CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220358Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 153819

MEETING PRELIMINARY COMMENTS

Vanda Pharmaceuticals, Inc.
Attention: Gunther Birznieks
Research and Development Committee Member
2200 Pennsylvania Ave, NW
Suite 300E
Washington, DC 20037

Dear Gunther Birznieks:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VHX-896.

We also refer to your correspondence, dated and received November 2, 2023, requesting a meeting to discuss the planned NDA submission seeking approval of the iloperidone metabolite, VHX-896, for the treatment of schizophrenia.

Our preliminary responses to your meeting questions are enclosed.

You should provide an electronic version of any materials (i.e., slides or handouts) to be presented or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, email me at Tiffanie.Taylor@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffanie Taylor, PharmD
Senior Regulatory Project Manager
Psychiatry Group
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 7, 2024, 11:00 a.m. to 12:00 p.m. (EST)
Meeting Location: Virtual meeting

Application Number: 153819
Product Name: VHX-896
Indication: Schizophrenia
Sponsor Name: Vanda Pharmaceuticals, Inc
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Tiffany R. Farchione MD	Director, Division of Psychiatry (DP)
Bernard Fischer, MD	Deputy Director, DP
Valentina Mantua, MD, PhD	Clinical Team Lead, DP
Roberta Rasetti, MD, PhD	Clinical Reviewer, DP
Venkateswaran ChithambaramPillai, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Nimishraj Panse, PhD	Clinical Pharmacology Reviewer, OCP
Aisar Atrakchi, PhD	Pharmacology/Toxicology Supervisor, Division of Pharmacology/Toxicology for Neuroscience (DPT-N)
Amy Avila, PhD	Pharmacology/Toxicology Team Leader, DPT-N
Sonia Tabacova, PhD	Pharmacology/Toxicology Reviewer, DPT-N
Peiling Yang, PhD	Biometrics Team Leader, Division of Biometrics I (DBI)
Tiffanie Taylor, PharmD	Senior Regulatory Project Manager, Division of Regulatory Operations for Neuroscience (DRON), Psychiatry Group

SPONSOR ATTENDEES

Mihael Polymeropoulos, MD	Chief Executive Officer
Christos Polymeropoulos, MD	Medical Director
Gunther Birznieks, MS	SVP, Business Development
Deepak Phadke, PhD	VP, Manufacturing
Rosarelis Torres, PhD	Sr. Director Clinical Affairs
Sean Chadwick, PhD	Clinical

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 7, 2024, 11:00 a.m. to 12:00 p.m., virtual meeting between Vanda Pharmaceuticals, Inc

and the Division of Psychiatry. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0. BACKGROUND

VHX-896 (P88) is the major active metabolite of iloperidone, an atypical antipsychotic initially approved in 2009 for the treatment of schizophrenia in adults (Fanapt, NDA 022192). The Sponsor's stated rationale for developing a VHX-896 oral formulation is (b) (4) The Sponsor is planning an NDA submission via the 505(b)(1) pathway.

The Sponsor initially completed a pharmacokinetic (PK) study, VP-VYV-683M-1201, and requested a Type B pre-IND meeting with the Agency. During the meeting (see the Meeting Preliminary Comments letter dated February 4, 2021), the Agency expressed general agreement with the approach to establish comparative bioavailability in healthy subjects; however, recommended a dose proportionality study to understand the PK linearity and dose-proportionality of VHX-896 and its metabolites in patients, and a study to evaluate the effect of food.

In support of the proposed NDA application, the Sponsor completed two additional studies:

- Study VP-VHX-896-1101 was a phase 1 single-center, single-dose, two-period, randomized, open-label, crossover study in 25 healthy subjects designed to evaluate the bioequivalence, safety, and tolerability of three 1 mg VHX-896 tablets relative to three 1 mg iloperidone tablets. The Sponsor states that VHX-896 and iloperidone showed comparable exposures (Cmax, AUC(0-t), and AUC(inf)) for iloperidone, VHX-896, and the sum of iloperidone and VHX-896).

- Study VP-VHX-896-1102 was an open-label, two-period, two-sequence, two-treatment randomized, single-dose, crossover study in 24 healthy subjects designed to evaluate the safety, tolerability, and food effect on the PK of VHX-896.

The Sponsor is not planning additional nonclinical studies.

The Sponsor's stated objective for this Type B pre-NDA meeting is to discuss and obtain concurrence with the Division on the adequacy of clinical and nonclinical data necessary to support the NDA filing and review of VHX-896 for the treatment of schizophrenia.

2.0. DISCUSSION

2.1. CLINICAL

Question 1: Vanda has conducted two studies demonstrating that VHX-896 and iloperidone are bioequivalent and characterizing the food effect of VHX-896. These two studies would comprise a complete clinical package, submitted as adequate and pivotal to an NDA filing referencing iloperidone data. Does the Division agree?

FDA Response to Question 1: *Your completed studies VP-VHX-896-1101 and VP-VHX-896-1102 appear sufficient for submission of an NDA relying, in part, on the listed drug iloperidone. However, a formal filing determination will be made after submission of the NDA.*

The adequacy of your completed Study VP-VHX-896-1101 to establish a scientific bridge between VHX-896 and iloperidone will be a matter of review at time of NDA submission.

We noted that the proposed product is available in only one strength (i.e., 1 mg). If you intend to develop higher strengths of VHX-896, you should consider:

- *Acceptable BA/BE data for the lower strength*
- *Compositional proportionality between a new, higher strength(s) and the strength on which the BA/BE data was generated*
- *All strengths are the same dosage form, have the same drug release mechanism and are made with the same manufacturing process*
- *Dissolution profile comparisons meet the f2 similarity requirements in three pH media (pH 1.2, 4.5, and 6.8)*
- *Evidence of linear pharmacokinetics over the proposed dose range*

The Agency would take the above into consideration when determining whether it would be appropriate to grant a waiver of the requirement to submit in vivo bioavailability or bioequivalence data for a higher strength, or whether additional data from an in vivo study would be needed to demonstrate dosage strength proportionality.

2.2. TOXICOLOGY AND PHARMACOLOGY

Question 2: Given the established bioequivalence between VHX-896 and iloperidone, Vanda plans to submit the NDA cross-referencing the existing nonclinical studies conducted in the iloperidone development program (i.e., IND 036827 and NDA 022192). Does the Division agree?

FDA Response to Question 2: *You may cross-reference the existing nonclinical study reports from IND 036827 and NDA 022192 for your proposed NDA submission. However, we recommend that you include lists of all nonclinical studies and tables of the results from the pivotal nonclinical studies in module 2 and include hyperlinks to the individual study reports. In addition, as we previously requested in the pre-IND meeting Preliminary Comments dated February 4, 2021, and in the May Proceed letter dated May 3, 2021, we remind you that "In order to potentially cross-reference toxicology data from the iloperidone development program, you should provide for our review the VHX-896 exposure data from chronic toxicity, reproductive/developmental toxicity, and carcinogenicity studies conducted in the iloperidone development program. Please submit this information in a table with exposure data from across animal species and human data from the iloperidone program" and human data from the recently completed comparative bioavailability study. We recommend you submit this information with the VHX-896 NDA and to the IND as well for our review in order to determine if any additional nonclinical studies would be needed to support your NDA submission.*

3.0. OTHER

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of

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

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

PRESCRIBING INFORMATION

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

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

[1] https://www.fda.gov/media/86340/download
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Highlights Indications and Usage heading

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

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/

TIFFANIE A TAYLOR
02/01/2024 02:53:27 PM