# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761150Orig1s000

# OTHER REVIEW(S)

Center for Drug Evaluation and Research
Office of Pharmaceutical Quality
Office of Biotechnology Products

# LABELS AND LABELING ASSESSMENT

| | |
|---|---|
| Date of Assessment: | November 23, 2020 |
| Assessor: | Vicky Borders-Hemphill, PharmD<br>Labeling Assessor<br>Office of Biotechnology Products (OBP) |
| Through: | Kathryn King, PhD, Product Quality Assessor<br>OBP/Division of Biotechnology Review and Research 1 |
| Application: | BLA 761150 |
| Applicant: | MacroGenics, Inc. |
| Submission Date: | December 18, 2019 |
| Product: | Margenza (margetuximab-cmkb) |
| Dosage form(s): | injection |
| Strength and Container-Closure: | 250 mg/10 mL (25 mg/mL) in a single-dose vial |
| Purpose of assessment: | The Applicant submitted a biologics license application Agency assessment. |
| **Recommendations:** | The prescribing information (submitted November 20, 2020), container labels (submitted August 19, 2020), and carton labeling (submitted August 13, 2020) are acceptable from an OBP 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 (submitted November 20, 2020), container labels (submitted August 19, 2020), and carton labeling (submitted August 13, 2020) are acceptable from an OBP labeling perspective (see Appendix C).

**APPENDICES**

**Appendix A**: Proposed Labeling

Prescribing Information (submitted on December 18, 2019
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Container Labels (submitted on December 18, 2019)

(b) (4)



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

**Appendix B**: Evaluation Tables
**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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (placement of dosage form below the proper name)* | ✓ Yes<br>☐ No<br>☐ N/A |

| **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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (using the qualifying phrase "Manufactured by:")* | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (U.S license number for container bearing a partial label[5])* | ✓ Yes<br>☐ No<br>☐ N/A |

| **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<br>☐ No<br>☐ N/A |

[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."

| **Expiration date (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: USP General Chapters <7> Labeling, Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 lines 178-184, which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |

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

| **Product Strength (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (expression of strength for injectable drugs) references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 176, which, when finalized, will represent FDA's current thinking on topic*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

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

| **Statement: "Rx only" (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (prominence of Rx Only statement) reference: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 line 147, which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |

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

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

| **No container label (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.60(d) | ☐ Yes<br>☐ No<br>☒ N/A |

| **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<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Per 3.2.P.7.1.3. submission the overseal contains a (b) (4) plastic top which is flipped off prior to use. There are no embossed words on the plastic top.

| **Visual inspection** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.60(e) | ✓ Yes<br>☐ No<br>☐ 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: MacroGenics confirms that an adequate uncovered area of the vial remains when the label is affixed that allows visual inspection of the vial content. Circumference of the vial is 74.6 mm; the length of the container label to be affixed is 70 mm. The area along the side of the vial remaining uncovered for visual inspection has a width of 4.6 mm and a length of 42 mm from the base of the vial to the vial shoulder*
*Applicant's response is acceptable*

| **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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)* | ✓ Yes<br>☐ No<br>☐ N/A |

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

| **Preparation instructions (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.5(g) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic* | ☐ Yes<br>☐ No<br>☒ N/A |

| **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)*<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |

| **Misleading statements (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.6 | ☐ Yes<br>☐ No<br>☒ N/A |

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

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

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

| **Bar code label requirements (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 201.25, 21 CFR 610.67 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011*<br>*Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786), which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |

| **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<br>☐ No<br>☒ N/A |

| **Net quantity (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.51 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic*<br>*Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)*<br>*USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).* | ✓ Yes<br>☐ No<br>☐ N/A |

| **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<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Consider revising the usual dosage statement from (b) (4) (b) (4) to read "Dosage: See Prescribing Information"
*The Applicant revised as requested*

| **Inactive ingredients (container label)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.100 | ☐ Yes<br>☐ No<br>☒ N/A |
| *Recommended labeling practices reference: USP General Chapters <1091> Labeling of Inactive Ingredients and USP General Chapters <7> Labeling* | ☐ Yes<br>☐ No<br>☒ N/A |

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

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

## 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (placement of dosage form below the proper name)* | ✓ Yes<br>☐ No<br>☐ N/A |

| **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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices (using the qualifying phrase "Manufactured by:")* | ✓ Yes<br>☐ No<br>☐ N/A |

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

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

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

[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.

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

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

| **Product Strength (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 176), which, when finalized, will represent FDA's current thinking on topic*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

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

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

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

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

| **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<br>☐ No<br>☒ N/A |

| **Inactive ingredients (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61, 21 CFR 201.100 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: USP General Chapters <1091> Labeling of Inactive Ingredients, USP General Chapters <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** Revise ingredient list to include each ingredient per mL and to list in alphabetical order "Each single-dose vial contains 250 mg in 10 mL of solution. 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.
*The Applicant revised as requested*

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

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

| **Rx only (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (line 147-149), which, when finalized, will represent FDA's current thinking on topic* | ✓ Yes<br>☐ No<br>☐ N/A |

| **Divided manufacturing (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) | ☐ Yes<br>☐ No<br>☒ N/A |

| **Distributor (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5) | ☐ Yes<br>☐ No<br>☒ N/A |

| **Bar code (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.67, 21 CFR 201.25 | ✓ Yes<br>☐ No<br>☐ N/A |
| Recommended labeling practices references: *Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011*<br>*Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 511-512), lines 780-786)* | ✓ Yes<br>☐ No<br>☐ N/A |

| **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<br>☐ No<br>☒ N/A |

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

| **Preparation instructions (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.5(g) and 21 CFR 610.61(i) | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013 (lines 426-430), which, when finalized, will represent FDA's current thinking on topic*<br>*USP General Chapters <7> Labeling* | ☐ Yes<br>☐ No<br>☒ N/A |

| **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)*<br>*USP chapter <659> Packaging and Storage Requirements* | ✓ Yes<br>☐ No<br>☐ N/A |

| **Misleading statements (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.6 | ☐ Yes<br>☐ No<br>☒ N/A |

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

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

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

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

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

| **Net quantity (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 201.51 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (line 461- 463) which, when finalized, will represent FDA's current thinking on topic*<br>*Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)*<br>*USP General Chapters <1151> Pharmaceutical Dosage Forms (Excess volume in injections).* | ✓ Yes<br>☐ No<br>☐ N/A |

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

**Comment/Recommendation:** Consider revising the usual dosage statement from (b) (4)

(b) (4) to read "Dosage: See Prescribing Information"

*The Applicant revised as requested*

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

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

## Prescribing Information Evaluation

**PRESCRIBING INFORMATION**

| **Highlights of Prescribing Information** | |
|---|---|
| **PRODUCT TITLE** | **Acceptable** |
| Regulation: 21 CFR 201.57(a)(2) | ✓ Yes<br>☐ No<br>☐ 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* | ✓ Yes<br>☐ No<br>☐ N/A |

| **Highlights of Prescribing Information** | |
|---|---|
| **DOSAGE AND ADMINISTRATION** | **Acceptable** |
| *Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions* | ☐ Yes<br>☐ No<br>☒ N/A |

| **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<br>☐ No<br>☐ 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)*<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

| Full Prescribing Information | |
|---|---|
| **2 DOSAGE AND ADMINISTRATION** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(3)(iv)]<br>*Confirm appropriateness of specific direction on dilution, preparation, and administration of the dosage form and storage conditions for stability of the reconstituted drug; confirm the appropriateness of infusion bags, infusion sets (e.g., tubing, infusion aids, or filter membranes); confirm product's incompatibilities, and 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<br>☐ No<br>☐ N/A |
| *Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products* | ✓ Yes<br>☐ No<br>☐ N/A |

| Full Prescribing Information | |
|---|---|
| **3 DOSAGE FORMS AND STRENGTHS** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(4) | ✓ Yes<br>☐ No<br>☐ 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)*<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** the identifying characteristics of the drug product have been added
*The Applicant revised as requested*

| 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) | ✓ Yes<br>☐ No<br>☐ N/A |

| | |
|---|---|
| *Recommended labeling practices references: USP General Chapters <1091>, USP General Chapters <7>* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:** the proprietary name has been deleted since this paragraph discusses the drug substance. *The Applicant revised as requested*
The mechanism of action has been deleted since it provided in section 12.1
*The Applicant revised as requested*
This information has been deleted since it is not required information for section 11 (b) (4)
(b) (4)
*The Applicant revised as requested*
Inactive ingredients have been revised to appear in alphabetical order and according amount per mL of solution. *The Applicant revised as requested*

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

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

**Comment/Recommendation:** identifying characteristics and package type term have been added. *The Applicant revised as requested*

| Full Prescribing Information | |
|---|---|
| **MANUFACTURER INFORMATION** | **Acceptable** |
| Regulations: 21 CFR 201.100(e), 21 CFR 201.1 | ✓ Yes<br>☐ No<br>☐ 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)* | ✓ Yes<br>☐ No<br>☐ N/A |

Medication Guide Evaluation (N/A)
Patient Information Labeling Evaluation (N/A)
Instructions for Use Evaluation (N/A)

**APPENDIX C. Acceptable Labels and Labeling**
Prescribing Information (submitted on November 20, 2020 \\CDSESUB1\evsprod\bla761150\0056\m1\us\114-labeling\114a-draft-label\1-14-1-3-draft-uspi-2020-11-20.pdf)

Container Labels (submitted on August 19, 2020)

(b) (4)

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

Kathryn King

Digitally signed by Kathryn King
Date: 11/23/2020 01:26:46PM
GUID: 508da6d70002631846fa22d677dd8d3c

Vicky Borders-Hemphill

Digitally signed by Vicky Borders-Hemphill
Date: 11/23/2020 11:40:27AM
GUID: 50814c7000007a3d59329f660d8ddf02

# Memorandum of Review

| | |
|---|---|
| Submission Tracking Number (STN): | BLA 761150 (SDN 1) |
| Subject: | Immunogenicity assay review for BLA 761150 |
| Stamp Date: | December 18, 2019 |
| Review/Revision Date: | November 16, 2020 |
| Primary Reviewer: | Anshu Rastogi, Ph.D., OBP, DBRR1 |
| Secondary Reviewer: | Brian Janelsins, Ph.D., OBP, DBRR1 |
| Tertiary Reviewer: | Wendy Weinberg, Ph.D., OBP, DBRR1 |
| RPM: | Anh-Thy Ly |
| Applicant: | MacroGenics, Inc. |
| Product: | Margenza (margetuximab) |
| 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 |
| Action Due Date: | December 18, 2020 |

**Summary Basis of Recommendation:**

1. **Recommendation:** BLA 761150 is recommended for approval with respect to OBP's evaluation of the immunogenicity assays. 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. A postmarketing commitment (PMC) will be issued for MacroGenics to develop and validate a suitable neutralizing antibody (nAb) assay that is tolerant to onboard levels of drug to further support the low immunogenicity risk of margetuximab.

2. **Justification:** MacroGenics is seeking licensure for margetuximab (referred to as MGAH22 herein) as a treatment for patients with metastatic HER2-positive breast cancer who received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. In support of their 351(a) BLA application (STN 761150), MacroGenics evaluated the immunogenicity of MGAH22 in their Phase 3 clinical study (CP-MGAH22-04) in a breast cancer patient population. Immunogenicity assays to screen and confirm for the presence of binding anti-drug antibodies (ADAs) and to determine antibody titer levels and the neutralizing capability of binding ADAs in confirmed positive samples were developed, validated, and used to assess the immunogenicity of MGAH22 in clinical samples. The BLA submission includes method validation data for each immunogenicity assay and the immunogenicity data derived from each clinical trial. During the course of the review, an information request (IR) was sent to the applicant (8/25/20) to obtain additional information and data to support the adequacy of the validation exercises for the assays used to analyze samples from the Phase 3 clinical study. The response (received on 9/2/20; SDN 0038) was adequate to allow for a complete review, and subsequently, it was determined that there were no significant deficiencies present for the binding ADA assay. As a result, the ADA incidences reported in the BLA and label are accurate. The data and

information provided to support the validation of the nAb assay was not sufficient; the assay is not reliable in the presence of onboard levels of drug. However, considering the proposed indication and that ADA incidence against MGAH22 is low, and based on internal discussions with the clinical pharmacology and clinical teams, the issue regarding the nAb assay is not considered an approvability issue. A PMC was agreed upon for MacroGenics to optimize the current nAb assay or develop a new assay that is tolerant to onboard levels of drug and to validate the selected assay. 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.

**PMC LANGUAGE**

XXXX-X 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.

| | |
|---|---|
| Study Completion: | October 2021 |
| Final Report Submission: | December 2021 |

**Review:**
*Note: Reviewer comments are in italicized text.*

**5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies**

MacroGenics, via (b) (4), evaluated the immunogenicity of MGAH22 in patients with breast cancer in their Phase 3 clinical study (Study CP-MGAH22-04). A multi-tiered approach was used to screen and confirm clinical samples for presence of binding ADAs via a binding antibody assay. Clinical samples that were confirmed positive for binding ADAs were then titered by the same assay to determine antibody levels and analyzed by a nAb assay to determine the presence of neutralizing ADAs. The binding antibody and nAb assays were developed and validated with reagents based on MGAH22; the methods and validation studies for these assays are discussed below.

***Reviewer comment****: An ELISA method was developed and validated for use to determine the incidence of binding ADAs in Phase 1 (CP-MGAH22-01) and Phase 2 (CP-MGAH22-02) clinical samples. Considering that the immunogenicity data that is used to support the BLA is mainly derived from the Phase 3 clinical study and the ADA incidences reported in the label are derived from the Phase 3 clinical study, the validation of the ELISA method is not discussed in this review.*

**Binding Antibody Assay Validation Report (Report RERE2)**

ADAs against MGAH22 were detected using an electrochemiluminescence (ECL) binding assay using Meso-Scale Discovery (MSD) technology, which was developed and validated for the detection, confirmation, and titration of binding ADAs against MGAH22 in breast cancer patient serum. Samples were initially evaluated in a screening assay, and positive samples from the

screening assay were then evaluated in a confirmatory assay to demonstrate that the ADA response is specific to MGAH22. The confirmed positive ADA samples were then titrated.

**Assay Principle**

Under the screening assay format, samples were diluted with acetic acid to dissociate the ADA:drug complexes in the serum. The samples were then neutralized with a master mix containing biotinylated-MGAH22 and Ru-MGAH22 to allow ADAs specific to MGAH22 to bind to the master mix components. The antibody complex was then added to a pre-blocked streptavidin-coated MSD plate and incubated. Read buffer containing tripropylamine was added to the plate. The ruthenium in the immune complexes produces an electrochemiluminescent (ECL) signal when voltage is applied to the plate; only samples containing Ru-MGAH22/anti-MGAH22/B-MGAH22 complexes generate a signal. The signal is directly proportional to the level of binding ADAs present in the sample. Samples with mean replicate response < the screening cut-point, the sample is reported as "negative", while samples with mean replicate response ≥ the screening cut-point are considered "potential positive" and are evaluated by the confirmatory assay. Under the confirmatory assay format, samples are left untreated or pre-treated with excess drug as a competitor to determine the specificity of the finding and whether samples that screened positive for ADAs are confirmed positive. Samples with %inhibition < confirmatory cut-point are reported as "negative", while samples with inhibition ≥ confirmatory cut-point are considered "confirmed positive." Under the titer assay format, confirmed positive ADA samples are titered prior to analysis under the screening assay format. The reciprocal of the last dilution (inclusive of assay MRD) resulting in the last positive response at or above the titration cut-point is reported as the sample titer. If the responses of the sample dilution series do not consistently stay below the titration cut point, the first dilution below the titration cut-point is considered the first "negative" dilution.

**Negative Control**

Drug-naïve human breast cancer serum samples (commercially sourced) were screened for ADAs. Seven samples negative for ADAs were pooled to serve as a matrix-based negative control (NC).

**Positive Control**

Stock solutions of anti-MGAH22 monoclonal antibodies (goat anti-MGAH22 Fv) were supplied by the sponsor as the positive control (PC), which were spiked into the NC pool at 25 ng/mL (low positive control; LPC), 100 ng/mL (mid positive control; MPC), and 20,000 ng/mL (high positive control; HPC).

**Screening Assay Cut**

The screening assay cut-point was derived from 50 drug-naïve human breast cancer serum samples. Data was collected from three assay runs by two analysts (n = 150 data points; Table 1). The distribution of the data was determined not to be normal (Shapiro-Wilk test) after identification and removal of outliers by the Tukey's Outlier Filter approach (outliers defined as values less than Q1 - 1.5 x IQR or greater than Q3 + 1.5 x IQR). Therefore, data transformation was performed (natural log) to normalize the data, followed by outlier identification and removal by Tukey's outlier filter approach. A parametric approach was applied to the screening cut-point determination (Cut point value (CPV) = exp(mean + z × SD) where z is 1.645 for the 95% upper prediction interval (5% false positive rate) and SD is the root mean square error). A floating cut-

point was determined to be most appropriate based on run means and variances. The normalization cut point factor (NCF; parametric cut-point value/negative control) was determined to be 1.19 at the 95% upper prediction interval. The screening cut point for sample analysis was calculated as the NCF multiplied by the geometric mean of NC for the in-study run (NC.IS), which is shown below:

Screening Assay Floating Cut-Point = NC.IS × NCF = (NC.IS x CPV)/NC.V

***Reviewer Comment:*** *The screening assay cut-point was derived from commercially available breast cancer samples and no additional data were provided to support that the validated cut-points are suitable to analyze the clinical breast cancer samples. An IR was sent to applicant (8/25/20) to provide data to support that the validated binding antibody assay screening cut-point results in an appropriate false positive rate for the analysis of the pre-dose clinical samples from study CPMGAH22-04. Additionally, the applicant was asked to compare the assay mean and variance of the pre-dose clinical samples from study CP-MGAH22-04 with those of the commercial breast cancer samples that were used to determine the validation cut points. In response (9/2/20), the applicant provided data from the analysis of pre-dose clinical samples from study CPMGAH22-04, which showed a false positive rate of 4.5% using the calculated screening cut-point derived from commercial breast cancer samples. Additionally, data was provided for comparison of assay statistics between pre-dose clinical samples and commercial breast cancer samples (Table 1 of the response), which shows a slightly higher mean value which could be attributed to n = 246 clinical samples analyzed vs. n = 50 commercial samples. The variance, however, is observed to be lower in pre-dose clinical samples (with confirmed positive samples excluded) compared to commercial breast cancer samples. The data provided is acceptable to support that the screening assay cut-point calculated from commercial breast cancer samples is appropriate to analyze the Phase 3 clinical samples.*

**Confirmatory Assay Cut-Point**

The confirmatory assay was run in a competitive binding format. The same 50 drug-naïve human breast cancer serum samples that were analyzed to determine the screening assay cut-point were left untreated or spiked with an excess (20.0 μg/mL) of MGAH22 during the acid dissociation step. Samples were then processed in the same manner as in the screening assay; data was collected from three assay runs by two analysts (n = 150 data points); the mean signal inhibition (%) was calculated for each sample (Table 2). The distribution of the data was determined not to be normal (Shapiro-Wilk) after outlier identification and removal by Tukey's Outlier Filter approach (outliers defined as values less than Q1 - 1.5 x IQR or greater than Q3 + 1.5 x IQR). Therefore, data transformation was performed (natural log) to normalize the data, and then outliers were identified and excluded by Tukey's outlier filter approach. A parametric approach was applied to determine the confirmatory cut-point (CCP, CCP = exp(mean - z × SD), z is 2.33 for the 99% upper prediction interval (1% false positive rate) and SD is the root mean square error). The percent inhibition was determined from subtracting the CCP from 1 and determined to be 16.0% inhibition at the 99% upper prediction interval:

Percent Inhibition = 100*(1-CCP) = 100*[1-(response with excess drug/response with no drug)]

***Reviewer Comment:*** *The confirmatory cut-point is acceptable.*

**Titer Assay Cut-Point**

***Reviewer comment:*** *A cut-point factor of 1.31 was chosen for the titer assay. However, information was not provided as to how the titer assay cut-point was derived. An IR was sent to the applicant (8/25/20) to provide data and information to support the titer cut-point. In response (9/2/20), the applicant provided additional information to state that the titer cut-point was derived using the analyses from the screening assay cut point. The cut-point normalization factor was found to be 1.31 at the 99.9% upper prediction interval (0.1% false positive rate), which was used as the titer assay cut-point. The information provided is acceptable.*

**Precision**

The precision of the assay was determined by evaluating the NC, LPC, MPC, and HPC multiple times; precision was expressed as the percent coefficient of variation (%CV) of each pool.

Intra-assay Precision

Intra-assay precision was evaluated by running the NC and PC pool samples 6 times each. Screening assay data was compiled from validation run 14RERE2, and confirmatory assay data were compiled from analytical runs 24RERE2 and 25RERE2. The intra-assay precision of the screening assay for the NC, LPC, MPC, and HPC was 5.91% CV, 3.62% CV, 5.73% CV, and 11.2% CV, respectively. For the confirmatory assay, the intra-assay precision of the NC, LPC, MPC, and HPC was 3.88% inhibition, 45.6% inhibition, 68.45% inhibition, and 99.3% inhibition, respectively (standard deviation < 2.69 for each). Results for the screening and confirmatory assays are provided in Tables 3A and 3B, respectively.

Inter-assay Precision

Inter-assay precision was calculated from the NC and PC pool samples from multiple validation runs by multiple analysts over the course of validation (i.e., on multiple days). The inter-assay precision of the screening assay for the NC, LPC, MPC, and HPC was 14.9% CV, 12.2% CV, 12.4% CV, and 12.8% CV, respectively. For the confirmatory assay, the inter-assay precision of the NC, LPC, MPC, and HPC was 14.9% CV, 12.2% CV, 12.4% CV, and 12.8% CV, respectively (standard deviation < 4.45 for each). Inter-assay precision data are provided in Tables 4A – 4D.

***Reviewer comment:*** *While intra- and inter-assay precision data were provided and determined to be acceptable for both the screening and confirmatory assays, precision data was not provided for the titer assay. An IR was sent to the applicant to provide intra- and inter-assay precision data for the titer assay. In response (9/2/20), the applicant stated that precision data are not available for the titer assay but can be interpreted from the sensitivity runs (11RERE2, 12RERE2, and 21RERE2; Table 5A) performed by two analysts on different days. Based on seven curves generated in the runs (20,000 ng/mL to 1.02 ng/mL dilution series), the CV at each dilution was <20% (i.e., 12 – 17.7%; Table 7, Appendix 4 of the response). The corresponding calculated titers at each dilution also had CV of <20% (i.e., 5.1 – 18.8%), and were within 1 dilution of the last positive titer result (i.e., 656100 and 218700); Table 8, Appendix 4 of the response). The data provided for ADA positive clinical patient samples show that reported titers range from <300 – 9600, which is within the range of dilutions tested (i.e., 300 – 5904900), therefore the analysis is appropriate. The data provided is acceptable to support the precision of the titer assay.*

**Sensitivity and LPC Calculations**

The sensitivity was evaluated in the screening assay by serially diluting the HPC (20,000 ng/mL) 1:3 to span the screening assay cut-point (3-fold to 19683-fold). An additional 59049-fold dilution was added since the dilution series did not span the cut point. The screening assay sensitivity was evaluated in validation runs 11RERE2 and 12RERE2, and with the additional dilution in validation run 21RERE2. The sensitivity of the confirmatory assay was evaluated similarly (27-fold to 59049-fold dilutions) in validation runs 26RERE2 and 29RERE2. Multiple analysts performed the runs for both assays. The assay sensitivity was reported as the lowest concentration of ADA that the control produced a positive response (i.e., ≥ the assay cut point). The sensitivity of the screening and confirmatory assays, interpolated from the dilution curves generated, was calculated to be 4.45 ng/mL and 6.68 ng/mL, respectively (Tables 5A and 5B). The assay sensitivity level was used to establish the LPC level targeting a 1% assay rejection rate, calculated as the mean concentration corresponding to assay sensitivity + (3.365 x SD). The screening and confirmatory LPC was calculated to be 9.00 ng/mL and 15.0 ng/mL, respectively (Tables 5C and 5D). Both LPCs were evaluated in qualification runs; the screening LPC failed 50% of the time and the confirmatory LPC passed 87.5% of the time, therefore the LPC for both assays was set to 15 ng/mL.

***Reviewer Comment:*** *The sensitivity of the binding antibody assay (screening, confirmatory, and titer) is acceptable as the assay is able to detect an adequate level of ADAs against MGAH22. In addition, the chosen concentration for the LPC provides adequate monitoring of assay performance near the cut-point level under both assay formats.*

**Stability**

The stability of the HPC and LPC was evaluated by comparing frozen control samples to samples subjected to 6 freeze thaw cycles (frozen at -80°C, thawed at room temperature (RT)) and samples thawed and stored at RT for 27 hours. After freeze/thaw, the LPC samples had 3.06% CV (frozen reference 2.43% CV) with 100% recovery, while the HPC samples had 4.19% CV (frozen reference 2.27% CV) with 106% recovery. After storage at RT, the LPC samples had 1.95% CV with 97.7% recovery, while the HPC samples had 1.95% CV with 97.4% recovery (Tables 6 and 7). The stability of the frozen controls was not evaluated. Recovery was calculated as:

%Recovery = (Mean of stability sample/Mean of reference control sample)*100.

***Reviewer Comment:*** *The provided data suggest that the PC preparations and clinical serum samples are stable without much deviation in assay responses for up to 6 freeze/thaw cycles from -80°C storage to RT, as well as stored at RT for 27 hours, which cover the working conditions for the assay. While data was not provided for the controls stored under long-term storage conditions (i.e., frozen), this is acceptable because antibodies are known to be stable over time when stored at -80°C. Sufficient information and data are provided to support the stability of the controls clinical serum samples during assay in-use conditions.*

**Effect of Hemolysis**

The effect of hemolysis on ADA detection was evaluated in the screening assay by evaluating blank, LPC, and HPC samples prepared in hemolyzed matrix containing 5% fully lysed whole blood, and similarly, in the confirmatory assay by analyzing uninhibited and inhibited blank, LPC,

and HPC samples prepared in hemolyzed and non-hemolyzed matrix. In the screening assay, the LPC samples had a 2.76% CV with a 97.5% recovery, while the HPC samples had a 7.07% CV with a 96.6% recovery, compared to non-hemolytic control samples at the same concentration. In the confirmatory assay, the inhibited LPC samples had a 3.26% CV with a 95.3% recovery and the HPC samples had a 3.62% CV with a 133% recovery. The corresponding uninhibited controls had a 6.65% CV and 4.17% CV for LPC and HPC, with recovery at 118% and 122%, respectively. Data is provided in Tables 8A and 8B.

***Reviewer comment:*** *The data show that the hemolyzed matrix did not affect the LPC and HPC samples in terms of detection of ADAs (%recovery). The data for hemolytic samples was comparable to non-hemolytic samples for both the screening and confirmatory assays.*

**Effect of Lipemia**

The effect of lipemia on ADA detection was evaluated in the screening assay by evaluating blank, LPC, and HPC samples prepared in lipemic matrix (> 300 mg/dL), and similarly, in the confirmatory assay by analyzing uninhibited and inhibited blank, LPC, and HPC samples prepared in lipemic and non-lipemic matrix. In the screening assay, the LPC samples had a 2.6% CV with a 108% recovery (re-analyzed samples), while the HPC samples had a 2.67% CV with a 104% recovery, compared to non-lipemic control samples at the same concentration. In the confirmatory assay, the inhibited LPC samples had a 4.08% CV with a 93.1% recovery and the HPC samples had a 1.96% CV with a 105% recovery. The corresponding uninhibited controls had a 3.77% CV and 2.83% CV for LPC and HPC, with recovery at 122% and 117%, respectively. Data is provided in Tables 9A – 9C.

***Reviewer comment:*** *The data show that lipemia did not interfere with the detection of ADAs in the LPC and HPC samples in both the screening and confirmatory assays. The data for lipemic samples was comparable to non-lipemic samples for both assays.*

**Matrix Interference**

Pooled NC and disease-state samples from 10 individuals were used to prepare blank, low, and high matrix interference controls using goat anti-MGAH22 antibody. These controls (i.e., low and high) were prepared at same levels as prepared for the LPC and HPC, respectively. Samples were evaluated in the screening and confirmatory assays. In the screening assay, serum samples spiked with HPC had 101% – 122% recovery (excluding two out of specification results that were >125%), while samples spiked with LPC had 84% – 124% recovery (including LPC re-run; excluding three out of specification results that were >125%) compared to respective spiked blank controls. In the confirmatory assay, the inhibited serum samples spiked with HPC had 98.5 – 121% recovery, while samples spike with LPC had 90.7 – 107% recovery, compared to respective inhibited matrix blank samples. Results are provided in Tables 10A – 10D for the screening assay and Tables 11A – 11E for the confirmatory assay.

***Reviewer comment:*** *The data show that matrix from breast cancer samples does not negatively interfere in ADA detection in both screening and confirmatory assays.*

**Drug Tolerance**

The drug tolerance of the assay was evaluated to determine the level of drug that would interfere with ADA detection in the assay. The NC (0 ng/mL), LPC (25 ng/mL), MPC (100 ng/mL), and HPC (20,000 ng/mL) were each spiked with drug at 10, 20, 50, and 100 µg/mL levels, and pre-incubated prior to analysis. The LPC, MPC, and HPC could be detected in the presence of up to 100 µg/mL of drug. Results are provided in Tables 12A -12D.

***Reviewer comment:*** *The drug tolerance of the binding assay was determined to be 100 µg/mL as the assay can detect an adequate level of ADAs (25 ng/ml) in the presence of 100 µg/mL of drug. Information provided in the submission shows that the reported onboard level of drug ($C_{trough}$) for clinical study CP-MGAH22-04 is approximately 100 µg/mL (Clinical Study Report CP-MGAH22-04, Module 5.3.5.1). Because the assay was not validated for drug concentrations higher than 100 µg/mL and it was unclear what percentage of patient samples have drug levels above $C_{trough}$, additional information was needed to support the established drug tolerance limit of the assay. An IR was sent to the applicant (8/25/20) to provide the complete range of drug levels observed in patient samples at the time of immunogenicity testing, as well as any additional drug tolerance data to support that onboard levels of drug higher than 100 µg/mL allow for detection of an adequate level of binding ADAs (e.g., 100 ng/mL). In response (9/2/20), the applicant stated that ADA incidence was determined in all patients and the range of drug was 0.894 – 986 µg/mL, with anywhere from 29.6 – 100% of patient samples having drug levels above 100 µg/mL over the course of testing (Appendix 3 of the response). Additional information was provided by the Clinical Pharmacology reviewer as to the onboard level of drug present in ADA positive patient samples. Two of the eleven positive confirmed samples had levels higher than 100 µg/mL (i.e., 110 and 119 µg/mL), therefore it appears that the assay is able to tolerate onboard levels of drug that are at least slightly higher than 100 µg/mL. Moreover, the assay was able to detect very low levels of ADAs (i.e., 25 ng/mL, exceeding the minimal expectation of 100 ng/mL) in the presence of 100 µg/mL of drug, which suggests that the assay can tolerate higher drug levels to obtain detection of 100 ng/mL of ADAs. Overall, the information provided is acceptable to support that the assay has acceptable drug tolerance to support the BLA.*

**Deviations**

There were no SOP deviations during the study; however, two validation plan deviations occurred, detailed in Appendix A. Seven lots, rather than 10, were pooled to make the NC pool sample. Additionally, a blank matrix pool was prepared for the LPC and HPC levels for the matrix interference analysis but was not prepared for the blank level. However, since an acceptance NC (blank matrix pool) was run on the same plate, this was evaluated as the blank matrix pool control.

***Reviewer comment:*** *The deviations do not impact the validation exercises for the binding assay.*

**Interim Analytical Report (Report RERH2)**

Patient serum samples from clinical study CP-MGAH22-04 were evaluated using the screening, confirmatory, and titer assays. Samples were obtained from patients receiving MGAH22 for immunogenicity testing at baseline, every 2 cycles, and at end of study therapy. All patients enrolled in the study received trastuzumab previously, and treatment-emergent anti-MGAH22 antibodies were observed in 4 patients (1.7%). Of these 4 patients, anti-MGAH22 antibodies were detected prior to Cycle 7 of dosing in 1 patient, and more than 2 months after the last dose in 3

patients. In the infusion sub-study, treatment-emergent anti-MGAH22 antibodies were observed in 2 patients (3.8%). Of these 2 patients, anti-MGAH22 antibodies were detected prior to Cycle 3 of dosing in 1 patient, and more than 6 months after the last dose in 1 patient. Titer levels were also reported for clinical samples confirmed positive for ADAs.

***Reviewer comment:*** *It was unclear whether the titers reported in the analysis report considered all possible dilutions in the titer assay. An IR was sent to the applicant (8/25/20) to clarify, and if necessary, update the report to include titer values that consider all possible dilutions. In response (9/2/20), the applicant clarified that all possible dilutions were not initially considered, and in combining all possible dilutions, a dilution factor of 1:300 will be factored into the revised titer calculation. Previously, sample titer results ranged from 1:1 to 1:32, but with all possible dilutions considered, the titer will be updated to 1:300 to 1:9600. The applicant provided the updated report on 10/14/20. The adequacy and relevance of the updated titer data is deferred to the clinical pharmacology review team.*

*New PC samples were prepared prior to analysis of the clinical samples; however, this would not impact the validated state of the assay. No changes in the assay methods were made during the analysis of the clinical samples.*

**System Suitability/Data Acceptance Criteria**

For a run to be considered acceptable, at least 75% (3/4) of the NC results and at least 50% (1/2) of the replicates at each control level must meet the following criteria based on the acceptable raw response: HPC > LPC > CP (cut point) > NC. Additionally, each PC or NC replicate must have a CV ≤ 20%. The mean NC replicate response must be below the plate specific or screening cut point, where at least three NC results are averaged to calculate the plate specific/screening cut point (1.19 x geometric mean of the NC in the run).

For the confirmatory assay, the percent inhibition of the HPC and LPC spiked with MGAH22 must be ≥ 16.0% (confirmatory cut point; CCP) compared to the uninhibited HPC and LPC. For the titration assay, a cut point was determined for each plate through multiplying the normalization factor of 1.31 by the geometric mean of acceptable negative controls on the plate. While sample replicates must have CV ≤ 20%, samples with CV > 20% are still acceptable, unless one duplicate is above, and the other duplicate is below the assay cut point. Additional method validation exercise criteria are included in Appendix A of the method validation report.

***Reviewer Comment****: System suitability was met during assay validation and clinical immunogenicity sample runs, demonstrating that the assay is capable of producing meaningful data to support the validated state of the assay and the clinical immunogenicity data, respectively.*

**Neutralizing Antibody Assay Validation Report (Report RERF2)**

Neutralizing antibodies (nAbs) against MGAH22 were detected using an antibody-dependent cell-mediated cytotoxicity (ADCC) assay in which the product binds to antigens on the surface of target cells and also binds to the FcγRIIIa receptors on the cell surface of effector cells leading to activation of ADCC and killing the target cells. The assay uses the human breast cancer SK-BR-3 cell line (target cells), and an engineered Jurkat cell line (effector cells) that stably expresses the FcγRIIIa receptor and contains a firefly luciferase expression system.

**Assay principle**

Target cells were plated and incubated for 22 ± 2 hours at 37°C. MGAH22 was incubated with samples and controls for 45 ± 15 minutes, then added to the cells and incubated for 55 ± 10 minutes, after which effector cells were added to the plate and incubated for 16-24 hours at 37°C. Bio-Glo reagent was added to the plate and luciferase activity in the effector cells was measured; if neutralizing antibodies were present in the serum samples, margetuximab would be unable to kill the target cells. Samples above the screening assay cut-point were considered "negative" for nAb, while samples at or above the screening assay cut-point were potentially positive ("confirmation required") and were further evaluated in the confirmatory assay. Under the confirmatory assay format, samples are left untreated or immunodepleted with protein A/G/L to confirm that the reduction in assay signal is due to antibodies and not due to non-specific matrix components. Confirmed positive samples were then titrated. Under the titer assay format, samples are diluted to determine a titer, prior to analysis under the screening assay format.

**Positive Control**

The LPC was prepared by spiking 300 ng/mL anti-MGAH22 antibodies (commercially sourced ( (b) (4) , lot AH004) neutralizing anti-trastuzumab antibody) in healthy human serum (HHS), while the HPC was prepared by spiking 3,000 ng/mL anti-MGAH22 antibodies into HHS. The LPC was later adjusted to 323 ng/mL based on assay sensitivity data. These are referred to as HHS PCs. Breast cancer controls were prepared at 1,410 ng/mL for the LPC and 12,000 ng/mL for the HPC, spiked into breast cancer serum (BCS).

**Screening Assay Cut-Point**

The HHS screening assay cut-point was derived from 50 HHS samples, and the BCS screening assay cut-point was derived from 50 female BCS samples. Data was collected from three assay runs by two analysts over several days, for each. The sample assay values (SAV) were defined as mean of sample/mean of the NC. The means and medians of each dataset were evaluated to determine whether they are comparable or not. The mean of the sample assay values were 0.914 for the BCS matrix and 0.933 for the HHS matrix (p value = 0.176) and the medians of the sample assay values were 0.906 for the BCS matrix and 0.937 for the HHS matrix (p value = 0.069), which are not statistically different. However, the MRD for the two cut-points are different, thus, the datasets were not pooled and separate cut-points were determined. The SAV dataset for the BSC samples was evaluated for outliers using Tukey's Outlier Filter approach (any value that is less than Q1 – 1.5 x IQR or greater than Q3 + 1.5 x IQR is defined as an outlier). Three samples were identified as outliers and were removed from the analysis. Shapiro-Wilk analysis of the dataset shows that the values are distributed normally ($P > 0.05$). The data was then evaluated to assess whether the means were equal across the study by ANOVA test, which showed a statistical difference (p value < 0.001). Levene's test for homogeneity of variances showed that there was no statistical difference between the variances across the study ($p = 0.362$). The cut-point was calculated as (CPV = mean – z x SD), where mean is the overall mean of the sample values, z is equal to 1.65 for a 5% false positive rate, and SD is the root mean square error. The HHS fixed assay cut-point was determined to be 0.711, which gave a false positive rate of 6.8%, while the BCS fixed assay cut-point was determined to be 0.757, which gave a false positive rate of 6.3%. The data are provided in Table 2 and 3, as well as Appendix D. The cut-point derived from BCS matrix was used to analyze clinical samples.

***Reviewer comment:*** *The screening cut-point for BCS gives approximately the desired false positive rate of 5%, therefore, the cut-point is appropriate.*

**Confirmatory Assay Cut-Point**

The confirmatory assay was performed in order to evaluate whether the reduction in signal is observed due to the presence of nAbs or due to non-specific matrix components. Samples were first immunodepleted with protein A/G/L; samples below the %depletion cut-point were defined as negative, while those above the cut-point were defined as positive. Fifty HHS samples were used to derive the HHS confirmatory cut point, while 50 female BCS samples were used to derive the BCS confirmatory cut point. Data was collected from three assay runs by two analysts over several days. The data was presented as a ratio of untreated sample response by treated sample response. The %depletion for each sample is calculated as %depletion = 100 x (1-ratio). Each ratio dataset identified and removed outliers using the same approach as described for determination of the screening assay cut-point. Each dataset was determined to be normally distributed (Shapiro-Wilk). The confirmatory cut-point was determined as (mean – z x SD), where mean is the overall mean of the ratios, z is equal to 2.33 for 1% false positive rate, and SD is the room mean square error. The corresponding %depletion cut-point was determined by subtracting the confirmatory cut-point by one ((1 - CCP) x 100). The HHS confirmatory assay cut-point was determined to be 43.1%, which gave a false positive rate of 2.7%, while the BCS confirmatory assay cut-point was determined to be 24.8%, which gave a false positive rate of 2.2%. The data are provided in Tables 4 and 5, as well as Appendix D. The cut-point derived from BCS matrix was used to analyze the clinical samples.

***Reviewer comment:*** *The false positive rate for the confirmatory cut-point for BCS is close to the desired false positive rate of 1%, therefore, the cut-point is appropriate.*

**Sensitivity and LPC Calculations**

The assay sensitivity was evaluated by serially spiking anti-MGAH22 antibody into the NC pool to create an antibody curve from 9600 ng/mL to 75 ng/mL (1:2 dilutions). Samples were analyzed at n = 2 per plate in HHS and BCS runs; samples were analyzed in three assays, by two analysts on at least two days. Six antibody curves were generated for each run type, and the SAV was calculated for each sample. The CV was 2.75% – 11.6% for the HHS dilutions, and 3.46% – 17.7% for BCS dilutions. The assay sensitivity, the lowest concentration at which the PC produced a positive result in all curves, was determined to be 300 ng/mL for HHS and 2,400 ng/mL for BCS. The 1,200 ng/ml concentration for BCS resulted in a positive response in only half of the curves. The 99% screening cut point was then set as an unknown sample and back calculated against the curves. The back calculated results were 323 ng/mL for HHS (16% CV) and 1,410 ng/mL for BCS (9.75% CV), which was subsequently set as the level of the LPC for HHS and BCS, respectively. Since the BCS LPC was lower than assay sensitivity, a different approach to determine assay sensitivity was used. The 95% screening cut point was set as an unknown sample and back-calculated against the curves. The resulting sensitivity was found to be 247 ng/mL for HHS (15.9% CV) and 1,130 ng/mL for BCS (15.3% CV). The data are provided in Tables 6 – 8.

***Reviewer comment:*** *The runs met the acceptance criteria of CV < 30%, and therefore are appropriate to calculate sensitivity and LPC levels. The sensitivity of the assay and the level of the LPC appear to be acceptable.*

**Matrix Interference**

The ability to detect anti-MGAH22 nAbs in the presence of matrix components was evaluated. The LPC (HHS and BCS) and HPC (HHS and BCS) were spiked into 10 HHS samples that had screened as negative, and then analyzed in the screening and confirmatory assays. Ten of ten unspiked samples were negative in both the screening and confirmatory assays, while ten of ten BCS LPC, and HHS and BCS HPC spiked samples were positive. Only nine of ten HHS LPC were positive. CV was ≤ 7.83% for all samples evaluated. Data are provided in Table 9 and 10.

***Reviewer comment:*** *The CV was < 30% for all samples in each run, and therefore the evaluation is acceptable. The data show that the detection of nAbs is not affected by the presence of serum from healthy and breast cancer subject samples.*

**Drug Tolerance**

The drug tolerance of the assay was evaluated to determine the potential of MGAH22 to interfere with the detection of nAbs. MGAH22 was prepared at 40,000 ng/mL, 10,000 ng/mL, 5,000 ng/mL, 1,000 ng/mL, 500 ng/mL, 200 ng/mL and 80 ng/mL in the NC pool. Anti-MGAH22 antibodies were prepared in the NC pool at 2X LPC, 2X MPC (set at 500 ng/mL for HHS and 2,500 ng/mL for BCS), and 2X HPC. Each PC sample was diluted with MGAH22 sample (1:1) and incubated for 1 hour. The level of MGAH22 that interferes with neutralizing activity was determined. For HHS, the LPC could be detected in the presence of 40 ng/mL of drug, the MPC could be detected in the presence of up to 100 ng/mL of drug, and the HPC could be detected in the presence of up to 500 ng/mL of excess drug. For BCS, the LPC could not be detected in the presence of drug, the MPC could be detected in the presence of 40 ng/mL of drug, and the HPC could be detected in the presence of up to 5,000 ng/mL of excess drug. Data are provided in Table 11 and 12.

***Reviewer comment:*** *The data provided does not support that the nAb assay can detect an adequate level of nAbs in the presence of onboard levels of drug. For example, intermediate levels of nAbs (2.5 µg/mL) in breast cancer samples could only be detected in the presence of up to 0.04 µg/mL of drug. An IR was sent to the applicant (8/25/20) to provide additional drug tolerance data to support that the nAb assay is capable of detecting adequate levels of nAbs (1 – 1.8 µg/mL) in the presence of onboard levels of drug (approximately 100 µg/mL). In response (9/2/20), the applicant stated that additional data is not available as higher drug concentrations were not investigated during validation and acknowledged that the data submitted does not support that the nAb assay can detect an adequate level of nAbs in the presence of onboard levels of drug.*

*Considering the proposed indication and that the overall binding ADA incidence has been observed to be low, this is not an approvability issue. It should be noted that the current nAb assay does not employ enrichment strategies to improve drug tolerance (e.g., acid dissociation or depletion steps). Therefore, the assay may be able to be optimized. A PMC was agreed upon (response received 11/3/20) for the applicant to optimize the current assay or develop a new assay that is validated to be sensitive, accurate, and reliable for the detection of nAbs in the presence of drug levels that are expected to be present at the time of patient sampling. This PMC is supported by the clinical pharmacology team, which could not definitively conclude (due to low ADA incidence) a lack of impact of ADAs on PK, safety, and efficacy from Study CP-MGAH22-04. As a result, the clinical pharmacology team will issue a PMC for the applicant to re-evaluate the*

*Study CP-MGAH22-04 samples using an appropriately validated nAb assay. An improved nAb assay may also support future indications proposed for the product.*

**Plate Homogeneity**

Plate homogeneity was evaluated by analyzing one plate of LPC at n = 26 for HHS and BCS. For an acceptable run, 90% of LPC sample SAVs had to be at or below the assay cut point. For both HHS and BCS, 100% of the SAVs were at or below the assay cut point. HHS samples had CV ≤ 8.05%, while BCS samples had CV ≤ 27.5%. Data are provided in Table 13 and 14.

***Reviewer comment:*** *The CV was ≤ 30% and the runs were acceptable; evaluation of plate homogeneity reveals that the nAb assay can adequately be run in the assay plates without deviation in values.*

**Titration Reproducibility**

The reproducibility of the titer calculation was evaluated and validated by spiking two individual HHS and BCS samples with anti-MGAH22 antibodies at respective HPC concentrations. The samples were diluted 2-fold in pooled normal human serum and evaluated in the screening assay. The HHS samples had a titer of 80 calculated from each run (CV ≤ 7.24% for all samples), while the BCS samples had titers of 320 and 640, which are within one dilution of each other (CV ≤ 7.03% for all samples). Data are provided in Tables 15 – 17.

***Reviewer comment:*** *The assay is able to reproducibly titrate the nAbs levels in BCS samples to within one dilution. This is acceptable for evaluation of clinical patient serum samples. It is unclear whether the applicant is including all dilutions when reporting nAb titers. This was not an issue in this review as no clinical samples were determined to be positive for nAbs. This should be evaluated in the response to the PMC.*

**Precision**

Intra-assay Precision

Intra-assay precision was evaluated by running six replicates of the LPC and HPC for HHS and BCS. All six replicates of LPC and HPC had SAVs below the respective assay cut-point for HHS and BCS. The CV for the LPC and HPC in HHS was 5.44% and 4.24%, respectively, and for BCS, the CV for the LPC and HPC was 9.40% and 3.95%, respectively. Data are provided in Table 18 and 19.

Inter-assay Precision

In order to evaluate inter-assay precision, the LPC and HPC controls were evaluated from all acceptable validations runs for both HHS and BCS. The CV for the LPC and HPC was 20.5% and 31.0%, respectively, for HHS. The CV for the LPC and HPC was 26.1% and 26.2%, respectively, for BCS. The data are presented in Table 20 (LPC) and Table 21 (HPC). Since the CV was > 30%, cell-line stability was evaluated; cell passages were restricted to 19 passages and runs using cells higher than passage 19 were removed from assessment. Re-evaluation of CV for HPC found 25.4% for HHS and 26.2% for BCS. Data are provided in Tables 20 – 30.

***Reviewer comment:*** *The intra- and inter-assay precision of the screening assay is adequate; the results for samples as well as for runs can be reproducibly obtained for the detection of nAbs.*

*Data for intra- and inter-assay precision was not provided for the confirmatory and titer assay formats. However, since an adequate nAb assay will be developed/optimized and validated as a PMC, this is currently not an issue. It is expected that the final study report provided in the PMC will include the complete set of precision data.*

**Cell Line Stability**
The stability of the cell-line was evaluated based on the ratio of drug control/negative control (DC/NC) from acceptable validation runs. Acceptable passage number was found to be between 6 and 19; runs with passage above 19 were excluded from analysis. Data are provided in Table 31.

**Stability**
The stability of the HPC and LPC for HHS and BCS (six replicates each) was evaluated by subjecting samples to 5 freeze thaw cycles (frozen at -80°C, thawed at RT) prior to analysis in the screening assay. All 6 replicates for LPC and HPC for HHS and BCS were ≤ the respective assay cut-points. Data are provided in Table 32 and 33.

Six replicates each were also evaluated after storage at RT for 24 hours or at 2 – 8°C for 24 hours, and then run in the screening assay. All 6 replicates for LPC and HPC for HHS and BCS were ≤ the respective assay cut-points. Data are provided in Tables 34 – 37.

***Reviewer Comment:*** *The data provided is acceptable and support the stability of clinical samples and PC controls that will be evaluated during execution of the assay.*

**Effect of Hemolysis**
The effect of hemolysis on nAb detection was evaluated in six replicates of pooled HHS. Lysed whole human blood was added to the samples to prepare hemolyzed matrix at 1%, 5%, and 10% levels. The samples were spiked with anti-MGAH22 antibodies at LPC and HPC levels for both HHS and BCS, and then evaluated in the screening and confirmatory assays. Hemolysis interference was found in samples with levels higher than 1% hemolyzed matrix. For HHS, six of six unspiked 1% hemolyzed samples were negative, and six of six LPC and HPC 1% spiked samples were positive. For BCS, six of six unspiked 1% hemolyzed samples were negative, and six of six HPC 1% spiked samples were positive. BCS LPC spiked with 1% hemolyzed matrix results had CV > 30% and therefore the run failed; the samples were not re-evaluated. Unspiked 5% and 10% hemolyzed samples had positive results, and therefore showed interference. Data are provided in Tables 38 – 43.

***Reviewer comment:*** *The data show that the hemolyzed matrix (higher than 5%) interferes with detection of low and high levels of nAbs. Therefore, the assay is not suitable for evaluation of samples with hemolysis above 1%. The method validation report stated that hemolyzed clinical samples will not be analyzed. This should be assessed during review of the response to the PMC.*

**Effect of Lipemia**
The effect of lipemia on nAb detection was evaluated in six human serum samples with triglycerides > 300 mg/dL, which were spiked with HHS LPC and HPC levels of anti-MGAH22 antibodies. One replicate of each sample (spiked and unspiked) was analyzed in the screening and confirmatory assays. All unspiked lipemic samples had a negative result, none of the spiked

samples had a positive result at the LPC level, and all six samples spiked at the HPC levels had a positive result.

Additionally, samples containing 200-249 mg/dL or 250-300 mg/dL triglycerides were spiked at the LPC level and evaluated. Only one of six LPC spiked samples was positive with 200-249 mg/dL triglycerides, and two of six LPC spiked samples were positive with 250-300 mg/dL triglycerides. Samples spiked with 500 ng/mL, 1000 ng/mL and 1500 ng/mL anti-MGAH22 antibodies were spiked into the six samples each with > 300 mg/dL triglycerides, 250-200 mg/dL triglycerides and 200-249 mg/dL triglycerides. All unspiked lipemic samples were negative, while all spiked lipemic samples with 1000 ng/mL and 1500 ng/mL anti-MGAH22 antibodies were positive. For samples spiked with 500 ng/mL anti-MGAH22 antibodies, five of six samples with 200-249 mg/dL triglycerides were positive, three of six samples with 250-300 mg/dL were positive, and two of six samples with > 300 mg/dL triglycerides were positive. Data are provided in Table 44 – 47.

***Reviewer comment:*** *The data show that there is interference from lipemic samples containing > 200 mg/dL triglycerides when spiked with low levels of nAbs. Interference was also observed in lipemic samples containing >249 mg/dL triglycerides when spiked with 500 ng/mL of anti-MGAH22 antibodies. Some interference in the assay may occur in lipemic samples containing > 300 mg/dL at antibody concentrations less than 1,000 ng/mL. The assay can be suitable for use with lipemic samples, though only at low levels of triglycerides or in samples with high levels of nAbs. It is unclear whether the clinical samples analyzed had samples containing triglycerides that would impact assay performance. This should be assessed during review of the response to the PMC.*

**Assay Acceptance Criteria**

All acceptable validation runs were evaluated to determine the final DC/NC ratio for plate acceptance. Acceptance criteria was established by considering: the mean DC/NC ratio of all acceptable runs – (1-3X SD) = lower limit of acceptance. The lowest DC/NC ratio obtained could also be used as acceptance ratio if the above calculation did not accurately reflect validation data. The best fit DC/NC ratio for plate acceptance was determined to be the lowest ratio obtained, which was 3.74. Data are provided in Tables 48 – 50.

For the assay controls, the mean response for all controls must have a CV $\leq$ 30.0%, and the screening assay value (SAV) of the positive controls (HPC/DC and LPC/DC) must be $\leq$ 0.757 (BCS screening assay cut point). In the confirmatory assay, %depletion must be $\geq$ 24.8% (BCS confirmatory assay cut point) for LPC and HPC, while the DC/NC ratio must be $\geq$ 3.74. For study samples, the mean response for samples must have a CV $\leq$ 30.0%.

***Reviewer Comment****: System suitability was met during assay validation (for acceptable runs that were used in evaluations). However, given the totality of information provided for the nAb assay, it is not adequate for the evaluation of clinical patient samples, as the drug tolerance of the assay is not sufficient to be able to allow detection of a suitable level of nAbs in the presence of onboard levels of drug.*

**Interim Analytical Report (Report RERI)**

Patient serum samples from clinical study CP-MGAH22-04 were first evaluated using the screening, confirmatory, and titer assays for detection of ADAs. Samples that were confirmed positive (n = 29) were analyzed using the cell-based nAb assay to detect nAbs. The validated methods were not modified during patient sample analysis.

***Reviewer comment:*** *Since the format of the assay does not appear to have the appropriate tolerance to be able to detect neutralizing antibodies in the presence of onboard levels of drug found in patient samples, it is unclear whether the level of nAbs reported is accurate. As a result,* (b) (4)

Anshu Rastogi

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Brian Janelsins

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Wendy Weinberg

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# MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

| | |
|---|---|
| Date of This Memorandum: | November 3, 2020 |
| Requesting Office or Division: | Division of Oncology 1 (DO1) |
| Application Type and Number: | BLA 761150 |
| Product Name and Strength: | Margenza (margetuximab-cmkb) Injection, 250 mg/10 mL |
| Applicant/Sponsor Name: | MacroGenics, Inc. |
| OSE RCM #: | 2019-2692-1 |
| DMEPA Team Leader: | Ashleigh Lowery, PharmD, BCCCP |

## 1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels received on August 13, 2020 for Margenza. Division of Oncology 1 (DO1) requested that we review the revised container label and carton labeling for Margenza (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations made in our previous label and labeling review[a].

## 2 CONCLUSION

The revised container label and carton labeling are acceptable and we have no additional recommendations at this time.

[a] Gao, T. Label and Labeling Review for Margenza (BLA 761150). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 JUL 09. RCM No.: 2019-2692.



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**FOOD AND DRUG ADMINISTRATION**
**Center for Drug Evaluation and Research**
**Office of Prescription Drug Promotion**

# ****Pre-decisional Agency Information****

# Memorandum

**Date:** October 28, 2020

**To:** Melanie Royce, MD, Clinical Reviewer
Division of Oncologic Diseases I (DO-1)

Duyen Mach, PharmD, Regulatory Project Manager, DO-1

William Pierce, PharmD, Associate Director for Labeling, DO-1

**From:** Maritsa Serlemitsos-Day, PharmD, BCPS, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

**CC:** Kevin Wright, PharmD, Team Leader, OPDP

**Subject:** OPDP Labeling Comments for MARGENZA™ (margetuximab-cmkb) injection, for intravenous use

**BLA**: 761150

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In response to DO-1's consult request dated August 1, 2020, OPDP has reviewed the proposed product labeling (PI) for the original NDA/BLA submission for MARGENZA™ (margetuximab-cmkb) injection, for intravenous use (Margenza) indicated, in combination with chemotherapy, for the treatment of adult 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.

OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DO-1 (Clara Lee) on October 19, 2020, and are provided below.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on August 19, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Maritsa Serlemitsos-Day at (301) 796-1760 or maritsa.serlemitsos-day@fda.hhs.gov.

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/s/

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MARITSA SERLEMITSOS-DAY
10/28/2020 04:04:10 PM

# Clinical Inspection Summary

| | |
|---|---|
| **Date** | August 10, 2020 |
| **From** | Tina Chang, M.D., Reviewer<br>Min Lu, M.D., M.P.H., Team Leader<br>Kassa Ayalew, M.D., M.P.H, Branch Chief<br>Good Clinical Practice Assessment Branch (GCPAB)<br>Division of Clinical Compliance Evaluation (DCCE)<br>Office of Scientific Investigations (OSI) |
| **To** | Melanie Royce, M.D., Medical Officer<br>Christy Osgood, M.D., Clinical Team Leader<br>Julia Beaver, M.D., Director<br>Tony Park, PharmD, Regulatory Project Manager<br>Division of Oncology 1 (DO1) |
| **NDA/BLA #** | 761150 |
| **Applicant** | MacroGenics, Inc. |
| **Drug** | Margenza (margetuximab) |
| **NME (Yes/No)** | Yes |
| **Therapeutic Classification** | Anti-HER2 chimeric antibody |
| **Proposed Indication(s)** | 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. |
| **Consultation Request Date** | January 28, 2020 (original); February 26, 2020 (revised) |
| **Summary Goal Date** | November 20, 2020 |
| **Action Goal Date** | December 18, 2020 |
| **PDUFA Date** | December 18, 2020 |

## I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigators, Dr. William Gradishar (Site# US025), Dr. Gail Wright (Site US043), and Dr. Raul Oyola (Site# US035) were inspected for one Phase 3 study, Study CP-MGAH22-04.

The study conduct and data derived from these three clinical sites, based on the results of the inspections, are considered acceptable in support of this biologics licensing application (BLA).

## II. BACKGROUND

Margetuximab is an Fc-engineered, anti-HER2 chimeric antibody. Its variable domains are from mouse monoclonal antibody (mAb) 4D5, the parent antibody of trastuzumab. Whereas

trastuzumab is humanized, margetuximab is chimeric [redacted (b) (4)]. Margetuximab and trastuzumab bind the same domain IV HER2 epitope with similar affinity.

The sponsor conducted a Phase 3 study (CP-MGAH22-04), to evaluate the efficacy of Margenza in combination with chemotherapy for treatment of patients with metastatic HER2-positive breast cancer who received two or more prior anti-HER2 regimens, at least one of which was for metastatic disease. Subjects received margetuximab or trastuzumab on Day 1 of a 3-week cycle. Chemotherapy was given on each agent's schedule, consistent with local practice, beginning on Day 1.

One Phase 3 study from Protocol CP-MGAH22-04 will form the basis for the regulatory decision-making process for this application.

**Study CP-MGAH22-04**

Study Title: A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs. Trastuzumab Plus Chemotherapy in the Treatment of Patients with HER2+ Metastatic Breast Cancer Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment

This was a Phase 3 randomized (1:1), open-label study that compared margetuximab to trastuzumab, each in combination with the Investigator's choice chemotherapy, for treatment of subjects, 18 years of age and older, with metastatic or locally advanced human epidermal growth factor receptor 2 positive (HER2+) treatment-resistant breast cancer. Before randomization, Investigators selected 1 of 4 chemotherapy agents for each subject to administer with anti-HER2 study therapy. Chemotherapy options included capecitabine, eribulin, gemcitabine, or vinorelbine. Subjects were then randomized 1:1 to receive either margetuximab or trastuzumab on Day 1 of a 3-week cycle with the selected chemotherapy. Randomization was stratified for chosen chemotherapy, number of prior therapies, and number of metastatic sites of disease. Chemotherapy was given on each agent's schedule, consistent with local practice, beginning on Day 1. Subjects received treatment until disease progression, death, withdrawal of consent, or request by the Investigator or subject to stop study treatment. After treatment discontinuation, subjects were to be followed for survival, as well as monitored for progression if discontinued for a reason other than disease progression.

Primary efficacy endpoints included progression-free survival (PFS) and overall survival (OS) and were analyzed sequentially where the PFS endpoint was analyzed first. If PFS achieved statistical significance, the OS would be analyzed. Progression-free survival was defined as the time from date of randomization to date of first documented disease progression or death from any cause, whichever occurred first. Disease response was determined using RECIST 1.1. Overall survival was defined as the time from date of randomization to date of death from any cause.

Subjects were evaluated regularly for disease progression. Tumor assessments were obtained using computed tomography (CT) and/or magnetic resonance imaging (MRI) scans of chest,

abdomen, and pelvis and were performed before treatment (baseline) and every 2 cycles for the first 24 weeks on study therapy. Bone scans were to be performed on all subjects at baseline, then as clinically indicated for assessment of bone metastasis. Disease response was determined both locally based on investigator interpretation of available studies and by central review using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

A Data Safety Monitoring Committee (DSMC) monitored safety via evaluation of unblinded data throughout the study. The DSMC reviewed efficacy data at interim analyses for PFS and OS. The first futility analysis was to be performed after occurrence of about 100 PFS events, followed by primary PFS analysis after occurrence of about 257 PFS events. Interim analysis of OS was to be performed at the same time as primary PFS analysis, then after occurrence of 270 deaths (70% of target OS events), and finally after occurrence of about 385 deaths.

The study randomized 536 subjects from 166 sites in 17 countries. The first subject was randomized on 26 August 2015 and the last patient completed the study on 10 October 2018 based on the first interim analysis.

**Rationale for Site Selection**

Three clinical investigators were selected for routine inspections: Dr. William Gradishar (Site# US025) was chosen for its large enrollment of subjects and history of a complaint issued on October 31, 2018 for not reducing the dose of capecitabine for a subject after the subject was diagnosed with Grade 2 Hand-Foot Syndrome (HFS), a side effect that is attributed to capecitabine. According to the protocol, each Grade 2 event requires a hold until the adverse event has resolved to Grade 1 or 0, followed by a 20% dose reduction. The Board determined the Sub-investigator administering the wrong dose after toxicity constituted serious noncompliance and required the clinical investigator to systematically retrain all study investigators after each protocol update.

Dr. Gail Wright (Site# US043) and Dr. Raul Oyola (Site# US035) were chosen for inspections for their large enrollment and higher response rates on efficacy endpoints compared to other sites for Study CP-MGAH22-04.

# III. RESULTS:

1. **Dr. William Gradishar, Site# US025 (Northwestern University Feinberg School of Medicine, 676 N Saint Clair Street, Suite 850, Chicago, IL 60611-3124; Inspection dates: February 20 – 28, 2020.)**

   For Study CP-MGAH22-04, this site screened 18 subjects and enrolled 9 subjects. The study was ongoing for follow-up at the time of the inspection. One subject withdrew consent before receiving the investigational product. All 9 of the enrolled subjects were reviewed comprehensively during the inspection.

The inspection evaluated the following documents: IRB approval letters and correspondence; monitoring reports; consent forms, subject medical records, financial disclosure reports, case report forms, drug accountability records, site signature and responsibility logs; and site training documentation.

The primary efficacy endpoint was verifiable for all subjects, except for Subject US025-(b) (6). Please see below. There was no under-reporting of adverse events.

At the end of the inspection, a Form FDA 483 was issued for the following observations:

1. An investigation was not conducted in accordance with the investigational plan.

   Specifically:

   a. The clinical investigator reported Subject US025-(b) (6), who was assigned to trastuzumab plus chemotherapy treatment group, as having progressive disease based on the CT scan performed on (b) (6) when neither the Response Evaluation Criteria in Solid Tumors (RECIST) worksheet and progress notes for the visits dated (b) (6) and (b) (6) indicated protocol defined progressive disease, and patient proceeded with treatment with Cycle 5 Day 1 on (b) (6).

      *Reviewer's comments: Dr. Gradishar responded in writing on March 19, 2020 and stated that progressive disease was entered incorrectly in eCRF for Subject US025-(b) (6), who was assigned to trastuzumab plus chemotherapy treatment group. The CT scan was performed on (b) (6) and was read by independent radiologist who questioned possible progression but did not call it unequivocal progression. The wrong response assessment, "progressive disease" was inadvertently entered incorrectly electronically in the eCRF by the data assistant. Although the clinical investigator signed off on the eCRF, the clinical investigator did not feel that there was any unequivocal progression after evaluating the CT scan and the patient's clinical status on physical exam and appropriately proceeded with treatment, Cycle 5 Day 1 with trastuzumab and eribulin on (b) (6) as documented in the RECIST worksheet and progress notes for the visits dated (b) (6) and (b) (6). This was reported as a protocol deviation in the study report in the submission. Dr. Gradishar stated he would contact the Sponsor to amend the correct response. This isolated incident in the control treatment group is unlikely to have a significant impact on overall results of the study safety or efficacy of this product.*

   b. For 4 subjects, Subjects US025-(b) (6), US025-(b) (6), US025-(b) (6), and US025-(b) (6), the RECIST worksheets were completed after the subjects' Cycle 1 Day 1 instead of before Cycle 1 Day 1 per inclusion criterion #9.

*Reviewer's comments: Dr. Gradishar responded that all 4 subjects, Subjects US025-(b) (6) and US025-(b) (6), who were assigned to trastuzumab plus chemotherapy treatment group, and Subjects US025-(b) (6) and US025-(b) (6), who were assigned to the margetuximab plus chemotherapy treatment group, were considered eligible based on the treating physician's review who was aware of RECIST 1.1 criteria, and a sponsor provided eligibility form, along with bone scan reports, pathology reports, and CT scan reports were submitted to the medical monitor for review and approval prior to study entry. RECIST worksheets were completed by an independent radiologist and because the RECIST worksheets were not standard of care, it was difficult to get the radiologists to prioritize completing the worksheets, and the screening RECIST 1.1 assessments for this study were delayed. These were not reported as protocol deviations in the clinical study report. The delay in completion of RECIST worksheets by the radiologist after Cycle 1 Day 1 is unlikely to have a significant impact on the efficacy or safety data of the study.*

2. Failure to prepare or maintain adequate case histories with respect to observations and data pertinent to the investigation

   Specifically:

   a. Failed to maintain copies of "Test Article Accountability Log" forms that identifies the person preparing the investigational product, the time of preparation, the mg/mL of investigational product used, and the storage conditions/times after preparation for 36 of 68 subject cycles.

      *Reviewer's comment: Although the clinical investigator did not maintain "Test Article Accountability Log" forms for 36 of 68 subject cycles, many of the elements of the Test Article Accountability Log form were captured in the hospital's electronic medical record (EMR). Specifically, the EMR Dispense Notes documented the ordered dose, route, dose calculations, administration instructions, and the time of the order. The EMR Infusion Visit Notes documented the actual time that the infusion was started and completed as well as any special orders/instructions for the infusion. The Study Product Accountability Records showed the subject number and initials for each intended kit, the date that allocated kits were retrieved by the Satellite Pharmacy from the Investigational Drug Service (IDS) Pharmacy and the date and number of vials retrieved from storage at the Satellite Pharmacy for test article preparation. Dr. Gradishar responded that as a preventive action, a worksheet will be required to capture all the preparation information and the IDS pharmacy is in the process of implementing an IV workflow solution for compounding pharmacies that will electronically store all*

*the preparation information and ultimately replace the worksheets by 4th quarter of 2020. The incident described above was not reported as protocol deviations and does not appear to have an impact on safety or efficacy data of the study.*

b. There is no source documentation for the cause of death for Subjects US025-(b) (6) and US025-(b) (6), both assigned to the margetuximab plus chemotherapy treatment group.

*Reviewer's comment: Dr. Gradishar states in his written response that although the obituary and telephone encounters did not specify cause of death, the clinical notes leading up to the individual dates of deaths support progression and need for initiating palliative and hospice care. Subject US025-(b) (6), who was assigned to the margetuximab plus chemotherapy treatment group, came off the protocol treatment on (b) (6) due to progressive disease and passed away on (b) (6). Subject US025-(b) (6), who was assigned to the margetuximab plus chemotherapy treatment group, came off protocol treatment on (b) (6) due to progressive disease and passed away on (b) (6) Both patients came off the study for progression of disease and passed not long after. Dr. Gradishar states that in the future, that if he is unable to obtain a death certificate with the cause of death listed, he will document it in the clinical notes. The events described above were not reported as protocol deviations and appear unlikely to have significant impact on the overall safety or efficacy data of the study with acceptable corrective action taken.*

In general, this clinical investigator appeared to be in compliance with Good Clinical Practices except for the observations described above. Data submitted by this clinical site appear acceptable in support of this application.

**2. Dr. Gail Wright, Site# US043 (Florida Cancer Specialists, 560 Jackson Street, Suite 220, St. Petersburg, FL 33705; Inspection dates: June 12- June 22, 2020.)**

For Protocol CP-MGAH22-04, this site screened 19 subjects and enrolled 16 subjects. Among the 16 enrolled subjects, 16 subjects completed the study treatment. All 16 subjects were reviewed comprehensively during the inspection.

The inspection evaluated the following documents: Protocols and amendments, monitoring visits and correspondence, informed consent forms, subject medical records, Dr. Wright's oversight of the study, site's training activities and implementation of study procedures, adherence to and documentation of protocol-required visits, administration of the investigational product, financial disclosure reports, case report forms, institutional review board approval letters and correspondence, notifications and correspondence between the sponsor and the Principal Investigator, delegation of study responsibilities,

drug accountability records, investigational product control, and storage, site signature and responsibility logs, and site training documentation.

Source documents for the raw data used to assess the primary endpoint were verifiable at the study site for Study CP-MGAH22-04. No under-reporting of adverse events was noted.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support of this application.

**3. Dr. Raul Oyola, Site# US035 (340 Kennestone Hospital Blvd, Suite 200, Marietta, GA 30060; Inspection dates: June 22 – June 25, 2020.)**

This was Dr. Oyola's second FDA inspection. The previous inspection was a For Cause inspection, conducted on 10/22-25/2018, and covered the same clinical study as the current inspection. The For Cause inspection was a result of a complaint, received by the Division of Good Clinical Practice Compliance, reporting that study nurse administered a drug at an incorrect dosage then falsely documented the dosage on source records. No Form FDA 483 (Inspectional Observations) was issued to Dr. Oyola and it was classified as NAI.

For Protocol CP-MGAH22-04, this site screened 9 subjects and enrolled 7 subjects. Among the 7 enrolled subjects, 4 subjects discontinued the study due to disease progression. All 7 subjects were reviewed comprehensively during the inspection.

Since this was the second inspection that covered this study, the inspection evaluated the primary endpoints, verification of line listings, adverse events, and study procedures that took place after the date of the previous inspection.

Source documents for the raw data used to assess the primary endpoint were verifiable at the study site for Study CP-MGAH22-04. No under-reporting of adverse events was noted.

This clinical investigator appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (Inspectional Observations) was not issued. Data submitted by this clinical site appear acceptable in support this application.
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CONCURRENCE:

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CC:

Central Doc. Rm.
Review Division /Division Director/
Review Division /Medical Team Leader/
Review Division /Project Manager/
Review Division/MO/
OSI/Office Director/
OSI/DCCE/ Division Director/
OSI/DCCE/Branch Chief/
OSI/DCCE/Team Leader/
OSI/DCCE/GCP Reviewer/
OSI/ GCP Program Analysts/
OSI/Database PM/Dana Walters

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

| | |
|---|---|
| Date of This Review: | July 9, 2020 |
| Requesting Office or Division: | Division of Oncology 1 (DO1) |
| Application Type and Number: | BLA 761150 |
| Product Name, Dosage Form, and Strength: | Margenza (margetuximab-xxxx)[a] Injection, 250 mg/10 mL |
| Product Type: | Single Ingredient Product |
| Rx or OTC: | Prescription (Rx) |
| Applicant/Sponsor Name: | MacroGenics, Inc. |
| FDA Received Date: | December 18, 2019 |
| OSE RCM #: | 2019-2692 |
| DMEPA Safety Evaluator: | Tingting Gao, PharmD |
| DMEPA Team Leader: | Chi-Ming (Alice) Tu, PharmD |

[a] Since the proper name for Margenza has not yet been determined, "margetuximab-xxxx" is used throughout this review as the nonproprietary name for this product.

## 1 REASON FOR REVIEW

As part of the review process for Margenza (margetuximab-xxxx) Injection, the Division of Oncology 1 (DO1) requested that we review the proposed Margenza prescribing information, container label, and carton labeling for areas of vulnerability that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

| Material Reviewed | Appendix Section (for Methods and Results) |
|---|---|
| Product Information/Prescribing Information | A |
| Previous DMEPA Reviews | B – N/A |
| Human Factors Study | C – N/A |
| ISMP Newsletters* | D – N/A |
| FDA Adverse Event Reporting System (FAERS)* | E – N/A |
| Other | F – N/A |
| Labels and Labeling | G |

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Margenza prescribing information, container label, and carton labeling and determined that they may be improved to ensure safe product use.

## 4 CONCLUSION & RECOMMENDATIONS

The proposed Margenza prescribing information, container label, and carton labeling may be improved to ensure safe product use. We provide specific recommendations in Section 4.1 and 4.2 below.

4.1 RECOMMENDATIONS FOR DIVISION OF ONCOLOGY 1 (DO1)

A. Prescribing Information

1. Dosage and Administration Section, Section 2.3 Preparation for Administration

a. There are several negative statements emphasized in bolded text (e.g., "Do not administer as an intravenous push or bolus. Do not mix MARGENZA with other drugs. etc) throughout Section 2.3. Since these negative statements are bolded and more prominent than the rest of the text, they may be misread as affirmative actions. Therefore, we recommend unbolding those negative statements to minimize the risk of these negative statements being read as affirmative actions.

b. Consider relocating the statement "Do not mix MARGENZA with other drugs." to the end of "Preparation for Intravenous Infusion" sub-section, and the statement "Do not administer as an intravenous push or bolus." to "Administration" sub-section instead of listing towards the beginning of section 2.3 to decrease prominence of these negative statements.

c. Consider deleting the second bulletin where it states "(b) (4) " since this sentence may be misinterpreted to mean that (b) (4)

d. Delete the abbreviation "(IV)" and spell out "IV" as "intravenous" to minimize misinterpretation.

e. As currently presented, this paragraph is lengthy and important information may get overlooked.

- Withdraw appropriate volume of MARGENZA solution from the vial(s). The calculated total dose volume should be rounded to the nearest 0.1 mL. Transfer MARGENZA into an intravenous (IV) bag containing 100 mL or 250 mL 0.9% Sodium Chloride injection (b) (4). Polyvinyl chloride (PVC) bags or (b) (4) may be used. The final concentration of the diluted solution should be between 0.5 to 7.2 mg/mL.

We recommend breaking up this lengthy paragraph into smaller bulletins. We also recommend adding instructions to instruct healthcare providers to calculate the dose and the total dose volume required for preparation of Margenza solution. For example:

- Calculate the required volume of MARGENZA needed to obtain the appropriate dose according to patient's body weight. The calculated total dose volume should be rounded to the nearest 0.1 mL.

- Withdraw appropriate volume of MARGENZA from the vial(s) using a syringe.
- Transfer MARGENZA into an intravenous bag containing 100 mL or 250 mL 0.9% Sodium Chloride Injection, USP. Polyvinyl chloride (PVC) bags or (b) (4) may be used.
- The final concentration of the final diluted solution should be between 0.5 mg/mL to 7.2 mg/mL.

f. We recommend the following comment be communicated to the Macrogenics:

> You stated that Margenza should be diluted in intravenous bags containing 100 mL or 250 mL of 0.9% Sodium Chloride Injection to a final concentration between 0.5 mg/mL to 7.2 mg/mL. However, if a 250 mL bag is used to achieve a concentration of 7.2 mg/L, a patient weighting more than 120 kg would require a dose greater than 1800 mg would exceed the concentration of 7.2 mg/mL if a 250 mg intravenous bag is used. Please clarify.

2. Dosage Forms and Strengths

   a. Provide information to facilitate identification of the dosage form, including information about color (e.g., clear solution) and other identifying characteristics.

3. How Supplied/Storage and Handling Section

   a. Provide information to facilitate identification of the dosage form, including information about color (e.g., clear solution) and other identifying characteristics.

   b. Revise the statement "(b) (4) " to "Store refrigerated at 2°C to 8°C (36°F to 46°F)" for consistency with the wording on the container label and carton labeling.

## 4.2 RECOMMENDATIONS FOR MACROGENICS, INC.

We recommend the following be implemented prior to approval of this BLA:

A. General Comments (Container label & Carton Labeling)

1. As currently presented, the NDC number is denoted by a placeholder. We request that you submit the actual NDC numbers for the container label and carton labeling to ensure that the product code numbers are not sequential. The similarity of the product code numbers has led to selecting and dispensing of the wrong strength and wrong drug. See *Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize*

*Medication Errors*, which, when finalized will represent the agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors.

2. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash to separate the portions of the expiration date. See *Draft Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers*, which, when finalized will represent the Agency's current thinking on the topics therein. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/product-identifiers-under-drug-supply-chain-security-act-questions-and-answers.

B. Container Label

1. Consider revise "(b) (4)" to "Store refrigerated at 2°C to 8°C (36°F to 46°F)." and delete the statement "(b) (4)" to reduce clutter.

C. Carton Labeling for carton of one vial and carton of four vials

1. Consider revise "(b) (4)" to "Store refrigerated at 2°C to 8°C (36°F to 46°F)." and delete the statement "(b) (4)" to reduce clutter.

2. If space permits, consider including instructions on the side panel that describes the required diluent to dilute Margenza. For example, add "Use 0.9% Sodium Chloride injection, USP to dilute Margenza." to the side panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Margenza received on December 18, 2019 from MacroGenics, Inc..

| Table 2. Relevant Product Information for Margenza | |
|---|---|
| Initial Approval Date | N/A |
| Nonproprietary Name | margetuximab-xxxx |
| Indication | in combination with chemotherapy, for the treatment 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. |
| Route of Administration | intravenous |
| Dosage Form | Injection |
| Strength | 250 mg/10 mL |
| Dose and Frequency | The recommended dose of MARGENZA is 15 mg/kg, administered as an intravenous infusion every 3 weeks (21-day cycle) until disease progression or unacceptable toxicity. |
| How Supplied | Carton of one single-dose vial<br>Carton of four single-dose vials |
| Storage | (b) (4) |
| Container Closure | 10 cc/20 mm (b) (4) clear glass vial with rubber stopper, 20 mm aluminum cap, and (b) (4) tope. |

## APPENDIX G. LABELS AND LABELING

### G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[b] along with postmarket medication error data, we reviewed the following Margenza labels and labeling submitted by MacroGenics, Inc.

- Container label received on December 18, 2019
- Carton labeling received on December 18, 2019
- Prescribing Information (Image not shown) received on December 18, 2019, available from \\cdsesub1\evsprod\bla761150\0001\m1\us\114-labeling\114a-draft-label\1-14-1-draft-uspi-2019-12-10.docx

### G.2 Label and Labeling Images

Container label

(b) (4)

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

[b] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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# Consult Memorandum

U.S. FOOD & DRUG ADMINISTRATION

**Date:** 7/8/2020
**To:** Melanie Royce, Clinical Reviewer, CDER
Christy Osgood, CDTL Lead, CDER
Kelly Duyen, Regulatory Project Manager, CDER
**From**: Banu Saritas-Yildirim, Ph.D. Scientific Reviewer, CDRH/OIR/DMGP/MPCB
**Through:** Soma Ghosh, Ph.D., Branch Chief, CDRH/OIR/DMGP/MPCB
Reena Philip, Ph.D., Director, CDRH/OIR/DMGP
**Subject:** CDER consult request for IND (b) (4)
**ICC Number:** ICC2000486
**BLA Number:** BLA 761150
**ICCR Number:** ICCR# 00019393
**Drug Name:** Margetuximab
**Drug Sponsor:** MacroGenics, Inc.
**Device:** Unknown
**Device Sponsor:** Unknown
**Analytes Detected:** HER2 overexpression/amplification
**Related Submissions:** N/A
**Protocol Title Supporting Drug Labelling: SOPHIA (NCT02492711)/CP-MGAH22-04** – A Phase 3, Randomized Study of Margetuximab Plus Chemotherapy vs Trastuzumab Plus Chemotherapy in the Treatment of Patients with HER2+ Metastatic Breast Cancer Who Have Received Prior Anti-HER2 Therapies and Require Systemic Treatment

## I. PURPOSE

CDER is currently reviewing the BLA application from MacroGenics Inc., for margetuximab and requested CDRH representation in the labelling meeting scheduled for July 9, 2020.

## II. BACKGROUND and RATIONALE

Among women, invasive adenocarcinoma of the breast is the most common nondermatological cancer and the second leading cause of death in the United States (US). While early detection and treatment have reduced the death rate associated with breast cancer, for women diagnosed with metastatic breast cancer (MBC) in the US, the overall prognosis remains poor, with an estimated 40,300 deaths due to this disease in 2014. In the US and elsewhere, several agents are approved for the treatment of HER2+ breast cancer. For patients who require systemic therapy as part of definitive surgical resection, either neo-adjuvant therapy with trastuzumab - and increasingly - pertuzumab, or adjuvant therapy with trastuzumab, both in combination with cytotoxic chemotherapy, is the treatment of choice. Treatment at the time of recurrence is determined in part by the length of the original treatment-free interval. Patients whose disease recurs late after adjuvant treatment are often treated with the same or similar anti-HER2 regimen (trastuzumab ± pertuzumab) used in the neo-adjuvant or adjuvant setting. Patients whose disease recurs shortly after initial neoadjuvant/adjuvant therapy (within 6 months) will often proceed to a second-line regimen, usually ado-trastuzumab emtansine (T-DM1) monotherapy. The recurrence of disease is common, and additional treatments are needed.

To date, no HER2-targeted agents have been approved in the US to specifically treat patients after two prior lines of treatment, although both lapatinib and trastuzumab are often used in this setting. The purpose of this study is to evaluate the activity of margetuximab in combination with standard of care chemotherapies in the setting of patients with metastatic HER2+ breast cancer who have received at least 2 prior lines of anti-HER2 directed therapy in the metastatic setting, or in case of having received (neo)adjuvant pertuzumab, at least 1 prior line of anti-HER2 directed therapy in the metastatic setting, and who have received at least one, and no more than three, lines of therapy overall in the metastatic setting. Because common practice is to treat these patients with an anti-HER2 agent in combination with chemotherapy, it is unethical to compare the effect of margetuximab with placebo, and therefore an active comparator was chosen. Trastuzumab is commonly used in this setting, and the comparison will directly evaluate whether a molecule that has been engineered to enhance ADCC produces superior clinical efficacy.

**Margetuximab**

Margetuximab-cmkb targets the HER2 antigen overexpressed on the surface of tumor cells. Upon binding to HER2, margetuximab-cmkb (1) inhibits tumor cell proliferation, (2) blocks shedding of the HER2 extracellular domain and (3) mediates tumor cell lysis by engaging immune effector cells.

The engineered Fc region of margetuximab-cmkb enables greater immune activation than trastuzumab, including in vitro antibody-dependent cellular cytotoxicity (ADCC) and NK cell activation. Margetuximab-cmkb treated patients have also shown an increase in adaptive immune responses, including elevations in HER2-specific T-cells and antibodies and increases in T-cell clonality.

In the trial, margetuximab was given intravenously at an initial dose of 15 mg/kg every 3 weeks over 120 minutes. Trastuzumab was given intravenously at an initial dose of 8 mg/kg over 90 minutes, followed by 6 mg/kg over 30 minutes every 3 weeks thereafter. Patients were treated with margetuximab or trastuzumab in combination with chemotherapy until disease progression, consent withdrawal, or unacceptable toxicity. The median number of 21-day cycles was 6.0 for MARGENZA and 5.0 for trastuzumab.

## III. COMPLETED SUPPORTING TRIALS

Study CP-MGAH22-01 is a Phase 1, open-label, single-arm, multicenter dose-escalation study to define the toxicity profile, maximum tolerated dose (MTD), immunogenicity, pharmacokinetic (PK), and potential anti-tumor activity of margetuximab in patients with refractory HER2+ breast cancers and patients with other carcinomas that overexpress HER2 for whom no standard therapy is available.

Study CP-MGAH22-02 is a single-arm, open-label, Phase 2 study of margetuximab in patients with relapsed or refractory breast cancer whose tumors express HER2 at a 2+ level by immunohistochemistry (IHC) and lack evidence of HER2 gene amplification by fluorescent in situ hybridization (FISH) or express HER2 at a 1+ level by IHC and have a value of >10.5 by HERmark® testing.

Although not designed as an efficacy study, the Phase 1 study demonstrated preliminary antitumor activity of margetuximab when used as a monotherapy in the treatment of patients with HER2+ tumors who had experienced multiple treatment failures with previous therapies. In particular, 4 of 21 patients with HER2+ MBC have experienced a partial response (PR) by RECIST criteria. Three of these 4 patients had received prior trastuzumab and lapatinib. No responses have been observed in the Phase 2 study of patients with MBC who express HER2 at the 2+ level by IHC or who have a HERMark® score of ≥10.5.

SOPHIA (NCT02492711) was a Phase 3 ,multicenter, open-label, comparator-controlled trial of 536 randomized patients with IHC 3+ or ISH-amplified HER2+ advanced breast cancer that have received prior treatment with

other anti-HER2 therapies. Patients were randomized (1:1) to margetuximab plus chemotherapy or trastuzumab plus chemotherapy.

Randomization was stratified by chemotherapy choice, number of lines of therapy in the metastatic setting, and number of metastatic sites. Patients were required to have progressed on or after the most recent line of therapy. Prior radiotherapy, hormonal therapy, and other anti-HER2 therapy were allowed.

Major efficacy endpoints were progression-free survival (PFS) by independent blinded review and overall survival (OS) of margetuximab plus chemotherapy, compared with trastuzumab plus chemotherapy.

Primary PFS analysis of the ITT population showed a 24% reduction in risk of disease progression (HR = 0.76, 95% CI: 0.59, 0.98; p = 0.033) in the margetuximab treated group compared to the trastuzumab treated group. Median PFS was 5.8 months on the margetuximab arm and 4.9 months on the trastuzumab arm.

## IV. HER2 BIOMARKER STATUS TESTING IN THE TRIALS

HER2 positivity was a prerequisite for enrollment to the Phase I, II, and III trials. Subjects should have histologically proven metastatic or locally advanced relapsed/refractory HER2+ (3+ by IHC or ISH-amplified as per American Society of Clinical Oncology [ASCO] and the College of American Pathologists [CAP] Guidelines) breast cancer based on the most recently available tumor biopsy collected from the patient. HER2 status must be documented from a reference laboratory that conforms to standards set for accreditation by CAP or an equivalent accreditation authority. Confirmatory IHC testing is not required for study entry. Tumors may be estrogen receptor (ER)/progesterone receptor (PgR) positive or negative.

Throughout the trials HER2 testing was performed using devices with various technologies: Immunohistochemistry (IHC), In Situ Hybridization (ISH), or HERmark score of ≥ 10.5. Phase II trial used an un-approved test, HERmark, for enrollment. Although the details were not clearly stated in the clinical protocol or the draft drug labelling, it seems like Phase III trial enrolled patients based on IHC with 3+ level or ISH-amplified HER2+. Whether MacroGenics used a FDA-approved device is unclear.

The draft labelling for margetuximab does not refer to use of an FDA-approved device for HER2 testing. It should be noted that FDA has approved several devices for HER2 testing.

## V. CDRH COMMENTS TO CDER

Please note that this evaluation is based on limited information provided in the study protocol and draft drug labelling:

MacroGenics Inc., trials for margetuximab enrolled patients based on HER2 positivity using various tests including IHC, ISH, or HERmark, or based on documented HER2 positivity. However, the clinical protocol CP-MGAH22-04 does not state which devices were used nor their FDA-approval status. It should be noted that HERmark test used in Phase II is not FDA-approved and we cannot comment to the meaning or relevance of HERmark score ≥ 10.5 for HER2+ patient selection. CDRH has no issue with this population of patients being selected for margetuximab treatment without a companion diagnostic device, since in the clinical setting patients were screened for HER2 amplification for previous HER2-directed therapies. However, CDRH would recommend including the following in Section 14.1 of the drug label with the following sentence:
*"HER2 positivity was based on archival or fresh tissue with HER2 positivity defined as HER2 IHC 3+ or ISH positive."*

If there are any questions regarding this review, please contact Banu Saritas-Yildirim, Ph.D. by phone at (301) 796 9613 or by email at Banu.Saritas@fda.hhs.gov

# Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOLOGY AND NEPHROLOGY

Date: April 16, 2020

From: Interdisciplinary Review Team for Cardiac Safety Studies

Through: Christine Garnett, Pharm.D.
Clinical Analyst
Division of Cardiology and Nephrology

To: Tony Park, RPM
OOD/DO1

Subject: QT-IRT Consult to BLA # 761150 (SDN # 001)

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

This memo responds to your consult to us dated 1/21/2020 regarding the proposed language in Section 12.2 of the label. The QT-IRT reviewed the following materials:

- Previous QT-IRT review for IND # 107768 dated 10/22/2018 in DARRTS (link); and
- Sponsor's proposed product label (SN0001 / SDN001; link).

## 1 IRT Responses

We propose not to include QT-related language in section 12.2 of the label. This recommendation is consistent with the labeling practice for the other monoclonal antibodies of which a dedicated QT study has not been conducted.

Please note, that this is a suggestion only and that we defer final labeling decisions to the Division.

| **12.2 Pharmacodynamics** |
|---|
| (b) (4) |

## 2 Internal Comments to the Division

- *The findings are consistent with our prior experience for monoclonal antibodies which have low likelihood of direct interaction with cardiac ion channels.*

## 3 BACKGROUND

### 3.1 Product Information

MacroGenics, Inc. is developing margetuximab for the treatment of patients with metastatic human epidermal growth factor receptor 2 protein (HER2)-positive breast cancer who have received two or more prior anti-HER2 regimens (BLA-761150). Margetuximab (margetuximab-cmkb; MW: ~149 kDa) is a chimeric, Fc-engineered IgG1 kappa monoclonal antibody produced by recombinant DNA technology and is expected to bind to the extracellular domain of HER2.

The product is formulated as a sterile solution for injection (Margenza injection) containing 250 mg margetuximab-cmkb (250 mg/10 mL; single dose vial) for intravenous administration. The proposed therapeutic dose for the present indication is 15 mg/kg to be administered as intravenous infusion (over 2 h for the initial dose, then over a minimum of 30 minutes) every 3 weeks (21-day cycle). It is suggested to evaluate the left ventricular ejection fraction before initiating and regularly during treatment. The peak concentrations of 466 ± 91 µg/mL (half-life ~19 days) are expected at steady-state in patients with metastatic breast cancer receiving 15 mg/kg every 3 weeks (Population PK; Study 04).

### 3.2 Sponsor's position related to the question

The sponsor did not conduct a dedicated QT study for margetuximab. The sponsor claims that intravenous administration of margetuximab in clinical studies was not associated with clinically relevant QT prolongation.

Study 04 compared margetuximab plus chemotherapy with trastuzumab plus chemotherapy effects on ECG parameters. Twelve-lead ECGs (in triplicate, about 1 minute apart) were obtained at Screening and Day 1 of each treatment cycle, before and at end of margetuximab or trastuzumab infusions, and at the End of Treatment visit. There were no requirements for fasting and no restrictions for fluid and food intake during the study. ECGs were to be obtained pre-meal, if possible, and after 5 to 10 minutes of rest following any coincident PK sample collection. Categorical analysis was performed for cardiac interval abnormalities, including heart rate, PR, QRS, and QTcF.

Treatment groups were balanced for PR interval, QRS duration, and QTcF interval. A majority in both groups had PR intervals ≤ 220 msec, QRS ≤ 120 msec, and QTcF ≤ 500 msec. Heart rate values were < 100 bpm for a majority in both groups. Notably, a higher proportion of subjects on margetuximab (36 [13.6%]) had heart rate > 100 bpm than those on trastuzumab (21 [7.9%]). Nine subjects on margetuximab had concomitant IRR and heart rate > 100 bpm. Few AEs related to changes in ECG intervals were observed (CSR Study 04), including no AEs related to QTc intervals.

ECG intervals revealed no marked differences between margetuximab and trastuzumab treatment groups. More subjects on margetuximab had heart rate > 100 bpm than those on trastuzumab, consistent with increased concomitant IRRs on margetuximab. There were no AEs related to QTc interval changes.

### 3.3 Nonclinical Cardiac Safety

Refer to the sponsor's non-clinical overview (m2.4) and previous IRT review for IND # 107768 dated 10/22/2018 in DARRTS.

### 3.4 Clinical Cardiac Safety

Refer to the sponsor's clinical overview (m2.5), summary of clinical safety (m2.7.4), and previous IRT review for IND # 107768 dated 10/22/2018 in DARRTS.

The Sponsor performed ECG monitoring in all margetuximab trials (CSR Study 01 - Section 12.5.2 and CSR Study 02 – Section 12.6).

In randomized Study 04 ECGs were compared by group for incidence of QTc elevations above 500 msec, QTc prolongation over baseline of at least 30 msec, and prolongation of at least 60 msec (Study 04 SAP – Section 5.2.3 and Section 6.4.3). The Sponsor also reviewed cardiac AEs, including arrhythmias, to assess potential QT effects for all trials included in this Summary of Clinical Safety.

None of the cardiotoxicity SMQs revealed potential margetuximab safety issues. The torsade/QTc prolongation SMQ did not identify potential safety issues for margetuximab.

### 3.5 Summary results of prior QTc assessments

Not available.

### 3.6 Relevant details of planned Phase 3 study

Not applicable.

Thank you for requesting our input into the development of this product. We welcome more discussion with you now and in the future. Please feel free to contact us via email at cderdcrpqt@fda.hhs.gov.

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/s/

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04/16/2020 10:42:53 AM

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04/16/2020 12:25:42 PM