

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761286Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 132407

MEETING PRELIMINARY COMMENTS

UCB, Inc.
Attention: Marian Saxon, PhD, MS
US Regulatory Lead
4000 Paramount Parkway, Suite 200
Morrisville, NC 27560

Dear Dr. Saxon:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for UCB7665.

We also refer to your May 23, 2022, correspondence, received May 23, 2022, requesting a meeting to discuss the proposed content and format of a planned BLA submission for UCB7665.

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 FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, contact me at Anhthu.Nguyen@fda.hhs.gov or at (240) 402-4460.

Sincerely,

{See appended electronic signature page}

Annie Nguyen, RPh
Senior Regulatory Project Manager
Neurology Group 1
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

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ENCLOSURE:

Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-BLA

Teleconference Date and Time: July 21, 2022, 11:00 am – 12:00 pm

Application Number: IND 132407
Product Name: UCB7665
Proposed Indication: Treatment of myasthenia gravis in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle specific tyrosine kinase (MuSK) antibody positive.
Sponsor Name: UCB, Inc.
Regulatory Pathway: 351(a) of the Public Health Service Act

FDA ATTENDEES (tentative)

Office of Neuroscience
Billy Dunn, MD, Director

Division of Neurology 1
Teresa Buracchio, MD, Director
Laura Jawidzik, MD, Deputy Director (Acting)
Emily Freilich, MD, Associate Director (Acting)
Ami Mankodi, MD, Clinical Reviewer

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

Office of Clinical Pharmacology
Bilal AbuAsal, PhD, Clinical Pharmacology Team Leader
Min Li, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD, Pharmacometrics Team Leader

Office of Biostatistics
Kun Jin, PhD, Team Leader, Division of Biometrics I
Jinnan Liu, PhD, Statistical Reviewer

Office of Biotechnology Products
Ashutosh Rao, PhD, Chief, Laboratory of Applied Biochemistry, Division of Biotechnology Review and Research III (DBRR III)
Thomas Biel, PhD, Quality/Product Quality Reviewer

Controlled Substances Staff

Neil Varshneya, PhD, CSS Reviewer

Office of Scientific Investigations

Cara Alfaro, PharmD, BCPP, Clinical Analyst

Division of Regulatory Operations for Neuroscience

Annie Nguyen, RPh, Senior Regulatory Project Manager

Roshell Weatherless-Strobes, PharmD, Regulatory Project Manager

SPONSOR ATTENDEES

TBD

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference scheduled for July 21, 2022, 11:00 am – 12:00 pm 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, Inc. is developing UCB7665 (rozanolixizumab) for treatment of patients with generalized myasthenia gravis (gMG) who are AChR or MuSK antibody positive. The product is a subcutaneous IgG4 humanized monoclonal antibody directed against the neonatal Fc receptor (FcRn) for IgG antibodies. UCB7665 is given once weekly via subcutaneous infusion. The development program for UCB7665 consists of a double-blind, placebo-controlled Phase 3 study which evaluated the use of UCB7665 once weekly for 6 weeks and an open-label extension study which evaluated the safety of UCB7665 given in cycles.

The Agency granted orphan drug designation for the use of UCB7665 for the treatment of gMG on February 1, 2019.

The sponsor has requested this Type B Pre-NDA meeting to discuss the content and format of a planned BLA submission for UCB7665.

The Agency's preliminary responses to the questions presented in the sponsor's background package dated June 17, 2022, are provided below.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1:

The Quality development program is summarized in Rozanolixizumab Overview of Product Development, (Appendix 1) Section 5 with extended details available in Module 3 of IND 132407.

Does the Agency agree that the CMC development program appears sufficient to support initial registration?

FDA Response to Question 1:

You provided high level information on your quality development program in the meeting package and requested feedback on its adequacy for supporting initial registration. The adequacy of the CMC development program to support registration is a review issue for the BLA. As noted in the FDA Guidance for Industry: *Formal Meetings Between the FDA and Sponsors or Applicants*¹, the content of a meeting package should provide summary information relevant to the product and supplementary information needed to develop responses to issues raised and should be organized in a question-by-question manner. However, the CMC question in your meeting package is too broad, and it is unclear whether you have questions about specific issues regarding your CMC development program. We recommend you request a CMC-only Type B pre-BLA meeting to discuss the specific aspects of your CMC program for the Agency to provide more targeted feedback. Please note that protocols, full study reports, or detailed data generally are not appropriate for meeting packages. In addition, we recommend that you consider existing FDA and ICH guidance documents related to product development and focus your questions on critical issues that, for example, may deviate from current guidance or practices or need additional discussion with the Agency. In addition, we recommend that you review the CMC Microbiology comments that were provided in a Type C meeting dated July 21, 2021.

2.2. Nonclinical

Question 2:

¹ <https://www.fda.gov/media/109951/download>

The comprehensive nonclinical program that has been conducted with rozanolixizumab is summarized in Appendix 1, Section 6 with extended details available in Section 4 of the Investigator's Brochure. Tabulated overviews of nonclinical studies conducted with rozanolixizumab are provided in Appendix 1, Section 6, Table 6-1, Table 6-2, and Table 6-3. Table of Contents for Module 2 and Module 4 of the BLA are provided in Appendix 4.

Does the Agency agree that the nonclinical program proposed for inclusion in the application and outlined in the briefing package appears sufficient for filing and review of the BLA?

FDA Response to Question 2:

The nonclinical studies of UCB7665, as described in the briefing document, appear sufficient to support filing of the BLA for treatment of adults with gMG. The adequacy of the studies will be a matter of review.

2.3. Clinical

Question 3:

Does the Agency concur that the overall clinical program, including the Phase 3 pivotal study MG0003, supports filing and review of the BLA?

FDA Response to Question 3:

The clinical program, as outlined in the Briefing Package, appears capable of supporting a BLA submission for the treatment of generalized myasthenia gravis (gMG). The adequacy of the data to support your proposed indication will be a matter of review.

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

Also, provide subgroup analyses of the AChR-ab positive population and the MuSK-ab positive population in your submission. Conduct the primary and secondary analyses (i.e., change from baseline on the MG-ADL and QMG) on these two subgroups and include the analyses in your BLA submission.

Question 4:

Does the Agency agree that the extent of long-term safety data supports submission of the BLA, in particular the number of study participants treated for ≥ 12 months who have received ≥ 6 cycles, the maximum number of cycles possible per year?

FDA Response to Question 4:

Your proposed safety database appears capable of supporting a BLA submission for the treatment of gMG. The adequacy of the drug exposure in terms of the number of infusions in a treatment cycle, the duration of a treatment cycle, the number of treatment cycles per year, and the time to initiate a repeat treatment cycle from the start of the previous treatment cycle will be a matter of review. Your submission should include information on the duration of treatment cycles in Pool S1. Populate the following table shell in your BLA submission:

Table 1. Duration of Cycles in Pool S1

Cycle X	Patients with at Least X Cycles		Cohort of Patients With a Maximum of X Cycles			
	N (%)	Individual Cycle Duration (days) ^a	N (%)	Duration of Follow up (Days) ^b		Average Cycle Duration (Days) Based on Median Follow-up ^c
		Median (Min/Max)		Mean (SD)	Median ^c (Min, Max)	
1						
2						
3						
4						
5						
6						
7						
8						
etc						

^aThe median number of days from the first infusion of a cycle to the first infusion of the next cycle or the data cutoff date, whichever comes first.

^bThe number of days from the first infusion to the end of the observation period (i.e., the end of the study or the data cutoff date, which comes first).

^cThe average cycle duration is calculated as the median duration of the follow-up divided by the number of cycles.

Include in your submission an evaluation of the key safety review issues for the drug class such as dyslipidemia and immunizations; in particular, include an evaluation of the timing of vaccine administration, and the safety and effectiveness of immunization with live and live-attenuated vaccines in your patient population.

We also refer you to Appendix B for a list of preferred safety analyses that should be included in your submission. We note that not all of the proposed analyses may be

appropriate for the study population; however, you should include the analyses that are appropriate to support your application.

Question 5:

Does the Agency agree that the proposed BIMO listings and data sets (ie, from MG0003) are sufficient for filing and review of the BLA?

FDA Response to Question 5:

Yes, we agree. For the efficacy endpoints, include individual item (as applicable) and total scores for all timepoints for each of the endpoints listed (not just the change from baseline to Day 43).

Question 6:

Does the Agency agree that rozanolixizumab lacks abuse potential and thus a full assessment of its abuse potential is not warranted, and that the Sponsor's plans as proposed herein will support filing and review of the BLA?

FDA Response to Question 6:

We agree that UCB7655 appears to lack abuse potential; therefore, additional animal and human studies of abuse potential are not warranted at this time. However, for all clinical studies you conduct with UCB7665, we recommend continued monitoring of adverse events (AEs) that may be indicative of CNS activity, e.g., AEs suggestive of euphoria or other abuse potential-associated AEs. See the guidance for industry *Assessment of Abuse Potential of Drugs*, section V.B., for additional details.²

Question 7:

Based on the described implementation of FDA's MIDD advice, does FDA agree in principle with UCB's intention to propose fixed doses of [REDACTED] (b) (4) and 420mg for patients weighing <50kg, acknowledging that the adequacy of the clinical efficacy and safety results and model-informed analyses for supporting a two-fixed dose regimen will be a matter of review?

FDA Response to Question 7:

Your general strategy as well as the plan for PK/PD and dose/exposure-response analyses to support the proposed two-fixed dose regimen appears to be acceptable. We recommend you also analyze the anti-AChR and anti-MuSK IgG data in addition to total

² <https://www.fda.gov/media/116739/download>

IgG for the PK/PD modeling and simulation to demonstrate clinical efficacy of the two-fixed dose regimen.

Question 8:

The proposed content for Modules 1, 2, 3, 4, and 5 are provided in the BLA Table of Contents (Appendix 4). Note: Only CTD sections that are planned to have documents are included in the Table of Contents.

Does the Agency agree:

- a. with the proposed overall content and format of the BLA as described in this package?
- b. that the proposed content of the marketing application, as described in this package, supports filing and review of a BLA for the treatment of generalized myasthenia gravis (gMG) in adult patients who are anti-acetylcholine receptor (AChR) or anti-muscle-specific tyrosine kinase (MuSK) antibody positive?

FDA Response to Question 8a:

We have the following technical comments related to the format of your proposed BLA:

Module 2

Module 2

2.3.S Drug Substance – One or multiple documents can be submitted at this level. Documents may NOT be submitted at the following sub-levels

- 2.3.S.1 General Information
- 2.3.S.2 Manufacture
- 2.3.S.3 Characterization
- 2.3.S.4 Control of Drug Substance
- 2.3.S.5 Reference Standards or Materials
- 2.3.S.6 Container Closure System
- 2.3.S.7 Stability

2.3.P Drug Product – One or multiple documents can be submitted at this level. Documents may NOT be submitted at the following sub-levels

- 2.3.P.1 Description and Composition of Drug Product
- 2.3.P.2 Pharmaceutical Development
- 2.3.P.3 Manufacture
- 2.3.P.4 Control of Excipients
- 2.3.P.5 Control of Drug Product
- 2.3.P.6 Reference Standards
- 2.3.P.7 Container Closure System
- 2.3.P.8 Stability

Module 3

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3.2.P.2 Pharmaceutical Development – One or multiple documents can be submitted at this level. Documents may NOT be submitted at the following sub-levels

- 3.2.P.2.1 Components of The Drug Product
- 3.2.P.2.2 Drug Product
- 3.2.P.2.3 Manufacturing Process Development
- 3.2.P.2.4 Container Closure System
- 3.2.P.2.5 Microbiological Attributes
- 3.2.P.2.6 Compatibility

Module 4

4.2.3.7 Other toxicity studies - Documents rolled up to this level are not considered appropriate. One or multiple documents can be submitted in one or more of the following sub-levels.

- 4.2.3.7.1 Antigenicity
- 4.2.3.7.2 Immunotoxicity
- 4.2.3.7.3 Mechanistic studies
- 4.2.3.7.4 Dependence
- 4.2.3.7.5 Metabolites
- 4.2.3.7.6 Impurities
- 4.2.3.7.7 Other

Refer to the [Comprehensive Table of Contents Headings and Hierarchy](#) and the [M4 Organization of the Common Technical Document for the Registration of Pharmaceuticals for Human Use Guidance for Industry](#) for more details on each section referred to in the FDA Response.

From a technical perspective (and not content related), all other sections proposed in the eCTD-BLA Table of Contents are acceptable.

FDA Response to Question 8b:

Whether the application is fileable will be a matter of review. See also the response to Question 1 regarding the CMC aspects of your application and additional clinical pharmacology comments below.

Question 9:

For the purposes of providing Investigator financial disclosure information, UCB proposes that the three Phase 3 studies (MG0003, MG0004, and MG0007) be considered the "covered clinical studies" for the BLA per 21 CFR 54.2(e).

UCB proposes to provide transfer of sponsor obligation information in the BLA for the proposed "covered clinical studies" (ie, MG0003, MG0004, MG0007).

Does the Agency agree that:

- a. providing financial disclosure information for MG0003, MG0004, and MG0007 is sufficient for filing and review?
- b. providing transfer of sponsor obligation information for MG0003, MG0004, and MG0007 is sufficient for filing and review?
- c. providing the list of clinical sites for MG0003, MG0004, and MG0007 is sufficient for filing and review?

FDA Response to Question 9:

We agree.

Question 10:

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

FDA Response to Question 10:

Your plan is acceptable; however, 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*.³

Should you choose to submit a proprietary name for consideration that is different than the one found previously conditionally acceptable (i.e., (b) (4)), please submit a request to withdraw the previous name.

We note that you included proposed suffixes for our consideration as part of your meeting package; however, submission of suffixes as part of a meeting package is not the appropriate mechanism to request the Agency's review. If you choose to submit suffixes for our review, please submit them to the IND as a General Correspondence instead. Also, please note that FDA reviews any submitted proposed suffixes as resources permit if submitted during the IND phase, or in accordance with any application milestones as part of BLA review if you submit them with your BLA.

³ <https://www.fda.gov/media/72144/download>

Additional Clinical Pharmacology Comments:

- As UCB7665 is an FcRn inhibitor, you should provide a plan to mitigate DDIs with other concomitant monoclonal antibody drugs because FcRn may involve the disposition of those drugs.
- Please provide a “review aid” for Clinical Pharmacology in the BLA submission. Please refer to the attached template in Appendix A.

3.0 ADDITIONAL INFORMATION**DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION**

As stated in our June 2, 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. 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.⁴

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

⁴ <https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>

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 Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ websites, which include:

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

Pursuant to the PLLR, you should include the following information with your application

⁵ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁶ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial

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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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.⁷

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.⁸

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

⁷ <http://www.fda.gov/ectd>

⁸ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

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 356h⁹ 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

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>

for commercial production and those used for product and manufacturing process development.

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

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 tretinoin, 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

¹¹ <https://www.fda.gov/media/85061/download>

particular clinical protocol should prospectively discuss this omission with the Division of Neurology 1.

APPENDIX A

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 t_{1/2} 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, C_{max} or C_{min} 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, C_{max} or C_{min} 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) C_{max} 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 [C_{max}, t_{max}, AUC, C_{max,ss}, C_{min,ss}, C_{max,ss}/C_{min,ss}, t_{max,ss}, AUC_{0-τ},

CL/F, V/F and $t_{1/2}$ (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, C_{max} , C_{min} , CL/F and $t_{1/2}$ 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, t_{max} , $t_{max,ss}$, C_{max} , $C_{max,ss}$ 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 $\geq 90\%$ 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/1.73m²) 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) C_{max} 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 AUC_{0-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 C_{max} and C_{min} 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, C_{max}, C_{min}) 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, C_{max}, clearance, volume of distribution and t_{1/2} 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 Cockcroft-Gaul- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} 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, C_{max} and CL/F on Cl_{cr} 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, C_{max}, t_{max} and t_{1/2} 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 C_{max}, 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 K_m , 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 K_i , IC_{50} and V_{max} 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 $[I]/K_i$ 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 $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} 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 $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} 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 C_{max} 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 C_{max}, AUC and C_{min} 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 C_{max}, AUC and C_{min} 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 $\leq -20^{\circ}\text{C}$.

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)?

Appendix B

General Clinical Safety Requests

General Submission Contents:

1. 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.
2. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
3. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
4. 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.
5. Include active hyperlinks from the lists of references to the referenced article.
6. 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](#)
7. Provide an assessment of safety as per the [FDA Guidance for Industry: Premarketing Risk Assessment](#)
8. 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.
9. 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)
10. 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](#)

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed “MedDRA Term Selection: Points to Consider” document accessible at [MedDRA](#)

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www.fda.gov

2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed “drug-related.”
5. Provide a table of treatment-emergent adverse events reported in $\geq 2\%$ of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies including the reasons for termination if this occurred. 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, all discontinuations, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
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 case report form and/or narrative.
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 lab 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 both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
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):
 - Patient age and gender
 - Adverse event onset and stop dates (presented as relative Study Day number)

- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- 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 data 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 $\geq 7\%$ from baseline and increase of $\geq 7\%$ 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. 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:
 - Age
 - Sex

- Dates of screening, randomization and starting therapy
- Whether the patient completed or did not complete the study, with dates and reason for withdrawal
- 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)
- Prior medications and concomitant medications with dates of start and end
- Vital signs and laboratories, sorted by date, with reference ranges *
- Full reports for radiologic studies, ECG, MRI, pathology results, and special studies with dates and reference ranges *
- Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)

* 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.

For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted to the IND.

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

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

/s/

ANHTU NGUYEN
07/19/2022 08:58:51 AM



IND 132407

MEETING MINUTES

UCB, Inc.
Attention: Justin Franklin, PharmD
Associate Director, Regulatory Affairs
1950 Lake Park Drive, Building 2100
Smyrna, GA 30080

Dear Dr. Franklin:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rozanolixizumab (UCB7665).

We also refer to the meeting between representatives of your firm and the FDA on May 22, 2019. The purpose of the meeting was to discuss the design and adequacy of your proposed Phase 3 study, MG0003.

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

If you have any questions, contact Annie Nguyen, Regulatory Project Manager, by email at Anhtu.Nguyen@fda.hhs.gov or by phone at (240) 402-4460.

Sincerely,

{See appended electronic signature page}

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

Enclosure:

- Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: May 22, 2019, 1:00 p.m. – 2:00 p.m., ET
Meeting Location: White Oak Building 22, Room 1309

Application Number: IND 132407
Product Name: Rozanolixizumab (UCB 7665)
Proposed Indication: [REDACTED] (b) (4)

Sponsor Name: UCB, Inc.

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Nick Kozauer, MD, Associate Director
Teresa Buracchio, MD, Clinical Team Leader
Christopher Breder, MD, PhD, Clinical Reviewer
Michelle Campbell, PhD, Senior Clinical Analyst
Annie Nguyen, RPh, Regulatory Project Manager

Office of Clinical Pharmacology

Sreedharan Sabarinath, PhD, Clinical Pharmacology Team Leader
Priya Brunsdon, PharmD, Clinical Pharmacology Reviewer

Office of Biostatistics

Kun Jin, PhD, Team Leader, Division of Biometrics I
Ling Xiang, PhD, Statistical Reviewer

Office of Biotechnology Products

Thomas Biel, PhD, Quality/Product Quality Reviewer
Ashutosh Rao, PhD, Chief, Laboratory of Applied Biochemistry, Division of
Biotechnology Review and Research III (DBRR III)

Clinical Outcome Assessments (COA) Staff

Yasmin Choudhry, MD, COA Reviewer
Sarrit Kovacs, PhD, COA Team Leader
Wen-Hung Chen, PhD, COA Team Leader

SPONSOR ATTENDEES

UCB, Inc.

Justin Franklin, PharmD, Lead Regulatory Scientist

Jacqui Morris, Global Regulatory Lead

Andrea Kiessling, PhD, MS, Director Nonclinical Safety

Fabian Somers, PhD, MBA, Senior Clinical Program Director

Ali Bozorg, MD, Program Physician

Peter Kiessling, PhD, Clinical Lead, Platform Development

Grant Langdon, PhD, Clinical Pharmacology Lead

Mark Morris, MSc, Project Lead Statistician

Ann-Christin Mork, Head Patient Centered Outcomes Research

Neil Davie, Platform Development Leader

Juan Ke, MD, Clinical Safety Lead

1.0 BACKGROUND

UCB, Inc. is developing rozanolixizumab (UCB7665)

(b) (4)

The sponsor states that rozanolixizumab is a recombinant, humanized, anti-FcRn IgG4P monoclonal antibody (mAb). The Agency granted orphan drug designation for rozanolixizumab for the treatment of myasthenia gravis on February 1, 2019.

The Division issued written responses to a pre-IND meeting request on December 9, 2016. IND 132407 was submitted on February 28, 2017. On March 29, 2017, the sponsor was informed that they may proceed with their clinical investigation. The sponsor states that a Phase 2a clinical study (MG0002) has been completed.

The sponsor has requested this Type B end-of-phase 2 meeting to seek Agency feedback on the design and adequacy of the proposed Phase 3 study, MG0003.

FDA sent Preliminary Comments to UCB on May 16, 2019.

2. DISCUSSION

2.1. Nonclinical

Question 1:

UCB has conducted a comprehensive nonclinical program of pharmacological, PK/PD, and toxicity studies for Rozimab. In addition, UCB has initiated an ePPND study in the Cynomolgus monkey that will be conducted in parallel to the proposed Phase 3

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development and UCB has completed a carcinogenicity assessment for the potential impact of Rozimab on cancer risk.

Does the agency agree that:

- a. The current nonclinical development program including submission of the carcinogenicity assessment document (waiver request), provides a sufficient assessment of Rozimab to support initiation of the proposed Phase 3 program in gMG?
- b. The current nonclinical development program appears sufficient to support the filing and review of a BLA for Rozimab in the proposed indication in gMG?

FDA Response to Question 1:

The completed nonclinical studies appear to be sufficient to support initiation of Phase 3 studies. The carcinogenicity study waiver request is under review. If a carcinogenicity assessment is determined to be unnecessary or infeasible, the completed and proposed nonclinical studies would be sufficient to support filing of a BLA for Rozimab. The adequacy of the nonclinical data will be a matter of review.

Discussion:

No discussion.

2.2. Clinical

Question 2:

UCB considers that MG0002 established supportive evidence of efficacy with Rozimab for the treatment of gMG. UCB intends to confirm the efficacy of Rozimab in patients with gMG with another randomized placebo-controlled study (MG0003), which will be followed by an OLE study MG0004. MG0003 is a randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of Rozimab in the treatment of subjects with gMG. Six weekly sc doses of Rozimab will be administered in subjects who experience moderate to severe symptoms, and are considered for treatment with intravenous infusion of IVIG or PEX.

Does the Agency agree the overall design of study MG0003 is adequate including the following:

- a. the assessment of 2 dose levels of Rozimab
- b. the proposed patient population and key inclusion/exclusion criteria

- c. the study duration (Treatment and Observation Periods)
- d. the acceptability of the adaptive design in terms of proposed sample size, sample size reassessment and futility analysis
- e. the primary and secondary efficacy variables and timing of assessments, including the proposed PROs
- f. the planned analyses of the primary and secondary efficacy endpoints, plans for sensitivity and supplementary analyses, and plans for handling missing data
- g. the proposed safety monitoring plan

FDA Response to Question 2:

- a.) The proposed 7 mg/kg dose appears reasonable; however, you have not provided sufficient information to support the selection of the 10 mg/kg dose level. Preliminary pharmacodynamic results from study TP0001 do not suggest that increase in exposure beyond 7 mg/kg results in a corresponding total IgG reduction or clinical benefit. Additionally, less frequent dosing intervals may be explored, based on the sustained reduction in total IgG observed after single-dose administration.
- b.) In general, the proposed study population appears acceptable. Based on the information you presented, the impact of impairment in organ function on the exposure to rozanolixizumab appears low. Therefore, you can include subjects with renal/hepatic function impairment in the proposed study.
- c.) The study duration appears reasonable.
- d.) In general, the study design appears acceptable. Please clarify whether patients who have not completed the double-blind treatment period will be unblinded and included in the interim analysis.
- e.) The proposed primary and secondary endpoints are acceptable. See the response to Question 4 regarding the proposed PRO.
- f.) In general, using a combination test for the proposed adaptive design is acceptable. However, you need to provide details on the testing procedure, the method for estimating the treatment effect and confidence interval, the use of other covariance structures if convergence is an issue, and the multiplicity adjustment for the secondary endpoints. Sensitivity analysis based on the assumption of missing not at random (MNAR) should be proposed. Please be reminded that citing references alone is not sufficient. The statistical analysis plan with key SAS codes and IDMC charter should be submitted well in advance of the interim analysis for our complete review.
- g.) The safety monitoring plan appears adequate.

Also, see response to Question 5 regarding the ability of Study MG002 to provide support for a marketing application.

Discussion:

Question 2a: The Agency encouraged the Sponsor to fully utilize the Phase 2 results from the Placebo-4 mg/kg cohort to assess dose-response and for dose selection. The Sponsor stated that the Phase 2 data was used for dose selection and that increased benefit, as measured by QMG, was observed with the higher dose. Additionally, the Sponsor stated that doses beyond 10 mg/kg did not result in greater reduction of IgG, based on results of other clinical studies. The Agency recommended that alternate dosing regimens, including an extended dosing interval, be explored prior to initiation of the Phase 3 study. The Sponsor indicated that other dosing intervals were explored through PK/PD simulations and were determined to be not optimal.

Question 2b: No discussion.

Question 2c: No discussion.

Question 2d: The sponsor clarified that patients who have not completed the double-blind treatment period will not be included in the interim analysis. The Agency agreed.

Question 2e: No discussion

Question 2f: No discussion

Question 2g: No discussion

Question 3:

Patients completing MG0003 will be given the opportunity to enter a randomized, long-term (52 week) OLE study (MG0004). The primary objective in this study will be to evaluate the long-term safety and tolerability of Rozimab in patients with gMG who have completed the Observation Period of MG0003 or who needed rescue medication during the Observation Period of MG0003. Study MG0004 is seen as supportive for the proposed indication (b) (4). MG0004 intends to evaluate the same 2 dose equivalents used in MG0003. Secondary objectives of the study will be to evaluate the longer-term effects of Rozimab on MGADL, MG-Composite, QMG scores, and disease-specific PROs. Data from MG0004 may be beneficial to prescribing physicians by providing information on continued treatment following an initial 6-week treatment course (in MG0003) with Rozimab.

Does the Agency agree with MG0004 study design including the following?

- a. the proposed objectives and study duration
- b. the randomization and dosing schedule

- c. the proposed safety and efficacy variables and timing of assessments, including the proposed PROs
- d. the proposed safety monitoring plan

FDA Response to Question 3:

The open-label extension study, MG0004, appears reasonable, based on the information provided.

Discussion:

No discussion.

Question 4:

UCB considers that its novel 'Myasthenia Gravis Symptoms Patient Reported Outcome' instrument offers the opportunity of a well-defined and reliable instrument that will adequately complement the existing MG outcomes measures and generate interpretable PRO data for the demonstration of treatment benefit in MG patients. Information on UCB MG PRO development was initially provided in the pre-IND meeting package. Further to FDA's pre-IND Written Responses, patient input informed UCB's decisions on item selection (and reduction) and response options. As a result, the two exploratory PRO instruments have been merged into a single, refined and shorter PRO instrument which UCB intends to utilize in the Phase 3 program. UCB acknowledges additional information including plans for validation and analyses will need to be provided to the Agency (b) (4).

(b) (4)
(b) (4), based on the comprehensive research conducted by UCB to date, does the agency agree with the following:

- a. That fatigability, physical fatigue, limb and axial weakness, and bulbar function – identified using literature review, expert interviews, and patient interviews – are appropriate concepts of interest for the demonstration of treatment benefit in gMG patients?
- b. The plan for the inclusion of the final set of items of the 'Myasthenia Gravis Symptoms PRO' instrument are appropriate to assess the concepts of fatigability, physical fatigue, limb and axial weakness, and bulbar function in patients with gMG?

FDA Response to Question 4a:

We acknowledge the use of exit interview data from interviews conducted with 36 patients with myasthenia gravis (MG) at the end of your phase 2b study (MG0002) to gain additional information on the relevant and important concepts for MG. Since the patient transcripts from the exit interviews were not included in the submission, we cannot fully comment on the appropriateness of the concepts that are included in the final version of the MG Symptoms PRO. Submit all interviewer scripts, and patient interview transcripts for Agency review and comment.

Exit interviews provide an opportunity to obtain patients' input on what they consider to be a meaningful score change. Also see Comment #1 under Additional comments.

While the concepts of fatigability, physical fatigue, limb and axial weakness, and bulbar function included in the MG Symptoms PRO appear to be relevant and important to patients, some content validity issues at the item level still remain. See FDA Response to Question 4b.

We do not agree with the approach that was used to conduct the Rasch analysis:

- Rasch analysis generally applies only to cross-sectional data. (b) (4)
 - (b) (4)
 - (b) (4)
- The Rasch analysis should be conducted on each domain (b) (4).

Therefore, we believe that the results of the Rasch analysis are inconclusive, at this time.

Discussion:

The sponsor indicated that they plan to submit the patient transcripts of the qualitative study and the results of the completed psychometric study. The sponsor also indicated that they plan to conduct exit interviews at the end of the Phase 3 study to determine what change in the Myasthenia Gravis Activities of Daily Living (MG-ADL) patients consider meaningful.

The Agency reiterated that the current version of the MG Symptoms PRO scale had several items that were clinically redundant.

The sponsor stated that they are not considering modifying the MG Symptoms PRO instrument prior to the start of the Phase 3 study (which will be initiated soon). However, the sponsor stated that once the Phase 3 study begins, they may consider some modifications to the scale (if needed) during the study. The Agency asked the sponsor whether they plan to cognitively test the instrument with patients, if they made any modifications to the instrument, to ensure that patients understand the modified item

wording, etc. The sponsor replied that they may consider cognitively testing the modified instrument with the patients in parallel with the phase 3 study. The sponsor also acknowledged that they planned to modify the analysis plan for the PRO based on their further evaluation of its psychometrics. The Agency reminded the sponsor to develop and describe in their SAP a missing data plan for both the instrument score and the endpoint since MG Symptoms PRO will not be modified prior to the start of the Phase 3 study. The sponsor acknowledged this advice, and indicated that they will consider requesting a Type C meeting with the Agency to discuss their plans prior to finalizing the SAP.

Post-meeting comment: The Agency strongly recommends that the sponsor use the same version of the MG Symptoms PRO instrument throughout the Phase 3 study. Modifications made to the instrument should only inform use of the instrument in future studies.

FDA Response to Question 4b:

We acknowledge your efforts at item reduction from 82 items included in the Muscle Weakness Severity and Fatigability Assessment/Fatigue PRO Instrument to 42 items in the MG Symptoms PRO, based on the qualitative and quantitative research and FDA comments.¹ Due to the vast number of clinical outcome assessments you plan to administer during your proposed trial, you should develop a pre-specified order of administration of your clinical outcome assessments to minimize the risk of missing data (e.g., due to respondent burden) and ensure you will have sufficient data to support your primary endpoint followed by your secondary endpoints.

While the current version of the MG Symptoms PRO is an improvement over the previous version of instruments, we are concerned that interpretability of MG Symptoms PRO data may be challenging due to the following reasons:

MG Symptoms PRO content:

1. The MG Symptoms PRO (42 items) is still quite lengthy and may be burdensome to patients whose physical condition may already be compromised because of fatigue. Particularly, when administration of other lengthy assessments [such as MG-Activities of Daily Living (MG-ADL; PRO), the MG-Composite (ClinRO), and the (QMG)] is also planned for phase 3.
2. There is still redundancy in the concepts being captured. Several items in the Physical Fatigue domain appear to have overlap with each other (e.g., legs were weak, body could not keep up with what you wanted to do, whole body was weak, drained, whole body was heavy, etc.).

¹FDA Meeting Minutes IND 132407 dated December 9, 2016.

While patients may have mentioned these terms in describing their physical fatigue, it may not be necessary to capture each and every term that patients use to describe their experience as a separate item. Some of the items (e.g., *body could not keep up with what you wanted to do*) are vague and may not lead to consistency in reporting across and within patients. We recommend you use your Phase 2 study data to look at internal consistency and reliability of this domain to see if it appears that one or more of the items should be removed from the domain. Similarly, it is also unclear what how “(b) (4)” is different from “(b) (4)” and how “(b) (4)” is different from “slurred speech”. You should look at the correlations between each of the items with each other and with the total score to see item-level descriptive statistics and determine whether any of the items are redundant and can either be combined into one item or one of the two can be chosen for retention and the other excluded from the instrument. Submit results from these analyses for Agency review.

We suggest that you review your qualitative research and examine whether using terms such as “felt physically tired,” “legs felt weak,” “arms felt weak,” “felt exhausted,” etc. as descriptors for the Physical Fatigue domain might be appropriate. Similarly, you should examine which descriptors may be considered appropriate for the domain of Muscle Weakness Fatigability.

3. We note that some domains contain items that are not clearly clinically meaningful, as they assess physical signs of the disease rather than the functional impairments that arise from these findings. For example, the ocular domain includes items such as “(b) (4)”, rather than the functional impairment that such a finding causes.
4. While very few participants indicated interpretation/clarity issues with the concepts included in the MG Symptoms PRO, the qualitative report indicated that a number of concepts were not supported by a fair number of the interview participants. Of the 36 participants,
 - a. Ten participants (28%) found the conceptual overlap for the concept of *pronouncing words*; and 7 participants (19%) found conceptual overlap for the concept of “(b) (4)”. However, the report does not mention which other concept(s) patients believed overlapped with *pronouncing words* and “(b) (4)”.
 - b. Five participants (14%) did not find the following concepts to be relevant to their condition: *Mouth drooping, swallowing food, and* “(b) (4)”.
 - c. Four participants (11%) did not find the following concepts to be relevant to their condition: “(b) (4)” and “(b) (4)”.
5. If you wish to use in future trials the Ocular and Respiratory domains of the MG Symptoms PRO, you should conduct cognitive testing of the new items added to

these domains to ensure understanding of the concepts and clarity of the wording.

6. As was conveyed to you in a written responses letter (dated December 9, 2016), we have a concern regarding the 7-day recall period. Patients may have difficulty averaging the score if they have had one bad day but the rest of the week was fine for them, particularly when there are so many concepts/items addressing different parts of the body/function (arms, legs, neck, breathing etc.). From your qualitative report, it is not clear whether patients were asked about the appropriateness of the 7-day recall period or questioned about their preference of a 7-day vs 24-hour recall (e.g., separate daily assessments that could then be aggregated to create a score).
7. Items 1-18 are rated on a severity scale, while items 19-42 are rated on a frequency scale. Based on analysis of your Phase 2 data, consider whether items corresponding to the proposed MG Symptoms PRO items 1-42 are sensitive in detecting a treatment effect. It is possible that for item scores that may not show any change during the Phase 2 study, the response option scale may be inappropriate, e.g., a severity scale was used rather than frequency scale or vice versa.
8. The briefing package indicates that you plan to evaluate the measurement properties of the MG Symptoms PRO. We recommend that you consider conducting your psychometric study using your Phase 2 data (i.e., focusing on the relevant items that are proposed for inclusion in the Phase 3 studies and recreating your proposed Phase 3 endpoints) and submit the results for Agency review and comment prior to initiation of Phase 3. Please submit your psychometric analysis protocol before conducting this study.
10. For the MG Symptoms PRO domains of interest, provide item-level descriptive analyses to allow evaluation of whether or not individual items are contributing more or less to the respective domain scores and whether any items should be combined or excluded. See also point #2 above.
11. We acknowledge your plan of linguistic validation of the MG Symptoms PRO in the MG0003 local languages before its use in the trial.
12. Patient interviews that you conducted indicated that not all patients experienced symptoms related to all four of the muscle symptom groups (bulbar, limbs/axial and respiratory). The report states that this may be due to the heterogeneous nature of the disease. Heterogeneity of the MG symptomatology can pose measurement challenges and generate missing data and/or lead to less sensitivity of the endpoint score in detecting a treatment effect. Explain how missing data will be handled.
13. Please confirm whether the version of the MG Symptoms PRO included in Section 6.11 page 110 of 114 (Appendix 11 Myasthenia Gravis Symptoms

Patient Reported Outcome (PRO) Instrument) is the final version that you propose for use in phase 3.

We recommend numbering the versions of the MG Symptoms PRO for clarity. We also recommend that you be consistent in the nomenclature (e.g., “MG PRO” versus “MG Symptoms PRO”).

Additional Comments:

1. It is not clear how you will determine what MS Symptoms PRO score change is considered meaningful to patients. We recommend that you consider conducting exit interviews at the end of your Phase 3 trial to help determine what score change patients would consider to be a meaningful improvement/worsening, and whether they believe that they experienced an improvement, no change, or worsening at the end of treatment.
2. We recommend you explore inclusion of multiple anchor scales in Phase 3 to help identify clinically meaningful within-patient score changes in the MG Symptoms PRO, from the patient perspective. The anchor scales should be assessed at comparable time points as, but completed after, the MG Symptoms PRO. We recommend you include at least the following anchor scales to generate a threshold for improvement that represents a meaningful amount of change in your target population:
 - Static, current state patient global impression of severity (PGIS) scale
 - Patient global impression of change (PGIC) scale

(Note: In contrast to the PGIC scale, the PGIS scale is not subject to recall error and can also be used to assess change from baseline data. The PGIS scale is the preferred anchor scale over the PGIC scale; however, there is no perfect anchor scale and it is helpful to include multiple anchor scales for anchor-based analyses.)

Examples of PGIS and PGIC scales are as follows:

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

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

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe

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

- ☐ None
- ☐ Mild
- ☐ Moderate
- ☐ Severe
- ☐ Very severe

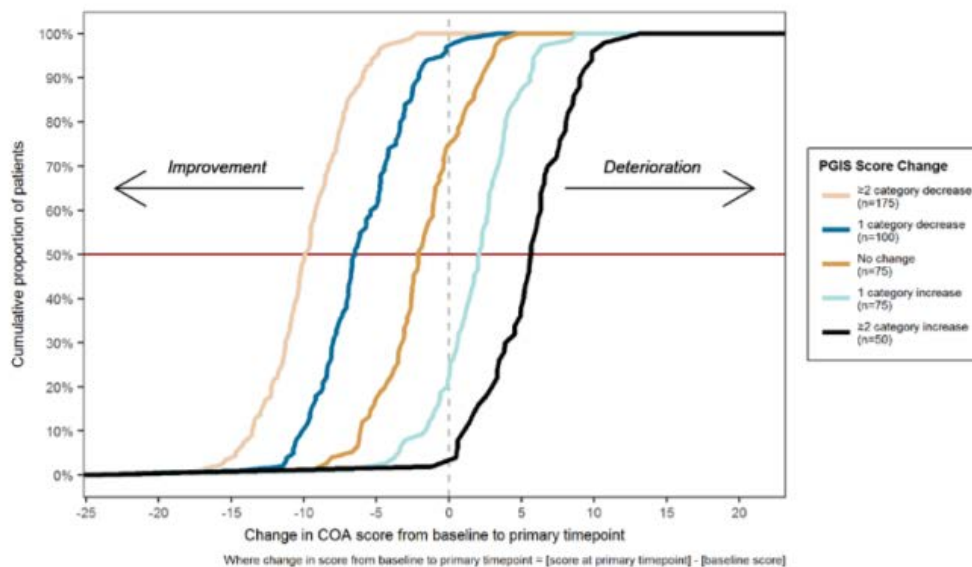
Example of a Patient Global Impression of Change (PGIC) Scale:

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

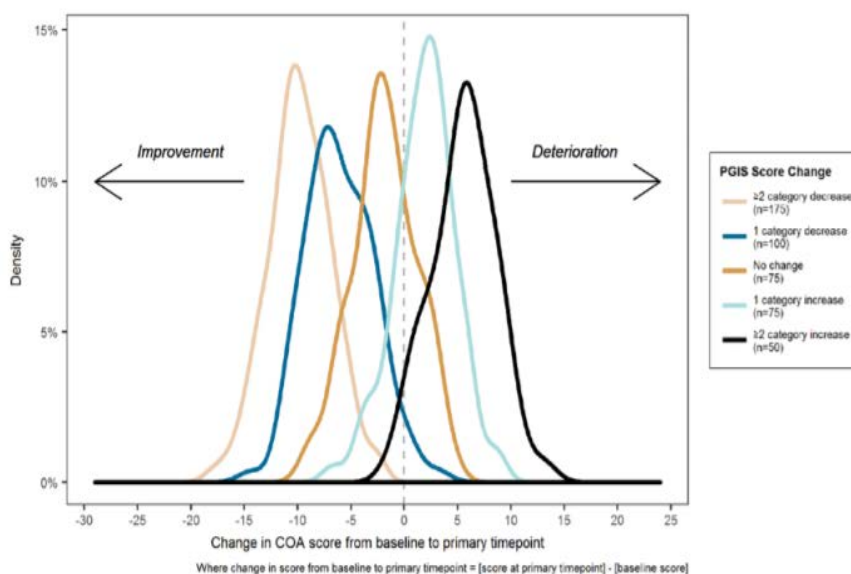
- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse

3. Please provide the Agency with the following anchor-based empirical cumulative distribution function (eCDF) and probability density function (PDF; many times estimated using kernel density estimation) curves, including the sample size and median score for each eCDF and PDF anchor curve in each figure's legend:
- For the PGIS scale: eCDFs and PDFs of MG Symptoms PRO change scores from baseline to Day 43 (Visit 10) for all patients (both treatment and placebo arms pooled) by the PGIS change scores between baseline and Day 43 (Visit 10) (e.g., +3 points change, +2 points change, +1 point change, 0 point change, -1 point change, -2 points change, -3 point change, etc.)
 - For the PGIC scale: eCDFs and PDFs of MG Symptoms PRO change scores from baseline to Day 43 (Visit 10) for all patients (both treatment and placebo arms pooled) by the different PGIC response options at Day 43 (Visit 10).
 - eCDFs and PDFs of MG Symptoms PRO change scores from baseline to Day 43 (Visit 10) by treatment arms (i.e., treatment vs. placebo)

Example of Empirical Cumulative Distribution Function (eCDF) Curves of Change in COA Score from Baseline to Primary Time Point by Change in Patient Global Impression of Severity (PGIS) score



Example of Probability Density Function (PDF; often estimated using kernel density estimation) Curves of Change in COA Score* from Baseline to Primary Time Point by Change in PGIS Score



Discussion: See discussion above for 4a.

Question 5:

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The clinical program to support the gMG filing for Rozimab will consist of the following studies: Phase 1 healthy volunteer studies (UP0018 and UP0060), the Phase 2a study MG0002, and the Phase 3 studies MG0003 and MG0004. A summary of the completed, planned, and ongoing studies in healthy volunteers and across all indications including gMG is provided in Table 4–4.

Understanding that data are a review issue, in principle could supportive data from the Phase 2a study MG0002 and confirmatory evidence from the proposed Phase 3, placebo-controlled study MG0003 together with results from an interim analysis from an ongoing OLE study (MG0004) be adequate for a BLA filing to support the proposed target indication for Rozimab (b) (4)

FDA Response to Question 5:

Since your Phase 2 study was not positive on the primary endpoint using the preplanned analysis, it cannot serve as an independent source of substantial evidence for effectiveness. In order for study MG0003 to support a marketing application as a single trial, this trial would need to fulfill the conditions described in the *Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*.²

Discussion:

No discussion.

Question 6:

UCB currently plans a safety database that will include a total of approximately 217 subjects with gMG exposed to 3 therapeutic doses of Rozimab (equivalent to 4mg/kg, 7mg and 10mg/kg). This will include approximately 126 subjects having at least 6 months exposure, and approximately 80 subjects having at least 1-year. It is anticipated that safety/exposure data will be available from clinical studies with Rozimab in other indications including Phase 2 studies in ITP (TP0001) and CIDP (CIDP01) and Phase 3 studies in ITP (TP0003 and TP0004), comprising approximately 164 patients with ITP and 28 patients with CIDP. In addition, further safety/exposure data (N=86) is planned from Phase 1 studies in healthy volunteers (UP0018 and UP0060).

Does the Agency agree in principle that the plan to provide safety data from the proposed studies in gMG, as well as additional data from other studies in healthy volunteers and other disease areas (ITP and CIDP) would be adequate to assess the

². <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/providing-clinical-evidence-effectiveness-human-drug-and-biological-products>

(b) (4): risk and to support the filing and review of a BLA with Rozimab for the treatment of gMG?

FDA Response to Question 6:

The proposed safety database appears reasonable. Whether the safety dataset is adequate for filing a BLA will depend on the safety profile after completion of your Phase 3 studies.

Discussion:

No discussion.

Question 7:

A non-cellular competitive ligand binding assay (CLBA) format to support assessment of the neutralizing potential of anti-Rozimab antibodies (ADA) is proposed for use in Phase 3. Does the Agency agree with this proposal?

FDA Response to Question 7:

While we appreciate the relative low ADA risk to a humanized IgG4, based on recommendations from the OBP Immunogenicity working group and the American Association of Pharmaceutical Scientists White Paper (Wu et al. 2016), a cell-based assay is recommended for the evaluation of ADAs when the MOA of the mAb is an antagonist for a receptor with complex binding requirements, such as the endosomal binding requirements of FcRn. Thus, a non-cellular assay would only be acceptable in cases where a cell-based assay is not feasible.

Discussion:

The Sponsor stated that they were having problems establishing the sensitivity of the cell-based assay and would like to request that other data, such as those collected during PK studies, be considered in lieu of cell-based assay. The Agency responded that since no data was submitted for the cell-based assay and its challenges, they could not agree with alternative methods. Furthermore, the scientific rationale for substitution of cell-based assay with PK data wasn't clear, and the Agency asked the Sponsor to submit this information and justification for review. The Sponsor agreed to submit this information.

Additional Comments:

- As part of your clinical development plan, you should provide information on how you plan to mitigate DDIs with other monoclonal antibody drugs.

Discussion:

The Agency clarified that the comment regarding a plan to mitigate DDIs with other mAbs refers to the overall clinical program, not the Phase 3 study where all other mAbs are excluded. The list of prohibited drugs in the proposed Phase 3 protocol appears reasonable.

3.0 ADDITIONAL INFORMATION**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.

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 (cdcr-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>. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA 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](https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM587505.pdf) 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>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA**, **ANDA**, **BLA**, **Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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.

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 tretinoin, 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submit the scientific rationale for substitution of cell-based assay with PK data	UCB	Received by FDA 6/13/2019

6.0 ATTACHMENTS AND HANDOUTS

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

/s/

ERIC P BASTINGS
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