

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

213137Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 121691

MEETING MINUTES

Global Blood Therapeutics, Inc.
Attention: Linda Yokoshima
Senior Director, Regulatory Affairs
171 Oyster Point Boulevard, Suite 300
South San Francisco, CA 94080

Dear Ms. Yokoshima:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for voxelotor (GBT440).

We also refer to the telephone conference between representatives of your firm and the FDA on February 26, 2019. The purpose of the meeting was to discuss the proposed studies to establish safety and efficacy of voxelotor in adults and adolescent subjects with sickle cell disease (SCD) to support your New Drug Application.

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

If you have any questions, contact Katie Chon, Regulatory Project Manager, at katie.chon@fda.hhs.gov or (240) 402-6578.

Sincerely,

{See appended electronic signature page}

Tanya Wroblewski, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: February 26, 2019 10:00 AM – 11:00 AM EST
Meeting Location: Teleconference

Application Number: IND 121691
Product Name: Voxelotor (GBT440)
Indication: Treatment of sickle cell disease
Sponsor/Applicant Name: Global Blood Therapeutics, Inc. (GBT)

Meeting Chair: Tanya Wroblewski, MD
Meeting Recorder: Katie Chon, PharmD, RPh

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP)

Ann Farrell, MD, Director
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
Tanya Wroblewski, MD, Clinical Team Leader
Patricia Oneal, MD, Medical Officer
Amy Baird, Chief Project Management Staff
Katie Chon, PharmD, RPh, Regulatory Project Manager

OHOP/Division of Hematology Oncology Toxicology (DHOT)

Chris Sheth, PhD, Pharmacology/Toxicology Team Leader

Office of Biostatistics/Division of Biometrics V

Yeh-Fong Chen, PhD, Statistical Team Leader
Kate Li Dwyer, PhD, Statistical Reviewer

Office of Pharmaceutical Quality

Sherita McLamore, PhD, Team Leader

Office of Clinical Pharmacology/Division of Clinical Pharmacology I

Ruby Leong, PharmD, Team Leader

SPONSOR ATTENDEES

Ted W. Love, MD, Chief Executive Officer
Josh Lehrer, MD, Senior Vice President, Development
Jonathan Sorof, MD, Senior Vice President, Medical and Regulatory Affairs
Nicholas Vlahakis, MD, Vice President, Clinical Development
Barbara Tong, PhD, Vice President, Biometrics
Michael Conner, DVM, Vice President, Toxicology
Linda Yokoshima, Senior Director, Regulatory Affairs

(b) (4) External
Consultant

1.0 BACKGROUND

Voxelotor is an oral, bioavailable oxygen affinity modulator which binds to hemoglobin and increases the Hgb-O₂ affinity and increases the bioavailability of oxygen in the blood which may slow polymerization of hemoglobin and hemolysis of red blood cells.

Voxelotor was granted orphan drug designation (#15-4997) on December 29, 2015, for treatment of sickle cell disease and breakthrough designation on January 3, 2018, for sickle cell disease in patients (b) (4).

The Sponsor has requested this Pre-NDA meeting to discuss the specific components need to support the review of the voxelotor application.

FDA sent Preliminary Comments to GBT on February 15, 2019.

2. DISCUSSION

2.1. Regulatory

Question 1: *Does the Agency agree with the proposal and timelines for a rolling NDA submission?*

FDA Response to Question 1: In general, the proposed timeline for submission for a rolling review appears reasonable.

The Agency's expectation is that the NDA submission should be complete at the time of original NDA submission. Submission of data during the review cycle should be avoided and is subject to extension of the PDUFA clock.

The review clock will not begin until the Applicant informs the Agency that a complete NDA was submitted and after the Agency is notified of the complete application, we will make a filing determination within the usual time frame. Please refer to *Guidance for Industry: Expedited Programs for Serious Conditions- Drugs and Biologics*

(<https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>)

See responses to Question 3 regarding CMC timeline submission and Question 20 regarding clinical pharmacology submissions.

Please provide the proposed data lock date of your pivotal trial, GBT440-031, for the NDA submission.

Meeting discussion: There was no discussion.

Question 2: *Does the Agency agree with the proposed content for Section 2.5 Clinical Overview?*

FDA Response to Question 2: Note that Section 2.5 Clinical Overview should include a brief discussion of product development rationale (Section 2.5.1), Overview of Biopharmaceutics (Section 2.5.2), and an Overview of Clinical Pharmacology (section 2.5.3).

Section 2.5 should include a high-level discussion of surrogate endpoints, the nature and magnitude of expected clinical benefit and the basis for these expectations. This section should include a high-level overview of the SIT and STOP study analyses and how this analysis demonstrates or will be expected to demonstrate an association between change in hemoglobin and transcranial Doppler flow velocity and stroke reduction. However, please note that we cannot agree with the proposed analyses plan for the SIT and STOP2 study included in this meeting package due to lack of information needed for us to form a conclusion. Please see response to Question 12.

Section 5 should contain the patient-level data analyses from the SIT and STOP trials.

The Benefit and Risk conclusions should integrate all the conclusions reached in previous sections of 2.5 and to provide an overall appraisal of the benefits and risks of its use in clinical practice.

Refer to the following guidance: *Guidance for Industry M4E: The CTD-Efficacy*
<https://www.fda.gov/downloads/Drugs/Guidances/ucm073290.pdf>.

Meeting discussion: The Sponsor clarified that the purpose of the SIT and STOP2 data analysis is to provide evidence to support hemoglobin as an acceptable surrogate endpoint that is reasonably likely to predict clinical benefit as demonstrated by reduction in TCD flow velocity consistent with the requirements for a Subpart H approval pathway. The Sponsor also provided a high-level overview of the goals for the analysis for the SIT and STOP data and stated that they will provide details of the analysis and preliminary analysis results at a future meeting with the Agency. The Sponsor stated that a summary of the relationship between TCD and stroke risk will be provided based on a literature review.

The Agency recommends that the Sponsor submit a meeting request to discuss the details of the analysis plan of the SIT and STOP2 data to provide evidence to support hemoglobin as an acceptable surrogate endpoint for TVD flow velocity. The Agency welcomes further discussion regarding the details of the proposed analysis.

We acknowledge the submission of Study GBT 440-032 in January 2019 and comments to the Sponsor regarding this study will be forthcoming.

Question 3: *Does the Agency agree with the proposed content of Section 2.7.3 Summary of Clinical Efficacy?*

FDA Response to Question 3: Even though an integrated database combining GBT440-031 and GBT440-007 datasets is not planned for the summary of efficacy due to differences in the study populations, please include a comparison and analyses of results across Study GBT440-031 and GBT440-007 and analysis of clinical information relevant to dosing recommendations.

We encourage you to refer to the following guidance: *Guidance for Industry M4E: The CTD-Efficacy* <https://www.fda.gov/downloads/Drugs/Guidances/ucm073290.pdf>.

Meeting discussion: **There was no discussion.**

Question 4: *Does the Agency agree with the proposed content of Section 2.7.4 Summary of Clinical Safety?*

FDA Response to Question 4: Please include exposure evaluation plan, analysis of adverse events, clinical laboratory evaluations, vital signs and other observations related to safety and safety in special groups and situations in the controlled studies and uncontrolled studies.

We encourage you to refer to the following guidance: *Guidance for Industry M4E: The CTD-Efficacy* <https://www.fda.gov/downloads/Drugs/Guidances/ucm073290.pdf>.

Meeting discussion: **There was no discussion.**

2.2. Chemistry, Manufacturing and Control

Question 5: *Does the Agency agree with this proposed stability data submission schedule?*

FDA Response to Question 5: Yes, we agree with the proposed drug product stability data submission schedule. Be advised that the shelf life of the drug product will be determined during the NDA review based on the totality of data submitted in the NDA and that stability data submitted after 30 calendar days after the submission of the original application may not be reviewed, depending on review timeline and available resources.

Meeting discussion: **There was no discussion.**

Question 6: *GBT proposes to [REDACTED] (b) (4). Does the Agency agree with this proposal?*

FDA Response to Question 6: No, we do not agree with your proposal to submit the [REDACTED] (b) (4)

Meeting discussion: There was no discussion.

2.3. Nonclinical

Question 7: *Does the Agency agree that the content and format of Module 4 support the submission of an NDA for voxelotor for SCD?*

FDA Response to Question 7: Yes, the content and format of Module 4 appears to support the submission of an NDA for voxelotor for SCD.

Meeting discussion: There was no discussion.

Question 8: *The Agency previously agreed that carcinogenicity study reports were not required for submission of the original NDA.*

- *The final study report for the 26-week carcinogenicity study in mice will be included the original NDA.*
- *The final study report for the [REDACTED] (b) (4)*

Does the Agency agree with this proposal?

FDA Response to Question 8: The Agency finds your proposal to submit the 26-week carcinogenicity study in mice with the original NDA to be acceptable. [REDACTED] (b) (4)

Meeting discussion: There was no discussion.

2.4. Clinical

Question 9: *Does the Agency agree that the content and format of Module 5, as outlined in Appendix 2, support the submission of an NDA for voxelotor for SCD?*

FDA Response to Question 9: The content and format outlined in Appendix 2 is acceptable to the Agency. Include the patient-level analyses from the SIT and STOP data in Module 5.

Meeting discussion: There was no discussion.

Question 10: *Does the Agency agree that the information in Section 2.7.3 Clinical Summary of Efficacy can be duplicated in Section 5.3.5.3 for the Integrated Analysis of Efficacy?*

FDA Response to Question 10: It is not clear if you are asking if Section 2.7.3 can serve as the ISE or if Section 2.7.3 can serve as the narrative portion of the ISE.

There may be situations in which sections 2.7.3, Summary of Clinical Efficacy and 2.7.4., Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the ISE and ISS, respectively, but still concise enough to meet the suggested size limitations for Module 2.

Refer to the following guidances: *Integrated Summaries of Effectiveness and Safety Location within the Common Technical Document*:

<https://www.fda.gov/downloads/drugs/guidances/ucm136174>. *Integrated Summary of Effectiveness*: <https://www.fda.gov/downloads/drugs/guidances/ucm079803.pdf>

Meeting discussion: There was no discussion.

Question 11: *Does the Agency agree that the information in Section 2.7.*

FDA Response to Question 11: No, Clinical Summary of Safety can be duplicated in Section 5.3.5.3 for the Integrated Analysis of Safety. Please refer to Question 10.

Meeting discussion: There was no discussion.

Question 12: *Does the Agency agree with the proposed plan for the analysis of SIT and STOP 2 data?*

FDA Response to Question 12: No. We cannot comment on your proposed analysis plan at this time as it is lacking in sufficient details.

It is also unclear why your proposed analysis for the SIT and STOP2 trials includes all subjects screened in both the SIT and STOP2 clinical trials versus those subjects who were randomized into both trials.

Your current statistical analysis plan in Appendix 4 to assess the relationship between hemoglobin level and TCD flow velocity and to support the TCD study is lacking in sufficient details. You will need to provide the justification for the chosen cut-off, study duration as well as the assumptions used for your sample size planning for the TCD study. We also recommend you conduct the pooled analyses from the SIT and STOP2 when feasible.

The Agency recommends that you submit a more detailed analysis plan and separate meeting request to discuss the full analysis plan and methods for the SIT and STOP2 data.

Meeting discussion: The Sponsor explained the rationale as to why they plan to analyze both the randomized and screened patients with the objective of understanding the hemoglobin and TCD relationship in general for different types of patients and a broader patient population.

Post-Meeting Comment: We acknowledge your plan to analyze the data of the SIT and STOP2 for both patients who were randomized and those who were screened (either separately or pooled). As a patient's status could have changed during the course of the study, we recommend that you also conduct analyses for different time points.

Question 13: *Does the Agency agree that OSI listings be provided for Study GBT440-031 at the time of the NDA submission?*

FDA Response to Question 13: We recommend to include subject-level listings for discontinuations (discontinued from study treatment and discontinuation from study completely), protocol-defined study population in which each subject was analyzed, inclusion and exclusion criteria, all adverse events (non-serious and serious adverse events including death, date of occurrence and time if collected, severity) and concomitant meds and safety monitoring.

Please refer to Bioresearch Monitoring Technical Conformance Guide
<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/formssubmissionrequirements/ucm332466.pdf>.

Meeting discussion: There was no discussion.

Question 14: *Does the Agency agree with the studies to support efficacy and safety, datasets and analysis programs proposed to be included in the NDA?*

FDA Response to Question 14:

The Agency agrees with your proposal to submit SDTM and ADaM datasets for studies GBT440-031 and GBT440-007.

In addition, the Agency recommends that you

- Submit an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission. Refer to the Study Data Technical Conformance Guide: Technical Specifications Document for additional details.
- Provide sufficient comments, adequate bookmarks, and hyperlinks in the define files to ensure efficient review.
- Provide standard alone SAS programs with adequate documentation to allow FDA to duplicate the analysis datasets derivation from raw datasets.
- Provide the SAS programs as well as format library files used for your efficacy and safety data analysis. If the SAS programs use any SAS macro, provide all necessary macro programs. These programs should be sufficient for the Agency to reproduce your efficacy and safety results.

Meeting discussion: There was no discussion.

Question 15: Does the Agency agree with a 90-day safety update?

FDA Response to Question 15:

The safety update should also contain updated adverse reaction datasets and case report forms for each patient who died or did not complete the study due to an adverse event.

Meeting discussion: There was no discussion.

Question 16: Does the Agency agree that the proposed NDA safety database is adequate to support an NDA for voxelotor for the treatment of SCD in adult (b) (4)
[REDACTED] ?

FDA Response to Question 16: The sufficiency of the safety database to support an indication for adolescent subjects will be a review issue.

Meeting discussion: There was no discussion.

Question 17: Does the Agency agree with the proposed plan to submit safety narratives for all deaths, voxelotor related serious adverse events, and TEAEs leading to study drug discontinuation in the original NDA?

FDA Response to Question 17: No, safety narratives should be submitted for all serious adverse events and not limited to voxelotor related serious adverse events. Please include detailed safety narratives from subjects who received voxelotor including those subjects who have received voxelotor through the expanded access program.

Meeting discussion: There was no discussion.

Question 18: Does the Agency agree that the proposed clinical pharmacology program as outlined in Appendix 2 supports the submission of an NDA for voxelotor for SCD?

FDA Response to Question 18: Your proposed clinical pharmacology program appears sufficient to support an NDA submission. However, the need for additional studies will be determined during the NDA review.

Meeting discussion: There was no discussion.

Question 19: Does the Agency agree that the PBPK modeling data are sufficient and obviate the need for additional clinical DDI studies at higher doses of voxelotor?

FDA Response to Question 19: We acknowledge your PBPK modeling data; however, the need for additional clinical DDI studies will be determined during the NDA review. We have the following comments regarding your PBPK model:

- a. About 86-fold difference was found in in vitro Ki values towards CYP3A4 using testosterone (1.3 µM) and midazolam (112 µM) as the substrate. In the DDI simulation to predict the effect of GBT440 on midazolam PK, it seems that you used in vitro Ki using testosterone as the substrate for CYP3A4. Provide the rationale for using the Ki value from a different substrate for DDI simulation.
- b. Submit all model files in your NDA submission.
- c. Submit model verification for substrates midazolam, caffeine, omeprazole, rosiglitazone, s-warfarin, and metoprolol in your NDA submission.

Meeting discussion: There was no discussion.

Question 20: *Does the Agency agree with the proposal to submit the final clinical study report from the planned P-gp inhibition interaction study (Digoxin as a probe substrate, GBT440-0116) during the review of the NDA (September 2019)?*

FDA Response to Question 20: It is the Agency's expectation that the NDA submission should be complete at the time of original NDA submission. Submission of data during the review cycle should be avoided and is subject to extension of the PDUFA clock. If you commit to submitting the final report for the planned P-gp drug-drug interaction study within 30 days after filing the NDA application, it will be reviewed.

Meeting discussion: There was no discussion.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:

1. We recommend the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA Guidance for Industry, "Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format" (available at <https://go.usa.gov/xn4qB>). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

2. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
3. What are the exposure-response relationships for efficacy, safety and biomarkers?
4. What is the effect of voxelotor on the QT/QTc interval?

5. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
6. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
7. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

8. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
 9. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean \pm standard deviation) and median with minimum and maximum values as appropriate.
 10. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
 - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
 - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
 11. Submit the following for the population pharmacokinetic analysis reports:
 - Standard model diagnostic plots
 - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
 - Model parameter names and units in tables.
 - Summary of the report describing the clinical application of modeling results.
- Refer to the following pharmacometric data and models submission guidelines
<http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm>.
12. Submit the following information and data to support the population pharmacokinetic analysis:
 - SAS transport files (*.xpt) for all datasets used for model development and validation

- A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
 - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submit these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)
13. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf> for population PK, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf> for exposure-response relationships, and <http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm> for pharmacometric data and models submission guidelines.
14. Include the purpose of the simulations, assumptions, detailed process of PBPK model building and verification, summary of model input parameters, version of software, simulation results, and conclusions in the study report. Provide the study report as PDF files (screenshots can be incorporated if required). Include the model files used to generate the final PBPK simulations. These files should be executable by FDA reviewers using the specified software. Include appropriate supporting documentations such as any special instructions and file definitions.
15. Include the following items when you submit your QT study report:
- a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed
 - b. Electronic copy of the study report
 - c. Electronic or hard copy of the clinical protocol
 - d. Electronic or hard copy of the Investigator's Brochure
 - e. Annotated CRF
 - f. A data definition file which describes the contents of the electronic data sets
 - g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
 - h. Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
 - i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point
 - j. Narrative summaries and case report forms for any:
 - i. Deaths
 - ii. Serious adverse events
 - iii. Episodes of ventricular tachycardia or fibrillation

- iv. Episodes of syncope
- v. Episodes of seizure
- vi. Adverse events resulting in the subject discontinuing from the study
- k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
- l. A completed Highlights of Clinical Pharmacology Table

Advancing in this field – and possibly reducing the burden of conducting QT studies – depends critically upon obtaining the most comprehensive understanding of existing data. Please consider making your data, at least placebo and positive control data, available for further research purposes; see, for examples, the Data Request Letter at <http://cardiac-safety.org/ecg-database/>

Meeting discussion: There was no discussion.

3. OTHER IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 21, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

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

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new

dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements/ Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

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

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

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

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

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

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

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

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential

and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

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

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

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

Corresponding names and titles of onsite contact:

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

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>.

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR: <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612927.htm>. In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- AssessmentAid:<https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/OCE/ucm612923.htm>

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached response document and slides to outline the specific issues to address.

41 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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/

TANYA M WROBLEWSKI
02/28/2019 04:06:42 PM

CDER Breakthrough Therapy Designation Determination Review Template

IND/NDA/BLA #	IND 121691
Request Receipt Date	November 6, 2017
Product	Voxelotor (GBT440)
Indication	Treatment of Sickle Cell Disease (SCD) in patients (b) (4)
Drug Class/Mechanism of Action	Small molecule/Oral bioavailable oxygen affinity modulator which binds to hemoglobin and increases the Hgb-O2 affinity and increases the bioavailability of oxygen in the blood
Sponsor	Global Blood Therapeutics, Inc.
ODE/Division	OHOP/DHP
Breakthrough Therapy Request(BTDR) Goal Date (within 60 days of receipt)	January 6, 2018

Note: This document *must* be uploaded into CDER's electronic document archival system as a **clinical review: REV-CLINICAL-24 (Breakthrough Therapy Designation Determination)** even if the review is attached to the MPC meeting minutes, and will serve as the official primary Clinical Review for the Breakthrough Therapy Designation Request (BTDR). Link this review to the incoming BTDR. Note: Signatory Authority is the Division Director.

Section I: Provide the following information to determine if the BTDR can be denied without Medical Policy Council (MPC) review.

1. Briefly describe the indication for which the product is intended (Describe clearly and concisely since the wording will be used in the designation decision letter): Treatment of Sickle Cell Disease (SCD) patients (b) (4) .
2. Are the data supporting the BTDR from trials/IND(s) which are on Clinical Hold? YES NO

If 2 above is checked "Yes," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "No", proceed with below:

3. Consideration of Breakthrough Therapy Criteria:

- a. Is the condition serious/life-threatening¹? YES NO

Beginning in childhood, patients with SCD suffer unpredictable and recurrent episodes of severe pain often leading to significant psychosocial and occupational disability, chronic pain medications, and recurrent hospitalizations. In addition to painful crises, a systemic vasculopathy leads to chronic and progressive tissue injury affecting all organ systems with a multitude of severe clinical consequences such as priapism, cognitive dysfunction and stroke, renal dysfunction, cardiopulmonary complications, leg ulcers as well as increased susceptibility to infections resulting in a decrease of approximately 25 to 30 years in life expectancy.

If 3a is checked "No," the BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off. If checked "Yes", proceed with below:

- b. Are the clinical data used to support preliminary clinical evidence that the drug may demonstrate substantial improvement over existing therapies on 1 or more clinically significant endpoints adequate and sufficiently complete to permit a substantive review?

¹ For a definition of serious and life threatening see Guidance for Industry: "Expedited Programs for Serious Conditions—Drugs and Biologics" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

- YES the BTDR is adequate and sufficiently complete to permit a substantive review
 Undetermined
 NO, the BTDR is inadequate and not sufficiently complete to permit a substantive review; therefore the request must be denied because (check one or more below):

- i. Only animal/nonclinical data submitted as evidence
- ii. Insufficient clinical data provided to evaluate the BTDR (e.g. only high-level summary of data provided, insufficient information about the protocol[s])
- iii. Uncontrolled clinical trial not interpretable because endpoints are not well-defined and the natural history of the disease is not relentlessly progressive (e.g. multiple sclerosis, depression)
- iv. Endpoint does not assess or is not plausibly related to a serious aspect of the disease (e.g., alopecia in cancer patients, erythema chronicum migrans in Lyme disease)
- v. No or minimal clinically meaningful improvement as compared to available therapy²/ historical experience (e.g., <5% improvement in FEV1 in cystic fibrosis, best available therapy changed by recent approval)

4. Provide below a brief description of the deficiencies for each box checked above in Section 3b:

If 3b is checked “No”, BTDR can be denied without MPC review. Skip to number 5 for clearance and sign-off (Note: The Division always has the option of taking the request to the MPC for review if the MPC’s input is desired. If this is the case, proceed with BTDR review and complete Section II). If MPC review is not required, email Miranda Raggio and Sandy Benton as soon as this determination is made so that the BTDR can be removed from the MPC calendar.

If 3b is checked “Yes” or “Undetermined”, proceed with BTDR review and complete Section II, as MPC review is required.

5. Clearance and Sign-Off (no MPC review)

Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
 Team Leader Signature: {See appended electronic signature page}
 Division Director Signature: {See appended electronic signature page}

Section II: If the BTDR cannot be denied without MPC review in accordance with numbers 1-3 above, or if the Division is recommending that the BTDR be granted, provide the following additional information needed by the MPC to evaluate the BTDR.

6. A brief description of the drug, the drug’s mechanism of action (if known), the drug’s relation to existing therapy(ies), and any relevant regulatory history. Consider the following in your response.

Voxelotor is a oral bioavailable oxygen affinity modulator which binds to hemoglobin and increases the Hgb-O₂ affinity and increases the bioavailability of oxygen in the blood. This modulation of oxygen affinity in sickle hemoglobin eventually slows the polymerization of hemoglobin and hemolysis of red blood cells in vitro studies. It is known that in patients with SCD continuous hemolysis mediated by free plasma heme and nitric oxide scavenging results in endothelial dysfunction and a systemic vasculopathy which predisposes individuals to leg ulcers, pulmonary hypertension, and stroke who are at the greatest risk for earlier morbidity and mortality. Improvements across the laboratory measures of

² For a definition of available therapy refer to Guidance for Industry: “Expedited Programs for Serious Conditions—Drugs and Biologics” <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>

intravascular hemolysis (i.e. unconjugated bilirubin, LDH and reticulocyte levels) in these patients may contribute to an increase in hemoglobin which can impact fatigue and reduce early mortality in SCD patients.

This IND was submitted on October 7, 2014. Orphan drug designation (#15-4997) was granted on December 29, 2015.

(b) (4)

Drug/Mechanism of Action: Oral bioavailable hemoglobin oxygen affinity modulator which increases Hb-O₂ affinity and increases the bioavailability of oxygen in the blood (delays in vitro HbS polymerization).

Indication/Disease: For the treatment of SCD in patients (b) (4)

Available therapies: (b) (4) Droxia (hydroxyurea) is approved for patients ≥ 18 years of age with SCD and Endari (L-glutamine) is approved for patients ≥ 5 years of age with SCD.

7. Information related to endpoints used in the available clinical data:

Approximately 229 patients have enrolled across three clinical trials using multiple doses of voxelotor (500, 700, 600, 900, 1000 and 1500 mg) in healthy volunteers as well as patients with all SCD variants.

In their dose finding studies, the Sponsor provided preliminary efficacy results showing an increase in hemoglobin by 1 g/dL among SCD adult patients at six weeks and up to 6 months of treatment. Thirty-three percent of the patients were on hydroxyurea (HU). Among GBT440 treated subjects, thirteen patients (46%) showed an increase in hemoglobin of 1 g/dL sustained for 90 days to 6 months compared to placebo. Reductions in hemolysis markers $\{-39.7\%$ $(-49.9,-32.2)\}$ and the number of irreversible sickle cells $\{-76.6\%$ $(-83.9,-63.0)\}$ were demonstrated across all treatment groups.

In their open label, Phase 2, multiple-dose study among adolescent patients with SCD (n=12), the Sponsor demonstrated efficacy results showing an increase in hemoglobin by 1 g/dL by 42% by 12-24 weeks of exposure compared to placebo. A reduction in unconjugated bilirubin and reticulocytes was also demonstrated at 12-24 weeks of treatment. Of note, ninety-two percent of the patients were on a stable doses of hydroxyurea.

In their ongoing Phase 3 registration study (n=19), improvements from baseline were observed for both hemoglobin and hemolysis. By Week 6, five patients had achieved a 0.9 g/dL increase in hemoglobin from baseline in the 900 mg arm and a 1.3 g/dL increase in hemoglobin from baseline in the 1500 mg arm compared to placebo (-0.4 g/dL). A reduction in unconjugated bilirubin and reticulocytes was seen at six weeks of treatment. In this trial, sixty-eight percent of the patients were stable HU users. This would suggest a possible additive effect of GBT 440 among HU users.

Expanded access of GBT 440 has been granted to seven patients since 2016. The duration of treatment has ranged from 3 to 15 months. Four of the seven patients did achieve a hemoglobin level of > 1 g/dL after 10 weeks of treatment. The number of transfusions (from 33 to 13) and hospitalizations due to vaso-occlusive crises (VOC) (from 28 to 9) were reduced over the 10 weeks of treatment. All of the patients reported improvement in their well-being, reduced fatigue as well as improvement in mood and depression status.

Based on the available data treatment, GBT440 has shown to effect a significant rise in hemoglobin (1 g/dL) in patients with SCD. Importantly, the achievement of at least one gram increase in the hemoglobin may translate into the avoidance of blood products (avoiding iron overload), less hospitalizations (higher hospitalizations are associated with higher rates of morbidity/mortality), and a reduction in fatigue (primary patient concern noted in FDA Public meeting on SCD in

February 2014). Improvements in the hemolysis markers have been noted with longer use of GBT-440, which may translate an improvement in endothelial dysfunction and may mitigate the systemic vasculopathy which in some SCD subtypes (i.e. patients with leg ulcers, pulmonary hypertension, and stroke) cause greatest risk for earlier morbidity and mortality. In addition, there may be an additive effect of GBT440 among hydroxyurea users. The Sponsor's Phase 3 registration study will also incorporate clinical outcome measures (i.e. reduction in vasoocclusive crises) through (b) (4) which is one of their primary secondary endpoints.

8. A brief description of available therapies, if any, including a table of the available Rx names, endpoint(s) used to establish efficacy, the magnitude of the treatment effects (including hazard ratio, if applicable), and the specific intended population. Consider the following in your response:

Droxia® (Hydroxyurea) (Approved for patients >18 years of age with SCD)¹

The mechanisms by which DROXIA produces its beneficial effects in patients with sickle cell disease are uncertain. The known pharmacologic effects of DROXIA that may contribute to its beneficial effects includes increasing hemoglobin F levels in red blood cells (RBCs), decreasing neutrophils, increasing the water content of RBCs, increasing deformability of sickled cells, and altering the adhesion of RBCs to endothelium. This translated in subjects showing a significant reduction in the incidence of painful events, acute chest syndrome, hospitalizations and the number of blood transfusions.

Table 2: Results from the Multicenter Study of Hydroxyurea in Sickle Cell Anemia

Event	Hydroxyurea (N=152)	Placebo (N=147)	Percent Change Versus Placebo	P-value
Median yearly rate of painful crises*	2.5	4.6	-46	=0.001
Median yearly rate of painful crises requiring hospitalization	1.0	2.5	-60	=0.0027
Median time to first painful crisis (months)	2.76	1.35	+104	=0.014
Median time to second painful crisis (months)	6.58	4.13	+59	=0.0024
Incidence of chest syndrome (# episodes)	56	101	-45	=0.003
Number of patients transfused	55	79	-30	=0.002
Number of units of blood transfused	423	670	-37	=0.003

* A painful crisis was defined in the study as acute sickling-related pain that resulted in a visit to a medical facility, that lasted more than 4 hours, and that required treatment with a parenteral narcotic or NSAID. Chest syndrome, priapism, and hepatic sequestration were also included in this definition.

Endari® (L-Glutamine) (Approved for adults and pediatric patients > 5 years of age with SCD)²

The mechanism of action of the amino acid L-glutamine in treating sickle cell disease (SCD) is not fully understood. We know that oxidative stress phenomena part of the pathophysiology of SCD where sickle red blood cells are more susceptible to oxidative damage than normal RBCs, which contribute to the chronic hemolysis and vaso-occlusive events associated with SCD. L-glutamine may improve the NAD redox potential in sickle RBCs through increasing the availability of reduced glutathione in preventing oxidative damage in RBCs. The efficacy of Endari demonstrated a reduction in the number of sickle cell crises as well as a lower incidence of acute chest syndrome.

Table 3. Results from the Endari Clinical Trial in Sickle Cell Disease

Event	Endari (n = 152)	Placebo (n = 78)
Median number of sickle cell crises (min,max) ¹	3 (0, 15)	4 (0, 15)
Median number of hospitalizations for sickle cell pain (min, max) ¹	2 (0, 14)	3 (0, 13)
Median cumulative days in hospital (min, max) ¹	6.5 (0, 94)	11 (0, 187)
Median time (days) to first sickle cell crisis (95% CI) ^{1,2}	84 (62, 109)	54 (31, 73)
Patients with occurrences of acute chest syndrome (%) ¹	13 (8.6%)	18 (23.1%)

¹. Measured through 48 weeks of treatment

². Hazard Ratio=0.69 (95% CI=0.52, 0.93), estimated based on unstratified Cox's proportional model. Median time and 95% CI were estimated based on the Kaplan Meier method.

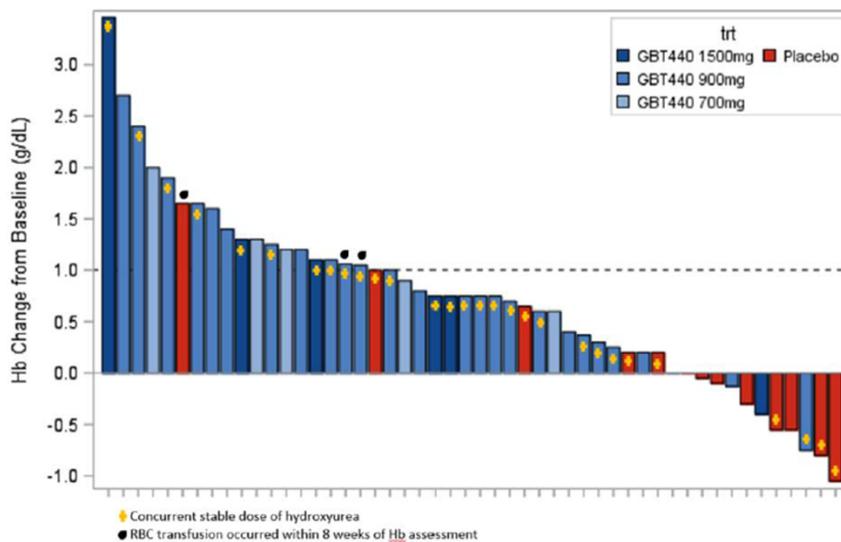
9. A brief description of any drugs being studied for the same indication, or very similar indication, that requested breakthrough therapy designation³.

Not applicable

10. Information related to the preliminary clinical evidence:

Achievement of the primary endpoint of a hemoglobin response > 1 g/dL from baseline:

Figure 1: Hemoglobin (g/dL) Change from Baseline with at least 6 Weeks of Treatment (Studies GBT440-001, GBT440-007 and GBT440-031)



The primary endpoint of GBT 440 has been demonstrated across all studies where the hemoglobin increase due to the treatment can be perceived as a prediction to the clinical benefit that GBT 440 may have on sickle cell disease. Improvements in hemolysis across all patient populations, dosages and duration may be interpreted of a treatment effect in VOC but most importantly a reduction in the vasculopathic complications of SCD which impacts mortality. Finally, the safety profile is limited to Grade 1-2 common adverse events such as headache, back pain, diarrhea, cough and rash.

³ Biweekly reports of all BTDRs, including the sponsor, drug, and indication, are generated and sent to all CPMSs.

11. Division's recommendation and rationale (pre-MPC review):

GRANT :

Provide brief summary of rationale for granting:

- Sickle cell disease is a serious condition where the available therapy may not be effective in all patients afflicted with this disease. Currently, there is a lack of overlap of available therapies for SCD patients. There are no available therapies for patients < 5 years of age. The sponsor plans to study patients aged (b) (4)
- The efficacy data has shown an increase in hemoglobin 1 g/dL among a significant number of SCD patients using GBT 440 by 24 weeks of treatment. The hemoglobin increase may translate into a reduction of transfusions, reduction in hospitalizations while improving the patients' sense of well being.
- Improvement in hemolysis parameters could especially benefit those SCD with high risk vasculopathy profiles. They may show a reduction in severe SCD complications and improvement in morbidity and mortality.
- The available safety data is favorable.
- Even in their expanded access program, data also shows a 1 g/dL increase in Hgb in 4/7 patients after 10 weeks of treatment while suggesting an improvement in functional status.

Note, if the substantial improvement is not obvious, or is based on surrogate/pharmacodynamic endpoint data rather than clinical data, explain further.

DENY:

Provide brief summary of rationale for denial:

Note that not looking as promising as other IND drugs is not a reason for denial; the relevant comparison is with available (generally FDA-approved) therapy. If the Division does not accept the biomarker/endpoint used as a basis for traditional approval or accelerated approval or as a basis for providing early clinical evidence of a substantial improvement over available therapy, explain why:

12. Division's next steps and sponsor's plan for future development:

- a. If recommendation is to grant the request, explain next steps and how the Division would advise the sponsor (for example, plans for phase 3, considerations for manufacturing and companion diagnostics, considerations for accelerated approval, recommending expanded access program):



13. List references, if any:

1. DROXIA® (hydroxyurea capsules, USP) Prescribing Information, https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016295s041s042lbl.pdf.
2. ENDARI® (L-glutamine oral powder) Prescribing Information https://www.accessdata.fda.gov/drugsatfda_docs/label/201E7/208587s000lbl.pdf.

14. Is the Division requesting a virtual MPC meeting via email in lieu of a face-to-face meeting? YES NO

15. Clearance and Sign-Off (after MPC review):

Grant Breakthrough Therapy Designation
Deny Breakthrough Therapy Designation

Reviewer Signature: {See appended electronic signature page}
Team Leader Signature: {See appended electronic signature page}
Division Director Signature: {See appended electronic signature page}

Revised 10/17/17/M. Raggio

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

/s/

WONME K CHON

12/27/2017

electronically signed by Katie Chon, PharmD, RPh

PATRICIA A ONEAL

12/27/2017

KATHY M ROBIE SUH

12/29/2017

ANN T FARRELL

01/02/2018



IND 121691

MEETING MINUTES

Global Blood Therapeutics, Inc.
Attention: Martine Kraus, PhD
Vice President, Regulatory Affairs and Quality Assurance
400 East Jamie Court, Suite 101
South San Francisco, CA 94080

Dear Dr. Kraus:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for GBT440.

We also refer to the meeting between representatives of your firm and the FDA on July 26, 2016. The purpose of the meeting was to discuss your Phase 3 study plan and proposed registration plan for GBT440 for the treatment of sickle cell disease (SCD) in adult and pediatric patients.

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

If you have any questions, call Jessica Boehmer, Senior Regulatory Project Manager at (301) 796-5357.

Sincerely,

{See appended electronic signature page}

Nicole Gormley, MD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



**FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: July 26, 2016; 3:00 PM – 4:00 PM ET
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1315
Silver Spring, Maryland 20903

Application Number: IND 121691
Product Name: GBT440
Indication: For the treatment of Sickle Cell Disease
Sponsor/Applicant Name: Global Blood Therapeutics, Inc.

Meeting Chair: Nicole Gormley, MD
Meeting Recorder: Jessica Boehmer, MBA

FDA ATTENDEES

Office of Hematology and Oncology Products/Division of Hematology Products

Ann Farrell, MD, Director
Edvardas Kaminskas, MD, Deputy Director
Nicole Gormley, MD, Team Leader, Acting
Hyon-Zu Lee, PharmD, Clinical Reviewer
Virginia Kwitkowski, MS, ACNP-BC, Clinical Team Leader, Associate Director for Labeling
Rachel Ershler, MD, Clinical Reviewer
Rosanna Setse, MD, Clinical Reviewer
Jessica Boehmer, MBA, Senior Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V

Lei Nie, PhD, Statistical Team Leader
Kyung Y. Lee, PhD, Statistical Reviewer

Division of Hematology Oncology Toxicology

Christopher Sheth, PhD, Supervisory Pharmacologist
Pedro Del Valle, PhD, Pharmacologist

Office of Clinical Pharmacology

Stacy Shord, PharmD, Clinical Pharmacology Team Leader
Guoxiang (George) Shen, PharmD, Clinical Pharmacology Reviewer

Lily (Yeruk) Mulugeta, PharmD, Pharmacometrics Reviewer

Office of the Commissioner / Office of Minority Health

Jonca Bull, MD, Director

Office of New Drugs (OND) / Immediate Office (IO) / Rare Diseases Program

Lucas Kempf, MD, Medical Officer

OND / IO / Clinical Outcomes Assessment Staff

Selena Daniels, PharmD, Team Leader

Office of Surveillance and Epidemiology

Sarah Harris, PharmD, RPh, Project Management Team Leader

SPONSOR ATTENDEES

Global Blood Therapeutics

Ted Love, MD, Chief Executive Officer

Eleanor Ramos, MD, Chief Medical Officer

Ken Bridges, MD, Vice President, Medical Affairs

Josh Lehrer, MD, Senior Director, Clinical Sciences

Margaret Tonda, PharmD, Senior Director, Clinical Sciences

Carla Washington, PhD, Senior Director, Clinical Pharmacology

Jitendra Ganju, PhD, Vice President, Biometrics

Athiwat Hutchaleelaha, PhD, Vice President, Drug Metabolism and Pharmacokinetics

(b) (4), Independent Pharmacology and Toxicology Consultant

Martine Kraus, PhD, Vice President, Regulatory Affairs and Quality Assurance

(b) (4) Clinical Pharmacology Consultant
(by telephone)

(b) (4)

1.0 BACKGROUND

The purpose of this meeting is to discuss the Phase 3 study plan and proposed registration plan for GBT440 for the treatment of sickle cell disease (SCD) in adult and pediatric patients.

GBT440 is an orally bioavailable hemoglobin (Hb) modifier. GBT440 is under clinical development for the treatment of SCD (IND 121691). A Phase 1/2 study evaluating GBT440 in adults (Study GBT440-001) is ongoing and several clinical pharmacology studies (including Studies GBT440-002, GBT440-003, GBT440-004, GBT440-005, and GBT440-008) are complete or are in progress at this time. Also in progress is a Phase 2a study in adolescents (Study GBT440-007).

GBT is evaluating GBT440 for the treatment of sickle cell disease (SCD) under IND 121691 (Division of Hematology Products). GBT440 for SCD has been granted fast track (October 7, 2015) designation and orphan product designation (December 29, 2015).

FDA sent Preliminary Comments to Global Blood Therapeutics, Inc. on July 19, 2016.

2. DISCUSSION

Preamble:

As currently proposed, your development plan has significant deficiencies. The Agency has the following concerns/questions which we hope to begin to address during the scheduled meeting:

- **The impact that your product will have on the clinical course of patients with sickle cell disease is not clear.**
- **The proposed [REDACTED] ^{(b) (4)} is not a measure of clinical benefit and has not been demonstrated to be a surrogate that is reasonably likely to predict clinical benefit.**
- **You have proposed for your phase 3 trial a patient population that has relatively mild disease (≥ 1 VOC in the preceding year). When evaluating diseases that have a relatively mild phenotype, there is a risk that it will be possible to demonstrate only minimal improvement as a result of the intervention. You should consider evaluating a more severely affected patient population which will make possible the measurement of an effect of therapy that is greater in magnitude. The same suggestion can be made for your [REDACTED] ^{(b) (4)} development.**
- **In the phase 1 study, there were several events of sickle cell anemia with crisis that occurred after discontinuation of GBT-440 or during treatment holds. These events are concerning and no explanation has been provided for these events. The effect of GBT-440 on erythropoietin, specifically the increases noted with higher dose levels, is also of concern and requires further explanation.**
- **Please also explain why the Hgb rise is minimal, while hemolysis is decreased.**

2.1. Clinical Questions

GBT has the following questions related to clinical development and statistical considerations:

Question 1: Does the Agency agree that the data from the ongoing Phase 1/2 study (GBT440-001) of the PK, safety, and treatment response of GBT440 in healthy subjects and subjects with SCD support further evaluation of GBT440 in the proposed Phase 3 study GBT440-031?

FDA Response to Question 1: No. Before commencing your Phase 3 trial, address the following:

- **Your observed dose response data indicate response to treatment may plateau at dose of 500 to 700 mg for reduction in % of irreversible sickle cells and LDH. In addition, the erythropoietin data show inverse U-shaped dose-response**

relationship between GBT440 dose and erythropoietin levels, indicating a potentially deleterious effect at high doses of GBT440. Therefore, there is no clear justification for the proposed 900 mg once daily dose. In order to assess whether there are C_{max} related toxicities, you will need to evaluate the data from 900 mg once daily dose in the ongoing Phase 1 trial (Study GBT440-001) before using this dose in a pivotal trial.

- Your dose-response analyses should also include safety endpoints. Your meeting package indicates adverse events including rash, gastrointestinal adverse effects (diarrhea, abdominal pain, etc.), and sickle cell anemia with crisis were observed. We noticed that in your ongoing and completed trials, 8 subjects in the treatment arm experienced sickle cell anemia with crisis; since GBT440 is intended for the treatment of sickle cell anemia, please explain this seemingly contradictory finding.
- In order to assess the therapeutic benefit of GBT440 at multiple dose levels, we recommend you evaluate two dose levels in your planned Phase 3 trial.
- Assess safety of GBT440 in adolescent patients using data from your ongoing trial (study GBT440-007) and add an additional cohort of 900 mg.

Discussion:

The Sponsor provided background on the safety and activity observed with GBT-440 thus far. The Sponsor also presented a revised proposal for a pivotal trial, which is designed as a phase 2/3 trial (see attached Sponsor slides). The phase 2 portion of the trial will enroll 3 dose cohorts (a placebo arm and two GBT-440 dose levels). The phase 3 portion will compare a placebo arm with the dose selected from phase 2. The proposed primary endpoint is (b) (4). The Agency stated that while it is advisable to conduct a phase 2 trial before initiating a pivotal phase 3 trial, the specific details of their proposed phase 2/3 will need to be carefully considered and discussed with the Agency before initiation. Specific concerns with the proposed design include how the (b) (4) will be validated in the phase 2 portion, carryover of some patients from the phase 2 portion to the phase 3 portion, and other concerns pertaining to the analysis of the phase 2 to inform the phase 3 trial.

With regards to the endpoint used, the Agency reiterated that the Sponsor should carefully consider the clinical benefit measurement(s) they expect their product to affect. This information will inform the choice of an appropriate trial endpoint for their pivotal trial. The Agency stated that it may be acceptable to use the (b) (4)

The Agency encouraged the Sponsor to continue development of their biomarker evaluations, as this may provide important supportive information. Please see post-meeting minutes below.

Question 2: The dose to be evaluated in Phase 3 study GBT440-031 was selected based on treatment response and safety data from Study GBT440-001 and PK/pharmacodynamic (PK/PD) modelling/simulation. The dose GBT440 900 mg was selected to achieve Hb modification in the range of 10% to 30%, an efficacy target which is genetically validated for

fetal hemoglobin. Does the Agency agree with the rationale provided and the dose GBT440 900 mg proposed for evaluation in Study GBT440-031?

FDA Response to Question 2: No. Provide a final summary table of safety and efficacy results of the multiple dosing cohorts from the GBT440-001 and GBT440-007 trials when available with the justification of the proposed dose (900 mg once daily) for the phase 3 trial (GBT440-31) that includes the adolescent population (12 to <18 years of age).

No, instead of using one endpoint (Hb modification), your dose selection should be based on all the evaluated PD markers (Hb increase, reticulocyte count, sickle cell reduction, LDH reduction, etc.). These PD markers indicate that maximum drug effect may be achieved at doses of 500 to 700 mg; therefore, there is no clear justification for the selected dose of 900 mg once daily. Also see response to Question 1.

Discussion:

The Sponsor provided additional safety data observed with 90 days GBT-440 treatment at 900 mg to support the safety of selected doses of 900 mg and 1500 mg. The Sponsor provided one subject's dose-response (biomarker) profiles during dose-adjustment to support the use of Hb occupancy >20% in selection a dose that may provide clinical benefit in patients with SCD. The Sponsor also clarified that pre-dose concentrations (Cmin) of GBT440 were used in the calculation of Hb occupancy. The Agency stated that the dose-response analyses are not conclusive due to the small number of subjects in each cohort, significant PK variability, and the narrow dose range investigated. The Agency recommended the Sponsor conduct model-based exposure-response analyses to potentially overcome the above issues and to support the Phase 2 dose selection. Additionally, the Agency recommended that the Sponsor include justification for the selected target Hb occupancy and a description of how Hb occupancy is determined in patients to support the Phase 2 dose selection. The Agency also suggested the Sponsor to consider alternative dosing regimens such as twice a day dosing regimen if high Cmax leads to significant adverse events. The Sponsor agreed to provide these analyses and information with the protocol for the proposed Phase2/3 trial.

Question 3: Does the Agency agree with the design of the proposed Phase 3 study (Study GBT440-031) including the study population (adults and adolescents), sample size, planned evaluations of efficacy and safety, plan for dose reduction/study drug discontinuation, and study duration?

FDA Response to Question 3: No. Your proposed (b) (4)

You have not provided any information/justification regarding the thresholds you have chosen and have not provided evidence that this (b) (4) is predictive of clinical benefit in sickle cell disease.

Discussion:

See discussion captured for Questions 1 and 2 and post-meeting note.

Question 4: Does the Agency agree with the proposed monitoring plan for Study GBT440-031 including safety assessments performed at each study visit, frequency of visits and the plan for Data Safety Monitoring Board (DSMB) oversight of the study?

FDA Response to Question 4: Yes.

Discussion:

No discussion occurred.

Question 5: Does the Agency agree with the proposed [REDACTED] (b) (4)

FDA Response to Question 5: No. See response to Question 3.

Discussion:

No discussion occurred.

Question 6: Does the Agency agree with the key secondary endpoint [REDACTED] (b) (4) and the proposed alpha-controlled secondary endpoints and multiple testing procedures as defining an improvement in clinical outcomes in Phase 3 Study GBT440-031?

FDA Response to Question 6: Your proposed endpoints of [REDACTED] (b) (4) the rate of VOC are measurements of clinical benefit and could be acceptable endpoints for registrational purposes depending on how they are defined and the validation of your [REDACTED] (b) (4). See also response to Question 3.

[REDACTED] (b) (4)

Discussion:

See discussion captured for Questions 1 and 2 and post-meeting note.

Additional Comment:

Question 7: Does the Agency agree that the proposed Phase 3 study (Study GBT440-031), if positive for both the primary and key secondary ^{(b) (4)} endpoints, together with confirmatory evidence from the Phase 2 program would together provide adequate evidence of effectiveness to support review of an NDA for this fast track and orphan drug designated therapy, according to the FDAMA 115 requirement of a single adequate and well controlled study together with confirmatory evidence?

FDA Response to Question 7: No. See response to Question 3.

Discussion:

No discussion occurred.

Question 8: Does the Agency agree that the proposed NDA safety database in adult and pediatric subjects is adequate to support an NDA for GBT440 for the treatment of SCD in adult patients and pediatric patients ^{(b) (4)}?

¹ Guidance for Industry: Electronic Source Data in Clinical Investigations
(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm328691.pdf>)

FDA Response to Question 8: Your proposal for the safety database appears acceptable at this time. However, this will be a review issue.

Discussion:

No discussion occurred.

Question 9: Does the Agency agree that the proposed plan to study GBT440 in adolescents and in adults with SCD in the proposed Phase 3 efficacy and safety study and to conduct single-dose PK and longer-term safety and PK/PD bridging studies (b) (4)

FDA Response to Question 9: The overall plan for pediatrics is not unreasonable.

(b) (4)

Discussion:

No discussion occurred.

Question 10: Does the Agency agree that available data in adults and forthcoming data in adolescent subjects (from Part B of Study GBT440-007 and planned Study GBT440-031) (b) (4) on the schedule described in Section 6 of the Meeting Background Package?

FDA Response to Question 10: Yes, the review of the adult and adolescent data may allow dosing of GBT440 in your planned single and multiple dose pediatric PK studies.

Discussion:

No discussion occurred.

Question 11: Does the Agency agree that the proposed Phase 2 study (Study (b) (4)), if positive in outcome for safety and efficacy across the primary endpoint, will support a request for breakthrough designation? Does the Agency have any comments about the study design?

FDA Response to Question 11:

(b) (4)

Discussion:

The Agency stated that as development continues with GBT-440 and the sponsor has preliminary clinical evidence suggesting that GBT-440 may demonstrate a substantial improvement on a clinically significant endpoint over available therapy, the Agency would be willing to provide preliminary breakthrough designation request advice before official submission of the breakthrough designation request.

2.2. Clinical Pharmacology Questions

GBT has the following specific questions related to clinical pharmacology:

Question 12: Apart from the data requirements for the new tablet formulation with which the proposed Phase 3 study is planned to be conducted, does the Agency agree that the proposed clinical pharmacology program supports initiation of the planned Phase 3 study (GBT440-031) and supports the submission of an NDA for GBT440 for SCD?

FDA Response to Question 12: No. Although the proposed clinical pharmacology program appears to be adequate to support the initiation of the planned Phase 3 study, if a dosing regimen higher than 600 mg QD is selected for the Phase 3 trial, additional DDI assessment for GBT440 as an inhibitor should be conducted at the Phase 3 study dose to support the submission of the NDA so that risk of DDI is not underestimated.

Discussion:

No discussion occurred.

Question 13: Does the Agency agree that measuring the concentration of GBT440 in blood and plasma in the proposed Phase 3 study is adequate and that measuring of the minor active metabolite representing 2.5% and 2.75% of the total exposures (AUC) in blood and plasma, respectively, is not necessary?

FDA Response to Question 13: Yes, we agree.

Discussion:

No discussion occurred.

Question 14: Does the Agency agree with the use of population PK analysis to evaluate the effects of gender, age, and other covariates on the disposition of GBT440?

FDA Response to Question 14: Yes, we agree.

Discussion:

No discussion occurred.

Question 15: Does the Agency agree that the electrocardiogram (ECG) exposure/response QTc analysis of data from Study GBT440-001 provided under separate forthcoming submission to IND 121691 (serial number to be assigned) exclude a QTc effect of concern and that therefore a thorough QTc study is not required to support an NDA for GBT440 for SCD?

FDA Response to Question 15: More information is needed to respond to this question.

Discussion:

No discussion occurred.

Question 16: Does the Agency agree that the planned drug-drug interaction (DDI) studies are adequate to support an NDA for GBT440 for use in the treatment of SCD?

FDA Response to Question 16: No. See response to Question 12.

Discussion:

No discussion occurred.

Question 17: Does the Agency agree that the planned studies in special populations are adequate to support an NDA for GBT440 for use in the treatment of SCD?

FDA Response to Question 17: No. Please provide rationale why subjects with severe hepatic impairment are excluded in the planned hepatic impairment study.

Additional Clinical Pharmacology Comments:

Regarding the proposed Phase 3 study GBT440-031:

- Please include the sampling time points for PK and 12-lead ECG assessment.
- Please include exclusion criteria for bilirubin so that subjects with moderate and severe hepatic impairment will be excluded.
- Patients should be advised to avoid taking GBT440 with high-fat meals.

Discussion:

No discussion occurred.

2.3. Nonclinical Pharmacology/Toxicology Questions

GBT has the following specific question related to nonclinical pharmacology/toxicology:

Question 18: Does the Agency agree that the nonclinical data package available at the time of the start of the Phase 3 study (including the proposal for provision of data from the chronic

studies as outlined in Section 7.1.3.4) is adequate to support the proposed Phase 3 study (GBT440-031)?

FDA Response to Question 18: The Agency is concerned with the findings from the ongoing 26-week rat and 39-week monkey studies that were summarized in the meeting package, specifically the moribundity/mortality that apparently began occurring at around 90 days of dosing at human equivalent doses that are lower than the proposed dose for Phase 3. We note that the safety margins based on AUC from 13-week monkey study are 2.1 and 1.8 in males and females, respectively. Safety margins based on body surface from 13-week monkey study area appear to be <1 (30 mg/kg in monkeys represents a HED of 9.73 mg/kg or 681.1 mg total per dose for a 70 kg patient compared to 900 mg dose for Phase 3).

The Agency expects that audited draft reports with signed anatomic pathology reports, or finalized study reports for the 26-week and 39-week repeat-dose studies in rats and monkeys, respectively, will be made available for FDA review before extending dosing in the Phase 3 clinical trial beyond 3 months.

Discussion:

No discussion occurred.

Question 19: Does the Agency agree that the nonclinical data package, including the standard battery of reproductive and chronic toxicity studies and the carcinogenicity study in the transgenic mouse (with submission of 2-year carcinogenicity data following the NDA action date) is adequate to support an NDA for GBT440 for SCD?

FDA Response to Question 19: The nonclinical data package appears reasonable to support an NDA. The adequacy of studies scheduled for future completion will be a review issue.

Discussion:

No discussion occurred.

Question 20: Does the Agency agree that a definitive juvenile toxicity study is not required as a stepwise approach to dosing in children is proposed in Section 6 (Plan for Evaluation of GBT440 in Pediatric Population – see Figure 22) of the background package?

FDA Response to Question 20: Yes, we agree.

Discussion:

No discussion occurred.

2.4. Regulatory Questions

GBT has the following specific question related to regulatory activities:

Question 21: Although orphan drug designation has been granted for GBT440 for the treatment of SCD and the NDA will be exempt from PREA (FDCA 505B) requirements [including the 210-day review of a Pediatric Study Plan (PSP)], (b) (4)

[REDACTED]

FDA Response to Question 21: No, the Agency is not in agreement with your proposed development plan.

Discussion:

No discussion occurred.

Question 22: Does the Agency agree that the proposed pediatric study plan will support a (b) (4)

[REDACTED]

FDA Response to Question 22: (b) (4)
[REDACTED] we cannot address this question.

Discussion:

No discussion occurred.

Question 23: Does the Agency agree that the separate EOP2/CMC-specific meeting to discuss chemistry and manufacturing considerations for GBT440 may be requested as a Type B meeting?

FDA Response to Question 23: Yes.

Discussion:

No discussion occurred.

Additional comments for your current design and analysis plan:

- **The efficacy endpoint analyses population should be intent-to-treat (ITT) population which includes all randomized subjects.**
- **In your current analysis plan, if the sample size in any strata is less than 5, the primary analysis (CMH test) will be replaced with Fisher's exact test. We note that CMH test works well with sparse data and recommend that you continue to use CMH test with pre-specified rules to combine extremely sparse data, e.g. strata with sample size less than 2. Fisher's exact test may be used as a sensitivity analysis.**
- **Please include age (adolescent versus adult) as a stratification factor.**
- **You noted that for the primary efficacy endpoint, missing data at week 24 will be imputed with data closest to the Week 24 visit but after Week 17 visit. We recommend the sensitivity analysis that considers missing Week 24 data as non-responders. Please also clarify whether data post Week 24 would be used for imputation.**
- **We recommend the sensitivity analysis considering subjects with rescue medications as non-responders for the primary endpoint.**
- **We note that missing at random (MAR) assumption you made in your analysis of SCD total score might not be reasonable. We recommend that you conduct sensitivity analyses assuming missing not at random (MNAR). We also recommend sensitivity analyses using alternative variance covariance structures for the MMRM you proposed.**
- **Every subject should be accounted for in the analysis by either being measured for the primary endpoint or properly accounted for if not measured for the primary endpoint. The number of subjects not measured for an endpoint should be kept to a minimum. Too much missing data undermine the reliability and confidence of the results. Sensitivity analyses should be performed to account for the limitation of the data and to examine the potential impact of any missing data. For further advice on missing data see the National Academies of Sciences report on The Prevention and Treatment of Missing Data in Clinical Trials.**

Post-Meeting Comment:

For products seeking an indication for the treatment of a life-threatening disease, we recommend a primary endpoint be an objective measure of the disease. In this case, the addition of a symptom benefit claim can provide important supportive data of clinical benefit.

3.0 OTHER IMPORTANT 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 start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a [Study Data Standards Resources](#) web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER

strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

See attached Sponsor handout/slides.

15 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

/s/

NICOLE J GORMLEY
08/08/2016