CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215206Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 114780

MEETING MINUTES

Allergan, LLC.
Attention: Lenh Mong, M.E., J.D., R.A.C.
5 Giralda Farms
Madison, NJ 07940

Dear Dr. Mong:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for atogepant (AGN-241689/MK-803).

We also refer to the teleconference between representatives of your firm and the FDA on September 22, 2020. The purpose of the meeting was to discuss your planned NDA.

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

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

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**B**
Meeting Category:	**Pre-NDA**
Meeting Date and Time:	**September 22, 2020 from 2:00-3:00pm EDT**
Meeting Location:	**Telecon**
Application Number:	**114780**
Product Name:	**Atogepant**
Proposed Indication:	(b) (4)
Sponsor Name:	**Allergan**
Regulatory Pathway:	**505(b)(1)**
Meeting Chair:	**Nick Kozauer, MD**
Meeting Recorder:	**Lana Chen RPh**

FDA ATTENDEES

Billy Dunn, MD, Director (Acting), Office of Neuroscience

Division of Neurology 2
Nick Kozauer, MD, Director
Paul Lee, MD, PhD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Viveca Livezey, MD, Clinical Reviewer
Lana Chen, RPh, Project Manager

SPONSOR ATTENDEES

Allergan
Ramesh Boinpally, PhD, Executive Director, Clinical Pharmacology
Matthew Butler, MD, Director, Medical Safety
Leslie Carter, PharmD, Vice President, Neuroscience,
Global Therapeutic Area Head, Global Regulatory Strategy
Michelle Finnegan, MPH, Executive Director, Clinical Development Neurosciences
Sharon Graham, Associate Director, Global Regulatory Strategy CMC
Hua Guo, PhD, Director, Biostatistics
Amjad Iqbal, PharmD, Executive Director, Global Regulatory Strategy
Jordan Lateiner, MS, MBA Asset Team Lead
Ann Lee, PharmD ,Regulatory Affairs Fellow
Steven Leili, PhD, Executive Director, Toxicology
Kaifeng Lu, PhD, Executive Director, Biostatistics
Lenh Mong, ME, JD, RAC, Director, Global Regulatory Strategy

Weining Robieson, PhD, Senior Director and Statistics Therapeutic
Area Head, Neuroscience
Manshi Shah, MS, RAC, Manager, Global Regulatory Strategy
Christoph Tacheci, PhD, Director, CMC Team Lead
Joel Trugman, MD Associate Vice President, Clinical Development Neurosciences

DISCUSSION

Question 1: Table of Contents

a. Does the Agency agree that the proposed content provides sufficient information to constitute a complete fileable NDA?

FDA Response:
On face, the content of your proposed NDA, as described in this briefing package, appears fileable; however, this determination can only be made during the review of your future application, at the time of filing.

Meeting Discussion: There was no meeting discussion.

b. Does the Agency agree that the proposed organization of the submission is acceptable?

FDA Response:
Overall, your proposed table of contents (TOC) follows the FDA eCTD Comprehensive Table of Contents Headings and Hierarchy (CTOC) with two exceptions:

- **Heading 3.2.R (subheadings/nodes listed)-** You included nodes/headings under 3.2.R which are not listed in FDA's CTOC. You should avoid creating nodes/headings in the eCTD that are not listed in FDA's CTOC.

- **Heading 5.3.2 (title)** – Your titled heading "Reports of Bioanalytical and Analytical Methods for Human Studies" instead of "Reports of studies pertinent to pharmacokinetics using human biomaterials" which is listed in FDA's CTOC.

You can access the FDA CTOC in the eCTD Submission Standards document at https://www.fda.gov/ectd.

Meeting Discussion: There was no meeting discussion.

Question 2: Financial Disclosure

Does the Agency agree with Allergan's proposed list of studies for which clinical investigator financial disclosures will be provided?

FDA Response:
This proposal appears acceptable.

Meeting Discussion: There was no meeting discussion.

Question 3: Day 120 Safety Update

Does the Agency agree with the content of the proposed 120-day safety update?

FDA Response:
The content appears acceptable. At the time of submission, your application should be complete and should include exposure of your product of at least 300 patients at 6 months and 100 patients at 1 year, with a substantial number of patients exposed at the highest planned marketed dose.

Meeting Discussion: There was no meeting discussion.

Question 4: Updated Safety Data for Ongoing Study 3101-309-002 to be Included in the 120-day Safety Update
Does the Agency agree with Allergan's proposal to provide updated safety analyses for Study 3101-309-002 in ISS Group 2 and Group 3 at the 120-day safety update?

FDA Response:
This plan appears acceptable.

In your package it was noted that some participants may be counted twice as independent participants due to a large gap between studies (e.g., CGP-MD-01 completers who then enrolled into Study 3101-302-002). Please ensure the tables with each Phase 2 and Phase 3 study clearly specify the number of unique patients for each dose level with duration of exposure. Please also confirm that the participant exposure table (Table 10-7 in your package) also has a column for unique participant exposures (i.e., in which participants are not counted twice) to better understand the exposure data.

We note several patients had elevated liver function tests in the pivotal studies. Please include patient narratives for all patients with liver function studies (ALT, AST) greater or equal to three times the upper limit of normal (ULN), or bilirubin greater than or equal to 2 times the ULN. When indicated, please include safety analyses to evaluate your product for possible hepatotoxicity. We refer you to the Guidance for Industry: Drug Induced Liver Injury.

We also refer you to our Attachment 1 of the Type C meeting minutes (January 2020), which includes our standard pre-NDA meeting clinical safety requests.

Meeting Discussion: The sponsor clarified that it would provide narratives for all participants with elevated liver function tests in the initial NDA, at the time of the 120-day safety update, and after the 120-day safety cutoff for patients that met criteria for providing narratives based on abnormal liver function tests. The Division agreed that this was acceptable.

The Division stated that exposure tables should be included in the NDA that clearly state how many unique subjects were exposed at distinct timepoints. The Division stated that including exposure tables for individual studies in the CSR is acceptable. The sponsor stated that there were 65 patients overall that were double-counted in the pooled exposure tables. The Division indicated that it had wanted to confirm that ICH exposure requirements were met without double counting patients.

Question 5: Advisory Committee Meeting
Considering that atogepant would not be the first CGRP receptor antagonist to be approved for the treatment of migraine, and the current data support a positive risk-benefit profile, does the Agency agree that an Advisory Committee Meeting is not required for the atogepant NDA?

FDA Response:
Whether an Advisory Committee meeting is required will be determined during the review of any future marketing application.

Meeting Discussion: There was no meeting discussion.

Question 6: Proposed Indication
Allergan intends to submit an NDA for the following indication:
Atogepant is indicated for [redacted (b) (4)].
Allergan understands that the indication statement will be a matter of review.
Could the Agency comment on the sufficiency of the data package to support this indication?

FDA Response:
This proposal does not appear to be supported by your available data. As previously noted in the Type C meeting minutes dated June 27, 2017, submitting two adequate and well-controlled studies for the preventive treatment of episodic migraine would support an indication of the preventive treatment of episodic migraine. Alternatively, a [redacted (b) (4)]

The acceptability of the specific language of any proposed indication statement will be determined during the review of any future marketing application.

Meeting Discussion: There was no meeting discussion.

Question 7: Clinical Pharmacology Package

Question 7a: Does the Agency agree that the clinical pharmacology data package is sufficient to support the NDA?

FDA Response:
The clinical pharmacology package provided appears adequate to support the NDA submission.

Meeting Discussion: There was no meeting discussion.

Question 7b: As recommended by the Agency, Allergan generated data to conclude that metabolite M23 is not an acyl glucuronide. Does the Agency agree that no additional studies on metabolite M23 are needed to support the NDA?

FDA Response:
Based on information provided, we agree that no additional studies on metabolite M23 are required.

Meeting Discussion: There was no meeting discussion.

Question 8: Clinical Package
Does the Agency agree that the proposed clinical data package will provide sufficient information to support the NDA?

FDA Response:
Please refer to our response to Question 1a.

Meeting Discussion: There was no meeting discussion.

Nonclinical
Question 9: Nonclinical Package
Does FDA agree that the proposed nonclinical data package is adequate to support the NDA and that no additional nonclinical studies are needed?

FDA Response:
The nonclinical package appears sufficient to support the NDA. The adequacy of the data will be a matter of review.

Meeting Discussion: There was no meeting discussion.

Question 10: Qualification of (b) (4) Impurity
Does the Agency agree that the (b) (4) impurity has been adequately characterized to support specification?

FDA Response:
While your approach generally appears reasonable, the adequacy of the nonclinical studies to support qualification of the (b) (4) impurity will be a matter of review (see Written Responses, February 14, 2020).

Meeting Discussion: There was no meeting discussion.

Question 11: Abuse Liability Profile
Does the Agency agree that the adverse event data from Study 3101-301-002 and ISS Group 2 (pooled long-term safety studies) continue to support that a human abuse potential study and a human physical dependence study will not be required in the proposed NDA?

FDA Response:
Yes, we agree. The receptor binding studies, nonclinical data, and abuse-related AE profile assessment do not suggest an abuse potential associated with atogepant. A human abuse potential study and clinical physical dependence study are not required in the proposed NDA.

Meeting Discussion: There was no meeting discussion.

Question 12: CSS Designation and Evaluation

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

FDA Response:
Yes, we agree.

Meeting Discussion: There was no meeting discussion.

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

FDA Response:
During an NDA review, the abuse-related data are reviewed by the Controlled Substance Staff (CSS). If we (CSS) determine that the drug has abuse potential and should be recommended for scheduling under the Controlled Substances Act (CSA), we will prepare a scientific and medical analysis of the drug, sometimes referred to as an "Eight Factor Analysis" (8FA). This document is

responsive to the requirements of the 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") established specific 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.

Meeting Discussion: There was no meeting 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-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, 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

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

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

period (i.e., method of assignment of study events to a specific study period).

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

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

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 guidance for industry *Assessment of Abuse Potential of Drugs*.[5]

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

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

Specifications.[6]

ATTACHMENTS AND HANDOUTS
Slides from Sponsor are attached.

11 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

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

/s/

NICHOLAS A KOZAUER
10/19/2020 11:15:44 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114,780

MEETING MINUTES

Allergan, LLC.
Attention: Terri Richmond, M.S., Ph.D.
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 atogepant (AGN-241689/MK-8031).

We also refer to the meeting between representatives of your firm and the FDA on November 19, 2018. The purpose of the meeting was to discuss your Phase 3 clinical development plan for the preventive treatment of migraine.

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

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	**B**
Meeting Category:	**End of Phase 2**
Meeting Date:	**November 19, 2018**
Meeting Location:	**FDA White Oak**
Application Number:	**IND 114,780**
Product Name:	**Atogepant (AGN-241689/MK-8031)**
Indication:	(b) (4)
Sponsor Name:	**Allergan**
Meeting Chair:	**Billy Dunn, MD**
Meeting Recorder:	**Lana Chen, RPh**

FDA ATTENDEES

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Heather Fitter, MD, Clinical Team Leader
Sally Yasuda, MD, PharmD, Safety Team Leader
Laura Jawidzik, MD, Clinical Reviewer
Viveca Livezey, MD, Clinical Reviewer
Kun Jin, PhD, Statistical Team Leader
Jinnan Liu, PhD, Statistical Reviewer
Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Priya Brunsdon PharmD, Clinical Pharmacology Reviewer
Katherine Bonson, PhD, CSS Reviewer
Lana Chen, RPh, Project Manager

Clinical Outcome Assessments (COA) Staff
Julia Jiu, PhD, COA Reviewer
Sarrit Kovacs, PhD, COA Team Leader

SPONSOR ATTENDEES

Allergan
Ramesh Boinpally, PhD Executive Director, Clinical Pharmacology
June Bray, MBA Senior Vice President, Global Regulatory Affairs
Michelle Finnegan, MPH Director, Clinical Development

Hassan Lakkis, PhD Associate VP, Biostatistics
Jordan Lateiner, MS, MBA Executive Director, Project Management
Ye Li, PhD Manager, Statistical Science
Kaifeng Lu, PhD Executive Director, Biostatistics
Lenh Mong, M.E., J.D., R.A.C. Director, Global Regulatory Affairs
Baldo Sforzolini, MD, PhD, MBA Senior Vice President, Clinical Development
Armin Szegedi, MD, PhD Vice President, Clinical Development CNS
Joel Trugman, MD Associate VP, Clinical Development CNS
Li Peng Yap, MS, PhD Manager, Global Regulatory Affairs

DISCUSSION

FDA sent Preliminary Comments to SPONSOR on November 14, 2018.

Question 1: Submission Package
Does the Agency agree that the completed, ongoing and planned clinical pharmacology studies provide an adequate basis to support the NDA?

FDA Response:
We agree that the ongoing and planned clinical pharmacology studies have the potential to support filing of an NDA. You should also consider the following comments:

1. If the final to-be-marketed formulation differs significantly from the formulations used in the pivotal efficacy studies, a pharmacokinetic (PK) bridging study may be required.

2. It is noted that atogepant is a P-gp substrate. The completed drug-drug interaction study with itraconazole assessed the combined impact of CYP3A4 and P-gp inhibition on atogepant PK. Please provide recommendations for dose adjustment for concomitant use of atogepant with medications that are P-gp inhibitors and not CYP3A4 inhibitors.

Meeting Discussion: The sponsor requested suggestions regarding the type of studies that would characterize the impact of P-gp inhibition (without CYP3A4 inhibition) on atogepant PK. The Division suggested conducting a clinical DDI study utilizing quinidine as a perpetrator, in addition to a PBPK model. Quinidine is a P-gp and CYP2D6 inhibitor. Atogepant is expected to be primarily metabolized by CYP3A4 with only a minor contribution from CYP2D6. The clinical DDI study with quinidine combined with a PBPK model would better inform any labeling recommendations regarding dose-adjustment when atogepant is taken with a concomitant P-gp inhibitor.

Question 2: Renal Impairment Study
Renal route being a minor route of elimination for atogepant, does the Agency agree that a renal impairment study is not required for registration?

FDA Response: Based on the preliminary human mass balance study results and the planned inclusion of patients with all degrees of renal impairment in the Phase 3 studies, we agree that a

dedicated renal impairment study is not required for NDA submission. We also agree with your proposal to use population-PK analyses to assess the impact of renal impairment on atogepant exposure from Phase 3 studies. However, the usefulness of this approach depends on ensuring enrollment of adequate number of subjects with renal impairment in these planned studies.

Meeting Discussion: There was no meeting discussion.

Question 3: TQT Study
Allergan is planning to test 60 mg QD atogepant as the highest dose in the Phase 3 efficacy studies and in the long-term safety study. Based on this and lack of accumulation upon QD dosing, does the Agency agree with the proposed supratherapeutic single dose of 300 mg atogepant for the TQT study (Study CGP-PK-04)?

FDA Response:
Yes, we agree with the proposed supratherapeutic single dose of 300 mg for the TQT study. Overall, the proposed study design and analysis plan appear acceptable to characterize the effects of your product on the QTc interval.

Additionally, we have the following comments for you to consider.
1) When you submit your QT study report, please include the following items:
    a. Statistical analysis plan
    b. Clinical study protocol
    c. Investigator's Brochure
    d. A completed Highlights of Clinical Pharmacology and Cardiac Safety Table
    e. Annotated CRF
    f. A data definition file which describes the contents of the electronic data sets
    g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), lead, and ECG ID (link to waveform files, if applicable).
    h. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
    i. Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.
    j. Narrative summaries and case report forms for any
        i. Deaths
        ii. Serious adverse events
        iii. Episodes of ventricular tachycardia or fibrillation
        iv. Episodes of syncope
        v. Episodes of seizure
        vi. Adverse events resulting in the subject discontinuing from the study

2) Submit all related ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
3) We are also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

Meeting Discussion: There was no meeting discussion.

Question 4: Study CGP-MD-01 – Episodic Migraine
Study CGP-MD-01 was a 12-week study of atogepant for the prevention of Episodic Migraine. The study demonstrated that atogepant is effective across multiple doses and dose regimens with a good safety and tolerability profile. Allergan considers Study CGP-MD-01 to be adequate and well-controlled. Does the Agency agree that Study CGP-MD-01 will be considered a pivotal study for the proposed Episodic Migraine indication?

FDA Response: Study CGP-MD-01 has many of the characteristics of an adequate and well-controlled pivotal efficacy trial. Ultimately, whether CGP-MD-01 contributes to establishing the effectiveness of atogepant for the (b) (4) will be a matter of review.

Meeting Discussion: There was no meeting discussion.

Question 5: Clinical Data Package – Episodic Migraine

a. Does the Agency agree that the current clinical development plan (including the number of studies, patient population, treatment durations, and overall study designs) is sufficient to support an NDA for the indication of the prevention of migraine in adults with Episodic Migraine?

   FDA Response: On face, your proposed plan appears acceptable. Further discussion regarding the adequacy of your package can take place at your pre-NDA meeting.

b. Since obtaining FDA feedback at the Type C meeting in June 2017 on the general study design for Study 3101-301-002 (Episodic Migraine study), there have been protocol modifications. Does the Agency agree with the current study design for Study 3101-301-002?

   FDA Response: We have no objections to the current study design. However, please refer to FDA's previous COA-related comments and recommendations dated 9/11/2018. Please address those comments before initiating your Phase 3 trials. Please see our "Additional FDA Comments" below regarding patient global impression of severity and change (PGIS and PGIC) scales.

c. Since obtaining FDA feedback at the Type C meeting in June 2017 on the general study design for Study 3101-302-002 (Long term safety study), there have been protocol

modifications. Does the Agency agree with the current study design, for Study 3101-302-002?

FDA Response: We remind you that an open-label long-term safety study is generally not designed adequately to obtain efficacy data. We agree with the selection of the highest dose (60 mg daily) planned for marketing for the Phase 3 long-term safety study.

Meeting Discussion: FDA pointed out that the current submission did not include a PGIS scale as part of the COA evaluation and the sponsor acknowledged this omission. FDA asked the sponsor to modify their protocol and assessment schedule to include a PGIS assessment. FDA acknowledged and accepted the sponsor's preference to use the 7-point PGIC scale over a 5-point scale, based on patients' preferences, and to keep the PGIC scale consistent with the version used in their Phase 2 trial. The sponsor indicated that they may collapse PGIC response categories in data analysis. FDA reiterated that the previous COA-related comments and recommendations from September 11, 2018, should be addressed by the sponsor before initiation of the Phase 3 trials. The sponsor agreed to submit their response to those comments after the current meeting.

Question 6: Pivotal Study Dose Selection - Episodic Migraine

a. Based on the results of CGP-MD-01, Allergan has selected 30 mg QD and 60 mg QD for evaluation in clinical Study 3101-301-002 (Episodic Migraine). Does the Agency agree that the proposed doses and dose regimen are appropriate to support registration?

FDA Response: Considering the similar efficacy seen in all the dosing arms of the Phase 2 trial, we also recommend including the 10-mg dose in the Phase 3 study, as this dose may provide a better safety profile than the higher doses selected.

b. Based on the results of CGP-MD-01, Allergan has selected 60 mg QD to evaluate long-term safety of atogepant. Does the Agency agree that atogepant 60 mg QD in clinical Study 3101-302-002 (Long-term Safety) is adequate to evaluate the long-term safety of atogepant for Episodic Migraine?

FDA Response: See the response to Question 5c.

c. Study CGP-MD-01 demonstrated statistically significant efficacy for all doses and dose regimens (10 mg QD, 30 mg QD, 60 mg QD, 30 mg BID, and 60 mg BID) tested against placebo, with a similar safety and tolerability profile across treatment arms. Given these results, and understanding that Study 3101-301-002 (Episodic Migraine) will evaluate atogepant 30 mg QD and 60 mg QD, does the Agency consider that the 10 mg QD and 30 mg BID doses tested in CGP-MD-01 could be approvable doses for the prevention of Episodic Migraine?

FDA Response: This would be a matter of review. If you plan to seek approval of the 10 mg QD and 30 mg BID doses, we recommend that you include these doses in your Phase 3 trial.

Meeting Discussion: [redacted] (b) (4) The sponsor discussed why they do not plan on studying the 10 mg dose in their Phase 3 trial. In summary, they considered the safety profile of all the doses to be similar, they thought that there were some secondary endpoints demonstrating superior efficacy on the 30 and 60 mg q day dosing regimen as compared to that of the 10 mg q day dose, and that the PK/PD modeling suggested lower exposures at 18- 24 hours for the 10 mg dose as compared to the 30 and 60 mg dose q day doses, thus possibly yielding a shorter duration of efficacy for the 10 mg q day dose compared to the higher doses. Regarding the use of bid dosing, the sponsor said that they received feedback from practitioners that bid dosing would be inconvenient and may reduce compliance.

The Division continued to recommend the inclusion of the 10 mg dose into the pivotal efficacy trials. The Division emphasized that the dose-response appears to be flat, and the sponsor should consider not only the efficacy observed with their product in completed studies, but also the possibility that later stage studies might identify a less favorable safety profile of the higher doses, making it important to fully understand the dose-response for efficacy. The Division also pointed out that due to the small sample size for some of the dose groups, the variability in the efficacy data makes it difficult to differentiate treatment effects between the dose groups. In a larger study, it may be more apparent that the efficacy of the 10 mg q day dose is similar to that of the 30 mg and 60 mg q day dose. Only empirical data could verify this, since modeling will only yield predictions. The 10 mg dose appears to provide efficacy and might be better tolerated, so it deserves more exploration in Phase 3. Identifying the lowest effective dose in a development program is important. Ultimately, which doses are studied in Phase 3 is the sponsor's decision, as all the doses appear safe to study further.

The Division acknowledged the sponsor's concerns about BID dosing, but suggested that if higher efficacy for a lower dose given bid vs q day was demonstrated, the benefit of the improved efficacy may balance out the inconvenience of bid dosing, and that it may be worthwhile to continue to explore bid dosing, specifically 10 mg bid or 30 mg bid.

Question 7: Statistical Analysis Strategy – Episodic Migraine

a. Does the Agency agree that the planned primary efficacy analysis, combined with the sensitivity analyses, is adequate to analyze the primary efficacy endpoint for Study 3101-301-002?

FDA Response: We recommend that the primary efficacy analysis be calculated based on the 3-month average of the mean monthly migraine days (MMD) rather than using the mixed effects model for repeated measures. Please clearly define how you derive the primary endpoint from the e-Diary data. In addition, report the amount of missing data and how you plan to handle missing data.

b. Does the Agency agree with the proposed secondary efficacy endpoints, corresponding planned statistical analysis, and graphic approach for multiplicity control for Study

3101-301-002?

FDA Response: In section 7.3.2 of the study protocol contained in the Appendix 4 of this meeting package, you stated that "A complete graph and details of the graphical multiple comparison procedure will be presented in the statistical analysis plan of this study." Since there was no statistical analysis plan (SAP) submitted in this meeting package, we will provide more detailed comments when you submit your SAP.

If you want to include the AIM-D results in the labeling, you will need to include a plan for control of the overall Type I error for that endpoint.

Meeting Discussion:

The sponsor stated that they would like to keep the MMRM as the primary analysis model, but would prefer to include the ANCOVA as a sensitivity analysis. The sponsor stated that the MMRM model has an advantage because it can include patients who only have 1 month data. The Division emphasized that the expectation is that there will be minimal missing data. The Division stated that the MMRM could be used as the primary efficacy analysis and the ANCOVA should be provided as a sensitivity analysis. Additional feedback could be provided when the Statistical Analysis Plan (SAP) is submitted.

The Division stated that a minimum of 14 days instead of 12 days of diary data is required for the 28-day periods to be counted as not missing. The observed 18% overall dropout rate in the 3-month Phase 2 study CGP-MD-01 is considered high, compared to other similar studies, and the Division encouraged the sponsor to minimize the dropout rate or any form of missing data through trial design, planning, and training for the planned Phase 3 studies.

Question 8: Safety Database

a. Does the Agency agree that the revised anticipated safety database would be adequate to support an NDA for the proposed Episodic Migraine indication?

FDA Response: On page 22 of the briefing booklet, you note that patients who complete study CGP-MD-01 and roll over to the long-term safety study will have a gap from the completion of Study CGP-MD-01 to the start of Study 302. That gap period should not be included in the total exposure time when counting patients for inclusion into the long-term safety database. Otherwise, on face, the numbers you have proposed in table 10 of the briefing booklet (≥1500 exposed for at least one dose, 300 for 6 months, and 100 for 12 months) appear adequate to support an initial NDA filing. As mentioned in our response to Question 5(c) above, exposure for the durations listed above must be for the highest dose proposed for marketing.

b. Does the Agency agree that the long-term safety database for the initial NDA submission can be supported by an interim database cut for Study 3101-302-002 (long-term safety) with the final long-term safety data being submitted in the Day 120 safety update report?

FDA Response: All information to support the review and approval of your application needs to be available at the time of submission of your application.

Please also refer to Attachment 1 for general standard safety requests regarding the safety content of an NDA.

Meeting Discussion: The sponsor clarified that they expect to have at least 1500 patients exposed to one dose of atogepant with 300 patients exposed for 6 months at the 60 mg dose, and 100 patients exposed for 1 year at the 60 mg dose. The sponsor clarified that this will be continuous exposure without breaks. The Division stated that this, on face, appears acceptable.

(b) (4)

(b) (4)

Question 10: Study Data Standardization Plan
Does the Agency agree with the Study Data Standardization Plan (SDSP) for the atogepant IND?

FDA Response: Yes. From a technical standpoint, the Study Data Standardization Plan (SDSP) for the atogepant NDA is acceptable.

Meeting Discussion: There was no meeting discussion.

Additional FDA Comments:

1. We recommend you explore including multiple anchor scales to provide an accumulation of evidence to help interpret a clinically meaningful within-patient change in the AIM-D scores from the patient perspective. We recommend you add a patient global impression of severity (PGIS) scale in addition to a patient global impression of change (PGIC) scale. In contrast to a PGIC scale, a PGIS scale is a static, current state scale, and is not subject to recall error; it can also be used to assess change from baseline data. The anchor scales should be assessed at comparable time points as, but completed after, the AIM-D. We have included examples of PGIS and PGIC scales below. We recommend that you use a 5-point PGIC scale rather than a 7-point scale as you have proposed for your Phase 3 trials.

Examples of Patient Global Impression of Severity (PGIS) Scales:

Please choose the response below that
best describes the severity of your
<SYMPTOM/OVERALL STATUS/ETC.>
over the past week.

□ None
□ Mild
□ Moderate
□ Severe
□ Very severe

Example of a Patient Global Impression of Change (PGIC) Scale:

Please choose the response below that
best describes the overall change in your
<SYMPTOM/OVERALL STATUS/ETC.>
since you started taking the study medication.

□ Much better
□ A little better
□ No change
□ A little worse
□ Much worse

2. In the "Drug Abuse and Dependence" section of the meeting package, you have the following statement: "No data are available at this time regarding the potential for drug abuse or dependence."

In March 2018, CSS provided feedback to you regarding the design of your proposed animal self-administration study. It is unclear from your statement in the EOP2 meeting package whether this study has been initiated or completed.

We remind you of our statement to you in 2017 regarding your overall proposal for an abuse potential assessment:

"The decision regarding whether a human abuse potential study will be necessary with atogepant will be based on nonclinical abuse-related studies such as the Irwin test and self-administration, as well as the abuse-related adverse event profile observed in healthy volunteers in Phase 1 and in patients in Phase 2. If there are no positive signals indicative of abuse in these studies, it may be possible that a HAP study will not need to be

conducted. If a HAP study is necessary, the supratherapeutic doses to be tested will be determined by safety considerations."

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.

DATA STANDARDS FOR STUDIES

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

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (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 started after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page 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 started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting

mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf.

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the 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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

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

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

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

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the Guidance for Industry, Collection of Race and Ethnicity Data in Clinical Trials (available at: https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm126396.pdf) and for more information.

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

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)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.

8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
5. Ensure that all adverse events are presented, and not only events deemed "drug-related."
6. Provide a table of treatment-emergent adverse events reported in $\geq$ 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. Please ensure that appropriate pediatric reference values are used for pediatric patients.
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.

ATTACHMENTS AND HANDOUTS
Sponsor provided attached slides

21 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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
12/18/2018