

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212728Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109886

MEETING MINUTES

Biohaven Pharmaceuticals
Attention: Marianne Frost
Vice President of Regulatory Affairs
215 Church Street
New Haven, CT 06510

Dear Ms. Frost:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rimegepant (BHV-3000).

We also refer to the meeting between representatives of your firm and the FDA on Monday, March 11, 2019. The purpose of the meeting was to discuss Chemistry, Manufacturing, and Controls Strategy in anticipation of NDA submission.

A copy of the official minutes of the meeting 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) 796-8427.

Sincerely,

{See appended electronic signature page}

Dahlia A. Walters
Regulatory Business Process Manager
Division of Neurology
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: Monday, March 11, 2019
Meeting Location: WO Building 22, Rm 1309

Application Number: 109886
Product Name: [Rimegepant \(BHV-3000, Formerly BMS-927711-11\)](#)
Indication: **Acute treatment of migraine in adults**

Sponsor/Applicant Name: Biohaven Pharmaceuticals
Meeting Chair: Wendy I. Wilson-Lee, Ph.D., Branch Chief
Meeting Recorder: Dahlia A. Walters, MS, PMP, RBPM

FDA ATTENDEES

Wendy I. Wilson-Lee, Ph.D., Branch Chief
Martha R. Heimann, Ph.D., CMC Lead Neurology
Rajan Pragani, Ph.D., Drug Substance Reviewer
Andrei Ponta, Ph.D., Drug Product Reviewer
Suong T Tran, Ph.D., Branch Chief
Peter Krommenhoek, Ph.D., Manufacturing Process Reviewer
Zhuojun Joan Zhao, Ph.D., Biopharmaceutics Reviewer
Ta-Chen Wu, Ph.D., Biopharmaceutics Lead
Dahlia A. Walters, M.S., PMP, RBPM

SPONSOR ATTENDEES

Vlad Coric, MD, Chief Executive Officer
Elyse Stock, MD., Chief of Portfolio Strategy and Development
Rajesh Kumar, Ph.D., Vice President, Chemistry, Manufacturing, and Controls
Robert Croop, MD., Chief Development Officer- Neurology
(b) (4) CMC Consultant to Biohaven Pharmaceuticals
Marianne Frost, MA., Vice President, Regulatory Affairs
Lisa Stocking, MSPH, Director of Regulatory Affairs and Operations
Charles Conway, Biohaven Pharmaceuticals

1.0 BACKGROUND

Rimegepant is a calcitonin gene-related peptide (CGRP) receptor antagonist in development for the treatment of migraine. Rimegepant offers a novel therapeutic mechanism for the acute treatment of migraine with the potential to address important unmet needs (e.g., durable efficacy, lack of rebound headaches, and no contraindications or warnings in patients with cardiovascular disease). The purpose of the meeting is to discuss the proposed 505(b)(1) NDA submission of Rimegepant (BHV-3000, BMS-927711) and specifically the chemistry, manufacturing, and controls (CMC) portions of the submission.

FDA sent Preliminary Comments to Biohaven Pharmaceuticals on Thursday, March 6, 2019.

2. DISCUSSION

Question 1: Based on the information provided regarding fully characterized simple structure, availability, literature precedence, propinquity, specifications, impurity purging, stability, and process controls, does the Agency agree with the proposal that [REDACTED] (b) (4) [REDACTED] are acceptable as designated regulatory starting materials for the commercial manufacture of BHV-3000 Drug Substance?

FDA Response to Question 1: We agree that [REDACTED] (b) (4) [REDACTED] are acceptable as designated regulatory starting materials for the commercial manufacture of BHV-3000 Drug Substance.

Q1 BHV RESPONSE

This response is clear, and no discussion is needed.

Meeting Comments: *No further discussion needed*

Question 2: The Sponsor would like to receive comments on the overall drug substance control plan for Tablet and ODT drug products and specifically the following items:

a. Does the Agency agree that the proposed approaches to drug substance specifications including testing attributes, methods and acceptance criteria, are acceptable to support commercial manufacture of BHV-3000?

Q2a BHV RESPONSE

Review of the synthetic schemes indicates that [REDACTED] (b) (4) [REDACTED]

[REDACTED] . These specification limits

conform to ICH Q3D guidance; therefore, we believe it is not necessary to include a test for these elemental impurities in BHV-3000 drug substance.

[REDACTED] (b) (4)
The results of these analyses will be provided in the NDA.

If the Agency agrees, then no discussion is needed.

Meeting Discussion: The Agency advised Biohaven Pharmaceuticals to provide justification as part of the NDA submission.

b. Does the Agency agree that the proposed approaches to RSMs and key intermediates specifications including testing attributes, methods and acceptance criteria, are acceptable to support commercial manufacture of BHV-3000?

Q2b BHV RESPONSE

This response is clear, and no discussion is needed.

Meeting Discussion: No further discussion needed

c. Does the Agency agree that the plan for assessing comparability between [REDACTED] (b) (4) manufactured drug substance is acceptable to further support the drug product registration batch representation by the two vendors and to, in part, support the approval of both vendors as commercial suppliers of BHV-3000?

Q2c BHV RESPONSE

This response is clear, and no discussion is needed.

Meeting Discussion: No further discussion needed

FDA Response to Question 2: It should be noted that the adequacy of the drug substance control plan will be assessed when the NDA is submitted. We have the following comments in response to your questions:

- a. Your proposed approach to the drug substance commercial specification appears reasonable. Provide a justification for [REDACTED] (b) (4)
- b. Your proposed approach to your RSMs and key intermediates specifications appears reasonable.

- c. Overall, there is one important problem with the approach. It should be noted that GMP begins at the designation of the regulatory starting materials. Therefore, (b) (4) should also be listed as a GMP manufacturer on the 356h form and in the NDA and should be ready for inspection. Information on (b) (4) process should be included in the NDA or referenced in a DMF. Otherwise, your approach for approval of both vendors as commercial suppliers of BHV-3000 appears reasonable. Furthermore, include information to show that drug product batches produced from each drug substance supplier is comparable.

Additionally, in the NDA, briefly provide information that lead to the selection of the (b) (4) for commercial drug product development. If other salt or polymorph forms were used in clinical trials, describe the different forms and if their properties affected drug product performance through clinical development. Also, ensure that a description of the (b) (4) is described in the NDA.

Meeting Discussion: Biohaven Pharmaceuticals will describe the process controls and provide justification for the form selection in the NDA submission.

Question 3: *Considering the registration batch genealogy regarding representation of regulatory starting materials and key intermediates sourcing, drug substance manufacturer representation, registration batch stability protocol, and availability of a minimum of 12 month stability data on each of three pilot scale drug substance batches manufactured by (b) (4) and (b) (4) at time of NDA submission, does the Agency agree that the drug substance registration batch stability plan will adequately support the NDA submission?*

FDA Response to Question 3: If a minimum of 12-month stability data on each of the three pilot-scale drug substance batches each manufactured by (b) (4) and (b) (4) is available at the time of NDA submission, we agree that the drug substance registration batch stability plan will appropriately support the NDA submission. Ensure appropriate tests for critical quality attributes are included in the stability specification, unless otherwise justified. Include a proposed retest period in the NDA submission. The adequacy of the stability data is an NDA review issue.

Q3 BHV RESPONSE

This response is clear, and no discussion is needed.

Meeting Discussion: No further discussion needed

Question 4:

(b) (4)
(b) (4)

(b) (4)

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(b) (4)

Meeting Discussion: The Agency indicated that supplements are reviewed by the Office of Lifecycle Drug Products (OLDP). As such, this question can be addressed during the NDA review cycle.

Question 6: *Does the Agency agree that the drug product control strategy for BHV-3000 orally disintegrating tablets is adequate in design to support the NDA and commercialization of BHV-3000? Specifically:*

- a. Are the in-process and release testing specifications, including the testing attributes, methods, acceptance criteria and method validation scope acceptable to support the NDA?*

FDA Response to Question 6: Please refer to our response to Question 4. In addition, we recommend monitoring friability as part of the in-process controls or release and stability specifications.

Q6 BHV RESPONSE

Biohaven would like to clarify that (b) (4) testing is not feasible nor applicable for this dosage form as it is a (b) (4) lyophilized ODT tablet. The drug product is formed directly in a blister pack and the dosage unit is removed from the blister as a unified form just prior to administration.

If the Agency agrees, then no further discussion is needed.

Meeting Discussion: The Agency indicated that the justification for omitting (b) (4) testing is acceptable.

Question 7: *Does the Agency agree with the manufacturing process and control strategy, release testing strategy and hold-time stability plans for (b) (4) in drug product manufacture?*

- a. Furthermore, does the Agency agree that the description of the (b) (4) sections of the NDA?*

FDA Response to Question 7: The adequacy of the manufacturing process and control strategy, release testing strategy and hold-time stability plans for (b) (4) BHV-3000 drug substance will be a matter for review; however, we have the following comments at this time:

- (b) (4)

(b) (4)

(b) (4)

Q7 BHV RESPONSE

The BHV-3000 ODT is prepared using a

(b) (4)

Bioequivalence was previously demonstrated for BHV-3000 tablets administered orally (BHV3000-110), which displayed an average D90 particle size approximately than the average API particle size used in ODT tablets, suggesting that particle size for oral tablets is unlikely to be a critical quality attribute.

We will provide in the NDA submission comparative dissolution results in a Figure format for n=12 dissolution testing results and test comparability by an f2 test comparing the pivotal clinical batch which had

(b) (4)

If the Agency agrees that this information would adequately demonstrate equivalency across the API particle size manufacturing range, then no further discussion is needed?

Meeting Discussion:

(b) (4)

The Agency recommended that the Sponsor provide dissolution profile data on drug product three batches along with the clinical and manufacturing batches. Additionally, for the dissolution comparison as proposed for batches with different D90 values, the Agency would like to see dissolution profile with sufficient time points prior to 15 minutes in view of the rapid dissolution. In addition to the figure format, the Sponsor should provide raw data and results of statistical analysis of the profile comparison.

The Sponsor inquired whether it is acceptable to rely on in vivo bioequivalence (BE) results demonstrating BE of these batches with different D90 particle size, instead of in vitro dissolution profile comparison. The Agency responded that it is acceptable to not provide the in vitro comparison results if in vivo BE results are available for these ODT batches with different particle sizes.

Question 8: *Does the Agency agree with the design of the BHV-3000 orally disintegrating*

tablets ongoing stability program and the proposed recommendation of storage at controlled room temperature, subject to review of additional data available at the time of the NDA filing? Specifically,

- a. Is it acceptable to file the NDA with (b) (4) registration batch stability data on three batches (manufactured using (u) (4) drug substance), with 12-month data to be submitted to the NDA within 30 days of the initial filing date (b) (4) (u) (4) manufactured with (u) (4) manufactured drug substance?

FDA Response to Question 8: No, we do not agree with the proposal to file the NDA with (b) (4) registration batch stability data. We expect the initial NDA to contain 6-month accelerated and at least 12-month long-term stability data for representative drug product batches manufactured using the proposed commercial manufacturing process and packaged in the proposed commercial container closure system. Submitting less than 12-months of long-term result in a refuse to file recommendation from the Office of Pharmaceutical Quality. For detailed recommendations regarding the batch selection, testing conditions, etc., refer to ICH Q1A (R2) Guidance “Stability Testing of New Drug Substances and Products.”

Q8 BHV RESPONSE

Biohaven now expects to have one clinical batch and one registration batch with at least 12-month stability data that will be included at the time of NDA submission. These batches were manufactured using the commercially representative unit operations.

In addition, the clinical batch will have 18 months data at the time of NDA submission. Trending suggest no detectable signs of degradation or other changes in CQAs that would suggest any risk of out-of-specifications results at 12 months. (b) (4) (u) (4) on each of three registration batches as well as on the supportive clinical batch.

To supplement the above, 2 additional registration batches will be included in the NDA with 11 months stability data. Twelve months stability data will be submitted for the remaining two batches within 30 days of the submission date (prior to NDA filing).

Given the totality of the above stability data from 4 batches with 11-18 months being submitted at the time of the NDA, would the OPQ agree that this revised plan is acceptable at the time of NDA submission?

If the Agency agrees, then no further discussion is needed.

Meeting Discussion: The Agency reiterated their recommendation to adhere to ICH guidelines of submitting 12 months of stability data for three registration batches at the time of NDA Submission. If less information is provided at the time of submission, it is likely to be a refuse to file issue.

If the drug product is granted breakthrough therapy designation or the clinical division otherwise deems that the product offers clinical benefit to address an unmet medical need, the Agency indicated that the Applicant can submit a question asking the Agency to reconsider this recommendation via a Type A written response only meeting request.

Question 9: [REDACTED] (b) (4)

FDA Response to Question 9: [REDACTED] (b) (4)

Q9 BHV RESPONSE

This response is clear and no discussion is needed.

[END OTHER IMPORTANT MEETING LANGUAGE SECTION]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
N/A	N/A	N/A
N/A	N/A	N/A

6.0 ATTACHMENTS AND HANDOUTS

No Handouts

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/

DAHLIA A WALTERS
03/19/2019 08:01:07 AM



IND 109,886

MEETING MINUTES

Biohaven Pharmaceuticals
Attention: Marianne Frost
234 Church Street, Suite 304
New Haven, CT 06510

Dear Ms. Frost:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rimegepant (BHV-3000, formerly BMS-927711).

We also refer to the meeting between representatives of your firm and the FDA on March 1, 2017. The purpose of the meeting was to discuss plans for your proposed Phase 3 program.

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

If you have any questions, call Lana Chen, Regulatory Project Manager at (301) 796-1056.

Sincerely,

{See appended electronic signature page}

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date: March 1, 2017
Meeting Location: FDA White Oak

Application Number: IND 109,886
Product Name: rimegepant (BHV-3000, formerly BMS-927711)
Indication: migraine
Sponsor/Applicant Name: Biohaven Pharmaceuticals

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Lana Chen, R.Ph.

FDA ATTENDEES

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Laura Jawidzik, MD, Clinical Reviewer
Lana Chen, RPh, Project Manager

Jinnan Liu, PhD, Statistical Reviewer
Kun Jin, PhD, Statistical Team Leader
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

Vlad Coric, MD, Chief Executive Officer
(b) (4), Migraine Clinical Consultant to Biohaven
(b) (4), Safety Consultant to Biohaven
Robert Berman, MD, Chief Medical Officer
Charlie Conway, PhD, Chief Scientific Officer
Kimberly Gentile, Vice President, Clinical Operations
Beth Morris, Executive Director, Clinical Operations
David Stock, PhD, Executive Director, Biostatistics
(b) (4), Toxicology Consultant to Biohaven
(b) (4) CMC Consultant to Biohaven
(b) (4) Safety Consultant to Biohaven

Marianne Frost, MA, Executive Director, Regulatory Affairs

DISCUSSION

Nonclinical

QUESTION 1

- a. An extensive nonclinical program has been conducted with rimegepant. These available nonclinical data support clinical trials in patients with migraine. Does the Agency agree that no additional nonclinical toxicology investigations with rimegepant are required to support registration?

FDA Response: Based on the information provided, the completed, ongoing, and planned nonclinical studies of rimegepant appear sufficient to support an NDA, with the following exceptions:

- A pre- and postnatal development study in one species should be provided in the NDA. You state that a fertility and early embryonic development study is ongoing and is to be included in the NDA. According to guidance, that study should be submitted to support initiation of Phase 3 studies (ICH M3(R2), January 2010); therefore, the final study report should be submitted to the IND as soon as possible.
- The results of an *ex vivo* human coronary artery study were described in your request for [REDACTED] ^{(b) (4)} however, we found no mention of it in the briefing package. We were also not able to locate the study in the IND. You should either provide its location in the IND or submit the study report to the IND as soon as possible.

The adequacy of the nonclinical studies will be a matter of review.

BHV RESPONSE

The fertility and embryonic development study will be submitted to the IND prior to the Phase 3 study start. In addition, a pre- and postnatal development study in one species will be provided in the NDA.

The results of the *ex vivo* human coronary artery study will be submitted shortly following the EOP2 meeting.

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

FDA Response: See response to Question 1a.

BHV RESPONSE

Discussion at the meeting is not needed.

- c. Does the Agency agree that the proposed 6-month rat and 9-month monkey studies are sufficient to support the 12-month, long-term, clinical safety study?

FDA Response: The 6-month rat and 9-month monkey studies are of sufficient duration to support a 12-month clinical study; the adequacy of the studies will be a matter of review.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion (1a-1c): None.

Clinical/Statistical

QUESTION 2

Does the Agency agree that the proposed entry criteria for the Phase 3 clinical trials adequately define the population for the proposed indication?

FDA Response: We have the following comments about the inclusion/exclusion criteria for your planned phase 3 trials:

1. We recommend that you do not exclude triptan nonresponders, as this would be an important population that may benefit from treatment with your product.
2. The rationale for excluding patients with hemiplegic migraine is not clear to us.
3. We encourage you to enroll a broad study population, including patients with vascular risk factors and/or vascular disease, unless there are information to suggest that your product could not be safely administered to these patients. As always, the safety experience (and its limitations) will inform labeling.

BHV RESPONSE

1. Triptan non-responders will be included in the Phase 3 trials.
2. Our goal is to study migraine with and without aura. Familial hemiplegic migraine is a distinct disorder with its own genetic underpinnings and biologic mechanisms. We excluded these patients to avoid heterogeneity.
3. We recognize that this is a patient population with high unmet need and plan to include patients in our Phase 3 trials with CV-related events, conditions, and procedures as well as multiple risk factors. The Phase 3 protocols will be submitted to the IND for review.

Meeting Discussion: None.

QUESTION 3

Assuming that the Phase 3, 75 mg ODT formulation yields PK that is comparable to the 75 mg formulation used in Phase 1 and Phase 2, does the Agency agree that a dose selection of 75 mg ODT is appropriate for use in the Phase 3 studies?

FDA Response: On face, we agree with your selection of the 75 mg dose to evaluate in your phase 3 program.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion: None.

QUESTION 4

- a. Does the Agency agree that the primary endpoints: (1) Pain Freedom and (2) freedom from the most bothersome symptom associated with migraine at 2 hours post-dose are appropriate for the assessment of efficacy for the proposed indication?

FDA Response: Yes, we agree with the co-primary endpoints of pain freedom and freedom from the most bothersome symptom at 2 hours post dose.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion: None.

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

FDA Response: For our general recommendations on the secondary endpoints that should be assessed in your efficacy trials, please see the Guidance for Industry, *"Migraine: Developing Drugs for Acute Treatment"* (October, 2014). Please note that we would describe study results on photophobia, phonophobia, and nausea at 2 hours post dose, regardless of statistical significance, so that it would not be necessary for you to spend some alpha on these endpoints

(b) (4)

(b) (4)

¹ <https://www.fda.gov/downloads/drugs/guidances/ucm193282.pdf>

BHV RESPONSE

If significance is reached on the most bothersome symptom endpoint, BHV will conduct follow-up analyses on nausea, phonophobia and photophobia that produce p-values and confidence intervals. This will be done without any alpha spend. BHV's understanding is that these nominal p-values and confidence intervals (calculated outside the statistical hierarchy) for photophobia, phonophobia, and nausea at 2 hours post dose (b) (4)

Meeting Discussion: The Division clarified that analyses done without Type I error control on nausea, phonophobia and photophobia (b) (4)

The Division clarified that it is also acceptable to evaluate the four co-primaries in the traditional way, with the acknowledgement that selecting an endpoint based on the four traditional co-primary endpoints instead of the co-primary endpoints pain freedom and freedom from the most bothersome symptom at 2 hours, may make it harder to reach statistical significance in the trial.

- c. Biohaven plans to select the most bothersome symptom (MBS) at the time of the treated attack and not at baseline. Does the Agency agree that the MBS can be selected at the time of the treated attack?

FDA Response: Patients may select their MBS at the time of the index migraine attack, as long as this selection is entered in the eDiary prior to dosing. The eDiary should clearly demonstrate that the MBS was identified by the patient prior to administration of the investigational product (IP). Please describe how you would prevent patients from identifying the MBS after they have taken the IP.

Preferably, patients may prospectively identify their most bothersome symptom (MBS) prior to randomization, and treat the first migraine attack that is associated with their prospectively selected MBS at onset.

BHV RESPONSE

BHV agrees and the eDiary will provide a mechanism that clearly indicates patient identification of MBS prior to taking the IP.

Meeting Discussion: None.

- d. A number of other supportive endpoints are being considered to further assess efficacy for the proposed indication. Does the Agency have any comments about these supportive endpoints?

FDA Response: See response to 4b.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion: None.

QUESTION 5

Does the Agency agree that a sample size of 850 subjects (425/arm) in the acute Phase 3 studies is appropriate to demonstrate efficacy?

FDA Response: On face, the proposed sample size seems adequate.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion: None.

QUESTION 6

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

FDA Response: The population for the primary efficacy analysis should be the modified intent-to-treat, [REDACTED] (b) (4)

[REDACTED] While we do not expect much missing data in a single attack migraine trial, a plan must be provided for how you will handle patients who treat a headache with the IP, but do not have the 2-hour efficacy measurement.

The proposed statistical analysis (with the exception described above) for the first co-primary endpoint seems adequate.

Please clarify whether you plan to stratify for the second co-primary endpoint. If so, provide details about what variable(s) you plan to stratify on. In addition, provide details about what categories you will select for each stratification variable.

In regard to the secondary endpoints, please provide details about how you plan to analyze these endpoints, the order you will use to test these variables, and how you plan to adjust for errors of multiplicity. Also see our response to Question 4.

In general, missing data for migraine studies is expected to be minimal. We strongly recommend minimizing missing data via good trial conduct.

BHV RESPONSE

We propose to use the mITT population, defined as treated subjects with at least one efficacy measurement, for all efficacy analyses. Missing data would be handled as (b) (4). This is an observed case analysis which we feel is justified since it is expected that very few patients will be missing. Sensitivity analyses would include (b) (4) and multiple imputations based on the reference group. If the FDA would prefer something other than (b) (4) for the primary analysis, the sponsor would consider using a single imputation method such as: (b) (4) or substitution based on the response rate in each group. Multiple imputation would remain as part of the sensitivity analyses.

The second co-primary endpoint, most bothersome symptom (MBS) at headache onset, will be stratified by a variable that identifies the subjects self-identified MBS. Thus, there would be three strata in the CMH test: nausea, phonophobia, and photophobia.

Based on your response to Question 4b, we now believe that the associated symptoms of nausea, phonophobia and photophobia can be tested for significance outside of the testing hierarchy. These endpoints will be tested using CHM tests, stratified on initial headache pain levels at baseline (severe vs other).

Without the necessity to include the 3 associated symptom endpoints, the remaining secondary endpoints to be tested can be reduced to the following testing hierarchy:

- Pain freedom from 2 to 24 hours
- Headache response at 2 hours post-dose
- Pain relief from 2 to 24 hours
- Pain freedom from 2 to 48 hours
- Pain relief from 2 to 48 hours

We expect to test these endpoints in the order shown above. However, the final ordering will appear in the finalized protocol.

Multiplicity will be controlled by testing the secondary endpoints in a fixed sequence after significance has been reached on the two co-primary endpoints. Hence, if the primary endpoints are significant, each secondary endpoint will be tested in turn at the 0.05 level. If any secondary endpoint fails to reach significance, the testing will stop at that point in the sequence. Any subsequent endpoints will not have the possibility of reaching statistical significance. The secondary endpoints will be tested using CMH tests stratified by initial pain severity. For measures of sustained pain freedom, subjects with pain observed in the period will be considered

to be failures regardless of the amount of data collected. Subjects with no pain observed in the period, but with some missing data, will be considered missing. Measures of sustained pain relief will be treated in an analogous manner.

In case significance is not achieved on all outcomes in this sequence, we wonder if it might be possible to, nevertheless, include point estimates and 95% CIs in a table in the clinical studies section for all outcomes, with an * noting those for which statistical significance was achieved. Such information may be informative for prescribers.

Meeting Discussion: The Division stated that we do not expect missing data in an acute migraine trial. The Division did not agree that (b) (4) but instead stated that “missing” should equal “failed”.

The primary analyses should be based on the ITT population, which should include all randomized patients. Because we expect minimal missing data, the difference in the results between the mITT population and the ITT population should be minimal. The proposed (b) (4) is not recommended. Please see the following reference: National Research Council (US) Panel on Handling Missing Data in Clinical Trials. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington (DC): National Academies Press (US); 2010. 1, Introduction and Background. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK209902/>)

QUESTION 7

Given the large safety margins demonstrated in nonclinical (e.g., hERG, rabbit Purkinje fibers, monkey telemetry cardiovascular safety pharmacology) and clinical (e.g., SAD/MAD) studies, does the Agency agree that a (b) (4) is not required for registration?

FDA Response: The large exposure margin observed in the SAD/MAD study appears to support that the study may serve as an alternative to a (b) (4). However, we cannot determine the adequacy of the doses studied before the impact of intrinsic and extrinsic factors have been fully characterized. In addition, the provided study report does not provide sufficient information to determine if robust high-quality ECGs (ICH E14 Q&A (R3) 5.1) were collected. Therefore, we cannot agree whether ECGs collected in the SAD/MAD study will be sufficient to serve as a replacement for a (b) (4) until the additional information has been provided.

BHV RESPONSE

BHV will follow up and provide additional information on the method by which the ECGs were collected in the SAD/MAD study.

Meeting Discussion: None.

QUESTION 8

Does the Agency agree with proposed design of the 12-month, long-term clinical safety study?

FDA Response: In general, the design of the 12-month long-term safety study seems acceptable, based on the synopsis you provided, but we suggest adding a measurement of liver function tests at 2 weeks post dose, as well as at the other time points you propose in the study schedule. All patients that have abnormal findings on liver function testing or other laboratory testing should be followed till resolution of the laboratory abnormality.

Also see answer to Question 10.

BHV RESPONSE

BHV agrees to add LFTs at 2 weeks and we will follow abnormal LFTs to clinical resolution.

Meeting Discussion: None.

QUESTION 9

Does the Agency have any comments on other aspects of these studies, based on the draft protocol synopses provided?

FDA Response: Not at this time. We recommend that you send the pivotal efficacy trials for Special Protocol Assessment.

BHV RESPONSE

BHV appreciates the opportunity for SPA review. Given that the Phase 3 program has been designed closely following the FDA's *Guidance for Industry Migraine: Developing Drugs for Acute Treatment (October 2014)* and the Division's response to Q12a indicates that on face the development program appears acceptable, BHV does not plan to submit the Phase 3 protocols for SPA. The full protocols will be submitted to the IND for review and feedback prior to initiating Phase 3 studies.

Are there any specific issues that are not covered in this EOP2 meeting that would be addressed by SPA?

Meeting Discussion: The Division stated that submission of a SPA for the phase 3 trials is not required. The sponsor agreed to submit the statistical analysis plans in addition to the full protocols so that the Division could provide feedback on the phase 3 trials prior to initiation of these studies.

QUESTION 10

Does the Agency agree that the proposed safety experience from planned and completed clinical studies with rimegepant, combined with the safety database for the long-term study, will be sufficient to evaluate the safety of rimegepant in support of registration for the indication of the acute treatment of migraine with or without aura in adults?

FDA Response:

At an End of Phase 1 meeting (on September 1, 2011), the Division discussed with BMS issues related to liver toxicity concerns with CGRP antagonists. At the time, BMS stated that nonclinical data from rats and monkeys indicate that the liver is a target organ. BMS indicated their plans to conduct a 3-month Phase 2 safety study in migraine patients. The study was to include up to 3 doses of your product or placebo. Patients were to receive double-blinded study drug daily for 3 months. The study was to be conducted prior to the initiation of Phase 3, in order to identify potential safety issues that could emerge with longer term frequent intermittent use. The division agreed with the plan to assess hepatotoxicity with chronic use of your product early in the development program, and indicated that the requirement for a safety database of patients with frequent chronic exposure was anticipated to be considerably higher than the typical ICH requirement. BMS also indicated that they anticipated the following number of patients to be exposed to the drug in the overall development program:

- Total exposure of > 6,000 patients
- Long term study will have about 1,400 patients
- At least 700 patients will be exposed to study drug for 6 months
- At least 300 patients will be exposed to study drug for 12 months.

The division reemphasized a concern about a potential liver signal with this class of drugs, and that any risk of liver injury has to be very low, and stated that exposure with the drug has to be sufficient to cap the risk of liver injury at a level acceptable for the migraine population. The division noted that patients are typically required to have treated, on average, at least 2 migraines attacks per month in order to be “counted” in the long-term safety database. However, the risk of liver injury should be assessed for higher frequencies of exposure, as it is well known that a fraction of patients uses acute treatment of migraine products on a daily or near-daily frequency.

We continue to believe that an NDA database for your product must address the safety of frequent (daily or near daily) use of the product, and cap the risk of liver toxicity to a level acceptable for the indication. The 3-month study with daily use that was proposed in 2011 would be an important part of the safety package. It is not clear to us that the study was ever conducted. The study should include at least 300 patients treated at the highest dose proposed for marketing.

In addition, your long-term safety experience should include at least 600 patients treated for 6 months, and 300 patients treated for 12 months. We would expect that out of these patients, at least 50% use of the product at the highest dose proposed for marketing, and that the study population be enriched for frequent users, e.g., patients with chronic migraine or frequent

episodic migraine. The identification of a signal for liver toxicity may trigger the need for a larger safety database.

Please note that the size of your proposed safety database is not clear from the briefing package. Although your package states that you plan to enroll 2000 patients into this trial, you expect to have 450 patients at 6 months and 150 patients at 12 months. It is unclear why there would only be an estimated 150 patients left in the study at one year from an initial enrollment. Also, that sample size would be insufficient (see above).

Also see answer to Question 8.

BHV RESPONSE

Biohaven agrees that the safety program for rimegepant should address the safety of the highest dose proposed for marketing and its planned indication. Subsequent to the BMS EOP1 meeting (September 2011) which discussed the 2011 Three-Month Safety Study, additional clinical and toxicology data have become available that warrant updating of the development plan for rimegepant:

- In 2011 at the time of the EOP1 meeting, the projected clinical doses were not yet determined and the MAD study was still underway. The BMS 2011 three-month safety study anticipated that potential marketed doses could be 150 mg, 300 mg and 600 mg. This is well above BHV's proposed marketed dose of 75 mg prn, which provides a more substantial safety margin compared to the preliminary BMS plan.
- As of 12/31/16, approximately 687 subjects have been dosed with rimegepant. In Phase 1 and 2b trials, approximately 600 subjects have received single doses of rimegepant up to 1500 mg; and approximately 87 subjects have received multiple doses of rimegepant up to 600 mg daily for up to 14 days.
 - The projected exposure achieved in 35 subjects treated for 8 to 14 days from Study CN170001 and CN170002 provided a > 30-fold therapeutic exposure over that achieved with a 75 mg dose. This amounts to the same exposure burden achieved with well over 200 doses of 75 mg rimegepant, but compressed into several days.
- In 2012, results of the Phase 2 randomized controlled trial (CN170003) identified 75 mg as the fully efficacious dose, effective in all four traditional co-primary endpoints. Biohaven has selected this dose as the highest dose intended for marketing.
 - At our highest planned dose of 75 mg, the NOEL/NOAEL doses in rats (30 mg/kg/day) and monkeys (50 mg/kg/day) in the pivotal 3-month nonclinical studies were associated with mean AUC exposures that were at least 23× (rat) and 56× (monkey) the anticipated human AUC at a 75 mg/day clinical dose, thus providing wide safety margins at the newly identified efficacious dose.
- Longer-term toxicology studies completed in 2012 revealed that the nonclinical hepatic finding of lipidosis at high doses was rodent specific (not found in monkeys).
 - The liver was the primary target organ in mice at levels of 100 mg/kg/day and greater, and in rats at levels of 60 mg/kg/day and greater. The primary hepatic

finding was lipidosis. These dosing levels were not associated with hepatocellular degeneration/necrosis, inflammation, or fibrosis.

- In 2012, study results became available from the 3-month monkey study and were submitted to the IND on October 17, 2012 (Seq #0029). The study tested 25, 50 and 100 mg/kg/day in monkeys. BHV-3000 was clinically tolerated by monkeys for 3 months at daily doses up to 100 mg/kg/day (mean sex-combined AUC in Week 13 of 460 $\mu\text{g}\cdot\text{h}/\text{mL}$). The high dose of 100 mg/kg/day produced a spectrum of clinical observations not correlated with liver toxicity in the 3-month GLP monkey study. There were no histopathologic liver findings in monkeys (refer to Section 10.2.3.3.7 in the Briefing document).
- Hepatic lipidosis previously identified in mouse and rat studies was determined to be rodent specific as it was not observed at rimegepant exposures in monkeys which exceeded those producing lipid effects in rats in the three-month pivotal studies.
- Further, results from in vitro transporter inhibition studies relevant to potential liver effects became available in 2016 (refer to Section 10.2.2.1 of the Briefing Document). These data demonstrate that the majority of normal transporter functions (BSEP, UGT1A1, OATP1B3) would remain intact with repeated clinical exposures of 75 mg rimegepant.

In summary, the currently proposed safety program reflects the incorporation of this additional clinical and toxicology data that was not available when this program was last discussed with the Division in 2011. We believe that the totality of the clinical and nonclinical data to date supports the advancement of rimegepant 75 mg prn into Phase 3 and the initiation of the Long-term Safety Study (clarified below) to provide the appropriate means of continued assessment of safety needed for registration. The high exposures assessed in previous clinical studies were generally well tolerated and any potential effects on the liver can be readily monitored in the efficacy and long-term safety studies.

We agree with the Division that the safety plan must also address the potential for frequent use of the highest intended dose of rimegepant (i.e., 75 mg). Consequently, we designed the long-term safety study to include a total of 2000 enrolled subjects, all of whom would be instructed to use rimegepant 75 mg as-needed up to once daily. The majority of patients with migraine would be expected to administer rimegepant 75 mg 2 – 4 times per month. However, to assess safety with more frequent use, 600 of these 2000 migraineurs would be required to have a history of 8 or more migraine days per month. Together with the freedom to dose daily as needed, this would allow the long-term safety assessment in patients who may use rimegepant in a daily or near daily basis. Of note, daily use and prevention of chronic migraines is not the intended use of this product. Overall, this data set will collect information with use of rimegepant in frequent migraineurs. To facilitate more frequent use, subjects in the safety study will be encouraged to administer rimegepant for mild, moderate or severe migraines.

To address concerns about capping the risk for liver toxicity, we note that the proposed long-term safety study has a robust number of subjects, well above the ICH guidelines and includes a population of subjects with frequent use who will be allowed to use rimegepant on a daily basis if warranted for the treatment of migraines. In addition, the clinical exposures achieved with a

75 mg dose of rimegepant are well below those where liver toxicities were observed in non-clinical testing.

We wish to clarify our proposed Long-Term Safety Study as follows:

- 2000 total subjects to be enrolled who will receive 75 mg rimegepant prn, up to once daily as needed.
- 600 of these subjects will be required to have a history of frequent migraines (i.e., 8 or more migraines per month) and encouraged to treat mild as well as moderate and severe migraines to assess high frequency use in patients on up to daily or near daily basis.
- All subjects (100%) will be administered the highest dose of rimegepant (i.e., 75 mg).
- At the time of filing, we will provide safety data on at least 450 subjects treated for six months at the highest dose (75 mg) – meeting the Division’s request for 50% of 600 subjects receiving the highest dose.
- In addition, we will also provide safety data on at least 150 subjects treated for 12 months at the highest dose (75 mg) – meeting the Division’s request for treating 50% of 300 subjects for 12 months.
- Of note, all subjects enrolled in the long-term safety study will have the opportunity to continue dosing for 12 months. The minimum exposure data provided at filing will include the 450 subjects treated for 6 months and 150 subjects dosed for 12 months; however, these subject numbers may be exceeded upon filing since we do not anticipate a high drop-out rate (additional experience will be included in the ongoing safety updates).

Table Summarizing Anticipated Safety Exposures at NDA Filing

	<i>Estimated Number of Subjects</i>
<i>Total Exposed to Rimegepant</i>	3,000
<i>Long-term (LT) Safety Study</i>	2,000
<i>Subset of LT Safety Study, High Frequency Users</i>	600
<i>Exposed to study drug for 6 months</i>	<ul style="list-style-type: none"> • <i>At least 450 at the time of NDA filing</i> • <i>Additional data from 1150 subjects will be available post NDA filing (assuming 20% attrition)</i>
<i>Exposed to study drug for 12 months</i>	<ul style="list-style-type: none"> • <i>At least 150 at the time of NDA filing</i> • <i>Additional data from ~1000 subjects will be available post NDA filing (assuming 35% attrition)</i>

In light of the new clinical efficacy and safety data, does the Division agree that we may proceed to Phase 3 trials with single dose 75 mg rimegepant for the acute treatment of migraine?

Given the clarifications provided above, does the Division agree that our currently proposed Long-Term Safety Study with 2000 enrolled subjects, with a subset of 600 high frequency

users, appropriately assesses the safety of 75 mg rimegepant in its anticipated indication and frequent dosing?

Meeting Discussion:

The sponsor summarized the three reasons why they thought that the safety database requested in the End of Phase 1 (EOP1) meeting minutes may not be necessary. The reasons are as follows:

- 1) The sponsor is evaluating a lower dose for the upcoming marketing application, than what was described at the time of the EOP1 meeting. At that time, doses up to 600 mg were considered; at this time, the sponsor plans to market only the 75 mg dose and this dose has a much wider safety margin, based on the findings in the nonclinical studies.
- 2) The sponsor reports that results from the toxicology studies in primates with up to 3 months of dosing do not show drug-related histopathology findings in the liver.
- 3) The sponsor reports that, at this time, there is more clinical data that suggests that the safety profile, in terms of an effect on liver function, may be different from that seen with other products in this class, such as telcagepant.

Although the estimates reported in the table above of the long-term database suggest that there may be a high dropout rate, the sponsor clarified that they are not expecting a high dropout rate in their open-label extension trial, and that they expect more safety data to be available after filing their NDA than what was listed in their briefing package.

The Division reiterated a concern that the proposed long-term safety study might not adequately address daily or near daily use of rimegepant. The Division stated that an expectation that the sponsor's safety database will include at least 300 patients using rimegepant daily or near daily for at least three months. The Division recommended that the sponsor conduct a 3-month safety study in patients using daily or near daily medication. The study could potentially provide both safety and efficacy data if the sponsor decided to evaluate the prophylaxis of migraine in this 3 month trial.

The sponsor proposed to enrich their long-term study with patients who have very frequent migraines. The Division stated that this would be at the sponsor's risk, and that they might not be able to meet the required numbers (i.e. 300 patients using daily or near daily medication for at least three months.)

The sponsor wanted clarification about whether they could proceed with phase 3 trials without doing this three-month safety study. The Division clarified that the sponsor could proceed to phase 3.

The sponsor described why they thought there was a chemical difference between rimegepant and telcagepant that may predict a lower hepatotoxicity risk of their product as compared to telcagepant. The sponsor stated that they compared their product head to head with telcagepant in vitro using transporter assays and demonstrated that their product was a less potent inhibitor than telcagepant. The sponsor stated that they believe

there is information that suggests hepatic bile salt transporter (BSEP) as well as other transporters may play a role in drug induced liver injury. The Division told the sponsor that they could provide any information they had about these markers as they relate to liver toxicity and the Division would review the information.

QUESTION 11

Does the Agency agree with the proposed plan to submit a pediatric study plan in patients (b) (4) years old?

FDA Response: Yes, we agree that your pediatric study plan should include a plan to study migraine patients 6-17 years old.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion: None.

Regulatory

QUESTION 12

- a. Does the Agency agree that data from the completed and planned clinical studies serve as an adequate basis for evaluation of rimegepant for the acute treatment of migraine with or without aura in adults?

FDA Response: On face, your plan to conduct two efficacy studies to support efficacy seems acceptable. Please refer to our other preliminary responses in the document about proposed study design issues, statistical analyses and safety evaluations.

BHV RESPONSE

Previous FDA guidance has suggested adaptive trial designs would not be considered registrational. Clinical Study CN170003 (n=885 randomized) demonstrated robust efficacy at multiple doses in Phase 2b. Nominal p-values, computed using CMH tests, found 75 mg rimegepant superior to placebo on all 4 co-primary endpoints. These p-values are still significant after a Bonferroni correction that adjusts for testing the 6 doses (see table below).

Endpoint	CMH p-value	Bonferroni Adjusted
Pain	0.0018	0.0108
Nausea	0.0074	0.0444
Phonophobia	<0.001	<0.006
Photophobia	0.0023	0.0138

Could BHV submit Clinical Study CN170003 when combined with one adequate and well-controlled Phase 3 trial as evidence for approval?

Meeting Discussion: The Division stated that the fact that the study used an adaptive design was not, in and of itself, a reason why this trial may not meet the requirements for a registration study. The Division would have to review the study to determine whether it could be considered a pivotal efficacy trial. An important factor to consider in this evaluation is whether there was a prospective plan in place for how adaptations would be made in the study. In addition, if there was a prospective statistical analysis plan to study the 4 key endpoints, then it would be more likely that this could be considered as a registration trial. The Division recommended that the sponsor submit their argument and documentation supporting the use of CN17003 as a pivotal trial if the sponsor thought that the study may meet these requirements.

- b. Does the Agency agree that Biohaven can submit the NDA with complete results from a 6-month transgenic (hTras) mouse carcinogenicity study and the in-life portion of the 2-year rat carcinogenicity study with a complete report including histopathology and tumor analysis to be submitted at completion of the report (i.e., during the NDA review period or as a post-approval commitment)?

FDA Response: Final reports for the 6-month and 2-year carcinogenicity studies will be required at the time of NDA submission.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion: None.

- c. If both Phase 3 studies with the ODT (one sublingual administration, one oral administration) met their primary efficacy endpoints, could the clinical trial package

support approval and labeling with the indication of rimegepant for the acute treatment of migraine when administered either sublingually or orally?

FDA Response: The two studies you proposed, if positive, could support efficacy of the product. However, we recommend you assess the PK characteristics of your product with sublingual or oral administration prior to conducting efficacy studies. We would also like to discuss with you the use of the term “sublingual” in labeling. Orally disintegrating tablets are intended to disintegrate rapidly within the mouth to provide a dispersion before the patient swallows the resulting slurry where the drug substance is intended for gastrointestinal delivery and/or absorption. Sublingual tablets are intended to be inserted beneath the tongue, where the drug substance is absorbed directly through the oral mucosa. The term used in labeling would therefore depend on the extent of mucosal absorption. In addition, assessment of local toxicity (mucosa) would be required to support sublingual administration.

BHV RESPONSE

BHV agrees and discussion at the meeting is not needed.

Meeting Discussion: None.

d.

[REDACTED] (b) (4)

FDA Response: We acknowledge receipt of your [REDACTED] (b) (4)
[REDACTED] We will review your submission and provide feedback once our review is complete.

BHV RESPONSE

Discussion at the meeting is not needed.

Meeting Discussion: None.

Additional Comments

Clinical Pharmacology:

- We note that you are planning to conduct a P1 study to assess the effect of BHV-3000 on renal function (BHV3000-106) and study BHV3000-107 to assess the effect of BHV-3000 on liver function. It is not clear to us whether these studies are clinical pharmacology studies to assess the effect of renal and hepatic impairment on the exposure of BHV-3000.

BHV RESPONSE

BHV appreciates the Division's feedback and an updated table will be sent in the weeks following the meeting.

Tables 5 and 14 of the background document list the following studies:

- BHV3000-106: Phase 1 study to assess the effects of BHV-3000 on renal function
 - BHV3000-107: Phase 1 study to assess the effects of BHV-3000 on liver function
- BHV would like to clarify that these studies should have been listed as follows:
- BHV3000-106: Phase 1 study to assess *PK in subjects with renal impairment*
 - BHV3000-107: Phase 1 study to assess *PK in subjects with hepatic impairment*
- You need to assess the drug interaction liability of BHV-3000 as a victim or perpetrator of other major CYP/transporters. Please refer to the FDA DDI guidance for more details²

BHV RESPONSE

BHV will ensure that the drug interaction information is consistent with the guideline.

- We remind you that FDA advises against using oral ketoconazole in drug interaction studies due to serious potential side effects. Other strong CYP3A4 inhibitor (e.g., clarithromycin) can be used instead.

BHV RESPONSE

No discussion needed.

- Please provide more information about the human plasma metabolic profiles for major and active metabolites in future submissions.

BHV RESPONSE

The metabolite profile was provided in the Highlights of Clinical Pharmacology and Safety Table requested by the Division.

CSS:

- For all phase 1, 2 and 3 studies, AEs associated with potential abuse or overdose should be documented. Case narratives of each of these AEs should be provided, especially for any patient with serious AEs (SAEs). These should include cases involving lack of compliance or patients who discontinue participation without returning the study medication. For additional details regarding the documentation

² <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

of AEs, consult the January 2017 CDER guidance for industry on Assessment of Abuse Potential of Drugs³.

- The incidence of abuse-related AEs in comparison to placebo in trials should be reported by study, population, dose, and displayed in tabular format. Tables should be created for abuse-related higher level MedDRA terms, even if there were few patients or subjects who experienced a particular AE.
- We also recommend that you monitor for possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical trials. Additionally, you should look for drug accountability discrepancies (e.g., missing medication, loss of drug, or non-compliance cases in which more investigational drug was used, as compared to expected use). Investigators should obtain more information and explanations from the subjects when there are drug accountability discrepancies.
- We remind you that metabolites formed at greater than 10 percent of total drug-related systemic exposure levels at steady state must be assessed for safety, including an assessment of abuse potential.

BHV RESPONSE

In the EOP1 meeting package, BMS described receptor binding studies, data suggesting the inability of rimegepant to enter the brain (e.g., brain penetration data), and the AE profile from select Phase 1 studies. In the EOP1 meeting minutes, the CSS concluded: “*A preliminary review of these data suggest that specific abuse potential studies (preclinical and clinical) are not necessary for the parent compound (BMS-927711) at this time.*” No new data has emerged that would change the CSS conclusion.

BHV agrees to document AEs associated with potential abuse or overdose in accordance with the January 2017 CDER guidance for industry on Assessment of Abuse Potential of Drugs. However, BHV’s understanding is that nonclinical and clinical studies to specifically address abuse potential are not needed.

Meeting Discussion (All Additional Comments): None.

³ <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm198650.pdf>

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* at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf>. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>.

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 (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See

<http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page 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.

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 start 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 Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

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](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

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 draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical

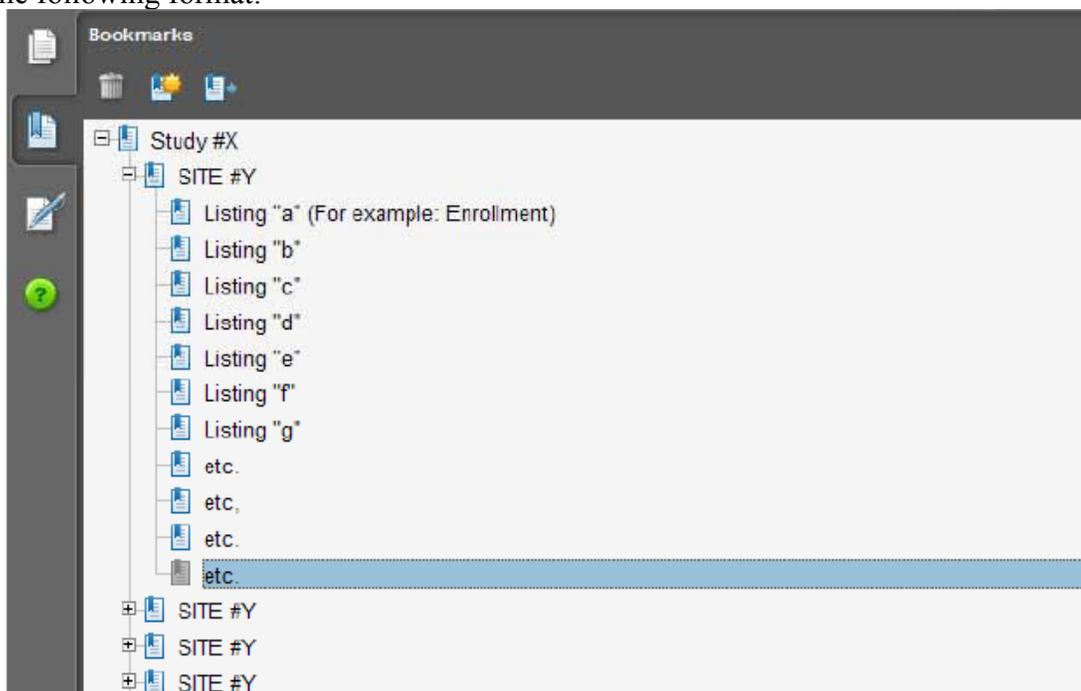
investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)

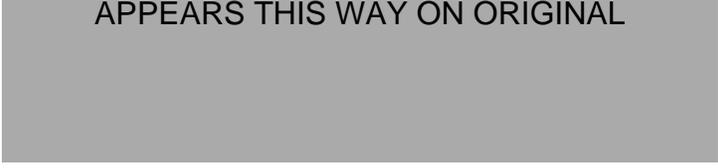
- f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

APPEARS THIS WAY ON ORIGINAL



Attachment 1

**Technical Instructions:
 Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item⁴	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

⁴ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page
(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIC P BASTINGS
03/27/2017