's BTDR submission – Clinical Information Amendment

Safety:

The safety profile of VX-548 is favorable, without any major safety concerns, and does not negatively impact the Division's recommendation. The following is a summary of the safety findings for the Phase 1 and Phase 2 studies.

A pooled analysis of adverse events was performed for the five Phase 1 studies in which dosing is complete. There were no deaths, SAEs or AEs leading to discontinuation. Of the 129 subjects who received at least 1 dose of VX-548, the most common AEs ($\geq 5.0\%$ incidence) were headache (10.9%), paresthesia (8.5%), dizziness (5.4%), and nausea (5.4%).

In Study 101 (bunionectomy), all AEs were mild or moderate in severity. No subjects had SAEs or AEs leading to treatment discontinuation or interruption. The most common AEs (occurring in $\geq 5\%$ of subjects in any treatment group) were headache, nausea, and vomiting, and the incidences in the VX-548 groups (three dose arms) were lower than those in the placebo group and similar to or lower than those in the HB/APAP group.

In Study 102 (abdominoplasty), the majority of AEs were mild or moderate in severity, however, SAEs occurred in 1 subject each in the placebo, HB/APAP, and VX-548 (60 mg/30 mg q12h) treatment arms. The subject in the Vertex arm experienced an SAE of pulmonary embolism. The Sponsor did not consider any SAEs related or possibly related to study drug. The most common AEs (occurring in $\geq 5\%$ of subjects in any treatment group) were nausea, headache, constipation, dizziness, hypoxia, vomiting, hyperhidrosis, and hypotension. Most AEs had similar or lower incidences in the VX-548 groups compared with the placebo and HB/APAP groups, except for headache, which had an incidence in the VX-548 100 mg/50 mg q12h group (14.5%) that was higher than in the placebo (6.5%) or HB/APAP (6.6%) groups.

12. Division's recommendation and rationale (pre-MPC review):

GRANT:

Provide brief summary of rationale for granting:

We recommend granting breakthrough therapy designation for VX-548 for the treatment of moderate-to-severe acute pain where an opioid is the only available standard-of-care therapy. The submitted data suggest favorable efficacy of high-dose (100 mg/50 mg q12h) VX-548 compared to placebo for the Phase 2 clinical studies. Moreover, there is a strong mechanistic rationale for less abuse potential as compared to opioids. The CSS review of nonclinical and clinical studies to date confirms this mechanistic rationale with CSS opining that it is unlikely that VX-548 has potential for abuse. Moreover, the clinical safety profile has been favorable without major safety concerns. Overall, VX-548, in combination with ibuprofen, has potential to serve as a replacement for an oral opioid after an outpatient surgical procedure to treat moderate-to-severe acute pain.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

13. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):

The Division has an EOP2 meeting with the Sponsor on July 14, 2022. The Sponsor is requesting input on the proposed development plan and Phase 3 clinical studies to support the registration of VX-548 for the indication of treatment of moderate-to-severe acute pain.

- b. If recommendation is to deny the request and the treatment looks promising, explain how the Division would advise the sponsor regarding subsequent development, including what would be needed for the Division to reconsider a breakthrough therapy designation:

N/A

14. List references, if any:

N/A

15. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

16. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}

Team Leader Signature: {See appended electronic signature page}

Division Director Signature: {See appended electronic signature page}

Revised 10/13/20 /M. Raggio

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/

TANYA L BRESCIA-ODDO
06/28/2022 08:45:50 PM

RIGOBERTO A ROCA
06/28/2022 10:19:45 PM