CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761354Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 142381

MEETING PRELIMINARY COMMENTS

Biogen MA Inc.
225 Binney Street
Cambridge, MA 02142

Attention: Rafael Dominguez Rodriguez, MSc, RAC
Senior Manager Regulatory Affairs

Dear Mr. Rodriguez:

Please refer to your pre-investigational new drug application (PIND) file for BAT1806.

We also refer to your correspondence, dated and received on April 29, 2022, requesting a meeting to gain alignment on the planned BLA submission.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call me at (240) 402-2925.

Sincerely,

{See appended electronic signature page}

Susie Choi, PharmD
Regulatory Project Manager
Rheumatology and Transplant Medicine
Division of Regulatory Operations-
Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD 4

Meeting Date and Time: June 28, 2022, 12:00-1:00 PM ET
Meeting Location: Teleconference

Application Number: pIND 142381
Product Name: BAT1806

Indication: BAT1806 is being developed for the same indications as approved for US-licensed Actemra
Sponsor Name: Biogen MA Inc.
Regulatory Pathway: 351(k) of the Public Health Service Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 28, 2022, 12:00- 1:00 PM ET, teleconference between Biogen MA Inc. and the Division of Rheumatology and Transplant Medicine. 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

Biogen MA Inc. (Biogen) is seeking advice on development plans for BAT1806 as a biosimilar to US-licensed Actemra through the 351(k) pathway. A meeting request was submitted on April 29, 2022. A teleconference was granted on May 27, 2022. Biogen's final questions included in the briefing package, dated April 29, 2022, are provided below in italics, followed by FDA responses in normal font.

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Biogen MA Inc. and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).

2.0 DISCUSSION

Question 1:
Is there an opportunity to leverage the inspection outcomes of the currently planned preapproval inspection (PAI) by the FDA for Bio-Thera's pending BLA for BAT1706 to support licensure of BIIB800 in lieu of requesting a separate PAI?

FDA Response to Question 1:

The facilities listed in each submission are evaluated using a risk-based approach at the time of submission. FDA will use all available tools and sources of information to support regulatory decisions on submitted applications. It is premature to comment on how any future inspections may impact the future assessment of the facilities for this product.

Question 2:
a) The Applicant believes that the pivotal and supportive non-clinical studies conducted with BAT1806 and RPs sourced from the US are sufficient to support a BLA submission for a biosimilar product. Does the Agency agree?

b) Does the Agency agree that all pivotal and supportive non-clinical studies conducted with BAT1806 and reference products sourced from the US, EU and China should be included in the tocilizumab biosimilar VIAL submission?

FDA Response to Question 2:

a) In general, the proposed *in vitro* biological and functional pharmacology studies comparing BAT1806 to US-licensed Actemra appear sufficient. A final determination will be made upon review of the BLA submission. Comparative analytical data of the proposed biosimilar and the reference product influence decisions about the animal and clinical data needed to support a demonstration of biosimilarity. If the comparative analytical data are considered inadequate, the Agency may advise additional physicochemical and functional testing and/or analysis of additional lots of the proposed biosimilar and reference product prior to considering whether an animal study would be appropriate to resolve remaining uncertainties.

   We also refer you to Nonclinical comment #8 in the Meeting Minutes dated July 30, 2020: "In the alternative, we note that you may wish to include in your application a justification for why animal studies are unnecessary (see section 351(k)(2)(A)(ii) of the PHS Act)."

b) If you ultimately choose to submit animal studies conducted with US-Actemra and/or EU-RoActemra, submission of nonclinical studies conducted with

BAT1806 and comparator products sourced from China would not be necessary for your BLA submission.

Question 3:
In the Tocilizumab biosimilar VIAL submission, the Applicant does not intend to provide Standard for Exchange of Nonclinical Data (SEND) for the 4-week repeat dose toxicity study conducted with BAT1806. Does the Agency agree that SEND datasets are not required for the toxicology studies conducted with BAT1806 to be included in the Tocilizumab biosimilar VIAL submission?

FDA Response to Question 3:
Refer to FDA Response to Question 2b.

Question 4:
a) For the tocilizumab biosimilar VIAL submission, the Applicant proposes to include the English translation (and certificate of translation) of all BAT1806 study reports written in Chinese, and all BAT1806 study reports written in English, with the original Chinese reports available on request. Does the Agency agree with this approach?

b) Should the Agency also require the original study reports in Chinese, advice is requested to specify how and where the study reports should be included in the eCTD modules of the tocilizumab biosimilar VIAL submission?

FDA Response to Question 4:
a) For all studies conducted under US-GLP, submit original language study reports. For *in vivo* animal studies, translated study reports should contain a certificate of translation as well as original language signature pages for US-GLP statements and summary tables and line listings for histopathology tables (as applicable).

b) An original language study report should be submitted under the same eCTD module as the translated study report. It may be helpful to title the submissions as “-English” or “-Chinese”.

Question 5:
The Applicant intends to submit a waiver for not conducting environmental risk assessment (ERA) studies with BAT1806. Does the Agency agree?

FDA Response to Question 5:
Your proposal to submit a waiver for not conducting environmental risk assessment to support your BLA appears acceptable. Note that your BLA should include an environmental assessment or a request for categorical exclusion as required by 21 CFR 314.50(d)(1)(iii). Refer to https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/environmental-impact-review-cder for more information.

Question 6:
The impact of the COVID-19 pandemic on study conduct was addressed in a post-hoc exploratory statistical analysis plan (SAP). The results are intended to be presented in Section 14 (Tables, Listings, and Figures) of the CSR, the SAP covering the post-hoc exploratory analysis is intended to be included in Section 16.1.9 (Documentation of Statistical Methods), and corresponding results will be labeled as 'exploratory analyses' in the CSR. Does the agency consider this approach acceptable?

FDA Response to Question 6:
We agree. However, we recommend that you label your "exploratory analyses" results that are post-hoc as "post-hoc exploratory analyses." We also recommend that you indicate which analyses are COVID-19 related and which are not.

Question 7:
BAT1806-002-CR CSR V1.0 has been updated to BAT1806-002-CSR V2.0 to include exploratory post-hoc analyses. The applicant intends to include only BAT1806-002-CR CSR V2.0 in the BLA/ MAA and would like to understand if the agency considers this an acceptable approach?

FDA Response to Question 7:
We recommend you submit both versions of the CSRs as well as the change log documenting the differences between them.

Question 8:
Methotrexate dosing changes were assessed in Phase 3 study BAT-1806-002-CR using an iteratively developed methodology, which will be reported in Section 16.1.9 (Documentation of Statistical Methods). The results will be displayed in Section 14 (Tables, Listings, and Figures). Does the agency consider that this approach is acceptable and in line with agency expectation?

FDA Response to Question 8:
This approach is reasonable.

Question 9:
The BLA will contain CDISC compliant data packages for Phase 1 study BAT-1806-001-CR, Phase 3 study BAT-1806-002-CR, integrated summary of immunogenicity (ISI) and Population (Pop) PK. NONMEM files used for Pop PK analysis will be part of the Pop PK data package. Is the data submission approach as fully outlined in the Draft Study Data Standardization Plan (SDSP) acceptable for the agency?

FDA Response to Question 9:
Your dataset submission approach is acceptable. Please note that the population PK analysis is not considered necessary to assess PK similarity between your product and US-Actemra. If you plan to submit Population PK, we recommend you submit

the datasets, codes/scripts, and output files. Refer to the following pharmacometric data and models submission guidelines for more information. (http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm).

Question 10:

The applicant intends to provide BIMO listings and datasets for the Pivotal Phase 3 study BAT-1806-002-CR as required by the FDA guidance. The applicant does not intend to provide BIMO listings and datasets for the Phase 1 study BAT-1806-001-CR as this was a single center study and the relevant information that would be presented in BIMO listings and datasets is already provided in Section 14 (Tables, Listings, and Figures) of the BAT-1806-002-CSR V2.0.

a) Does the agency agree that the pivotal Phase 3 study requires BIMO listing and datasets to be included?

b) Does the agency agree that the single center Phase 1 study does not require BIMO listings and datasets to be included?

FDA Response to Question 10:

BIMO data should be submitted for all major studies used to support comparison of safety and efficacy in your application. We agree with your plan to submit BIMO data only for study BAT-1806-002-CR, as study BAT-1806-001-CR is a single center study and relevant data will be included in the CSR. BIMO data should be submitted according 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). Please also refer to the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications: https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf

Question 11:

The Phase 1 (BAT-1806-001-CR) and Phase 3 (BAT-1806-002-CR) clinical studies included an assessment of the response to anti-drug antibodies (ADA). The applicant has reported the results in the Integrated Summary of Immunogenicity (ISI). The ISI will be included in M.5.3.5.3 of the BLA filing. An integrated discussion of safety will be included in Module 2.7.4 and a separate Integrated Summary of Safety (ISS) will not be provided. Does the Agency agree?

FDA Response to Question 11:

The integrated summary of safety (ISS) located in Module 5 is a detailed integrated analysis of all relevant data from clinical study reports and is required by the regulations. However, we acknowledge that the two clinical studies have different study designs and were conducted in different populations (healthy subjects and RA patients), and would not be integrated in the ISS. If you believe that the Integrated

Summary of Immunogenicity (ISI) in Module 5 and Summary of Safety in Module 2.7.4 would be sufficiently detailed, then you may place the summary safety portion of your assessment in Module 2 and provide an explanation in both Module 2 and Module 5.

Additional Comment:
In your Integrated Summary of Immunogenicity, provide your analysis of the observed numerical differences of immunogenicity between BAT-1806 and US-Actemra. The ISI should also include analysis of any product quality attributes that could impact immunogenicity. These analyses and justification should support a demonstration of biosimilarity between BAT-1806 and US-Actemra.

Question 12:
The reference product Actemra has been granted an EUA (Emergency Use Authorization) for the treatment of coronavirus disease 2019 (COVID-19) in hospitalized adults and pediatric patients (2 years of age and older). Can the agency advise if this indication:
a) can also be extrapolated to for BIIB800 biosimilar BLA, and if so, should a COVID-19 Fact Sheet be prepared?

b) should be added to the initial Pediatric Study Plan (iPSP)

FDA Response to Question 12:
As noted, Actemra (tocilizumab) is currently authorized for emergency use under EUA for the treatment of COVID-19 in certain adults and pediatric patients. The criteria for issuance of an EUA are specified in section 564 of the Federal Food, Drug and Cosmetic Act. The Agency's issuance of an EUA is not the same as FDA approval or licensure of a drug or biological product, and as such, a COVID-19 Fact Sheet is not required as part of the development of your proposed biosimilar to Actemra. Indications included in the iPSP for a biosimilar would similarly be applicable only to those indications for which the reference product is licensed. (See A.I.16 in the guidance for industry, Questions and Answers on Biosimilar Development and the BPCI Act (September 2021).[1])

Question 13:
The reference product (Actemra) is available in three vial sizes 80 mg/ 4mL, 200 mg/ 10mL, 400 mg/ 20mL (20mg/mL) each with a different vial cap color. Similarly, the biosimilar product will have the same vial sizes also with different vial cap colors, however the biosimilar cap colors/ shades will be different to the reference product cap colors. Does the agency agree with this approach?

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

FDA Response to Question 13:

The cap color for your proposed product line is a business decision; from a medication error perspective we recommend that you take into consideration the possibility of product strength errors which may occur due to confirmation bias based on the reference products' vial cap color scheme and mitigate these through adequate differentiation across your product line and as compared to the reference product.

3.0 OTHER IMPORTANT MEETING LANGUAGE SECTION:

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA II. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) 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.[2]

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 a pediatric assessment to support dosing,

[2] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For additional information on how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*.

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[3]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

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)[4]

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

and 201.57[5] 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 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

[5] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1
[6] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[7] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.[8]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

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

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.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

STUDIES IN HUMANS MAY NOT BE CONDUCTED UNDER THIS PIND

Before you may conduct studies in humans, you must submit a full Investigational New Drug Application (IND, see 21 CFR Part 312[1]) by amending this PIND with the required information. Include the above PIND number in Box 6 of the form FDA 1571 submitted with your IND. Send your IND submission in eCTD format through the ESG.

[8] 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.

Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov[9].

SECURE EMAIL COMMUNICATIONS

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

[9] http://www.fda.gov/ectd

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/

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