CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761324Orig1s000

PRODUCT QUALITY REVIEW(S)

BLA Executive Summary
Assessment Date: 4/13/2023

1. Application/Product Information

BLA number	761324
Submission Type	Original Submission
Regulatory Pathway	351(a)
Associated IND/BLA	IND135659
Review Designation	Priority
Applicant	Genmab A/S
Indication	For the treatment of adult patients with relapsed or refractory large B-cell lymphoma (LBCL)
Rx/OTC dispensed	Rx
Drug Product Name	**Proprietary Name:** EPKINLY
	Non-proprietary Name/Code Name: Epcoritamab-bysp
	OBP Naming: BsMAB: MAB HUMANIZED (IGG1) ANTI P11836 (CD20_HUMAN) & ANTI P07766 (CD3E_HUMAN) [GEN3013]
Drug Product Description	EPKINLY (epcoritamab-bysp) is a humanized bi-specific IgG1 monoclonal antibody targeting human CD20 and CD3. Epcoritamab is generated (b) (4) EPKINLY is a preservative-free and sterile liquid, clear to slightly opalescent, colorless to slightly yellow solution, free of visible particles supplied in a single dose 2 mL (b) (4) glass vial in two presentations (5 mg/mL (4 mg/0.8 mL) and 60 mg/mL (48 mg/0.8 mL) vials).

	Each dose of EPKINLY (4 mg/0.8 mL) vial contains epcoritamab (4 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5. Each dose of EPKINLY (48 mg/0.8 mL) vial contains epcoritamab (48 mg), acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP. The pH is 5.5.		
Dosage Form	Liquid		
Strength	Injection: 4 mg/0.8 mL in a single-dose vial for dilution prior to use Injection: 48 mg/0.8 mL in a single-dose vial for use without dilution		
Route of Administration	Subcutaneous injection		
Primary Container Closure System	Vial ([(b) (4)] glass sealed with [(b) (4)] rubber stopper and secured with an aluminum flip off cap)		
Device Information	None		
Co-packaged Product Information	None		
OPQ Review Team	**Discipline**	**Primary**	**Secondary**
	Drug substance Drug product Immunogenicity Assay	Leiyun Boone (OPQ/OBP/DBRR IV)	Samuel Mindaye (OPQ/OBP/DBRR IV)
	Facility	Wendy Tan (Drug product) Charles Kuo (Drug substance)	Zhong Li (CDER/OPQ/OPMA/DBM)

	Microbiology	Wendy Tan (Drug product) Charles Kuo (Drug substance)	Maxwell Van Tassel (CDER/OPQ/OPMA),
	RBPM	Janell Artis (OPQ/OPRO)	
	ATL	Samuel Mindaye (OPQ/OBP/DBRR IV)	
OPQ Issued Consults	**None**		

Multidisciplinary Assessment Team:

Discipline	Assessor	Office/Division
RPM	Natasha Kormanik	CDER/OND/ORO/DRO-OD
Cross-disciplinary Team Lead	Nicholas Richardson	CDER/OND/OOD/DHM2
Medical Officer	Nicole Sunseri	CDER/OND/OOD/DHM2
Pharmacology/Toxicology	Michael Manning/Brenda Gehrke, TL	CDER/OND/OOD/DHOT
Clinical Pharmacology	Sriram Subramaniam/ Xiling Jiang, TL	CDER/OTS/OCP/DCPI
Pharmacometrics	Robyn Konicki/ Jiang Liu, TL	CDER/OTS/OCP/DPM
Statistics	Mohamad Megheib/ Lola Luo, TL	CDER/OTS/OB/DBIX

Submissions Assessed:

Submission	Date Received
STN 761324/0001– Submission of Modules 1, 2, 4, and 5	09/21/2022
STN 761324/0002 Quality/Response to Information Request	10/12/2022
STN 761324/0003 Quality/Response to Information Request	10/18/2022
STN 761324/0004 (Stability update) Simple stability updates	10/20/2022
STN 761324/0005 Quality/Response to Information Request	10/21/2022
STN 761324/0009 Quality/Response to Information Request	12/07/2022
STN 761324/0017 Quality/ Response to Information Request	01/20/2023
STN 761324/0024 Quality/Response to Information Request	02/08/2023
STN 761324/0026 Quality/Response to Information Request	02/13/2023
STN 761324/0028 Quality/Response to Information Request	02/16/2023
STN 761324/0029 Labeling/Response to Information Request	02/16/2023
STN 761324/0031 Quality/Response to Information Request	02/24/2023

STN 761324/0032 Quality/Response to Information Request	03/08/2023
STN 761324/0035 Quality/Response to Information Request	03/27/2023
STN 761324/0036 Quality/Response to Information Request	03/28/2023
STN 761324/0037 Labeling/Package Insert Draft	03/28/2023
STN 761324/0039 Quality/Response to Information Request	04/04/2023
STN 761324/0040 Quality/Response to Information Request	04/05/2023
STN 761324/0041 Quality/Response to Information Request	04/07/2023
STN 761324/0042 Quality/Response to Information Request	04/11/2023
STN 761324/0043 Quality/Response to Information Request	04/12/2023
STN 761324/0045 Labeling/Response to Information Request	04/27/2023
STN 761324/0046 Quality/Response to Information Request	04/27/2023

Related/Supporting Documents: DMFs

DMF#	DMF Holder	Item Referenced	Letter of Cross-Reference	Comments (status)
(b) (4) (Type III)	(b) (4)	(b) (4)	Yes	No further reviews were performed because adequate nformation is provided in the application.
(b) (4) (Type III)			Yes	
(b) (4) (Type III)			Yes	

2. Recommendation and Conclusion on Approvability

Recommendation: Approval

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761324 for EPKINLY manufactured by Genmab A/S. The data submitted in this application are adequate to support the conclusion that the manufacture of EPKINLY 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)

(b) (4)

(b) (4)
FEI (b) (4)

- **Drug Product:**
  (b) (4)
  FEI: (b) (4)

b. Fill size and dosage form: EPKINLY is provided as 4 mg/0.8 mL in a single-dose vial for dilution prior to use and 48 mg/0.8 mL in a single-dose vial.

c. Dating Period:

- **Drug Product:** 24 months at 2°C - 8°C for both 5 mg/mL and 60 mg/mL
- **Drug Substance:** (b) (4) months at (b) (4) °C
  (b) (4)
- **For packaged products:** None
- **Stability Option:**
  - For stability protocols:
    - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your drug substance and/or drug product under 21 CFR 601.12.

d. Exempt from lot release:

- Yes
- Rationale, if exempted: EPKINLY is exempted from lot release per FR 95-29960. The overall control strategy, including manufacturing and release controls, is adequate to control lot-to-lot variability and product quality over the proposed shelf-life.

e. Benefit/Risk Management Steps

The assessment of manufacturing information provided in the application concluded that the methodologies and processes used for (b) (4) epcoritamab drug substance, and drug product manufacturing, release and stability testing are robust and sufficiently controlled to produce product with consistent quality and safety profile. The manufacturing process is robust for inactivation and removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

Pre-licensing inspections or assessments were conducted for (b) (4) (b) (4) manufacturing, (b) (4) epcoritamab DS, (b) (4) and EPKINLY, (b) (4) (b) (4) The facilities were found acceptable for the proposed operations.

f. Recommendation on Phase 4 (Post-Marketing) Commitments,

PMC-1: Develop, validate, and implement an assay to evaluate the neutralizing capacity of epcoritamab anti-drug-antibodies (ADAs) detected in the patient samples. The assay should be capable of sensitively detecting neutralizing ADAs in the presence of epcoritamab levels that are expected to be present in serum at the time of patient sampling. The final report should include assay validation report and assay SOP.

Final report submission: 06/30/2023

PMC-2: Develop, validate, and implement a CIEX-HPLC method to assess charge heterogeneity at release and stability testing of epcoritamab drug substance and drug product. Genmab should submit the method validation report and update the epcoritamab drug substance and drug product specifications and other relevant BLA sections.

Final report submission: 08/31/2023

PMC-3: Conduct additional validation study to support linearity, range, and accuracy of the A280 protein concentration method using representative epcoritamab (b) (4) drug substance and drug product samples. In addition, Genmab should conduct additional validation study to support the range and accuracy of the protein assay (b) (4). (b) (4) to support suitability of the method at this site. Genmab should submit the method validation report and update the relevant BLA sections of the epcoritamab drug substance and drug product .

Final report submission: 12/31/2023

PMC-4: Re-evaluate and update the acceptance criteria for biological activity of both epcoritamab drug substance and drug products after 10 additional commercial drug product batches have been released. Genmab will submit the reanalysis final report and update the epcoritamab drug substance and drug product specifications and other relevant BLA sections.

Final report submission: 12/31/2024

4. Basis for Recommendation

a) Summary of Quality assessments:

Critical quality attribute (CQA) Identification, Risk and Lifecycle Knowledge Management

Provided below is summary of critical quality attributes and the associated control strategies for attributes that are relevant to active pharmaceutical ingredient (Table 1), epcoritamab [redacted] drug substance (Table 3), and EPKINLY drug product (Table 4). For additional information, see the primary reviews, including the [redacted] DS, and DP Quality Review by OBP/DBRRIV and the DS Microbiology Review and the DP Microbiology Review by OPMA/DBM.

(i) Active Pharmaceutical Ingredient Quality Summary

Table 1: Active pharmaceutical ingredient CQA identification, risk and lifecycle knowledge management

Epcoritamab CQAs	Origin	Risk	Controlled
Identity (primary structure)	Intrinsic to molecule	Biological activity and safety	[redacted]
Biological and immunological activities (T-cell activation, CD3 antigen binding, CD20 antigen binding, FcRn binding, T-cell mediated cytotoxicity)	Intrinsic to molecule, formulation, stability and manufacturing process	Efficacy, immunogenicity, and safety	
Size related variants (LMWS including LC and HC)	Formulation, stability and manufacturing process and stability	Efficacy, Pharmacokinetics and immunogenicity	
Size related variants (HMWS) (dimer and oligomer)	Formulation, stability and manufacturing process and stability	Efficacy, Safety and immunogenicity	

Charge-related variants (Acidic and basic forms) product-related impurity	DS manufacturing process, formulation, and stability, deamidation in CDR in particular	Efficacy, Pharmacokinetics and immunogenicity	(b) (4)
Disulfide linkages	DS manufacturing process and storage conditions	Biological activity and safety	
Post-translational modifications (oxidation, deamidation, N- and C-terminal deamidation, glycation, and glycosylation heterogeneity)	Formulation, processing, and stability	Efficacy, immunogenicity pharmacokinetics, and safety	

(b) (4)

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(b) (4)

(iii) Drug Substance quality summary

Table 3: Drug Substance CQA Identification, Risk and Lifecycle Knowledge Management

Epcoritamab CQAs	**Origin**	**Risk**	**Control steps and control strategy**
Protein concentration	Formulation	Biological activity and safety	(b) (4)
Appearance (Color and Opalescence)	Formulation and manufacturing process	Stability and safety	
Microbial contamination	Manufacturing process, failure of the container closure integrity	Safety, purity, and efficacy	
Bacterial endotoxins	Raw material, manufacturing process	safety	
Osmolality	Formulation, manufacturing process, and stability	Safety	

(b) (4) content	Manufacturing process	Stability and safety	(b) (4)
pH	Formulation, manufacturing process, and stability	Biological activity and safety	
(b) (4) (process-related impurity)	Manufacturing process	Efficacy and safety	
(b) (4)	Raw material and process	Safety	

Description: Epcoritamab is a humanized bispecific anti-CD3 and anti-CD20 antibody generated by (b) (4)

Mechanism of action (MoA): Epcoritamab simultaneously binds to CD3 on T cells and CD20 on malignant B cells thereby inducing activation and cytotoxic activity of T cells and enables killing of target lymphoma cells. With this MoA epcoritamab induces cytolytic synapse formation and kills CD20-positive target cells, independent of ligation of a peptide-MHC complex by the T cell receptor.

Potency assay: The biological activity of epcoritamab is determined in a surrogate T-cell activation assay using GloResponse NFAT-Luc2 Jurkat cells expressing CD3 and Daudi cells expressing CD20. Co-binding of epcoritamab to the Daudi and Jurkat cells activates the NFAT pathway and leads to luciferase expression. The bioluminescent signal is detected and is proportional to the activity level. The result is reported as % relative EC50 to a reference standard (RS).

Reference Materials: A two-tiered reference material system consisting of the primary reference standard (PRS) and working reference standard (WRS) has been established for epcoritamab per ICH Q6B recommendations. (b) (4)

(b) (4) he PRS was qualified against the previous RS and will be used to qualify future WRS batches. The WRS will be used for release, stability and characterization testing of epcoritamab DS and DP. The current reference standards are suitable for their intended use. The current PRS and WRS will be requalified (protocols are acceptable) biannually and trending analysis will be performed for the requalification results as well as routine in-use testing results. Protocols have been provided for the qualification of future PRS and WRS and the protocol contains adequate testing and acceptance criteria. The implementation of a new reference standard will be reported in annual report.

Critical starting materials: Epcoritamab is generated (b) (4) Summary of critical materials used in the production of epcoritamab (b) (4) is provided in earlier section. Overall, raw materials used in commercial manufacture are animal- and human-component free. All compendial raw materials and excipients comply with the requirements of the relevant monographs and are purchased from qualified suppliers with certificates of analysis. All non-compendial materials are purchased from approved suppliers and are tested against the defined set of acceptance criteria.

Manufacturing process of DS: The manufacture of epcoritamab DS involves (b) (4)

Container closure system: (b) (4)

Dating period and storage conditions: (b) (4) months at (b) (4) °C.

(iv) Drug product (EPKINLY) quality summary

Table 4: Drug product CQA Identification, Risk and Lifecycle Knowledge Management

CQA type	Origin	Risk	Control steps and control strategy
Protein concentration	Formulation	Biological activity and safety	(b) (4)
Particles (sub-visible)	Formulation, manufacturing process, and degradation	Stability and safety	
Appearance (Color)			
Appearance (Opalescence)			
Appearance (Visible particles)			
Sterility (contaminant)	Manufacturing process, failure of the container closure integrity	Safety, purity, and efficacy	
Endotoxins	Raw material, manufacturing process	Safety, purity and immunogenicity	
Container closure integrity	breaches during storage	Safety	
Extractable volume	Filling/storage	Inaccurate dosing/ Safety/efficacy	
Osmolality	Formulation, manufacturing process, and stability	Safety	
Polysorbate content	Formulation manufacturing process, and stability	Stability and safety	
pH	Formulation, manufacturing process, and stability	Biological activity and safety	
Identity	Intrinsic to molecule	Biological activity and safety	
Potency	Intrinsic to molecule, altered by formulation, stability	Efficacy, safety, immunogenicity	

Description (summary of product design): EPKINLY is a sterile, preservative-free liquid supplied in a single dose 2 mL (b) (4) glass vial. The vial is sealed with (b) (4) rubber stopper and secured with an aluminum flip off cap. EPKINLY is presented as 5 mg/mL and 60 mg/mL vials. The nominal quantity per vial is 4 mg for 5 mg/mL vial and 48 mg for 60 mg/mL vial based on an extractable volume of 0.8 mL each. The target fill volume is (b) (4) mL (target (b) (4) mL) to ensure a minimum of (b) (4) mL overfill (target (b) (4) mL) for both presentations. The 5 mg/mL DP is a concentrate for injection and is diluted in sterile saline (0.9% sodium chloride) to the target final concentration (0.16 and 0.8 mg/mL) prior to subcutaneous injection. The saline diluent is not provided with the DP. The 60 mg/mL DP is a solution for subcutaneous injection (without a dilution step).

Potency and Strength: EPKINLY contains epcoritamab DS of 4 mg for 5 mg/mL vial and 48 mg for 60 mg/mL vial. The potency assays are the same as those described in the DS section of this review.

List of excipients: excipients in each single-dose 5 mg/mL and 60 mg/mL EPKINLY vial include acetic acid (0.19 mg), polysorbate 80 (0.32 mg), sodium acetate (1.7 mg), sorbitol (21.9 mg) and Water for Injection, USP.

Reference Materials: The same reference standard is used for DP as for DS. Refer to the Drug Substance reference standard section above.

Manufacturing process summary: The epcoritamab drug product manufacturing process involves (b) (4) Container closure integrity testing using a validated method is included in the stability program.

The validated commercial batch size is (b) (4) and at least three consecutive batches at the commercial scale were manufactured and analyzed to validate the manufacturing process. Process parameters were within pre-specified parameters, and product quality attributes were within specification limits. These data support a well-controlled process that will consistently produce a high-quality product and that is adequate from a product quality

review perspective. OPMA recommends approval of the DP manufacturing process from a product quality microbiology and sterility assurance perspective.

Container closure: The container closure system consists of a 2 ml clear (b) (4) glass vial, a (b) (4) rubber stopper and an aluminum cap with flip-off top.

Dating period and storage conditions: 24 months at 2°C - 8°C.

(v) Any Special Product Quality Labeling Recommendations:

- Store EPKINLY vials refrigerated at 2°C to 8°C (36°F to 46°F). Keep in the original carton to protect from light. Do not freeze. Do not shake.

Preparation for administration

- EPKINLY 4 mg/0.8 mL vial:
    - Dilute required amount of EPKINLY in 0.9% sodium chloride solution for injection following the steps outlined in the package insert.
    - Use diluted EPKINLY solution immediately. If not used immediately, store the solution refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours or at room temperature at 20°C to 25°C (68°F to 77°F) for up to 12h.
    - The total storage time from the start of dose preparation to administration should not exceed 24 hours. Protect from direct sunlight.
    - Allow EPKINLY solution to equilibrate to room temperature for not more than 1 hour before administration.
    - Discard unused EPKINLY solution beyond the allowable storage time.
- EPKINLY 48 mg/0.8 mL vial is supplied as ready-to-use solution that does not need dilution prior to administration.

(vi) Establishment Information:

Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
(b) (4)					
Drug Substance					
Manufacture of drug substance Release testing, Stability testing, storage	(b) (4)		On-site pre-license inspection needed	6-item 483 was issued	Approved based on inspection
Release testing, Stability testing, storage			Approve based on previous history	N/A	Approve based on previous history
Release testing for DS and DP (b) (4)					
Drug Product					
Manufacture of drug product Visual inspection, Release testing, Stability testing	(b) (4)		On-site pre-license inspection needed	2-item 483 was issued	Approve based on inspection

Release testing, Stability testing	[redacted] (b) (4)		N/A	N/A	Approve based on previous history
Release testing, Stability testing			N/A	N/A	
Release testing, Stability testing			N/A	N/A	
Visual inspection, Labelling and packaging			N/A	N/A	
Visual inspection, Storage of drug product and finished goods, Stability testing (Container closure integrity)			N/A	N/A	
Labelling and packaging			N/A	N/A	No evaluation was necessary
Storage of finished goods	(b) (4)	N/A	N/A	N/A	
Storage of drug product and finished goods		N/A	N/A	N/A	
Shipment of drug product and finished goods, Batch disposition of finished goods	Genmab A/S a Kalvebod Brygge 43 1560 Copenhagen V, Denmark Genmab Inc. 777 Scudders Mill Road, Bldg. 2, 4th Floor Plainsboro, NJ 08536, USA	N/A	N/A	N/A	

Facilities:

1. A pre-licensure inspection (PLI) was conducted (b) (4) a five-item FDA Form 483 was issued with an initial field recommendation of VAI. Upon review of the 483 responses, the Compliance Team concurs with the initial field recommendation of VAI. The 483 responses were reviewed and found acceptable. This facility was recommended for approval.

2. A PLI for epcoritamab drug substance (DS) was conducted for epcoritamab DS manufacturer (b) (4) At the conclusion of the PLI, a 6-item 483 was issued with an initial field recommendation is VAI. Upon review of the 483 responses, the Compliance Team concurs with the initial field recommendation of VAI. The 483 responses were reviewed and found acceptable. This facility was recommended for approval.

3. A PLI for epcoritamab drug product (DP) was conducted for epcoritamab DP manufacturer (b) (4) A two-item FDA Form 483 was issued to the firm. Initial field recommendation of the inspection was VAI. The 483 responses were reviewed and found acceptable. This facility was recommended for approval.

b) Subdiscipline Recommendation:

Drug Substance	**-**	**Adequate**
Drug Product	**-**	**Adequate**
Immunogenicity Assay	**-**	**Adequate**
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 EPKINLY (i.e., there is no specific test method described in regulation for EPKINLY that establishes an official standard of potency). We next considered whether potency is a factor for EPKINLY 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 EPKINLY for purposes of § 610.61(r) because lot variability is not a concern for EPKINLY as the 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. (b) (4)

c. Drug Substance:

i. Protocols approved:
   1. (b) (4) Lifetime Validation: 3.2.S.2.5 (b) (4) epcoritamab DS
   2. Qualification of New Primary Reference Standard: 3.2.S.5 Primary Reference Standard – epcoritamab DS
   3. Qualification of New Working Reference Standard: 3.2.S.5 Working Reference Standard – epcoritamab DS
   4. Post-approval Stability Protocol: 3.2.S.7.2 Post-Approval Stability Protocol and Stability Commitment – epcoritamab DS

ii. Residual risk: None

iii. Future inspection points to consider: None

d. Drug Product:

i. Protocols approved:
   1. Post-approval Stability Protocol: 3.2.P.8.2 Drug product post-approval stability protocol and stability commitment

ii. Residual risk: None

iii. Future inspection points to consider: None

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/

SAMUEL MINDAYE
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