CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761352Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: November 15, 2024

1. Application/Product Information

BLA number	761352
Submission Type	Original Submission
Regulatory Pathway	NME 351(a); Fast Track, Breakthrough, Orphan
Associated IND/BLA	IND 131752 IND 156484 IND 165120
Review Designation	Priority
Applicant	Merus N.V.
Indication	• 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
Rx/OTC dispensed	Rx
Drug Product Name	Proprietary Name Bizengri
	Non-proprietary Name/Code Name zenocutuzumab-zbco/MCLA-128
	OBP Naming BsMAB: MAB HUMANIZED (IGG1) ANTI P04626 (ERBB2_HUMAN) & ANTI P21860 (ERBB3_HUMAN) [MCLA128]
Drug Product Description	Bizengri (zenocutuzumab-zbco) is supplied as two sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free injection for intravenous infusion in single-dose vials, where each vial contains

	375 mg/18.75 mL (20 mg/mL) MCLA-128, 34.9 mg histidine, 51.1 mg L-histidine hydrochloride monohydrate, 3.7 mg polysorbate 20, 1412 mg trehalose, and water for injection at pH 6.0. Zenocutuzumab-zbco is a humanized IgG1-based bispecific monoclonal antibody containing two identical light chains and two different humanized heavy chains (HCs) containing different complementarity-determining regions (CDRs), targeting human epidermal growth factor receptor 2 (HER2) and human epidermal growth factor receptor 3 (HER3).		
Dosage Form	Liquid		
Strength	375 mg/18.75 mL (20 mg/mL)		
Route of Administration	Intravenous (IV) infusion		
Primary Container Closure System	Vial		
Device Information	Not applicable		
Co-packaged Product Information	Not applicable		
OPQ Review Team	Discipline	Primary	Secondary
	Drug substance (DS)	Tamanna Azam	Phillip Angart
	Drug product (DP)	Xiaoyan Zou	
	Immunogenicity Assay		
	Facility	Hamet Touré	Virginia Carroll
	Microbiology	Hamet Touré (DS) / Reyes	

		Candau-Chacon (DP)	
	DS Site Inspection	Abigail Marella / Lindsey Brown / Yun Wu / Chandan Thomas / Phillip Angart	
	RBPM	Kelly Ballard (OPRO)	
	ATL	Phillip Angart	
OPQ Issued Consults	None		

2. Recommendation and Conclusion on Approvability
Recommendation: Approval with PMCs/PMRs

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761352 for BIZENGRI manufactured by Merus N.V. The data submitted in this application are adequate to support the conclusion that the manufacture of BIZENGRI is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert.

3. CMC Information for Action Letter
   a. Manufacturing Location:
      - Drug Substance: (b) (4)
      - Drug Product: (b) (4)
   b. Fill size and dosage form: Bizengri is supplied as a single-dose vial of 375 mg/18.75 mL (20 mg/mL) as a sterile liquid for intravenous infusion; each carton contains 2 vials.
   c. Dating Period:
      - Drug Product: 18 months at 5 ± 3 °C
      - Drug Substance: (b) (4) months at (b) (4) °C
      - For packaged products: Not packaged
      - Stability Option: We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance under 21 CFR 601.12.
   d. Exempt from lot release:
      - Yes

- Rationale, if exempted: specified product
  Bizengri is exempted from lot release per FR 95-29960.

e. Draft Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, as applicable

The following post-marketing commitments (PMCs) were discussed and agreed to by the Applicant during the BLA review.

1. 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.

   Fulfillment date: December 31, 2025

2. 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.

   Fulfilment date: March 31, 2025

3. 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.

   Fulfillment date: March 31, 2025

4. 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.

   Fulfillment date: December 15, 2025

5. 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 [redacted] (b) (4) impurities by the drug product imaged capillary isoelectric focusing method.

Fulfillment date: July 31, 2025

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

   Fulfillment Date: April 30, 2025

7. 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.

   Fulfillment Date: March 31, 2025

8. 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.

   Fulfillment Date: July 31, 2025

9. 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.

   Fulfillment Date: June 30, 2025

4. Basis for Recommendation
   a. Summary:

Bizengri (zenocutuzumab-zbco; MCLA-128) is a humanized immunoglobulin G1 (IgG1) bispecific antibody with two identical light chains and two unique heavy chains (HCs), with charge-based substitutions in the CH3 region of the IgG1 to facilitate preferential pairing of the two different HCs, covalently linked via disulfide linkages. The complementarity-determining regions (CDR) within the heavy chain variable domain 1 (HC1) is directed against the extracellular domain of human epidermal growth factor receptor 2 (HER2). The CDR within the heavy chain variable domain 2 (HC2) is directed against the extracellular domain of human epidermal growth factor receptor 3 (HER3). Zenocutuzumab-zbco is characterized as low-fucose due to the

(b) (4) Chinese hamster ovary (CHO) cell line used for expression of zenocutuzumab-zbco, (b) (4) preventing metabolization of the fucose for glycan synthesis.

Zenocutuzumab-zbco binds to the extracellular domains of HER2 and HER3, inhibiting HER2:HER3 dimerization and preventing *NRG1* binding to HER3, thereby preventing activation of the phosphoinositide (P13K)-AKT-mammalian target of rapamycin (mTOR) oncogenic signaling pathway, suppression of tumor cell proliferation, and tumor cell survival. Zenocutuzumab-zbco also mediates antibody-dependent cell-mediated cytotoxicity (ADCC) leading to elimination of tumor cells. The biological activity of zenocutuzumab-zbco is evaluated based on its ability to individually bind HER2, HER3, and cluster of differentiation 16 (CD16) and an ADCC reporter assay. All potency results are reported as percentage relative to a qualified reference material.

The zenocutuzumab-zbco drug substance (DS) manufacturing process consists of (b) (4) DS is stored frozen at (b) (4) °C to (b) (4) °C.

The zenocutuzumab-zbco drug product (DP) manufacturing process includes, (b) (4) and stoppering, capping, visual inspection, and labeling and packaging. Zenocutuzumab-zbco DP is a sterile, clear to slightly opalescent, colorless to slightly yellow, preservative-free concentrate for infusion, formulated as 375 mg/18.75 mL (20 mg/mL) zenocutuzumab-zbco, 34.9 mg histidine, 51.1 mg L-histidine hydrochloride monohydrate, 3.7 mg polysorbate 20, 1412 mg trehalose, and water for injection at pH 6.0. Zenocutuzumab-zbco DP is provided in a Type (b) (4) glass vial, stoppered with an elastomeric stopper, and sealed with an aluminum cap stored at the long-term storage condition of 2 °C to 8 °C. Each carton contains two vials of zenocutuzumab-zbco DP for one 750 mg dose.

The anti-drug antibody (ADA) assay used for immunogenicity assessment in the clinical studies to support this application is adequately validated and suitable for its intended purpose. A post-marketing commitment (PMC) to validate a neutralizing antibody assay for assessment of ADA positive samples was negotiated and will be issued by the clinical pharmacology review team.

The microbial control and sterility assurance strategy is sufficient to support consistent manufacture of a sterile product. The DP is sterilized using a validated filtration process and (b) (4)

The pre-license inspection (PLI) of (b) (4) , responsible for manufacturing and testing of zenocutuzumab-zbco DS resulted in a facility recommendation of approval. The PLI of the DP manufacturing facility (b) (4) was waived based on satisfactory inspection history.

Nine non-506B reportable CMC PMCs were negotiated with the Applicant during the review cycle (listed in Section 3.e, above). PMCs 1-8 are related to the improvements in the analytical methods and acceptance criteria used in the control of DS and DP. PMC 9 is a commitment to conduct a supplemental DP fill homogeneity assessment. There is residual risk that there may be inhomogeneity in excipients and product attributes that can be impacted by (b) (4). Critical attributes were assessed in the DP fill homogeneity assessment provided in the BLA submission to support the management of this additional study as a PMC.

A review extension was issued on November 4, 2024 to extend the Prescription Drug User Fee Act (PDUFA) goal date from November 4, 2024 to February 4, 2025. The basis for review extension is the submission of additional chemistry, manufacturing, and control (CMC) information on October 30, 2024 which required additional time to review. The information was related to: (1) resolution of discrepancies identified between the drug substance manufacturing site and the filed BLA and (2) additional information related to the DP stability trends to support the proposed shelf-life. The first issue could not be fully resolved until the facility review was complete. The second issue was only identified after the receipt of a stability update on

September 5, 2024. Both issues were fully resolved and support the final OPQ recommendation.

The overall zenocutuzumab-zbco control strategy incorporates controls over raw materials, facilities and equipment, the manufacturing process, adventitious agents, microbial contamination, and release and stability of the DS and DP. The manufacturing processes and overall control strategies for zenocutuzumab-zbco are appropriately established to ensure consistency and quality of the final product; therefore, lot variability is not a concern. The assessment of manufacturing information provided in this application has concluded that the methodologies and processes used for the DS and DP manufacturing, release, and stability testing are sufficiently robust and controlled to ensure the consistent manufacture of a safe, pure, and potent product.

Individual assessments for each OPQ subdiscipline are located in separate documents in Panorama.

b. Subdiscipline Recommendation:

Drug Substance	-	Adequate with PMCs/PMRs
Drug Product	-	Adequate with PMCs/PMRs
Immunogenicity Assay	-	Adequate with PMCs/PMRs
Facilities	-	Adequate
Microbiology	-	Adequate

c. Environmental Assessment (EA):
Categorical exclusion is claimed by the applicant and deemed acceptable.

d. Potency Assessment for Labeling:
As an initial matter, we determined that no U.S. standard of potency has been prescribed for zenocutuzumab (i.e., there is no specific test method described in regulation for zenocutuzumab that establishes an official standard of potency). We next considered whether potency is a factor for zenocutuzumab within the meaning of 21 CFR 610.61(r), which requires a statement about potency on the package (carton) label if “potency is a factor” and “no U.S. standard of potency has been prescribed.” We have determined that potency is not a factor for Bizengri for purposes of § 610.61(r) because lot variability is not a concern for Bizengri as Bizengri’s manufacturing process is appropriately controlled to ensure the consistency and quality of the final product.

5. Life-Cycle Considerations
   a. Established Conditions based on ICH Q12 principles: No

   b. Drug Substance:
      i. Protocols approved:
         1. Working cell bank qualification
         2. (b) (4) lifetime cycle concurrent validation at manufacturing scale
         3. Membrane life cycle concurrent validation at manufacturing scale
         4. Concurrent process validation for (b) (4)
         5. Concurrent process validation for (b) (4)
         6. Working reference standard qualification and re-qualification
         7. Stability protocol for shelf-life extension
         8. Post-approval stability commitment
      ii. Residual risk: See Sections 3.e and 4.a above
      iii. Future inspection points to consider: None

   c. Drug Product:
      i. Protocols approved:
         1. Real time leachables study
         2. Post-approval stability commitment
      ii. Residual risk: See Sections 3.e and 4.a above
      iii. Future inspection points to consider:
         1. Evaluate trending procedures for DP stability samples.
         2. Verify that the procedures for evaluating stability data results and procedures for investigation of out of trend results have well established and reasonable timelines for completion.

FOIA statement: More detailed assessments of the BLA submission, which are not included in this integrated quality assessment, may be requested via a Freedom of Information Act (FOIA) request.

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/

PHILLIP A ANGART
11/15/2024 01:13:30 PM

YAN WANG
11/15/2024 01:19:31 PM

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11/15/2024 01:30:38 PM

LABELS AND LABELING ASSESSMENT

Date of Assessment:	October 17, 2024
Assessor:	Diana Pei, PharmD Labeling Assessor Office of Product Quality Assessment III (OPQA III)
Through:	Xiaoyan Zou, PhD Product Quality Assessor OPQA III/Division of Product Quality Assessment XIV
Application:	BLA 761352
Applicant:	Merus N.V.
Submission Date:	March 4, 2024
Product:	Bizengri (zencutuzumab-zbco)
Dosage form(s):	Injection
Strength and Container-Closure:	375 mg/18.75 mL (20 mg/ml) single-dose vial
Purpose of assessment:	The Applicant submitted a biologics license application to seek approval of Bizengri (zencutuzumab-zbco) for the treatment of patients with advanced unresectable or metastatic non-small cell lung cancer harboring a neuregulin 1 (NRG1 + NSCLC) or pancreatic adenocarcinoma haboring a neuregulin 1 (NRG1 + PDAC) following progression with prior systemic therapy (b) (4)
Recommendations:	The prescribing information, patient labeling, container labels, and carton labeling are acceptable from an OPQA III labeling perspective.

Materials Considered for this Label and Labeling Assessment	
Materials Assessed	**Appendix Section**
Proposed Labels and Labeling	A
Evaluation Tables	B
Acceptable Labels and Labeling	C

n/a = not applicable for this assessment

DISCUSSION

We assessed the proposed labels and labeling for compliance with applicable requirements in the Code of Federal Regulations. Also, we assessed the proposed labels and labeling for consistency with recommended labeling practices (see Appendix B).

CONCLUSION

The prescribing information, patient labeling, container labels, and carton labeling submitted on October 8, 2024, July 31, 2024, and August 29, 2024 respectively were assessed and found to be acceptable (see Appendix C) from an OPQA III Labeling perspective.

APPENDICES

Appendix A: Proposed Labeling

- Prescribing Information and Patient Information (submitted on March 4, 2024)
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- Container Labels (submitted on March 4, 2024)

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

Evaluation Tables: Label[1,2] and Labeling[3] Standards

Container[4] Label Evaluation

Proper Name (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(1), 21 CFR 201.10(g)(2), 21 CFR 610.62(a), 21 CFR 610.62(b), 21 CFR 610.62(c), 21 CFR 610.60(c), 21 CFR 201.50(b), 21 CFR 201.10(a), 21 CFR 201.10(h)(2)(i)(1)(i)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	

Comment/Recommendation:

Manufacturer name, address, and license number (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(2), 21 CFR 201.1(a), 21 CFR 610.60(c), 21 CFR 201.10(h)(2)(i)(1)(iv), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	
Recommended labeling practices (U.S license number for container bearing a partial label[5])	

Comment/Recommendation:
The name, address, and license number of the manufacturer shall appear on the container label per 21 CFR 610.60 (a)(2). For biologic products, the Applicant's name as listed in field 2 of Form FDA 356h "Merus N.V." is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. If necessary, correct this on your form FDA 356h. Revise the manufacturer statement using the following qualifying phrase "Manufactured by". Clarify the role of "Merus US, Inc.", if it is the distributor, it may appear on the container label using the appropriate qualifying phrase provided that the name, address, and license number of the manufacturer also appears on the label. See 21 CFR 610.64 for qualifying phrases for the distributor.

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.

[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.

[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.

[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.

[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

The licensed manufacturer should appear as:

Manufactured by:
Applicant name as listed in field 2 of Form FDA 356h
Address as listed on line 5 of Form FDA 356h
U.S. License Number XXXX

Applicant revised as recommended.

Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

Lot number or other lot identification (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(3), 21 CFR 610.60(c), 21 CFR 201.18, 21 CFR 201.100(b)(6), 21 CFR 201.10(h)(2)(i)(1)(iii)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <7> Labeling, Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (container label)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Product Strength (container label)	**Acceptable**
Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (expression of strength for injectable drugs) references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	

Comment/Recommendation:
We refer to your 3.2.P.1 Description and Composition of the Drug Product submitted on February 16, 2024. The product strength for injectable drugs should be expressed as the strength per total volume (total drug content supplied in container) followed in close proximity by a parenthetical that includes the strength/mL in label/labeling. See *USP General Chapter <7> Labeling* for single-dose injectable drug products with containers that supply a volume of drug greater than 1 mL. Revise the product strength to read: "375 mg/18.75 mL (20 mg/mL)"

Applicant revised as recommended.

Multiple-dose containers (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55 *(recommended individual dose)*	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Statement: "Rx only" (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (prominence of Rx Only statement) reference: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	

Comment/Recommendation:

Medication Guide (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The product does not need a Medication Guide.

No Package for container (container label)	**Acceptable**
Regulation: 21 CFR 610.60(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The container is enclosed in a package.

No container label (container label)	**Acceptable**
Regulation: 21 CFR 610.60(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The product contains a container label.

Ferrule and cap overseal *(for vials only)*	**Acceptable**
Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Confirm there is no text on the ferrule and cap overseal of the vials.

Applicant's response: The sponsor confirms that there is no printed text on the ferrule and cap over seal of the (b) (4) *vials with zenocutuzumab.*

Visual inspection	**Acceptable**
Regulation: 21 CFR 610.60(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Confirm that sufficient area of the container remains uncovered for its full length or circumference to allow for visual inspection when the label is affixed to the container and indicate where the visual area of inspection is located.

Applicant's response: The (b) (4) *vials with zenocutuzumab are labeled with a 88.9 x 31.75 mm label with an open space perimeter of 5.30 mm between both ends of the affixed label. In addition, to the label, 3.25 mm above and below the label remains uncovered to permit visual inspection of the contents.*

Section 3.2.P.7 (container closure systems) has been updated with the commercial label for zenocutuzumab. The updated section is attached to this response document. In addition, the updated section is included in the formal submission of the response to the BLA.

Additional update(s) included in this version of the carton/container:

Carton	
Previous version in SN003	Updated version included
Outer tab: "SN"	"S/N"
No 2D barcode for placement	2D barcode added for placement

(b) (4)

[redacted]

Route of administration (container label)	**Acceptable**
Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	

Comment/Recommendation:

NDC numbers **(container label)**	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Preparation instructions (container label)	**Acceptable**
Regulation: 21 CFR 201.5(g)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	

Comment/Recommendation:

Package type term (container label)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Revise to the appropriate package-type term for this product, "single-dose".

Applicant revised as recommended.

No misleading statements (container label)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Prominence of required label statements (container label)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (container label)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (container label)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Bar code label requirements (container label)	**Acceptable**
Regulations: 21 CFR 201.25, 21 CFR 610.67	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Net quantity (container label)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	

Comment/Recommendation:
Add the net quantity statement "18.75 mL" to the container label.

Applicant revised as recommended.

Statement of Dosage (container label)	**Acceptable**
Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation: The label is small and could be considered a partial label. Thus, a dosage statement is not required.

Inactive ingredients (container label)	**Acceptable**
Regulation: 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling	

Comment/Recommendation: The label is small and could be considered a partial label. Thus, an inactive ingredient statement is not required.

Storage requirements (container label)	**Acceptable**
Recommended labeling practices references: USP General Chapters <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dispensing container (container label)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Package[6] Labeling Evaluation

Proper name (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (placement of dosage form outside of parenthesis and/or below the proper name)	

Comment/Recommendation:

[6] Per 21 CFR 600.3(cc) *Package* means the immediate carton, receptacle, or wrapper, including all labeling matter therein and thereon, and the contents of the one or more enclosed containers. If no package, as defined in the preceding sentence, is used, the container shall be deemed to be the package. Thus, this includes the carton, prescribing information, and patient labeling.

Manufacturer name, address, and license number (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (using the qualifying phrase "Manufactured by:")	

Comment/Recommendation:

Note the applicant does not have a U.S. License number so the labeling contains a placeholder, xxxx. The U.S. License number will be issued at the time of the licensure of the BLA.

The name, address, and license number of the manufacturer shall appear on the container label per 21 CFR 610.60 (a)(2). For biologic products, the Applicant's name as listed in field 2 of Form FDA 356h "Merus N.V." is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder to both container label and carton labeling. If necessary, correct this on your form FDA 356h. Revise the manufacturer statement using the following qualifying phrase "Manufactured by". Clarify the role of "Merus US, Inc.", if it is the distributor, it may appear on the container label and carton labeling using the appropriate qualifying phrase provided that the name, address, and license number of the manufacturer also appears on the label. See 21 CFR 610.64 for qualifying phrases for the distributor.
The licensed manufacturer should appear as:

Manufactured by:
Applicant name as listed in field 2 of Form FDA 356h
Address as listed on line 5 of Form FDA 356h
U.S. License Number XXXX

Applicant revised as recommended.

Lot number or other lot identification (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(c), 21 CFR 201.18	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Expiration date (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(d), 21 CFR 201.17	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Beyond Use Date (Multiple-dose containers) (package labeling)	**Acceptable**
Recommended labeling practices: USP General Chapters: <659> Packaging and Storage Requirements and <7> Labeling	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Preservative (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(e)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Number of containers (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(f)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Product Strength (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters: <7> Labeling*	

Comment/Recommendation:
We refer to your 3.2.P.1 Description and Composition of the Drug Product submitted on February 16, 2024. The product strength should be expressed as the strength per total volume (total drug content supplied in container) followed in close proximity by a parenthetical that includes the strength/mL in the label and labeling. See *USP General Chapter <7> Labeling* for single-dose injectable drug products with containers that supply a volume of drug greater than 1 mL. Revise the product strength to read: "375 mg/18.75 mL (20 mg/mL)".

Applicant revised as recommended.

Storage temperature/requirements (package labeling)	**Acceptable**

Regulation: 21 CFR 610.61(h)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP General Chapters: <7> Labeling, USP General Chapters <659> Packaging and Storage Requirements	

Comment/Recommendation:

Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(i)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Multiple dose containers (recommended individual dose) (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(j)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Route of administration (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)	

Comment/Recommendation:

Known sensitizing substances (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product is not made with latex (natural rubber latex, dry natural rubber or synthetic derivatives of natural rubber latex).

Inactive ingredients (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61, 21 CFR 201.100, FD&C Act section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling	

Comment/Recommendation:
To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e), the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, histidine, polysorbate 20, and trehalose. Revise the ingredient information to the compendial names and definitions. (b) (4)

per the USP monograph definition. Revise (b) (4) trehalose (1412.3 mg). Please confirm the calculated amount trehalose (b) (4) per the monograph definition. Submit an updated Description and Composition Table in section 3.2.P.1 adding a footnote to the table that includes the calculation (b) (4) (b) (4) The footnote should serve as a link between the names and quantities presented in section 3.2.P.1 to the names and quantities presented in the Prescribing Information and carton labeling. Ensure that all inactive ingredients with a USP monograph are provided as such.

Revise the inactive ingredients list to read as:
"Each vial contains 375 mg (20 mg/mL) zenocutuzumab-zbco, histidine (34.9 mg), L-histidine hydrochloride monohydrate (51.1 mg), polysorbate 20 (3.7 mg), trehalose (1412.3 mg), water for injection."

The Applicant accepted the revisions for the inactive ingredients and their quantities except for trehalose. The Applicant proposed to revise the trehalose quantity to 1412 mg which is acceptable.

Source of the product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(p)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Minimum potency of product (package labeling)	**Acceptable**
Regulation: 21 CFR 610.61(r)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Based on CDER's current interpretation of 21 CFR 610.61(r) and after consultation with Product Quality assessors, this regulation does not apply to this product because 1) no U.S. standard of potency has been prescribed for **zenocutuzumab** products (i.e., there is no specific test method described in regulation for **zenocutuzumab** products that establishes an official standard of potency) and 2) Product Quality assessors have determined that potency is not a factor within the meaning of § 610.61(r) for **Bizengri** because lot variability is not a concern as the manufacturing process is appropriately controlled to ensure the consistency and quality of the final product. Accordingly, the phrase "No U.S. standard of potency" is not required to appear on the carton labeling.

Remove the statement "No U.S. standard of potency" from the carton labeling because our view is that 21 CFR 610.61(r) is not applicable."

Applicant revised as recommended.

Rx only (package labeling)	**Acceptable**
Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	

Comment/Recommendation:

Divided manufacturing (package labeling)	**Acceptable**
Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) (Also refer to the Guidance for Industry, Cooperative Manufacturing Arrangements for Licensed Biologics)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Distributor (package labeling)	**Acceptable**
Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Bar code (package labeling)	**Acceptable**
Regulations: 21 CFR 610.67, 21 CFR 201.25	✓ Yes

	☐ No
Recommended labeling practices references: Guidance for Industry *Bar Code Label Requirements Questions and Answers* (August 2011) Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)	☐ N/A

Comment/Recommendation:

Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)	**Acceptable**
Regulations: 21 CFR 610.68, 21 CFR 201.26	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

NDC numbers (package labeling)	**Acceptable**
Regulations: 21 CFR 201.2, 21 CFR 207.35	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Preparation instructions (package labeling)	**Acceptable**
Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i)	☐ Yes ☐ No ☒ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) *USP General Chapters <7> Labeling*	

Comment/Recommendation:

Package type term (package labeling)	**Acceptable**
Recommended labeling practices: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements*	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
Revise to the appropriate package-type term for this product, "single-dose". A single-dose

container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/ infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose.

Applicant revised as recommended.

No misleading statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.6	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Prominence of required label statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.15	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Spanish-language (Drugs) (package labeling)	**Acceptable**
Regulation: 21 CFR 201.16	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The label does not display text in Spanish.

FD&C Yellow No. 5 and/or FD&C Yellow No. 6 (package labeling)	**Acceptable**
Regulation: 21 CFR 201.20	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain FD&C Yellow No. 5 or 6.

Phenylalanine as a component of aspartame (package labeling)	**Acceptable**
Regulation: 21 CFR 201.21(c)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain phenylalanine.

Sulfites; required warning statements (package labeling)	**Acceptable**
Regulation: 21 CFR 201.22(b)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation: The drug product does not contain sulfites.

Net quantity (package labeling)	**Acceptable**
Regulation: 21 CFR 201.51	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022) Guidance for Industry *Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products* (June 2015) *USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).*	

Comment/Recommendation:

Statement of Dosage (package labeling)	**Acceptable**
Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Dispensing container (package labeling)	**Acceptable**
Regulation: 21 CFR 201.100(b)(7)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Medication Guide (package labeling)	**Acceptable**
Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Other (package labeling)	**Acceptable**
	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Prescribing Information Evaluation

PRESCRIBING INFORMATION

Highlights of Prescribing Information	
PRODUCT TITLE	**Acceptable**
Regulation: 21 CFR 201.57(a)(2)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: Draft Guidance for Industry on Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format (January 2018), which, when finalized, will represent FDA's current thinking on topic	

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE AND ADMINISTRATION	**Acceptable**
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

Highlights of Prescribing Information	
DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018)	

USP chapter <659> Packaging and Storage Requirements *USP General Chapters: <7> Labeling*	

Comment/Recommendation: We refer to your IR responses under Seq#0012 submitted on May 24, 2024. The product strength has been revised to the strength per total volume (total drug content supplied in container) followed in close proximity by a parenthetical that includes the strength/mL in the prescribing information. See *USP General Chapter <7> Labeling* for single-dose injectable drug products with containers that supply a volume of drug greater than 1 mL.

Descriptors of the product appearance that appear in DOSAGE FORMS AND STRENGTHS in the full Prescribing Information should not appear in Highlights. See *Guidance for Industry: Labeling for Human Prescription Drug and Biological Products – Implementing the PLR Content and Format Requirements* (February 2013).

We revised to the appropriate package type term. The appropriate package-type term for this product is "single-dose". A single-dose container is a container of a sterile medication for parenteral administration (injection or infusion) that is not required to meet the antimicrobial effectiveness testing requirements. A single-dose container is designed for use with a single patient as a single injection/infusion. Use of the term "single-dose" container does not imply the entire contents of the container constitute a single dose. In some instances, a single-dose container may contain more drug than is required for a single dose or multiple vials may be needed to obtain a single dose. See *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018).

(b) (4)

Applicant made revisions as recommended.

Full Prescribing Information	
2 DOSAGE AND ADMINISTRATION	**Acceptable**
Regulation: 21 CFR 201.57(c)(3)(iv) *Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted or diluted drug; ensure verbatim statement for parenterals: "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit."*	✓ Yes ☐ No ☐ N/A
Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products; confirm the appropriateness of infusion bags, infusion sets (e.g.,	

tubing, infusion aids, or filter membranes) incompatibilities with these components Draft Guidance *Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry* (January 2023)	

Comment/Recommendation:
We included clarity so that the identifying characteristics is consistent throughout the prescribing information.

(b) (4)

Applicant revised as recommended.

We refer to your CMC IR response dated on June 5, 2024. Updated the storage time to "6 hours" of the infusion solution at room temperature (15°C to 25°C / 59°F to 77°F) including infusion time based on the evaluation of the submitted data.
Applicant revised as recommended.

Full Prescribing Information	
3 DOSAGE FORMS AND STRENGTHS	**Acceptable**
Regulation: 21 CFR 201.57(c)(4)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: Guidance for Industry *Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use* (October 2018) *USP chapter <659> Packaging and Storage Requirements* *USP General Chapters: <7> Labeling*	

Comment/Recommendation:
We revised to remove the term (b) (4) to avoid confusion with the appropriate dosage form "injection" for this drug product and removed information that is not required in this section.

As currently presented, the volume is not listed in collaboration with the strength. The product strength should be expressed as the strength per total volume (total drug content

supplied in container) followed in close proximity by a parenthetical that includes the strength/mL in the prescribing information. See *USP General Chapter <7> Labeling* for single-dose injectable drug products with containers that supply a volume of drug greater than 1 mL.

(b) (4)

Applicant revised as recommended.

Full Prescribing Information	
11 DESCRIPTION	**Acceptable**
Regulations: 21 CFR 201.57(c)(12), 21 CFR 610.61 (m), 21 CFR 610.61(o), 21 CFR 610.61 (p), 21 CFR 610.61 (q), FD&C Act Section 502(e)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>	

Comment/Recommendation:
We deleted the statement (b) (4) throughout the prescribing information and replaced with the appropriate dosage form "injection". In addition, we revised to the appropriate package type term for the container.

(b) (4)

To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e), the inactive ingredient list has been revised by using established names for drugs (i.e., drug products and ingredients). The established names for inactive ingredients in your products are the USP/NF monographs titles, histidine, polysorbate 20, and trehalose.
Revise the ingredient information to the compendial names and definitions. (b) (4)

(b) (4)

per the USP monograph definition. Revise (b) (4) trehalose (1412.3 mg). Please confirm the calculated amount trehalose (b) (4) per the monograph definition. Submit an updated Description and Composition Table in section 3.2.P.1 adding a footnote to the table that includes the calculation (b) (4)

(b) (4) The footnote should serve as a link between the names and quantities presented in section 3.2.P.1 to the names and quantities presented in the Prescribing Information and carton labeling. Ensure that all inactive ingredients with a USP monograph are provided as such.

Inactive ingredients names have been revised to appear in alphabetical order in accordance with *USP General Chapters <1091> Labeling.*

(b) (4)

Applicant revised as recommended.

Full Prescribing Information	
15 & 16 Hazardous Drug	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)(iv) Section 15: References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html* Section 16: xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1]	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

Full Prescribing Information	
16 HOW SUPPLIED/ STORAGE AND HANDLING	**Acceptable**
Regulation: 21 CFR 201.57(c)(17)	✓ Yes ☐ No ☐ N/A
Recommended labeling practices: to ensure placement of detailed storage conditions for reconstituted and diluted products	

Comment/Recommendation:
As currently presented, the volume is not listed in collaboration with the strength. The product strength should be expressed as the strength per total volume (total drug content supplied in container) followed in close proximity by a parenthetical that includes the strength/mL in the prescribing information. See *USP General Chapter <7> Labeling* for single-dose injectable drug products with containers that supply a volume of drug greater than 1 mL.

(b) (4)

Applicant revised as recommended.

Full Prescribing Information	
MANUFACTURER INFORMATION	**Acceptable**
Regulations: 21 CFR 201.100(e), 21 CFR 201.1	✓ Yes ☐ No ☐ N/A
Recommended labeling practices references: 21 CFR 610.61(b) (add the US license number for consistency with the carton labeling), and 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	

Comment/Recommendation:
We noticed there is a discrepancy in the way you have listed the manufacturer name on the submitted Form FDA 356h and in proposed label/labeling. FDA's biological product regulations (21 CFR 600.3(t)) define "manufacturer" as "any legal person or entity engaged in the manufacture of a product subject to license under the PHS Act," including "any legal person or entity who is an applicant for a license where the applicant assumes responsibility for compliance with the applicable product and establishment standards". Thus, the Applicant's name as listed in field 2 of Form FDA 356h "Merus N.V." is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. If necessary, correct this on your form FDA 356h. Revise the manufacturer statement using the following qualifying phrase: "Manufactured by:" **Clarify** the role of "Merus US, Inc.", if it's the distributor, revise to the appropriate qualifying phrase "Marketed by:". See 21 CFR 610.64 for qualifying phrase examples. We also relocated the US license number with the manufacturer information.

(b) (4)

Applicant revised as recommended.

Patient Information Labeling Evaluation

PATIENT INFORMATION LABELING	
TITLE (NAMES AND DOSAGE FORM)	**Acceptable**
Recommended Labeling Practices references: To ensure consistency with the product title in the Highlights of Prescribing Information (see Draft Product Title and Initial U.S. Approval in the Highlights of Prescribing Information for Human Prescription Drug and Biological Products - Content and Format Guidance for Industry (January 2018). For the recommended dosage form (see USP General Chapters: <1> Injections, Nomenclature and Definitions, Nomenclature form).	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING	
STORAGE AND HANDLING	**Acceptable**
Recommended labeling practices for Patient Labeling: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)	☐ Yes ☐ No ☒ N/A

Comment/Recommendation:

PATIENT INFORMATION LABELING	
INGREDIENTS	**Acceptable**

Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)	✓ Yes ☐ No ☐ N/A

Comment/Recommendation:
To ensure that all FDA approved labeling fulfills the Federal Food, Drug, and Cosmetic Act (FD&C Act) section 502(e) by using established names for drugs (i.e., drug products and ingredients), the established names for inactive ingredients in your products are revised according to the USP/NF monographs titles.
Also, inactive ingredients names have been revised to appear in alphabetical order in accordance with *USP General Chapters <1091> Labeling*.
Applicant revised as recommended.

PATIENT INFORMATION LABELING	
MANUFACTURER INFORMATION	**Acceptable**
21 CFR 201.1, 19 CFR 134.11	✓ Yes ☐ No ☐ N/A
21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)	

Comment/Recommendation:
For biologic products, the Applicant's name as listed in field 2 of Form FDA 356h "Merus N.V." is the name of the person or legal entity to whom the license is issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder. If necessary, correct this on your form FDA 356h. Revise the manufacturer statement using the following qualifying phrase "Manufactured by:" See 21 CFR 610.64 for qualifying examples. We also relocated the US license number with the manufacturer information.
Applicant revised as recommended.

APPENDIX C. Acceptable Labels and Labeling

- Prescribing Information (submitted on October 8, 2024)
  \\CDSESUB1\EVSPROD\bla761352\0045\m1\us\114-labeling\114a-draft-label\draft-uspi-bizengri-20241007.pdf

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

Diana Pei

Digitally signed by Diana Pei
Date: 10/21/2024 10:37:30AM
GUID: 6352da2c009ad0777a2c3b47ec094b9a

Xiaoyan Zou

Digitally signed by Xiaoyan Zou
Date: 10/21/2024 10:46:22AM
GUID: 642462e4006b9879988dc8a30849fc96