CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

220152Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 141315

MEETING MINUTES

Vanda Pharmaceuticals Inc.
Attention: Vasilios Polymeropoulos, M.D.
Medical Director
2200 Pennsylvania Ave NW
Suite 300 E
Washington, D.C. 20037

Dear Dr. Polymeropoulos:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tradipitant (VLY-686).

We also refer to the teleconference between representatives of your firm and the FDA on November 8, 2023. The purpose of the meeting was to discuss the plan for filing a New Drug Application.

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

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, Pharm.D.
Senior Regulatory Health Project Manager
Gastroenterology
Division of Regulatory Operations for
Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

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

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B Teleconference
Meeting Category: Pre-NDA

Meeting Date and Time: November 8, 2023, 1:00 PM- 2:00 PM EST

Application Number: IND 141315
Product Name: tradipitant (VLY-686)

Indication: prevention of vomiting induced by motion
Sponsor Name: Vanda Pharmaceuticals Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Matthew Kowalik, M.D.
Meeting Recorder: Mary Chung, Pharm.D.

FDA ATTENDEES

Office of Immunology and Inflammation
Nikolay Nikolov, M.D., Director

Division of Gastroenterology, Office of Immunology and Inflammation
Jessica Lee, M.D., M.M.Sc., Director
Juli Tomaino, M.D., M.S., Deputy Director
Matthew Kowalik, M.D., Clinical Team Lead
Christopher St. Clair, Pharm.D., Clinical Reviewer

Division of Pharmacology and Toxicology for Immunology and Inflammation
Andrew Goodwin, Ph.D., Director
Sushanta Chakder, Ph.D., Supervisory Pharmacologist
Jackye Peretz, Ph.D., Lead Toxicologist
Sarah Morgan, Ph.D., Pharmacologist

Office of Biostatistics/ Division of Biostatistics III
Paul Imbriano, Ph.D., Team Lead

Office of Clinical Pharmacology / Division of Inflammation and Immune Pharmacology
Insook Kim, Ph.D., Clinical Pharmacology Team Lead
Lei He, Ph.D., Clinical Pharmacology Reviewer

Office of New Drug Policy, Division of Regulatory Policy
James Myers, J.D., Director
Richard Ishihara, MEM, Policy Advisor

Division of Regulatory Operations for Immunology and Inflammation, Office of Regulatory Operations
Mary Chung, Pharm.D. Senior Regulatory Health Project Manager

SPONSOR ATTENDEES

Mihael Polymeropoulos, M.D., Chief Executive Officer, Vanda Pharmaceuticals
Gunther Birznieks, Research and Development Committee Member, Vanda Pharmaceuticals
Christos Polymeropoulos, M.D., Research and Development Committee Member, Vanda Pharmaceuticals
Vasilios Polymeropoulos, M.D., Medical Director, Vanda Pharmaceuticals
Derek Xiao, Ph.D., Head of Biometrics, Vanda Pharmaceuticals
Timothy Williams, General Counsel, Vanda Pharmaceuticals
(b) (4)

1.0 BACKGROUND

On May 13, 2020, an End of Phase 2 meeting was held between Vanda Pharmaceuticals and FDA on IND 141315 tradipitant (VLY-686). Tradipitant is an inhibitor of neurokinin-1 receptor (NK-1) that is administered orally.

On September 14, 2023, the Sponsor submitted a pre-NDA meeting request. Under IND 141315, tradipitant is currently proposed for prevention of vomiting induced by motion. This meeting request was granted and the background package was received on October 9, 2023.

FDA sent Preliminary Comments to Vanda Pharmaceuticals on November 6, 2023.

2.0 DISCUSSION

Question 1:
Given the robust effect of tradipitant in the prevention of vomiting induced by motion displayed over two studies (VP-VLY-686-2401, VP-VLY-686-3401), does FDA agree that these two studies would be adequate to support the NDA filing and review of efficacy of tradipitant for the prevention of vomiting induced by motion?

FDA Response to Question 1:
The determination that an NDA is sufficiently complete for filing is made within 60 days after receipt of the NDA.

We have the following comments:

1. **We are concerned that the design of study VP-VLY-686-2401 has several limitations that may impact the interpretability of the results. We have the following comments regarding VP-VLY-686-2401.**

    a. **It appears that VP-VLY-686-2401 had two primary endpoints: 1) "The most severe motion sickness severity during vehicle travel" as measured by the Motion Sickness Severity Scale (MSSS), and 2) "Percentage of vomiting, which is defined as subjects ever vomited (MSSS=6) or terminated early due to severity during the vehicle travel." It is unclear which primary endpoint was tested first, as the statistical analysis plan (SAP), which was submitted alongside the clinical study report (CSR), does not specify the testing hierarchy and no adjustments were made for multiplicity. Furthermore, the most severe motion sickness endpoint was not statistically significantly different between tradipitant and placebo. As a result, the analyses for the primary endpoint do not control the overall type I error rate at a two-sided alpha of 0.05. Furthermore, testing multiple endpoints and then selecting an endpoint based on which endpoint showed the most favorable results could produce a biased assessment of efficacy results. Therefore, efficacy results from study VP-VLY-686-2401 may not be appropriate to inform regulatory decision making.**

    b. **Study VP-VLY-686-2401 assessed the primary endpoints with the MSSS. We note that the MSSS asks subjects** (b) (4) **" We are concerned that, based on the specific language in the question that was asked, a subject may not report vomiting if it occurred between MSSS measurements (i.e., every 30 minutes)** (b) (4) **Therefore, we are concerned that the incidence of vomiting as measured by the MSSS may be difficult to interpret and may not reliably capture data to inform your proposed indication of prevention of vomiting induced by motion. Refer to our advice letters dated December 19, 2018, and March 12, 2019, and the end of phase 2 meeting minutes dated May 21, 2020.**

2. **The CSR and SAP for VP-VLY-686-3401 was submitted after your pre-NDA meeting request and background package. Our review of the VP-VLY-686-3401 CSR and SAP is ongoing; however, we have the following comments:**

    a. **It appears that a fixed-sequence multiple testing procedure was used in your analyses. The SAP specifies that the following endpoints will be assessed sequentially in the following order:**
        i. **The percentage of vomiting in the tradipitant 170 mg group compared to placebo (i.e., the primary endpoint)**
        ii. **The worst nausea in tradipitant 170 mg group compared to placebo**
        iii. **The percentage of vomiting in the tradipitant 85 mg group compared to placebo**
        iv. **The worst nausea in tradipitant 85 mg group compared to placebo**

    Based on the CSR, it appears that the worst nausea in tradipitant 170 mg was not statistically significantly different from placebo. Therefore, according to the multiple testing procedure, hypotheses tested after this endpoint are not controlled for type I error. This may impact the ability of VP-VLY-686-3401 to support a future marketing application.

3. **It is unclear from your meeting package which dose(s) you intend to propose for marketing in a future NDA submission. We note that VP-VLY-686-2401 only assessed tradipitant at the 170 mg dose, whereas studies VP-VLY-686-3401 and VP-VLY-686-3404 both assess tradipitant at 85 mg and 170 mg doses. Without data from VP-VLY-686-3404, it appears that the results for the 85 mg dose would not be substantiated. The efficacy and safety data from VP-VLY-686-3404 will be important to inform the benefit-risk assessment of each dose level for the proposed indication. In general, we recommend that the lowest effective dose be identified to increase the likelihood of a favorable benefit-risk assessment. We recommend that you submit the SAP for VP-VLY-686-3404 prior to unblinding and analyzing the data in order to allow for our review and feedback.**

Therefore, based on the concerns outlined above, including that the phase 2 study (VP-VLY-686-2401) assessed vomiting in a different way from the phase 3 study (VP-VLY-686-3401), we recommend completing the ongoing phase 3 study VP-VLY-686-3404 ("Motion Serifos: A randomized, double-blind, placebo-controlled study to investigate the efficacy of tradipitant in participants affected by motion sickness during travel") prior to a future NDA submission to potentially provide additional data to support your proposed indication of prevention of vomiting induced by motion.

Meeting Discussion:
The Sponsor provided a draft document with additional questions for the Agency, which was received November 8, 2023. The Sponsor referred to this document during the discussion. Refer to Section 4.0 Attachments and Handouts.

In response to the Agency's preliminary comment 1a that stated testing multiple endpoints and then selecting an endpoint based on which endpoint showed the most favorable results could produce a biased assessment of efficacy results, the Sponsor stated that the statistical analysis plan (SAP) for study 2401 was updated to include the primary endpoint of "Percentage of vomiting, which is defined as subjects ever vomited (MSSS=6) or terminated early due to severity during the vehicle travel." The Sponsor inquired whether this update to the SAP may lessen the potential for interpretation bias. The Agency stated that it was premature to agree and may provide a post-meeting comment.

Post-Meeting Comment:
You stated that the efficacy endpoint of "Percentage of vomiting, defined as subjects ever vomited (MSSS=6) or terminated early due to severity during the vehicle travel" was added to the SAP following our comments provided in an advice letter dated March 12, 2019. We note that the SAP was not submitted prior to unblinding. The SAP that was provided with the clinical study report, received April 24, 2020, does not specify which primary endpoint was tested first or the testing hierarchy and whether adjustments were made for multiplicity. Therefore, we are unable to agree that the information provided above addresses our concern about potential bias without a clearly prespecified multiple testing procedure. Ultimately, the adequacy of the data will be determined during review of the NDA.

In response to the Agency's preliminary comment 1b, the Sponsor clarified that the MSSS used in study 2401 was modified so that subjects were queried "In the last 30 minutes, how severe is your motion sickness." The Sponsor asked if this addresses the Agency's concerns. The Agency requested copies of the COAs that used the modified question and any information available to support the use of the COA, and they would consider it as part of the NDA submission.

In response to the Agency's preliminary comment 2a, the Sponsor stated that both the tradipitant 170 mg and 85 mg dose arms achieved p-values < 0.0001 on the endpoint of the percentage of vomiting. The Sponsor asked if the Agency agreed that both of these results would be considered statistically significant at p < 0.05 if the Bonferroni method had been used. The Agency stated that statistical significance is determined based on the pre-specified multiple testing procedure. While alternative multiple testing procedures could lead to different conclusions, the type I error rate is only controlled using the pre-specified multiple testing procedure. The Sponsor asked if the results from the analyses of the tradipitant 85 mg dose arm on the percentage of vomiting would not be considered by the

Agency. The Agency indicated that any efficacy data submitted as part of a future NDA would be considered but that the type I error control is an important aspect of the assessment of efficacy.

Question 2:
Does FDA agree that the proposed safety database would be adequate to support the NDA filing and review of tradipitant for the prevention of vomiting induced by motion?

FDA Response to Question 2:
Refer to FDA Response to Question 1 and Question 3. The determination that an NDA is sufficiently complete for filing is made within 60 days after receipt of the NDA.

We note that our safety assessment will focus on controlled data from the intended-use population. According to the meeting background package, it appears you intend to submit data from the following studies conducted in subjects with vomiting induced by motion: VP-VLY-686-2401, VP-VLY-686-3401, VP-VLY-686-3403,[2] and VP-VLY-686-3404. This will result in controlled safety data for a single dose of tradipitant 85 mg and 170 mg from an estimated 223 and 283 subjects, respectively.[3] The size of the proposed safety database may be reasonable for the proposed indication; however, the appropriateness of the size of the safety database will depend on a number of factors including the intended use population, the condition being treated, and the risks identified in the development program, during the review of the NDA.

Meeting Discussion:
The Sponsor provided a draft document with additional questions for the Agency, which was received November 8, 2023. The Sponsor referred to this document during the discussion. Refer to Section 4.0 Attachments and Handouts.

The Sponsor stated that they will provide justification for the adequacy of the safety evaluations in the NDA. The Agency reiterated that in general, safety data obtained from controlled clinical trials conducted in the target population who received the to-be-marketed dose, is the most relevant to assess the safety of tradipitant for the proposed use. The Agency stated that the Sponsor may submit additional safety data with justification for the Agency's consideration in the future NDA submission.

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[2] VP-VLY-686-3403 "Motion Delos: An open label study to investigate the safety and efficacy of tradipitant in participants affected by motion sickness during travel." The Agency previously conveyed the concern that the open-label, uncontrolled design of VP-VLY-686-3403 will not be interpretable. The Agency also stated that data from an uncontrolled, open-label study will not replace the need for data from controlled investigations to support a determination of safety and effectiveness. Refer to the advice letter dated February 28, 2023.
[3] This estimate is based on Tables 11 and 12 from the meeting background package with the exclusion of data from VP-VLY-686-3403.

Question 3:
Does FDA agree that the proposed preclinical safety database is adequate for the filing and review of this application for the prevention of vomiting induced by motion?

FDA Response to Question 3:
The determination that an NDA is sufficiently complete for filing is made within 60 days after receipt of the NDA. We note, however, that the proposed nonclinical safety database may not be adequate to inform the repeated use of tradipitant for the prevention of vomiting induced by motion. While vomiting induced by motion may occur intermittently, it is likely that a patient will require multiple courses of treatment. It will be important to adequately characterize the risks of cumulative toxicity following repeated short-term exposures to tradipitant. Refer to Advice Letter dated February 28, 2023.

(b) (4)

If you believe you have a suitable alternative approach to our recommendations in the context of this NDA, you may propose an alternative approach and provide rationale to support why the data are sufficient as part of the NDA submission.

Meeting Discussion:
No further discussion.

FDA Additional Comments:

Pediatrics

1. **An initial pediatric study plan (iPSP) has not been submitted. See Section 3.0 Other Important Information, PREA Requirements below.**

Clinical Pharmacology

2. **Address dosing for patients with hepatic impairment or renal impairment. It is unclear whether dedicated hepatic or renal impairment studies have been conducted.**

3. **The ICH E14 (Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs) recommends evaluation of QT interval prolongation risk for new drugs having systemic bioavailability. It is unclear whether a thorough QT study has been conducted. Regarding the QT evaluation report, include a completed**

version of the most recent "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt).

4. **Provide adequate PK data for single dose and multiple doses with the to-be-marketed formulation for the proposed drug and its major metabolites. We note that tradipitant and its major metabolites M2, M3, M4, and M8, account for approximately 43% of the circulating material in human plasma based on the radiolabeled ADME study described in the background package. In the NDA submission, provide an explanation for the radioactivity that was unaccounted for in human plasma.**

5. **Characterize food effect on the to-be-marketed formulation and dosing instruction respective of food intake.**

6. **Provide a complete assessment of drug-drug interaction for tradipitant and its major metabolite(s), if applicable. We recommend you address the potential effects of concomitant inhibitors of tradipitant metabolizing enzymes on the PK of tradipitant. Refer to the guidance for industry *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020) and *Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020).** Error! Bookmark not defined.

7. **Submit electronic datasets for the PK concentration data, PK parameters, and complete bioanalytical reports for the proposed drug and its major metabolites, including assay method validation reports and in-study bioanalytical assay reports for all studies with PK components in the NDA submission.**

8. **Additionally, if the to-be-marketed formulation is different from the formulation used in the trial(s) intended to support the marketing application, a relative bioavailability study may be needed to support a bridge between the two formulations.**

Data Submission and Format

9. **Refer to the Study Data Technical Conformance Guide: Technical Specification Document (available at: https://www.fda.gov/industry/fdadata-standards-advisory-board/study-data-standards-resources) for specifications, recommendations, and general considerations on how to submit standardized study data using FDA-supported data standards.**

10. **The meeting background package did not specify whether you intend to submit an integrated summary of effectiveness (ISE) and an integrated summary of safety (ISS). Include in your NDA submission an ISE and ISS (21 CFR 314.50(d)(5)). Refer to the guidances for industry *Integrated Summary Effectiveness* (October 2015) and *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* (April 2009). Additionally, we recommend that you submit the SAPs for both the ISE and ISS.**

11. **Submit all codes (including any macros) and datasets (along with data dictionaries) used to create the analyses to support a determination of efficacy or safety. The submitted datasets should be structured to allow replication of efficacy and safety analyses without excess data manipulation.**

12. **All data for a given domain or dataset (e.g., ADLB) should be contained in one dataset. The dataset should include flags to permit evaluation of the relevant analysis populations as outlined in the SAP.**

13. **Include flags in the ADSL dataset to indicate if a narrative, CRF, or adjudication package has been submitted for each patient.**

14. **Narratives and CRFs should be submitted for all deaths, serious adverse events (SAEs), adverse events of special interest (AESIs), adverse events leading to permanent treatment discontinuation regardless of attribution to the investigational drug product or treatment arm and for patients who experienced treatment emergent pregnancy.**

15. **Narrative format and content:**

    a. **The subject's unique identifier should be used as the title of the document and the file name. These names are used to assist reviewers in finding the narratives for an individual.**

    b. **Narrative summaries should provide a complete synthesis of available relevant clinical data and an informed discussion of the case. This summary should include, but not limited to, the patient's medical history, medical/surgical management of the event, the outcome, study treatment and enrollment disposition, and the event's potential relationship to the investigational treatment.**

    c. **Narratives should be comprehensive enough for the reader to be able to reach a reasonable conclusion regarding the subject and the adverse event.**

d. **For subjects who had more than one related event requiring a narrative (whether in the same trial or in the core study and an extension), present a single narrative for each subject rather than separate narratives for the various events. Unrelated events that are separated in time may be submitted as separate narratives.**

16. **Although Système International (SI) units may be the standard reporting mechanism globally, we recommend laboratory test results be presented in both SI and US conventional units in a single domain or data set to minimize conversion needs during review.**

17. **Submit a dataset that contains all subjects who were unblinded. The dataset should include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.**

18. **When creating the disposition dataset, for discontinuations due to "other," perform medical review to ensure appropriate categorization e.g., discontinuation due to AE or meeting study discontinuation criteria, etc. For discontinuations due to "other" that are not appropriate for predefined categories, provide the specific reason.**

19. **For the safety analyses, provide a prioritized list of AESIs including those previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any MedDRA SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.**

20. **For each study, provide a flag in the AE dataset or a separate dataset that maps preferred terms to the AESIs.**

21. **In addition to presenting the adverse event data by preferred terms, evaluate adverse events based on logical groupings of preferred terms using standard MedDRA queries or other appropriate means. Include in the submission the procedures and rationale used for grouping of preferred terms.**

22. **Analysis of liver safety should be included in the overall safety assessments. You should incorporate and summarize investigator reports and PTs related to potential hepatic injury not limited to the specific liver biochemistry elevations. Refer to FDA guidance for *industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation* and relevant sections from *Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH)* for additional guidance on liver safety data submission.** Error! Bookmark not defined.

Meeting Discussion:
No further discussion.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[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]

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

[4] 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.
[5] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

you to review the labeling review resources on the PLR Requirements for Prescribing Information[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

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

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

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.[8]

[6] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[7] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule
[8] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

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 (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[9] 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.

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

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 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[10]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[11].

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[12]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[13]

[10] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[11] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[12] http://www.fda.gov/ectd
[13] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[14] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[15]. Submit all

[14] https://www.fda.gov/media/84223/download
[15] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

Office of Scientific Investigations (OSI) Requests

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[16]

4.0 ATTACHMENTS AND HANDOUTS

The Sponsor's draft document received November 8, 2023, attached.

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

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY H CHUNG
12/08/2023 03:13:01 PM

IND 141315

MEETING MINUTES

Vanda Pharmaceuticals Inc.
Attention: Vasilios Polymeropoulos, M.D.
Director of Medical Analytics
2200 Pennsylvania Ave NW
Suite 300 E
Washington, D.C. 20037

Dear Dr. Polymeropoulos:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tradipitant (VLY-686).

We also refer to the telecon between representatives of your firm and the FDA on May 13, 2020. The purpose of the meeting was to discuss aspects of the clinical development of tradipitant (VLY-686).

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

If you have any questions, call me at (301) 796-0260.

Sincerely,

{See appended electronic signature page}

Mary Chung, Pharm.D.
Senior Regulatory Health Project Manager
Gastroenterology
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[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.

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B, Teleconference
Meeting Category: End of Phase 2

Meeting Date and Time: May 13, 2020 1:00- 2:00 PM EST

Application Number: IND 141315
Product Name: tradipitant (VLY-686)

Indication: Sponsor's proposed indication is (b) (4) prevention of vomiting associated with motion (b) (4)

Sponsor Name: Vanda Pharmaceuticals Inc.
Regulatory Pathway: 505(b)(1)

Meeting Chair: Erica Lyons, M.D.
Meeting Recorder: Mary Chung, Pharm.D.

FDA ATTENDEES

Division of Gastroenterology

Joyce Korvick, M.D.	Deputy Director for Safety
Erica Lyons, M.D.	Medical Team Lead
Matthew Kowalik, M.D.	Medical Officer

Division of Pharmacology and Toxicology for Immunology and Inflammation

Sushanta Chakder, Ph.D.	Pharmacology Team Lead
Yolanda Branch, Ph.D.	Pharmacology Reviewer

Office of Clinical Pharmacology, Division of Inflammation and Immune Pharmacology

Insook Kim, Ph.D.	Clinical Pharmacology Team Lead
Jie Cheng, Ph.D.	Clinical Pharmacology Reviewer

Office of New Drug Policy, Division of Regulatory Policy

James Myers, J.D.	Director

Office of Biostatistics, Division of Biostatistics III

David Petullo, M.S.	Statistical Team Lead
Sara Jimenez, Ph.D.	Statistical Reviewer
Scott Komo, Ph.D.	Statistical Team Lead
Xin Yuan, Ph.D.	Statistical Reviewer

Division of Clinical Outcome Assessment
Sarrit Kovacs, Ph.D. Team Lead
Christopher St. Clair, Pharm.D. Reviewer

SPONSOR ATTENDEES
Mihael Polymeropoulos, M.D., Chief Executive Officer
Gunther Birznieks, Research and Development Committee Member
Christos Polymeropoulos, M.D., Vice President Medical Director
Vasilios Polymeropoulos, M.D., Director of Medical Analytics/ Clinical Program Lead
Derek Xiao, Ph.D., Head of Biometrics
Tim Williams, Vanda General Counsel
(b) (4) Outside Legal Counsel
Lauren Van Draanen, Clinical

1.0 BACKGROUND

On January 16, 2020, the Sponsor submitted a meeting request for IND 141315 tradipitant (VLY-686). Tradipitant is an inhibitor of neurokinin-1 receptor (NK-1) that is administered orally. (b) (4)

The Sponsor's January 16, 2020 meeting request, the first meeting request for IND 141315, was submitted as an End of Phase 2 meeting request. This meeting request was granted and the background package was received March 24, 2020.

2.0 DISCUSSION

The format of these minutes provides for Vanda Pharmaceutical's questions in regular typeface, followed by the Agency's May 7, 2020 responses in **bolded** print. The May 13, 2020 meeting discussion summary is presented in ***italic and bolded*** print.

Meeting Discussion:
The Sponsor expressed understanding of FDA's assessment that their development program may be adequate to support an indication for the prevention of vomiting induced by motion and voiced their intent to pursue this indication.

Regarding FDA's recommendation to utilize an endpoint of the absence of vomiting or rescue medication use in a pre-specified time period to evaluate the efficacy of tradipitant for the prevention of vomiting induced by motion, the Sponsor stated that their current study design does not allow for the use of rescue medication and provided their justification and rationale to maintain the

current design. FDA acknowledged their rationale and committed to provide feedback on this proposal as a post-meeting comment.

> ***Post-meeting Comment:***
> ***We acknowledge you intend to evaluate vomiting in the absence of rescue medication use as your primary endpoint and agree with your proposal to not allow for rescue medication use in study VP-VLY-686-3401.***

The Sponsor stated that they intend to introduce a new assessment tool to evaluate the primary efficacy endpoint, consisting of a questionnaire to document whether a participant has vomited over the last 30 minutes that will be administered every 30 minutes. FDA requested that an exact copy of the questionnaire be submitted for FDA review, and the Sponsor agreed.

The Sponsor stated that they will continue to collect data with the MSSS, MSAQ, and PGIS. The Sponsor also informed FDA of their intent to introduce a nausea severity scale as a secondary assessment.

FDA referred the Sponsor to advice and recommendations provided during previous communications on the use and support of COA tools within their development program as this advice would be applicable to novel PRO assessments as well. FDA requested that exact copies of all questionnaires and instruments be submitted for FDA review, and the Sponsor agreed.

The Sponsor inquired as to FDA's recommendation for the addition of a (b) (4) ***without a baseline assessment and with a single treatment period in the study design. FDA agreed to provide additional information regarding the recommendations to include a*** (b) (4) ***as a post-meeting comment.***

> ***Post-meeting Comment:***
> ***We acknowledge that it may be difficult to incorporate a*** (b) (4) ***assessment into your proposed study design. Therefore, in this specific circumstance, we do not object to omitting*** (b) (4)
>
> ***We acknowledge your plan to include an assessment of nausea severity. We recommend use of a verbal rating scale (VRS; e.g., none, mild, moderate, severe)*** (b) (4)

The Sponsor provided rationale for their proposal (b) (4)

[redacted] ***FDA committed to internally discuss this proposal and provide a post-meeting comment.***

> ***Post-meeting Comment:***
> ***We acknowledge your rationale*** [redacted] ***we continue to recommend you explore the effect of tradipitant in all sea conditions to support the generalizability of the results of your study.***

The Sponsor clarified that they intend to submit safety data from a cohort of between 150-200 patients treated with a dose of 170 mg of tradipitant in studies assessing the prevention of vomiting induced by motion. Additionally, the Sponsor requested clarification on the inclusion of safety information from patients treated with tradipitant for other indications ([redacted] ***.***

FDA referred to the preliminary comments and stated that the adequacy of the safety database will be determined at the time of review. However, the data from patients treated with tradipitant for other indications would be considered supportive, and not part of the primary safety database.

The Sponsor restated that they were pursuing an indication of the prevention of vomiting induced by motion and inquired whether FDA would be supportive of an indication of [redacted]

FDA stated that they did not agree that the indication of [redacted] ***would be appropriate for their development program as currently designed.***

FDA asked about the status of the current phase 3 study.

The Sponsor stated that enrollment has been temporarily paused due to challenges related to the COVID-19 pandemic.

FDA thanked the Sponsor for providing comments and clarifications and committed to having additional internal discussion and providing post-meeting comments as agreed upon during the meeting.

Introductory Comments

We are providing these comments to encourage collaboration and increase the likelihood of a successful development program for tradipitant. Based on our preliminary review of the data from your phase 2 study and ongoing phase 3

protocol, it is our assessment that your development program, as currently designed, may be adequate to support an application for the indication of the prevention of vomiting induced by motion.

We acknowledge the submission of your phase 2 clinical study report and that your presented summary data appears supportive of a reduced incidence of vomiting in patients who received tradipitant compared to placebo. (b) (4)

We refer you to our previous recommendations for analyses and resulting data that would be needed to support (b) (4) **the demonstration of efficacy for this indication or be considered for inclusion into the prescribing information.**

Reference is made to the Advice/Information Request from December 19, 2018 and the Advice/Information Request from March 8, 2019, which detailed our concerns with your phase 2 study (i.e., VP-VLY-686-2401) and provided recommendations for how to resolve the noted deficiencies. We do not agree that these issues have been satisfactorily addressed or resolved. This introduces significant limitations on the interpretability of the data from your development program and the potential for the data to support a successful marketing application (b) (4)

1. (b) (4) **We refer you to the concerns conveyed in the December 19, 2018 Advice/Information Request (** (b) (4) **Clinical Outcome Assessments (COAs) must be well-defined and reliable in order to support regulatory decision-making and labeling claims.[2]**

2. **At this time, we do not agree that the** (b) (4) **is acceptable** (b) (4) **as you have not provided sufficient information to demonstrate that this instrument is fit-for-purpose and, if so, what degree of change is clinically meaningful to patients. You may refer to the FDA Guidance for Industry: *Patient-Reported***

[2] 21 CFR Part 314.126(b)(6). Available from https://www.ecfr.gov/cgi-bin/text-idx?SID=26f86f78bf3a7293101aa3f952237cce&mc=true&node=pt21.5.314&rgn=div5#se21.5.314_1126

***Outcome Measures: Use in Medical Product Development to Support Labeling Claims*[3] regarding fit-for-purpose clinical outcome assessments.**

3. **We continue to recommend that you include a (b) (4) anchor scale in addition to a PGI-S anchor scale to determine a clinically meaningful change in your endpoints. We recommend that anchor scales such as the PGI-S and (b) (4) be positioned as exploratory endpoints rather than secondary endpoints.**

4. **We continue to recommend you utilize an endpoint of the absence of vomiting or rescue medication use in a pre-specified time period to demonstrate the efficacy of tradipitant for the prevention of vomiting induced by motion.**

Furthermore, we request clarification regarding your intent to seek an indication for (b) (4)

Additionally, we note that your protocol proposed (b) (4) was eliminated without an update to the protocol or amendment. Please confirm that the most current version of the protocol has been submitted to the IND.

Question 1:

Does the Division agree that the Phase III clinical protocol outlined in this briefing book is able to support an indication of either:

1. (b) (4)
2. (b) (4)

Please also comment on the adequacy of the following study characteristics:

- Population selection
- Primary endpoint selection
- Dose selection
- Inclusion/exclusion criteria selection

Does the Division agree that this program would be sufficient for NDA filing?

[3] FDA Guidance documents available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents.

FDA Response to Question 1:

No, we do not agree. Please see Introductory Comments above. We have significant concerns regarding your proposed indications, the interpretability of the data from study VP-VLY-686-2401, and the phase 3 protocol for study VP-VLY-686-3401.

Regarding the adequacy of the following characteristics for study VP-VLY-686-3401:

1. **In general, your population selection appears reasonable; however, we have the following recommendations:**
   a. **In your phase 3 protocol,** [redacted] (b) (4) **We recommend you evaluate tradipitant in all wave height conditions to support the generalizability of the results of your study.**
   b. **Provide a copy of the contents of** [redacted] (b) (4)

2. **Regarding your primary endpoint selection, please refer to our Introductory Comments above for additional data needed to support your proposed primary endpoint.**

3. **Your dose selection appears reasonable from a safety perspective, and your proposal to study two dose levels is acceptable.**

4. **In general, your eligibility criteria appear reasonable.**
   a. **We acknowledge your plan to conduct a hepatic impairment study. We recommend you exclude patients with hepatic impairment (a history of cirrhosis and patients with cirrhosis with Child-Pugh B and C classes) until additional information becomes available to support dosing in these populations because tradipitant undergoes extensive metabolism and apparent biliary excretion.**
   b. **We acknowledge that you plan to conduct a renal impairment study. We recommend you specify inclusion/exclusion criteria based on renal function using eGFR and provide a rationale with supporting data to support the inclusion patients with renal impairment in the phase 3 trial.**
   c. [redacted] (b) (4) **Per your backgrounder, M2, one of major metabolites is a substrate of CYP3A4.**

5. **You should include individual study stopping criteria such that patients have the option of receiving rescue therapy (e.g., pharmacologic, behavioral, or environmental). (b) (4) Additionally, we recommend that you establish study stopping criteria based upon Common Terminology Criteria for Adverse Event v5.0 criteria.**

With the above described limitations, and in consideration of the current status of your program, it is premature to agree that this program would be sufficient for NDA filing (b) (4) Please see our Introductory Comments and past Advice/Information Requests for recommendations to increase the likelihood of a successful NDA filing and review. We do not agree that study VP-VLY-686-2401, as conducted, or study VP-VLY-686-3401, as currently designed, would be considered adequate to support an application for your proposed indications.

Question 2:
Does the division believe that the proposed safety database would be sufficient to characterize the safety of tradipitant (b) (4) and support the NDA filing?

FDA Response to Question 2:

We acknowledge your proposed safety database for tradipitant (b) (4) includes 63 patients from your phase 2 study and a proposed 300 patients in your phase 3 study (of which patients will be randomized 1:1:1 to placebo, tradipitant 85 mg, or tradipitant 170 mg). Please note that the data from patients treated with 85 mg of tradipitant will not be considered sufficient to support of the safety of the 170 mg dose (see response to Question 3 below). Ultimately, the adequacy of the safety database will be determined during review of the application; however, we recommend that you submit additional justification for the proposed size of your safety database.

Question 3:
Does the division agree with utilizing additional safety data across all studied indications with tradipitant to support the NDA filing safety data package?

FDA Response to Question 3:

While we agree that safety data from patients treated with tradipitant for indications (b) (4) could be considered supportive of the overall safety profile of tradipitant, the primary safety database for a marketing

application should consist of patients from the intended use population treated with the dose intended to be marketed. We do not agree with your proposal to include patients from other development programs in the primary safety database (b) (4)

3.0 ADDITIONAL COMMENTS

Clinical Outcome Assessments

In accordance with comments conveyed in the December 19, 2018 Advice/Information Request with regard to submitting information to the Agency prior to initiating your phase 2a study, we have the following comments.

For any COA that you propose as a pre-specified alpha-controlled efficacy endpoint intended to be fit-for-purpose to support regulatory decision-making and labeling claims, we recommend that you provide the following for Agency review and comment prior to initiating your phase 3 trial:

- **Conceptual framework of the instrument**
- **Evidence of content validity obtained for this specific context of use (e.g., qualitative research with patients matching clinical trial eligibility criteria)**
- **Exact copy of the instrument as it will be administered during the clinical trial (e.g., electronic screenshots) and any associated training materials and user manuals**
- **Proposed scoring algorithm(s) with rationale and corresponding information on how the instrument's scores will be analyzed as part of an endpoint**
- **Plans for, and results from, evaluation of the psychometric properties and performance of the instrument (i.e., reliability, validity, and ability to detect change) after content validity has been established**
- **Pre-specified plans for handling missing data**
- ***A priori* threshold (or range of thresholds) representing clinically meaningful within-patient improvement in the instrument's scores**

Clinical Pharmacology

- **We recommend you collect PK blood samples and explore the exposure-response relationship in the phase 3 study.**
- **If the to-be-marketed formulation is different from the formulation used in the clinical studies, provide information for how you intend to support a bridge between the clinical trial formulation and the to-be-marketed formulation.**
- **We recommend you conduct a thorough QT study to address the potential effects of tradipitant on the QT interval.**

- **We recommend that you provide a tabulated summary of in vitro drug-drug interaction study results with a prediction of in vivo drug-drug interaction potential.**
- **We recommend that you conduct an in vivo drug-drug interaction study with strong CYP3A4 inhibitors. Please further clarify the metabolizing enzymes for tradipitant into various metabolites.**
- **We request that you provide a comprehensive summary of clinical pharmacology information to support the dose and regimen selected for study.**

PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[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]

[4] 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.

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

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.[6]

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,[7] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[8] 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

[6] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm
[7] https://www.fda.gov/media/88173/download
[8] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm

(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.[9] 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[10] (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.[11] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[12]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[13] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[14]

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[9] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[10] https://www.fda.gov/media/88173/download
[11] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[12] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[13] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[14] https://www.fda.gov/media/109533/download

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[15]

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY H CHUNG
05/21/2020 04:45:06 PM