CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216834Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 134340

MEETING PRELIMINARY COMMENTS

Ra Pharmaceuticals now part of UCB, Inc
Attention: Robert McNeill, PhD, RAC
Regulatory Affairs Lead
1950 Lake Park Drive, Building 2100
Smyrna, GA 30080

Dear Dr. McNeill:[1]

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

We also refer to your March 4, 2022, correspondence, received March 4, 2022, requesting a meeting to discuss components of the planned new drug application (NDA) for the treatment of generalized myasthenia gravis (gMG).

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, contact me via email at Michael.Matthews@fda.hhs.gov or via telephone at (301) 796-3047.

Sincerely,

{See appended electronic signature page}

Michael Matthews
Regulatory Project Manager
Neurology Group 1
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

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

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: May 5, 2022
3:00 PM to 4:00 PM Eastern Time
Meeting Location: Teleconference
Application Number: IND 134340
Product Name: Zilucoplan
Indication: For the treatment of generalized myasthenia gravis (gMG).
Sponsor Name: Ra Pharmaceuticals now part of UCB, Inc
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES (tentative)

Office of Neuroscience
Billy Dunn, MD, Director

Division of Neurology 1
Teresa Buracchio, MD, Director
Laura Jawidzik, MD, Clinical Team Lead and Deputy Director (Acting)
Daniel Foster, DO, Clinical Reviewer
Sally Jo Yasuda, MS, PharmD – Safety Team Lead
Natalie Branagan, MD, Clinical Safety Reviewer

Division of Pharmacology/Toxicology - Neuroscience
Lois Freed, PhD, Director
Barbara Wilcox, PhD, Reviewer

Office of Biostatistics
Kun Jin, PhD, Statistical Team Leader
Jinnan (Joanne) Liu, PhD, Statistical Reviewer

Office of Clinical Pharmacology
Bilal AbuAsal, PhD, Clinical Pharmacology Team Leader
Poonam Delvadia, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD, Pharmacology Team Lead, Division of Pharmacometrics

Office of Pharmaceutical Quality
Martha Heimann, PhD, CMC Lead for Neurology Products
Katie Duncan, PhD, CMC Reviewer

Controlled Substances Staff
Chad Reissig, PhD, Supervisory Pharmacologist
Joshua Lloyd, MD, Medical Officer Team Leader
Neil Varshneya, PhD, Pharmacologist

Office of Surveillance and Epidemiology
Lopa Thambi, PharmD, Senior Regulatory Health Project Manager
Wendy Brown, PharmD, BCACP, Senior Regulatory Project Manager, REMS
Chad (John) Morris, PharmD, MPH, DMEPA2 Reviewer
Stephanie DeGraw, PharmD, DMEPA2 Team Leader
Jacqueline Sheppard, PharmD, Team Leader, DRM
Anahita Tavakoli, MA, Health Communications Analyst, DRM
Donella Fitzgerald, PharmD, Senior Risk Management Analyst, DRM
Shelly Harris, ScD, MPH, Team Leader, REMS

Office of Scientific Investigations
Phillip Kronstein, MD, GCP Team Lead,
Cara Alfaro, PharmD, BCPP Clinical Analyst

Center for Devices and Radiological Health (CDRH)
Alan Stevens, MS, Assistant Director, Injection Devices Team Leader
Courtney Evans, MS, Reviewer Division of Drug Delivery and General Hospital Devices (DHT3C)

Division of Regulatory Operations for Neuroscience
Heather Bullock, RN, Chief, Project Management Staff
Michael Matthews, Regulatory Project Manager, Neurology 1

SPONSOR ATTENDEES

To be determined

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for May 5, 2022, from 3:00 PM to 4:00 PM Eastern Time between UCB and the Division of Neurology 1. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to

your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

UCB is developing zilucoplan (a 15-amino acid macrocyclic peptide) for the treatment of adults with generalized myasthenia gravis (gMG) who are anti-acetylcholine receptor (AchR) antibody positive. The type B, end-of-phase 2 final minutes were provided to the sponsor on March 29, 2019. Orphan drug designation was received on August 26, 2019. Type C written responses were provided on September 13, 2021, to discuss the statistical analysis plan and integrated statistical analysis plan for the overall efficacy and safety data for the phase 3 study MG0010.

The purpose of this type B, pre-NDA meeting is to discuss content and format of a new drug application (NDA) which is targeted to be submitted late August 2022.

The Agency's preliminary responses to the questions contained in the sponsor's April 1, 2022, background package follow below.

2.0 DISCUSSION

2.1. Quality/Chemistry, Manufacturing, and Controls (CMC)

Question 1: Does the Agency agree that the CMC development program is sufficient to support filing and initial registration?

FDA Response to Question 1:

The drug substance information appears reasonable to support an NDA submission. A final determination of the adequacy of the drug substance manufacturing process, control strategy, control of materials, release specification, and analytical methods will be made during the review of the NDA. The determination of the retest period will be based on the evaluation of the available stability data according to ICH Q1E.

We have the following recommendations for the NDA submission:

- Provide a side-by-side comparison of the manufacturing process changes made between [redacted] (b) (4) Provide data (batch analyses and stability data) to demonstrate the comparability of the material manufactured by both processes and at both [redacted] (b) (4) sites.

- We acknowledge the intention [redacted] (b) (4) We recommend [redacted] (b) (4)

[redacted] as regulatory starting materials to ensure enough of the manufacturing process is conducted under cGMP. The Agency evaluates regulatory starting materials based on the principles of ICH Q11 and the associated Questions and Answers Guideline. Justification of the regulatory starting materials in the NDA should address all of the considerations described in the ICH Q11 Q&A Guideline.

- Provide adequate justification for the proposed acceptance criteria for related substance impurities, including batch history, stability data, and available nonclinical studies. The acceptability of the impurity control strategy will be determined in collaboration with our Pharmacology/Toxicology review team during the review of the full NDA submission.

- Provide justification for [redacted] in the drug substance specification.

- Include a risk assessment for the formation of [redacted] impurities. Refer to the [redacted]

- Add [redacted]

- We acknowledge your proposal to provide additional drug substance stability data after the initial NDA submission. While we will accept additional data within the first 30 days of submission, we cannot guarantee review of any additional data during the review cycle due to our internal review timelines.

From a drug product perspective, the CMC development program appears adequate to support an NDA submission. The adequacy of the information to support approval is a matter for review.

2.2. Nonclinical

Question 2: Does the Agency agree that the nonclinical studies proposed for inclusion in the application, and outlined in the briefing package, are sufficient for filing and review of the application?

FDA Response to Question 2:

The nonclinical studies proposed for inclusion appear sufficient to support filing of an NDA.

[2] https://www.fda.gov/media/141720/download.

2.3. Clinical

Question 3: Does the Agency agree that the overall clinical program, notably the Phase 3 pivotal study MG0010, supports filing and review of the application?

FDA Response to Question 3:

We agree that the efficacy data from study MG0010 appears capable of supporting an NDA submission for the treatment of gMG. However, your proposed long-term safety database appears inadequate to support an NDA submission. Please see response to question 5.

Please clarify how you intend you meet the substantial evidence of effectiveness standard in your submission (i.e., based on one adequate and well-controlled large multicenter study or one adequate and well-controlled study plus confirmatory evidence).

Question 4: Does the Agency agree that the proposal to provide CIOMS forms for SAEs reported for ZLP exposed COVID-19 associated respiratory syndrome participants and blinded SAEs for ALS study participants is sufficient for filing and review of the application?

FDA Response to Question 4:

We do not agree with your proposal to submit only CIOMS forms from the COVID-19 and ALS clinical studies. In addition to the CIOMS forms, provide the following information in your submission. Provide summaries of the safety analyses from those programs. If the studies are still blinded at the time of the NDA submission, submit a list of deaths, serious adverse events (SAEs), discontinuations due to adverse events (AEs), from those studies, as well as line listings of AEs of special interest. If unblinded data is available, provide narratives for deaths, SAEs, discontinuations due to AEs, in addition to the CIOMS forms that you propose to provide.

Question 5: Does the Agency agree that the safety database, comprised of exposures in gMG, supported by data from other disease indications and healthy study participants, is sufficient to support filing and review of the application?

FDA Response to Question 5:

Your proposed safety database does not appear to be adequate to support a BLA submission. You have proposed a safety database for gMG of 84 patients exposed

to at least 12 months of dosing at the proposed dose (0.3 mg/kg/d) at the time of the initial NDA submission, with an additional 54 patients (138 total) exposed for ≥12 months in the 120-day safety update. Typically, we require a minimum of 100 patients treated for approximately 1 year at the proposed marketed dose to support a marketing application for a rare disease such as myasthenia gravis, which needs to be provided in the initial NDA submission and not as part of the 120-day safety update. Additionally, the submission of safety data for an additional 54 patients for the 120-day safety update appears to be excessive, as this is almost double the number of exposures you have proposed for the initial submission and could substantially impact the safety review. You will need to provide an adequate number of exposures to characterize the safety of your product at the time of the initial NDA submission.

Question 6: Does the Agency agree that the proposed clinical safety narrative criteria and corresponding CRFs are sufficient for filing and review of the application?

FDA Response to Question 6:

You propose narratives and CRFs for SAEs, deaths, discontinuations, pregnancy, and Neisseria infections. Your top-line safety results suggest several additional AEs of potential concern.

In addition to the narratives that you propose, provide narratives and CRFs for the following:

- hepatic events
- pancreatitis
- elevated amylase or lipase
- infections (serious and non-serious)
- injection site reactions

Also, please refer to the standard pre-NDA safety requests in Attachment 1. We note that not all requests may be applicable to your program. However, you should attempt to address the requests that are applicable.

Question 7: Does the Agency agree that the proposed BIMO datasets and listings (i.e., from MG0009 and MG0010) are sufficient for filing and review of the NDA?

FDA Response to Question 7:

Your plan to submit clinical study-level Information, data line listings by site, and summary-level clinical site datasets for Studies MG0009 and MG0010 is acceptable.

Question 8: Does the Agency agree that the datasets and SAS programs proposed for inclusion in the application are sufficient to support filing and review of the application?

FDA Response to Question 8:

From a technical perspective the datasets and SAS programs proposed for inclusion in the application are acceptable.

The proposed submission includes datasets (SDTM, ADAM) and SAS programs for the primary study MG0010 and the phase 2 study MG0009, and the final clinical study reports (CSRs) for both studies. On face, this is acceptable.

Clinical Pharmacology:

We acknowledge your plan to develop population pharmacokinetic (PopPK) model and conduct of exposure-efficacy analysis for zilucoplan. Please refer to the general expectations for submitting pharmacometrics data and models that should be considered for your NDA[3].

Question 9: Does the Agency agree with the proposed content, including the datasets, for the 120-Day Safety Update?

FDA Response to Question 9:

Please refer to our response to question 5.

Question 10: Does the Agency agree that the proposed REMS is adequate to mitigate the potential risk of meningococcal infections?

FDA Response to Question 10:

You did not submit a proposed REMS as part of your meeting package; therefore, we are unable to provide feedback on whether your proposal is acceptable. We note that while you did not report any cases of *Neisseria meningitidis* in your clinical trial, your protocol did require that patients were vaccinated against *N. meningitidis* prior to study entry with a quadrivalent meningococcal vaccine; and patients were counseled and provided a safety card with instructions regarding signs and symptoms of infection and what steps to take if these occur.

[3] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format

If you plan to submit a REMS proposal with your New Drug Application (NDA) it should include your rationale for the proposed REMS elements. We refer to the requirements of the Empaveli REMS on REMS@FDA which was recently approved to mitigate the occurrence and morbidity associated with encapsulated bacterial infections. The basic requirements of the Empaveli REMS might serve as a model for how your proposed REMS might serve as a model for how your proposed REMS could be structured.

You may also wish to refer to our draft guidance, *Format and Content of a REMS Document* in preparation of your proposal. A complete review of the proposed REMS, including whether a REMS is necessary to ensure the benefits of the drug outweigh its risks, will occur in conjunction with the full clinical review of your NDA.

2.4. Abuse Potential Assessment

Question 11: Does the Agency agree that the proposed plan regarding assessment for abuse potential and liability will support filing and review of the application?

FDA Response to Question 11:

Yes, we agree. However, if in vitro screening reveals that RA101495 or its metabolites bind to receptors associated with abuse-related effects or if adverse events in clinical studies suggest a signal of abuse potential, non-clinical abuse potential assessments and/or a human drug abuse potential study may be required.

2.5. Regulatory

Question 12: Does the Agency agree that:

a) providing financial disclosure information for MG0009 and MG0010 is sufficient for filing and review?

b) providing transfer of sponsor obligations information for MG0009 and MG0010 is sufficient for filing and review?

FDA Response to Question 12:

a). Your proposal for providing financial disclosure information for MG0009 and MG0010 is acceptable.

b). Your proposal for providing transfer of sponsor obligations information for MG0009 and MG0010 is acceptable.

Question 13: Does the Agency agree that the plan for providing foreign data supporting information, as applicable, for MG0010 and MG0011 is sufficient for filing and review?

FDA Response to Question 13:

When the foreign clinical study is not conducted under an IND, the sponsor must ensure that the study complies with the requirements in 21 CFR 312.120 in order to use the study as support for an application for marketing approval. Under 21 CFR 312.120, FDA will accept a well-designed, well-conducted, non-IND foreign study as support for an IND or application for marketing approval if the study was conducted in accordance with GCP and if FDA is able to validate the data from the study through an onsite inspection, if necessary. Refer to Guidance for Industry and FDA Staff on FDA Acceptance of Foreign Clinical Studies Not Conducted Under an IND Frequently Asked Questions.

Question 14: Regarding the required comprehensive list of clinical sites, does the Agency agree that providing a list of all clinical sites in studies MG0009, MG0010, and MG0011 will be adequate to support filing and review of the NDA?

FDA Response to Question 14:

Your proposal for the comprehensive list of clinical studies is acceptable.

Question 15: Does the Agency agree with submission of the supporting information in the NDA followed by a subsequent request for review of the proposed proprietary name?

FDA Response to Question 15:

You may submit your marketing application and request for proprietary name review concurrently. For more information on submitting requests for proprietary name review, we refer you to the following: Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names[4];

Question 16: Does the Agency agree that the proposed content of the marketing application, as described in this package, supports filing and review of an NDA for the treatment of gMG in adult patients who are AChR antibody positive?

[4] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

FDA Response to Question 16:

Please see responses to Questions 3 and 5 regarding the adequacy of the safety database to support an application. We also refer you to the additional comments from Clinical Pharmacology and Center for Devices and Radiological Health.

2.6. Additional comments

Clinical Pharmacology:

1. In your NDA, summarize bioanalytical methods for each clinical pharmacology study that involved pharmacokinetic concentration evaluation, as outlined in Bioanalytical Methods Templates, Guidance for Industry Technical Specifications Document (September 2019).[5]

2. Due to the absence of human ADME study in your drug development program, we recommend you submit all available information about metabolism of zilucoplan and route of elimination of zilucoplan and its metabolites.

3. Reference is made to clinical pharmacology summary aid (Attachment 2) to facilitate creation of summary pertaining to clinical pharmacology findings.

Center for Devices and Radiological Health:

Your proposed content appears acceptable from the device constituent perspective. Please ensure that your design verification testing of the final finished combination product includes evaluation of all device essential performance requirements (including needle safety activation and override forces, if applicable) following preconditioning (e.g. simulated shipping/transportation and drop testing per ASTM D4169-16 and ISO 11608-1). Please see additional comments below.

Device content for marketing application

Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).

[5] https://www.fda.gov/media/131425/download

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1. Device Description Documentation
   a. Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.
   b. Describe the principles of operation of your device.
   c. Describe any accessories or other devices labeled for use with your device.

2. Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the FDA Design Control Guidance for Medical Device Manufacturers, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf. We recommend that the design control information provided in your application include the following:

   a. Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)
   b. Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)
   c. Design Verification Plan/Summary Report, supporting data and traceability
   d. Design Validation Plan/Summary Report, supporting data and traceability
   e. Risk Management File

3. Essential Performance – Identify essential performance requirements (EPR) for the device.

For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.

Example auto-injectors EPRs:

- Delivered Volume Accuracy
- Activation Force
- Injection Time
- Extended Needle Length
- Audible/Visual Feedback

Please refer to the FDA Guidance titled Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products issued in June 2013 (https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm147095.pdf) for more details.

4. Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.

5. Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.

6. Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.

7. Quality System
The marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 9, 2022, 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 FDA.gov.[6]

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[7] and Pregnancy and Lactation Labeling Final Rule[8] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.

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

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

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

1. Drugs that affect the central nervous system (CNS), 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 NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of NDA submission, see the Guidance for Industry, Assessment of Abuse Potential of Drugs (https://www.fda.gov/media/116739/download). You will be required to provide a formal proposal, usually in in Section 1.11.4 of the eCTD submission as to the appropriate schedule for your proposed product. You will need to provide and discuss all relevant abuse-related data in your NDA submission to support your proposals.

2. Capture CNS-related adverse events (AEs) during clinical studies and provide

detailed narratives for AEs that are particularly suggestive of a signal of abuse potential. Provide a list of terms that will prompt these reports (including abuse potential-related AE terms such as euphoria, dissociative effects, hallucinations, psychosis, changes in mood, impaired cognition, attention, and psychomotor effects, inappropriate affect, patient dropouts, overdoses; misuse, and lost or unaccounted-for medication and unjustified dose increases). Include time of onset and duration of the event, dose of drug taken, severity and outcome in the narratives. If available, provide pharmacokinetic values for each individual subject who experienced these AEs to understand if there is a temporal correlation between drug plasma levels and AEs.

3. Monitor for possible cases of drug abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical trials and look for drug accountability discrepancies (e.g., missing medication, loss of drug, or non-compliance cases in which more investigational drug was used, as compared to expected use). Additionally:

    a. Train investigators to capture cases of abuse, misuse, addiction and to monitor for drug accountability discrepancies before starting trials. Instruct investigators to obtain more information and explanations from the subjects when there are drug accountability discrepancies.

    b. Provide data in tabular form for all reports of abuse, overuse, lost/stolen/missing or unaccounted product that occurred in clinical trials (Phase 1, 2 and 3). Include the study number and type of study, subject ID number, narratives, case description, and other available details.

    c. Provide narratives for cases where the patients drop out from studies for reasons that might be coded as “protocol violation,” “lack of efficacy,” (to eliminate the possibility of aberrant behaviors behavior in patients who drop out of the study supposedly due to lack of efficacy), “lost to follow up,” “non-compliance to study medication or procedures,” “over compliance,” or for “other.” Provide case reports separately.

    d. Report any use of the investigational formulation by individuals other than the patients (family member, health care practitioner, etc.).

    e. Report any instances of drug accountability discrepancies that may have occurred at the study site level and identify the origin of the discrepancy and individuals involved.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing

facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

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

Attachment 1.

DN1 Pre-BLA and 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.
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.

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.

Attachment 2.

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address. A special Section of the Clinical Pharmacology Summary should identify and discuss the critical findings and issues and indicate how the unresolved issues are addressed.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies*)* and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal t1/2 and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness

relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, Cmax or Cmin is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive

adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [Cmax, tmax, AUC, Cmax,ss, Cmin,ss, Cmax,ss/Cmin,ss, tmax,ss, AUC0-τ, CL/F, V/F and t1/2 (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, Cmax, Cmin, CL/F and t1/2 of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, tmax, tmax,ss, Cmax, Cmax,ss and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for ≥ 90% of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and

patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m^2) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) Cmax and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC0-τ at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether Cmax and Cmin of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, Cmax, clearance, volume of distribution and t1/2 for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both)) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, Cmax and t1/2 of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, Cmax and CL/F on Clcr for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, Cmax, tmax and t1/2 of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of Cmax, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the

subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?
Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?
Summarize the results of the in vitro studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction

study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to Km, controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the in vitro findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for Ki, IC_{50} and Vmax for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/Ki ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of

the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report t1/2, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and Cmax for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and Cmax after

single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?
Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?
Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on Cmax, AUC and Cmin of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the

fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in Cmax, AUC and Cmin than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?
Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?
Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?
If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?
List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?
Indicate whether free, bound or total (bound+unbound) concentrations of the drug of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at ≤ –20° C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

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/

MICHAEL A MATTHEWS
05/03/2022 07:43:47 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 134340

MEETING PRELIMINARY COMMENTS

Ra Pharmaceuticals, Inc.
Attention: Peter DiRoma
SVP Head of Regulatory, Quality, and Government Affairs
87 Cambridge Park Drive
Cambridge, MA 02140

Dear Mr. DiRoma:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for RA101495 (zilucoplan).

We also refer to your January 18, 2019, correspondence, received January 18, 2019, requesting an End-of-Phase 2 meeting to discuss the design of the nonclinical, clinical pharmacology, and clinical development programs to support a New Drug Application for the proposed indication of generalized myasthenia gravis.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, contact me at heather.bullock@fda.hhs.gov or (301) 796-1126.

Sincerely,

{See appended electronic signature page}

Heather M. Bullock, RN, BSN, MSHS
Commander, United States Public Health Service
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	End of Phase 2
Meeting Date and Time:	April 4, 2019; 11:00 a.m. to 12:00 p.m. EST
Meeting Location:	FDA White Oak Building 22, Room 1313 Silver Spring, MD
Application Number:	IND 134340
Product Name:	RA101495 (zilucoplan)
Proposed Indication:	generalized myasthenia gravis
Sponsor Name:	Ra Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for April 4, 2019; 11:00 a.m. to 12:00 p.m. EST at the FDA White Oak campus between Ra Pharmaceuticals, Inc. and the Division of Neurology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager [RPM]). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Ra Pharmaceuticals, Inc. (sponsor) is developing RA101495 (zilucoplan) for the treatment of generalized myasthenia gravis under IND 134340. RA101495 (zilucoplan) is a sterile, preservative-free, aqueous solution for subcutaneous (SC) injection. (b) (4)

On March 13, 2017, the sponsor submitted a PIND meeting request. The meeting was granted as written responses only on March 22, 2017; and the Division provided written responses on May 11, 2017.

On September 1, 2017, the sponsor submitted the initial IND application; and on September 29, 2017, the sponsor was notified via telephone that they may proceed with their proposed clinical investigation for the treatment of myasthenia gravis. The Study May Proceed letter with non-hold comments was sent on October 26, 2017.

On July 9, 2018, the sponsor requested a waiver of institutional review board requirements und 21 CFR Part 56 for the use of RA101495 in a foreign investigational study or all foreign investigational studies conducted under this IND. The IRB waiver was granted on August 30, 2018.

On January 18, 2019, the sponsor requested an End-of-Phase 2 meeting to discuss the design of the nonclinical, clinical pharmacology, and clinical development programs to support a New Drug Application for the proposed indication of generalized myasthenia gravis. The meeting request was granted on January 23, 2019.

2.0 DISCUSSION

Question 1:

Is the design of the proposed Phase 3 study (Protocol RA101495-02.301) of zilucoplan in patients with gMG suitable to support NDA approval of zilucoplan for treatment of gMG? We ask that the FDA comment if the following design elements of the proposed study protocol are acceptable in regards to: a) use of the 0.3 mg/kg/day dose, b) eligibility criteria, c) suitability of change from baseline in MG-ADL score as the primary study endpoint, d) proposed secondary clinical endpoints, e) acceptability of a 12-week study duration for the placebo-controlled period, and f) the adequacy of the proposed study sample size, significance level (2-sided p-value <0.05), and statistical analysis plan summary (SAP) to assess the safety and efficacy of zilucoplan in this patient population.

FDA Response to Question 1:

a) The justification for the proposed once-daily dosing regimen is not clear. Please provide information on the duration of the pharmacodynamic (PD) effect (i.e., complement C5 concentration time-course of inhibition of the cleavage to C5a and C5b) and on whether there is any dose-, exposure-PD relationship for zilucoplan. Based on the results from the single- and multiple-ascending dose PK studies, the elimination half-life of zilucoplan is about 7 days. Therefore, it appears that a less frequent dosing regimen than the currently proposed daily regimen may be more appropriate for the Phase 3 study.

   We recommend evaluating more than one dose in the Phase 3 trial, in order to further assess dose-response.

b) Subjects with thymectomy within 6 months of the study are excluded. We recommend that the study exclude all thymectomy patients because gradual improvement could be due to the thymectomy and not the drug.

   Based on the information you provided, we recommend that you consider inclusion of patients with renal impairment in your Phase 3 study.

   If you think patients with mild and moderate hepatic impairment do not require any dose adjustment (based on your current proposed plan to assess the impact of hepatic impairment only in severe hepatic impairment), you may include such patients in your Phase 3 study.

   The study design should also standardize the concomitant therapies given during the study and stratify randomization based on them, as imbalances in background medications could affect the interpretability of the study results. Concomitant therapies should also be kept stable throughout the trial unless a safety reason requires otherwise.

c) We agree with change from baseline in MG-ADL score as the primary study endpoint.

d) You propose the following secondary endpoints: QMG, MG – Quality of Life 15 (revised) (MG-QOL15r), MG Composite (MGC), the proportion of subjects who receive rescue therapy with IVIG or plasma exchange (PLEX), and the proportion of subjects who reach MSE (i.e., an MG-ADL score of 0 or 1). These proposed secondary endpoints are reasonable.

e) A 12-week placebo-controlled efficacy study duration would be acceptable. See the response to Question 2 regarding long-term safety assessment.

f) Your statistical analysis plan (SAP) summary appears reasonable. You need to submit the final SAP with full details well in advance of data unblinding for our complete review.

Question 2:

Is the proposed cumulative clinical safety database regarding the overall number of patients and duration of exposures acceptable to support the NDA for gMG?

FDA Response to Question 2:

Your proposal for a safety database of 130 subjects in Protocol RA101495-02.301 with up to 1.8 years of exposure, including a planned long-term open label extension, appears reasonable. You should specify how many additional subjects from prior studies will also have exposure data at the same dose(s) as your planned Phase 3 trial.

Question 3:

Is the design of the proposed anti-drug antibody (ADA) Binding Assay for zilucoplan which will be used to assess presence of ADA's in Phase 3 clinical studies acceptable?

FDA Response to Question 3:

FDA does not review assays within the context of meetings as the timeframe is too short. A brief assessment of the screening and confirmatory assays indicates that they may be suitable for testing samples from pivotal trials; however, no determination can be made until the data is examined.

We have the following general comments on the immunogenicity assessment plan:

- You should characterize the development of anti-drug antibodies (ADA) to your drug, including rate, titer, neutralizing capacity, duration, and effect on the pharmacokinetics, pharmacodynamics, efficacy and safety of your drug.
- You should include a plan to test the impact of increased lipidemia on assay sensitivity.
- There is no plan to discriminate whether the product induces anti-PEG antibodies. An assay to assess these antibodies needs to be implemented.

- Since you are using biotin-drug extraction and acid dissociation in your assay, the dilutions corresponding to these processes should be taken into consideration when calculating Ab titers.
- You should also clearly describe the sampling times in the Phase 3 study protocol in your immunogenicity assessment plan. The briefing package states that you are planning to take samples to assess immunogenicity at Days 0, 8, 29, 84 and 168 in your Phase 3 study. We recommend that you add an additional timepoint 4 weeks after the last dose or explain why this should not be added.
- We remind you that until your assays have been formally reviewed, you should retain sufficient samples to be able to re-test if necessary.
- Please refer to the following guidance for more information:
    - Assay Development for Immunogenicity Testing of Therapeutic Proteins
    - Immunogenicity Assessment for Therapeutic Protein Products

Question 4a:

Does the FDA agree that a drug-drug interaction (DDI) study is not necessary to evaluate the potential for DDI with zilucoplan as an inhibitor or inducer of CYP isoforms?

FDA Response to Question 4a:

Your proposal appears acceptable, on face.

We have the following recommendations for *in vitro* DDI assessments:

- You should evaluate the potential for DDI with zilucoplan as a victim (substrate) for transporters.
- You should also evaluate the DDI liability with the major metabolites of zilucoplan as perpetrator and victim for various CYP isoforms and transporters.
- Please refer to the following guidance for more information on *in vitro* DDI assessments: https://www.fda.gov/downloads/Drugs/Guidances/UCM581965.pdf

Question 4b:

Does the FDA agree that a DDI study is not necessary to evaluate the potential for DDI due to the interaction of zilucoplan with transporters, either as a substrate or an inhibitor?

FDA Response to Question 4b:

Your proposal appears acceptable, on face. Please see our response for Question 4a.

Question 4c:

Does the FDA agree that DDI studies are not necessary or feasible to evaluate the potential for DDI due to the effect of CYP4F2 inhibitors or inducers on zilucoplan?

FDA Response to Question 4c:

Your proposal appears acceptable, on face.

Question 4d:

Does the FDA agree with the Sponsor's position that a dedicated radiolabeled human absorption, distribution, metabolism and excretion (ADME) study is not warranted given the unexpectedly long label recovery kinetics in rats, and with the agreement that the Sponsor will conduct a hepatic impairment study prior to registration?

FDA Response to Question 4d:

Your proposal appears acceptable, on face. However, it is necessary to identify and confirm all the major metabolites in humans (>10% of total circulating drug related material). Additionally, the safety of all major human metabolites will need to be demonstrated in the appropriate nonclinical studies (cf. ICH M3(R2), January 2010; ICH M3(R2) Questions and Answers, February 2013).

Question 5:

Does the FDA agree that the proposed pre-clinical program is suitable to support the NDA for gMG?

FDA Response to Question 5:

Based on the information provided in the briefing document, it appears the proposed nonclinical program would be sufficient to support an NDA for zilucoplan for the treatment of gMG. However, you should submit justification, with all supportive data, for your plan not to assess the carcinogenic potential of zilucoplan.

Question 6:

[redacted] (b) (4) the FDA DMEPA recommended we submit our plans for a Human Factors (HF) assessment program. We would like to have the FDA comment on our timeline and plan for discussions with the FDA to reach agreement on that plan as well as our proposal to conduct HF testing in the gMG population.

FDA Response to Question 6:

We understand that you are planning to use RA101495 (zilucoplan) to treat generalized myasthenia gravis (gMG). We note that you intend to complete formative human factors (HF) testing and an HF validation study. However, you have not submitted a comprehensive risk analysis.

We recommend you conduct a comprehensive use-related risk analysis if you have not already completed one. The comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

The risk analysis can be used to inform the design of a human factors validation study protocol for your product. We note that you intend to request a Type C meeting to discuss the HF validation study protocol design prior to initiation of the study. Please note that submitting your study protocol as part of a meeting package is not the best mechanism to obtain comprehensive feedback from the Agency. We ask that the study protocol be submitted as a separate submission to the IND. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

[redacted] (b) (4)

(b) (4)

Please refer to our draft guidance titled "Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications" for the content of a human factors validation study protocol submission. The guidance is available online at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:
http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

3.0 ADDITIONAL INFORMATION

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR 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.

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.

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/

HEATHER M BULLOCK
03/29/2019 10:20:10 AM