# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761210Orig1s000

# PRODUCT QUALITY REVIEW(S)

# QUALITY EXECUTIVE SUMMARY REVIEW ADDENDUM

Recommendation: Approval

BLA/NDA Number: 761210
Assessment Number: First Round
Assessment Date: 04/28/2021
Addendum Date: 5/20/2021

| | |
|---|---|
| Drug Name/Dosage Form | RYBREVANT (amivantamab-vmjw), injection |
| Strength/Potency | 50 mg/mL (350 mg/vial) |
| Route of Administration | For intravenous infusion |
| Rx/OTC dispensed | Rx |
| Indication | for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy |
| Applicant/Sponsor | Janssen |

## Quality Executive Summary Review Addendum:

The Quality Executive Summary memo filed on April 28, 2021 made a preliminary recommendation pending the outcome of the pre-license inspection (PLI) for the drug substance manufacturer Janssen Sciences Ireland UC, Cork, Ireland (FEI 3007029098). This Review Addendum summarizes the outcome of this PLI, summarizes the final Facilities recommendation, and provides a final approval recommendation from the OPQ team. *The updated review sections are below, with key changes highlighted in red text. Refer to the April 28, 2021 Quality Executive Summary memo for all other review sections and recommendations for the action letter*.

## I. Recommendations:

### A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761210 for RYBREVANT manufactured by Janssen Biotech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of

RYBREVANT is well-controlled and leads to a product that is pure and potent. *It is recommended that this product be approved for human use under conditions specified in the package insert*.

## II. Summary of Quality Assessments:

### F. Establishment Information:

| Overall Recommendation: | | | | | |
|---|---|---|---|---|---|
| DRUG SUBSTANCE | | | | | |
| Function | Site Information | DUNS/FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |
| Drug Substance Manufacturer | Janssen Sciences Ireland UC, Cork, Ireland | 3007029098 | PLI needed | *1) Invalid assays are not adequately investigated.* | *Approve – Based on Inspection* |
| Parental Antibody Manufacturer | (b) (4) | | 704 (a) (4) records review | NA | Approve-Based on 704 (a) (4) |
| Analytical Testing for Drug Substance | | | NA | NA | Approve – Based on Previous History |
| DRUG PRODUCT | | | | | |
| Function | Site Information | DUNS/FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |
| Drug Product Manufacturer, Analytical Testing for Drug Substance | Cilag AG, Schaffhausen, Switzerland | 3002806695 | PLI waiver assessment; firm has other FDA-approved BLAs; good inspection history | NA | PLI waiver granted |

| | | | | | |
|---|---|---|---|---|---|
| Analytical Testing for Drug Substance and Drug Product | Janssen Biologics B.V., Leiden, The Netherlands | 3002806632 | NA | NA | Approve – Based on Previous History |

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for [redacted] (b) (4) Janssen Sciences Ireland UC (FEI 3007029098) (both are proposed for DS manufacture) and Cilag AG (FEI 3002806695), proposed for DP manufacture. *All proposed manufacturing and testing facilities are acceptable based on pre-license inspection, their currently acceptable CGMP compliance status, recent relevant inspectional coverage, and 704 (a) (4) records review, as applicable*.

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# PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
# Memorandum of Review to the File

| | |
|---|---|
| **Application ID** | BLA 761210 |
| **Submission Type** | Original BLA |
| **Drug Product Name** | JNJ-61186372 (amivantamab) |
| **Strengths** | 350 mg |
| **Dosage Form** | Solution for dilution |
| **Administration Route** | Intravenous |
| **Indication** | Treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy |
| **Applicant Name** | Janssen Biotech, Inc. |
| **US License Number** | 1864 |
| **Application Type** | 351 (a) |
| **Primary Reviewer** | Amy Devlin, Ph.D., Microbiologist, OPQ/OPMA/DBM1 |
| **Secondary Reviewer** | Maxwell Van Tassell, Ph.D., SPQA,<br>Zhong Li, Ph.D., SPQA, OPQ/OPMA/DBM1 |
| **Goal Date** | July 24, 2021 |

## Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective and is recommended for Approval.
- Manufacturing Facility Assessment Recommendation: Approval.
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

### Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4) (b) (4). Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process and at DS release. Microbial control (b) (4) (b) (4) was demonstrated by microbial monitoring in their lifetime studies. Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) (b) (4) (b) (4) Janssen Sciences Ireland UC (FEI 3007029098), proposed for JNJ-61186372 (amivantamab) DS manufacture. All proposed manufacturing and testing facilities are acceptable based on their current cGMP compliance status and recent relevant inspectional coverage.

**Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:**

| CQA (type) | Risk | Origin | Control Strategy |
|---|---|---|---|
| Endotoxin | Safety, Purity | Raw materials, manufacturing process | (b) (4) |
| Bioburden | Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination | Raw materials, manufacturing process | |

**List Submissions being assessed (Table):**

| Document Description (SD #) | Date Received |
|---|---|
| Original submission (0002) | 11/24/2020 |
| Response to FDA IR sent 04/01/2021 (0035) | 04/14/2021 |
| Response to FDA IR sent 04/12/2021 (0036) | 04/19/2021 |

# MODULE 3.2.S

**Module 3.2.S Lifecycle Management Considerations**

| | |
|---|---|
| **Lifecycle considerations:** | No |
| **Post-approval inspection?** | No |

## S.1 General Information

Amivantamab is a low-fucose, human IgG1-based EGFR-MET bispecific antibody that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications by binding to the extracellular domains of EGFR and MET. Amivantamab consists of two heavy and two light chains joined by disulfide bonds. The relative molecular mass of the molecule is 148209 Da for the major glycoform. Amivantamab is manufactured using two recombinant CHO cell lines.

***Reviewer's Comment: For Information***

## S.2 Manufacture

(b) (4)



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Maxwell Van Tassell

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Zhong Li

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

# LABELS AND LABELING ASSESSMENT

| | |
|---|---|
| Date of Assessment: | May 19, 2021 |
| Assessor: | Jim Barlow, RPh<br>Labeling Assessor<br>Office of Biotechnology Products (OBP) |
| Through: | Andrea Franco, PhD, Product Quality Assessor<br>OBP/Division of Biotechnology Review and Research 4 |
| Application: | BLA 761210 |
| Applicant: | Janssen Biotech, Inc. |
| Submission Date: | 11/24/2020 |
| Product: | Rybrevant (amivantamab-vmjw) |
| Dosage form(s): | Injection |
| Strength and Container-Closure: | 350 mg/7 mL (50 mg/mL)<br>in a single-dose vial |
| Purpose of assessment: | The Applicant submitted a biologics license application to seek approval of amivantamab for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy. |
| **Recommendations:** | The prescribing information, patient labeling, container labels, and carton labeling are **acceptable** from an OBP labeling perspective. |

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

n/a = not applicable for this assessment

## DISCUSSION

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

## CONCLUSION

The prescribing information and patient labeling submitted on May 17, 2021 and the container and carton labels and labeling submitted on May 13, 2021 were assessed and found to be acceptable from an OBP labeling perspective.

**APPENDICES**

**Appendix A**: Proposed Labeling

- Prescribing Information and Patient Information (submitted on 11/24/2020)
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- Container Labels (submitted on 11/24/2020)

(b) (4)

- Carton Labeling (submitted on 11/24/2020)

(b) (4)

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

**Container[4] Label Evaluation**

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

**Comment/Recommendation:**
**To applicant:** Recommend increasing the prominence of the proper name to be at least the same font as the proposed drug strength.

**Applicant response**: (Acceptable)
The font size of the proper name "amivantamab-vmjw" has been increased relative to the size of the proprietary name "Rybrevant". The proper name is now in 5.5 point font, and the proprietary name is in 9 point font.

Suffix approved 4/22/2021 (vmjw)

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

[1] Per 21 CFR 1.3(b) *Label* means any display of written, printed, or graphic matter on the immediate container of any article, or any such matter affixed to any consumer commodity or affixed to or appearing upon a package containing any consumer commodity.
[2] Per CFR 600.3(dd) *Label* means any written, printed, or graphic matter on the container or package or any such matter clearly visible through the immediate carton, receptacle, or wrapper.
[3] Per 21 CFR 1.3(a) *Labeling* includes all written, printed, or graphic matter accompanying an article at any time while such article is in interstate commerce or held for sale after shipment or delivery in interstate commerce.
[4] Per 21 CFR 600.3(bb) *Container* (referred to also as "final container") is the immediate unit, bottle, vial, ampule, tube, or other receptacle containing the product as distributed for sale, barter, or exchange.
[5] Per 21 CFR 610.60(c) *Partial Label.* If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label."

| **Comment/Recommendation:** All regulations required are met. Acceptable |
|---|

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

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

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

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

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

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

| | |
|---|---|
| | |

**Comment/Recommendation:**
**To applicant:** Recommend relocating to the bottom left corner of the PDP on the container and decrease the prominence.

**Applicant response: (Acceptable)**
The "Rx only" statement has been relocated in accordance with the revised layout accommodating the increase in font size of the proper name.

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

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

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

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

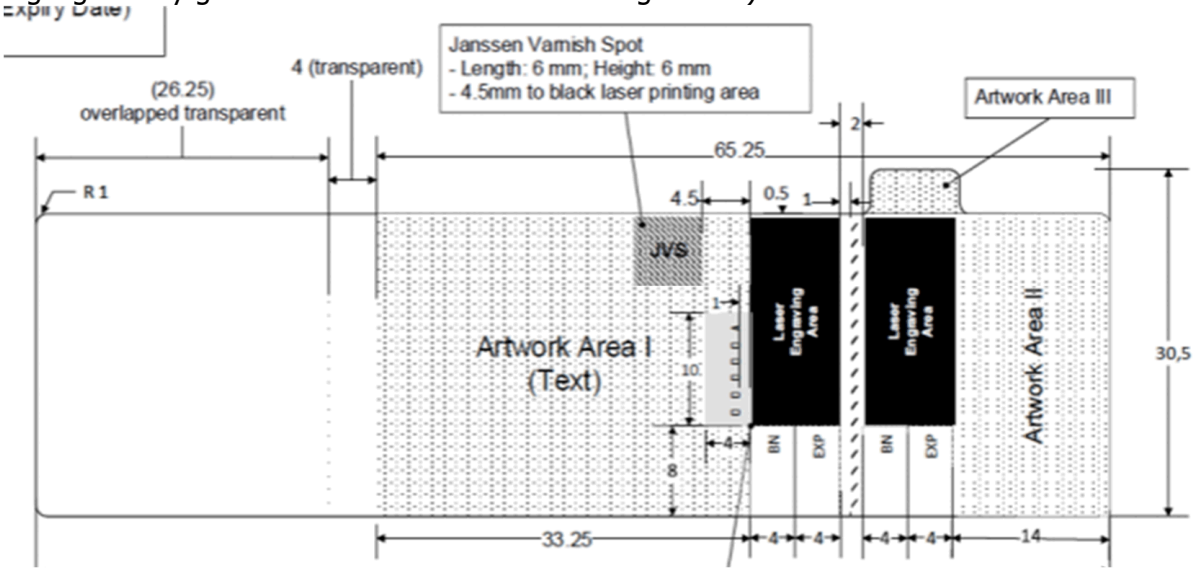
**Comment/Recommendation:** Confirm there is no text on the ferrule and cap overseal of the vials.

**Applicant response (Acceptable)**
Janssen confirms that the top surface of the vial, including the ferrule and cap overseal, will not contain text. The side of the ferrule will have the lot number (batch name) printed on it, consistent with FDA's draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (April 2013).

| **Visual inspection** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.60(e) | ✓ Yes<br>☐ No<br>☐ N/A |

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

**Applicant response (Acceptable)**
Janssen confirms sufficient area of the vial remains uncovered for its full length to allow for visual inspection when the label is affixed to the vial. The width of this area 4 mm. (See area highlighted by green box on the technical drawing below.)




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

**Comment/Recommendation:**

**To applicant:** Revise to read "For Intravenous Infusion after Dilution" to be in alignment with recommended labeling practices and be consistent with recently approved FDA labeling.

**Applicant response: (Acceptable)**
Janssen would like to maintain consistency with how the route of administration is expressed in the HIGHLIGHTS section of the USPI, i.e., "for intravenous use". By adding "Dilute before" "intravenous infusion", consistency is no longer achieved, and the emphasis of each statement is lessened. Additionally, the metadata in the Structured Product Labeling will only allow the route of administration to be expressed as "Intravenous Infusion". Therefore,

| |
|---|
| consistency between how this is stated on the carton and what is displayed on DailyMed will be lost. |

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

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

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

**Comment/Recommendation:**

**To applicant:** Remove the (b) (4) positioned directly above the package-type term to avoid clutter.

**Applicant response: (Acceptable)**
(b) (4) has been removed.

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

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

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

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

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

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

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

**Comment/Recommendation:**
**To applicant:** Revise to include "Single-dose vial. Discard unused portion."

**Applicant response: (Acceptable)**
Revised to read "Single-dose vial. Discard unused portion." to correct package-type term.

| **Statement of Dosage (container label)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.60(a)(5), 21 CFR 610.60(c), 21 CFR 201.55, 21 CFR 201.100(b)(2) | ✓ Yes<br>☐ No |

| | |
|---|---|
| | ☐ N/A |

**Comment/Recommendation:**
**To applicant:** Recommend revising to read "Dosage: See Prescribing Information." to be in alignment with PLR labeling.

**Applicant response: (Acceptable)**
The Statement of Dosage has been revised to read "Dosage: See Prescribing Information".

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

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

**Comment/Recommendation:**
**To applicant:**
Revise to read "Store refrigerated at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light." for consistency.

**Applicant response: (Acceptable)**
Storage statements have been revised to read "Store refrigerated at 2°C to 8°C (36°F to 46°F).
Do not freeze. Protect from light".

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

## Package[6] Labeling Evaluation

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

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

**Comment/Recommendation:** Acceptable

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

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

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

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

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

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

| **Product Strength (package labeling)** | **Acceptable** |
|---|---|

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

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

**Comment/Recommendation:**

**To applicant:** To highlight important storage information, we recommend revising the storage information to read, "**Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze**."

**Applicant response: (Acceptable)**

To highlight important storage information, we recommend revising the storage information to read, "Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze."

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

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

| **Route of administration (package labeling)** | **Acceptable** |
|---|---|
| Regulations: 21 CFR 610.61(k), 21 CFR 201.5(f), 21 CFR 201.100(d)(1) | ✓ Yes |

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

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

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

**Comment/Recommendation:**

**To applicant:** Revise the ingredient statement to be consistent with the Prescribing Information to read: "Each vial contains 350 mg (50 mg/mL) amivantamab-xxxx, EDTA disodium salt dihydrate (0.14 mg), L-histidine (2.3 mg), L-histidine hydrochloride monohydrate (8.6 mg), L methionine (7 mg), polysorbate 80 (4.2 mg), sucrose (595 mg), and water for injection, USP.". Please refer to 21 CFR 201.100(b)(5) and USP <1091> Labeling of Inactive and include the name of the pH adjuster – consider providing as "xx may be added to adjust the pH."

**Applicants response: (Acceptable)**
Janssen has combined the active and inactive ingredients into a single statement. A hyphen has been reinserted in "L-methionine" where it appears to have been inadvertently removed by FDA, "7.0 mg" was updated on the carton label to "7 mg" and "USP" has been added after "water for injection".

Naming of a pH adjuster is not applicable, (b) (4) (b) (4)

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

| **Minimum potency of product (package labeling)** | **Acceptable** |
|---|---|

| | |
|---|---|
| Regulation: 21 CFR 610.61(r) | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:**
**To applicant:** Revise to include minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency." to be in alignment with CFR 610.61(r).

**Applicant response: (Acceptable)**
No U.S. standard of potency has been prescribed. The words "No U.S. standard of potency" have been added.

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

**Comment/Recommendation:**
**To applicant:** Recommend locating to the bottom left corner of the PDP on the carton.

**Response (Acceptable)**
Janssen's internal design standard places "Rx only" in the lower left corner of the Principal Display Panel above the net quantity statement. The rationale for this placement is to provide generous separation between the product net quantity and the product strength. FDA's draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors (April 2013) recommends that "the net quantity statement appear on the PDP but separate from and less prominent than the statement of strength (e.g., not highlighted, boxed, or bolded)." Janssen would prefer not to deviate from internal design standards and to maintain a greater separation between the product strength and net quantity.

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

| **Distributor (package labeling)** | **Acceptable** |
|---|---|
| Regulation: 21 CFR 610.64, 21 CFR 201.1(h)(5) | ☐ Yes |

| | |
|---|---|
| | ☐ No<br>☒ N/A |

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

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

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

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

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

**Comment/Recommendation:**
**To applicant:** Revise to correct package type term

Applicant response: (Acceptable)

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

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

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

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

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

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

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

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

**Comment/Recommendation:**

**To applicant:** Recommend revising the Statement of Dosage to read "Dosage: See Prescribing Information." to be in alignment with PLR labeling and avoid clutter.

**Applicant response: (Acceptable)**

The Statement of Dosage has been revised to read "Dosage: See Prescribing Information".

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

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

| Other (package labeling) | Acceptable |
|---|---|
| | ☐ Yes<br>☐ No<br>☒ N/A |

**Prescribing Information Evaluation**

**PRESCRIBING INFORMATION**

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

| Highlights of Prescribing Information | |
|---|---|
| **DOSAGE AND ADMINISTRATION** | **Acceptable** |

| | |
|---|---|
| *Recommended labeling practices reference: USP nomenclature for diluents and intravenous solutions* | ✓ Yes<br>☐ No<br>☐ N/A |

| **Highlights of Prescribing Information** | |
|---|---|
| **DOSAGE FORMS AND STRENGTHS** | **Acceptable** |
| Regulations: 21 CFR 201.57(a)(8), 21 CFR 201.10, 21 CFR 201.100 | ✓ Yes<br>☐ No<br>☐ N/A |
| *Recommended labeling practices references: Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use Containers for Human Use (October 2018)*<br>*USP chapter <659> Packaging and Storage Requirements*<br>*USP General Chapters: <7> Labeling* | ✓ Yes<br>☐ No<br>☐ N/A |

**Comment/Recommendation:**
**To applicant:** Revise to utilize correct package-type term.

**Applicant response:** Firm revised as requested. Acceptable

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

**To applicant:**
Revise to correct package-type term.
Revise to be in alignment with USP nomenclature.
Revise to include "59°F to 77°F" for clarity and to prevent possible storage mistakes

**Applicant response**: Revised as requested. Acceptable

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

**Comment/Recommendation:**
**To applicant:** Revise to utilize correct package-type term.

**Applicant response**: Revised as requested. Acceptable

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

**Comment/Recommendation:**
**To applicant:** Revise to include suffix.
Revise to utilize correct package-type term.
Delete terminal zero (7 mg) rather than (7.0 mg).

**Applicant response:** Revised as requested. Acceptable
The Applicant also proposed the following language be included in the first sentence of the DESCRIPTION section "low-fucose" to accurately describe the drug substance. This was found to be acceptable.

| Full Prescribing Information | |
|---|---|
| **15 & 16 Hazardous Drug** | **Acceptable** |
| Regulation: 21 CFR 201.57(c)(17)(iv)<br><br>Section 15: | ☐ Yes<br>☐ No<br>☒ N/A |

| | |
|---|---|
| References 1. OSHA Hazardous Drugs. OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*<br><br>Section 16:<br>xxxx is a hazardous drug. Follow applicable special handling and disposal procedures.[1] | |

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

**Comment/Recommendation:**
**To applicant:**
Revise to include suffix.
Revise to include "sterile" per 201.57 and restructured sentence to be in alignment with more recently approved FDA labeling.

**Applicant response:** Revised as requested. Acceptable

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

**Comment/Recommendation:**
Firm correctly lists the license holder on the 356h form per *21 CFR 610.60(a)(2)*.
For biologic products, the name of Applicant in Field 2 of the form FDA 356h is the name of the person or legal entity to whom the license will be issued. Ensure that the manufacturer name and address appear exactly as intended for the US license holder.

Acceptable

**Medication Guide Evaluation N/A**

**Patient Information Labeling Evaluation**

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

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

| PATIENT INFORMATION LABELING | |
|---|---|
| **INGREDIENTS** | **Acceptable** |
| *Recommended labeling practice: To ensure labeling of inactive ingredients are in alphabetical order (see USP General Chapters <1091>)* | ✓ Yes<br>☐ No<br>☐ N/A |

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

**Comment/Recommendation:**
**To applicant:** Revise per 21 CFR 610.61 (add the US license number for consistency with the carton labeling).
**Applicant response:** Revised as requested. Acceptable

**Instructions for Use Evaluation**

**APPENDIX C. Acceptable Labels and Labeling**

- Prescribing Information (submitted on May 17, 2021)
  \\CDSESUB1\evsprod\bla761210\0045\m1\us\draft-labeling-pi.doc

- Patient Information (submitted on May 17, 2021)
  \\CDSESUB1\evsprod\bla761210\0045\m1\us\draft-labeling-ppi.doc

- Container Labels (submitted on May 13, 2021)


- Carton Labeling (submitted on May 13, 2021)


(b) (4)

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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SHARON K SICKAFUSE
05/19/2021 01:24:15 PM

Recommendation:
Approval (Pending outcome of pre-license inspection of Janssen Sciences Ireland manufacturing facility)

BLA/NDA Number: 761210
Assessment Number: First Round
Assessment Date: 04/28/2021

| | |
|---|---|
| Drug Name/Dosage Form | RYBREVANT (amivantamab-vmjw), injection |
| Strength/Potency | 50 mg/mL (350 mg/vial) |
| Route of Administration | For intravenous infusion |
| Rx/OTC dispensed | Rx |
| Indication | for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutation whose disease has progressed on or after platinum-based chemotherapy |
| Applicant/Sponsor | Janssen |

## Product Overview:

Amivantamab (JNJ-61186372, also known as CNTO 4424) is a low-fucose, fully-human, IgG1- based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumor with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET. Amivantamab is produced by mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of amivantamab is approximately 148 kDa.

The amivantamab final drug product (DP), RYBREVANT, is supplied in a vial as a sterile, colorless to pale yellow preservative-free solution, 50 mg/mL liquid concentrated solution for infusion. The pH is 5.7. Each single-use vial contains 350 mg of amivantamab, EDTA disodium salt dihydrate (0.14 mg), L-histidine (2.3 mg), L-histidine hydrochloride monohydrate (8.6 mg), L-methionine (7.0 mg), polysorbate 80 (4.2 mg), sucrose (595 mg), and water for injection. RYBREVANT must be diluted with either 5% dextrose solution or 0.9% sodium chloride solution.

## Quality Assessment Team:

| Discipline | Assessor | Branch/Division |
|---|---|---|
| Drug Substance (DS) | Andrea Franco | CDER/OPQ/OBP/DBRR IV |
| Drug Product (DP) | | |
| Immunogenicity assays | | |
| Labeling | CDR James Barlow | CDER/OPQ/OBP |

| | | |
|---|---|---|
| Microbiology and Facilities | Amy Devlin (DS)<br>Jeanne Finger (DP) | CDER/OPQ/OPMA/DBM |
| Team Leads | LCDR Leslie A. Rivera Rosado (Product Quality)<br>Frederick Mills (Immunogenicity)<br>Zhong Li (Facilities)<br>Maxwell Van Tassell (Micro) | CDER/OPQ/OBP/DBRR IV<br><br>CDER/OPQ/OPMA/DBM<br>CDER/OPQ/OPMA/DBM |
| Application Technical Lead | LCDR Leslie A. Rivera Rosado | CDER/OPQ/OBP/DBRR IV |
| Regulatory Business Project Manager | Anita Brown | CDER/OPQ/OPRO |

Multidisciplinary Assessment Team:

| Discipline | Reviewer | Office/Division |
|---|---|---|
| RPM | Sharon K. Sickafuse | OND/ORO/DROOD |
| Cross-disciplinary Team Lead | Erin Larkins (CDTL) | OOD/DO2 |
| Medical Officer | Katie Chon, Erin Larkins (CDTL) | OOO/DO2 |
| Pharm/Tox | Stephanie L. Aungst, Whitney S. Helms (TL) | OOO/DHOT |
| Clinical Pharmacology | Sriram Subramaniam, Hong Zhao (TL) | OCP/DCPI |
| Pharmacometrics | Yangbing Li, Jiang Liu (TL) | OCP/DPM |
| Genomics | Jielin Sun, Rosane Charlab Orbach (TL) | OCP/DTPM |
| Biostatistics | Somak Chatterjee, Pallavi Mishra-Kalyani (TL) | OB/DBV |
| OSI | Lee Pai-Scherf, Karen Bleich (TL) | OSI |
| OSE PM | Latonia Ford | OSE PM |
| OSE/DMEPA | Sali Mahmoud, Ashleigh Lowery (TL)<br>Ebony Whaley; Colleen Little (TL) | OSE/DMEPA |
| OSE/DRISK | Joyce Weaver, Naomi Boston (TL) | OSE/RISK |
| OSE/OPE/DEPI | Kate Gelperin, Steven Bird (TL) | OSE/OPE/DEPI |
| OSE/OPE/DVP | Peter Waldron, Afrouz Nayernama (TL) | OSE/OPE/DVP II |
| Labeling | Susan Redwood, Barbara Fuller (TL) | OMP/OMPI/DMPP |
| OPDP | Nazia Fatima | OPDP |

1. Names:

   a. Proprietary Name: RYBREVANT
   b. Trade Name: RYBREVANT
   c. Non-Proprietary Name/USAN/INN: amivantamab- vmjw

d. CAS registry number: 2171511-58-1
e. Common Name: Human IgG1 bispecific mAb against EGF and cMET receptors
f. Company Name(s): amivantamab, CNTO 4424, JNJ 61186372
g. Compendial Name: N/A
h. OBP systematic name: BsMAB HUMAN (IGG1) ANTI P00533 (EGFR_HUMAN) & ANTI P08581 (MET_HUMAN) [JNJ61186372]

Submissions Assessed:

| Submission(s) Reviewed | Document Date | Review Completed (Yes/No) |
|---|---|---|
| BLA 761210/1 (Original Submission) | 11/24/20020 | Yes |
| BLA 761210/6 (stability updates) | 12/21/2020 | Yes |
| BLA 761210/8 (Quality Response to Information Request) | 12/29/2020 | Yes |
| BLA 761210/15 (Updated Manufacturing Schedule) | 1/27/2021 | Yes |
| BLA 761210/35 (Quality Response to Information Request) | 4/14/2021 | Yes |
| BLA 761210/36 (Quality Response to Information Request) | 4/20/2021 | Yes |

# Quality Assessment Data Sheet:

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

A. DMFs:

| DMF # | DMF Type | DMF Holder | Item referenced | Code[1] | Status[2] | Date Assessment Completed | Comments |
|---|---|---|---|---|---|---|---|
| (b) (4) | | | | 3 | Adequate | 3-31-2021 | |
| | | | | 3 | Adequate | 3-31-2021 | |
| | | | | 3 | Adequate | 3-31-2021 | |
| | | | | 3 | Adequate | 3-31-2021 | |
| | | | | 3 | Adequate | 3-31-2021 | |
| | | | | 3 | Adequate | 3-31-2021 | |

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

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

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

| Document | Application Number | Description |
|---|---|---|
| IND | 135405 | IND submitted to the U.S. Food and Drug Administration (FDA) by Janssen Research and Development, LLC |
| PMA | P200010/S001 | Guardant Health's PMA supplemental (sPMA) application (P200010/S001) |
| | | (b) (4) |

3. Consults: None

4. Environmental Assessment of Claim of Categorical Exclusion:
Janssen Research & Development (a division of Janssen Pharmaceutica NV), Beerse Belgium, certifies that the referenced action meets the criteria for a categorical exclusion defined in the regulations (21 CFR 25.31[c]), and that to the knowledge of Janssen R&D, no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed.

# Executive Summary:

## I. Recommendations:

### A. Recommendation and Conclusion on Approvability:

The Office of Pharmaceutical Quality (OPQ), CDER, recommends approval of STN 761210 for RYBREVANT manufactured by Janssen Biotech, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of RYBREVANT is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. This recommendation is pending the pre-license inspection (PLI) of the Janssen Sciences Ireland UC, Cork, Ireland manufacturing facility.

### B. Approval Action Letter Language:

- Manufacturing location:
  (b) (4)
  - Drug Substance:
    - Janssen Sciences Ireland, UC (JSI): Barnahely, Ringaskiddy, Co. Cork, Ireland
  - Drug Product:
    - Cilag AG: Hochstrasse 201, 8200 Schaffhausen, Switzerland

- Dosage form and fill size:
  - Injection: 350 mg/7 mL solution in a single-use vial

- Dating period:
  - Drug Product: 18 months: 2-8 °C
  - Drug Substance: (b) (4)
    (b) (4)
  - Stability Option:
    - Limited stability data [less than 3 full scale lots (and the applicant is committed to continue stability testing)]

- Results of on-going stability should be submitted throughout the dating period, as they become available, including the results of stability studies from the first three production lots.

- For stability protocols:
  - We have approved the stability protocol(s) in your license application for the purpose of extending the expiration dating of your (b) (4) drug substance, and drug product under 21 CFR 601.12.

- Exempt from lot release:
  - Yes
  - Rationale, if exempted: RYBREVANT (amivantamab-vmjw) is exempted from lot release per FR 95-29960.

C. Benefit/Risk Considerations:

The review of manufacturing information provided in the application has concluded that the methodologies and processes used for drug substance and drug product manufacturing, release and stability testing are robust and sufficiently controlled to result in a consistent and safe product. The drug substance manufacturing process is robust for removal of adventitious agents. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

The amivantamab (b) (4) drug substance (DS) will be manufactured at Janssen Sciences Ireland UC (JSI) Barnahely Ringaskiddy, Co. Cork, Ireland (FEI# 3007029098) (Stages 6-14 of the manufacturing process), and the drug product (DP) will be manufactured at Cilag AG: Hochstrasse 201, 8200 Schaffhausen, Switzerland (FEI# 3002806695). Pre-licensing inspection was conducted at JSI and record review in lieu of an on-site inspection was performed (b) (4). The facilities were found acceptable for the proposed operations. At the time this document was finalized, the pre-license inspection at JSI was not completed.

The immunogenicity assays are sufficiently sensitive to detect anti-drug antibodies (ADA) in the presence of amivantamab at plasma concentrations.

Individual reviews for each discipline, (1) Drug Product Quality Review (which includes review of drug substance intermediates, drug substance, and drug product quality and review of immunogenicity assays), (2) Microbiology Quality Review (which includes microbiological control of drug substance and drug product), (3) Facilities Quality Review, and (4) Quality Labeling Review are located as separate documents in Panorama (link).

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

None.

## II. Summary of Quality Assessments:

### A. CQA Identification, Risk and Lifecycle Knowledge Management

Table 1 is a summary of product-related critical quality attributes, intrinsic to the molecule, that are relevant to both drug substance (DS) and drug product (DP). The table includes the identification of the various attributes along with their risk management.

Table 1: Active Pharmaceutical Ingredient CQA Identification, Risk and Lifecycle Knowledge Management (see example in Attachment 1)

| CQA (type) | CQA | Risk (efficacy, PK/PD, immunogenicity and safety | Origin | Control Strategy |
|---|---|---|---|---|
| Identity | Identity (dot blot) | safety | Intrinsic to molecule | (b) (4) |
| Potency (biological activity) | cMET binding (cMET binding assay) (TR-FRET assay) | Efficacy | Intrinsic to molecule | |
| | EGFR binding (EGFR binding assay) (TR-FRET assay) | Efficacy | Intrinsic to molecule | |
| | EGFR ADCC (EGFR ADCC assay) | Efficacy | Intrinsic to molecule | |
| | FcγRI and FcγRIIa (FcγRI and FcγRIIa binding assay) | Efficacy | Intrinsic to molecule | |

| | | | |
|---|---|---|---|
| | FcγRIIIa testing (FcγRIIIa binding assay) | Efficacy | Intrinsic to molecule |
| | FcRn (FcRn binding assay) | PK | Intrinsic to molecule |
| Product related variants/impurities | Charge variants (cIEF) | Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA | (b) (4) |
| | (b) (4) | Efficacy | |
| | High molecular weight species (HMWS) (SE-HPLC) | Efficacy or immunogenicity | |
| | Low molecular weight species (LMWS) (cSDS) | Efficacy | |
| | Higher Order Protein Structure (CD, DSC, AUC) | Efficacy | Intrinsic to the molecule |
| | (b) (4) Oxidation (b) (4) (b) (4) | Efficacy | (b) (4) |

| | | | |
|---|---|---|---|
| Protein Structure | (b) (4) Oxidation and (b) (4) Oxidation, (b) (4) (b) (4) | Efficacy | (b) (4) |
| | (b) (4) (b) (4) Oxidation (b) (4) | PK | |
| | (b) (4) Oxidation (b) (4) | PK | |
| | (b) (4) Deamidation (b) (4) | Efficacy | |
| | Isomerization (b) (4) (b) (4) | Efficacy | |
| | Sequence Variant (b) (4) (b) (4) | Classified as pCQA due to knowledge uncertainty and treated as CQA for commercial production. | Cell line (WCB lot) (b) (4) |
| Carbohydrate Structure | AGHC (b) (4) | Efficacy | (b) (4) |
| | Fucosylation, galactosylation, and (b) (4) (b) (4) (HILIC) | Efficacy for fucosylation. galactosylation and (b) (4) are Classified as pCQA due to knowledge uncertainty and treated as CQA for commercial production. | |
| Disulfide Structure | Disulfide Structure (b) (4) (b) (4) | Efficacy | |

| | | | |
|---|---|---|---|
| | (b) (4) | Efficacy | (b) (4) |

DS: Drug Substance; DP: Drug Product: CQA: Critical Quality Attribute; MCB: Master Cell Bank; WCB: Working Cell Bank; ADCC: Antibody Dependent Cellular Cytotoxicity; (b) (4) SE-HPLC: Size exclusion high performance liquid chromatography; cIEF: Capillary isoelectric focusing; AUC: Analytical ultracentrifugation, CD: Circular dichroism; DSC: Differential scanning calorimetry; FAE: Fab-arm exchange; PK/PD: Pharmacokinetic/Pharmacodynamic; cMET: Mesenchymal-epithelial transition factor; EGFR: Epidermal growth factor receptor; HILIC: Hydrophilic interaction liquid chromatography; AGHC: Aglycosylated heavy chain; TR-FRET: time-resolved fluorescence resonance energy transfer.

## B. Drug Substance Amivantamab Quality Summary

Table 2 provides a summary of the identification, risk, and lifecycle knowledge management for drug substance CQAs that derive from the drug substance manufacturing process and general drug substance attributes, including process-related impurities.

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

| CQA (type) | CQA | Risk | Origin | Control Strategy |
|---|---|---|---|---|
| Process-Related Impurities | (b) (4) | Safety | (b) (4) | (b) (4) |
| | | Safety | | |
| | | Safety | | |

| | | | | |
|---|---|---|---|---|
| | (b) (4) | Efficacy | | (b) (4) |
| | Microbial contamination (bioburden/sterility) (bioburden, sterility, CCIT) | Safety | | |
| | Endotoxin/ pyrogen | Safety | | |
| | Adventitious Virus | Safety | | |
| | Mycoplasma | Safety | | |
| | Endogenous virus (TEM) | Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA | | |
| | Color of solution | Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA | Intrinsic to the molecule | (b) (4) |

| | | | |
|---|---|---|---|
| Composition and Strength | pH | Safety | (b) (4) |
| | Osmolality | Safety | |
| | Protein Concentration (b) (4) | Efficacy | |

DS: Drug Substance; DP: Drug Product; (b) (4) MCB: Master Cell Bank; WCB: Working Cell Bank; CQA: Critical Quality Attribute; PK/PD: Pharmacokinetic/Pharmacodynamic; TEM: Transmission Electron Microscopy.

- Description:
  Amivantamab is a human low-fucose IgG1 bispecific antibody against EGF and cMET receptors. Amivantamab is produced by cultivation of recombinant CHO cells with specificity for EGFR and cMET and has a molecular mass of 148209 Da for the major glycoform. Amivantamab consists of 2 heavy chains (HC) and 2 light chains (LC), joined by disulfide bonds. It is prepared by (b) (4)
  (b) (4)

- Mechanism of Action (MoA):
  Amivantamab binds to the extracellular domains of EGFR and MET, with immune cell-directing activity that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab disrupts EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumor growth and progression. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

- Potency Assays:
  - ADCC bioactivity: The determination of antibody dependent cell-mediated cytotoxicity (ADCC) bioactivity (relative potency) of amivantamab drug substance (DS) and drug product (DP) test articles is measured using a commercially available gene reporter kit, which uses engineered Jurkat cells that express the FcγRIIIa receptor. Amivantamab binds to antigens on the cell-surface of target cells. The FcγRIIIa receptors on the effector cells recognize the target cell-bound antibodies and trigger a signal transduction cascade through the

nuclear factor of activated T-cells (NFAT) pathway activating firefly luciferase expression. The luciferase activity in the effector cells is quantified by measuring the luminescence, which is related to the degree of effector cell FcγRIIIa receptor binding to the antibody co-engaged with target cells and serves as surrogate for cellular ADCC activity. The signal obtained is plotted against amivantamab concentration and analyzed by a 4-parameter curve fit. The potency of test articles is calculated relative to the amivantamab reference material (RM) and expressed as a percentage.

- cMET binding: The structural integrity of the c-mesenchymal-epithelial transition factor receptor (cMET) binding Fab portion of amivantamab is assessed by a cMET binding assay. In vitro binding of amivantamab to cMET is demonstrated using a competitive time-resolved fluorescence resonance energy transfer (TR-FRET) assay format. Varying concentrations of unlabeled test article compete with donor fluorophore (Europium (Eu) chelate) labeled amivantamab for binding to an acceptor fluorophore (Cy5) labeled cMET. Excitation of the donor fluorophore results in a transfer of energy to the bound acceptor fluorophore. The resultant fluorescence resonance energy transfer (FRET) is detected as the emission of light at 665 nm using a microplate reader capable of measuring time-resolved fluorescence. The signal obtained is plotted against amivantamab concentration and the potency calculated relative to the reference material and expressed as a percentage.

- Reference Materials:

(b) (4)

- Critical starting materials:

(b) (4)

- (b) (4)

- Manufacturing process summary:

(b) (4)

- Container closure:
  - The container closure system used (b) (4) is a single use, (b) (4) container with a (b) (4) closure (b) (4).

- Dating period and storage conditions:
  - Drug Substance: (b) (4) (b) (4)

C. Drug Product Rybrevant Quality Summary:

Table 3 provides a summary of the identification, risk, and lifecycle knowledge management for drug product CQAs that derive from the drug product manufacturing process and general drug product attributes.

Table 3: Drug Product CQA Identification, Risk, and Lifecycle Management (see example in Attachment 3)

| CQA (type) | CQA | Risk | Origin | Control Strategy |
|---|---|---|---|---|
| Particles (product or process related impurities) | Visible foreign particles (visual inspection) | Safety, Immunogenicity | DP manufacturing process, CCS, and product | (b) (4) |
| | Visible translucent particles (MIDI) | Safety, Immunogenicity | DP manufacturing process, CCS, product, and DP storage | |
| | Sub-visible particles (HIAC) | Safety, Immunogenicity | DP manufacturing process, CCS and product | |
| Volume in container | Extractable Volume | Efficacy | DP process (b) (4) | |
| Contamination | Microbial contamination (sterility) (sterility and CCIT) | Safety, purity, and efficacy (degradation or modification of the product by contaminating microorganisms) | DP manufacturing process, container closure integrity failure | |
| | Bacterial endotoxin | Safety, purity, and immunogenicity | Raw materials, contamination during DP manufacturing process | |

| | | | | |
|---|---|---|---|---|
| | Container closure integrity (CCIT) | Safety (maintenance of sterility during shelf-life) | Container closure breaches during manufacturing or storage. May be impacted by storage conditions. | (b) (4) |
| Composition and strength | Protein Concentration (b) (4) | Efficacy (bioactivity) | DP manufacturing process | |
| | pH | Safety | Formulation | |
| | (b) (4) | Stability, aggregate formation | Formulation | |
| | Appearance of primary container | Although it does not have impact on efficacy, PK/PD, immunogenicity, and safety, it is classified as CQA | DP manufacturing process and raw material | |
| | Color | Safety | Intrinsic to the molecule, formulation | |
| | Osmolality | Safety, stability, bioactivity | Formulation | |
| | Excipient concentration (histidine, sucrose, EDTA, and methionine) (HPLC/UHPLC excipient assays) | Stability and product oxidation | Formulation | |
| | Turbidity | Safety | Formulation, (b) (4) | |

CCIT: container closure integrity testing; CCS: container closure system; DP: Drug Product; MIDI: microflow digital imaging; EDTA: Ethylenediaminetetraacetic acid; (b) (4).

- Potency and Strength: 50 mg/mL liquid concentrate for infusion
- Summary of Product Design: Each vial contains 350 mg of amivantamab in a 7.0 mL nominal fill volume and an excess volume (b) (4). The proposed excess volume of (b) (4) is the USP<1151> recommended excess volume for (b) (4) The DP is intended for administration by the intravenous (IV) route after dilution in commercially available 5% dextrose (glucose) or 0.9% Normal Saline (NS).

- List of Excipients: (b) (4) L-histidine, (b) (4) L-histidine Hydrochloride Monohydrate, (b) (4) sucrose, (b) (4) (b) (4) Polysorbate-80 (b) (4) (b) (4) L-methionine, (b) (4) EDTA Disodium Salt Dihydrate.
- Reference Materials: (b) (4).
- Manufacturing process summary: (b) (4)
- Container closure: 8 mL Type 1 glass vial closed with a (b) (4) stopper and (b) (4) aluminum seal with a flip-off cap.
- Dating period and storage conditions: The shelf life of the DP is 18 months when stored at the recommended storage condition of 5 ± 3 °C and protected from light.

D. Novel Approaches/Precedents:
None.

E. Any Special Product Quality Labeling Recommendations:
- Single-dose vials
- Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light.
- Visually inspect RYBREVANT for particles or discoloration prior to administration.

F. Establishment Information:

| Overall Recommendation: | | | | | |
|---|---|---|---|---|---|
| DRUG SUBSTANCE | | | | | |
| Function | Site Information | DUNS/FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |
| Drug Substance Manufacturer | Janssen Sciences Ireland UC, Cork, Ireland | 3007029098 | PLI needed | | Pending PLI |
| Parental Antibody Manufacturer | (b) (4) | | 704 (a) (4) records review | NA | Approve- Based on 704 (a) (4) |

| | | | | | |
|---|---|---|---|---|---|
| Analytical Testing for Drug Substance | [redacted] (b) (4) | | NA | NA | Approve – Based on Previous History |
| DRUG PRODUCT | | | | | |
| Function | Site Information | DUNS/FEI Number | Preliminary Assessment | Inspectional Observations | Final Recommendation |
| Drug Product Manufacturer, Analytical Testing for Drug Substance | Cilag AG, Schaffhausen, Switzerland | 3002806695 | PLI waiver assessment; firm has other FDA-approved BLAs; good inspection history | NA | PLI waiver granted |
| Analytical Testing for Drug Substance and Drug Product | Janssen Biologics B.V., Leiden, The Netherlands | 3002806632 | NA | NA | Approve – Based on Previous History |

G. Facilities:

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for [redacted] (b) (4) Janssen Sciences Ireland UC (FEI 3007029098) (both are proposed for DS manufacture) and Cilag AG (FEI 3002806695), proposed for DP manufacture. All proposed manufacturing and testing facilities except the DS site Janssen Sciences Ireland UC (FEI 3007029098) are acceptable based on their currently acceptable CGMP compliance status, recent relevant inspectional coverage, and 704 (a) (4) records review, as applicable. The facilities recommendation is currently pending the PLI at the DS site Janssen Sciences Ireland UC (FEI 3007029098).

H. Lifecycle Knowledge Management:

1. Protocols submitted to the BLA

| Items | Purpose of the Protocol | BLA link | Reporting category |
|---|---|---|---|
| Primary and Working Reference Materials | Preparation and qualification of future primary and working reference materials | Section 3.2.S.5 Future Primary and Working reference Materials Preparation and Qualification | Annual Report |
| (b) (4) | | Section 3.2.S.7.2 Post-approval Stability Commitment | Annual Report |
| Amivantamab Drug Product | Shelf-life extension based on full shelf-life data on three commercial-scale batches | Section 3.2.P.8.2 Stability Commitment | Annual Report |
| Introduction of new product at JSI | Comparability protocol for the introduction of new products at JSI | Section 3.2.R Comparability Protocol, New Product Introduction-JSI | Annual Report |
| Introduction of new product at Cilag AG | Comparability protocol for the introduction of new products at Cilag AG | Section 32.R Comparability Protocol, New Product Introduction-Cilag | Annual Report |

2. Outstanding assessment issues/residual risk: None identified
3. Future inspection points to consider: Review the performance of the analytical methods used for release, stability, and in-process testing.

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**This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.**

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/s/

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CHRISTOPHER D DOWNEY
04/28/2021 06:02:51 PM

# PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
# Memorandum of Review to the File

| | |
|---|---|
| **Application ID** | BLA 761210 |
| **Submission Type** | Original BLA |
| **Drug Product Name** | JNJ-61186372 (amivantamab) |
| **Strengths** | 350 mg |
| **Dosage Form** | Solution for dilution |
| **Administration Route** | Intravenous |
| **Indication** | Treatment of patients with metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy |
| **Applicant Name** | Janssen Biotech, Inc. |
| **US License Number** | 1864 |
| **Application Type** | 351 (a) |
| **Primary Reviewer** | Amy Devlin, Ph.D., Microbiologist, OPQ/OPMA/DBM1 |
| **Secondary Reviewer** | Maxwell Van Tassell, Ph.D., SPQA,<br>Zhong Li, Ph.D., SPQA, OPQ/OPMA/DBM1 |
| **Goal Date** | July 24, 2021 |

## Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective and is recommended for Approval.
- Manufacturing Facility Assessment Recommendation: Pending PLI.
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

### Summary Basis of Recommendation (DS):

Overall, the process is under adequate microbial control. Microbial quality is controlled at each step of the manufacturing process (b) (4) (b) (4). Bioburden and endotoxin samples are monitored at each critical step of the manufacturing process and at DS release. Microbial control (b) (4) (b) (4) was demonstrated by microbial monitoring in their lifetime studies. Adequate controls are in place to maintain microbiological product quality during maximum hold periods and throughout the manufacturing process.

Adequate descriptions of the facilities, equipment, environmental controls, cleaning and contamination control strategy were provided for (b) (4) (b) (4) (b) (4) Janssen Sciences Ireland UC (FEI 3007029098), proposed for JNJ-61186372 (amivantamab) DS manufacture. All proposed manufacturing and testing facilities are acceptable (pending Janssen Sciences Ireland UC PLI outcome) based on their current cGMP compliance status and recent relevant inspectional coverage.

**Drug Substance CQA Process Risk Identification and Lifecycle Knowledge Management:**

| CQA (type) | Risk | Origin | Control Strategy |
|---|---|---|---|
| Endotoxin | Safety, Purity | Raw materials, manufacturing process | (b) (4) [redacted] |
| Bioburden | Safety, Purity and Efficacy due to degradation or modification of the product by microbial contamination | Raw materials, manufacturing process | |

**List Submissions being assessed (Table):**

| Document Description (SD #) | Date Received |
|---|---|
| Original submission (0002) | 11/24/2020 |
| Response to FDA IR sent 04/01/2021 (0035) | 04/14/2021 |
| Response to FDA IR sent 04/12/2021 (0036) | 04/19/2021 |

# MODULE 3.2.S

**Module 3.2.S Lifecycle Management Considerations**

| | |
|---|---|
| **Lifecycle considerations:** | No |
| **Post-approval inspection?** | No |

## S.1 General Information

Amivantamab is a low-fucose, human IgG1-based EGFR-MET bispecific antibody that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications by binding to the extracellular domains of EGFR and MET. Amivantamab consists of two heavy and two light chains joined by disulfide bonds. The relative molecular mass of the molecule is 148209 Da for the major glycoform. Amivantamab is manufactured using two recombinant CHO cell lines.

***Reviewer's Comment: For Information***

## S.2 Manufacture

(b) (4) [redacted]

Amy Devlin

Digitally signed by Amy Devlin
Date: 4/27/2021 10:19:52PM
GUID: 5bad1e590013e11cfb94f1c3a1ef8f84

Zhong Li

Digitally signed by Zhong Li
Date: 4/27/2021 10:20:15PM
GUID: 5452326f000475beaec6af628762212a

Maxwell Van Tassell

Digitally signed by Maxwell Van Tassell
Date: 4/28/2021 07:26:42AM
GUID: 588f9a18000bb6ac3ec7300751755758

# BLA STN 761210

**Rybrevant (amivantamab- vmjw)**

**Janssen Biotech, Inc.**

**Andrea Franco, Ph.D., Staff Fellow**
**Frederick Mills, Ph.D., Biologist**
**Leslie A. Rivera Rosado, Ph.D., Team Lead**
**Christopher Downey, Ph.D., Review Chief**

**Office of Biotechnology Product**
**Division of Biotechnology Review and Research IV**

# OBP CMC Review Data Sheet

1. **BLA#:** STN 761210

2. **REVIEW DATE:** 4/19/2021

3. **PRIMARY PRODUCT QUALITY REVIEW TEAM:**

| Discipline | Reviewer | Branch/Division |
|---|---|---|
| Drug Substance (DS), Drug Product (DP), and Immunogenicity assays | Andrea Franco | OPQ/OBP/DBRR IV |
| Inspection of DS site | LCDR Leslie Ann Rivera Rosado | OPQ/OBP/DBRR IV |
| Labeling | CDR James Barlow | OPQ/OBP |
| DS Facilities/ Microbiology | Amy Devlin | OPQ/OPMA/DBM |
| DP Facility/Microbiology | Jeanne Finger | OPQ/OPMA/DBM |
| Team Leads | LCDR Leslie A. Rivera Rosado (Product quality)<br>Frederick Mills (Immunogenicity assays)<br>Zhong Li (Facility)<br>Maxwell Van Tassell (Microbiology) | OPQ/OBP/DBRR IV<br>OPQ/OBP/DBRR IV<br>OPQ/OPMA/DBM<br>OPQ/OPMA/DBM |
| OPQ RBPM | Anita Brown | OPQ/OPRO |
| Application Technical Lead | LCDR Leslie A. Rivera Rosado | OPQ/OBP/DBRR IV |

**Multidisciplinary Review Team:**

| Discipline | Reviewer | Office/Division |
|---|---|---|
| RPM | Sharon K. Sickafuse | OND/ORO/DROOD |
| Cross-disciplinary Team Lead | Erin Larkins (CDTL) | OOD/DO2 |
| Medical Officer | Katie Chon, Erin Larkins (CDTL) | OOO/DO2 |
| Pharm/Tox | Stephanie L. Aungst, Whitney S. Helms (TL) | OOO/DHOT |
| Clinical Pharmacology | Sriram Subramaniam, Hong Zhao (TL) | OCP/DCPI |
| Pharmacometrics | Yangbing Li, Jiang Liu (TL) | OCP/DPM |
| Genomics | Jielin Sun, Rosane Charlab Orbach (TL) | OCP/DTPM |
| Biostatistics | Somak Chatterjee, Pallavi Mishra-Kalyani (TL) | OB/DBV |
| OSI | Lee Pai-Scherf, Karen Bleich (TL) | OSI |
| OSE PM | Latonia Ford | OSE PM |
| OSE/DMEPA | Sali Mahmoud, Ashleigh Lowery (TL)<br>Ebony Whaley; Colleen Little (TL) | OSE/DMEPA |
| OSE/DRISK | Joyce Weaver, Naomi Boston (TL) | OSE/RISK |
| OSE/OPE/DEPI | Kate Gelperin, Steven Bird (TL) | OSE/OPE/DEPI |
| OSE/OPE/DVP | Peter Waldron, Afrouz Nayernama (TL) | OSE/OPE/DVP II |
| Labeling | Susan Redwood, Barbara Fuller (TL) | OMP/OMPI/DMPP |
| OPDP | Nazia Fatima | OPDP |

4. **MAJOR GRMP DEADLINES**

**Filing Meeting:** 11-1-2021
**Mid-Cycle Meeting:** 2-24-2021 (internal); 3-10-2021 (meeting with Janssen)
**Wrap-Up Meeting: N/A**
**Primary Review Due:** 4-23-2021
**Secondary Review Due:** 4-28-2021
**CDTL Memo Due:** 5-7-2021
**PDUFA Action Date:** 7-23-2021 (target action date 5-21-2021)

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

| Communication/Document | Date |
|---|---|
| CMC Pre-BLA Meeting | Meeting requested on 6/2/2020. The meeting was canceled by Janssen on 7/30/2020 |
| Filing meeting with OND | 12/15/2020 |
| Orientation meeting with Janssen | 12/18/2020 |
| Information request #1 (OPMA) | 12/22/2020 |
| Filing meeting with Janssen | 1/11/2021 |
| Midcycle meeting with OND | 2/24/2021 |
| Midcycle meeting with Janssen | 3/10/2021 |
| Labeling meeting with OND | 3/15/2021 |
| Information request #2 (OPMA and OBP) | 4/1/2021 |
| Information request #3 (OPMA and OBP) | 4/12/2021 |

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

| Submission | Date Received | Review Completed (Yes/No) |
|---|---|---|
| STN 761210/2 | 11/24/2020 | Yes |
| STN 761210 /6 (Stability updates and results for oligosaccharide map from process validation lots 966554C and 966881C) | 12/21/2020 | Yes |
| STN 761210 /8 (response to IR #1 - OPMA) | 12/29/2020 | Yes |
| STN 761210/15 (updated manufacturing schedule) | 1/27/2021 | Yes |
| STN 761210/35 (response to IR #2 - OPMA and OBP) | 4/12/2021 (file in docuBridge dated 4/14/2021) | Yes |
| STN 761210/36 (response to IR #3 – OPMA and OBP) | 4/19/2021 (file in docuBridge dated 4/20/2021) | Yes |

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

a. Proprietary Name: Rybrevant
b. Trade Name: Rybrevant
c. Non-Proprietary/USAN: Amivantamab-xxx

d. CAS name: 2171511-58-1
e. Common name: JNJ-61186372
f. INN Name: Amivantamab
g. Compendial Name: N/A
h. OBP systematic name: BsMAB HUMAN (IGG1) ANTI P00533 (EGFR_HUMAN) & ANTI P08581 (MET_HUMAN) [JNJ61186372]
i. Other Names: JNJ-61186372

8. **PHARMACOLOGICAL CATEGORY:** Anti-neoplastic

9. **DOSAGE FORM:** Injection

10. **STRENGTH/POTENCY:**
(i) The concentration/strength of the Drug Product: 50 mg/mL / 150 mg and 350 mg
(ii) Type of potency assay (s): EGFR antigen dependent cellular cytotoxicity (ADCC) cell-based assay and cMET competitive time-resolved fluorescence resonance energy transfer (TR-FRET) assay

11. **ROUTE OF ADMINISTRATION:** Intravenous Infusion

12. **REFERENCED MASTER FILES:**

| DMF # | HOLDER | ITEM REFERENCED | Letter of Cross-Reference | COMMENTS (STATUS) |
|---|---|---|---|---|
| (b) (4) | | | yes | No review required as all the relevant information related to compatibility with the product was in the BLA. |
| | | | yes | No review required as all the relevant information related to compatibility with the product was in the BLA. |
| | | | yes | No review required as all the relevant information related to compatibility with the product was in the BLA. |
| | | | yes | No review required as all the relevant information related to compatibility with the product was in the BLA. |

| | | |
|---|---|---|
| (b) (4) | yes | No review required as all the relevant information related to compatibility with the product was in the BLA. |
| | yes | No review required as all the relevant information related to compatibility with the product was in the BLA. |

## 13. INSPECTIONAL ACTIVITIES

The amivantamab drug substance (DS) is manufactured at (b) (4) (b) (4) and at Janssen Sciences Ireland UC (JSI) (FEI# 3007029098) (stages 6 -14). The drug product (DP) is manufactured at Cilag AG (FEI# 3002806695). Pre-license inspection were conducted at JSI on April 26 – 30, 2021, by Dr. Sarah Johnson and Dr. Madushini Dharmasena, and record review in lieu of an on-site inspection was performed for (b) (4). The pre-license inspection for Cilag AG was waved. At the time this document was finalized, the pre-license inspection at JSI and the record review for the (b) (4) site were not completed.

## 14. CONSULTS REQUESTED BY OBP

None

## 15. QUALITY BY DESIGN ELEMENTS

The following was submitted in the identification of QbD elements (check all that apply):

| | |
|---|---|
| | Design Space |
| | Design of Experiments |
| x | Formal Risk Assessment / Risk Management |
| | Multivariate Statistical Process Control |
| | Process Analytical Technology |
| | Expanded Change Protocol |

Risk assessments to identify critical quality attributes of amivantamab and to identify process parameters for assessment in process characterization studies were performed according to methods described in the submission and review of Module 3.

## 16. PRECEDENTS

None

## 17. ADMINISTRATIVE

A. Signature Block

| Name and Title | Signature and Date |
|---|---|
| **Christopher Downey, Ph.D.**<br>Review Chief<br>Division of Biotechnology Review and Research IV (DBRR IV)<br>Office of Biotechnology Products (OBP)<br>Office of Pharmaceutical Quality (OPQ) | See attached |
| **Christopher Downey, on behalf of LCDR Leslie Ann Rivera Rosado, Ph.D.**<br>Product Quality Team Leader<br>DBRR IV, OBP, OPQ | See attached |
| **Frederick Mills, Ph.D.**<br>Biologist<br>DBRR IV, OBP, OPQ | See attached |
| **Andrea Franco, Ph.D.**<br>Product Quality Reviewer<br>DBRR IV, OBP, OPQ | See attached |

B. CC Block

| Recipient | Date |
|---|---|
| Sharon K. Sickafuse<br>Clinical Division BLA RPM | |
| OBP/DBRR IV<br>File/BLA STN 761210 | |

# SUMMARY OF QUALITY ASSESSMENTS

I. Primary Reviewer Summary Recommendation

The Office of Biotechnology Products recommends approval of BLA 761210 for Rybrevant (amivantamab- vmjw) manufactured by Janssen Biotech, Inc. from a product quality perspective based on the review of the information and data provided in the application.

II. List Of Deficiencies To Be Communicated

Not applicable.

III. List Of Post-Marketing Commitments/Requirement

In response to the Information Request response received on 4/12/2021, Janssen committed to submit an updated protocol for the qualification of new working cell banks (WCBs) at future time as prior approval supplement (PAS) to the approved BLA.

IV. Review Of Common Technical Document-Quality Module 1

A. Environmental Assessment Or Claim Of Categorical Exclusion

In Module 1 (1.12.14 Environmental Assessment – Claim for Categorical Exclusion), Janssen claims categorical exclusion, in accordance with 21 CFR 25.31(c), from the requirement to prepare an Environmental Assessment as Janssen Research & Development (a division of Janssen Pharmaceutica NV), Beerse Belgium, certifies that the referenced action meets the criteria for a categorical exclusion defined in the regulations (21 CFR 25.31[c]), and that to the knowledge of Janssen R&D, no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed.

***Assessor's Comment**: The claim of categorical exclusion is acceptable.*

V. Primary Container Labeling Review

Refer to review by CDR James Barlow.

VI. Review Of Common Technical Document-Quality Module 3.2

This document.

VII. Review Of Immunogenicity Assays – Module 5.3.1.4

This document.

# Contents

**DESCRIPTION OF DRUG SUBSTANCE AND DRUG PRODUCT**

Rybrevant is indicated for the treatment of patients with metastatic non-small cell lung cancer with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy. On 3/9/2021, Rybrevant was granted a breakthrough therapy designation and on 1/25/2021 was granted a priority review.

## S. DRUG SUBSTANCE

(b) (4)

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Frederick Mills

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Christopher Downey

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# PRODUCT QUALITY MICROBIOLOGY/FACILITY ASSESSMENT
# Memorandum of Review to the File

| | |
|---|---|
| **Application ID** | BLA 761210 |
| **Submission Type** | Original BLA |
| **Drug Product Name** | amivantamab |
| **Strengths** | 350 mg per vial |
| **Dosage Form** | solution for dilution in vial |
| **Administration Route** | intravenous infusion |
| **Indication** | Metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy |
| **Applicant Name** | Janssen Biotech, Inc. |
| **US License Number** | 1864 |
| **Application Type** | 351 (a) |
| **Primary Reviewer** | Jeanne Fringer, CDER/OPQ/OPMA/DBM/Branch 1 |
| **Secondary Reviewer** | Maxwell Van Tassell (micro), CDER/OPQ/OPMA/DBM/Branch 1<br>Zhong Li (facilities), CDER/OPQ/OPMA/DBM/Branch 1 |
| **Goal Date** | 23Jul2021 |

## Recommendation for Approvability:

- This BLA was reviewed from a product quality microbiology perspective and sterility assurance perspective and is recommended for Approval.
- Drug Product Manufacturing Facility Assessment Recommendation: Approval
- Product quality aspects not related to microbial control and facilities should be reviewed by OBP.

## Summary Basis of Recommendation (DP):

All sterile drug product-contact equipment and components are sterilized and depyrogenated using validated processes. The drug product is sterilized using a validated (b) (4) process and (b) (4) is integrity tested after use. (b) (4) (b) (4) (b) (4). Bioburden and endotoxin are tested during manufacture, and sterility and endotoxin are tested at release. Container closure integrity testing using a validated method is included in the stability program.

**Drug Product CQA Process Risk Identification and Lifecycle Knowledge Management:**

| CQA (type) | Risk | Origin | Control Strategy | Other |
|---|---|---|---|---|
| Sterility (Contaminant) | Safety, Purity, and Efficacy | Manufacturing process, failure of the container closure integrity | (b) (4) | |

| | | | | |
|---|---|---|---|---|
| Endotoxin (Contaminant) | Safety, Purity | Raw materials, manufacturing process | (b) (4) | |
| Container closure integrity (Sterility assurance) | Safety (Sterility assurance) | Breach during manufacture or storage | | |

**List Submissions being assessed (Table):**

| Document Description (SD #) | Date Received |
|---|---|
| BLA-761210-ORIG-1 (001) | 06Nov2020 |
| Quality/Response to IR (SD#008) | 29Dec2020 |
| Quality/Response to IR (SD#0035) | 14Apr2021 |

**List of DMFs assessed (Table):**

| DMF # | Date Reviewed | Finding | Document Reference |
|---|---|---|---|
| (b) (4) | 04/09/2018 | Adequate | (b) (4) m06r01.docx |

# Application Submission Background

***Reviewer's Comment: For Information***
BLA-761210 is submitted by Janssen Biotech, Inc., for the approval of amivantamab, 350mg solution for infusion, manufactured in 8mL vials. The application is a priority review for the treatment of lung cancer. The DP is manufactured at Cilag AG in Switzerland. The DP facility was given an inspection waiver due to having other FDA approved BLAs on the same (b) (4) line, its use of (b) (4), and a good history of inspection.

# MODULE 1
## 1.14 LABELING
***Reconstitution and Dilution Instructions***
Dosage and administration is of the DP shown below in Table 1:

**Table 1: Recommended Dose of TRADENAME**

| Body Weight of Patient at Baseline* | Recommended Dose | Number of 350 mg/7 mL TRADENAME Vials |
|---|---|---|
| Less than 80 kg | 1050 mg | 3 |
| Greater than or equal to 80 kg | 1400 mg | 4 |

* Dose adjustments not required for subsequent body weight changes.

Infusion rates are shown in Table 3:

Table 3: Infusion Rates for TRADENAME Administration

| 1050 mg Dose | | | |
|---|---|---|---|
| **Week** | **Dose (per 250 mL bag)** | **Initial Infusion Rate** | **Subsequent Infusion Rate†** |
| **Week 1 (split dose infusion)** | | | |
| Week 1 *Day 1* | 350 mg | 50 mL/hr | 75 mL/hr |
| Week 1 *Day 2* | 700 mg | 50 mL/hr | 75 mL/hr |
| **Week 2** | 1050 mg | 85 mL/hr | |
| **Subsequent weeks*** | 1050 mg | 125 mL/hr | |
| **1400 mg Dose** | | | |
| **Week** | **Dose (per 250 mL bag)** | **Initial Infusion Rate** | **Subsequent Infusion Rate†** |
| **Week 1 (split dose infusion)** | | | |
| Week 1 *Day 1* | 350 mg | 50 mL/hr | 75 mL/hr |
| Week 1 *Day 2* | 1050 mg | 35 mL/hr | 50 mL/hr |
| **Week 2** | 1400 mg | 65 mL/hr | |
| **Week 3** | 1400 mg | 85 mL/hr | |
| **Subsequent weeks*** | 1400 mg | 125 mL/hr | |

* After Week 4, patients are dosed every 2 weeks.

† Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.

For administration, 7 mL should be withdrawn from either 5% dextrose solution or 0.9% sodium chloride solution from a 250 mL infusion bag, then 7 mL should be withdrawn from the DP vial and added to the infusion bag. The diluted solutions should be administered within 10h (including infusion time) at room temperature (15°C to 25°C). The intravenous infusion set must include an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer).

***Reviewer's Comment:*** *See P.2.6 microbial challenge studies in support of the storage conditions for DP.*

# MODULE 3.2.P

**Module 3.2.P Lifecycle Management Considerations**

| | |
|---|---|
| **Lifecycle considerations:** | No |
| **Post-approval inspection?** | No |

# P.1 Description and Composition of the Drug Product

Amivantamab (JNJ-61186372) is 7 mL, 350mg/mL DP in an 8 mL Type 1 glass vial with an elastomeric closure and an aluminum seal with a flip off cap. It is diluted in 5% dextrose (glucose) or 0.9% Normal Saline (NS) for infusion. The composition of DP consists of 350mg amivantamab, 2.3mg L-histidine, 8.6mg L-histidine hydrochloride, 595mg monohydrate sucrose, 4.2mg polysorbate 80 (b) (4), 7.0mg L-Methionine, 0.14mg EDTA, and WFI. Final pH is 5.7. DP is (b) (4).

***Reviewer's Comment: For Information***

# P.2 Pharmaceutical Development

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Jeanne Fringer

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Zhong Li

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Maxwell Van Tassell

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