BLA 761352

BLA ACCELERATED APPROVAL

Merus N.V.
Attention: Penny Ng, DRSc, MBA, RAC
Executive Director, Global Regulatory Affairs
139 Mains Street, Suite 302
Cambridge, MA 02142

Dear Dr. Ng:

Please refer to your biologics license application (BLA) dated and received March 4, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for BIZENGRI (zenocutuzumab-zbco) injection.

We acknowledge receipt of your major amendment dated October 30, 2024, which extended the goal date by three months.

LICENSING

We are issuing Department of Health and Human Services U.S. License No. 2310 to Merus N.V., Cambridge, Massachusetts, 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 BIZENGRI (zenocutuzumab-zbco). BIZENGRI is indicated for adults with advanced, unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (NRG1) gene fusion with disease progression on or after prior systemic therapy; and adults with advanced, unresectable or metastatic pancreatic adenocarcinoma harboring an NRG1 gene fusion with disease progression on or after prior systemic therapy.

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture zenocutuzumab-zbco drug substance at (b) (4). The final formulated drug product will be manufactured, filled, labeled, and packaged at (b) (4) You may label your product with the proprietary name, BIZENGRI, and market it in 375 mg per 18.75 mL injection.

DATING PERIOD

The dating period for BIZENGRI shall be 18 months from the date of manufacture when stored at 2 °C to 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 at (b) (4) °C to -32 °C.

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

FDA LOT RELEASE

You are not currently required to submit samples of future lots of BIZENGRI 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 BIZENGRI, 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 accelerated approval pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 CFR 601.41, effective on the date of this letter, for use as recommended in the enclosed agreed-upon approved labeling. This BLA provides for the use of BIZENGRI for:

- Adults with advanced, unresectable or metastatic non-small cell lung cancer (NSCLC) harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy.
- Adults with advanced, unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (*NRG1*) gene fusion with disease progression on or after prior systemic therapy.

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

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, as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information and Patient Package Insert). Information on submitting SPL files using eLIST may be found in the draft 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 25, 2024, submission containing final printed carton and container labeling.

ADVISORY COMMITTEE

Your application for zenocutuzumab-zbco was not referred to an FDA advisory committee because the application did not raise significant safety or efficacy issues that were unexpected in the intended population.

ACCELERATED APPROVAL REQUIREMENTS

Pursuant to section 506(c) of the FDCA and 21 CFR 601.41, you are required to conduct further adequate and well-controlled clinical trials intended to verify and describe clinical benefit. You are required to conduct such clinical trial(s) with due diligence. If required postmarketing clinical trial(s) fail to verify clinical benefit or are not conducted with due diligence, including with respect to the conditions set forth below, we may withdraw this approval. We remind you of your postmarketing requirements specified in your submission dated November 27, 2024. These requirements are listed below.

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

[2] When final, this guidance will represent FDA's current thinking on this topic. 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.

4727-1 Complete a clinical trial intended to verify and describe the clinical benefit of zenocutuzumab 750 mg intravenously every two weeks in at least 100 evaluable adult patients with advanced unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy. To characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

The timetable you submitted on November 27, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	02/2026
Final Report Submission:	08/2026

4727-2 Complete a clinical trial intended to verify and describe the clinical benefit of zenocutuzumab 750 mg intravenously every two weeks in at least 50 evaluable adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy (or who are not eligible for standard of care therapy). To characterize response rate and duration, patients will be followed for at least 12 months from the onset of response.

The timetable you submitted on November 27, 2024, states that you will conduct this trial according to the following schedule:

Trial Completion:	02/2026
Final Report Submission:	08/2026

Submit clinical protocols to your IND 156484 for this product. 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.

You must submit reports of the progress of each clinical trial required under section 506(c) (listed above) to this BLA 180 days after the date of approval of this BLA and approximately every 180 days thereafter (see section 506B(a)(2) of the FDCA) (hereinafter “180-day reports”).

You are required to submit two 180-day reports per year for each open study or clinical trial required under 506(c). The initial report will be a standalone submission and the subsequent report will be combined with your application’s annual status report (ASR) required under section 506B(a)(1) of the FDCA and 21 CFR 601.70. The standalone 180-day report will be due 180 days after the date of approval (with a 60-day grace period). Submit the subsequent 180-day report with your application’s ASR. Submit both

of these 180-day reports each year until the final report for the corresponding study or clinical trial is submitted[3].

Your 180-day reports must include the information listed in 21 CFR 601.70(b). FDA recommends that you use FORM FDA 3989, *PMR/PMC Annual Status Report for Drugs and Biologics,* to submit your 180-day reports.[4]

180-day reports must be clearly designated "**BLA 761352 180-Day AA PMR Progress Report**."

FDA will consider the submission of your application's ASR under section 506B(a)(1) and 21 CFR 601.70, in addition to the submission of reports 180 days after the date of approval each year (subject to a 60-day grace period), to satisfy the periodic reporting requirement under section 506B(a)(2).

Submit final reports to this BLA as a supplemental application. For administrative purposes, the cover page of 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.

We are waiving the pediatric study requirement because necessary studies are impossible or highly impracticable to conduct due to the rarity of the condition in children.

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the FDCA 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 the

[3] You are required to submit information related to your confirmatory trial as part of your annual reporting requirement under section 506B(a)(1) until the FDA notifies you, in writing, that the Agency concurs that the study requirement has been fulfilled or that the study either is no longer feasible or would no longer provide useful information.
[4] FORM FDA 3989, along with instructions for completing this form, is available on the FDA Forms web page at https://www.fda.gov/about-fda/reports-manuals-forms/forms.

known serious risks of infusion-related reactions/hypersensitivity/anaphylaxis, interstitial lung disease/pneumonitis, and left ventricular dysfunction.

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 these serious risks.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess these serious risks.

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

4727-3 Conduct a comprehensive integrated safety analysis in a sufficient number of adult patients from clinical trials to adequately characterize the known serious risks of infusion-related reactions/hypersensitivity/anaphylaxis, interstitial lung disease/pneumonitis, and left ventricular dysfunction following exposure to zenocutuzumab. The integrated safety analysis should include all adverse events, major safety events, dose-reductions, dose interruptions, and withdrawals, when all patients have completed at least two years of treatment with zenocutuzumab or withdrew earlier.

The timetable you submitted on November 27, 2024, states that you will conduct this trial according to the following schedule:

Draft Protocol Submission (Analysis Plan):	01/2025
Final Protocol Submission (Analysis Plan):	05/2025
Study Completion:	12/2026
Final Submission:	06/2027

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.[5]

Submit clinical protocol(s) to your IND 156484 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) 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

[5] 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.

periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) 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(a)(1) 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.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

4727-4 Develop and validate a neutralizing antibody (NAb) assay and submit a full validation report of the developed NAb assay. The assay format should be adequately justified to be suitable for the detection of NAbs. This NAb assay will be used to test available confirmed anti-drug antibody positive samples from banked and ongoing clinical studies. Include the updated NAb results analyzed using the validated NAb assay to address the effects of neutralizing antibody on the pharmacokinetics, pharmacodynamics, safety, and effectiveness of zenocutuzumab.

The timetable you submitted on November 27, 2024, states that you will conduct this study according to the following schedule:

Draft Protocol Submission (Analysis Plan):	01/2025
Final Protocol Submission (Analysis Plan):	05/2025
Study Completion:	06/2025
Final Report Submission:	08/2025

4727-5 Conduct an appropriate analytical and clinical validation study to establish and support the availability of an in vitro diagnostic device using clinical trial data that demonstrates the device is essential to the safe and effective use of zenocutuzumab for the treatment of adult patients with advanced unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy.

The timetable you submitted on November 27, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2028

4727-6 Conduct an appropriate analytical and clinical validation study to establish and support the availability of an in vitro diagnostic device using clinical trial data that demonstrates the device is essential to the safe and effective use of zenocutuzumab for the treatment of adult patients with advanced unresectable or metastatic pancreatic adenocarcinoma harboring a neuregulin 1 (*NRG1)* gene fusion with disease progression on or after prior systemic therapy.

The timetable you submitted on November 27, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/2028

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.

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

We remind you of your postmarketing commitments:

4727-7 Develop a validated functional cell-based assay representative of the mechanism of action of zenocutuzumab, including blocking of NRG1:HER3 binding and HER2:HER3 dimerization, for drug substance and drug product release and stability testing of potency and establish acceptance criteria for release and stability for this test. Analyze sample retains from clinical batches and stability samples to support proposed acceptance criteria.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/31/2025

4727-8 Validate an appropriate test to control for zenocutuzumab (b) (4) and establish a drug substance release acceptance criterion based on the levels of the (b) (4) observed in clinical batches.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/31/2025

4727-9 Analyze zenocutuzumab drug substance and drug product sample retains for the antibody dependent cell-mediated cytotoxicity (ADCC) reporter assay activity using a qualified reference standard. Reevaluate drug substance and drug product release and stability acceptance criteria for the ADCC reporter assay based on available retain, release, and stability results. Provide a justification to support selection of the revised acceptance criteria.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/31/2025

4727-10 Optimize and re-validate the HER3 binding assay for drug substance and drug product release and stability testing of potency. Robustness assessments for critical reagents and parameters for the HER3 binding assay in the re-validation will be included.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/15/2025

4727-11 Perform a supplemental validation for the imaged capillary isoelectric focusing and ultra-performance size exclusion chromatography drug substance and drug product methods to confirm the reportable range in accordance with ICH Q2(R2). Validate a lower limit of quantification (LLOQ) for (b) (4) impurities by the drug product imaged capillary isoelectric focusing method.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/31/2025

4727-12 Establish an appropriate drug substance release acceptance criterion for Oligosaccharide mapping test based on levels of relevant glycosylated species observed in clinical batches.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/30/2025

4727-13 Establish appropriate drug substance and drug product release and stability specifications for total impurities by reduced capillary gel electrophoresis methods based on levels observed in clinical batches.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 03/31/2025

4727-14 Establish appropriate drug substance and drug product release and stability specifications for total impurities by non-reduced capillary gel electrophoresis methods based on levels observed in clinical batches.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 07/31/2025

4727-15 Conduct a supplemental drug product validation study to reassess the homogeneity of the fill study. Include formulation and product critical quality attributes that could be impacted by the fill process in your assessment.

The timetable you submitted on November 21, 2024, states that you will conduct this study according to the following schedule:

Final Report Submission: 06/30/2025

Submit clinical protocols to your IND 156484 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/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

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*.[6]

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:

[6] 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, email Maritsa Stephenson, Regulatory Health Project Manager, at maritsa.stephenson@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Paul Kluetz, M.D.
Supervisory Associate Director (acting)
Office of Oncologic Diseases
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Patient Package Insert
- 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/

PAUL G KLUETZ
12/04/2024 02:41:25 PM