

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**761163Orig1s000**

**PRODUCT QUALITY REVIEW(S)**



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

**LABELS AND LABELING ASSESSMENT**

|                                 |                                                                                                                                                                                                                                                                                                                                   |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Date of Assessment:             | July 21, 2020                                                                                                                                                                                                                                                                                                                     |
| Assessor:                       | Jim Barlow, RPh, Labeling Assessor<br>Office of Biotechnology Products (OBP)                                                                                                                                                                                                                                                      |
| Through:                        | Massod Rahimi, PhD, Product Quality Reviewer<br>OBP/Division of Biotechnology Review and Research 4                                                                                                                                                                                                                               |
| Application:                    | BLA 761163                                                                                                                                                                                                                                                                                                                        |
| Applicant:                      | MorphoSys US Inc.                                                                                                                                                                                                                                                                                                                 |
| Submission Dates:               | December 30, 2019                                                                                                                                                                                                                                                                                                                 |
| Product:                        | MONJUVI (tafasitamab-cxix)                                                                                                                                                                                                                                                                                                        |
| Dosage form:                    | For injection                                                                                                                                                                                                                                                                                                                     |
| Strength and Container-Closure: | 200 mg/vial                                                                                                                                                                                                                                                                                                                       |
| Purpose of assessment:          | The Applicant submitted a biologics license application seeking approval of tafasitamab-cxix for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL), including DLBCL arising from low grade lymphoma, and who are not eligible for (b) (4) autologous stem cell transplant (ASCT). |
| <b>Recommendations:</b>         | The prescribing information and patient information labeling (submitted July 21, 2020) and container label and carton labeling (submitted May 29, 2020) are <b>acceptable</b> from an OBP labeling perspective.                                                                                                                   |

| <b>Materials Considered for this Label and Labeling Assessment</b> |                         |
|--------------------------------------------------------------------|-------------------------|
| <b>Materials Assessed</b>                                          | <b>Appendix Section</b> |
| Proposed Labels and Labeling                                       | A                       |
| Evaluation Tables                                                  | B                       |
| Acceptable Labels and Labeling                                     | C                       |

**DISCUSSION**

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

**CONCLUSION**

The prescribing information and patient information labeling (submitted July 21, 2020) and container label and carton labeling (submitted May 29, 2020) are **acceptable** from an OBP labeling perspective (see Appendix C).

**APPENDICES**

**Appendix A: Proposed Labeling**

- Prescribing Information (submitted on December 30, 2019)  
<\\cdsesub1\evsprod\bla761163\0003\m1\us\draft-labeling-text.doc>
- Patient Information (submitted on June 10, 2020)  
<\\cdsesub1\evsprod\bla761163\0036\m1\us\draft-labeling-patient-pkg-insert-monjuvi-text.doc>
- Container Label (submitted on December 30, 2019)



- Carton Labeling (submitted on December 30, 2019)



**Appendix B: Evaluation Tables**

**Evaluation Tables: Label<sup>1,2</sup> and Labeling<sup>3</sup> Standards**

**Container<sup>4</sup> Label Evaluation**

| <b>Proper Name (container label)</b>                                                                                                                                                            | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 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) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (placement of dosage form below the proper name)</i>                                                                                                          | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Manufacturer name, address, and license number (container label)</b>                                               | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 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) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (using the qualifying phrase "Manufactured by:")</i>                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (U.S license number for container bearing a partial label<sup>5</sup>)</i>          | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Comment/Recommendation:</b>                                                                                                                                                                                                                                                                                                                                                                                          |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comment to Applicant: Revise the phrase <span style="background-color: #cccccc; padding: 0 20px;">(b)(4)</span> to read "Manufacturer by" which corresponds with the name and address of the applicant as it appears on FDA form 356h. Please refer to 21 CFR 600.3(t) for the definition of a manufacturer of biologic products. If space permits, consider including the U.S. License number per 21 CFR 610.60(a)(2). |

<sup>1</sup> 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.

<sup>2</sup> 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.

<sup>3</sup> 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.

<sup>4</sup> 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.

<sup>5</sup> 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.

Please note if the only manufacturer information on the label is the licensed manufacturer, then "Manufactured by" phrase as well as the address may be omitted if additional space is needed for other important information per 21 CFR 610.60(c).

May 29, 2020: The applicant included the phrase "Manufactured by" on the container label. However, due to space limitation the U.S. license number remains only on the carton.

FDA Response: The applicant's revision is acceptable.

This label is considered a partial label, so 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 per 21 CFR 610.60 (c).

| <b>Lot number or other lot identification (container label)</b>                                                         | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| 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) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Expiration date (container label)</b>                                                                                                                                                                                                                                                                       | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(4), 21 CFR 201.17                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;7&gt; 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</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Beyond Use Date (Multiple-dose containers) (container label)</b>                                                                | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: USP General Chapters: &lt;659&gt; Packaging and Storage Requirements and &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

This regulation does not apply, because this product is supplied as a single-dose container.

| <b>Product Strength (container label)</b>                                                                                                                                                                                                                                                                                                                       | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4)                                                                                                                                                                                                                                                                                                          | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (expression of strength for injectable drugs)<br/>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: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Multiple-dose containers (container label)</b>                                       | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 201.55<br><i>(recommended individual dose)</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This regulation does not apply, because this product is supplied as a single-dose container.

| <b>Statement: "Rx only" (container label)</b>                                                                                                                                                                                                                                                         | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(6), 21 CFR 201.100(b)(1)                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (prominence of Rx Only statement)<br/>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</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Medication Guide (container label)</b>          | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This product is not required to provide a Medication Guide, so this regulation does not apply.

| <b>No Package for container (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(b)                      | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This product has a carton, so this regulation does not apply.

| <b>No container label (container label)</b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(d)                | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This product contains a container label.

| <b>Ferrule and cap overseal (for vials only)</b>                                                                                                     | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices references: United States Pharmacopeia (USP) General Chapters: &lt;7&gt; Labeling (Ferrules and Cap Overseals)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Confirm there is no text on the ferrule and cap overseal of the vials. Refer to United States Pharmacopeia (USP) General Chapters: <7> Labeling (Ferrules and Cap Overseals).  
May 29, 2020: The applicant confirmed the no text appears on the top (circle) surface of the ferrule and cap overseal of tafasitamab vials.  
In order to unambiguously control tafasitamab identity and ensure traceability of individual bulk drug product (DP) lots prior to labeling and packaging, vials are coded with the bulk DP lot number on the side (skirt) surface of the ferrule.  
FDA Response: The applicant's response is acceptable.

| <b>Visual inspection</b>     | <b>Acceptable</b>                                                                                      |
|------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.60(e) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: 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 per 21 CFR 610.60(e).  
May 29, 2020: The applicant confirmed that once the label is affixed to the vial, an area remains uncovered to allow a visual inspection of the content. The visual area represents a surface of approximately 9.2 mm (0.36 in) per 32 mm (1.26 in) for the width and height, respectively.  
FDA Response: The applicant's response is acceptable.

| <b>Route of administration (container label)</b>                         | <b>Acceptable</b>                       |
|--------------------------------------------------------------------------|-----------------------------------------|
| Regulations: 21 CFR 201.5(f), 21 CFR 201.100(b)(3), 21 CFR 201.100(d)(1) | <input checked="" type="checkbox"/> Yes |

|                                                                                                                                                 |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
|                                                                                                                                                 | <input type="checkbox"/> No<br><input type="checkbox"/> N/A                                            |
| <i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

| <b><i>NDC numbers (container label)</i></b> | <b>Acceptable</b>                                                                                      |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.2, 21 CFR 207.35    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Please include the NDC numbers for this product.  
  
May 29, 2020: The applicant included the NDC 73535–208–01 on the label.  
  
FDA Response: The applicant’s revision is acceptable.

| <b><i>Preparation instructions (container label)</i></b>                                                                                                                                                                                                     | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.5(g)                                                                                                                                                                                                                                  | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This label is considered a partial label, which implies space is limited. The limited space does not allow the applicant to include the preparation instructions, which is acceptable.

| <b><i>Package type term (container label)</i></b>                                                                                                                                                                                                                                                                                            | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018) USP chapter &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b><i>Misleading statements (container label)</i></b> | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.6                              | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

Comment to Applicant: Consider revising the statement (b) (4) to read "Product of Germany". Refer to the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11.

May 29, 2020: The applicant responded that MONJUVI (tafasitamab-cxix) is manufactured in Germany, There is no substantial transformation in another country. The applicant changed the statement to "Product of Germany".

FDA Response: The applicant's revision is acceptable.

|                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Prominence of required label statements (container label)</b>                                                                                                                                                                                                                                                                                                                                      | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.15                                                                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <b>Spanish-language (Drugs) (container label)</b>                                                                                                                                                                                                                                                                                                                                                     | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.16                                                                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <b>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6 (container label)</b>                                                                                                                                                                                                                                                                                                                           | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.20                                                                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <b>Bar code label requirements (container label)</b>                                                                                                                                                                                                                                                                                                                                                  | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.25, 21 CFR 610.67                                                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: Guidance for Industry: Bar Code Label Requirements Questions and Answers, August 2011</i><br><i>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</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (container label)</b>                                                                                                                                                                                                                                                                   | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 610.68, 21 CFR 201.26                                                                                                                                                                                                                                                                                                                                                             | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |
| <b>Net quantity (container label)</b>                                                                                                                                                                                                                                                                                                                                                                 | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.51                                                                                                                                                                                                                                                                                                                                                                             | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No                                 |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <input type="checkbox"/> N/A                                                                           |
| <i>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 Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99) USP General Chapters &lt;1151&gt; Pharmaceutical Dosage Forms (Excess volume in injections).</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                         |                                                                                                        |
|-----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Statement of Dosage (container label)</b>                                            | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Comment/Recommendation:</b><br/> Comment to Applicant: Consider revising the statement, (b) (4) to "Dosage: See Prescribing Information."<br/> May 29, 2020: The applicant revised the statement to read "Dosage: see Prescribing Information."<br/> FDA Response: The applicant's revision is acceptable.</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                                                                                                                                 |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Inactive ingredients (container label)</b>                                                                                                                   | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.100                                                                                                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients and USP General Chapters &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                                                                                                                                                                              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Comment/Recommendation:</b><br/> The label is considered a partial label per 21 CFR 610.60 (c). Thus, the applicant will not be requested to add an inactive ingredient statement.</p> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                                                                                                                                                                |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Storage requirements (container label)</b>                                                                                                                  | <b>Acceptable</b>                                                                                      |
| <i>Recommended labeling practices references: USP General Chapters &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                       |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Comment/Recommendation:</b><br/> Comment to Applicant: Revise and bold the statement from, (b) (4) to <b>"Store refrigerated at 36°F to 46°F (2°C to 8°C)</b> in the carton to protect from</p> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

light.” We recommend this to increase prominence of this important information and minimize the risk of the storage information being overlooked. If space permits, please consider include the statement “Do not shake or freeze”. Please note the Prescribing Information will be revised to present the Fahrenheit temperatures before the Celsius temperatures.

May 29, 2020: The applicant revised and bolded the statement “**Store refrigerated at 36°F to 46°F (2°C to 8°C) in the carton to protect from light**”. The statement “**Do not shake or freeze**” was added below the storage conditions.

FDA Response: The applicant’s revisions are acceptable.

| <b>Dispensing container (container label)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.100(b)(7)              | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

### Package<sup>6</sup> Labeling Evaluation

| <b>Proper name (package labeling)</b>                                | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(a), 21 CFR 201.50(b), 21 CFR 201.10(g)(2) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Manufacturer name, address, and license number (package labeling)</b>               | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(b), 21 CFR 201.1(a), 21 CFR 201.1(i), 21 CFR 201.100(e)     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices (using the qualifying phrase “Manufactured by:”)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

Comment to Applicant: Revise the phrase (b)(4) to read “Manufacturer by” which corresponds with the name and address of the applicant as it appears on FDA form 356h. Please refer to 21 CFR 600.3(t) for the definition of a manufacturer of biologic products. Include the zip code for Boston, MA. Please relocate the U.S. License number to appear directly below the manufacturer information and above the country of origin statement.

<sup>6</sup> 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.

May 29, 2020: The applicant revised the manufacturing information as requested, and indicated the U.S. License number will be updated, upon issuance.

FDA Response: The applicant's revisions are acceptable.

| <b>Lot number or other lot identification (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(c), 21 CFR 201.18                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Expiration date (package labeling)</b>    | <b>Acceptable</b>                                                                                      |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(d), 21 CFR 201.17 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Beyond Use Date (Multiple-dose containers) (package labeling)</b>                                                               | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>Recommended labeling practices: USP General Chapters: &lt;659&gt; Packaging and Storage Requirements and &lt;7&gt; Labeling</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

This regulation does not apply, because this product is supplied as a single-dose container.

| <b>Preservative (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(e)           | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

Comment to Applicant: Revise the phrase (b) (4) to read "No preservative", refer to 21 CFR 610.61(e).

May 29, 2020: The applicant revised the statement to read "No preservative".

FDA Response: The applicant's revision is acceptable.

| <b>Number of containers (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(f)                   | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Product Strength (package labeling)</b>                               | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(g), 21 CFR 201.10(d)(1), 21 CFR 201.100(b)(4) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                                                 |                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>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: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|

| <b>Storage temperature/requirements (package labeling)</b>                                                                                                     | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(h)                                                                                                                                   | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP General Chapters: &lt;7&gt; Labeling, USP General Chapters &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Revise and bold the storage statement to read "**Store refrigerated at 36°F to 46°F (2°C to 8°C)** in the carton to protect from light. Do not shake. Do not freeze." We recommend this to increase prominence of this important information and minimize the risk of the storage information being overlooked. Please note the Prescribing Information will be revised to present the Fahrenheit temperatures before the Celsius temperatures.

May 29, 2020: The applicant revised and bolded the statement to read: "**Store refrigerated at 36°F to 46°F (2°C to 8°C) in the carton to protect from light. Do not shake. Do not freeze.**"

FDA Response: The applicant's revision is acceptable.

| <b>Handling: "Do Not Shake", "Do not Freeze" or equivalent (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(i)                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Multiple dose containers (recommended individual dose) (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.61(j)                                                     | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This regulation does not apply, because this product is supplied as a single-dose container.

| <b>Route of administration (package labeling)</b>                    | <b>Acceptable</b>                       |
|----------------------------------------------------------------------|-----------------------------------------|
| Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1) | <input checked="" type="checkbox"/> Yes |

|                                                                                                                                                 |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
|                                                                                                                                                 | <input type="checkbox"/> No<br><input type="checkbox"/> N/A                                            |
| <i>Recommended labeling practices (route of administration statement to appear after the strength statement on the principal display panel)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                       |                                                                                                        |
|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Known sensitizing substances (package labeling)</b>                                                | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 610.61(l), 21 CFR 801.437 (User labeling for devices that contain natural rubber) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
The product was not made with natural rubber latex or dry natural rubber.

|                                                                                                                                                               |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Inactive ingredients (package labeling)</b>                                                                                                                | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 610.61, 21 CFR 201.100                                                                                                                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;1091&gt; Labeling of Inactive Ingredients, USP General Chapters &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Include an inactive ingredient statement per 21 CFR 201.100(b)(5) as follows: "Each single-dose vial contains 200 mg tafasitamab-cxix, citric acid monohydrate (3.7 mg), polysorbate 20 (1 mg), sodium citrate dihydrate (31.6 mg) and trehalose dihydrate (378.3 mg).  
May 29, 2020: The applicant included the inactive ingredient statement as requested.  
FDA Response: The applicant's revision is acceptable.

|                                                 |                                                                                                        |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Source of the product (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 610.61(p)                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
The source is not a safety factor.

|                                                      |                                                                                                        |
|------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Minimum potency of product (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 610.61(r)                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

Comment to Applicant: Include the statement "No U.S. Standard of Potency" per 21 CFR 610.61(r).

May 29, 2020: The applicant included the statement "No U.S. Standard of Potency".

FDA Response: The applicant's revision is acceptable.

| <b>Rx only (package labeling)</b>                                                                                                                                                                                                                                      | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.61(s), 21 CFR 201.100(b)(1)                                                                                                                                                                                                                    | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Divided manufacturing (package labeling)</b>                              | <b>Acceptable</b>                                                                                      |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.63 (Divided manufacturing responsibility to be shown) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

| <b>Distributor (package labeling)</b>         | <b>Acceptable</b>                                                                                      |
|-----------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**

No distributor is listed on the package labeling.

| <b>Bar code (package labeling)</b>                                                                                                                                                                                                                                                                                       | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 610.67, 21 CFR 201.25                                                                                                                                                                                                                                                                                | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Strategic National Stockpile (exceptions or alternatives to labeling requirements for human drug products) (package labeling)</b> | <b>Acceptable</b>                                           |
|--------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| Regulations: 21 CFR 610.68, 21 CFR 201.26                                                                                            | <input type="checkbox"/> Yes<br><input type="checkbox"/> No |

|  |                                         |
|--|-----------------------------------------|
|  | <input checked="" type="checkbox"/> N/A |
|--|-----------------------------------------|

**Comment/Recommendation:**  
This product is not seeking exceptions to labeling per 21 CFR 610.68.

| <b>NDC numbers (package labeling)</b>    | <b>Acceptable</b>                                                                                      |
|------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.2, 21 CFR 207.35 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Please include the NDC numbers for this product.  
  
May 29, 2020: The applicant included the NDC 73535-208-01.  
  
FDA Response: The applicant's revision is acceptable.

| <b>Preparation instructions (package labeling)</b>                                                                                                                                                                                                                                                                  | <b>Acceptable</b>                                                                                      |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.5(g)                                                                                                                                                                                                                                                                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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 &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Package type term (package labeling)</b>                                                                                                                                                                                                                                                                                                      | <b>Acceptable</b>                                                                                      |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <i>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 &lt;659&gt; Packaging and Storage Requirements</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Misleading statements (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.6                        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Consider revising the statement (b) (4) to read "Product of Germany". Refer to the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11.

May 29, 2020: The applicant responded that MONJUVI (tafasitamab-cxix) is manufactured in Germany; there is no substantial transformation in another country. The applicant changed the statement to "Product of Germany".

FDA Response: The applicant's revision is acceptable.

|                                                                   |                                                                                                        |
|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Prominence of required label statements (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.15                                         | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                    |                                                                                                        |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Spanish-language (Drugs) (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.16                          | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                                                              |                                                                                                        |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>FD&amp;C Yellow No. 5 and/or FD&amp;C Yellow No. 6 (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.20                                                    | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                                                     |                                                                                                        |
|---------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Phenylalanine as a component of aspartame (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.21(c)                                        | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                                                 |                                                                                                        |
|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Sulfites; required warning statements (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.22(b)                                    | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Net quantity (package labeling)</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.51                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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</i><br><i>Allowable Excess Volume and Labeled Vial Fill Size in Injectable Drug and Biological Products Guidance for Industry, June 2015 (line 68, 93-99)</i><br><i>USP General Chapters &lt;1151&gt; Pharmaceutical Dosage Forms (Excess volume in injections).</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                               |                   |
|-----------------------------------------------|-------------------|
| <b>Statement of Dosage (package labeling)</b> | <b>Acceptable</b> |
|-----------------------------------------------|-------------------|

|                                                  |                                                                                                        |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulations: 21 CFR 201.55, 21 CFR 201.100(b)(2) | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
|--------------------------------------------------|--------------------------------------------------------------------------------------------------------|

**Comment/Recommendation:**  
Comment to applicant: Consider revising the statement, (b) (4) (b) (4) to "Dosage: See Prescribing Information."  
May 29, 2020: The applicant revised the statement to read "Dosage and storage: see Prescribing Information."  
FDA Response: The applicant's revision is acceptable.

|                                                |                                                                                                        |
|------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Dispensing container (package labeling)</b> | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.100(b)(7)               | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

|                                                    |                                                                                                        |
|----------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Medication Guide (package labeling)</b>         | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 610.60(a)(7), 21 CFR 208.24(d) | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This product is not required to provide a Medication Guide.

|                                 |                                                                                                        |
|---------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Other (package labeling)</b> | <b>Acceptable</b>                                                                                      |
|                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Consider revising your reconstituted statement to include the final concentration of the reconstituted solution. Consider revising the statement to read: Reconstitute with 5 mL of Sterile Water for Injection, USP, resulting in a concentration of 40 mg/mL. Do not shake.  
May 29, 2020: The applicant revised the reconstituting statement as requested.  
FDA Response: The applicant's revision is acceptable.

**Prescribing Information Evaluation**

**PRESCRIBING INFORMATION**

| <b>Highlights of Prescribing Information</b>                                                                                                                                                                                                                                                                                        |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>PRODUCT TITLE</b>                                                                                                                                                                                                                                                                                                                | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(a)(2)                                                                                                                                                                                                                                                                                                     | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
 Comment to Applicant: Revised the dosage form (b) (4) to read "for injection".  
 June 10, 2020: The applicant revised the dosage form to read "for injection".  
 FDA Response: The applicant's revision is acceptable.

| <b>Highlights of Prescribing Information</b>                                                             |                                                                                                        |
|----------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>DOSAGE AND ADMINISTRATION</b>                                                                         | <b>Acceptable</b>                                                                                      |
| <i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Highlights of Prescribing Information</b>                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>DOSAGE FORMS AND STRENGTHS</b>                                                                                                                                                                                                                                                                                                                                                                                          | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100                                                                                                                                                                                                                                                                                                                                                            | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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 &lt;659&gt; Packaging and Storage Requirements<br/>         USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

| <b>Full Prescribing Information</b> |                   |
|-------------------------------------|-------------------|
| <b>2 DOSAGE AND ADMINISTRATION</b>  | <b>Acceptable</b> |

|                                                                                                                                                                          |                                                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Regulation: 21 CFR 201.57(c)(3)(iv)                                                                                                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions and storage instructions for reconstituted and diluted products</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

Reconstitution subsection:

Dr. Rahimi and Dr. Fringer confirmed the reconstituted drug product can be stored for up to 12 hours at 2°C to 25°C from a stability and microbiology perspective.

Dr. Rahimi confirmed the drug product should be reconstituted with sterile water for injection, and the reconstituted solution should not be shaken or frozen and the reconstituted solution appears colorless to slightly yellow.

Dr. Rahimi confirmed the reconstituted drug product could be exposed to light during the reconstitution process but not for the 12-hour room temperature storage time. Thus, a "Protect from light during storage" was added to the reconstituted subsection.

Comment to Applicant: Your in-use stability data does not support the reconstituted and diluted infusion solutions being exposed to light for extended period of time (e.g. 12 plus hours). Thus, protect from light handling conditions were added to the reconstitution and dilution subsections.

Comment to Applicant: Revised the temperature designation to help inform this reconstituted solution can be stored in either under refrigerated or room temperature conditions.

The sentence was revised to read: "The reconstituted solution in the vial can be stored for a maximum of 12 hours refrigerated at 36°F to 46°F (2°C to 8°C) or room temperature at 68°F to 77°F (20°C to 25°C) before dilution."

June 10, 2020: The applicant accepted FDA's proposed revisions and inserted the word "either" to increase the clarity of the sentence to read in part "... for a maximum of 12 hours either refrigerated ....."

FDA Response: The applicant's revisions are acceptable.

Dilution subsection:

Dr. Rahimi and Dr. Fringer confirmed the reconstituted drug product diluted in an infusion bag with 0.9% sodium chloride injection can be stored for up to 18 hours at 2°C to 8°C and then up to 12 hours at 20°C to 25°C from a stability and microbiology perspective.

Dr. Rahimi confirmed the diluted Monjuvi infusion solution should not be shaken or frozen, and the final concentration between 2 mg/mL to 8 mg/mL was acceptable.

Dr. Rahimi confirmed the diluted drug product could be exposed to light during the dilution process and administration but not for the 18 plus 12-hour proposed storage time for the diluted infusion solution. Thus, a "Protect from light during storage" was added to the dilution subsection.

Comment to Applicant: Revised the wording for clarity and consistency.

The sentence was revised to read: If not used immediately, the diluted MONJUVI infusion solution can be stored refrigerated for up to 18 hours at 36°F to 46°F (2°C to 8°C), and/or at room temperature for up to 12 hours at 68°F to 77°F (20°C to 25°C). The room temperature storage includes time for infusion.

June 10, 2020: The applicant accepted FDA's proposed revisions.

FDA Response: The applicant's revisions are acceptable.

Administration subsection:

Dr. Rahimi confirmed that no incompatibilities were identified between MONJUVI and infusion containers made of polypropylene (PP), polyvinylchloride (PVC), polyethylene (PE), polyethyleneterephthalate (PET), or glass and infusion sets made of polyurethane (PUR) or PVC.

Comment to Applicant: Known compatibility information was added to assist healthcare providers with the preparation and administration of the drug product.

June 10, 2020: The applicant accepted FDA's proposed revisions to include compatibility information.

FDA Response: The applicant's revision is acceptable.

| <b>Full Prescribing Information</b>                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>3 DOSAGE FORMS AND STRENGTHS</b>                                                                                                                                                                                                                                                                                                                                                                                  | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(4)                                                                                                                                                                                                                                                                                                                                                                                      | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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)</i><br><i>USP chapter &lt;659&gt; Packaging and Storage Requirements</i><br><i>USP General Chapters: &lt;7&gt; Labeling</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**

Dr. Rahimi confirmed the identifying characteristics of the lyophilized powder are white to slightly yellowish.

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| Full Prescribing Information                                                                                        |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>11 DESCRIPTION</b>                                                                                               | <b>Acceptable</b>                                                                                      |
| 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)        | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>Recommended labeling practices references: USP General Chapters &lt;1091&gt;, USP General Chapters &lt;7&gt;</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Comment/Recommendation:</b></p> <p>Dr. Rahimi confirmed tafasitamab-xxxx is a humanized CD19 targeting monoclonal antibody, it is produced in Chinese hamster ovary, no antibiotics were used in the production bioreactor, and the molecular weight is 150 kDa.</p> <p>Dr. Rahimi confirmed the finished drug product is sterile, preservative-free, after reconstitution the resulting pH is 6, and the qualitative and quantitative information is acceptable.</p> <p>Comments to the Applicant:<br/>Revised to include the molecular weight.</p> <p>Revised to include the dosage formulation per 21 CFR 201.57(c)(12).</p> <p>Revised to include the resulting concentration after reconstitution commonly included for reconstituted products and the pH per 21 CFR 201.57(c)(12)(ii).</p> <p>Placed the inactive ingredients to appear in alphabetical order per USP General Chapters &lt;1091&gt;: Labeling of inactive ingredients.</p> <p>June 10, 2020: The applicant accepted FDA’s proposed revisions.</p> <p>FDA Response: The applicant’s revisions are acceptable.</p> <p>July 21, 2020: In response to removal of [REDACTED] (b) (4) statement, the applicant accepted the deletion and added the following statement “to modify the Fc-mediated functions of the antibody” in its place to provide description and rationale for the structural change in 2 amino acids.</p> <p>FDA: Applicants revision is acceptable.</p> |
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|                                     |  |
|-------------------------------------|--|
| <b>Full Prescribing Information</b> |  |
|-------------------------------------|--|

|                                                                                                                                                                                                                                                                                                                      |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>15 Cytotoxic Drug reference</b>                                                                                                                                                                                                                                                                                   | <b>Acceptable</b>                                                                                      |
| Regulation: 21 CFR 201.57(c)(17)(iv)<br><br>xxxx is a cytotoxic drug. Follow applicable special handling and disposal procedures.1 1.OSHA Hazardous Drugs. OSHA. [Accessed on June 9, 2017, from <a href="http://www.osha.gov/SLTC/hazardousdrugs/index.html">http://www.osha.gov/SLTC/hazardousdrugs/index.html</a> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:** This antibody is not cytotoxic.

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

**Comment/Recommendation:**  
Dr. Rahimi confirmed the drug product should be refrigerated, protected from light, not shaken or frozen, and no dry natural rubber or natural rubber latex was used with the drug product components.

Comments to the Applicant:  
Added do not shake and freeze handling and storage condition statements due to the lack of supporting data.

Section 16 should provide information concerning the commercial drug product. (b) (4)  
(b) (4)

June 10, 2020: The applicant accepted FDA's proposed revisions.

FDA Response: The applicant's revisions are acceptable.

|                                                                                                                                                            |                                                                                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>Full Prescribing Information</b>                                                                                                                        |                                                                                                        |
| <b>MANUFACTURER INFORMATION</b>                                                                                                                            | <b>Acceptable</b>                                                                                      |
| Regulations: 21 CFR 201.100(e), 21 CFR 201.1                                                                                                               | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>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</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

(Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)

**Comment/Recommendation:**

**Comments to the Applicant:**

Revised the (b) (4) phrase to read "manufacturer by". Please refer to 21 CFR 600.3(t) for the definition of a manufacturer of biologic products. The U.S. License number was also included, because it is commonly located directly below the address in the prescribing information.

The name of a distributor may also be included, refer to 21 CFR 610.64.

Per 21 CFR 201.1(i) and 21 CFR 201.100(e), the name and location of business listed here (street address, city, state, and zip code) is required in labeling. The street address may be omitted if it is shown in a current city directory or telephone directory. Please consider including the street address to the prescribing information.

Consider revising this statement to read "Product of Germany". Refer to the Country of Origin per U.S. Customs Border and Protection regulations 19 CFR 134.11.

June 10, 2020: The applicant accepted FDA's proposed revisions and revised the country of origin statement to read "Product of Germany"

FDA Response: The applicant's revisions are acceptable.

**Patient Information Labeling Evaluation**

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

**Comment/Recommendation:**

Edited the title block to include the suffix and the dosage form

July 21, 2020 Applicants Response: Included suffix as requested by the Agency.

FDA Response: The applicant's revisions are acceptable

| <b>PATIENT INFORMATION LABELING</b>                                                                                                                                                                                                                                                                   |                                                                                                        |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>STORAGE AND HANDLING</b>                                                                                                                                                                                                                                                                           | <b>Acceptable</b>                                                                                      |
| <i>Recommended labeling practices for Patient Labeling or IFU: To ensure that applicable storage and handling requirements are consistent with the information provided in the PI (Reference: Section 2 (Dosage and Administration) and Section 16 (How Supplied Storage and Handling) of the PI)</i> | <input type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input checked="" type="checkbox"/> N/A |

**Comment/Recommendation:**  
This product is prepared and administered in a health care setting. Thus, no storage and handling information is needed.

| <b>PATIENT INFORMATION LABELING</b>                                                                                                                |                                                                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>INGREDIENTS</b>                                                                                                                                 | <b>Acceptable</b>                                                                                      |
| <i>Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters &lt;1091&gt;)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: Placed the inactive ingredients to appear in alphabetical order per USP General Chapters <1091>: Labeling of inactive ingredients, which is also consistent with the Prescribing Information.  
  
July 21, 2020 Applicants Response: Firm revised as requested by the Agency.  
  
FDA Response: These revisions are acceptable.

| <b>PATIENT INFORMATION LABELING</b>                                                                                                                                                                                                         |                                                                                                        |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| <b>MANUFACTURER INFORMATION</b>                                                                                                                                                                                                             | <b>Acceptable</b>                                                                                      |
| 21 CFR 201.1, 19 CFR 134.11                                                                                                                                                                                                                 | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |
| <i>21 CFR 610.61 (add the US license number for consistency with the carton labeling), 21 CFR 610.64 (Name and address of distributor may appear and use a qualifying phrase for consistency with the carton labeling, when applicable)</i> | <input checked="" type="checkbox"/> Yes<br><input type="checkbox"/> No<br><input type="checkbox"/> N/A |

**Comment/Recommendation:**  
Comment to Applicant: The manufacturer information is added per 21 CFR 201.1 and the U.S. license number for consistency with the carton labeling.  
  
July 21, 2020 Applicants Response: Revised as requested by the Agency.  
  
FDA Response: Revisions made by the firm are acceptable

**APPENDIX C. Acceptable Labels and Labeling**

- Prescribing Information (submitted on 7/21/2020)  
<\\cdsesub1\evsprod\bla761163\0046\m1\us\draft-labeling-text-uspi-clean-version.doc>
- Patient Information (submitted on 7/21/2020)  
<\\cdsesub1\evsprod\bla761163\0046\m1\us\draft-labeling-text-ppi-clean-version.doc>
- Container Labels (submitted on May 29, 2020)



- Carton Labeling (submitted on May 29, 2020)





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Barlow

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**BLA STN 761163**

**MONJUVI™ (tafasitamab-cxix)**

**Manufacturer: MorphoSys US Inc.**

Massod Rahimi, Ph.D., Primary Reviewer  
Bazarragchaa Damdinsuren, M.D., Ph.D., Application Technical Lead  
Christopher Downey, Ph.D., Review Chief

Division of Biotechnology Review and Research IV (DBRR IV)  
Office of Biotechnology Products (OBP)  
Office of Pharmaceutical Quality (OPQ)  
Center for Drug Evaluation and Research (CDER)

**OBP CMC Review Data Sheet**

- 1. BLA#:** STN 761163
- 2. REVIEW DATE:** June 5, 2020
- 3. PRIMARY REVIEW TEAM:**  
**Product Quality Team:**  
**OPQ/OBP:** Massod Rahimi (DS/DP), Li Lu (Immunogenicity), Scott Dallas (Labeling), Bazarragchaa Damdinsuren (ATL), Christopher Downey (RC)  
**OPQ/OPMA:** Wayne Seifert (Facility reviewer), Thuy Thanh Nguyen (Facility TL/BC), Maxwell Van Tassell (DS Microbiology reviewer), Jeanne Fringer (DP Microbiology reviewer), Candace Gomez-Broughton (Microbiology TL)  
**OPQ/OPRO:** Anita Brown (RBPM)  
**Clinical:** Alex Schwarsin, Bindu Kanapuru (CDTL), Jennifer Lee (RPM)  
**Pharmacology/Toxicology:** Rama Gudi, Brenda Gehrke (TL)  
**Statistics:** Kunthel By, Yu-Te Wu (TL)  
**Clinical Pharmacology:** Vicky Hsu, Ruby Leong (TL), Bernadette Johnson-Williams (RPM)  
**OOD Safety:** Shanti Marur, Felicia Diggs (SRPM)

- 4. MAJOR GRMP DEADLINES:**  
 Filing Meeting: February 25, 2020  
 Mid-Cycle Meeting: April 15, 2020  
 Wrap-Up Meeting: June 30, 2020  
 Primary Review Due: June 5, 2020  
 CDTL Memo Due: July 15, 2020  
 PDUFA Goal Date: August 30, 2020 (Planned Action Date: July 30, 2020)

**5. COMMUNICATIONS WITH SPONSOR AND OND:**

| Communication/Document: | Date:            |
|-------------------------|------------------|
| Information Request #1  | January 14, 2020 |
| Information Request #2  | February 6, 2020 |
| Information Request #3  | April 1, 2020    |
| Information Request #4  | April 21, 2020   |
| Information Request #5  | April 27, 2020   |
| Information Request #6  | May 5, 2020      |
| Information Request #7  | May 11, 2020     |
| Information Request #8  | May 22, 2020     |

**6. SUBMISSION(S) REVIEWED:**

| Submission:                             | Date Received:    | Review Completed (yes or no) |
|-----------------------------------------|-------------------|------------------------------|
| STN 761163 / SN0003                     | December 30, 2019 | Yes                          |
| STN 761163 / SN0004 (Response to IR #1) | January 21, 2020  | Yes                          |

|                                                              |                   |     |
|--------------------------------------------------------------|-------------------|-----|
| STN 761163 / SN0006                                          | January 27, 2020  | Yes |
| STN 761163 / SN0009 (Response to IR #2)                      | February 11, 2020 | Yes |
| STN 761163 / SN0016 (Response to IR #3)                      | April 9, 2020     | Yes |
| STN 761163 / SN0020 (Response to IR #4)                      | April 30, 2020    | Yes |
| STN 761163 / SN0022 (Response to IR #5)                      | May 11, 2020      | Yes |
| STN 761163 / SN0024 (Response to IR #6)                      | May 14, 2020      | Yes |
| STN 761163 / SN0026 (Response to IR #5)                      | May 18, 2020      | Yes |
| STN 761163 / SN0027 (Response to IR #7)                      | May 20, 2020      | Yes |
| STN 761163 / SN0030 (Response to IR #7)                      | May 28, 2020      | Yes |
| STN 761163 / update is pending (Response to IR #8 via email) | June 5, 2020      | Yes |

**7. DRUG PRODUCT NAME/CODE/TYPE:**

- a. Proprietary Name: MONJUVI
- b. Trade Name: MONJUVI™
- c. Non-Proprietary/USAN: tafasitamab-cxix/tafasitamab
- d. CAS Registry Number: 1422527-84-1
- e. Common Name: MOR00208
- f. INN Name: tafasitamab
- 1. OBP Systematic Name: MAB HUMANIZED (IGG1/2) ANTI P15391 (CD19\_HUMAN) [MOR00208]

**8. PHARMACOLOGICAL CATEGORY:** Recombinant humanized monoclonal IgG1/2κ antibody against human CD19

**9. DOSAGE FORM:** For injection, lyophilized powder in a single-dose vial

**10. STRENGTH/POTENCY:**

- (i) The strength/concentration of the Drug Product: 200 mg (40 mg/mL after reconstitution with 5 mL SWFI)
- (ii) Type of potency assays: FACS-based CD19 binding assay, ADCC cell-killing assay

**11. REFERENCES MASTER FILES:** None

**12. ROUTE OF ADMINISTRATION:** Intravenous infusion

**13. INSPECTIONAL ACTIVITIES:**

In lieu of a pre-license on-site inspection (PLI) for the drug substance manufacturing facility (b) (4), a review of manufacturing site records under Section 704(a)(4) was conducted and found adequate. The proposed drug substance manufacturing facility is found to be acceptable to support the approval of BLA 761163.

The PLI of the drug product manufacturing site, (b) (4) was waived as the fill line is used for the commercial manufacture of license products and the facility has an acceptable compliance history.

**14. CONSULTS REQUESTED BY OBP:** None

**15. QUALITY BY DESIGN ELEMENTS:** None

**16. PRECEDENTS:** None

**17. ADMINISTRATIVE:**

Signature Block

| Name and Title                                                                       | Signature and Date |
|--------------------------------------------------------------------------------------|--------------------|
| Christopher Downey, Ph.D.<br>Review Chief, DBRR IV/OBP/OPQ                           | See attached       |
| Bazarragchaa Damdinsuren, M.D., Ph.D.<br>Application Technical Lead, DBRR IV/OBP/OPQ | See attached       |
| Massod Rahimi, Ph.D.<br>Primary Reviewer, DBRR IV/OBP/OPQ                            | See attached       |

CC Block

| Recipient                               |
|-----------------------------------------|
| Jennifer Lee, Clinical Division BLA RPM |
| OBP/DBRR IV File/BLA STN 761163         |

## Summary of Quality Assessments

- I. Primary Reviewer Summary Recommendation:  
*I recommend approval of this 351(a) BLA application for MONJUVI (tafasitamab-cxix). The manufacturing process is well-controlled and leads to a product that is pure and potent. The product is free from endogenous and adventitious infectious agents and meets the standards recommended by FDA. The conditions used in the manufacturing process were adequately validated, and the product was consistently manufactured from multiple production runs.*
- II. List of Deficiencies to be Communicated:  
*There are no CMC-related deficiencies precluding approval of this BLA.*
- III. List of Post-Marketing Commitments/Requirements:  
*PMC #1: Re-evaluate the drug substance and drug product lot release and stability acceptance criteria for the ADCC assay after release data from 25 drug substance lots and corresponding drug product lots are available, and with consideration of available stability data. The final report should include the corresponding data, the analysis thereof, and any proposed changes to the drug substance and drug product release or stability specifications resulting from the assessment.*
- IV. Review of Common Technical Document- Quality Module 1  
A. Environmental Assessment of Claim of Categorical Exclusion:  
*MorphoSys claims a categorical exclusion per 21 CFR 25.31(b) from the environmental assessment requirements of 21 CFR 25.20. Approval of this BLA will increase the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion. The request for categorical exclusion is acceptable.*
- V. Primary Container Labeling Review:  
*Reviewed by Scott Dallas. A separate review is uploaded in Panorama.*
- VI. Review of Common Technical Document- Quality Module 3.2:  
*The review of Module 3.2 is included in this review memorandum.*
- VII. Review of Immunogenicity Assays- Module 5.3.1.4  
*Reviewed by Li Lu. A separate review is uploaded in Panorama.*

EDR: [BLA 761163](#)

*Unless otherwise noted, figures and tables in the review are adapted or copied directly from the submission. Some of the figures and tables in the submission were updated during the review cycle, the review contains only the updated final versions. Reviewer comments are distinguished by use of italic font.*

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## Description of Drug Substance and Drug Product

### Clinical Information Summary

*Note that the following is based on the information provided in the original submission and may not reflect modifications proposed during the BLA review.*

Diffuse large B-cell lymphoma (DLBCL) is the most common high-grade non-Hodgkin lymphoma. The median age at diagnosis for DLBCL is 64 years and the majority of patients present with advanced disease. The current standard of care for DLBCL is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy with the CD20-targeted monoclonal antibody (mAb) rituximab (R-CHOP). Approximately 20 – 40% of treated patients will ultimately relapse or progress. In patients with progressive or relapsed disease, salvage chemotherapy, followed by high dose chemotherapy (HDC) with autologous stem cell transplantation (ASCT) offer a potential for cure. Although HDC with ASCT improves disease-free survival and overall survival in patients with refractory/relapsed DLBCL (R/R DLBCL), this aggressive approach is not appropriate in patients with comorbidities or older age and is used for a small percentage of patients. Second-line combination therapies with limited success are then used. New therapies that have been approved for DLBCL patients who have progressed after second-line therapy include CD19-targeting chimeric antigen receptor (CAR) T-cell therapies (Yescarta™ and Kymriah™) and the antibody-drug conjugate polatuzumab vedotin (Polivy™) targeting CD79b in combination with bendamustine and rituximab.

Tafasitamab under IND 114856 was granted Fast Track, Orphan Drug, and Breakthrough Therapy designations for R/R DLBCL. Tafasitamab in combination with lenalidomide (25 mg) followed by tafasitamab alone is seeking indication for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for, (b) (4) ASCT. The recommended tafasitamab dose is 12 mg/kg body weight administered as an intravenous infusion over 2 hours.

The clinical study to demonstrate efficacy was the pivotal trial MOR208C203 (L-MIND), a single arm Phase 2 trial of the combination of tafasitamab and lenalidomide followed by tafasitamab monotherapy until progression (conducted in Europe and in the US). The MOR208C206 (RE-MIND) observational, retrospective study with real-world patient-level data was used to assess the effectiveness of lenalidomide monotherapy and compare the activity of single-agent lenalidomide to that of tafasitamab in combination with lenalidomide studied in L-MIND. Additional efficacy data was provided by MOR208C201, a tafasitamab monotherapy clinical study in which the effectiveness of tafasitamab monotherapy in a clinical trial cohort of DLBCL patients was assessed. Additional safety data was provided from on-going clinical studies investigating tafasitamab monotherapy or tafasitamab in combination with other agents in patients with various B-cell hematological malignancies, including DLBCL.

Tafasitamab from CMC2 and CMC4 processes was used in the pivotal L-MIND study and no differences in PK or immunogenicity were detected. The terminal elimination half-life of tafasitamab was determined to be 16.9 days. In all studies, tafasitamab led to a marked reduction in peripheral B-cell counts, and in the L-MIND study, compared to baseline, the combination of tafasitamab and lenalidomide increased the number of peripheral NK cells. *The following table summarizes the results of the tafasitamab efficacy studies (prepared by the reviewer based on data from the submission):*

| Efficacy endpoint | Clinical Study             |         |                  |                           |
|-------------------|----------------------------|---------|------------------|---------------------------|
|                   | L-MIND<br>Tafasitamab/Len. | RE-MIND |                  | MOR208C201<br>Tafasitamab |
|                   |                            | Len.    | Tafasitamab/Len. |                           |
|                   |                            |         |                  |                           |

|                     | (n = 80)                    | (n = 76)                      | (n = 76)                      | (n = 35)                      |
|---------------------|-----------------------------|-------------------------------|-------------------------------|-------------------------------|
| CR or PR (ORR)      | 60%<br>(95% CI: 48.4, 70.8) | 34.2%<br>(95% CI: 23.7, 46.0) | 67.1%<br>(95% CI: 55.4, 77.5) | 25.7%<br>(95% CI: 12.5, 43.3) |
| DoR (median months) | 21.7<br>(95% CI: 21.7, NR)  | 6.6<br>(95% CI: 4.1, 17.2)    | 20.5<br>(95% CI: 12.3, NR)    | 20.1<br>(95% CI: 1.1, NR)     |
| PFS (median months) | 12.1<br>(95% CI: 5.7, NR)   | 4.0<br>(95% CI: 3.1, 7.4)     | 12.1<br>(95% CI: 5.9, NR)     | 2.7<br>(95% CI: 2.1, 13.2)    |
| OS (median months)  | NR<br>(95% CI: 18.3, NR)    | 9.4<br>(95% CI: 5.1, 20.0)    | NR<br>(95% CI: 15.5, NR)      | NA                            |

CR = complete response/remission; PR = partial response/remission; ORR = overall/objective response rate; DoR = duration of response; PFS = progression-free survival; OS = overall survival; Len. = lenalidomide; NR = not reached; NA = not available

While pre-existing anti-drug antibodies (ADAs) were detected (6.9%; 17/245), no treatment-emergent or treatment-boostered ADAs were observed, and the presence of ADAs had no impact on the PK, efficacy, or safety. In the L-MIND study, the most common hematological treatment-emergent adverse events (TEAEs) were neutropenia, anemia, thrombocytopenia, and leukopenia, and the most common non-hematological TEAEs were diarrhea, asthenia, pyrexia, peripheral edema, and decreased appetite. Infusion-related reactions were uncommon (6.2%; 5/81) and low-grade, and no anaphylaxis, hepatic injury, or cytokine release syndrome were reported.

**S. Drug Substance (DS)**



218 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

### 3.2.A.1 Facilities and Equipment

**Reviewer's Comments:** I read the report in this section, however, the review is deferred to the OPMA. The Applicant provided a list of product classes (recombinant proteins, monoclonal antibodies and cytokines) manufactured in the manufacturing facilities, (b) (4). However, a complete list of products manufactured in these facilities was provided in a document obtained from (b) (4) through FD&C 704(a)(4) in lieu of an on-site inspection. The identity assay for tafasitamab (b) (4) (b) (4) is able to distinguish this product from all other products manufactured in the DS and DP facilities.

### 3.2.R Regional Information (USA)

Comparability protocols (b) (4) (b) (4), the protocol for shipping performance qualification, adventitious agent reports, the executed batch records for DS PPQ batch MOR208-A4G-147 and DP PPQ lot MOR208-B4G-143, and method validation reports were provided.

**Reviewer's Comments:** The Applicant did not provide blank/master batch records. However, batch record information can be deduced from the executed batch records. The review of the materials in 3.2.R have been incorporated in the appropriate sections of this review, except the following comparability protocol.

**Comparability protocol for the introduction of new licensed products or investigational products to the (b) (4) manufacturing site:**

Under this protocol, a risk assessment will be performed and a determination that the introduction of the new product will not impact the tafasitamab product quality must be made. Only in situations fulfilling all the following requirements, the product will be introduced and reported in the BLA annual report:

- if specific tests exist to differentiate tafasitamab from all products manufactured at the facility,
- no change to the existing validated (b) (4) procedures (b) (4) (b) (4) is needed,
- no additional containment or product segregation requirements are needed, and
- the product to be introduced does not represent an additional level of risk and belongs to the same class of substances as already approved by the FDA.

If the new product does not fulfill the mentioned requirements, the submission classification will be re-evaluated and additional information will be provided to support the change. This comparability protocol is acceptable.



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Christopher  
Downey

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## Review Memorandum

|                             |                                                                                                                                                                                                                                         |
|-----------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>STN</b>                  | BLA761163                                                                                                                                                                                                                               |
| <b>Subject</b>              | <b>Immunogenicity Assay Review</b>                                                                                                                                                                                                      |
| <b>Submission Date:</b>     | December 30, 2019                                                                                                                                                                                                                       |
| <b>Review/Revision Date</b> | April 30, 2020; June 4, 2020                                                                                                                                                                                                            |
| <b>Primary Assessor</b>     | Li Lu, PhD, Product Quality Reviewer, OPQ/OBP/DBRR IV                                                                                                                                                                                   |
| <b>Secondary Assessor</b>   | Bazarragchaa Damdinsuren, MD, PhD, Team Leader                                                                                                                                                                                          |
| <b>Tertiary Assessor</b>    | Christopher Downey, PhD, Review Chief                                                                                                                                                                                                   |
| <b>Applicant</b>            | MorphoSys US Inc.                                                                                                                                                                                                                       |
| <b>Product</b>              | Tafasitamab (MOR00208, MOR208)                                                                                                                                                                                                          |
| <b>Indications</b>          | In combination with lenalidomide followed by tafasitamab monotherapy for the treatment of adult patients with relapsed or refractory DLBCL, including DLBCL arising from low grade lymphoma, and who are not eligible for, (b) (4) ASCT |
| <b>PDUFA Due Date</b>       | August 30, 2020                                                                                                                                                                                                                         |

### Summary

Tafasitamab is a recombinant humanized anti-CD19 IgG1/IgG2 hybrid mAb produced in CHO cells. The tafasitamab Fc S243D and I336E amino acid changes lead to increased binding to FcγRs (e.g., FcγRIIa and FcγRIIIa) and enhanced effector functions such as antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP).

The Applicant is seeking approval for tafasitamab in combination with lenalidomide (25 mg) followed by tafasitamab alone for the treatment of adult patients with relapsed or refractory (R/R) Diffuse Large B-cell Lymphoma (DLBCL). To evaluate the immunogenicity of tafasitamab, an electrochemiluminescent (ECL), solution-phase, bridging immunoassay that employs Meso Scale Discovery technology was developed and used for detection, confirmation and titration of anti-drug antibodies (ADA) in patient serum samples. The ADA-positive samples from L-MIND study were further characterized in a neutralizing Ab (NAb) bioassay based on the main mode of action of tafasitamab, antibody dependent cellular cytotoxicity (ADCC).

The evaluation of tafasitamab immunogenicity is based on data from the following 5 clinical studies in this BLA:

- 1) Study L-MIND (MOR208C203): Phase 2 in combination with lenalidomide, R/R DLBCL, includes 81 subjects
- 2) Study XmAb5574-01: Phase I, R/R CLL/SLL, 27 subjects
- 3) Study MOR208C201: Phase 2, R/R NHL (DLBCL, follicular lymphoma (FL), indolent non-Hodgkin's lymphoma (iNHL), mantle cell lymphoma (MCL)), 92 subjects
- 4) Study MOR208C202: Phase 2, R/R ALL, 22 subjects
- 5) Study COSMOS (MOR208C205): Phase 2, R/R CLL/SLL, 24 subjects

In the 1st and 2nd generation ADA assays used in the clinical studies XmAb5574-01, MOR208C201,

MOR208C202, COSMOS, an acid dissociation step was employed to reduce the interference of residual serum tafasitamab levels on the detectability of ADA. To further reduce free-drug interference, a solid-phase extraction followed by acid dissociation (SPEAD) sample pre-treatment step was implemented in the 3rd generation ADA assay which is employed in the L-MIND trial. This modification allowed more sensitive detection of ADA at tafasitamab serum concentrations observed at the corresponding ADA sampling time points. The 3rd generation ADA assay is used for the immunogenicity claims of tafasitamab (from the L-MIND study) thus validation of this assay is assessed in this review.

The ADA assay validation evaluated assay sensitivity, specificity, precision, selectivity, stability and drug tolerance. The results support that the ADA assay has acceptable precision for screening, conformation and titration, intermediate precision, repeatability, selectivity, specificity, and matrix stability. The validation results support that the assay is sufficiently sensitive in the presence of tafasitamab (based on serum trough of <250 µg/mL during weekly dosing) to detect 100 ng/mL of 6B11-E5 (protein G purified mouse monoclonal anti-tafasitamab antibody) but has some limitations (the drug level should be ≤ 120 µg/mL) to detect the same level of Cynomolgus anti-tafasitamab antibody. Based on these results, the drug tolerance of the 3rd generation ADA assay is considered adequate to detect ADA in clinical trial samples from L-MIND.

The NAb assay validation evaluated the assay precision, selectivity, specificity, stability, prozone and drug interference. The detected drug tolerance of the NAb assay is low compared to the expected tafasitamab concentration in patient samples and is not capable to detect NAb in the patient sample. However, no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed based on the ADA results, and the pre-existing ADA titer detected in the patient sera was low with sample dilutions of 1:4 and 1:32. In addition, based on the clinical immunogenicity results, no clinically meaningful differences in the PKs, efficacy, or safety profile were observed for tafasitamab. Thus, the NAb assay without a sufficient drug tolerance appears of low risk in this circumstance. We defer the regulatory decision to the BLA review team to consider the totality of the evidence.

Overall, the 3rd generation ADA assay is adequate to use and evaluate the ADAs to tafasitamab for the proposed indication.

## Review

**1. Anti-drug antibody (ADA) assay for screening, confirmatory, specificity and titer** [from Integrated Summary of Immunogenicity (MOR208L037), Immunoassay Validation Report (MOR208L024), Addendum I and Addendum II provided in Module 5.3.1.4]

### 1.1 Overview of ADA method development and validation

Overall, three generations of ADA assays were applied for clinical sample analyses:

- First generation ADA assay: Homogenous bridging ligand-binding assay based on Electrochemiluminescence (ECL) using biotinylated and Sulfo-tagged tafasitamab (screening, confirmatory, and titer tiers); specificity tier in this assay was validated by using MOR00208-IgG1 and MOR00208-IgG1/2 to discriminate potential ADA reactivity towards constant vs variable regions.
- Second generation ADA assay: The assay format identical to first generation assay and was validated for NHL/CLL/DLBCL subjects and tafasitamab CMC2/CMC3 reference material.
- Third generation ADA assay: Solid-Phase Extraction Followed by Acid Dissociation (SPEAD) (Smith et al. 2007) followed by a homogenous bridging ligand-binding assay in order to increase drug tolerance to residual tafasitamab serum concentrations; The assay was validated for

screening, confirmatory, titer, and specificity tiers using tafasitamab CMC2/CMC3/CMC4 reference materials.

## 1.2 Summary of ADA method development - 3<sup>rd</sup> generation ADA assay

A hierarchical test scheme was employed for ADA analysis (Figure 3 in the submission); Samples were first assessed in the screening assay based on a 5% false positive rate (FPR). Samples that screened positive were subsequently tested in the confirmatory assay (based on a 1% FPR for the 3<sup>rd</sup> generation assay). Samples that tested positive in the confirmatory assay were reported as ADA-positive, and titer and specificity (i.e., using MOR00208- hIgG1 and MOR00208-hIgG1/2 in order to discriminate potential ADA reactivity towards constant vs variable regions) were assessed. In L-MIND study, ADA-positive samples were also subjected to neutralizing Ab (NAb) analysis.

*Assessor's comments: The multi-tiered testing approach is utilized in the immunogenicity assessment, which is acceptable.*

*As described above, three generations of ADA assays have been developed and the 3<sup>rd</sup> generation of ADA assay has been used in the pivotal clinical study (L-MIND), which is a phase 2 clinical trial in combination with lenalidomide for R/R DLBCL patients. In this study, 501 ADA samples from 81 subjects were assessed. The draft USPI describes that no treatment-emergent or treatment-boosted anti-tafasitamab antibodies were observed. No clinically meaningful differences in the PKs, efficacy, or safety profile of tafasitamab were observed in 2.5% of 81 patients with relapsed or refractory DLBCL with pre-existing anti-tafasitamab antibodies in L-MIND.*

In order to estimate the degree of potential anti-MOR00208 antibodies towards the IgG1/IgG2 hybrid heavy chain region as well as towards the modified single amino acids within the CH2 domain, confirmed positive samples were additionally analyzed in two different specificity confirmation assays. In these assays the samples were pre-incubated independently with the following two control antibodies and they used for the testing:

- MOR00208-IgG1, an antibody comprised of the identical Fab-region as MOR00208 and a human IgG1 Fc-region
- MOR00208-IgG1/2, an antibody comprised of the identical Fab-region and the identical IgG1/IgG2 hybrid heavy chain region as for MOR00208 excluding the single amino acid mutations S239D, I332E and G327A.

## 1.3 ADA assay method description - 3<sup>rd</sup> generation ADA assay

The ADA assay format is an ECL-based bridging assay utilizing Mesoscale Discovery platform (MSD<sup>®</sup>), which employs a ruthenium metal chelate (Sulfo-Tag) as the ECL label. The samples are pre-treated to remove drug product (DP) potentially present in study samples using a SPEAD method (Smith et al. 2007). Briefly, the samples are diluted with 300mM acetic acid to disrupt pre-formed drug-ADA complex, and then incubated with biotinylated tafasitamab and then added to a Streptavidin-coated high binding plate containing 600 mM Tris neutralization buffer. The high binding plate is washed to remove the DP presented in the sample. The isolated ADAs are then eluted off the plate with 300 mM acetic acid and added directly to a polypropylene transfer plate containing Tris pH 10.0 for neutralization and biotinylated and sulfo-tagged tafasitamab for the homogenous bridging assay. The bridging complex is captured on a streptavidin coated microplate and signal measured by the MSD Quickplex instrument. The Applicant states that the signal intensity is proportional to the amount of anti-tafasitamab antibodies present in the samples. Samples that

screened positive were subsequently tested in the confirmatory assay. Samples that tested positive in the confirmatory assay were reported as ADA-positive, and titer and specificity were assessed. In L-MIND study, the ADA-positive samples were also subjected to NAb analysis. Additional information regarding the reagents and concentrations in the ADA method is provided in the following table.

**Table 1: Method information of the ADA assay**

|                                        |                                                                                    |
|----------------------------------------|------------------------------------------------------------------------------------|
| Positive Control (PC)                  | Protein G Purified Antibody Cell Line 6B11-E5                                      |
| Negative Control (NC)                  | Pooled Human Serum                                                                 |
| Confirmatory Molecule                  | MOR00208-CMC3                                                                      |
| Specificity Molecule #1                | MOR00208hIgG1                                                                      |
| Specificity Molecule #2                | MOR00208hIgG1/2                                                                    |
| Matrix                                 | Pooled Human Serum                                                                 |
| MRD                                    | SPEAD-treated samples are tested undiluted                                         |
| High (HPC) Concentration               | 1,000 ng/mL                                                                        |
| Mid PC (MPC) Concentration             | 100 ng/mL                                                                          |
| Low PC (LPC) Concentration             | 2.00 ng/mL                                                                         |
| Confirmatory Buffer Concentration      | 100 µg/mL                                                                          |
| Specificity #1 Buffer Concentration    | 100 µg/mL                                                                          |
| Specificity #2 Buffer Concentration    | 100 µg/mL                                                                          |
| Method Type                            | ECL assay employing solid-phase extraction followed by acid dissociation (SPEAD)   |
| Method Instrument                      | MSD QuickPlex SQ 120                                                               |
| Analytical System Software and Version | Gen5 Secure Software v. 1.08 or higher<br>JMP Statistical Software, Version 11.1.1 |

The acceptance criteria for ADA assay runs are summarized in the assessor-generated table below.

**Assessor’s Table 1 System Suitability and Sample Suitability Criteria for ADA Screening, Confirmatory and Specificity Assays**

| Controls                                | Acceptance Criteria                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Comment               |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
|-----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------|-------|-----------------------|--------|-----------------------|--------|----------------|-------|-----------------------|-------|-----------------------|--------|-----------------------|--------|----------------|-------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Screening, confirmatory and titer assay |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| Positive Quality Controls               | <p>1) Plate acceptance criteria for sample assessment using new conjugates (from MOR208L024 Addendum I): (at least 4 of the 6 replicates of each PC must meet the acceptable limit)</p> <table border="1"> <tr> <td>HPC normalized signal</td> <td>≥ 309</td> </tr> <tr> <td>MPC normalized signal</td> <td>≥ 33.0</td> </tr> <tr> <td>LPC normalized signal</td> <td>≥ 1.46</td> </tr> <tr> <td>PNC raw signal</td> <td>≤ 231</td> </tr> </table> <p>Note: the original acceptance criteria:</p> <table border="1"> <tr> <td>HPC normalized signal</td> <td>≥ 215</td> </tr> <tr> <td>MPC normalized signal</td> <td>≥ 26.2</td> </tr> <tr> <td>LPC normalized signal</td> <td>≥ 1.43</td> </tr> <tr> <td>PNC raw signal</td> <td>≤ 148</td> </tr> </table> <p>2) At least 4 out of 6 ratios (and at least 1 of 2 at each level) for the 2 sets each of HPC, MPC, and LPC normalized to mean PNC must be positive with CV ≤20.0%.</p> <p>3) If there is a set of PNC duplicates that show %CV &gt;20.0% and any PNC is above the screening cut point, the plate should be rejected.</p> | HPC normalized signal | ≥ 309 | MPC normalized signal | ≥ 33.0 | LPC normalized signal | ≥ 1.46 | PNC raw signal | ≤ 231 | HPC normalized signal | ≥ 215 | MPC normalized signal | ≥ 26.2 | LPC normalized signal | ≥ 1.43 | PNC raw signal | ≤ 148 | <p><i>The establishment of the lower limit for HPC, MPC and LPC, and the upper limit for PNC are supported by the data provided in Table 2 in this report and Table 2 in Addendum I.</i></p> |
| HPC normalized signal                   | ≥ 309                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| MPC normalized signal                   | ≥ 33.0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| LPC normalized signal                   | ≥ 1.46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| PNC raw signal                          | ≤ 231                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| HPC normalized signal                   | ≥ 215                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| MPC normalized signal                   | ≥ 26.2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| LPC normalized signal                   | ≥ 1.43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| PNC raw signal                          | ≤ 148                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| Screening Assay                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                       |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |
| Sample acceptance                       | The %CV of sample duplicates must be ≤20.0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <i>Acceptable.</i>    |       |                       |        |                       |        |                |       |                       |       |                       |        |                       |        |                |       |                                                                                                                                                                                              |

|                       |                                                                                                                                                   |                   |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| Confirmatory Assay    |                                                                                                                                                   |                   |
| Confirmatory Controls | The HPC and LPC must have percent inhibition greater than or equal to the confirmatory assay cut point.                                           | <i>Acceptable</i> |
| Sample acceptance     | The %CV of sample duplicates must be ≤20.0%                                                                                                       | <i>Acceptable</i> |
| Specificity Assay     |                                                                                                                                                   |                   |
| HPC and LPC           | The HPC and LPC (as specificity controls) must have percent signal inhibition greater than or equal to the respective specificity assay cut point | <i>Acceptable</i> |

*LPC - low positive control (PC), MPC - medium PC, HPC - high PC, PNS - pooled negative control*

*Note: details for the controls and qualifications of the cut points are discussed in the Validation section below.*

Protein G-purified mouse monoclonal idiotypic anti-tafasitamab antibody, 6B11-E5, was used as primary PC. This antibody was generated by immunization of mice with XmAb5574/tafasitamab and subsequent expression from a cloned hybridoma and purification via Protein G.

Cynomolgus monkey anti-tafasitamab antibodies were used as a secondary PC (i.e., for determination of sensitivity in the screening and confirmatory setup, as well as for determination of drug tolerance). The polyclonal PC was affinity-purified using a column coupled with tafasitamab from serum of cynomolgus monkey immunized with tafasitamab.

The LPC for the both PCs was selected at 2 ng/mL during method development to be very close to background of the assay (approximately 2-fold above background). MPC (100 ng/mL) and HPC (1000 ng/mL) were selected to provide a medium and high response based on the dose-response curve. The PNC was made from pooling of normal human serum (NHS).

*Assessor's comment: Overall the assay controls appear acceptable.*

#### 1.4 Validated performance characteristics - 3<sup>rd</sup> generation ADA assay

Validation study for 3<sup>rd</sup> generation ADA assay was performed at (b) (4) and provided in the Validation Report MOR208L024, Addendum I and Addendum II.

Note that the screening, confirmatory and end-point titer (EPT) cut points were re-established using baseline samples from L-MIND study as new batches of labelled tafasitamab reagents were used for the sample assessment in L-MIND study since the initial method validation (report MOR208L024). The change in labelled tafasitamab reagents also led to revision of the plate acceptance criteria (limits for the PCs and for PNC) in Addendum I.

*The validation results are summarized in the following table 2 and the parameters are elucidated individually below.*

**Assessor's Table 2. ADA Method Validation Summary.**

| Validation Parameter                 | Results                                                |
|--------------------------------------|--------------------------------------------------------|
| Screening assay cut point factor (X) | NHS: 1.06                                              |
|                                      | DLBCL patient serum: 1.05                              |
| EPT assay cut point (XEPT)           | NHS: 1.14                                              |
|                                      | DLBCL patient serum: 1.12                              |
|                                      | NHS: 17.3% (MOR00208hIgG1) and 16.6% (MOR00208hIgG1/2) |

|                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|----------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Confirmatory assay cut point (% signal inhibition)                                     | DLBCL serum: 19.7% (MOR00208hIgG1) and 20.9% (MOR00208hIgG1/2)                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Assay Sensitivity                                                                      | For 6B11-E5 (Protein G purified mouse monoclonal anti-idiotypic MOR00208 antibody) PC:<br>- Screening assay (95% CI): 0.398 ng/mL PC<br>- Confirmatory assay (95% CI): 0.606 ng/mL PC<br><br>For Cynomolgus anti-MOR00208 (polyclonal purified) PC:<br>- Screening assay (95% CI): 1.29 ng/mL PC<br>- Confirmatory assay (95% CI): 1.83 ng/mL PC                                                                                                                                                        |
| Recovery (assessed in screening and confirmatory assay using individual lots of serum) | NHS:<br>At 1,000 ng/mL PC, 10/10 lots met the criteria.<br>At 2.00 ng/mL PC, 10/10 lots met the criteria.<br>At 0.00 ng/mL PC, 8/10 lots met the criteria.<br>DLBCL human serum:<br>At 1,000 ng/mL PC, 10/10 lots met the criteria.<br>At 2.00 ng/mL PC, 10/10 lots met the criteria.<br>At 0.00 ng/mL PC, 7/10 lots met the criteria.<br>Hemolysis and Lipemia Assessment:<br>No effect was observed with 2.5% or 5.00% hemolysate or 2% (v/v) Intralipid® 20% Emulsion when spiked at the HPC and LPC |
| Free Drug Interference (concentration required to cause a false negative)              | Concentration of MOR00208 tolerated (i.e. still resulting in a screening-positive signal):<br>At 1,000 ng/mL 6B11-E5: > 1,000 µg/mL MOR00208<br>At 100 ng/mL 6B11-E5: > 1,000 µg/mL MOR00208<br>At 2.00 ng/mL 6B11-E5: at 57.7 µg/mL MOR00208                                                                                                                                                                                                                                                           |
| Prozone                                                                                | No hook effect was observed by spiking the PC at up to 200,000 ng/mL concentration                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Confirmatory Testing with MOR00208-CMC2 and MOR00208-CMC4 at 100 µg/mL                 | All (3/3) samples were above the confirmatory cut point of 12.0% at the HPC and LPC levels. All (3/3) samples were below the confirmatory cut point of 12.0% at the PNC level.                                                                                                                                                                                                                                                                                                                          |
| Confirmatory Testing with Human Gamma Globulin                                         | At least 2/3 samples spiked with Human gamma globulin instead of MOR00208 were below the confirmatory cut point of 12.0% at the HPC, LPC, and PNC levels.                                                                                                                                                                                                                                                                                                                                               |
| Interference Testing with Concomitant Drugs                                            | No interference observed with 10.0 µg/mL of Bendamustine Hydrochloride Hydrate or 1.00 µg/mL of Lenalidomide, since 3/3 samples at HPC and LPC levels were assessed positive and 3/3 PNC samples were assessed negative in screening and confirmatory setup.                                                                                                                                                                                                                                            |

### 1. Precision/PC acceptance criteria

For validation, the LPC, MPC and HPCs (2 PC samples in duplicate, i.e., 4 wells, per PC level in 100% serum) and the PNC (4 samples in duplicate) were analyzed in 84 analysis runs performed over 14 days by 2 analysts. Plate acceptance criteria and precision was evaluated in all plates (see the Assessor’s Table 3). Precision of the method, defined by the percent coefficient of variation (%CV = [(standard deviation / mean) x 100]), was determined from the normalized results of the PCs and from the raw signal of the PNC.

The pre-defined criteria for validation was set as the inter-assay precision should not exceed (b) (4)%, with (b) (4)% as the normal target, thus the PC and PNC sample results met the acceptance criteria.

The overall intra-assay precision of the raw signals for the PC samples and PNC was respectively ≤8.01% and 4.90% (Table 4 of the report). These results met the validation criteria of the intra-assay

precision ( $\leq$  (b) (4) %).

The mean normalized signals of the PCs and the raw signal for the PNC were used to determine the acceptance criteria for runs (*the plate acceptance criteria are summarized in Assessor's Table 1 above and Table 2 of the report*). Note that due to the use of the new batches of conjugates with the biotinylated tafasitamab and the sulfo-tagged tafasitamab, the new positive and negative control acceptance criteria were re-established (in report MOR208L024 Addendum I). With the new conjugates, the lower limits (expressed as ratios to PNC) for the PC samples were calculated (*Reviewer's Table 1 above and Addendum I, Table 2*). Table 3 below summarizes the validation results for assay precision.

**Assessor's Table 3 Precision Validation Results**

| Precision (Range in biological matrix, %CV, n = 84 runs)            | HPC        | MPC        | LPC        | PNC        |
|---------------------------------------------------------------------|------------|------------|------------|------------|
| Intra-assay Precision in biological matrix (%CV) (over n = 84 runs) | 0.471-4.44 | 0.430-2.80 | 0.507-4.50 | 0.609-3.72 |
| Inter-assay Precision (over n = 84 runs)                            | 23.8       | 20.6       | 11.8       | 11.3       |
| Intra-assay Precision (over n = 24 runs with new conjugates)*       | 1.99       | 1.89       | 2.39       | 3.11       |
| Inter-assay Precision (over n = 24 runs with new conjugates)*       | 14.4       | 13.9       | 9.74       | 12.3       |

\* - Data from Amendment 1 to report MOR208L024 generated using new lots of labelled tafasitamab reagents

*Assessor's comments: The intra- and inter-assay precisions for the ADA assays with new conjugate batches are within the recommended limit of %CV of  $\leq 20\%$  in the FDA Guidance for Industry: Immunogenicity Testing of Therapeutic Proteins - Developing and Validating Assays for Anti-Drug Antibody Detection, thus these are acceptable.*

*Note that the inter-assay precision for HPC and MPC with the prior conjugate batches were higher than the recommended limit. The applicant stated that the inter-assay precision is targeting (b) (4) %, and it will be considered acceptable up to a limit of (b) (4) %. These values show that the assay results might have slightly higher variability between different runs.*

**2. Normal Screening and End Point Titer Cut Points**

Fifty individual lots of NHS (from healthy volunteers) were evaluated for screening and end point titer (EPT) cut point analysis. EPT cut point is used in the determination of the ADA titer which are confirmed positive in the confirmatory assay. The lots were analyzed in 2 replicates on 6 separate days by 2 analysts for a total of 6 assays. The mean signal and normalized results from these analyses are presented in Table 2 of Appendix 2. Briefly, the 600 data points were tested for normality and the preponderance of data indicated that parametric analysis was appropriate and a parametric cut point factors were calculated.

For NHS, a screening cut point factor (X) at the 95% percentile and an EPT cut point factor (XEPT) at the 99.9% percentile were calculated using the following formulas:

$$\text{Screening Cut Point Factor (X)} = \text{Mean Normalized Response} + (1.645 * \text{SD Normalized Response}) = 1.06$$

$$\text{EPT Cut Point Factor (XEPT)} = \text{Mean Normalized Response} + (3.09 * \text{SD Normalized Response}) = 1.14$$

Thus, for all screening and titer ADA assays, the cut points will be calculated on a run-by-run basis using the following formulas:

$$\text{Screening cut point} = 1.06 * \text{PNC}_{\text{Plate}}$$

$$\text{EPT cut point} = 1.14 * \text{PNC}_{\text{Plate}}$$

*Assessor's comment: The applicant's approach for the determination of the screening and EPT cut points are acceptable.*

3. Normal Confirmatory and Specificity Cut Points with MOR00208, MOR00208 hIgG1, and MOR00208 hIgG1/2

- Confirmatory Cut Point:

For this assessment, each sample was spiked with buffer or excess drug (100 µg/mL MOR00208 from CMC3 production process) and analyzed in duplicate in 6 independent analyses performed by 2 analysts. The confirmatory assay cut point was calculated from the ratio values of individual serum samples spiked with MOR00208 to the corresponding sample with buffer (see the equation below) from the 50 individual serum lots.

$$\% \text{Signal inhibition} = [1 - (\text{Mean signal spiked with drug} / \text{Mean signal spiked with buffer})] \times 100$$

The confirmatory cut point was calculated to be 12.0% inhibition for NHS using the box-plot approach to remove the outlier (Table 4 in the report) and was set to provide a false-positive rate of 1%.

- Specificity Cut Point with MOR00208 hIgG1 and MOR00208 hIgG1/2:

To discriminate potential ADA reactivity towards tafasitamab constant or variable regions the samples were tested for specificity using MOR00208 hIgG1 and MOR00208 hIgG1/2 antibodies. To determine the cut points, all individual serum lots were analyzed with and without a spike of 100 µg/mL of MOR00208 hIgG1 and MOR00208 hIgG1/2 antibodies in duplicates on 4 separate days by 2 analysts for a total of 3 assays and the results calculated for each antibody using the same equation shown above (the results are in Tables 6 and 8 of Appendix 2). The MOR00208 hIgG1 and MOR00208 hIgG1/2 specificity assay cut points were determined to be 17.3% and 16.6% respectively.

*Assessor's comment: The applicant's approaches for the determination of the confirmatory assay cut point and of the specificity cut points with MOR00208 hIgG1 and MOR00208 hIgG1/2 antibodies are acceptable.*

4. DLBCL Screening and End Point Titer Cut Points

Fifty individual lots of serum from DLBCL patients were evaluated for screening and EPT cut point analysis. Each sample was analyzed in duplicate in 6 independent analyses performed by 2 analysts. The mean signal results and normalized results from these analyses are presented in Table 10 of Appendix 2. The same assessments as presented in section 2. Normal Screening and End Point Titer Cut Points were performed. Parametric assessment of the screening cut point data resulted in a screening cut point factor of 1.05 and an EPT cut point factor of 1.12 for DLBCL serum. Thus, for all screening and titer ADA assays, the cut points will be calculated on a run-by-run basis using the following formulas:

$$\text{Screening cut point} = 1.05 * \text{PNC}_{\text{Plate}}$$

$$\text{EPT cut point} = 1.12 * \text{PNC}_{\text{Plate}}$$

*Assessor's comment: The applicant's approach for the determination of the screening and titer cut points for DLBCL patient serum analyses is acceptable.*

5. DLBCL Confirmatory and Specificity Cut Points with MOR00208, MOR00208 hIgG1, and MOR00208 hIgG1/2

The same procedure used for determining cut points with NHS was used to determine the confirmatory

and specificity cut points with DLBCL patient serum. Each sample was spiked with buffer or excess drug (100 µg/mL MOR00208, or MOR00208 hIgG1, or MOR00208 hIgG1/2) and analyzed in duplicate in 6 independent analyses performed by 2 analysts.

The cut points for DLBCL patient serum were calculated to be (all targeting false-positive rate of 1%):

- For the confirmatory assay as 9.98% inhibition, (Table 12 of the report) ,
- For the MOR00208 hIgG1 specificity as 19.7% (Appendix 2: Table 14),
- For the MOR00208 hIgG1/2 specificity as 20.9% (Appendix 2: Table 16).

*Assessor’s comment: The applicant’s approach for the determination of the confirmatory assay cut point, the specificity cut points with MOR00208 hIgG1 and MOR00208 hIgG1/2 antibodies for DLBCL patient serum are acceptable.*

**6. Free Drug Interference**

Free drug interference in NHS was evaluated by measuring the impact of increased concentration of MOR00208 (0, 25, 50, 57.7, 120, 250, 500, and 1000 µg/mL) on the detection of anti-MOR00208 PCs (6B11-E5 or cynomolgus anti-MOR00208, 1000, 100, and 2.00 ng/mL in 100% serum). The drug-spiked PC samples were incubated at room temperature for at least one hour and then assayed in duplicates. The mean response, SD and %CV for each sample were reported. The concentration of drug that reduces the signal below the screening cut point (i.e., convert a positive sample to a negative sample) was determined, and the results are provided in this report, Tables 7 and 3 in Addendum II. A summary of the results of the free drug interference using 6B11-E5 and polyclonal PC antibody is copied below.

|                                                                              |                                                                                                                                                                                                                                                    |
|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| FREE DRUG INTERFERENCE<br>(concentration required to cause a false negative) | Concentration of MOR00208-CMC3 tolerated (i.e. still resulting in a screening-positive signal):<br>At 1,000 ng/mL 6B11-E5: > 1,000 µg/mL MOR00208<br>At 100 ng/mL 6B11-E5: > 1,000 µg/mL MOR00208<br>At 2.00 ng/mL 6B11-E5: at 57.7 µg/mL MOR00208 |
|------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

|                        |                                                                                                                                                                                                                                                                                                             |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Free Drug Interference | Concentration of MOR00208-CMC3 tolerated (i.e. still resulting in a screening-positive signal):<br>At 1,000 ng/mL Cynomolgus anti-MOR00208: 1,000 µg/mL MOR00208-CMC3<br>At 100 ng/mL Cynomolgus anti-MOR00208: 120 µg/mL MOR00208-CMC3<br>At 5.00 ng/mL Cynomolgus anti-MOR00208: 12.5 µg/mL MOR00208-CMC3 |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

*Assessor’s comments: These results with the mouse PC 6B11-E5 suggest that for the ADA levels more than 100 ng/mL (i.e., MPC), the screening assay can still result in a positive signal in presence of at least 1000 µg/mL tafasitamab, for the ADA as low as 2 ng/mL (i.e., LPC), the drug concentration up to 57.7 µg/mL can still result in a positive signal. In the case of cynomolgus PC antibody, for the ADA level more than 100 ng/mL, the screening assay can still result in a positive signal in the presence of at least 120 µg/mL tafasitamab. Based on serum Ctrough of <250 µg/mL during weekly dosing of tafasitamab, the screening assay is sufficiently sensitive with mouse mAb 6B11-E5 (per the FDA guidance).*

**7. Sensitivity**

- Screening Assay Sensitivity Using Monoclonal Positive Control 6B11-E5

The experiment was performed on 9 plates by analyzing PC titer/signal curves prepared in pooled NHS. Screening assay sensitivity was calculated using a linear regression based on the concentration and signal responses directly above and below the plate specific screening cut point. The results were evaluated using the screening cut point factor of 1.06. The mean screening assay sensitivity was determined to be 0.206 ng/mL with 95% confidence to be 0.398 ng/mL, and an LPC concentration at the 99% confidence level was determined to be 0.504 ng/mL (Table 8 in the report).

- Confirmatory Assay Sensitivity Using Monoclonal Positive Control 6B11-E5

The experiment was performed on 9 plates by analyzing PC titer curves prepared in pooled NHS assayed with and without a spike of 100 µg/mL of MOR00208. Confirmatory assay sensitivity was calculated using a linear regression based on the PC concentration and percent inhibition directly above and below the confirmatory cut point. Each curve was analyzed in duplicate and the results were evaluated using the confirmatory cut point of 12.0%. The mean confirmatory assay sensitivity was determined to be 0.277 ng/mL with the 95% confidence to be 0.606 ng/mL, and an LPC concentration at the 99% confidence level was determined to be 0.790 ng/mL (Table 8 in the report).

- Screening and Confirmatory Assay Sensitivity Using Cynomolgus anti-MOR00208 PC

The sensitivity was also determined using the purified, polyclonal cynomolgus anti-MOR00208 antibodies.

The screening assay sensitivity was performed on 3 plates (run 92, run 99, and run 100) by analyzing cynomolgus anti-MOR00208 signal curves prepared in pooled NHS. The results were evaluated using the screening cut point factor of 1.06 to determine the concentration of antibody that produced an assay response equal to the plate specific cut point. The mean screening assay sensitivity was determined to be 0.979 ng/mL with the 95% confidence to be 1.29 ng/mL (Table 22 of the report).

The confirmatory assay sensitivity was performed on 3 plates by analyzing cynomolgus anti-MOR00208 titer curves prepared in pooled NHS and analyzed with and without a spike of 100 µg/mL of MOR00208. Each curve was analyzed in duplicate and the results were evaluated using the confirmatory cut point of 12.0%. The mean confirmatory assay sensitivity was determined to be 0.972 ng/mL with the 95% confidence to be 1.83 ng/mL (Table 22 of the report).

Note: Throughout the MOR208 ADA assay lifecycle (i.e., 1<sup>st</sup>, 2<sup>nd</sup> and 3<sup>rd</sup> generation assays), assay sensitivities can be compared via the cynomolgus anti-tafasitamab PC, which was employed in all assay validations. Mean reported sensitivity in the screening assay was 2.44 ng/mL in the 1<sup>st</sup> generation ADA assay, 11.4 or 7.90 ng/mL in the 2<sup>nd</sup> generation; and was improved to 1.29 ng/mL (95% CI) in the 3<sup>rd</sup> generation ADA assay employed SPEAD.

*Assessor's comments: The validation results show that the assay sensitivity (in NHS without tafasitamab) is 0.398 ng/mL and 0.606 ng/mL when used the mouse monoclonal PC 6B11-E5 in screening and confirmatory assay respectively. The assay sensitivity is 1.29 ng/mL and 1.83 ng/mL for cynomolgus polyclonal PC in screening assay and confirmatory assay respectively.*

8. Normal Human Serum Recovery, Specificity and Selectivity

- Selectivity (Recovery in Individual Lots of Serum)

HPC and LPC samples were spiked into 10 individual lots of NHS. All results with the both PCs showed positive (10 out of the 10) in screening and confirmatory assays and met the acceptance criterion (≥8 of the 10 spiked lots are assessed as positive when compared to the screening and confirmatory cut points).

*Assessor's comment: Based on the results, the selectivity assessment is considered acceptable for*

*both the screening and confirmatory assays.*

- Specificity (Evaluation of Blank Individual Sera)

Ten individual lots of NHS (without PC antibody) and the PNC were analyzed in duplicate. The results presented in Tables 9 -12 of the report show that 10 of the 10 individual lots were determined to be negative in the screening assay on plates 68b, 69b, and 88a, and 8 of the 10 individual lots on plate 89a.

*Assessor's comment: Based on the results, the specificity evaluation with PNC in NHS is acceptable since it met the assay acceptance criteria listed above in Table 1 and at least eight of the ten blank lots are assessed as negative when compared to the screening cut point.*

- Specificity (Confirmatory Assessment with Human Gamma Globulin)

A specificity assessment was performed in the confirmatory assay by analyzing the HPC, LPC and the PNC with a spike of 100 µg/mL of Human gamma globulin. The results showed positive confirmatory controls as positive and the negative control as negative (Table 23 in the report). The specificity has been shown since % signal inhibition above the confirmatory cut point was only observed by spiking HPC or LPC with MOR00208, but not with gamma globulin.

*Assessor's comment: The assay acceptance criteria for this evaluation is met, and the confirmation of specificity is acceptable.*

- Hemolyzed And Lipemic Sample Evaluation

The HPC and LPC samples were spiked into pooled NHS that had been supplemented with different amounts of hemolysate (0 - 5.0%) or 2% (v/v) intralipid® (20%-emulsion). The results in Tables 13 and 14 showed that there was no observed effect with hemolysate and intralipid.

*Assessor's comments: I agree that the assay is not sensitive to tested levels of hemolyzed or lipemic samples.*

- Interference with Bendamustine Hydrochloride Hydrate

The assay interference was evaluated by measuring the impact of 10.0 µg/mL of Bendamustine hydrochloride hydrate on the detection of the HPC, LPC, and PNC in NHS in the screening and confirmatory assay. The results in Table 20 showed that the addition of Bendamustine hydrochloride hydrate did not affect the positive and negative determinations of the controls.

*Assessor's comment: The results suggest that the serum presence of Bendamustine hydrochloride hydrate (up to 10 µg/mL) due to the combination regimen has no interference on the results of the screening and confirmatory assay.*

- Interference with Lenalidomide

The assay interference was evaluated by measuring the impact of 1.0 µg/mL of Lenalidomide on the detection of the HPC, LPC, and PNC in NHS in the screening and confirmatory assay. The results in Table 21 showed that the presence of Lenalidomide did not affect the positive and negative determinations of the controls tested in the screening and confirmatory analyses.

*Assessor's comment: The results suggest that the serum presence of Lenalidomide (up to 1.0 µg/mL) due to the combination regimen has no interference on the results of the screening and confirmatory assay.*

## 9. DLBCL Serum Recover, Specificity and Selectivity

- Selectivity (Recovery in Individual Serum Lots)

The HPC and LPC were spiked into 10 individual lots of DLBCL patient sera. All 10 individual lots with HPC and LPC were assessed as positive in the screening and confirmatory assay (Tables 15

and 16 in the report).

*Assessor's comments: Based on the presented results, the selectivity assessment in DLBCL patient sera is considered acceptable for both the screening and confirmatory assays.*

- Specificity (Evaluation of Blank Individual Sera)

Ten lots of DLBCL serum and the PNC (without the PC antibody) were analyzed in duplicate. The results in Table 15 showed, 7 of the 10 individual lots on plate 78b were determined to be negative in the screening assay, which did not meet the acceptance criterion (as 8 out of 10 should be negative).

*Assessor's comments: Plate 78b Lot 9 blank showed as positive with mean signal of 118 (duplicate signal as 117, 118), which is same as the screening cut point determined for this plate. The sponsor stated that the mean PNC<sub>plate</sub> for this sample as shown in Table 15 is chosen in a conservative way (i.e., the higher value) and should be confirmed negative when proceeded into the confirmatory evaluation. The justification is acceptable.*

*Such false positivity of the screening assay is acceptable as the positively screened samples will go further confirmatory assessment.*

*Overall, the selectivity and specificity of the assay when tested in DLBCL patient serum are acceptable, and support that this method is suitable for testing of ADAs in DLBCL patient serum.*

## 10. Stability

The HPC and LPC were subjected to 5 freeze/thaw cycles (between -70°C and ambient temperature). The freeze/thaw and fresh PC samples were diluted, processed, and analyzed in replicates. The percent differences as calculated by  $\% \text{Difference} = ([\text{Mean Response}_{\text{stressed}} / \text{Mean Response}_{\text{fresh}}] - 1) \times 100$ , for the HPC and LPC were -8.02% and -8.13%, respectively.

The HPC and LPC were also tested when stored for 4 hours at ambient temperature. After storage, the stored, fresh and frozen (1 freeze / thaw cycle as the control) samples were diluted, processed, and analyzed in replicates. The percent differences (calculated same as above) for the HPC and LPC were -13.7% and 5.17%, respectively.

These results showed that the PC samples are measured within 25% of the mean value of the non-freeze-thaw controls (which is the acceptance criterion). The applicant stated that the long-term stability is not routinely assessed since a GMP reference calibrator is rarely available for ADAs.

*Assessor's comment: The analyte stability results support that PCs in NHS are stable as exposed to 5 freeze/thaw cycles or been stored at room temperature for up to 4 hours (as the worst cases).*

## 11. Prozone

The prozone effect was assessed in both the screening and confirmatory assays by spiking the PC at concentrations between 200,000 ng/mL and 823 ng/mL (3-fold serial dilutions in 100% human serum). The results are provided in Table 19. The applicant stated that prozone effects were not observed in the screening assay and in the confirmatory assay respectively since all samples showed mean signals greater than the plate cut point and all samples showed percent inhibition results greater than or equal to the confirmatory cut point (12.0%).

**Table 19 Prozone Assessment**

| Conc. (ng/mL) in 100% matrix | Run/Version       |      | % Inhibition |
|------------------------------|-------------------|------|--------------|
|                              | 72                | 72   |              |
|                              | Mean Response RLU |      |              |
|                              | Buffer            | Drug |              |
| 200000                       | 1520483           | 3659 | 99.8         |
| 66667                        | 1424306           | 3374 | 99.8         |
| 22222                        | 1016470           | 2185 | 99.8         |
| 7407                         | 431325            | 949  | 99.8         |
| 2469                         | 145403            | 353  | 99.8         |
| 823                          | 33614             | 144  | 99.6         |
| Cutpoint <sup>(a)</sup>      | 157               | 157  |              |
| X = 1.06                     |                   |      |              |
| Mean PNC <sub>Plate</sub>    | 148               | 148  |              |

(a) Mean PNC<sub>Plate</sub> \* Screening Cut Point (X)  
Drug = 100 µg/mL spike of MOR00208-CMC3  
Buffer = Diluent Buffer  
Screening Cut Point = 1.06  
Confirmatory Cut Point = 12.0%

*Assessor's comments: I plotted the data from Table 19 and found that the signal was not proportional increase at the highest concentrations of 66,667 ng/mL and 200,000 ng/mL and plateaued, while it showed good linearity in concentration ranges 823 - 22,222 ng/mL. Thus, the sample concentration of 22,222 ng/mL should be considered to monitor the prozone effects, however in the ADA assay, the PC concentration (up to 1000 ng/mL) is far below the stated concentration. Overall, prozone effect is not a concern in this case.*

*Assessor's Additional Comment: Overall, the 3<sup>rd</sup> generation ADA assay is adequate to use and evaluate the ADAs to tafasitamab for the proposed indication.*

## 2. Validation of ADCC cell-based assay for the detection of neutralizing anti-tafasitamab antibodies in human serum [Validation Report MOR208L019]

The NAb assay measures the ADCC effect on MEC-1 target cells employing an ADCC Reporter Bioassay (b) (4). Tafasitamab binds to CD19 antigen expressed on MEC-1 cell and thereby recruits CD16-expressing effector cells (a genetically engineered cell line derived from the human T-cell leukemia Jurkat line) via their Fc portion. This trimeric complex induces the transcription of luciferase enzyme through the activation of the NFAT (nuclear factor of activated T-cells) signaling pathway in the effector cells. After addition of the substrate, a bioluminescent signal can be measured, which corresponds to the activation of the effector cells and thus is representative for the main mechanism of action (MOA) of tafasitamab.

*Assessor's comment: The ADCC assay reflects the primary MOA of tafasitamab and is appropriate to use as a NAb assay.*

### 2.2 Method Development

A summary of method development work is presented in the protocol (refer to Appendix IV). This is briefly summarized here:

- The estimated tafasitamab/MOR208 concentration to be used as ADCC inducer in the assay

was determined as 1.0 ng/mL, which is in the upper linear portion of the titration curve as illustrated by the curve bend points.

- The biotinylated MOR208 conjugate concentration used for the assay with SPEAD sample pre-treatment titrations led to an estimated assay sensitivity below 100 ng/mL and a HPC level set at 200 ng/mL.
- Assay specificity was demonstrated as the neutralizing activity of the PC antibody was specifically depleted by the presence of an excess tafasitamab but not by the presence of the same excess of non-specific purified human IgG antibodies.

*Assessor's comments: Based on the data provided in Figure 2-5 in Appendix IV, the method development study support the concentration selection of MOR208, biotinylated MOR208, and the titration of the anti-MOR208 PC antibody. The specificity of the assay is also demonstrated in the development study.*

### **2.3 Validation Assessment**

The validation acceptance criteria are the following:

- Unless otherwise mentioned, applicable run acceptance criteria specified in the analytical procedure must be met prior to the evaluation of each validation assessment.
- Sets refer to sets of duplicates. For calculations, the mean RLU of the duplicate values will be used.
- For a set to be acceptable, CV of the mean RLU (i.e., between the duplicates) must be  $\leq$  20%, otherwise the value is not included in the assessment unless otherwise mentioned.

Details of the method validation work is presented in the protocol (refer to Appendix IV) and summarized in Table B:

**Table B** Method Validation Summary

| <i>Assessment</i>                            | <i>Results</i>                                                                                                                                                                                                           |                                |                                            |
|----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|--------------------------------------------|
|                                              | <i>Matrix</i>                                                                                                                                                                                                            | <i>False-positive rate (%)</i> | <i>Cut-point</i>                           |
| Screening cut-points                         | NHS                                                                                                                                                                                                                      | 1.0                            | 0.759 (ratio to AC)                        |
|                                              | HS-DLBCL                                                                                                                                                                                                                 | 1.0                            | 0.819 (ratio to AC)                        |
| LOD level                                    | 69.3 ng/mL (95.0% consistency level)                                                                                                                                                                                     |                                |                                            |
| LPC level                                    | 99.9 ng/mL (1.0% failure rate)                                                                                                                                                                                           |                                |                                            |
| Hook effect                                  | None up to 10000.0 ng/mL PC antibody                                                                                                                                                                                     |                                |                                            |
| Precision of LPC and HPC sample measurements | <u>Intra-run and inter-run</u> : 6 runs, 6 sets per run                                                                                                                                                                  |                                |                                            |
|                                              | <ul style="list-style-type: none"> <li>• Intra-run CV: ≤ 10.2% in all 6 runs</li> <li>• Inter-run CV: ≤ 9.9%</li> </ul>                                                                                                  |                                |                                            |
| Control sample thresholds                    | <i>Control sample</i>                                                                                                                                                                                                    | <i>Failure rate (%)</i>        | <i>Value</i>                               |
|                                              | AC                                                                                                                                                                                                                       | 0.1                            | 4.6 (ratio to NC)                          |
|                                              | LPC                                                                                                                                                                                                                      | 1.0                            | 0.759 (ratio to AC, i.e. must be positive) |
|                                              | HPC                                                                                                                                                                                                                      | 1.0                            | 0.441 (ratio to AC)                        |
| MOR208 drug tolerance                        | <i>PC level</i>                                                                                                                                                                                                          | <i>Drug level</i>              |                                            |
|                                              | LPC                                                                                                                                                                                                                      | 2.5 µg/mL                      |                                            |
|                                              | HPC                                                                                                                                                                                                                      | 8.3 µg/mL                      |                                            |
|                                              | PC at 500 ng/mL                                                                                                                                                                                                          | 13.3 µg/mL                     |                                            |
| Concomitant drug interference                | Assay tolerates at least 10.0 µg/mL Bendamustine and at least 1.0 µg/mL Lenalidomide                                                                                                                                     |                                |                                            |
| Hemolyzed and lipemic serum interference     | <ul style="list-style-type: none"> <li>• Highly hemolyzed serum (3+ on visual scale) does not interfere with the assay</li> <li>• Highly lipemic serum (3+ on visual scale) does not interfere with the assay</li> </ul> |                                |                                            |
| Stability of PC samples (MOR208 in PNHS)     | <ul style="list-style-type: none"> <li>• Freeze-thaw: 5 cycles (-80°C/RT)</li> <li>• Bench top: 21 h 06 min at RT</li> <li>• Long term: 178 days (-80°C)</li> </ul>                                                      |                                |                                            |
| Stability of the MOR208 Stock 1 (10.0 mg/mL) | 210 days at -80°C                                                                                                                                                                                                        |                                |                                            |

### 2.3.1 MOR208 Titration

MOR208 was tested at various concentrations (4-fold serial dilution) ranging from 50.0 to 0.003 ng/mL. Based on the results provided in Figure 1 of the Method Validation Protocol, a final in-well MOR208 concentration of 1.0 ng/mL was selected since it is in the upper linear portion of the titration curve and shows high signal to noise (~6x) in the assay.

*Assessor's comment: The selection of MOR208 concentration of 1 ng/mL is acceptable as justified and this concentration is sensitive to inhibition.*

### 2.3.2 Screening Cut-Points (NHS, DLBCL)

For the screening cut-point determinations, 30 individual lots of NHS or 30 individual serum lots from DLBCL patients were tested in duplicates by 2 analysts on 3 different days. Each cut-point run included 2 sets of ADCC control (AC) and the negative control (NC) samples prepared in pooled NHS (PNHS). The ADCC control is the PNHS with tafasitamab (from CMC3 production process) at 1.0 ng/mL final.

Based on the data presented in Table 2C (in Appendix I), the distribution of readout 178 log-transformed ratios to AC (after outlier removal) was quasi-normal which led to the use of an alternative equation (details are in described on page 91 of the report) to establish a screening cut-point at 0.759 (ratio to AC) for NHS.

Similarly based on the data presented in Table 3C (in Appendix I), a screening cut-point was decided at 0.819 (ratio to AC) for DLBCL serum.

*Assessor's comment: The cut point determination approach aligns with the recommendation in the FDA guidance and the determined screening cut points are acceptable.*

### 2.3.3 Assay Sensitivity (LOD), LPC Level Determination and Hook Effect

#### - Titration of Positive Control Antibodies:

The anti-MOR208 PC antibody was prepared at HPC level of 200.0 ng/mL and 2-fold serially diluted to 3.1 ng/mL in PNHS. Titration of the PC antibody along with AC and NC samples was performed in 4 runs by 2 analysts, where each run consisted of at least two titration curves. The PC antibody titrations (ratio to AC) were analyzed using the same 4-PL curve fit for all titration curves.

#### - LOD Determination:

The LOD of the assay was determined based on the method by Shankar et al. (2008) to obtain a statistical 95% consistency level. The screening cut-point (discussed in 2.3.2) was interpolated on all accepted PC titration curves. Based on the data presented in Table 4 (in Appendix I), the LOD was estimated at 84.6 ng/mL. The estimated LOD, as well as 2 additional PC concentrations (1 below and 1 above) were fortified in 10 individual NHS lots (PNHS as a spike control) and tested as 1 set along with 1 set of the serum lot non-mixed and 2 sets of AC and NC samples. Based on the data presented in Table 5 (Appendix I), the LOD was confirmed at 69.3 ng/mL.

#### - LPC Level Establishment:

The LPC level of the assay was estimated based on the method by Shankar et al. (2008) to obtain a statistical 1.0% failure rate. Based on the data presented in Table 4 (in Appendix I), the LPC was estimated at 99.9 ng/mL. Since the assay LOD level (69.3 ng/mL) was below the estimated LPC level (99.9 ng/mL), the LPC level was decided as 99.9 ng/mL.

#### - Hook Effect:

One titration curve with the antibody concentration ranging from 1.0 µg/mL to 10 µg/mL was plotted to assess the presence of any hook effect. Based on the data presented in Table 6 and Figure 2 (Appendix I), there was no hook effect for PC antibody concentrations up to 1000 ng/mL.

*Assessor's comment: The approaches used are acceptable. I reviewed these data and the data supported the determined LOD and LPC level, as well no hook effect for the PC from 3.1 ng/mL to 1000 ng/mL.*

### 2.3.4 Assay Precision and Assay Robustness

The intra- and inter-assay precision was evaluated over 3 independent assay runs by 2 analysts over

multiple days (total of 6 independent runs). Assay robustness was also evaluated in the precision runs by testing 3 lots of the effector cells (note that a single lot of “thaw and use” MEC-1 target cells were used throughout method validation). Each run (i.e. assay plate) included 6 sets of LPC and HPC samples and 2 sets of AC and NC samples. The precision was calculated on the ratio to AC values. The results provided in Table 7 (in Appendix I) showed intra-assay precision with CVs  $\leq 10.2\%$  in all runs, and inter-assay precision with CVs  $\leq 9.9\%$ ; thus, met the validation acceptance criteria. These results also supported assay robustness for use of different lots of effector cells.

*Assessor’s comment: The results support that the NAb assay is reproducible with acceptable variabilities (i.e., analysts, days, different lots of effector cells).*

### 2.3.5 Establishment of In-Study Acceptance Criteria for NC, AC, LPC and HPC Samples

#### - AC/NC Threshold:

A preliminary AC/NC threshold of 4.5 (based on development data) was used during the method validation. The final AC/NC threshold was determined (as  $\leq 15\%$ ) using the AC/NC data from all acceptable validation runs, excluding long term stability assessment runs and MOR208 stock 1 stability runs. Determination of the threshold was based on a 0.1% failure rate (1.0% failure rate was not selected due to limited data/variability) and calculated as 4.6 (Table 8 in Appendix I).

#### - Criteria for LPC and HPC Thresholds:

The final threshold acceptance criterion for the HPC sample was based on a 1.0% failure rate and was derived using HPC results (excluding spike control samples used for validation assessments of drug tolerance, stability, and concomitant drugs) with acceptable CV from all accepted runs. Similarly, the final threshold acceptance criterion for the LPC was calculated using LPC results.

The HPC/AC and LPC/AC thresholds are calculated as 0.441 and 0.759, respectively (Table 9 in Appendix I).

*Assessor’s comment: I reviewed these data and the data supported the determined AC/NC, LPC/AC and HPC/AC threshold criteria.*

### 2.3.6. MOR208 Drug Tolerance

The drug tolerance was evaluated from 3 independent assessments on different days at each PC level. The LPC, HPC and PC 500 ng/mL concentrations were tested using the 2-fold serial dilution MOR208 concentrations respectively up to 20, 40, and 80  $\mu\text{g/mL}$ .

The PC antibody and tafasitamab mixtures in PNHS were incubated at 37°C for 30 - 60 minutes with 500 rpm shaking. These samples were tested in duplicates along with AC, NC, LPC and HPC samples for the run control. The drug tolerance level was determined as the lowest tested concentration of tafasitamab that does not interfere with the assay.

The results presented in Table 10 (in Appendix I) show that the cynomolgus PC antibody LPC level (99.9 ng/mL) can tolerate up to 2.5  $\mu\text{g/mL}$  of tafasitamab, the HPC (200.0 ng/mL) level can tolerate up to 8.3  $\mu\text{g/mL}$  of tafasitamab, and the PC 500 ng/mL can tolerate up to 13.3  $\mu\text{g/mL}$  of tafasitamab.

*Assessor’s comments: The drug tolerance values were determined using the screening cut point of 0.759 for the NHS. When determined using the SCP of 0.819 for DLBCL sera, the drug tolerance levels of the assay could be slightly higher based on the same dataset provided in Table 10. The reported serum trough level of tafasitamab is  $< 250 \mu\text{g/mL}$ , which is much higher than the highest tolerated level*

*as 13.3 µg/mL, thus, the NAb assay may not detect the NABs in the patient serum and may under-report the NAb occurrence. However, according to the clinical immunogenicity result, no clinically meaningful differences in the PKs, efficacy, or safety profile of tafasitamab were observed in patients' samples (only 2 subjects were ADA positive, and both were identified as "negative" for NAb response) with DLBCL with pre-existing anti-tafasitamab antibodies. The ADA titer detected in the patient sera was low with sample dilutions of 1:4 and 1:32. Considering low ADA occurrence with lower titer and no observed clinical effect, the risk of the low drug tolerance of the NAb assay is low.*

*Finally, tafasitamab is a recombinant humanized IgG1/IgG2 hybrid mAb and is not an analogue of human endogenous protein. Therefore, the presence NABs to tafasitamab does not impose a significant safety risk to patients (i.e., due to cross-neutralization of native endogenous proteins), if such ADAs with neutralizing capacity develop.*

### 2.3.7 Concomitant Drug Interference

To evaluate interference of Bendamustine and Lenalidomide in the assay the following samples were used (tested as 3 sets along with applicable AC, NC, LPC and HPC samples):

- AC control (PNHS without PC) with 10.0 µg/mL Bendamustine or with 1.0 µg/mL Lenalidomide
- LPC and HPC samples with and without 10.0 µg/mL Bendamustine or 1.0 µg/mL Lenalidomide.

The data provided in Table 11 (in Appendix I) show that the AC with concomitant drug remains negative and the positive control with the concomitant drug remains positive, thus neither Bendamustine nor Lenalidomide interfered with the assay.

*Assessor's comment: The results in Table 11 suggest that the serum presence of Bendamustine or Lenalidomide (at the tested concentrations) due to the combination regimens has no interference on the results of the NAb assay.*

### 2.3.8 Hemolyzed and Lipemic Serum Interference

Hemolyzed and lipemic serum interference was evaluated using 5 different lots each of highly hemolyzed NHS and of highly lipemic NHS (both 3+ by visual scale) mixed with PC antibody at the LPC and HPC levels.

As presented in Tables 12A and 12B (Appendix I), the results show that high hemolysis levels and high lipemia levels did not interfere with the assay as all serum lots without PCs were screened negative, and opposite with the PCs.

*Assessor's comment: The assay met the assay acceptance criteria. I agree that the assay is not sensitive to tested levels of hemolyzed or lipemic samples.*

### 2.3.9 Stability of Positive Control Antibody in PNHS

Stability PC samples were prepared at LPC and HPC levels and stored at -80°C for at least 24 hours prior to being submitted to various stability treatments. They were analyzed in 3 sets, each set from different stability PC aliquots.

For freeze-thaw stability evaluation, the stability PC samples underwent 5 freeze-thaw cycles (results are provided in Table 13A in Appendix I).

For bench top stability testing, the stability samples (thawed unassisted) kept at room temperature for 21 hr 6 min prior to testing (results are in Table 13B).

For long term stability assessment, the stability samples were stored for 178 days at -80°C (results are in Table 13C).

*Assessor's comments: Based on the data provided in Tables 13A - 13C:*

- *The stability of the PC samples for 5 freeze-thaw cycles was demonstrated as the %differences between the fresh and stability samples were within  $\pm 6.9\%$ ,*
- *The stability of the samples at room temperature was confirmed for 21 hrs as the %differences between the fresh and stability PC samples were within  $\pm 21.9\%$ ,*
- *The %difference between the fresh and the long-term stored PC samples were within  $\pm 7.3\%$  supporting storage for up to 178 days at -80°C.*

*All the results met the assay acceptance criteria, thus support the assay stability listed in the three conditions studied.*

*Assessor's Additional Comment: Overall, the NAb assay may not be sufficiently sensitive to evaluate the ADAs to tafasitamab for their neutralizing property in the proposed indication.*



Li  
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