CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761198Orig1s000

OTHER ACTION LETTERS

BLA 761198

COMPLETE RESPONSE

Bio-Thera Solutions Ltd.
Attention: Lan Mu, Ph.D., RAC
Vice President Global Regulatory Affairs
34 Vanderveer Drive
Basking Ridge, New Jersey 07920

Dear Dr. Mu:

Please refer to your biologics license application (BLA) submitted and received on November 27, 2020, submitted under section 351(k) of the Public Health Service Act for BAT1706.

We acknowledge receipt of your amendments dated September 30, 2021, October 8, 2021, and October 29, 2021 which were not reviewed by all disciplines for this action. You may incorporate applicable sections of the amendments by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

CLINICAL PHARMACOLOGY

1. Selectivity data from the experiments conducted in normal human serum during the validation of the bioanalytical method to quantitate concentrations of BAT1706 and EU-Avastin did not meet the acceptance criteria, which may suggest the presence of interference that may impact the ability to accurately measure the BAT1706 and EU-Avastin concentrations. Therefore, the PK data from Study BAT1706-001-CR could not be used to support a demonstration of biosimilarity or establish the PK component of the scientific bridge to support the relevance of data generated using EU-Avastin as the comparator product in study BAT1706-003-CR. As a result, there is insufficient PK data to conclude that BAT1706 has no clinically meaningful differences from US-Avastin in terms of safety, purity, and potency.

   To address this deficiency, repeat experiments at the lower limit of quantitation (LLOQ) and high quality control (HQC) to establish the selectivity of the bioanalytical method for BAT1706 and EU-Avastin.

MICROBIOLOGY

2.

3.

4.

(b) (4)

PRODUCT QUALITY

Drug Substance (DS) and DP Manufacturing and Control Strategy

5.

(b) (4)

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

(b) (4)

PRESCRIBING INFORMATION

7. We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[1] and Pregnancy and Lactation Labeling Final Rule[2] websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances. In addition, we encourage you to review the FDA guidance for industry *Labeling for Biosimilar Products*.

CARTON AND CONTAINER LABELING

8. We reserve comment on the proposed labeling until the application is otherwise adequate.

PROPRIETARY NAME

9. The review of your proposed proprietary name has been stopped due to the deficiencies with the application as described in this letter. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

10. When you respond to the above deficiencies, include a safety update. As applicable, the safety update should include data from all nonclinical and clinical studies of the product under consideration regardless of indication, dosage form, or dose level.

    a. Describe in detail any significant changes or findings in the safety profile and their relevance, if any, to whether there may be clinically meaningful differences between the proposed biosimilar product and the U.S.-licensed reference product.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[2] https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

b. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the clinical studies for the proposed indication using the same format as the original BLA submission.
- Present tabulations of the new safety data combined with the original BLA data.
- Include tables that compare frequencies of adverse events in the original BLA with the retabulated frequencies described in the bullet above.

c. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.

d. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.

e. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original BLA data.

f. Provide updated exposure information for the clinical studies (e.g., number of subjects, person time).

g. Provide a summary of worldwide experience on the safety of this product, including adverse events known to be associated with the use of the product and immunogenicity. Include an updated estimate of use for this product marketed in other countries.

h. Provide English translations of current approved foreign labeling not previously submitted.

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

FACILITY INSPECTIONS

11. In addition to the deficiencies presented above, please note and acknowledge the following comment in your response. An inspection of the Bio-Thera Solutions, Ltd. facility at Guangzhou, China, FEI: 3017231337 is required before

this application can be approved. FDA must assess the ability of that facility to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to complete an inspection during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspection is conducted and any findings are assessed regarding your application. We will continue to monitor the public health situation as well as travel restrictions.

Please see the FDA's "Resiliency Roadmap for FDA Inspectional Oversight" for more information on FDA's plan to resume inspections (https://www.fda.gov/media/148197/download). Also see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

MICROBIOLOGY

12. Update Section 3.2.P.3.3 of the BLA with information on BAT1706 DP shipping to the US warehouse/distribution sites, including information for the shipping routes and temperature, shipper (e.g., details of the active shipper), minimum and maximum loads, temperature monitoring during routine shipments, and the validated shipping duration.

13. Provide shipping validation data (using the active shipper (b) (4)) to cover the shipments of BAT1706 DP from Bio-Thera in Guangzhou, P. R. China to the US warehouse/distribution sites from temperature control perspective.

14. The low endotoxin recovery (LER) study was conducted for (b) (4) which is not representative of the product storage during DP manufacturing (b) (4) Conduct a new LER study to account for the DP manufacturing time and provide the summary data and report, including endotoxin level recovered and percentage of recovery for all the test points.

15. The bacterial retention study of the BAT1706 DP sterilizing filter was conducted inadequately (b) (4) However, if the DP batch size is

increased in the future, the bacterial retention study should be repeated and the volume throughput for each testing filter should be directly measured.

PRODUCT QUALITY

DS and DP Manufacturing and Control Strategy

16. (b) (4)

17.

18.

Analytical Methods

19. Reference is made to the information provided in the BLA and to your response to FDA IR dated September 13, 2021, concerning the validation data for the glycosylation by HILIC method. System suitability failures were reported in the robustness study for the results generated using the (b) (4) labeling reagent due to the presence of interfering peaks. Therefore, it does not appear that the results support that the method is

robust with respect to the use of these specific sources of labeling reagents. Provide additional data (e.g., robustness data) to support the performance of the HILIC method with respect to the use of different sources of the (b) (4) labeling reagent. Alternatively, revise the analytical method description to specify the source of the labeling reagent used as part of the analytical method validation. Update the appropriate Sections of the BLA accordingly.

CLINICAL PHARMACOLOGY

20. During the validation of the bioanalytical method to quantitate concentrations of BAT1706, US-Avastin, and EU-Avastin from Studies BAT1706-001-CR and BAT1706-003-CR, the bioanalytical cross-validation comparability between the BAT1706, US-Avastin, and EU-Avastin were not considered optimal. To address this comment, conduct precision and accuracy experiments to assess bias using QC samples and calibration curves prepared from the three products (BAT1706, EU-Avastin, and US-Avastin).

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 601.3(b)). If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 601.3(c). You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

BsUFA II APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review

Transparency and Communication for Original 351(k) BLAs under BsUFA II ('the Program'). The BsUFA II Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a BsUFA II applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Haroon Vohra, Regulatory Health Project Manager, at 240-402-4471.

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director (Acting)
Division of Oncology 3
Office of Oncologic Diseases
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/

STEVEN J LEMERY
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