CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211765Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS
IND 113924

MEETING MINUTES

Allergan Sales, LLC
Attention: Terri Richmond, MS, PhD
2525 Dupont Drive
Irvine, CA 92612

Dear Dr. Richmond:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ubrogepant (MK-1602; AGN-241688).

We also refer to the meeting between representatives of your firm and the FDA on August 30, 2018. The purpose of the meeting was to discuss the development plan for ubrogepant and come to agreement on the proposed format and content of the planned New Drug Application.

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, contact E. Andrew Papanastasiou via email at emilios.papanastasiou@fda.hhs.gov, or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

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

Enclosure:
Meeting Minutes
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 30, 2018, from 1:00 PM to 2:00 PM EDT
Meeting Location: FDA White Oak

Application Number: 113924
Product Name: Ubrogepant (MK-1602; AGN-241688)
Indication: Acute treatment of migraine with or without aura in adults.
Sponsor/Applicant Name: Allergan

FDA ATTENDEES

Eric Bastings, MD, Deputy Director, Division of Neurology Products (DNP)
Nick Kozauer, MD, Associate Director, DNP
Heather Fitter, MD, Clinical Team Leader, DNP
Laura Jawidzik, MD, Clinical Reviewer, DNP
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer
Priya Brunsdon, PhD, Clinical Pharmacology Reviewer
Sally Yasuda, MS, PharmD, Safety Team Leader, DNP
Kun Jin, PhD, Statistics Team Leader
Jinnan (Joanne) Liu, PhD, Statistical Reviewer
Andrei Ponta, PhD, Pharmaceutical Quality Reviewer

SPONSOR ATTENDEES

June Bray, MBA, Senior Vice President, Global Regulatory Affairs
Erin Collins, MS, Senior Manager, Global Regulatory Affairs
Abhijeet Jakate, PhD, Director, Clinical Pharmacology
Hassan Lakkis, PhD, Associate VP, Statistical Science
Jordan Lateiner, MS, MBA, Executive Director, Project Management
Kaifeng Lu, PhD, Executive Director, Biostatistics
Carol Patterson, PhD, Executive Director, Regulatory Affairs (CMC)
Terri Richmond, MS, PhD, Executive Director, Global Regulatory Affairs
Brenda Smith, PhD, DABT, Director, Toxicology
Armin Szegedi, MD, PhD, Vice President, Clinical Development CNS
Christoph Tacheci, PhD, Associate Director, CMC Team Lead
Joel Trugman, MD, Associate VP, Clinical Development CNS
1.0 BACKGROUND

On June 5, 2018, Allergan Sales, LLC requested a Type B Pre-NDA meeting to discuss the content and format of a planned NDA for ubrogepant, proposed for the acute treatment of migraine with or without aura in adults. The sponsor plans to submit their NDA for ubrogepant in December of 2018. Topline results from two pivotal studies, UBR-MD-01 and UBR-MD-02, which were designed to evaluate the safety, efficacy, and tolerability of ubrogepant compared to placebo, are presented in the briefing package. In addition to these studies, two ongoing studies are being conducted, a long-term safety study (UBR-MD-04), and a hepatic safety study (3110-105-002).

FDA sent Preliminary Comments to Allergan on August 28, 2018.

2. DISCUSSION

Question 1: Does the Agency agree that the proposed organization of the submission is acceptable? If the Agency does not agree, please provide any recommendations.

FDA Response to Question 1:

From a technical standpoint, the proposed organization of the submission is acceptable. However, please see the additional comments below:

a) Study Data Standardization Plan (SDSP) should be placed in m1.13.9 (not m1.2), with a clear leaf title that is indicative of the content.

b) You may cross-reference information submitted to the same application or another application (if any), either by placing a cross-reference document under module m1.4.4 (cross reference to other applications), or using cross-application links.

c) To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (non- eCTD or paper) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document.

d) To use the second option (cross-application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. xlink:href="../../indXXXXXX/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the words “cross reference to” and the application number (e.g., Cross Ref to
indXXXXXX). The cross-reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross-application linking in an application and to ensure successful use of cross-application links, it is recommended that you submit an "eCTD cross application links" sample. However, if you have used the cross-application linking previously, there is no need for a cross-application sample.

To submit an eCTD cross-application links sample, you would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf

Discussion: None

**Question 2:** Does the Agency agree with Allergan’s proposed list of studies for which clinical investigator financial disclosures will be provided?

**FDA Response to Question 2:**

Yes, we agree. We may request additional financial disclosure information during the review of the application, if needed.

Discussion: None

**Question 3:** Does the Agency agree with the content of the proposed 120-day safety update?

**FDA Response to Question 3:**

Please clarify whether the exposures described in Table 10 (page 24) represent the safety data you will have at filing, or at the 120-day safety update. If this table refers to the exposure at the time of filing, please also provide a table of exposures at the time of the 120-day safety update, in a format similar to Table 10.

Discussion: The sponsor clarified that Table 10 represents the safety data they will have at the time of their NDA application. The sponsor agreed to provide an updated version of this table at the time of the 120-day safety update.

**Question 4:** Does the Agency consider that an Advisory Committee would not be required for NDA 211765?
**FDA Response to Question 4:**

The final decision regarding the need for an Advisory Committee meeting will be made at the time of filing.

**Discussion:** None

**Question 5:** Does the Agency agree that the ubrogepant NDA could be eligible for Priority Review?

**FDA Response to Question 5:**

Priority review decisions are made after the application is submitted. Provide your rationale for requesting a Priority Review Designation in your NDA submission, and we will review your request at that time.

**Discussion:** None

**Question 6:** Does the Agency agree that the clinical pharmacology data package will provide sufficient information to constitute a complete NDA?

**FDA Response to Question 6:**

Please refer to the attached review aid for the requirement of a complete clinical pharmacology package. If the following comments are addressed and included in the NDA submission, the clinical pharmacology package appears, on face, acceptable:

1. Study P009 (Table 11-5) shows that metabolite M15 may be a major metabolite, at 30.4% of the circulating drug-related material. The Pre-NDA Meeting Package states that there are no major metabolites. This discrepancy must be addressed. If M15 is a major metabolite, you should conduct in-vitro studies to assess the DDI potential of the metabolite for any CYPs that were not already investigated in a clinical DDI study.

2. Based on in-vitro results that show ubrogepant is a substrate of P-gp, BCRP, OATPB1, and OATPB3, clinical transporter DDI studies should be performed for these transporters. Alternatively, you may provide a compelling argument that these DDIs are not clinically relevant. Please refer to the FDA Guidance on In-Vitro Metabolism and Transporter-Mediated DDI Studies.

3. Please ensure that the ongoing BE bridging study report (3110-103-002) and associated datasets are included at the time of NDA submission.

Also, see responses to Questions 8 and 19.
As part of your planned population PK and PK/PD analysis, you should address the following points:

1. At the End-of-Phase 2 meeting, we noted that food effect studies demonstrated a reduction in ubrogepant exposure, and a delay in the time to reach maximum plasma concentrations during the fed state. Your PK/PD analysis should incorporate the potential of meals to impact the efficacy of ubrogepant during a migraine attack, and any implications for your proposed dosing recommendations.

2. To inform dosing recommendations in patients with renal impairment, your population PK analysis should also be used to explore the effect of renal function on the pharmacokinetics of ubrogepant.

3. If you are pooling PK data from Phase 1, 2 and 3 studies for your population PK analysis, your model should account for potential differences between the DBS and plasma assays.

4. The results of your population PK/PD analysis should be used to support your proposed dosing recommendations. To the extent the data allows, the analysis should also inform the efficacy and safety of a second dose (at a minimum of 2 hours after the first dose, if needed).

**Discussion:**

The sponsor stated that M15 is not a major metabolite and it is more polar than the parent drug. As a result, the sponsor will not conduct in-vitro studies to evaluate M15 as a major inhibitor. FDA acknowledged this proposal.

FDA clarified with the sponsor that the clinical DDI study with rifampin is not sufficient to elucidate the potential DDI with OATP. There was no DDI evaluation after the first dose of rifampin; therefore, the effect of OATP inhibition cannot be determined.

FDA clarified that this is not a filing issue. However, the sponsor needs to address concomitant use of OATP inhibitors in the clinical pharmacology package and the label. Additional clinical DDI studies may be requested after approval.

**Question 7:**

a) Does the Agency agree that the proposed phase 2/phase 3 clinical data package will provide sufficient information to constitute a complete NDA?

b) Does the Agency agree that efficacy data from the open-label, long-term safety study, UBR-MD-04, is not required to support approval of the ubrogepant NDA?
**FDA Response to Question 7:**

a) We are unable to provide a response without clarification about the number of patients you expect to have in your database at 6 months, 1 year, and the overall exposure at the time of filing. Please see our response to Question 3. In addition, please also populate the table shell below with information from your development program for ubrogepant expected at the time of filing.

Table 1: Safety Population, Size and Denominators

<table>
<thead>
<tr>
<th>Clinical Trial Groups</th>
<th>New Drug (n=)</th>
<th>Placebo (n=)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy volunteers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled trials conducted for this indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All other trials conducted for this indication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Controlled trials conducted for other indications</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

b) Please clarify how many patients in each arm have successfully completed the hepatic safety study 3110-105-002.

c) We agree that efficacy data from the open-label, long-term safety study is not required to support approval. You may include this information in your submission if it is available at the time of filing.

**Discussion:** See the response to Question 3. The sponsor clarified the size of the safety database that will be available at the time of the NDA application, including the number of patients who have completed the hepatic safety study. On face, the size of the safety database that the sponsor described in the slide presentation at the beginning of this meeting appears sufficient for filing. Whether the application is ultimately fileable will be a matter of review. Please refer to the slide presentation at the end of the meeting minutes.

**Question 8:** Does the Agency agree that the Phase 3 study (UBR-MD-01 and UBR-MD-02) population captures adequate safety and efficacy information in a renally impaired population to support review of the proposed NDA?
**FDA Response to Question 8:**

The safety and efficacy information in the renally impaired population that was obtained in Phase 3 studies seems sufficient for review. However, whether a dedicated renal impairment PK study may be needed will be a matter of review.

**Discussion:** None

**Question 9:** Does the Agency agree with the proposed eCRFs and narratives to include in the NDA?

**FDA Response to Question 9:**

In addition to the narratives you have already proposed to include, we request the following additional narratives:

- For Phase 3 studies, include narratives for patients with cardiovascular AEs.
- For Phase 2 studies, include narratives for the patients with cardiovascular AEs and for patients with transaminase elevations greater than 3xULN.
- For Phase 1 studies, provide narratives for the following: death, discontinuations due to AEs, SAEs, events of clinical interest, pregnancies, and cardiovascular AEs.

Please also see the attachment “General Clinical Safety Requests” for a description of the expected content for the narratives.

**Discussion:** None

**Question 10:** Does the Agency agree with Allergan’s proposed ISS SAP?

**FDA Response to Question 10:**

For ISS groups 1a and 1+2, you should perform the same analyses as you have planned for ISS groups 1, 2, and 3.

On page 41 of the ISS SAP, you state that an AE will be allocated to the long-term safety study if the AE occurs on or after randomization into the long-term safety study. If the AE occurs within 5 half-lives of the last treatment in the double-blind period, you should allocate that AE to the controlled study, even if the patient has already initiated their participation in the long-term safety study.

**Discussion:** The sponsor proposed to incorporate the additional ISS analyses on group 1a, but not to group 1+2. The sponsor provided the following table to summarize the planned ISS analyses including additional proposed analyses:
The sponsor explained that since group 1 included short-term controlled data and group 2 included long-term data, combining this data for the analyses above may not provide useful additional data to the analyses they plan to provide for group 1 and group 2 individually.

The sponsor clarified that there would be a 4-week follow-up visit after the last dose of investigational product in the controlled portion of the Phase 3 efficacy trials, and that AEs occurring up to this time would be attributed to the controlled trial, rather than the long-term safety study. FDA stated that this was acceptable.

**Post meeting comment:** FDA had additional internal discussion about the sponsor’s proposal to not conduct the full set of safety analyses in the combined group 1+2 and decided that this proposal is acceptable.

**Question 11:** Does the Agency agree with Allergan’s proposed ISE SAP?

**FDA Response to Question 11:**

The ISE should be an overall integrated analysis that comprehensively examines the effectiveness data derived from individual clinical studies. Therefore, this analysis would include a thoughtful synthesis of the evidence supporting efficacy based on the totality of the evidence provided from the various individual trials presented. It is not intended to include only analyses of pooled efficacy data from multiple studies. There are situations when pooled analyses may be useful, such as when evaluating effectiveness in relation to demographics, and such an analysis could be presented in the ISE. Please refer to the Guidance for Industry: Integrated Summary of Effectiveness:
Discussion: None

Question 12: Based on the submitted draft SDTM dataset definition file, draft ADaM dataset definition file, and annotated eCRF for Protocol UBR-MD-01, does the Agency have any suggestions on the data format from an NDA review perspective?

FDA Response to Question 12:

On face, the data formats are acceptable.

Discussion: None

Question 13:

a) Does the Agency agree that a PRO dossier will not be required in the ubrogepant NDA?

b) Does the Agency request any additional support for the functionality of the eDiary in the ubrogepant NDA?

FDA Response to Question 13:

a) We agree.

b) For Protocols UBR-MD-01 and UBR-MD-02, please describe how the self-reported headache data was handled from the time of entry into the electronic diary device by the subjects until the data reached the study database. Include the roles of the clinical investigator, CRO/vendor (if any), and the sponsor in the process. Please describe the process for making any changes to these data after entry as well as whether audit trails and data clarification forms were in use. In addition, please indicate if and how the self-reported headache data from the electronic diaries were made available to the clinical investigator at their sites throughout the study and after study completion.

Discussion: None

Question 14: Does the Agency agree that summary level clinical site data can be provided only for the pivotal studies, UBR-MD-01 and UBR-MD-02?

FDA Response to Question 14:

Please also provide subject-level data line listings by clinical site as described in the FDA 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) for Protocols UBR-MD-01 and UBR-MD-02. These data listings should include all raw e-diary scores for each subject used to calculate study endpoints.

**Discussion:** None

**Question 15:** Does the Agency agree that the UBR-MD-01 and UBR-MD-02 safety profile continues to support that a human abuse potential study and a human physical dependence study will not be required in the proposed NDA?

**FDA Response to Question 15:**

Yes, we agree that it will not be necessary to conduct a human abuse potential study and a human physical dependence study prior to NDA submission. The need for those studies was predicated on the appearance of a significant signal from abuse-related adverse events in the Phase 3 clinical studies. Given that the incidence of euphoria-related adverse events was < 0.5% (based on the summary of adverse events you submitted in the meeting package), there is no evidence that ubrogepant induces abuse potential.

However, if the NDA review of the abuse-related adverse events in the clinical studies with ubrogepant shows a significant euphoria-related signal, this may indicate a safety concern with ubrogepant that could result in the need for additional studies.

**Discussion:** None

**Question 16:**

a) Does the Agency agree with the proposed content and format of the abuse potential assessment for ubrogepant?

b) Can the Agency please comment on the timeline for review activities associated with a scheduling recommendation for ubrogepant under the CSA?

**FDA Response to Question 16:**

a) Yes. The nonclinical abuse-related studies and the abuse-related adverse event assessment of clinical studies appears comprehensive.

b) During an NDA review, the abuse-related data are reviewed by the Controlled Substance Staff (CSS). If CSS determines that the drug has abuse potential and should be recommended for scheduling under the Controlled Substances Act (CSA), they will prepare a scientific and medical analysis of the drug’s abuse potential in an “Eight Factor Analysis” (8FA). This document is responsive to the requirements of the Controlled Substances Act (CSA) and is prepared in conjunction with the National Institute on Drug Abuse (NIDA) on behalf of the
Assistant Secretary for Health (ASH) at the Department of Health and Human Services (HHS).

The 2015 Improving Regulatory Transparency for New Medical Therapies Act (“the Act”) streamlined the scheduling process by establishing time lines for DEA scheduling actions in relation to NDA approval actions. Under the Act, FDA approval of an NDA for a drug with abuse potential may not take effect until DEA issues an interim final rule under 21 U.S.C. 811(j) establishing a temporary scheduling placement for the drug, in accordance with 21 U.S.C. 355(x). DEA has 90 days to publish the interim final rule in the Federal Register, once both of the following events have occurred (in any order): 1) FDA has approved the NDA and formally notified DEA of the approval, and 2) the 8FA for the drug has been transmitted from the ASH to the DEA. Once the interim rule has been issued, the new drug applicant may update their product labeling to reflect the scheduling action (through supplement submission to their NDA) and then market their drug. Subsequently, DEA will issue a final rule that permanently places the drug under the CSA.

**Discussion:** None

**Question 17:** Does the Agency agree that the non-clinical data package will provide sufficient information to constitute a complete NDA?

**FDA Response to Question 17:**
Based on the information provided in the briefing document, the completed and planned nonclinical studies appear sufficient to support an NDA. However, you will need to ensure that impurity-related issues are adequately addressed (see response to Question 18). The adequacy of the nonclinical data and the need for any additional nonclinical studies will be a matter of review.

**Discussion:** None

**Question 18:** Does the Agency agree that (b) (4) should be considered as a regular process-related impurity and that it is not necessary to test (b) (4) in the drug substance during commercial manufacturing?

**FDA Response to Question 18:**
You will need to provide sufficient justification for (b) (4) to be considered a regular process-related impurity, as recommended by ICH M7(R1), March 2018. Published literature does not typically provide sufficient detail to allow for an independent review of the data; therefore, an Ames assay will be needed to assess (b) (4). In the absence of a negative Ames assay, (b) (4) should be controlled to 1.5 µg/day.

**Discussion:** The sponsor provided additional information to support designating (b) (4) as a non-mutagenic impurity. The FDA indicated that the decision to classify (b) (4) as a non-
mutagenic impurity and determining its limits is a review issue. The FDA recommended that the sponsor include their justification for treating (b) (4) as a regular process-related impurity and omitting (b) (4) testing on release of the drug product in the NDA submission.

**Question 19:** Does the Agency agree that Allergan can include a short summary of bioanalytical methods within the eCTD according to previous practice?

**FDA Response to Question 19:**

No, we do not agree. Your report should be consistent with the 2018 FDA Guidance for Bioanalytical Method Validation. The contents of the 2018 guidance are similar to the contents of the 2010 Draft Bioanalytical Guidance. A summary table of the assay validation results should be included.

**Discussion:** None.

**Question 20:** Does the Agency agree with the study data standardization plan for the proposed ubrogepant NDA?

**FDA Response to Question 20:**

From a technical standpoint, the study data standardization plan (SDSP) for nonclinical and clinical data is acceptable.

**Discussion:** None

**Additional Meeting Discussion:**

The sponsor reminded FDA that during a CMC pre-NDA meeting on May 23, 2018, the issue of the proposed stability package to support 24-month shelf-life was discussed. FDA stated that the drug product expiry is a matter of review, but FDA did agree that nine months of stability data at submission with an update of 12 months of stability data within 30 days of initial submission was acceptable.
3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our June 16, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan, as well as a timeline for review activities associated with a scheduling recommendation under the Controlled Substances Act for drugs with abuse potential. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

**PRESCRIBING INFORMATION**

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy
registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

**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:


Attachment 1.
DNP Pre-NDA Meetings
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)
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:

1. 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.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.

3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

4.0 ATTACHMENTS AND HANDOUTS
Attached are the slides presented by Allergan at the August 30, 2018, meeting at the FDA White Oak Campus.
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/

ERIC P BASTINGS
09/28/2018
IND 113,924

MEETING MINUTES

Allergan
Attention: Edward Burd, Ph.D.
2525 Dupont Drive
P.O. Box 19534
Irvine, CA 92623-9534

Dear Dr. Burd:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-1602.

We also refer to the meeting between representatives of your firm and the FDA on March 17, 2016. The purpose of the meeting was to discuss your Phase 3 development 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

Reference ID: 3913187
MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2
Meeting Date: March 17, 2016
Meeting Location: FDA White Oak
Application Number: IND 113,924
Product Name: MK-1602
Indication: Migraine
Sponsor/Applicant Name: Allergan
Meeting Chair: Eric Bastings, M.D.
Meeting Recorder: Lana Chen, R.Ph.

FDA ATTENDEES

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Suhail Kasim, MD, Clinical Reviewer
Laura Jawidzik, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Kun Jin, PhD, Statistical Team Leader
Qiu, Junshan, PhD, Statistical Reviewer
Sabarinath Sreedharan, PhD, Clinical Pharmacology Team Leader
Xinning Yang PhD, Clinical Pharmacology Reviewer
Kevin Krudys, PhD, Pharmacometrics Team Leader
Lana Chen, RPh, Project Manager
Katherine Bonson, Ph.D., Pharmacologist, Controlled Substance Staff
Robert Temple, MD, Deputy Director, ODE1
Naomi Lowy, MD, Associate Director for Regulatory Science (Acting), ODE 1

Reference ID: 3913187
SPONSOR ATTENDEES

Allergan
Joel Trugman, MD, Senior Director, Clinical Development CNS
Michelle Finnegan, MPH, Director, Clinical Development
Kaifeng Lu, PhD, Director, Biostatistics
Abhijeet Jakate, PhD, Senior Principal Scientist, Clinical Pharmacology
Ed Burd, PhD, Director, Global Regulatory Affairs
Erin Collins, MS, Senior Specialist, Global Regulatory Affairs
Hassan Lakkis, Executive Director Biostatistics
Baldo Sforzolini, MD, PhD, MBA, Senior Vice President, Clinical Development
Armin Szegedi, MD, PhD, Vice President, Clinical Development CNS
David Hovland, PhD, Vice President, Global Regulatory Affairs

DISCUSSION
Clinical Program

Question 1a
The planned Phase 3 development program will consist of two identical, randomized, double-blind, placebo-controlled, single-attack studies; and a 52-week, randomized, open-label, extension study to support the indication of acute treatment of migraine with or without aura in adults. This Phase 3 program has been designed to support approval.

Does the Agency agree that the proposed clinical development plan is sufficient to support an NDA for the indication of acute treatment of migraine with or without aura in adults? If the Agency does not agree, please explain.

FDA Preliminary Response: In general, two adequate and well controlled clinical trials would suffice to support an NDA. On face, your proposed clinical development plan has the potential to support an indication of “acute treatment of migraine in adults”.

In addition, we note that Study P006 has many of the characteristics of a pivotal efficacy trial. We are open to an argument that Study P006 could be used in support of a marketing application for your product, along with one of the other proposed pivotal studies, provided the results of the second study are robust, in particular for the “most bothersome migraine-associated symptom” endpoint.

Allergan Response

Allergan appreciates the Agency’s comments and will consider Study P006 as part of our overall registration-supporting program.

Meeting Discussion: FDA stated that any final determination about whether the phase 2 trial would qualify as a registration trial would be made after a complete review of the trial. If the
analysis for the primary outcome measure was prespecified and the study met the other key features of a registration trial, then it may qualify. On face, based on what was presented, it seemed to have features of such a trial.

**Question 1b**

**Allergan Response**
Allergan acknowledges the Agency’s advice.

**Meeting Discussion:** No further discussion.

**Question 1c**

Does the Agency agree with the study design of each of the proposed studies as adequate and well-controlled to support an NDA for the indication of acute treatment of migraine with or without aura in adults? If not, please explain the areas where the Agency does not agree with the design.

**FDA Preliminary Response:** Please note that in the absence of a full protocol, our response is limited to review of the submitted study synopses. We recommend you send protocols for any pivotal efficacy study as a special protocol assessment (SPA).

We have the following comments at this time:

1. In your proposed phase 3 studies, eligible patients during randomization will be stratified by the patient’s previous response to triptans based on the patient's history (triptan responder, triptan insufficient responder, and triptan naïve). In order to support a specific claim for ubrogepant use in patients who responded poorly to or are unsatisfied with triptan therapy (i.e., essentially a superiority claim over triptans), evidence would need to come from a superiority study in which patients with a history of failing triptan therapy would be randomized to ubrogepant or to a
tripatan. We also further refer you to the discussion in Section V.E. of the draft Guidance for Industry: Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products which deals specifically with the issue of enrichment with treatment nonresponders. (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332181.pdf).

2. We note that in your phase 2 trial, the 25 mg dose also demonstrated efficacy. We suggest that you continue to explore the 25 mg dose in your phase 3 trial(s).

**Allergan Response**

Allergan acknowledges the Agency’s advice. We plan to submit the protocols to FDA for review and welcome your comments and feedback, however we do not plan to formally submit for a Special Protocol Assessment.

1. Allergan confirms that we are not pursuing a specific labeling claim for the treatment of inadequate triptan responders.

2. Allergan plans to include the 25 mg dose in one of the pivotal Phase 3 studies. Does the Agency agree with this strategy?

**Meeting Discussion:** FDA agreed that including a 25 mg dose in at least one of the pivotal trials would be wise. It is possible that data from the Phase 2 trial could support positive efficacy findings from a 25 mg dose arm in the Phase 3 trial. In addition, the presence of a dose response within the trial would provide additional support of the efficacy of a low dose, such as 25 mg, studied in that trial. FDA stated that studying a lower dose in this case may also be useful if unexpected safety findings were identified later in the development program for the higher doses.

FDA asked the sponsor what their rationale was for not studying triptan non-responders as per the referenced guidance above on enrichment strategies. There was an exchange of information about what was described in the guidance.

FDA reminded the sponsor that a trial incorporating an enrichment strategy as discussed was not required.

**Question 1d**

**Does the Agency agree with the overall study design for the long-term safety study, specifically the inclusion of a usual-care arm to contextualize any safety findings seen with ubrogepant and the collection of efficacy in the ubrogepant arms only?**

FDA Preliminary Response: We have no objection to including patients randomized to a usual-care arm in your open-label long-term safety study. In general, such a study would be valuable to obtain safety information for the two proposed doses as compared to standard care, but such a
study would not provide interpretable efficacy information due to the open-label nature of the trial.

**Allergan Response**

Allergan acknowledges the Agency’s advice.

**Meeting Discussion**: No further discussion.

**Co-Primary Endpoints**

**Question 2**

Allergan intends to demonstrate the efficacy of ubrogepant using validated efficacy measures. Allergan proposes the following two co-primary endpoints for ubrogepant pivotal studies: (1) having no headache pain at 2 hours after dosing, and (2) absence of the most bothersome migraine-associated symptom at 2 hours after dose. Each of the pivotal studies will be considered positive if at least one of the ubrogepant doses is demonstrated to be superior to placebo on both co-primary endpoints. Details on the primary endpoints and statistical methods are presented in Section 12.2.1 of the protocol summary provided in Appendix 1.

Does the Agency agree with the proposed co-primary endpoints, statistical analyses, and study success criteria? If the Agency does not agree, please explain.

**FDA Preliminary Response**: Without a full protocol and a statistical analysis plan, our following statistical comments are preliminary.

1. Generally, the graphical approach can be used to control overall type I error for multiple comparisons across the ubrogepant doses and the primary and secondary efficacy endpoints. However, details on how to implement the graphical approach are needed for further review. Please note that both co-primaries must be positive for the same dose in order to consider the primary analysis as positive.

2. We agree that Firth’s penalized likelihood method can be used to handle the situation of quasi-complete or complete separation. However, we have concerns about making a valid inference based on this method. Please clearly state the statistics for inference and justify its validity.

3. Note that the proposed last-observation carried-forward (LOCF) approach for imputing missing post treatment values may not be optimal. However, it is acceptable as long as the amount of missing data is minimal. In addition, we recommend performing sensitivity analyses to test whether the analysis results are sensitive to the methods selected for handling missing data.
**Allergan Response**

Allergan acknowledges the Agency’s comments.

1. The details of the multiple comparison procedure, including the graph that depicts the strategy, will be provided in the SAP. The null hypothesis associated with the secondary endpoints cannot be rejected unless the null hypothesis associated with both coprimary endpoints have been rejected for the same dose.

2. The Firth’s penalized likelihood method provides a more conservative inference about treatment effect. We will provide a full justification in the SAP and submit it to the Agency for consideration. We request clarification regarding the Agency’s concerns about making valid inference based on this method.

3. We expect the amount of missing data to be minimal based on historical information from Study P006. As a sensitivity analysis, we will imput subjects with missing data at the 2-hour timepoint as non-responders. We will provide full details in the SAP and submit it to the Agency for consideration.

**Meeting Discussion:** The sponsor clarified that they will use a profile likelihood approach to make inferences and FDA agreed with this approach. The sponsor agreed to send the statistical analysis plan for FDA review.

**Secondary Endpoints**

Allergan proposes the following secondary efficacy endpoints for ubrogepant pivotal studies:

- Sustained pain freedom from 2-24 hours post dose, defined as pain freedom at 2 hours, with no administration of either rescue medication or the second dose of the investigational product, and with no occurrence thereafter of a mild/moderate/severe headache during the relevant number of hours after dosing with the investigational product

- Pain relief at 2 hours post dose, defined as the reduction of a moderate/severe migraine headache to a mild headache or to no headache, at 2 hours post dose

- Sustained pain relief from 2-24 hours post dose, defined as pain relief at 2 hours, with no administration of either rescue medication or the second dose of the investigational product, and with no occurrence thereafter of a moderate/severe headache during the relevant number of hours after dosing with the investigational product

- Absence of photophobia at 2 hours post dose
Absence of phonophobia at 2 hours post dose

Absence of nausea at 2 hours post dose

For all the endpoints, the data will be expressed as the proportion of patients meeting each endpoint.

A graphical approach by Bretz et al. (2009) will be used to control the overall type I error rate for multiple comparisons across the ubrogepant doses and the primary and secondary efficacy endpoints. The two co-primary efficacy endpoints will serve as the gatekeeper for the secondary efficacy endpoints. Details on the secondary endpoints and statistical methods are presented in Section 12.2.2 of the protocol summary provided in Appendix 1.

Question 3a

Does the Agency agree with the proposed secondary efficacy endpoints, statistical analyses, and multiplicity strategy? If the Agency does not agree, please explain.

FDA Preliminary Response: See response to Question 2.

Allergan Response

Allergan acknowledges the Agency’s comments. We will provide full details in the SAP and submit it to the Agency for consideration.

Meeting Discussion: No further discussion.

Question 3b

Does the Agency agree that the secondary endpoints can be described in the label if they are positive (after multiplicity control) and replicated across studies? If the Agency does not agree, please explain.

FDA Preliminary Response: Yes, except for sustained pain relief, which is redundant to sustained pain-free.

Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: No further discussion.

Phase 3 Dosing (50 & 100 mg)

Question 4

Allergan proposes to evaluate the efficacy and safety of 50- and 100-mg doses of ubrogepant in the Phase 3 clinical trials.
Does the Agency agree? If the Agency does not agree, please explain.

FDA Preliminary Response: Please see the response to Question 1c.

Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: No further discussion.

Safety Database

Question 5

The safety database will consist of approximately 3000 patients exposed to at least one dose of ubrogepant. Of these, we expect to have approximately 800 patients complete 6 months of intermittent treatment and 400 patients complete 12 months of intermittent treatment. We expect that 640 patients will have treated, on average, at least 2 migraine attacks per month for 6 months and 320 patients will have treated, on average, at least 2 attacks per month for 12 months.

Does the Agency agree that the anticipated safety database would be adequate to support an NDA for the acute treatment of migraine? If the Agency does not agree, please explain.

FDA Preliminary Response: On face, the proposed safety database appears acceptable. There must be adequate experience in a substantial number of migraineurs, i.e., 50% or more, at the maximal recommended ubrogepant dose proposed for registration.

Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: FDA suggested that the sponsor carefully characterize AEs to identify possible safety signals since CGRP has a proposed compensatory effect of vasodilation on the vascular system and CGRP antagonism may have potential end organ effects. A thorough workup of patients with adverse events in the controlled portion of the clinical trials is needed to inform labeling.
Hepatic Effects

Question 6

To evaluate potential hepatic effects, liver monitoring will be implemented in the Phase 3 studies, as follows:

- Clinical laboratory assessment of ALT, AST, alkaline phosphatase, and total bilirubin at the following study visits in the single-attack studies: Visit 1 (Screening), Visit 3 (4 days post dose), and Visit 4 (4 weeks post dose) (see Schedule of Evaluations in Section 11 of the Protocol Summary provided in Appendix 1 of this briefing package). In the long-term safety study, clinical laboratory testing will be performed at all visits (monthly visits for the entire 12 months) including the follow-up visit at 4 weeks after the last dose.
- Any cases with ALT or AST values ≥ 3 × the upper limit of normal (ULN) and potential Hy’s law cases will require immediate reporting by the Investigator and appropriate medical evaluation and follow-up will be conducted.
- An independent Clinical Adjudication Committee (CAC) will evaluate all cases with ALT or AST levels ≥ 3 × ULN for their possible relationship to investigational product as specified in an established CAC charter. For details, please refer to Section 13.1.4 of the Protocol Summary provided in Appendix 1.
- An independent Data Safety Monitoring Board will also be established to evaluate the safety of patients enrolled in the Phase 3 studies and will be authorized to make recommendations, including modification or termination of the studies. For details please refer to Section 13.4 of the Protocol Summary provided in Appendix 1.

Does the Agency agree with the proposed liver monitoring plan, including clinical laboratory test collection schedule and independent monitoring of any cases of ALT or AST elevation ≥ 3 × ULN? If not, please describe any missing elements in the proposal.

FDA Preliminary Response: On face, your plan appears acceptable. In addition, all patients identified as having abnormal liver function testing in your proposed trial must be followed until full resolution of the liver injury. Include in your protocol the battery of testing required to evaluate patients with abnormal liver function testing. Include specific plans for whether and in what conditions a re-challenge of study drug may be allowed.
Allergan Response

Allergan confirms that patients identified as having abnormal liver function testing will be followed until full resolution of the liver injury. We will include in the protocols the battery of testing required to evaluate patients with abnormal liver function. For the long-term safety study, we are considering the inclusion of a re-challenge option, which will be presented in the full clinical protocol.

Meeting Discussion: No further discussion.

Repeat Dosing in Labeling

Question 7

Does the Agency agree that an option to repeat the dose (at a minimum of 2 hours after the first dose, if needed) can be included in the label provided no safety/tolerability concerns are identified in the studies? If the Agency does not agree, please explain.

Pre-Meeting Communication Comment

FDA Preliminary Response: Information of a second dose may be described in labeling, provided there sufficient information supporting the safety and efficacy of redosing.

Allergan Response

Allergan acknowledges the Agency’s comment.

Can the Agency please provide clarification on what kind of efficacy data they would like to see presented?

Meeting Discussion: As proposed in the submitted protocol synopsis for the Phase 3 studies, in order to include efficacy data in the label for a second dose, patients that received active study drug would have to be re-randomized if a second dose of medication was used and evaluated for pain-freedom at 2 hours post-dose. The study does not need to be powered to test this endpoint, thus a numerical trend may be sufficient to describe the use of a second dose in labeling.

CV Risk

Question 8

The proposed Phase 3 studies will exclude patients with known clinically significant cardiovascular disease, but will include patients with varying degrees of cardiovascular risk (low, moderate, and high) as assessed by the National Cholesterol Education Program (NCEP) guideline. Integrated safety analyses are planned across the program for each of the CV risk subgroups.
FDA Preliminary Response: In order to include information in labeling regarding patients with cardiovascular risk factors, you should enroll such patients in your proposed pivotal trials, provided you have sufficient evidence (e.g., nonclinical) to support the safety of this approach. In particular, you should not exclude patients with coronary artery disease, arrhythmia and uncontrolled hypertension, unless there is a safety concern to do so.

Allergan Response

We wish to clarify our intention with regard to the patient population that will be studied. Patients with CV disease will be included in the program. The protocols will exclude patients with clinically significant CV disease, per the judgment of the investigator. While the intent is to leave this judgement to the investigator, the protocols give specific examples of conditions which will exclude the patients from participation in this program because they are medically unstable. For example, patients with heart failure defined as New York Heart Association functional classification system, Class III or IV, will be excluded.

Patients with all degrees of CV risk (low, moderate, and high) will be included in the Phase 3 program.

Meeting Discussion: The sponsor stated that they are including patients with various levels of cardiovascular risk but are excluding patients with a recent MI or stroke since these patients may be more unstable. FDA asked about the rationale for excluding these patients and suggested the sponsor enroll the broadest population possible unless there is information to suggest this would not be safe. FDA stated that this would be a review issue and could not prospectively provide a number. FDA suggested enrichment of the study population with patients with documented coronary artery disease.

The sponsor will submit information from a previously conducted in-vivo non-clinical study to determine the effect of triptan vs. ubrogepant on coronary artery diameter. In addition, FDA recommended that the ECG exclusionary criteria be more specific and detailed so investigators could be consistent in exclusion of patients with ECG abnormalities.
Secondary Endpoint in Label

Question 9

Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: No further discussion.

eDiary & COA Plan

Question 10

Allergan will develop an eDiary that will be used to record the endpoints in the upcoming clinical trials. This eDiary will be developed in accordance with the Agency’s recommendations (Guidance for Industry. Migraine: Developing Drugs for Acute Treatment) to develop a headache diary that is well defined and reliable for the target population, based on the PRO guidance for industry (Patient-Reported 204 Outcome Measures: Use in Medical Product Development to Support Labeling Claims). Allergan will prepare a Clinical Outcomes Assessment (COA) Plan, which will outline the research planned to develop the eDiary for use in the clinical trial population. Allergan will present the COA Plan at a future consultation (i.e., Type C meeting) with the Division and COA Staff.

Does the Agency agree with this proposal? If the Agency does not agree, please explain.

FDA Preliminary Response: In order to respond to this question, we need additional information about your plan. If your intention is to use an eDiary to record the outcomes described in your submission, we have no objection and only request that you provide details to the Division on the functionality of the eDiary. If you plan to develop a PRO and use the eDiary to capture the data from the PRO, you should submit the PRO to the Division and we will let you know appropriate next steps.

We note that food effect studies with ubrogepant showed a reduction in maximum plasma concentration \( (C_{\text{max}}) \) and systemic exposure during the first two hours (AUC\(0-2h\)) after oral administration in fed state. The time to reach maximal plasma concentration was also delayed by about 2 hours in the fed state. These changes in systemic exposure may impact the efficacy of
ubrogepant during a migraine attack. Therefore, we recommend that you include in the eDiary the details of patient's diet on the day of the migraine attack as well as on the day of PK sampling at Visit 3. This information can help in better understanding the exposure-efficacy relationship of ubrogepant from these studies.

**Allergan Response**

We confirm that the eDiary will only be used to collect the outcomes described in the protocols; we will not be developing a new instrument for ubrogepant. We will provide details on the functionality of the eDiary to the Division in due course. We plan to collect details about the patient’s diet on the day of the migraine attack and on Visit 3.

**Meeting Discussion:** No further discussion.

**Clinical Pharmacology**

**Question 11**

Does the Agency agree with the design of the planned hepatic impairment study? If the Agency does not agree, please explain.

**FDA Preliminary Response:** On face, your proposal is acceptable.

**Allergan Response**

Allergan acknowledges the Agency’s comment.

**Meeting Discussion:** No further discussion.

**Question 12**

Since less than 10% of drug is excreted in urine, Allergan plans not to perform a PK study in renal-impaired subjects.

**Does the Agency agree? If not, please explain.**

**FDA Preliminary Response:** You need to provide more information on the fraction of parent drug and metabolites excreted in feces and urine samples before we can assess the need for a dedicated renal impairment study. An 83% of radiolabeled dose recovered in feces, as you reported in the meeting package, does not necessarily mean that metabolism is the major elimination pathway.

Based on your current proposal, it seems that you don’t anticipate renal function impairment to significantly alter the pharmacokinetics of ubrogepant. If you have adequate justification, we recommend that you include patients with renal impairment
in your proposed Phase 3 studies to provide information on safety and efficacy of ubrogepant in this population.

**Allergan Response**

Please refer to study report P009, Table 11-6 and 11-7, for radiolabeled dose recovered in feces and urine. Of the 9.5% in the urine, 5.6% is unchanged parent compound AGN-241688 and 4% is inactive metabolites. Based on these data, we consider a PK study in renally impaired patients is not necessary. Does the Agency agree?

We will modify the protocols to not exclude patients with moderate and severe renal impairment in the Phase 3 program.

**Meeting Discussion:**

FDA responded that the report for Study 009 was not provided in the meeting package or in the investigator brochure in the IND. Based on the additional information provided by the sponsor during the meeting, it appears that renal elimination is a minor pathway for ubrogepant. Thus, it is reasonable to include patients with moderate or severe renal impairment in the trials.

Whether a dedicated renal impairment study using reduced design is needed (e.g., in patients with severe renal impairment) will be a review issue. This will depend on various factors such as the number of subjects with renal function impairment included in the Phase 3 studies, PK results from these patients, efficacy and safety in this sub-population, and the relationship between exposure or dose and efficacy/safety of ubrogepant in general. FDA reminded the sponsor that the Phase 3 studies should include an adequate number of patients with renal function impairment (moderate or severe) to enable safety/efficacy/PK evaluation in this patient population. The sponsor acknowledged the FDA’s recommendation and stated that PK samples will be collected from these patients in the proposed trials.

The sponsor also clarified that the results from the mass-balance study (009) showed that 62% of the radioactivity in feces was present as the parent drug. So, about half of the administered dose was recovered as unchanged drug in feces.

**TQT Design**

**Question 13**

Does the Agency agree with the planned design of the thorough QT study? If not, please explain.

FDA Preliminary Response: Yes, we agree with the planned design of the thorough QT (TQT) study.
Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: No further discussion.

Abuse Liability

Question 14

Based on the results from the nonclinical and clinical studies conducted to date, Allergan does not plan to conduct clinical abuse liability or drug dependence studies with ubrogepant.

Does the Agency agree? If not, please explain.

FDA Preliminary Response:
Ubrogepant is a new molecular entity with a novel mechanism of action. To date, there are no calcitonin gene-related peptide receptor antagonists that have been approved for marketing by FDA, so it is not possible to determine whether this class of drugs has abuse potential. Thus, it may be necessary for you to conduct a human abuse potential study.

Insufficient information was provided in the meeting package to make this determination. Therefore, you should submit:

- A comprehensive receptor binding study of CNS-related sites.
- Full preclinical protocols and complete data summaries for each drug and dose tested in each of the animal behavioral studies (including the Irwin test conducted during toxicological screening).
- Pharmacokinetic data from animal studies showing plasma levels achieved by each dose/route of administration used in the animal abuse-related studies and a comparison to the plasma levels produced by the highest proposed therapeutic dose in humans.
- A complete list of all abuse-related adverse events (especially ones that are related to euphoria or hallucinogenic properties) occurring in all clinical studies conducted to date. The data should provide abuse-related adverse event data on study drug and placebo, separated by phase 1 and phase 2/3 studies, by subject and patient population, by drug dose, and by length of treatment with study drug. Do not truncate representation of data by a cut-off percentage.

A clinical assessment of physical dependence is a safety assessment that is conducted for all drugs, in order to determine whether discontinuation of the drug produces withdrawal signs or symptoms. You may conduct an assessment of physical dependence at the conclusion of a clinical efficacy trial by following migraineurs for 2 weeks following abrupt discontinuation of ubrogepant. CSS is available to provide feedback on the proposed protocol.

Allergan Response
Based on review of available data and the intended acute intermittent use of ubrogepant, we believe the potential for human abuse is limited. Per the Agency’s request, we will provide a comprehensive evaluation of abuse liability, including consideration of the requested data components for Agency comment.

Meeting Discussion: The Sponsor questioned whether an abuse potential assessment was necessary for ubrogepant, since they believe it has limited abuse potential. CSS reiterated that it is important to fully evaluate a CNS-active NME with a novel mechanism of action for abuse potential. Once the Sponsor submits the requested abuse-related information, CSS will determine if a human abuse potential study with ubrogepant will be necessary. If there are no abuse-related signals in the animal or human studies conducted to date, a human abuse potential study will not be required. However, an assessment of physical dependence is necessary for any CNS-active drug. Such an assessment can be conducted in the weeks after a clinical trial is completed, when patients are discontinued from ubrogepant.

Clinical Pharmacology Development Plan

Question 15

In conjunction with the planned hepatic-impairment study and TQT study, does the Agency agree with the adequacy of the Clinical Pharmacology development plan to support NDA filing? If the Agency does not agree, please explain.

FDA Preliminary Response: We recommend the following studies be included in your clinical development program:

1. Ubrogepant is a CYP3A4 substrate. Therefore, you should conduct a drug-drug interaction (DDI) study with CYP3A/P-gp inducers.

2. There is limited information provided in the meeting package on the solubility of ubrogepant. If the solubility is pH-dependent, there may be a potential DDI with anti-acid drugs (e.g., proton pump inhibitors). Please note that you had excluded such drugs in your previous Phase 2 studies. Yet, in the current proposal for the Phase 3 trials, you do not propose to have such exclusion. Please also refer to our previous comments about this issue conveyed to you by email on September 17, 2013 in response to your June 28, 2013 submission.

3. There is uncertainty about the extent of absorption of ubrogepant. Please provide the information about the fraction of parent and metabolites in feces and urine samples. If the data indicate limited oral absorption, you may need to conduct a DDI study with P-gp and BCRP inhibitor (e.g., cyclosporine).

4. If the to-be-market formulation is significantly different from the clinical formulation used in the Phase 3 trials, you need to conduct a PK bridging study.
**Allergan Response**

1) We plan to conduct a drug-drug interaction (DDI) study with a CYP3A/P-gp inducer (CYP3A4).

2) We will prohibit concomitant use of PPIs and antacids for 48 hours prior to the qualifying migraine. In addition, we plan to conduct a DDI study with a PPI.

3) We acknowledge the Agency’s comment. Information about the fraction of metabolites is available in Study Report P009, Table 11-6. In this study, 83% of the radioactive material was in the feces (9.5% in urine). Of the total radioactivity, 62% is unchanged parent compound in the feces.

4) We acknowledge the Agency’s comment. We agree that if the to-be-marketed formulation is significantly different from the clinical formulation used in the Phase 3 trials, then we will conduct a PK bridging study.

**Meeting Discussion:** No further discussion.

**Dried Blood Spot Sampling**

**Question 16**

Based on the good correlation demonstrated between the ubrogepant concentrations obtained from dried blood spot (DBS; fingerstick blood) and plasma (Adjusted R^2 = 0.96, Pearson’s correlation coefficient = 0.98), Allergan plans to use DBS (fingerstick blood) PK sampling to assess the PK of ubrogepant in the proposed Phase 3 clinical studies.

**Does the Agency agree? If the Agency does not agree, please explain.**

**FDA Preliminary Response:** Based on the information provided in the meeting package, your proposal to use dried blood sampling technique in the phase 3 studies is acceptable. However, you should capture the time of drug administration and blood sampling times accurately in all patients. Also, you state that the pharmacokinetic (PK) sampling will be performed in a subset of patients. We encourage you to include PK sampling in as many subjects as possible on the day of migraine attack and from all subjects on the scheduled Visit 3 where the subjects take a single dose of ubrogepant. The sampling on Visit 3 could be sparse for those patients who decide not to participate in PK sampling on the day of migraine attack.
Allergan Response

Allergan accepts the Agency’s recommendations. We agree to include PK sampling in as many subjects as possible.

Meeting Discussion: No further discussion.

Nonclinical

Question 17

Allergan considers that the in vitro nonclinical DMPK studies conducted to date are sufficient to support NDA filing.

Does the Agency agree? If not, please explain.

FDA Preliminary Response: We recommend that you conduct a study to evaluate whether ubrogepant is a substrate of OATP1B1 and OATP1B3 transporters.

Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: No further discussion.

Question 18

In addition to the nonclinical toxicology studies already completed (see Table 8), Allergan plans to complete a pre/postnatal development study in rats to enable registration.

Does the Agency agree? If not, what additional studies are proposed?

FDA Preliminary Response: In addition to the completed nonclinical studies and the planned pre- and postnatal development study, you should conduct an in vitro study to evaluate the potential for AGN 241688 to cause vasoconstriction of coronary arteries.

Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: No further discussion.

Question 19

Allergan considers the studies completed to date to cover the age requirements for juvenile animal toxicology to support pediatric development.
Does the Agency agree? If the Agency does not agree, please explain.

FDA Preliminary Response: The completed nonclinical studies, by design, do not provide an adequate assessment of potential drug-related effects on developmental parameters. Therefore, to support clinical development in children <12 years of age, you will need to conduct a juvenile animal toxicology study in one species, with justification provided for selection of species. In addition to standard parameters, the study should assess reproductive function, neurobehavioral development, and bone growth. It is strongly recommended that a study protocol be submitted for feedback prior to study initiation.

Allergan Response

Allergan acknowledges the Agency’s comment. Regarding juvenile studies, we request clarification of which reproductive function endpoints the Agency recommends which are not covered by the standard reproductive toxicity study endpoints. We will submit a study protocol for Agency comment prior to study initiation.

Meeting Discussion: No further discussion.

Regulatory: Pediatric Study Plan

Question 20

In the Pediatric Study Plan that Allergan will submit, we plan to request a waiver for children ages <6 years in accordance with 21 CFR 314.55(c)(3). Allergan plans to request a deferral for children ages 6 to 17 years in the Pediatric Study Plan in accordance with 21 CFR 314.55(b) until after approval of the adult indication.

Does the Agency agree? If the Agency does not agree, please explain.

FDA Preliminary Response: On face, we agree with your plan for a deferral of studies in children age 6-17 until after the approval of the adult indication, but any final determination will be made after review of your Pediatric Study Plan with the Pediatric Review Committee (PeRC).

Allergan Response

Allergan acknowledges the Agency’s comment.

Meeting Discussion: No further discussion.

Target Product Profile

Question 21

Does the Agency have any comments on the proposed Target Product Profile?

FDA Preliminary Response: No.
**Allergan Response**

Allergan acknowledges the Agency’s comment.

**Meeting Discussion:** No further discussion.

**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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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.


**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](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 (cder-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.

Prospective Suicidality Assessments in Clinical Protocols

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

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.
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.”

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<th>DSI Pre-NDA Request Item¹</th>
<th>STF File Tag</th>
<th>Used For</th>
<th>Allowable File Formats</th>
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<td>Data listings, by study (Line listings, by site)</td>
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<tr>
<td>III</td>
<td>data-listing-dataset</td>
<td>Site-level datasets, across studies</td>
<td>.xpt</td>
</tr>
</tbody>
</table>

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

```
.mkdir [m5]
.mkdir datasets
.mkdir bimo
.mkdir site-level
```

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.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files
PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient’s perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA’s guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.
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
04/06/2016