CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216386Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 134120

MEETING PRELIMINARY COMMENTS

Biohaven Pharmaceuticals
Attention: Lisa Stocking
234 Church Street, Suite 304
New Haven, CT 06510

Dear Ms. Stocking:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BHV-3500.

We also refer to your correspondence dated and received January 13, 2020, requesting a meeting to discuss plans for your Phase 3 program.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Lana Y. Chen, R.Ph.
Senior Regulatory Project Manager
Neurology 2
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	**B**
Meeting Category:	**End of Phase 2**
Meeting Date and Time:	**March 18, 2020 from 10:00-11:00am EDT**
Meeting Location:	**FDA White Oak Bldg 22, Conference Rm 1311**
Application Number:	**134120**
Product Name:	**BHV-3500**
Indication:	**Acute treatment of migraine in adults**
Sponsor Name:	**Biohaven Pharmaceuticals**

FDA ATTENDEES (tentative)

Division of Neurology 2
Nick Kozauer, MD, Acting Director
Heather Fitter, MD, Clinical Team Leader
Laura Jawidzik, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Edmund Nesti, PhD, Nonclinical Reviewer
Martha Heimann, PhD, CMC Lead
Kun Jin, PhD, Statistical Team Leader
Jinnan Liu, PhD, Statistical Reviewer
Angela Men, PhD, Clinical Pharmacology Team Leader
Dawei Li, PhD, Clinical Pharmacology Reviewer
Lana Chen, RPh, Project Manager

SPONSOR ATTENDEES

Biohaven Pharmaceuticals
Vlad Coric, MD, Chief Executive Officer
Elyse Stock, MD, Chief Medical Officer
Charlie Conway, PhD, Chief Scientific Officer
Robert Croop, MD, Chief Development Officer – Neurology
Marianne Frost, MA,Vice President, Regulatory Affairs
David Stock, PhD, Vice President, Biostatistics
Richard Bertz, PhD,Vice President, Clinical Pharmacology and Pharmacometrics
(b) (4) Clinical Pharmacology Consultant to Biohaven
Beth Morris, BA, Executive Director, Clinical Operations
Francine Healy, BS, Executive Director, Scientific Writing and Regulatory Submissions
Lisa Stocking, MSPH, Director, Regulatory Affairs and Operations
(b) (4) Toxicology Consultant to Biohaven

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 March 18, 2020 between Biohaven Pharmaceuticals and the Division of Neurology 2. 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 and/or changing the format of the meeting (e.g., from face to face to teleconference). 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 DISCUSSION

QUESTION 1 (Nonclinical):

a. An extensive nonclinical program has been conducted with vazegepant. The available nonclinical data support clinical studies in subjects with migraine. Does the Agency agree that no additional nonclinical toxicology investigations with vazegepant are required to support registration?

FDA Response: Based on the information provided in the briefing document, we have the following comments on your nonclinical program:

- It does not appear that you plan to conduct chronic toxicology studies of vazegepant. We refer you to our August 1, 2017, Pre-IND Written Responses (WR) for comments on the need for chronic toxicity studies and on other aspects of the nonclinical program. We note the chronic toxicity study in nonrodent is to be 9 months in duration, rather than 12 months as stated in the WR.

- Based on the available receptor binding data, it is unlikely that the potential for vazegepant to have adverse developmental effects through CGRP antagonism would be assessed in mouse, rat, or rabbit. Previously (see August 1, 2017, WR, Appendix, Updated question for discussion of 25 Apr 2006), there was discussion of conducting an embryofetal development study in which CGRP(8-37) peptide antagonist would be administered to pregnant rats. We found no mention of such a study in the briefing document. You should provide justification for whatever approach you propose to address this issue.

b. Biohaven is conducting a 6-month transgenic mouse carcinogenicity study along with a 2-year rat carcinogenicity study (both ongoing). Does the Agency agree that this carcinogenicity package is acceptable for NDA submission?

FDA Response: We were unable to locate in the briefing document what transgenic mouse model is being used to assess the carcinogenic potential of vazegepant. In general, a 6-month carcinogenicity study in the Tg.rasH2 mouse and a 2-year carcinogenicity study in rat would constitute a sufficient evaluation of carcinogenic potential. The adequacy of the studies will be a matter of review.

QUESTION 2 (Clinical – Clinical Pharmacology Program):

Does the Agency agree that the clinical pharmacology investigations planned with vazegepant (Table 2) are sufficient to support registration?

a. Does the Agency agree that the planned cQT assessment of vazegepant from assessments in the SAD and MAD studies is adequate to support registration?

FDA Response: We cannot answer this question until we have reviewed your QT assessment report. We request that you submit your QT assessment report including clinical study reports for Study # BHV3500-101 and Study # BHV3500-102.

Additionally, we have the following comments:

1. The adequacy of the highest dose used in the study will be a review issue depending on the final choice of highest therapeutic dose and whether there exists a sufficiently high exposure margin (at least 2-fold of the worst-case scenario exposure) to waive the requirement for a positive control for assay sensitivity (refer to ICH E14 Q&A (R3), Section 5.1).
2. We are also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

3. When you submit your QT evaluation report, please include a completed version of the "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).

b. Does the Agency agree that a clinical interaction study of vazegepant and metformin is not needed to assess an interaction with the MATE1 transporter?

FDA Response: Yes, we agree that the assessment of MATE1 transporter mediated DDI is not needed at your proposed dosing regimen for Phase 3 study. If the 20 mg dose will be evaluated, you may need to conduct a clinical study to assess MATE1 transporter mediated DDI. For more detailed information, please refer to Guidance for Industry: In Vitro Drug Interaction Studies —Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions (January 2020). https://www.fda.gov/media/134582/download

c. Does the Agency agree that based on the preliminary assessment that vazegepant undergoes low metabolism, no study of hepatic impairment will be required prior to filing?

FDA Response: Whether a hepatic impairment study is necessary will rely on the results from your planed clinical mass balance study.

d. Does the Agency agree that a renal impairment study is not required given that vazegepant is a low dose (10 mg recommended) drug intended for acute intermittent use?

FDA Response: Whether a renal impairment study is necessary will rely on the results from your planed clinical mass balance study.

QUESTION 3 (Clinical – Dose Selection for Proposed Phase 3 Study):

Does the Agency agree that a dose selection of vazegepant 10 mg is appropriate for use in the proposed Phase 3 study for the acute treatment of migraine?

FDA Response: We have no objection to your proposed dose.

QUESTION 4 (Clinical – Patient Population in Proposed Phase 3 Study):
Does the Agency agree that the proposed entry criteria for the Phase 3 clinical study adequately defines the population for the proposed indication?

FDA Response: We have no objections to your proposed inclusion criteria.

In terms of your exclusion criteria, we encourage you to enroll the broadest population in your studies, unless you have safety information to suggest that your product could not be administered safely to a subset of patients. Please provide a rationale for excluding patients with a BMI ≥35 kg/m².

QUESTION 5 (Clinical – Endpoints in Proposed Phase 3 Study):

a. Does the Agency agree that the coprimary endpoints: (1) pain freedom at 2 hours postdose and (2) freedom from the most bothersome symptom associated with migraine at 2 hours postdose are appropriate for the assessment of efficacy for the proposed indication?

FDA Response: Yes, we agree with your proposed co-primary endpoints.

b. Does the Agency agree that the secondary endpoints are appropriate to provide additional evidence to support efficacy for the proposed indication?

FDA Response: The secondary endpoints that we consider supportive of efficacy are outlined in the Guidance for Industry, "Migraine: Developing Drugs for Acute Treatment." In general, we do not recommend the use of the endpoints (b) (4) at various time points. You should evaluate pain freedom at various time points, including sustained pain freedom at either 24 or 48 hours. If you are using a hierarchical approach to analyze your secondary endpoints, then the endpoints should be ordered according to their clinical meaningfulness.

c. Does the Agency agree that for statistically significant secondary endpoints in the pivotal Phase 3 study (BHV3500-301), those results plus the weight of evidence from the pivotal dose-ranging study (BHV3500-201), would be adequate to have these endpoints considered for labeling?

FDA Response: It is premature to comment on the contents of labeling.

QUESTION 6 (Statistics – Phase 3 Study):

Does the Agency agree with the proposed statistical plan including the sample size, analysis populations, plans to protect against Type I error and handling of missing data?

FDA Response: You plan to randomize 1400 patients with 700 per group. Assuming 90% will have a qualified migraine attack, there should be approximately 630 evaluable patients per group. The planned sample size of 630 per arm appears to be adequate.

Your plan to use the mITT population as the efficacy analysis population is acceptable.

Your plan to control Type 1 error by a hierarchical gate-keeping procedure appears to be adequate. However, see the response to Question 5(b) regarding the selection of the secondary endpoints, themselves. You will also need to pre-specify the list and testing order of the secondary endpoints in the study protocol and SAP.

Your plan to treat missing data as failures in the primary analyses seems reasonable. We expect to see minimal missing data for acute migraine trials since the primary efficacy data collection occurs 2 hours post-dosing.

QUESTION 7 (Clinical – General Aspect of Proposed Phase 3 Study):
Does the Agency have any comments on other aspects of this study, based on the draft protocol provided?

FDA Response: Yes, we have the following comments:

1. Please clarify why triptans are not permitted for 48 hours after taking the investigational product (IP). In general, we recommend that patients be allowed to use their standard of care medications two hours after the patient has taken the IP and has provided their two-hour efficacy data.

2. We suggest you modify your definition of menopause. Women who enroll in your clinical studies who still menstruate should still be considered women of child bearing potential and should practice effective birth control.

3. Please clarify how (i.e., electronic or paper diary) and for what time period you are collecting adverse events for Study 301.

QUESTION 8 (Clinical – Long-term Safety Study):
Does the Agency agree with proposed design of the 52-week, long-term clinical safety study?

FDA Response: On face, the design of the 52-week study appears adequate with the exception of your planned safety experience. We may have additional comments regarding the design of the long-term safety study once results from the multiple ascending dose study are available. Please also see our response to Question 9 regarding the evaluation of possible hepatotoxicity with your product.

QUESTION 9 (Clinical – General Aspect of Proposed Long-term Safety Study):
Does the Agency have any comments on other aspects of this study, based on the draft protocol provided?

FDA Response: Please see our responses to Questions 8 and 10.

QUESTION 10 (Clinical – Safety Database):
Does the Agency agree that the proposed safety experience from planned and completed clinical studies with vazegepant, combined with the safety database for the long-term study, will be sufficient to evaluate the safety of vazegepant in support of registration for the indication of the acute treatment of migraine with or without aura in adults?

FDA Response: No, we do not agree. Due to safety concerns of possible hepatotoxicity regarding the use of small molecule CGRP receptor antagonists, we require that you characterize the hepatic liability of the daily or near daily use of your product. The safety database you describe as part of your proposed development program is insufficient to adequately address the hepatic safety of your product for patients who use acute migraine medication on a near daily basis. We recommend that you conduct a two to three-month safety study in which 300 migraine patients or healthy volunteers use your product on a near daily basis and that this study includes a comparator arm.

Please also refer to Attachment 1: DN2 General Clinical Safety Requests for planned NDAs.

QUESTION 11 (Regulatory):
Does the Agency agree that data from the completed pivotal Phase 2/3 clinical study, together with data from the planned pivotal Phase 3 study (BHV3500-301), serve as an adequate basis for evaluation of vazegepant in a 505(b)(1) NDA for the acute treatment of migraine with or without aura in adults?

FDA Response: This question is premature. On face, Study 201 has many of the characteristics of an adequate and well-controlled study, but whether this trial can serve as one of your pivotal trials would be a matter of review. The acceptability of future studies, such as your planned Phase 3 study, to support drug approval depends on the study results and cannot be determined prospectively.

PREA REQUIREMENTS

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

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

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

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic*

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

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,[4] 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[5] 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.[6] 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

[4] https://www.fda.gov/media/88173/download
[5] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[6] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[7] (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.[8] 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.[9]

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

[7] https://www.fda.gov/media/88173/download
[8] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[9] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

randomization ratio imbalances, study populations, etc.).

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

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

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

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[10] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[11]

ABUSE POTENTIAL ASSESSMENT

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

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

guidance for industry *Assessment of Abuse Potential of Drugs*.[12]

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* (February 2018) and the associated *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*.[13]

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

(1) Study phase

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

[12] 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.
[13] https://www.fda.gov/media/85061/download

changes

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

(4) Population

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

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

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

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

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

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

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

Attachment 1.

DN2 General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment
3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
   a. Title of the table or figure in the application
   b. A hyperlink to the location of the table or figure with page number
   c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.
8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder

for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.

6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data
    k) For events without a definitive diagnosis, a list of the differential diagnoses
    l) Treatment provided
    m) Re-challenge results (if performed)
    n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units.
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
    • Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
    • Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
    • Pulse Rate: <60 bpm, >100 bpm
    • Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
    • Temperature: >38.0 °C, <36.0 °C
    • Respiratory rate: <12 breaths/min, > 20 breaths/min

6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

Patient profiles:

Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:

a) Age
b) Sex
c) Dates of screening, randomization and starting therapy
d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
f) Prior medications and concomitant medications with dates of start and end
g) Vital signs and laboratories, sorted by date, with reference ranges *
h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

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/

LANA Y CHEN
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