CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761150Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: *APPROVAL*

BLA/NDA Number: 761150
ADDENDUM to IQA memo dated November 23, 2020
Final Assessment Date: December 8, 2020

Drug Name/Dosage Form	Margetuximab-cmkb (MARGENZA)/injection
Strength/Potency	250mg/10ml (25 mg/ml) in a single dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment (in combination with chemotherapy) of patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease
Applicant/Sponsor	MacroGenics, Inc.

Background to Addendum:

At the time the initial ATL IQA memo was finalized, this BLA was recommended for Approval from the perspective of microbial control and product quality by both OPMA and OBP. The inspection was conducted from (b) (4); the firm was classified Official Action Indicated (OAI) with a recommendation to withhold approval based on the inspectional findings. Therefore, the Drug Substance Facility Assessment Recommendation was pending final review of the firm's written response to the Form 483 issued at the PLI.

UPDATED Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

a. Recommendation: *APPROVAL*

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761150 for MARGENZA manufactured by MacroGenics, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of MARGENZA 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.

B. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: (b) (4)
  - Drug Product: (b) (4)
- Fill size and dosage form: 250 mg/10 mL (25 mg/mL) in a single-dose vial; injection
- Dating period:

- Drug Product: 36 months: 2-8°C
- Drug Substance: (b) (4) months: (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.

- Exempt from lot release:
  - Yes
  - Rationale, if exempted: specified product in accordance with 21 CFR 601.2a
    Note: MARGENZA is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

An additional post-marketing commitment (PMC) was established due to corrective actions identified by (b) (4) following the pre-license inspection held at (b) (4) on (b) (4) and (b) (4). Form 483 from the pre-license inspection states as Observation #1 that (b) (4). The response received from (b) (4) to the Agency's Request for additional information indicated that, (b) (4) must be revalidated and the resulting (b) (4) shown to be consistent with that from the original process. This will be managed under (b) (4), which has a due date of 12/31/2021.

D. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:
In addition to the 6 CMC post-marketing commitments discussed in the IQA dated November 23, 2020 to support licensure of MARGENZA, the Sponsor has agreed to the following post-marketing commitment based on the outcome of the (b) (4) facility review and the corrective action commitment made by (b) (4)

- Prospectively revalidate the (b) (4) operation as per Agency communications with (b) (4) following the 2020 pre-license inspection of the drug substance manufacturing facility. In addition, confirm that (b) (4) Submit the results to the BLA as a Prior Approval Supplement (PAS).

Summary of updated information: Compliance status of drug substance manufacturing site

A. Establishment Information:

Overall Recommendation:					
DRUG SUBSTANCE					
Function	Site Information	DUNS/FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation

Margetuximab drug substance production, release and stability testing	(b) (4)	(b) (4)	Pre-license inspection requested	WITHHOLD	APPROVE

Facilities: A 6-item Form FDA 483 was issued to (b) (4) on (b) (4) for the following observations: (b) (4) The inspection team recommended withholding approval of the BLA because (b) (4) (items 1-3). (b) (4) responded to the Form 483 items on (b) (4). The responses to items 3-6 were deemed adequate, however, the responses to items 1 and 2 were deemed inadequate due to insufficient information regarding (b) (4) A request for additional information (RAI) was issued to the firm on (b) (4). Additional responses received on (b) (4) adequately addressed the remaining concerns, with (b) (4) (items 1,2) and establishment of a PMC for re-validation (b) (4) (item 1).

B. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved: Refer to IQA dated November 23, 2020
ii. Outstanding assessment issues/residual risk: None
iii. Future inspection points to consider ((b) (4)
Verify corrective actions to Form 483 Observations 1 and 2

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/

WENDY C WEINBERG
12/09/2020 01:40:19 PM

THUY T NGUYEN
12/09/2020 01:50:13 PM

KATHLEEN A CLOUSE STREBEL
12/09/2020 08:07:26 PM

Recommendation: Pending final review of Drug Substance Manufacturing Facility (delayed due to global pandemic)

INTEGRATED PRODUCT QUALITY ASSESSMENT

BLA Number 761150
Assessment Number: First Round
Assessment Date: November 23, 2020

Drug Name/Dosage Form	Margetuximab-cmkb (MARGENZA)/injection
Strength/Potency	250mg/10ml (25 mg/ml) in a single dose vial
Route of Administration	Intravenous infusion
Rx/OTC dispensed	Rx
Indication	Treatment (in combination with chemotherapy) of patients with metastatic HER2-positive breast cancer who have received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease
Applicant/Sponsor	MacroGenics, Inc.

Product Overview:

Margetuximab-cmkb is a chimeric Fc-engineered IgG1 kappa monoclonal antibody that binds to the extracellular domain IV of the human epidermal growth factor receptor 2 protein (HER2). The variable domains are derived from the same murine precursor antibody as trastuzumab. Upon binding to HER2-expressing tumor cells, margetuximab-cmkb acts as a HER2 receptor antagonist, leading to an inhibition of tumor cell proliferation and decreased shedding of the HER2 extracellular domain. The Fc portion of margetuximab-cmkb is distinct from trastuzumab in that it has been engineered to increase antibody-dependent cellular cytotoxicity (ADCC) and immune function via enhanced binding to both low (158F) and high (158V) affinity variants of activating receptor FcγRIIIa (CD16A), and decreased binding to the inhibitory Fc receptor FcγR2b (CD32B).

Margetuximab-cmkb is produced in genetically engineered mammalian cell (Chinese Hamster Ovary) culture and purified using standard biotechnology processes. It is supplied as a sterile, preservative-free aqueous solution in single use vials containing 10 ml recoverable fill volume. Each ml of solution contains 25 mg of margetuximab-cmkb, L-arginine hydrochloride (11 mg), polysorbate 80 (0.1 mg), sodium chloride (2.9 mg), sodium phosphate dibasic, heptahydrate (0.58 mg), sodium phosphate monobasic, monohydrate (1.1 mg), sucrose (30 mg), and Water for Injection, USP at a pH of approximately 6.1. The vialed solution is clear to slightly opalescent, colorless to pale yellow or pale brown solution. Some visible, translucent, inherent proteinaceous particles may be present. It is administered by intravenous infusion following dilution with 0.9% Sodium Chloride for Injection, USP through a 0.2 um pore size polyethersulfone (PES) inline filter.

Quality Assessment Team:

Discipline	Assessor	Office/Division
RBPM	Anh-Thy Ly	OPQ/OPRO
Product Quality - Drug Substance (DS)	Kathryn King	OBP/DBRR1
Product Quality - Drug Product (DP)	Kathryn King	OBP/DBRR1
Product Quality DS, DP Secondary Assessor	Wendy Weinberg	OBP/DBRR1

Immunogenicity	Anshu Rastogi	OBP/DBRR1
Immunogenicity Secondary Assessor	Brian Janelsins	OBP/DBRR1
Labeling	Vicky Borders-Hemphill	OBP/IO
Microbiology/Facilities Reviewer - DS	Zhong Li	OPMA/DBM
Microbiology/Facilities Reviewer - DP	Lindsey Brown	OPMA/DBM
Microbiology DS and DP Secondary Assessor	Candace Gomez-Broughton	OPMA/DBM
Facilities – DS & DP Secondary Assessor	Thuy Thanh Nguyen	OPMA/DBM
DBM Director	Zhihao Peter Qiu	OPMA/DBM
Application Team Lead	Wendy Weinberg	OBP/DBRR1
DBRR1 Division Director (Tertiary Assessor)	Kathleen A. Clouse	OBP/DBRR1

Multidisciplinary Assessment Team:

Signatory Authority for Division: Laleh Amiri-Kordestani, OOD/DO1 Signatory Authority for Office: Julia Beaver, OOD		
Discipline	Assessor	Office/Division
Regulatory Project Manager	Kelly Chiang Clara Lee	DRO-OD DRO-OD
Clinical Reviewer	Melanie Royce	DO1
Clinical Team Leader Cross-disciplinary Team Lead	Christy Osgood	DO1
Pharmacologist/Toxicologist Reviewer	Ching-Jey (George) Chang	DHOT
Pharmacology/Toxicology Team Lead	Tiffany Ricks	DHOT
Clinical Pharmacology Reviewer	Krithika Shetty	DCPV
Clinical Pharmacology Team Leader	Pengfei Song	DCPV
Biometrics Reviewer	Anup Amatya	DBV
Biometrics Team Leader (Acting)	Mallorie Fiero	DBV
Genomics Reviewer	Jeffrey Kraft	DTPM
Genomics Team Leader	Rosane Charlab Orbach	DTPM

1. Names:

   a. Proprietary Name: MARGENZA
   b. Trade Name: MARGENZA
   c. Non-Proprietary Name: margetuximab-cmkb
   d. CAS Registry Number: 1350624-75-7
   e. Common Name: MGAH22; H22 (DS CMO manufacturing site code)
   f. USAN/INN Name: margetuximab
   g. Compendial Name: not applicable
   h. OBP systematic name: MAB CHIMERIC (IGG1) ANTI P04626 (ERBB2_Human) [MGAH22]

Submissions Assessed:

Submission(s) Assessed			Document Date
SDN 1	Original Submission	OBP, OPMA	12/18/2020
SDN 7	Response to IR1	OBP	
SDN 9	Response to IR2 regarding CMO manufacturing and inspection planning	OBP, OPMA	03/26/2020
SDN 20	Response to IR3; request for teleconference to discuss inspection planning	OBP, OPMA	05/07/2020
SDN 27	Response to IR4	OPMA	06/15/2020
SDN 31	Response to IR5	OPMA	07/23/2020
SDN 33	Response to IR6 OBP	OBP	07/31/2020
SDN 39	Response to IR8 production plan at (b) (4)	OBP, OPMA	09/04/2020
SDN 40	Response to IR10	OBP	09/14/2020
SDN 42	Response to IR10	OBP, OPMA	09/18/2020
SDN 47	Response to IR11	OBP, OPMA	10/16/2020
SDN 48	Response to IR 9	OPMA	10/23/2020
SDN 49	Response to IR12	OBP, OPMA	11/02/2020
SDN 50	Response to PMC IR1	OBP	11/03/2020
SDN 52	Response to IR13	OBP	11/09/2020
SDN 53	Response to IR14	OBP	11/13/2020
SDN 54	Response to IR15	OBP	11/13/2020
SDN 55	Response to PMC IR2	OBP	11/19 2020

Quality Assessment Data Sheet:

1. Legal Basis for Submission: 351(a)
2. Related/Supporting Documents:

A. DMFs:

DMF #	DMF Type	DMF Holder	Item referenced	Code[1]	Status[2]	Date Assessment Completed	Comments
(b) (4)	III		(b) (4)	3	N/A		
	II			3	N/A		
	III			3	N/A		
	III			3	N/A		
	V			3	N/A		
	V			3	N/A		
	V			1	Adequate	1/29/2020	

1. Action codes for DMF Table: 1- DMF Assessed; Other codes indicate why the DMF was not assessed, as follows: 2- Assessed previously and no revision since last assessment; 3- Sufficient information in application; 4- Authority to reference not granted; 5- DMF not available; 6- Other (explain under "comments")

2. Action codes for Status column: Adequate, Adequate with Information Request, Deficient, or N/A (There are enough data in the application; therefore, the DMF did not need to be assessed.

B. Other documents: IND, Referenced Listed Drug (RLD), or sister application.

Document	Application Number	Description
Referenced IND	107768	Clinical development of margetuximab in breast cancer
Referenced IND	(b) (4)	

3. Consults: none

4. Environmental Assessment of Claim of Categorical Exclusion:
In accordance with 21 CFR 25.31(c), MacroGenics, Inc. claimed a categorical exclusion from the requirement under 21 CFR 25.20 to prepare an environmental assessment.

Executive Summary:

I. Recommendations:

A. Recommendation and Conclusion on Approvability:

Recommendation: PENDING

This BLA is recommended for Approval from the perspective of microbial control, sterility assurance, and product quality by both OPMA and OBP.
The Drug Substance Facility Assessment Recommendation is pending review of the firm's written response to the FDA-483 issued during the Pre-license Inspection (PLI) of (b) (4) (FEI (b) (4)) conducted from (b) (4). (b) (4) is the proposed site for Margetuximab DS manufacture.

If deemed acceptable for an approval, the following language can be used:

The Office of Pharmaceutical Quality, CDER, recommends approval of STN 761150 for MARGENZA manufactured by MacroGenics, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of MARGENZA 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.

In case of an OPQ recommendation of non-approval (Complete Response [CR]) due to CMC issues:

The Office of Biotechnology Products, OPQ, CDER, has completed assessment of STN 761150 for margetuximab-cmkb manufactured by MacroGenics, Inc. The data submitted in this application are not sufficient to support a conclusion that the manufacture of MARGENZA is well-controlled and will lead to a product that is pure and potent for the duration of the shelf-life. From a CMC standpoint, OBP is recommending a Complete Response letter be issued to MacroGenics, Inc. to outline the deficiencies noted below and the information and data that will be required to support approval.

B. Summary of Complete Response Issues: PENDING.

C. Approval Action Letter Language:

- Manufacturing location:
  - Drug Substance: (b) (4) A
  - Drug Product: (b) (4)
- Fill size and dosage form: 250 mg/10 mL (25 mg/mL) in a single-dose vial; injection
- Dating period:
  - Drug Product: 36 months: 2-8°C

  - Drug Substance: (b) (4) months: (b) (4) °C
  - For packaged products: Not packaged
  - Stability Option (select one below):
    - 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.
- Exempt from lot release:
  - Yes
  - Rationale, if exempted: Specified product in accordance with 21 CFR 601.2a
    Note: MARGENZA is exempted from lot release per FR 95-29960.

D. Benefit/Risk Considerations:

Margetuximab-cmkb is proposed for the treatment of patients with metastatic HER2 positive breast cancer who have received two or more prior anti-HER2 regimens, as least one of which was for metastatic disease. Overall, based on the information supplied in the BLA and through information amendments provided throughout the course of the review, the manufacturing process and control of margetuximab-cmkb are deemed adequate to support that MARGENZA drug product meets current standards for purity and potency. The drug substance and drug product are well-characterized and critical quality attributes are well-defined and adequately controlled. Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing and release processes.

Media fills have not been performed specifically for the DP primary container closure system (10ml/20mm vial). A PMC is being established to provide data from one media fill using the product-specific parts, (b) (4) and equipment, to further support (b) (4) the 10ml/20mm stopper combination use for margetuximab-cmkb DP. As media fills conducted using the 2ml/13mm and 20ml/10mm vials demonstrate the ability to (b) (4) , adequate information from media fills provided in the BLA submission justify the implementation of a PMC to obtain these data.

No real time leachables data were provided in the BLA. A PMC is being established to monitor leachables from the DP container closure system in real time stability studies with the goal of demonstrating the absence of significant leachables over the product shelf life. This product was developed to address an unmet medical need, and fulfilment of this PMC will involve long term data acquisition. Sufficient supportive data were provided from extractables studies, justifying the implementation of this study as a PMC.

The supportive DP shipping information relied mainly on a simulated shipping study. A PMC is being established to conduct a Drug Product (DP) shipping validation study on one lot of commercial DP shipped via commercial lanes to the selected third-party logistics warehouse to confirm that DP shipping does not result in product impact. The ISTA study data provided adequate assurance to support that further qualification of DP shipping can be conducted as a PMC.

The presumed mechanism of action/efficacy of margetuximab-cmkb relies on functions mediated by both the Fab and Fc portions of the IgG1 antibody molecule, and 3 assays are in

use to monitor and control for product potency: CGI Bioassay, HER2 Binding ELISA and FcγRIIIa Binding ELISA. Release testing results for these assays are reported relative to reference standard, and the Sponsor stated that they were optimized for this reporting approach. However, stability testing results for the reference standard are reported by IC_{50} and EC_{50} values, which are very wide and may not on their own allow detection of stability failures. A PMC is being implemented to optimize the direct measurement of absolute potency as IC_{50}/EC_{50} values, and to tighten IC_{50} and EC_{50} acceptance criteria for reference standard stability assessment based on the study results. Additional assays, IE-HPLC % main peak and SE-HPLC % monomer, are currently in place and correlate with potency by the CGI bioassay and FcγRIIIa binding, respectively. The available data support reference standard stability in the interim and justify that these studies are suitable to be conducted as a PMC.

The current DS and DP lot release and stability specifications for margetuximab-cmkb are based on both clinical experience and limited manufacturing experience with the commercial DS and DP manufacturing processes. A PMC is being established to reassess release and stability specifications for a subset of margetuximab-cmkb drug substance and drug product assays once additional manufacturing experience is gained (by December 30, 2022 or following manufacture of 30 lots, if earlier). The assays included are the following: N-glycosylation (DS), residual host cell protein levels (DS), potency by CGI bioassay, HER2 binding ELISA, and FcγRIIIa binding ELISA (DS and DP), visible particles (DP) and protein content (DP). This re-assessment will be used to tighten or support the current specifications, as appropriate, and to provide further control to maintain limits within clinical experience. Long term data from multiple runs are needed, thus this is appropriate as a PMC.

Regarding immunogenicity risk, sufficient information and data were provided to support the suitability of the binding anti-drug antibody (ADA) assay that was used to generate clinical ADA data in support of the BLA, and the safety profile observed in the clinical studies indicates that the low incidence of binding antibodies to MARGENZA does not appear to be a significant safety issue. However, the development, validation, and implementation of an adequate assay for detecting neutralizing antibodies to MARGENZA would provide a better assessment and characterization of immune responses to MARGENZA in patients. This will be pursued as a post-marketing commitment. Furthermore, a PMC will be issued by the clinical pharmacology team for Macrogenics to use the adequately optimized and validated nAb assay to analyze the clinical samples that tested positive for binding antibodies in study CP-MGAH22-04.

Additional PMC may be implemented depending on the outcome of the PLI review.

Detailed technical assessments by OBP (including DS/DP quality; immunogenicity assays) and OPMA (including microbiological quality DS and DP, facilities DS and DP) have been uploaded as separate documents to Panorama.

E. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps, if approvable:

The Sponsor has agreed to the following post-marketing commitments (PMC). Depending on the outcome of the (b) (4) facility review, additional PMCs may be deemed necessary and, if so, will be noted in the final review addendum.

1. Provide data from one media fill using the product-specific change parts, (b) (4) and equipment to support (b) (4) the 10 mL vial/20 mm stopper combination that is used for margetuximab DP.

2. Conduct a Drug Product (DP) shipping validation study of commercial DP shipped via commercial lanes to the selected third-party logistics warehouse. The study will include analytical characterization and cell-based potency determination of the DP both pre- and post-shipping. Submit results to the BLA as a final study report.

3. Conduct a DP leachables study to evaluate the DP container closure system through the end of shelf-life when stored under the recommended conditions of 2-8°C. Analyses will include appropriate methods to detect organic non-volatile (e.g., HPLC-UV-MS), volatile (e.g., headspace GC-MS), semi-volatile (e.g., GC-MS) species and metals (e.g., ICP-MS), including their chemical identification and quantitation. Testing will be performed at regular intervals throughout the shelf life with study results to be updated annually in the BLA Annual Report. The final report to be submitted to the BLA will include the complete data and risk evaluation for the potential impact of leachables on product safety and quality.

4. Reassess release and stability specifications for margetuximab drug substance and/or drug product, as appropriate, by December 30, 2022 or following manufacture of 30 lots (if earlier) for the following assays: N-glycosylation (DS), residual host cell protein levels (DS), potency by CGI bioassay, HER2 binding ELISA, and FcγRIIIa binding ELISA (DS and DP), visible particles (DP), and protein content (DP). Submit the final report as a Changes Being Effected-30 Supplement (CBE-30).

5. Conduct studies to optimize the three potency assays (CGI bioassay, HER2 binding ELISA, FcγRIIIa binding ELISA) for IC_{50} and EC_{50} reporting; tighten IC_{50} and EC_{50} acceptance criteria for reference standard stability assessment based on the study results. Submit the final report as a Prior Approval Supplement (PAS).

6. Develop and validate a sensitive, accurate, and reliable assay for the detection of neutralizing antibodies to Margenza in the presence of drug levels that are expected to be present in the serum at the time of patient sampling. The neutralizing antibody assay procedure and method validation protocol and report should be submitted to the BLA as a final study report.

II. Summary of Quality Assessments:

A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1, below, presents CQAs intrinsic to margituximab-cmkb, potential associated risks, and aspects of the control strategy to minimize these risks. Features of the parameters assessed are noted in the table ("other"). Residual risks are addressed through PMCs (refer to Section ID, Risk/Benefit Considerations, above).

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk, and Lifecycle Management

CQA	Risk	Origin	Control Strategy	Other
HER2 binding (potency)	Efficacy	Intrinsic to molecule. Impacted in-process	(b) (4)	The CGI bioassay (below) incorporates

		and on stability (aggregation including dimer, fragmentation and potentially deamidation. Slight decline on DP (liquid) storage.	(b) (4)	HER2 binding. HER2 binding shows a shallower decline in potency than that shown by the bioassay, which is more sensitive.
Proliferation inhibition (potency)	Efficacy	Intrinsic to molecule. Impacted in-process and on stability (aggregation including dimer, fragmentation and potentially deamidation. Declines on DP (liquid storage).		N/A
ADCC activity (potency)	Efficacy	Intrinsic to the molecule. Impacted by glycosylation, aggregation and fragmentation. Slight increase in surrogate end point (FcγRIIIa binding) observed on stability, likely due to increased aggregation.		FcγRIIIa binding activity was correlated to ADCC activity in PBMCs and linked (generally) to glycosylation status as part of characterization.
Identity (identity)	Safety and Efficacy	Intrinsic to molecule		N/A
Protein Content (content)	Efficacy and safety	Manufacturing process		N/A
HMWS, including dimer (product related impurities)	Efficacy-impact of high levels on HER2 binding and ADCC, Safety-immunogenicity, Anaphylaxis; PK, PD (because of potential ADA)	Manufacturing process. Exposure to heat or light. Minimal increase expected on long term stability.		N/A
LMWS,	Efficacy, PK	Manufacturing process. Exposure to heat and light.		N/A

(product related impurities)		Levels historically very low. Minimal increase expected on long term stability.	(b) (4)	
N-Glycosylation % HM, CNF, CF (product heterogeneity)	Efficacy (ADCC), PK	Fermentation. No change anticipated due to (b) (4) or storage. CNF can impact FcγRIIIa binding and ADCC activity. HM can impact both FcγRIIIa binding and PK (literature).		Different types of glycovariants were correlated with ADCC reporter gene and PBMC ADCC activity under characterization.
Acidic variants Including LC CDR1 (N30) deamidation (product related impurities)	Efficacy	Fermentation, in process and stability. Decline in %MP and increase in AP (especially AP2, N30 deamidation) expected on DP stability. Change in %MP correlates with decreased potency on cell growth inhibition bioassay.		N/A
Basic variants including HC CDR3 (D102) isomerization (product related impurities)	Efficacy	Fermentation, in process and stability. Decline in %MP and increase in BP (especially BP1- D102 isomerization) expected on DP stability. Change in %MP correlates with decreased potency on cell growth inhibition bioassay.		N/A

B. Drug Substance [margetuximab] Quality Summary

CQA Identification, Risk, and Lifecycle Knowledge Management

The following table presents CQAs derived from the drug substance manufacturing process and general drug substance attributes, as well as control strategies in place. Residual risks are addressed through PMC (refer to Sections ID and IE of this review).

Table 2 Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management*

CQA	Risk	Origin	Control Strategy	Other
Host cell proteins (process related impurity)	Safety (immunogenicity)	Process – (b) (4)	(b) (4)	N/A
Host cell DNA (process related impurity)	Safety (infectivity, oncogenicity)	Process- (b) (4)		N/A
(b) (4) (process related impurity)	Safety (immunogenicity)	Process- (b) (4)		N/A
(b) (4) (process related impurity)	Safety (allergenicity)	Process, from (b) (4) .		N/A

(b) (4) (process related impurity)	Safety (immunogenicity)	Process, (b) (4) .	(b) (4)	N/A
Small molecules clearance	Safety	Process, (b) (4) (b) (4)		N/A
Leachables (process related impurity	Safety	Process- Contact surfaces		An extractables study was done on the DP container closure, but not on DS. Levels of extractables identified from the risk assessment combined with the DP extractables study were deemed sufficient for a real time DP leachables study to be a PMC. This study would capture leachables from the entire process.
Adventitious virus (contaminant)	Safety and purity	Process (raw materials, (b) (4) (b) (4), environment, operator (b) (4)		N/A
Mycoplasma(contaminant)	Safety and purity	Process- most likely stage,		N/A

		(b) (4)	(b) (4)	
Osmolality	Safety and Efficacy (b) (4)	Formulation		N/A
pH	Safety and Efficacy	Formulation		N/A
(b) (4)	Safety and efficacy (b) (4)	Formulation		N/A

*Control strategies for standard CQAs for which there are no unexpected risks are as follows: 1) Appearance – general test. Indicator of drug product failure. Intrinsic to DS. Tested on DS and DP lot release. 1) Bioburden – contaminant. Risk to safety, purity and efficacy due to degradation or modification of the product by microbial contamination. Introduction via raw materials, manufacturing process. Controlled by (b) (4) . Bioburden is monitored in process and at release; DS release specification is: [TAMC + TYMC] ≤ 1 cfu/10 ml. 2) Endotoxin – contaminant. Risk to safety, purity. Introduced through raw materials, manufacturing process. Controlled by the bioburden-control strategy and input materials. Endotoxin is monitored in-process and at DS release; DS release specification is < (b) (4) EU/ml.

- Description:
  Margetuximab-cmkb is a chimeric IgG1 kappa monoclonal antibody that binds to the extracellular domain IV of HER2. The variable domains of the Fab are derived from the murine precursor of trastuzumab (4D5), and margetuximab-cmkb exhibits similar Fab activity to trastuzumab *in vitro*. Five amino acid changes were introduced in the Fc domain (L235V, F243L, R292P, Y300L and P396L) to mediate increased binding to the activating FcγRIIIa receptor and decreased binding to the inhibitory FcγRIIb receptor.

  The theoretical extinction coefficient of margetuximab-cmkb at A_{280} was calculated to be 1.42 (mg/mL)-1cm -1. It was verified experimentally using the amino acid analysis for primary RS lot QC15019 to be 1.41 (mg/mL)-1cm -1 and for the working reference standard parent lot 14-0066 to be 1.40 (mg/mL)-1cm -1. The approximate molecular weight is 149 kDa.

  Margetuximab-cmkb is intended for third line therapy of patients with HER2 positive breast cancers that have progressed.

- Mechanism of Action (MoA):

  HER2 is a transmembrane glycoprotein with intrinsic tyrosine kinase activity. Overexpression of HER2 has been reported in ~20% of breast cancers and is associated with a poor prognosis.

Like trastuzumab, margetuximab-cmkb binds HER2 protein that is overexpressed on certain cancer cells via the Fab domains. This can block downstream signaling events and inhibit HER2 shedding, leading to inhibition of tumor cell proliferation.

Additionally, in conjunction with binding of margetuximab-cmkb to HER2 on cancer cells, engagement of the Fc domain with FcγRIIIa receptors on NK cells in the tumor microenvironment can mediate cell death of HER2-positive tumor cells via antibody-dependent cellular cytotoxicity (ADCC). Margetuximab was designed to have enhanced ADCC activity relative to trastuzumab due to enhanced binding of the engineered Fc domain to FcγRIIIa receptors on NK cells in the tumor microenvironment. Polymorphisms in FcγRIIIa have been correlated with trastuzumab clinical outcome, with the 158F variant reported to show poorer clinical response. Margetuximab displayed increased binding affinity to both the high affinity (158V) and lower affinity (158F) allotypes relative to trastuzumab. Fc engineering also conferred decreased affinity of margetuximab to the inhibitory FcγR2b receptor (CD32B) relative to the wildtype antibody by ~8 fold. Decreased binding to the FcγR2b receptor was intended to enhance adaptive immunity by activating antigen presenting cells and stimulating cell-mediated anti-tumor responses.

While margetuximab-cmkb demonstrated 13-fold enhanced binding to C1q, no CDC activity was observed with margetuximab-cmkb in SKFR-3 or N87 breast cancer cell lines. This was attributed to the known expression of complement regulatory proteins CD55 and CD59 on solid cancer cell lines, which is believed to protect them from complement mediated lysis.

- Potency Assay:
  Three potency assays have been incorporated into the control strategy for margetuximab-cmkb, to capture the multiple mechanisms of action.

    - Fab-mediated functional assays:

The Cell Growth Inhibition (CGI) Bioassay (TME-0575) is a cell-based assay that captures the ability of margetuximab-cmkb to bind HER2 on overexpressing cancer cells, thereby inhibiting HER2-mediated cell proliferation in a dose-dependent manner. HER2-overexpressing BT-474 cell cultures are incubated with test article or reference standard for 6 days at 37°C. The number of viable cells at the end of the incubation is quantified based on the amount of ATP present, as detected by a luminescent signal using the Cell Titer Glo Luminescent Cell Viability assay kit from Promega. The result is reported as relative potency of the test article to that of the reference standard. The assay has been validated for: specificity, repeatability, intermediate precision, accuracy, linearity, range, and robustness. The CGI Bioassay is used for both release and stability testing of DS and DP.

HER2 Binding ELISA is an indirect ELISA method to quantitate the ability of margetuximab-cmkb to bind HER2. Microtiter plates (96 well) are coated with soluble HER2 fusion protein as a capture reagent, and dilution series of the RS and test article are added and allowed to bind to the coated plate to generate a dose response curve. An alkaline phosphatase-conjugated goat anti-human kappa antibody is then added, and quantitation of the bound conjugated antibody is visualized by addition of a colorimetric AP substrate by reading the plates at an absorbance of 405nm on a microplate reader. The result is reported as relative potency of the test article to that of the reference standard. The HER2 Binding ELISA has been validated for specificity, repeatability, intermediate precision, accuracy, linearity, range, and robustness. The HER2 Binding ELISA is part of release testing for potency and identity of DS and DP. Potency results by the CGI bioassay and

the HER2 ELISA assay generally correlate. The CGI bioassay appears more stability-indicating at 2-8°C than the HER2 Binding ELISA.

Fab-mediated activity is also indirectly controlled by IE-HPLC % main peak, which was shown to correlate with potency as measured by the CGI Bioassay.

- Fc-mediated function is measured by a FcγRIIIa Binding ELISA assay:

The FcγRIIIa Binding ELISA is an indirect competitive binding ELISA assay that quantitates the binding of margetuximab to recombinant FcγRIIIa that has been immobilized on 96-well assay plates. FcγRIIIa binding was shown to correlate with ADCC activity (both by PBMC mediated cell death and reporter gene assays) and therefore is used as a surrogate assay for ADCC activity. Dilution series of test articles and RS are added to the plate in the presence of a constant concentration of biotin labelled margetuximab (margetuximab-BT) as competitor. Margetuximab-BT bound to the plate is detected by addition of streptavidin conjugated alkaline phosphatase (AP) followed by a colorimetric AP substrate. A dose response curve is generated for the dilution series and margetuximab-BT levels bound are proportional to the color signal as detected by a microplate reader. A control antibody with wildtype Fc was used to validate specificity and demonstrated a dissimilar curve shape and relative potency of 0.15. Potency for this assay is reported relative to RS. The FcγRIIIa Binding ELISA assay has been validated for specificity, repeatability, intermediate precision, accuracy, linearity, range, and robustness. It is used for both release and stability testing of DS and DP.

Fc-mediated activity is also controlled in DS release by a specification for glycan variants, which have been shown to mediate FcγRIIIa binding activity.

- Reference Materials:

(b) (4)

(b) (4)

Protocol 19-010 for Selection, Manufacture and Qualification of a New Margetuximab Working Reference Standard is recommended for approved with this BLA. A PMC will be established to optimize the EC50/IC50 reporting of the reference standard potency assays (refer to Sections ID and IE of this review).

- Critical starting materials or intermediates: (b) (4)

(b) (4)

- Manufacturing process summary:

(b) (4)

- Container closure:

  Margetuximab DS is stored in (b) (4)

(b) (4)

- Dating period and storage conditions: (b) (4) months at (b) (4) °C.
  The DS is monitored by ongoing real time stability studies using (b) (4) .

C. Drug Product [MARGENZA] Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes. Residual risks are addressed through PMC (refer to Section ID, Risk/Benefit Considerations, above).

Table 3: Drug Product CQA Identification, Risk and Lifecycle Management

CQA	Risk	Origin	Control Strategy (b) (4)	Other
Appearance Clarity and Color (general)	Safety	Manufacturing process		N/A
Appearance Visible Particles (product or process related impurities)	Safety and Efficacy (immunogenicity)	Manufacturing process		Part of a PMC to reassess specification after the earlier of 30 lots or 2 years.
Subvisible particles (Product or process related impurities)	Safety and Efficacy (immunogenicity)	Manufacturing process		N/A
Deliverable Content (general)	Efficacy/Dosing	Manufacturing Process		N/A

Leachables (process related impurities)	Safety	Manufacturing equipment and container closure	(b) (4)	Data provided were deemed sufficient for the real time DP leachables study to be a PMC.
Osmolality	Safety and Efficacy (b) (4)	Formulation		N/A
pH	Safety and Efficacy	Formulation		N/A
Polysorbate-80	Safety and efficacy (b) (4)	Formulation		N/A
Endotoxin	Safety, purity, immunogenicity	Contaminant could be introduced throughout DP manufacturing process and through raw materials.		N/A
Sterility	Safety risk to patients (infection); purity and efficacy (degradation or modification of the product by	Contaminants could be introduced throughout DP manufacturing or by container closure integrity failure.		

	microorganisms or their byproducts)		(b) (4)
Container Closure Integrity (sterility Assurance)	Safety (Failure in closure integrity may lead to contamination through a loss of sterility, or evaporation/ leakage impacting concentration or content)	Potential breaches during storage. May be impacted by storage conditions.	

- Potency and Strength:
  250mg/10ml (25 mg/ml concentration)

- Summary of Product Design:
  A sterile, preservative-free, clear to slightly opalescent, colorless to pale yellow or pale brown solution. Some visible, translucent, inherent proteinaceous particles may be present. Drug product is presented in single dose vials and requires dilution prior to use.

- List of Excipients:
  Each ml of solution contains the following:
  - L-arginine hydrochloride (11 mg)
  - Polysorbate 80 (0.1 mg)
  - Sodium chloride (2.9 mg)
  - Sodium phosphate dibasic, heptahydrate (0.58 mg)
  - Sodium phosphate monobasic, monohydrate (1.1 mg)
  - Sucrose (30 mg)
  - Water for Injection, USP

- Reference Materials: Same as the margetuximab-cmkb DS reference standards

- Manufacturing process summary: Margetuximab DS is (b) (4)
  (b) (4)

(b) (4)

- Container closure: The primary container closure system for margetuximab DP is a 10 cc/20mm glass vial that is stoppered with a 20 mm (b) (4) rubber stopper. The stoppered vial is them crimped with a 20 mm aluminum cap overseals.

- Dating period and storage conditions: 36 months at the intended storage condition of 2-8ºC. As indicated in the USPI, vials are to be stored in the original carton to protect from light until time of use. Following dilution, the infusion solution can be stored at room temperature up to 4 hours or refrigerated at 2°C to 8°C (36°F to 46°F) up to 24 hours.

D. Novel Approaches/Precedents: None

E. Any Special Product Quality Labeling Recommendations:

The following product quality labeling recommendations are provided in the USPI:

- Storage and Handling:

  Vials are to be stored at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Instructions are provided to not freeze or shake the vials.

- Preparation:
  Vialed product should be examined visually prior to use for particulate matter and discoloration. The USPI describes the appearance in the vial as “clear to slightly opalescent, colorless to (b) (4) pale yellow or (b) (4) pale brown. Some visible, translucent, inherent proteinaceous particles may be present.”

  Intravenous bags composed of the following materials may be used for dilution and administration of MARGENZA: Polyvinyl chloride (PVC), polyolefins (polyethylene and polypropylene) and polyamide, polyolefins only or copolymer of olefins.

  Drug product is to be diluted with 0.9% Sodium Chloride Injection, USP and gently inverted to mix. Dextrose solution should not be used for dilution.

- Storage of diluted solution:

  If not used immediately, diluted solution may be held at room temperature up to 4 hours or at 2°C to 8°C (36°F to 46°F) up to 24 hours. If refrigerated, the diluted solution should be brought to room temperature prior to administration. The diluted solution is not to be frozen.

- Administration: Diluted product is to be administered through an intravenous line containing a sterile, non-pyrogenic, low-protein binding polyethersulfone (PES) 0.2 micron in-line or add-on filter.

F. Establishment Information:

Overall Recommendation: PENDING REVIEW OF THE PLI OF THE DS MANUFACTURING SITE					
DRUG SUBSTANCE					
Function	Site Information	FEI Number	Preliminary Assessment	Inspectional Observations	Final Recommendation
Margetuximab drug substance production, release and stability testing	(b) (4)		Pre-license inspection requested	WITHHOLD	PENDING
Residual DNA drug substance release testing			Acceptable based on previous history	N/A	Approve
MCB and WCB production and characterization Unprocessed bulk testing – in vitro viral safety testing			Acceptable based on previous history	N/A	Approve
Cell bank characterization testing; Unprocessed bulk release testing – mycoplasma			Acceptable based on previous history	N/A	Approve
Storage of drug substance, Master Cell Bank, and Working Cell Bank			Acceptable based on previous history	N/A	Approve
In vivo safety testing of Master Cell Bank and Working Cell Bank			No evaluation necessary	N/A	No evaluation necessary
Cell bank sterility testing			No evaluation necessary	N/A	No evaluation necessary

	(b) (4)			
Transmission electron microscopy of Master Cell Bank and Working Cell Bank		No evaluation necessary	N/A	No evaluation necessary
DRUG PRODUCT				
Function	Site Information	Preliminary Assessment	Inspectional Observations	Final Recommendation
Contract manufacturing site for drug product fill and (b) (4) Contract testing site for drug product sterility and endotoxin release tests Packaging and labeling of drug product	(b) (4)	Acceptable based on previous history	N/A	Approve
Contract testing site for drug product release and drug product stability testing		Acceptable based on previous history	N/A	Approve

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for the (b) (4) (FEI (b) (4)).

As of 11/16/2020, the facility review is pending the review of the (b) (4) pre-license inspection that was conducted at the (b) (4) (FEI (b) (4)), proposed for Margetuximab (MGAH22) DS manufacture.

H. Lifecycle Knowledge Management:

a. Drug Substance:

i. Protocols approved:
   - PQ-0074, (b) (4) – Lifetime Validation Protocol
   - PQ-0098, (b) (4) – Lifetime Validation Protocol
   - PQ-0077, (b) (4) – Lifetime Validation Protocol
   - PQ-0144, Protocol for (b) (4) During Commercial Production
   - PQ-0128, Reprocessing Protocol for (b) (4)
   - PQ-0129, Reprocessing Protocol for (b) (4)
   - PRO-19-011, Stability Evaluation of Commercial Margetuximab Drug Substance
   - Information provided in BLA Sections S.2.3.4.5.1, S.2.3.4.5.2, Tables S.2.3.4-17, S.2.3.4-18: Requalification of Production Working Cell Banks
   - PRO-19-010, Selection, Manufacture, and Qualification of a New Margetuximab Working Reference Standard

ii. Outstanding assessment issues/residual risk: None
iii. Future inspection points to consider: None

b. Drug Product

i. Protocols approved:
   - PRO-19-012, Stability Evaluation of Commercial Margetuximab Drug Product
   - VLD-19-543: DP Shipping PQ Protocol

ii. Outstanding assessment issues/residual risk: None
iii. Future inspection points to consider: None

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/s/

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