BLA 761171

BLA ACCELERATED APPROVAL

Y-mAbs Therapeutics, Incorporated
Attention: Lynda Sutton, B.S.
Chief Regulatory Officer; U.S. Agent for Y-mAbs Therapeutics
Cato Research Limited
Westpark Corporate Center
4364 South Alston Avenue
Durham, NC 27713-2220

Dear Ms. Sutton:

Please refer to your biologics license application (BLA) dated and received March 31, 2020, and your amendments, submitted under section 351(a) of the Public Health Service Act for DANYELZA (naxitamab-gqgk) injection for intravenous use.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2209 to Y-mAbs Therapeutics, Incorporated, New York, New York, under the provisions of section 351(a) 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 DANYELZA (naxitamab-gqgk). DANYELZA is indicated, in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF), for the treatment of pediatric patients 1 year of age and older and adult patients with relapsed or refractory high-risk neuroblastoma in the bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture naxitamab-gqgk drug substance at (b) (4). The final formulated product will be manufactured, filled, labeled, and packaged at (b) (4) (b) (4). You may label your product with the proprietary name DANYELZA and will market it in 40 mg in 10 mL (4 mg/mL) solution for intravenous infusion.

DATING PERIOD

The dating period for DANYELZA 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) months from the date of manufacture when stored (b) (4) (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 process performance qualification drug substance batches and drug product lots.

We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of DANYELZA 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 DANYELZA, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL AND LABELING

We have completed our review of this application, as amended. It is approved under the provisions of accelerated approval regulations (21 CFR 601.41), effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

Marketing of this drug product and related activities must adhere to the substance and procedures of the referenced accelerated approval regulations.

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, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Prescribing Information and Patient 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*.[2]

The SPL will be accessible via publicly available labeling repositories.

CARTON AND CONTAINER LABELING

We acknowledge your October 23, 2020, submission containing final printed carton and container labeling.

RARE PEDIATRIC DISEASE PRIORITY REVIEW VOUCHER

We also inform you that you have been granted a rare pediatric disease priority review voucher, as provided under section 529 of the Federal Food, Drug, and Cosmetic Act (FDCA). This priority review voucher (PRV) has been assigned a tracking number, PRV BLA 761171 All correspondences related to this voucher should refer to this tracking number.

This voucher entitles you to designate a single human drug application submitted under section 505(b)(I) of the FDCA or a single biologic application submitted under section 351(a) of the Public Health Service Act as qualifying for a priority review. Such an application would not have to meet any other requirements for a priority review. The list below describes the sponsor responsibilities and the parameters for using and transferring a rare pediatric disease priority review voucher.

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”

- The sponsor who redeems the priority review voucher must notify FDA of its intent to submit an application with a priority review voucher at least 90 days before submission of the application and must include the date the sponsor intends to submit the application. This notification should be prominently marked, “Notification of Intent to Submit an Application with a Rare Pediatric Disease Priority Review Voucher.”

- This priority review voucher may be transferred, including by sale, by you to another sponsor of a human drug or biologic application. There is no limit on the number of times that the priority review voucher may be transferred, but each

[2] 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.

person to whom the priority review voucher is transferred must notify FDA of the change in ownership of the voucher not later than 30 days after the transfer. If you retain and redeem this priority review voucher, you should refer to this letter as an official record of the voucher. If the priority review voucher is transferred, the sponsor to whom the priority review voucher has been transferred should include a copy of this letter (which will be posted on our Website as are all approval letters) and proof that the priority review voucher was transferred.

- FDA may revoke the priority review voucher if the rare pediatric disease product for which the priority review voucher was awarded is not marketed in the U.S. within 1 year following the date of approval.

- The sponsor of an approved rare pediatric disease product application who is awarded a priority review voucher must submit a report to FDA no later than 5 years after approval that addresses, for each of the first 4 post-approval years:
    - the estimated population in the U.S. suffering from the rare pediatric disease for which the product was approved (both the entire population and the population aged 0 through 18 years),
    - the estimated demand in the U.S. for the product, and
    - the actual amount of product distributed in the U.S.

- You may also review the requirements related to this program by visiting FDA's Rare Pediatric Disease Priority Review Voucher Program web page.[3]

ADVISORY COMMITTEE

Your application for DANYELZA was not referred to an FDA advisory committee because the safety profile is acceptable for the treatment of the indicated population and the application did not raise significant public health questions regarding the role of naxitamab for this indication.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled clinical trials to verify and describe clinical benefit. You are required to conduct such clinical trials with due diligence. If postmarketing clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated November 23, 2020. This requirement, along with required completion dates, is listed below.

[3] https://www.fda.gov/industry/developing-products-rare-diseases-conditions/rare-pediatric-disease-rpd-designation-and-voucher-programs

3950-1 Submit the final report, including datasets, from an ongoing multicenter clinical trial to verify and further characterize the clinical benefit of naxitamab for the treatment of patients with relapsed or refractory neuroblastoma in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) in bone or bone marrow who have demonstrated a partial response, minor response, or stable disease to prior therapy; and to provide a more precise estimation of overall response rate and duration of response (according to the revised International Neuroblastoma Response Criteria by blinded independent review). Enroll a minimum of 80 patients with evaluable disease and systematically follow all responding patients for at least 12 months from the onset of response, or until disease progression, whichever comes first. Include subgroup analyses of overall response rate and duration of response by prior anti-GD2 exposure, disease status (refractory vs. relapsed disease), anti-drug antibody (ADA) status (neutralizing antibody [nAb] positive versus nAb negative, ADA positive versus ADA negative), and area of disease involvement (bone marrow vs. bone) in the final report reflecting a sufficient number of patients in relevant subgroups. Derive the clinical data from a minimum of six study sites, with at least five patients enrolled per site in at least five sites.

Draft Protocol Submission:	06/2021
Final Protocol Submission:	12/2021
Trial Completion:	03/2027
Final Report Submission:	09/2027

Submit clinical protocols to your IND 132793 for this product. In addition, under 21 CFR 601.70 you should include a status summary of each requirement in your annual report 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 entered into each study/trial.

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement(s)**."

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of serious infusion reactions and adequately characterize the risk of toxicity particularly neuropathic pain and nerve damage associated with the use of patients receiving Danyleza.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

3950-2 Conduct a comprehensive analysis evaluating and characterizing the incidence, clinical presentation, management, and outcome of the potential serious risk of naxitamab-associated infusion-related reactions in a sufficient number of patients to adequately characterize the risk. Submit an integrated final report containing data using the preferred terms included in product labelling from patient-level and pooled analyses of on-going and completed clinical trials, post-marketing reports and/or literature reports and a comprehensive pharmacovigilance assessment for this potential serious risk. The report should also include an analysis of premedication administered. The results from this report may inform product labelling.

The timetable you submitted on October 13, 2020 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	03/2021
Final Protocol Submission:	06/2021
Trial Completion:	03/2027
Final Report Submission:	09/2027

3950-3 Conduct a repeat-dose juvenile animal toxicology study (a minimum of 2 cycles) in a pharmacologically relevant species that is also relevant for the toxicological analysis of an antibody with immune-mediated effects that will measure the toxicity associated with the use of naxitamab, particularly

effects on the central and peripheral nervous system. Administration of naxitamab should be reflective of the clinical administration schedule. Incorporate an evaluation of the effect of treatment on the proximal and distal nerves, and evaluation of the C1 level of the spinal cord in this study and include 7-8 slices for histopathological assessment of the brain. Evaluate the potential for effects on nociception and pain threshold, both acute and long-term, both during the study and at the end of an appropriate recovery period.

The timetable you submitted on October 13, 2020 states that you will conduct this trial according to the following schedule:

Draft Protocol Submission:	01/2022
Final Protocol Submission:	03/2022
Trial Completion:	01/2023
Final Report Submission:	07/2023

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocols to your IND 132793 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **Required Postmarketing Protocol Under 505(o), Required Postmarketing Final Report Under 505(o), Required Postmarketing Correspondence Under 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

POSTMARKETING COMMITMENT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3950-4 Conduct immunogenicity testing in all patients enrolled in the ongoing multicenter clinical trial (Trial 201) of naxitamab using the validated assays to adequately characterize the incidence of anti-drug antibody (ADA) and neutralizing antibodies against naxitamab and assess the impact of ADA on the pharmacokinetics (PK), safety and efficacy of naxitamab in accordance with FDA Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products available at https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf. Submit the integrated immunogenicity assessment report in the final report submission. The results from this study may inform product labeling.

The timetable you submitted on October 13, 2020, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2021
Final Protocol Submission:	12/2021
Trial Completion:	03/2027
Final Report Submission:	09/2027

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

We remind you of your postmarketing commitments:

3950-5 Conduct an analysis of the clonality of the naxitamab master cell bank using a suitable method such as "Next Generation Sequencing".

Final Report Submission: 04/2021

3950-6 Perform an additional in-use compatibility study with the specific purpose of testing aggregation and particulates. Samples from the in-use study will also be tested for visible particles and subvisible particles.

Final Report Submission: Annual report covering 05/2021

3950-7 Submit the validation report for the (b) (4) container closure integrity testing (b) (4).

Final Report Submission: 10/2020 (submitted)

3950-8 Perform container closure integrity testing on at least 500 units from one lot of drug product using the (b) (4) method, which is sensitive enough to detect breaches ≤ (b) (4) µm in size.

Final Report Submission: 12/2020

3950-9 Submit bioburden method verification data with testing volume of 100 mL for three drug product batches.

Final Report Submission: 02/2021

3950-10 Repeat the bacterial retention study with naxitamab drug product to include measurement of (b) (4). Implement routine monitoring of (b) (4)

and include a [redacted] parameter [redacted]. Submit a report that includes [redacted] results from three drug product batches.

Final Report Submission: 12/2021

3950-11 Provide data to demonstrate that shipping temperature is maintained within the shippers for drug product when exposed to worst-case conditions of temperature (summer and winter).

Final Report Submission: 10/2020 (submitted)

3950-12 Conduct a low endotoxin recovery study [redacted] to ensure the release test method can reliably detect endotoxin in naxitamab drug product. In case the study shows endotoxin recovery below [redacted], develop an alternative endotoxin testing method to mitigate LER.

Final Report Submission: 11/2020

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 clinical protocols to your IND 132793 for this product. 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 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

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved Prescribing Information, Medication Guide, and Patient Package Insert (as applicable).

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*.[5]

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (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 for licensed biological products (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:

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.

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

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

If you have any questions, call Rebecca Cohen, Regulatory Project Manager, at 240-402-4998.

Sincerely,

{See appended electronic signature page}

Marc Theoret, M.D.
Acting Supervisory Associate Director
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Patient 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/

MARC R THEORET
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