CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761367Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BLA 761367

REFUSAL TO FILE

CSL Behring LLC
1020 First Avenue
P.O. Box 61501
King of Prussia, PA 19406-0901

Attention: Loren Kohrs, MS, RAC
Associate Director, Global Regulatory Affairs

Dear Loren Kohrs:[1]

Please refer to your biologics license application (BLA), dated June 29, 2023, received June 29, 2023, under section 351(a) of the Public Health Service Act for garadacimab.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 601.2(a) for the following reasons:

- The results of the Rabbit Pyrogen Test conducted on three batches of garadacimab drug product in accordance with 21 CFR 610.13(b) were not available for our review at the time of submission or at the time of filing.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

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

PROPRIETARY NAME

The review of your proposed proprietary name has been terminated due to the refuse to file reasons as described in this letter. Please resubmit the proposed proprietary name if the application is resubmitted. If you do not have a conditionally acceptable proprietary name, you may submit a Request for Proprietary Name Review to your IND.

If you have any questions, call Katherine Won, Regulatory Project Manager, at 301-796-7568.

Sincerely yours,

{See appended electronic signature page}

Kelly Stone, MD, PhD
Associate Director for Therapeutic Review
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/

KELLY D STONE
08/28/2023 02:56:48 PM

IND 139936

MEETING PRELIMINARY COMMENTS

CSL Behring LLC
1020 First Avenue
P.O. Box 61501
King of Prussia, PA 19406-0901

Attention: Loren Kohrs
Associate Director, Global Regulatory Affairs

Dear Ms. Kohrs:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for CSL312 (garadacimab).

We also refer to your December 22, 2022, correspondence requesting a pre-BLA meeting to obtain feedback on the key elements to be included in a marketing application planned for 2023.

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.

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

If you have any questions, call me at (301) 796-1230.

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonology, Allergy, and Critical Care
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: March 22, 2023, 4 PM – 5 PM EST
Meeting Location: Teleconference

Application Number: IND 139936
Product Name: garadacimab

Indication: Hereditary Angioedema
Sponsor Name: CSL Behring

Regulatory Pathway: 351(a) of the Public Health Service Act

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 22, 2023, from 4 PM to 5 PM EST, via teleconference between CSL Behring and the Division of Pulmonology, Allergy, and Critical Care. 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

CSL Behring (CSLB) submitted a Type B meeting request on December 22, 2022, to obtain feedback on the key elements to be included in a marketing application planned for 2023. The Division granted the meeting on January 23, 2023. CSLB submitted the briefing package on February 17, 2023. The expected outcome of the meeting is to clarify questions outlined in the briefing package. CSLB's questions from the briefing package are printed in ***bold italics font*** and FDA's responses are in normal font.

2.0 DISCUSSION

2.1. Combination Product

2.1.1. *Question 1*

Does the Agency agree with the proposed Human Factors (HF) validation package submission plan and timeline for the autoinjector (AI) including submission of the supplementary study no later than 30 days after submission of the original BLA?

FDA Response to Question 1:
We generally expect that the submission to be complete at the time of filing. As such, we request that you submit the HF validation package for the AI presentation when you submit your original BLA for the AI presentation.

2.2. Quality

2.2.1 *Question 2*

CSL Behring LLC (CSLB) plans to submit 24-month stability data with the initial Biologics License Application (BLA) and 36-month stability data during BLA review. Does the Agency agree to accept the additional 36-month stability data during BLA review?

FDA Response to Question 2:
Considering that garadacimab was granted Orphan Drug Designation as well as Fast Track Designation, from a product quality perspective, your plan to submit 36-month stability data obtained from CSL312 semifinished product (SFP) 200 mg and CSL312 final combination drug product (DP) 200 mg with needle safety device (NSD) under (b) (4) during the BLA review cycle appears reasonable. However, to ensure that we have sufficient time to review your stability updates submitted during BLA review, only simple stability updates (i.e., stability data and analyses performed under the same conditions for the same batches in the same container closure system(s) using the same tabular presentation as in the initial BLA submission) submitted up to month 7 for a standard submission and month 4 for a priority submission will be reviewed and considered in shelf-life determinations.

2.3. Clinical

2.3.1. *Question 3*

CSL Behring LLC (CSLB) believes that the safety data package meets the requirements as previously communicated by the Agency to support the initial Biologics License Application (BLA). Does the Agency agree?

FDA Response to Question 3:
You propose to submit a safety database derived from 3 clinical trials – Study 2001 (phase 2 dose-ranging), Study 3001 (phase 3 pivotal), and Study 3002 (ongoing open label extension). Your safety database will consist of 13 weeks of controlled data from 16 subjects (8 garadacimab, 8 placebo) from Study 2001, 6 months of controlled data from 65 subjects (39 garadacimab, 26 placebo) in Study 3001, and up to 16 months of data in 161 subjects in the OLE, including 12 months of garadacimab exposure in 41 subjects. In terms of pediatric exposure, there will be 6 months of controlled data from 4 adolescents in Study 3001 and up to 16 months of exposure in 10 adolescents including 12 months of exposure in 2 adolescents from Study 3002. The safety database appears sufficient to support filing, but the adequacy of the safety database will be a review issue.

2.3.2. *Question 4*

In line with Food and Drug Administration input at the End of Phase 2 meeting in July 2020, the 4-Month Safety Update (4MSU) will include the safety data set from ~130 study participants with at least 12 months of exposure to assess the long-term safety of garadacimab. Does the Agency agree with the proposed approach and content for the 4MSU?

FDA Response to Question 4:
Your 4 month/120-day safety update will include an additional 5 months of data (September 2022 – February 2023) from Study 3002 (open-label extension), which will provide at least 12 months of garadacimab exposure in 130 subjects. The submission will include an updated cumulative pooled ISS dataset along with interim study report and appendices for Study 3002. Your proposal for the 4-month safety update appears reasonable.

2.3.3. *Question 5*

It is CSL Behring LLC's (CSLB) position that garadacimab does not meet the criteria for a Risk Evaluation and Mitigation Strategy (REMS). Does the Agency agree?

FDA Response to Question 5:
Based on the limited information available, we have not identified a safety concern that appears to warrant a risk evaluation and mitigation strategy; however, a final determination will be made during the BLA review.

2.4. Regulatory

2.4.1. *Question 6*

CSL Behring LLC (CSLB) plans to include the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) within the Summaries of Clinical Efficacy and Safety in the electronic Common Technical Document (eCTD) of this application. Does the Agency agree?

FDA Response to Question 6:
Yes, we agree with your plan to submit the ISE and ISS within the Summaries of Clinical Efficacy and Safety in the eCTD provided that the information fits within the space constraints of Module 2.

Regarding submission of immunogenicity data, we recommend that you provide an Integrated Summary of Immunogenicity in eCTD subsection 2.7.2.4. This Integrated Summary of Immunogenicity should include:

a. An immunogenicity risk assessment specific to your product

b. Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods used in the program

c. Links to method development and validation reports for the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from the pivotal clinical study(ies)

d. Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed

e. Summary results of immunogenicity analysis for all clinical studies that collected immunogenicity data, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse events) data

f. Traceability of DP lots used in all your clinical studies

g. All immunogenicity assays, that were used during clinical development and a description of which assays were used for which studies or patient groups.

2.4.2. *Question 7*

Does the Agency agree that the planned content of electronic Common Technical Document (eCTD) sections 3.2.P and 3.2.R of the initial Biologics License Application (BLA), as displayed in the proposed Module 3.2.P/3.2.R table of contents, including the proposed placement of the combination product/device information, is appropriate for this initial application?

FDA Response to Question 7:
The planned content and proposed placement of the combination product/device information appears appropriate for your initial application. Note that the acceptability of the contents contained within each module to support approvability of your application is a review issue. Ensure that your demonstration of device verification and validation includes evaluation of the device essential performance requirements following representative preconditioning, particularly after simulated shipping per ASTM D4169 and accelerated aging per ASTM F1980. Ensure that your evaluation of performance following preconditioning also includes verification of performance of the safety critical attributes of the needle safety device for each proposed device constituent (e.g., needle safety activation and override forces) to a recommended confidence and reliability interval of 95%/99%, using an attribute or variable sampling strategy.

2.4.3. *Question 8*

CSL Behring LLC (CSLB) has included an overview of the complete nonclinical package and the Study Data Standardization Plan (SDSP). Does the Agency agree that the nonclinical data package and planned data format are adequate to support registration of garadacimab?

FDA Response to Question 8:
The adequacy of your nonclinical program to support an eventual BLA is a review issue. Upon preliminary review, we agree that the content of your nonclinical package is supportive.

Additional Statistics and Data Standards Comments:

1. Page 16 of the ISS SAP, General Considerations notes that SDTM and ADAM datasets for the ISS will be pooled across the 3 trials (Study 2001, Study 3001, and Study 3002). Given the differences in study designs and duration and lack of blinding and a control arm in some studies or study periods, we anticipate that Study 3001 will serve as the primary source for our safety assessment. However, to facilitate our review of the ISS data, we request that you consider the following as you assemble your data package:

a. Include your 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.)

b. Study 2001 includes multiple treatment periods. Revise your ISS SAP to include planned criteria for analyses across the clinical program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

2. Within the ISS dataset, include a flag for the participants who rolled over from Study 2001 and 3001 into Study 3002.

3. The ISS must include all deaths, serious adverse events (SAE), adverse events of special interest (AESI), and adverse events (AE) leading to discontinuation for all controlled trials regardless of the drug studied.

4. In the Study Data Standardization Plan, multiple MedDRA versions are listed: v21.0/24.1 for Study 2001, v23.0/25.0 for Study 3001, v23.1/25.1 for Study 3002, and v25.1 for the ISS. To facilitate the safety assessment, the same version of MedDRA should be used across Studies 2001, 3001, 3002, and the ISS.

5. For Studies 2001, 3001, and 3002, provide a flag in the AE dataset or a separate dataset that maps preferred terms to the adverse events of special interest (AESIs).

6. Page 18 of the ISS SAP includes a description for summarizing results for subjects treated with 75 mg CSL312 or 400 mg CSL312 q2wk in Study CSL312_2001. Include deaths and AEs leading to discontinuation (if any) in this list of summary tables in your plan.

7. For the planned subgroup analyses (page 19 of the ISS SAP), include the subgroups of age, sex, race, and ethnic origin.

8. Page 26 of the ISS SAP describes that risk differences and 95% confidence intervals will be calculated to compare the 200 mg CSL312 treatment arm with the placebo arm for AESIs and SAEs. In addition, summarize AE preferred terms greater than 3% in this manner.

9. The data definition file (i.e., Define.xml) should include adequate detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. Submit corresponding Define.pdf files in addition to the Define.xml files.

10. For pivotal Study 3001, provide a table that contains the following:

    a. Dates of first patient and last patient visits

    b. Dates of data lock

    c. Dates of the initial protocol and all revisions with a hyperlink to the protocol and each revision; include a hyperlink to Summary of Changes for each version

    d. Dates of all versions of the Statistical Analysis Plan (SAP) with a hyperlink to each SAP; include a hyperlink to Summary of Changes for each version and specify the number of subjects enrolled in the trial at the time of each protocol change.

11. Submit a table detailing all the tables and figures featured in the main clinical efficacy and safety sections (not the appendix) of the BLA. The table should contain the following:

    a. Title of the table or figure in BLA

    b. A page number hyperlink to the location of the table or figure

    c. A name hyperlink to the code (and/or macros) used to create the table or figure

    d. Names of the datasets used to create the table or figure (hyperlinks are useful but not necessary).

12. For derived (analysis) datasets used to conduct your analyses, indicate the case report form (CRF) pages and tabulation datasets from which the information was derived.

13. For all derived datasets, submit all scripts/programs used to create the analysis datasets. The scripts and define files should be sufficient to facilitate understanding of how the analysis datasets were created. If variables are inadequately described in the define files, you may need to also submit all datasets (and associated define files) used to derive your analysis datasets.

14. All data for a given domain or data set (e.g., ADLB) should be contained in one dataset. The dataset should include flags to permit evaluation of the relevant analysis populations as outlined in the ISS SAP and CSR.

15. Submit a dataset that contains all subjects that were unblinded prior to data lock. The dataset should include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

16. Evaluate all AEs based on logical groupings of preferred terms (PTs) using standard MedDRA queries or other appropriate groupings of PTs. Include in your submission the procedures and rationale used for grouping of PTs. The intent of safety analyses based on grouped PTs is to avoid splitting of PTs so that adverse events are adequately captured (e.g., “ABDOMINAL PAIN, UPPER”, “ABDOMINAL PAIN, LOWER”, “ABDOMINAL PAIN” should be grouped together in the assessment for abdominal pain).

17. DILI: Analysis of liver safety should be included in your overall safety assessments. Incorporate and summarize investigator reports and PTs related to potential hepatic injury not limited to the specific liver biochemistry elevations. Refer to FDA guidance for industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation[2] and relevant sections from Technical Specifications for Submitting Clinical Trial Data Sets for Treatment of Noncirrhotic Nonalcoholic Steatohepatitis (NASH)[3] for additional guidance on liver safety data submission.

18. Submit an annotated CRF (aCRF) for each study.

19. Submit narratives and CRFs or all deaths, serious adverse events (SAEs), AESIs, adverse events leading to permanent treatment discontinuation and patients who experienced treatment emergent pregnancy regardless of attribution to the investigational drug product or treatment arm.

20. For Study 3001, provide a table in the CSR with summary statistics for the mean, median, and range of aPTT, PT, and bleeding time by treatment arm and by study visit.

Additional Clinical Comments:

1. We note that your proposed indication is for prophylaxis to prevent HAE attacks in adolescents and adult patients. We recognize that Type III HAE is rare and has unmet need with no approved therapies. However, we note that your pivotal trial only evaluated subjects with Types I and II HAE. Whether or not your BLA

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/drug-induced-liver-injury-premarketing-clinical-evaluation
[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/technical-specifications-submitting-clinical-trial-data-sets-treatment-noncirrhotic-nonalcoholic

submission contains sufficient evidence to support the proposed indication will be a review issue.

2. We acknowledge your plan to request a priority review of your BLA submission. To receive priority review, the program needs to clearly demonstrate significant improvement in safety or efficacy compared to currently available therapies. We refer you to the FDA Guidance on Expedited Programs.[4] A determination regarding priority or standard review will be made at the time of filing.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our January 23, 2023, 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 VII. 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.[5]

[4] https://www.fda.gov/files/drugs/published/Expedited-Programs-for-Serious-Conditions-Drugs-and-Biologics.pdf
[5] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

APPEARS THIS WAY ON ORIGINAL

REQUIRED PEDIATRIC ASSESSMENTS

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because your indication has orphan drug designation, you are exempt from this requirement.

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[6] and Pregnancy and Lactation Labeling Final Rule[7] 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

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

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.

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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*.[10]

[8] https://www.fda.gov/media/84223/download
[9] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[10] https://www.fda.gov/media/85061/download

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

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/

ELAINE SIT
03/17/2023 08:52:08 PM
Signed on behalf of Colette Jackson

IND 139936

MEETING MINUTES

CSL Behring LLC
1020 First Avenue
P.O. Box 61501
King of Prussa, PA 19406-0901

Attention: Ron Carnal
Regulatory Senior Manager, Global Regulatory Affairs

Dear Mr. Carnal:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CSL312

We also refer to the teleconference between representatives of your firm and the FDA on July 7, 2020. The purpose of the meeting was to discuss the adequacy of the overall safety data package, clinical pharmacology assessments, and nonclinical pharmaco-toxicology evaluation to support a BLA.

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

Sincerely,

{See appended electronic signature page}

Colette Jackson
Senior Regulatory Health Project Manager
Division of Pulmonary, Allergy, and Critical Care
Office of Immunology and Inflammation
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: July 7, 2020 from 12 PM to 1 PM EST
Meeting Location: via teleconference

Application Number: IND 139936
Product Name: CSL312

Indication: Hereditary Angioedema
Sponsor Name: CSL Behring LLC

Meeting Chair: Sally Seymour, M.D.
Meeting Recorder: Colette Jackson

FDA ATTENDEES

Sally Seymour, M.D., Division Director, DPACC
Banu Karimi-Shah, M.D., Deputy Division Director, DPACC
Stacy Chin, M.D., Clinical Team Leader, DPACC
Kelly Stone, M.D., Ph.D., Clinical Reviewer, DPACC
Colette Jackson, Senior Regulatory Health Project Manager, DPACC
Carol Galvis, Ph.D., Pharmacology/Toxicology Team Leader
Jessica Bonzo, Ph.D., Pharmacology/Toxicology Reviewer
Yunzhao Ren, Ph.D., Clinical Pharmacology Reviewer
Bavna Saluja, Ph.D., Clinical Pharmacology Team Leader
Pick-Wei Lau, Ph.D., Product Quality Reviewer
Yongman Kim, Ph.D., Statistical Team Leader
Susan Duke, Ph.D., Statistical Reviewer

SPONSOR ATTENDEES

Mitte Doyle, M.D., Vice President, Clinical and Therapeutic Area Strategy
Mihai Alexandru Bica, M.D., Director, Global Clinical Safety and Pharmacovigilance
Gerald Hoebarth, Ph.D., Senior Manager, Pharmacology & Toxicology
John-Philip Lawo, MS, Director, Biostatistics
Dipti Pawaskar, Ph.D., Director, Clinical Pharmacology and Translational Development
Lee Severson, Pharm.D., Global Regulatory Lead, Global Product Strategy
Tara Chapman, Pharm.D., Senior Director, Global Regulatory Affairs
Loren Kohrs, MS, Manager, Global Regulatory Affairs Region North America

1.0 BACKGROUND

CSL Behring (CSLB) submitted a Type B meeting request on February 10, 2020, to seek advice from the Agency on clinical development of the CSL 312 prior to initiating a pivotal phase 3 study. The Division granted the meeting on March 4, 2020. CSLB provided the briefing package on March 16, 2020. Specific topics to discuss and the expected outcome of the meeting is to clarify the study design and primary endpoint to support the target indication, the dosing regimen, sample size, and inclusion of adolescent (12-17 years of age) patients for the phase 3 pivotal study. In addition, CSLB would like to obtain agreement on the adequacy of the overall safety data package, clinical pharmacology assessments, and nonclinical pharmacotoxicology evaluation to support a new product registration. The FDA sent Preliminary Comments to CSLB on June 30, 2020. CSLB provided their points of discussion document via email on July 2, 2020. This was also officially submitted to their IND on July 2, 2020, and is included as an attachment under Section 6 in these meeting minutes.

2.0 DISCUSSION

Introductory Comments:
You propose to investigate the efficacy and safety of self-administered CSL312 in the prophylaxis of acute attacks of hereditary angioedema (type 1 or type 2), using a phase 3, randomized (1:1), double-blind, placebo-controlled, two-arm trial design, enrolling (b) (4) *patients. You also propose an open label extension study, the details for which were not provided. CSL312 is a new molecular entity that binds to and inhibits the catalytic domain of Factor XIIa. Factor XIIa is a mediator of the kallikrein-kinin, coagulation, and complement systems, and promotes cytokine production. Based on this product being a new molecular entity (NME) with broad biologic effects, the safety assessment is a critical element of your development program and your trial will need to have a larger safety database than proposed to support a licensing application.*

Question 1: Proposed Phase 3 Study Design

The Sponsor plans to conduct a single pivotal phase 3 study with CSL312 in HAE to support an indication for prophylaxis to prevent HAE attacks. Does the agency agree that the proposed phase 3 study design and clinical development program are adequate to support registration for the target indication?

FDA Response:
Conceptually, a single adequate and well-controlled phase 3 trial, in a rare disease such as HAE, might be sufficient to support a licensing application. However, the acceptability of this approach depends on the strength of the study design, robustness of the treatment effect, and adequacy of the safety database to inform the benefit/risk assessment. Based on your current proposal, we cannot necessarily agree that a single pivotal trial will be acceptable.

In general, evidence from at least two adequate and well-controlled studies is required to establish effectiveness. The FDA Guidance for Industry Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM078749.pdf) describes some settings where a single, properly designed and analyzed study may be sufficient to support a marketing application, in particular, when there is independent substantiation of effectiveness from related data or when evidence from the single study is both clinically and statistically very persuasive.

To ensure the adequacy of safety assessments and durability of treatment effect, we strongly recommend that you design your trial as a 26-week, randomized (1:1), double-blind, placebo-controlled, two-arm trial, with the primary efficacy endpoint assessed at 26 weeks. While we acknowledge your concern with placebo treatment beyond (b) (4) months, we believe that a 26-week treatment period is both feasible and necessary to adequately assess safety and efficacy for licensing. All patients should be provided with treatments for acute attacks as part of the trial.

Discussion:

CSLB referred to their points of clarification document that provided an overview of the phase 3 program and asked if the agency concurred with their assessment that the phase 3 trial, as designed, along with the open-label extension study, is sufficient to provide the clinical evidence required for registration. While the study design for the proposed (b) (4) month, placebo-controlled trial may be adequate to demonstrate efficacy, the FDA stated that (b) (4) months of placebo-controlled safety data will be insufficient to support a licensing application. The FDA acknowledged that the open-label extension study will provide additional safety data; however, uncontrolled safety data is often difficult to interpret and therefore limited in its utility. As a result, the FDA recommends a 6-month placebo-controlled trial to provide sufficient safety and efficacy data from a single trial to support the BLA. (b) (4) The FDA (b) (4) and re-emphasized the need for a 6-month placebo-controlled trial to provide adequate safety data to support licensing.

With regard to the proposed sample size for the pivotal phase 3 trial, the FDA acknowledged the Sponsor's increase from a total of (b) (4) to (b) (4) subjects but noted that (b) (4) subjects is still on the low end for a typical HAE development program. Recognizing that (b) (4) subjects may be sufficient to demonstrate efficacy and that the Phase 3b open label extension study will include additional long-term safety data for approximately (b) (4) subjects, the FDA reiterated the importance of controlled safety data to support a licensing application.

[redacted] While the overall number of subjects with long-term exposure might be acceptable, provided no significant safety issues are identified, the FDA stated the need for a longer duration of controlled safety data remains. The FDA acknowledged the rarity of HAE and small pool of patients available to study but noted that other programs have been able to provide 6 months of placebo data for both efficacy and safety at the time of an NDA or BLA submission. A placebo-controlled trial gives an advantage in case of safety issues that may arise and gives reassurance if the issue is not attributed to the drug. A 6-month placebo-controlled trial is required for the BLA submission.

Question 2: Primary Endpoint

The proposed primary endpoint is the time-normalized number of HAE attacks in subjects treated with once a month CSL312 or placebo from Day 0 through Day (b) (4). Does the agency agree that the proposed primary endpoint and efficacy analyses will provide sufficient and clinically meaningful results to support registration for the target indication?

FDA Response:

We agree with your primary efficacy endpoint of time-normalized number of HAE attacks, comparing patients treated with CSL312 to placebo treatment. However, we have the following recommendations:

1) *You do not provide criteria for defining an HAE attack in your protocol. Your protocol should include clear criteria for defining an HAE attack, including swelling that is characteristic of HAE, to prevent the premature use of rescue medications, such as for prodromal symptoms.*

2) *In your description of the run-in period, [redacted] We recommend that patients have ≥2 HAE attacks during the run-in period, ideally within a 4-week period, with a minimum observation period of 1 month and a maximum observation period of 2 months, to ensure adequate signal for efficacy assessment.*

3) *You propose to evaluate your primary efficacy endpoint through Day (b) (4). Although you select for patients with frequent HAE attacks during your run-in period, we have concerns about whether patients will have a sufficient number of attacks during the (b) (4) month treatment period to see clinically meaningful differences between the 2 groups. As noted in our response to Question 1, we recommend that the primary efficacy endpoint be assessed through Week 26.*

4) *We are unclear about your planned primary and secondary efficacy analyses. You state that you anticipate the data is distributed as a Poisson distribution, but you do not appear to be analyzing it with that distribution in mind. Consider analyzing using a negative binomial or Poisson regression model as a primary or a supportive analysis. For example, the lanadelumab analysis used a generalized linear model (GLM) for count data assuming a Poisson distribution with a log link function and Pearson chi-square scaling of standard errors to account for potential over dispersion.[1] The model included fixed effects for treatment group (categorical) and the normalized baseline attack rate (continuous), and the logarithm of time in days each subject was observed during the treatment period was used as an offset variable in the model.*

5) *Include in your protocol a plan for Type I error control for primary and any secondary efficacy endpoints that are of potential interest for the label.*

Discussion:

CSLB stated they will assess the primary endpoint at the end of the proposed double-blind period and asked if it is acceptable to have the primary endpoint assessed at month (b) (4). The FDA emphasized the need for a 6-month, placebo-controlled trial and recommended that the primary efficacy endpoint assessment be performed at the end of the 6-month period.

Question 3: Dosing Regimen

Does the agency agree with the proposed dose and dosing interval of CSL312 for the phase 3 Study CSL312_3001?

FDA Response:

1) *While the proposed dose and dose interval are supported by your phase 2 dose-ranging study, we note that a formulation of 200 mg/1.2mL will be used in the Phase 3 Study CSL312_3001, which is different from the formulation used in Studies CSL312_1001 and CSL312_2001 (100 mg/mL). Caution should be exercised when utilizing exposure-response analysis and extrapolation of findings from studies conducted with different drug product formulations. Therefore, the choice of the proposed dose and dosing interval, i.e., 400 mg SC for the first dose followed by 200 mg Q1M, in the Phase 3 study is at your own risk and discretion.*

2) *Provide justification for the use of a loading dose.*

3) *Your Study Design Figure in Section 3 should be updated to more clearly indicate the proposed loading dose.*

[1] Drugs@FDA, Lanadelumab Multidisciplinary Review
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/761090Orig1s000MultidisciplineR.pdf

Discussion:
The FDA referred to CSLB's points of clarification document and asked CSLB to clarify treatment for the placebo arm, specifically if a "loading dose" will be administered and how many injections will be given. The FDA is concerned with breaking the blind. CSLB clarified that the placebo group will receive "loading dose" treatment, which includes 2 injections at Week 1. The FDA responded that this is acceptable.

Question 4: Sample Size

Does the agency agree that the proposed sample size for the phase 3 Study CSL312_3001 will provide adequate confirmatory evidence to support registration of CSL312 for the target indication?

FDA Response:
No, we do not agree that your proposed sample size for Study CSL312_3001 will provide adequate confirmatory evidence of safety and efficacy to support registration. The size of your trial should be large enough to allow for an adequate safety assessment, including a sufficient comparison to placebo and adequate number of adolescent subjects, particularly given the broad biologic effects of CSL312. Your phase 1 trial included 32 patients who received CSL312 and your phase 2 study included 32 patients who received CSL312. Although you have estimated that (b) (4) patients will provide adequate power for assessing the primary efficacy endpoint in your phase 3 trial, neither the size nor duration of controlled safety data is sufficient for a new molecular entity intended for chronic, life-long use.

That said, we concur with your sample size calculations for efficacy.

a. *By our calculations (b) (4) total, not including the extra patients added in case of discontinuations) achieves 99% power. The reason for the small sample size is due to the large difference between treatment arms (1.5 in placebo and 0.3 in active).*

b. *With respect to power, instead of a (Poisson) model-based (monthly attack) rate ratio calculation, you are calculating a patient-level rate per month and using the non-parametric Wilcoxon rank sum test to compare rates between arms. We do not have concerns about bias of the comparison, but this might be less powerful because of the less sensitive non-parametric approach and no adjustment for baseline covariates. Therefore, we recommend negative binomial regression analysis as a supportive analysis (or for your consideration as a primary analysis) to see how the two results compare.*

Additional Statistics Comments:

1) *It is important to distinguish between treatment discontinuation and study discontinuation, and your handling of missing data in each of these scenarios.*

2) *Consider whether there are any intercurrent events and if so, describe in your protocol's statistics section as the estimand for your pivotal study's primary endpoint, time-normalized number of HAE attacks in subjects treated with once a month CSL312 or placebo (treatment descriptions, population, endpoint, summary measure and intercurrent events).*

3) *We recommend that you include a sensitivity analysis of the primary endpoint to address missing data in your SAP. We are interested to review your SAP and have adequate time to provide feedback prior to database lock.*

4) *Include definitions for ITT and PP populations in your protocol.*

Discussion:
See discussion under Question 1.

Question 5: Study Population

Does the agency agree that the proposed study population (i.e., inclusion/exclusion criteria) supports the target indication, and the planned enrolment of adolescent patients in the phase 3 Study CSL312_3001 is appropriate?

FDA Response:
We agree with your proposed study population. However, we have the following recommendations:

1) *In addition to previous comments, to ensure adequate signal, we recommend that patients have ≥2 HAE attacks within a consecutive 4-week period during the run-in period to be eligible for randomization, consistent with your phase 2 trial.*

2) *Provide justification for exclusion of patients* (b) (4).

3) *In your inclusion criteria "C4 antigen concentration below the lower limit of reference range", specify if this is at baseline, with HAE attacks, or either.*

4) *For your exclusion criteria, given the defined adverse events of special interest, include exclusion for patients with for bleeding or thrombotic disorders, or justify its omission.*

5) *Under Section 7.2, Prohibited Medications/Therapies, you prohibit the use of angiotensin-converting enzyme inhibitors,* (b) (4), *and estrogen-containing medications. Prohibition of these medications will limit the generalizability of the trial findings and would be included on the product label. Provide justification for prohibition, and if included in your final protocol, include as exclusionary criteria.*

Discussion:
The FDA stated a stronger justification will be needed to exclude patients (b) (4). CSLB stated they will review and provide a stronger justification. The FDA recommended stratifying randomization by age, particularly for adolescents, in order to obtain reasonable estimates in the lowest and highest age groups and to minimize imbalance within a stratum expected to be small in size. CSLB asked the FDA for the minimum number of adolescents needed in the trial. The FDA stated a specific target number cannot be provided, but suggested aiming to have an adequate representation of adolescent subjects across the age range, especially for the lower bound of 12 years of age.

Question 6: Safety evaluation, Number of Subjects & Duration

CSLB plans to generate additional data with CSL312 by conducting an open-label extension study CSL312_3002, which will enroll naïve subjects and rollover subjects from the previous phase 2 and phase 3 studies. The overall safety exposure database planned at the time of submission will include approximately (b) (4) patients with greater than 6 months exposure, and at least (b) (4) patients with greater than 12 months exposure to CSL312.

Does the agency agree that the proposed safety database is sufficient for registration of CSL312 for the target indication?

FDA Response:
We do not agree. Your pivotal trial will need to include at least 26 weeks of controlled safety data in larger number of subjects to allow for an adequate assessment of safety. We agree with your proposed open-label extension study to provide additional and long-term safety data to support a licensing application.

We have the following specific recommendations:

1) *You should have an external, independent Data Monitoring Committee (IDMC) for this trial and the DMC charter should be submitted to the IND prior to initiation of the trial.*

2) *Clarify in your protocol and DMC Charter that an independent statistician will be included as a full member (advising on further conduct of the study) on your IDMC.*

3) *Your protocol should specify the criteria used for grading the severity of adverse events. Since patients are healthy between HAE attacks, we recommend criteria appropriate for this population, such as the such as the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials: https://www.fda.gov/media/73679/download*

4) *Your protocol should include clear criteria for discontinuation of investigational product for individual patients, based on severity of adverse events, and study stopping rules for safety.*

5) *To ensure a reliable safety evaluation and to support the benefit-risk assessment, we recommend you submit the following:*

   a. *Identification of key potential benefits and risks, e.g., in a value tree.*

   b. *A discussion of the sufficiency of the sample size and duration of studies in the development program to reliably evaluate safety. In particular, for your adverse events of special interest (AESIs), consider in your safety planning the sufficiency of the sample size to reliably evaluate safety and benefit-risk. Also consider your method of data collection, including whether each outcome will be ascertained based on specific items in a structured checklist/questionnaire (active ascertainment) or based on a planned grouping of specific PTs mapped from voluntary participant responses to open-ended questions (passive ascertainment).*

   c. *A plan for defining identified safety outcomes, including any planned groupings of AEs, e.g., with Standardized MedDRA Queries (SMQs) or preferred terms (PTs) or System Organ Classes (SOCs) or some other grouping of multiple events/PTs representing the same or similar underlying concepts.*

   d. *A plan for analyzing adverse events, both within studies and integrated across studies. For serious adverse events and AESIs, we recommend prospectively planned analyses that compare treatment groups with respect to risk, e.g., with a rate ratio, risk difference, hazard ratio, or relative risk, along with a confidence interval for the chosen metric to help quantify the uncertainty in the treatment comparison (no hypothesis testing is necessary).*

   e. *A plan for evaluating and communicating results for key benefit and risk outcomes.*

      i. *One source for useful safety graphs is: https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome, particularly the adverse event plot with frequency and risk differences plotted together for the most common adverse events in the HAE study.*

Discussion:

See discussion under Question 1.

Question 7: Clinical Pharmacology Package

Does the FDA agree that the current clinical pharmacology package is adequate and no further specific clinical pharmacology studies are necessary to support the registration of CSL312 for HAE?

FDA Response:

1) *Your proposed approach to not conduct drug-drug interaction studies, hepatic/renal impairment studies, and thorough QT study appears reasonable. However, you should provide adequate justification for not conducting these studies in your BLA submission.*

2) *Since you propose a different drug product formulation and a subcutaneous loading dose of 400 mg that has not been studied previously, we recommend that you adopt more intensive PK sampling scheme in the proposed Phase 3 study to sufficiently characterize the PK profile following the loading dose and one dose at steady-state for the to-be-marketed product. You should also characterize the time to reach PK steady-state.*

3) *You should evaluate the impact of immunogenicity on PK, PD, efficacy, and safety in the study report.*

Discussion:

CSLB referred to their points of clarification document and asked if the justification for PK sampling for the phase 3 trial is acceptable. The FDA referred to 21CFR 314.50 which mandates providing bioavailability information from the to-be-marketed formulation. The new formulation to be used in phase 3 trials has a higher osmolality than the previous one and it is uncertain if this will affect the absorption of the drug.

In addition, the FDA indicated that CSLB will also need to characterize the PK profile of the 400 mg SC loading dose as this has not been studied previously. The plan to collect (b) (4) is not sufficient for this purpose. CSLB could achieve this by either collecting more PK samples during the phase 3 study (i.e., Day 7, 14, 21 following the loading dose) or introduce an additional arm with 400 mg SC dose in a planned phase 1 study. CSLB stated they will take this into consideration as they move into their phase 3 program.

Question 8: Nonclinical Pharmacology and Toxicology

Does the FDA agree that the current nonclinical package presented below and in the Nonclinical Background Information (Section 15.3) is adequate and no further, specific pharmacology or toxicology studies are necessary to support registration of CSL312?

FDA Response:

The adequacy of your nonclinical program to support an eventual BLA is a review issue. Upon preliminary review, we agree that the supportive nonclinical pharmacology studies and repeat dose toxicity studies are sufficient. We have the following comments regarding your nonclinical program:

1. *Submit the final study report for the completed Local Tolerance and Bioequivalence study in rabbits (Study Number (b) (4)) prior to the start of your proposed Phase 3 clinical study.*

2. *Per the ICH S6(R1) guidance, when a biotechnology-derived product is active in rodents and rabbits, both species should be used for embryo-fetal development (EFD) studies, unless embryo-fetal lethality or teratogenicity has been identified in one species. Per summary Table 6 in the meeting package (p27), you have only conducted an EFD study in rabbits. Your primary pharmacology data indicates that rodents may be pharmacologically relevant species. Provide justification in the IND for the use of a single species in evaluation of the embryo-fetal developmental toxicity. If your justification is found inadequate, an additional study in a second (rodent) species might be needed.*

3. *We consider Type III HAE to be a serious disease with unmet medical need; therefore, regulatory flexibility with regard to the timing of submission of study reports may be warranted. We agree with your proposal to conduct the PPND study in parallel with your proposed clinical Phase 3 study. We acknowledge your intent to submit the carcinogenicity risk assessment prior to the start of your proposed clinical Phase 3 study.*

Discussion:

CSLB referred to their points of clarification document and asked the FDA if the justification outlined is sufficient to preclude CSLB from conducting an additional EFD study in a second rodent species. The FDA stated that the justification appears sufficient; however, the data and study reports must be submitted for review with the BLA. CSLB must also clearly identify and provide the rat binding data. CSLB stated they will provide this information in an amendment to the IND.

3.0 OTHER IMPORTANT MEETING 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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

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.[4]

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[4] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[5] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are 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[6] 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.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

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 FDA Study Data Technical 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 FDA.gov.[7] 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.

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[5] https://www.fda.gov/media/88173/download
[6] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[7] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

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[8] (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.[9] 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 FDA.gov.[10]

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).

[8] https://www.fda.gov/media/88173/download
[9] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[10] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

- 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[11] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[12]

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*.[13]

[11] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[12] https://www.fda.gov/media/109533/download
[13] https://www.fda.gov/media/85061/download

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified at the meeting.

6.0 ATTACHMENTS AND HANDOUTS

CSLB's points of clarification document provided via email on July 2, 2020, which was also officially submitted to the IND on July 2, 2020.

84 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

COLETTE C JACKSON
10/17/2020 11:23:17 AM