U.S. FOOD & DRUG ADMINISTRATION

BLA 761198

BLA APPROVAL

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

Dear Dr. Mu

Please refer to your biologics license application (BLA) dated November 27, 2020, and your amendments submitted under section 351(k) of the Public Health Service Act for Avzivi (bevacizumab-tnjn) injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL) for intravenous infusion as a biosimilar to US-licensed Avastin (bevacizumab) injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL) for intravenous infusion. Avzivi (bevacizumab-tnjn) injection, 100 mg/4 mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL) for intravenous infusion are available in a single-dose vial presentation.

We acknowledge receipt of your resubmission dated October 28, 2022, which constituted a complete response to our November 19, 2021, action letter.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2218 to Bio-Thera Solutions, Ltd., Guangzhou, China, under the provisions of section 351(k) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product Avzivi (bevacizumab-tnjn). Avzivi is indicated for the treatment of:

- Metastatic colorectal cancer in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment.
- Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab product-containing regimen.

  Limitation of Use: not indicated for adjuvant treatment of colon cancer.

- Unresectable, locally advanced, recurrent or metastatic non-squamous non-small cell lung cancer, in combination with carboplatin and paclitaxel for first-line treatment.
- Recurrent glioblastoma in adults.
- Metastatic renal cell carcinoma in combination with interferon alfa.
- Persistent, recurrent, or metastatic cervical cancer, in combination with paclitaxel and cisplatin, or paclitaxel and topotecan.
- Epithelial ovarian, fallopian tube, or primary peritoneal cancer in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan for platinum-resistant recurrent disease who received no more than 2 prior chemotherapy regimens.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture bevacizumab-tnjn drug substance, at Bio-Thera Solutions, Ltd., in Guangzhou, China (FEI: 3017231337). The final formulated drug product will be manufactured and filled at Bio-Thera Solutions, Ltd., in Guangzhou, China. The final labeling and secondary packaging will be performed at Bio-Thera Solutions, Ltd., in Guangzhou, China. You may label your product with the proprietary name, Avzivi, and market it in as 100 mg/4 mL and 400mg/16 mL single-dose vials, injection.

DATING PERIOD

The dating period for Avzivi shall be 12 months from the date of manufacture when stored at 2-8 °C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated drug product. The dating period for your drug substance shall be (b) (4) from the date of manufacture when stored (b) (4)

Results of ongoing stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Avzivi to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Avzivi, or in the manufacturing facilities, will require the submission of information to your BLA for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format.[1] Content of labeling must be identical to the enclosed labeling text for the Prescribing Information. Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As (October 2009)*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your November 20, 2023, submission containing final printed carton and container labeling.

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

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

The Agency has determined that, at this time, no pediatric study(ies) will be required under PREA for this BLA.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4521-1 Perform a method validation study to confirm the suitability of the UPLC-MS assay for the control of (b) (4) in BAT1706 drug product during storage. Submit the validation results in a final study report to the BLA.

The timetable you submitted on September 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 4/24

4521-2 Perform a thorough evaluation to elucidate (b) (4) (b) (4) (b) (4) BAT1706 drug product during storage. Based on the results of this product-specific evaluation, reassess the BAT1706 control strategy (b) (4) (b) (4) (b) (4) to confirm the adequacy of overall controls. Submit the assessment as a final study report to the BLA.

The timetable you submitted on September 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/24

4521-3 Implement (b) (4) raw material sourced from a qualified vendor that supplies the material with a (b) (4) container closure (b) (4) during raw material storage. Report this change to the BLA in an annual report.

The timetable you submitted on September 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/24

4521-4 Implement a two-tiered reference standard program that includes the qualification of a working reference standard to be used for BAT1706 primary reference standard stability testing, routine drug substance and drug product process and product controls. Submit the qualification results of the working reference standard and associated changes to BAT1706 reference standard program to the BLA in a prior-approval supplement.

The timetable you submitted on September 22, 2023, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/24

A final submitted protocol is one that the FDA has reviewed and commented upon, and you have revised as needed to meet the goal of the study or clinical trial.

Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients/subjects entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled "**Postmarketing Commitment Protocol**," "**Postmarketing Commitment Final Report**," or "**Postmarketing Commitment Correspondence**."

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs*.[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements at 21 CFR 600.80.

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements at 21 CFR 600.81.

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA 3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4207
Silver Spring, MD 20903

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

Sincerely,

{See appended electronic signature page}

Steven Lemery, M.D., M.H.S.
Director
Division of Oncology 3
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Carton and Container Labeling

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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