CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761210Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABELING

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 14, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761210
Product Name and Strength:	Rybrevant (amivantamab-vmjw) injection, 350 mg/7 mL (50 mg/mL)
Applicant/Sponsor Name:	Janssen Biotech, Inc.
OSE RCM #:	2020-2485-1
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Colleen Little, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 13, 2021 for Rybrevant. The Division of Oncology 2 (DO2) requested that we review the revised container label and carton labeling for Rybrevant (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Whaley, E. Human Factors Results and Labels and Labeling Review for Rybrevant (BLA 761210). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAR 24. RCM No.: 2020-2485 and 2020-2615.

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

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

Memorandum

Date: May 10, 2021

To: Sharon Sickafuse
Regulatory Project Manager
Division of Oncology 2 (DO2)

From: Nazia Fatima
Consumer Safety Officer
Office of Prescription Drug Promotion (OPDP)

CC: Kevin Wright, Team Leader, OPDP

Subject: OPDP Labeling Comments for RYBREVANT™ (amivantamab-vmjw) injection, for intravenous use (Rybrevant)

BLA: 761210

In response to DO2 consult request dated December 14, 2020, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI) and carton and container labeling for the original NDA submission for RYBREVANT™ (amivantamab-vmjw) injection, for intravenous use (Rybrevant).

OPDP's comment on the proposed labeling are based on the draft labeling received by electronic mail from DO2 on May 10, 2021 and OPDP's comment is listed below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI were sent under separate cover on May 4, 2021.

OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on April 27, 2021, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Nazia Fatima at 240-402-5041 or nazia.fatima@fda.hhs.gov.

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NAZIA FATIMA
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	May 4, 2021
To:	Sharon Sickafuse, M.S Senior Regulatory Project Manager **Division of Oncology II (DO2)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, CWOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Nazia Fatima, PharmD, MBA, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI)
Drug Name (established name):	TRADENAME (amivantamab-xxxx)
Dosage Form and Route:	injection, for intravenous use
Application Type/Number:	BLA 761210
Applicant:	Janssen Biotech, Inc.

1 INTRODUCTION

On November 24, 2020, Janssen Biotech, Inc., submitted for the Agency's review the second and final rolling part of Biologics Licensing Application (BLA) 761210 for TRADENAME (amivantamab-xxxx) injection, for intravenous use. The Applicant seeks approval of TRADENAME (amivantamab-xxxx) 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Oncology II (DO2) on December 4, 2020, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TRADENAME (amivantamab-xxxx) injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft TRADENAME (amivantamab-xxxx) injection PPI received on November 24, 2020, and received by DMPP and OPDP on April 22, 2021.
- Draft TRADENAME (amivantamab-xxxx) injection Prescribing Information (PI) received on November 24, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on April 22, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/

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Clinical Inspection Summary

Date	April 22, 2021
From	Lee Pai-Scherf, MD Karen Bleich, MD Kassa Ayalew, MD, MPH Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Katie Chon, Clinical Reviewer Erin Larkins, MD, Team Lead Harpreet Singh, MD, Division Director Division of Oncology 2 Office of Oncologic Products
BLA #	761210
Applicant	Janssen Biotech, Inc.
Drug	Amivantamab
NME (Yes/No)	Yes
Therapeutic Classification	Monoclonal Antibody
Proposed Indication(s)	Metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertion mutation, whose disease has progressed on or after platinum-based chemotherapy
Consultation Request Date	January 4, 2021
Summary Goal Date	April 15, 2021, extended to April 30, 2021
Action Goal Date	May 21, 2021
PDUFA Date	July 23, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Study 61186372EDI1001 were submitted to the Agency in support of a Biological License Application (BLA 761210) for amivantamab for the above proposed indication. Three clinical investigators (Drs. Eric Haura, Dr. Rachel Sanborn and Dr. Joshua Sabari) were selected for clinical inspection, as well as the central imaging contract research organization (CRO), (b) (4).

The inspections revealed no significant findings at the audited clinical investigator sites or the imaging CRO site. There was no evidence of underreporting of serious adverse events or significant protocol deviations. Based on the results of these inspections, the Study 61186372EDI1001 overall appears to have been conducted adequately the data generated by the inspected clinical investigators and the imaging CRO appear acceptable in support of the respective indication in the BLA.

II. BACKGROUND

Janssen Biotech, Inc seeks approval for amivantamab for the treatment of patients with metastatic NSCLC with EGFR Exon 20 insertion mutation (Exon 20ins), whose disease has progressed on or after platinum-based chemotherapy. Amivantamab is a new molecular entity and was granted Breakthrough Therapy Designation for the proposed indication.

Clinical data from an ongoing, first-in-human, single arm, dose-escalation (Part 1) and dose expansion cohort (Part 2) study of amivantamab in patients with advanced NSCLC (61186372EDI1001) was submitted to support this BLA.

The application includes safety data from 362 subjects enrolled in Part 1 and Part 2 of the study who received at least one dose of amivantamab. The efficacy population for this application consists of 81 subjects with Exon 20ins NSCLC enrolled in Cohort D (Part 1 or Part 2) who received amivantamab at the recommended phase 2 dose and had received prior platinum-based chemotherapy. The primary efficacy endpoint is overall response rate (ORR), as determined by a Blinded Independent Central Review (BICR) according to RECIST v 1.1.

Subjects with metastatic NSCLC were required to sign an informed consent prior to any screening procedure. Baseline tumor assessment was performed at screening (within 28 days of initiation of study drug) and every 6 weeks following cycle 1, day 1 until documented radiological disease progression.

The first subject was enrolled on May 27, 2016 and the data cutoff date for the BLA is June 8, 2020. At the time of the data cutoff, the study was being conducted at 53 study centers in 10 countries: Australia, Canada, China, France, Japan, Korea, Spain, Taiwan, United Kingdom and United States (28% of the subjects were enrolled in 13 study centers in the US).

Five clinical investigators, including one alternate site, were initially identified for inspection by the review division (DO2) and OSI: two domestic sites, Dr. Eric Haura, site US10001 (Tampa, FL), Dr. Rachel Sanborn, site US 10012 (Portland, OR), and two international sites, Dr. Byoung Chul Cho, site KR10003 (Seoul, Korea), and Dr. Keunchil Park, site KR10001 (Seoul, Korea). In addition, Dr. Joshua Sabari, site US10009 (New York, NY) was selected as an alternate site for inspection. Clinical site selection used a risk-based approach taking into consideration the total number of subjects enrolled and safety and efficacy parameters. OSI's Clinical Investigators Site Selection Tool (CISST) was utilized to assist with site selection. Inspections for Dr. Cho and Dr. Park could not be conducted because of the ongoing COVID-19 pandemic as the ORA inspectors could not travel to the site due to restricted entry into the country. In addition, due to regulatory and institutional requirements, remote regulatory assessment of the sites could not be conducted. In collaboration with the review division, Dr. Joshua Sabari (site US10009) was chosen to replace the requested inspection of the Drs. Cho and Park.

(b) (4) the central imaging facility responsible for central review of images, was chosen for evaluation of the conduct of the central imaging review and for evaluation of the primary efficacy endpoint of a larger number of subjects.

III. RESULTS (by site):

1. **Dr. Eric Haura** (Site # US10001)
   H. Lee Moffitt Cancer Center and Research Institute
   12902 USF Magnolia Dr # Srb4
   Tampa, FL
   USA 33612
   Inspection dates: 02/17 – 02/22/21

   Dr. Eric Haura was inspected as a surveillance inspection for Study 61186372EDI1001. This was the first FDA inspection for this investigator.

   At the time of the inspection, the investigator had screened 29 subjects (14 in Part 1, 15 in Part 2) and enrolled 15 subjects (11 in Part 1, 4 in Part 2). Five subjects (3 in Part 1, 2 in Part 2) remain on follow-up and no subjects were on active treatment.

   Source records of all 15 enrolled subjects were reviewed and compared to the line listings included in the BLA submission. Records reviewed include informed consent form, eligibility checklist, disease assessment, pre-treatment biomarker analysis for the purpose of cohort assignment, medical history, visit cycles and dates, tumor measurement worksheet, laboratory results, oxygen saturation and ECG results, adverse events, concomitant medications and procedures.

   In addition, adverse events, protocol deviation logs, financial disclosures, IRB communications, monitoring logs, records related to control of the investigational product, and electronic records access and audit trail procedures were reviewed.

   Computer tomography (CT) scans were performed every six weeks to verify the primary endpoint were verifiable. Images were assessed at the site by Dr. Haura, per RECIST 1.1 for response or progression according to the protocol and submitted to the Sponsor for Blinded Independent Central Review. There were no scans at the site that were not submitted to the Sponsor for central review.

   The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Haura at the conclusion of the inspection. The data
   generated by Dr. Haura appear to be acceptable in support of the BLA.

2. **Dr. Rachel Sanborn** (Site # US10012)
Providence Portland Medical Center
4805 NE Glisan Street, 2N-35
Portland, OR
USA 97213
Inspection dates: 02/16 – 02/19/21 and 02/22 - 02/24/21

Dr. Sanborn was inspected as a surveillance inspection for Study 61186372EDI1001. This was the first FDA inspection for this investigator.

At the time of the inspection, the investigator had screened 30 subjects and enrolled 11 subjects into the study. Of the 11 subjects, data from the 8 subjects enrolled prior to the data cutoff were included in the BLA. Five of 8 subjects had discontinued treatment (4 due to disease progression, 1 withdrew consent to receive treatment close to home). Two subjects were part of the efficacy population pertinent to this submission (Subjects (b) (6)).

Source records of all 8 subjects were reviewed in detail and compared to the line listings included in the BLA submission. Records reviewed include informed consent form, inclusion/exclusion criteria, adverse events, treatment with investigational product and efficacy endpoint data.

The primary endpoint data was reviewed and consists of imaging scans performed every 6 weeks per protocol. Scans were documented in a running log, which include a results report. There were no unreported scans noted for the timeframe reviewed (data cutoff 06/08/2020).

Adverse events logs, protocol deviation logs, financial disclosures forms, IRB communications, monitoring logs, records related to the control of the investigational product, electronic records access and audit trail procedures were reviewed.

A single unreported adverse event was identified during the inspection. According to the source records at the site, Subject (b) (6) had hypotension reported in a family medicine clinic note dated 11/21/2019. The blood pressure measurement is not included in the note. As documented in the clinical note, the subject's blood pressure medication (losartan) was held in response to the hypotension. Hypotension is not included in the CRF nor in the submitted data listing for adverse events for this subject. Records at the site indicate that Subject (b) (6) had normal blood pressure documented in the subsequent study visit.

Reviewer comment: The adverse event was documented in the electronic medical record system and the site failed to transcribe the adverse event into their AE log and to the CRF. The unreported adverse event appears to be an isolated incident at the site. There is no evidence of harm to the subject related to this unreported AE.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Sanborn at the conclusion of the inspection.

3. **Dr. Joshua Sabari** (Site # US 10009)
New York University Langone Health
Perlmutter Cancer Center
160 East 34th Street, 8th Floor
New York, NY
USA 10016
Inspection dates: 03/02/21- 03/08/21

Dr. Sabari was inspected as a surveillance inspection for Study 61186372EDI1001. This was the first FDA inspection for this investigator.

At the time of the inspection, the investigator had screened 38 subjects (16 screen failures) and enrolled 22 subjects. Four subjects remain on study (18 subjects off study).
Source documents for all enrolled subjects were reviewed. All subjects met protocol specified inclusion and exclusion criteria, signed informed consent, and that the clinical investigator and sub investigators evaluated overall response and targeted/non-targeted evaluations per protocol. There was no underreporting of adverse events or serious AEs or protocol deviation. In addition, there was no evidence of unreported scans or images.

Other documents reviewed during the inspection include training records, delegation log, drug accountability, electronic records, including signatures and audit trails, and other source documents. All versions of the protocol were submitted to the IRB for approval. No discrepancies or regulatory violations were observed.

The inspection found no regulatory violations at the site. No Form FDA 483 was issued to Dr. Sabari at the conclusion of the inspection.

4. (b) (4) **CRO)**

Inspection dates: 01/19/21– 02/05/21

(b) (4) was inspected as data audit and surveillance inspection for Study 61186372EDI1001. This CRO has been previously inspected on 12/10/14, 01/28/15, 07/24/15, 06/08/17, and 09/26/19, all classified as NAI.

The inspection included the review of the following records: contract agreements, written procedures/ charters, training records, record retention, and the process of acquiring scans or images from study sites, evaluation by independent readers and data transfer activities to the sponsor.

For Study 61186372EDI1001, the radiographic images were shipped to (b) (4) by the Sponsor in hard drives and uploaded to the system (b) (4) and made available to independent readers and oncologist for evaluation. The inspector confirmed that the independent readers had no access to each other's evaluation. When a case needed adjudication, (b) (4) had adjudicators to review both readers' evaluations.

During the inspection, the primary endpoint data, consisting of tumor assessments for all 81 subjects included in the efficacy population from the Individual Efficacy Response Data listing (data cutoff of June 6, 2020) were reviewed. There were no discrepancies noted,

There were no data discrepancies identified for the primary endpoint assessment. The firm followed all procedures for conducting study related activities. The inspection found no regulatory violations at the site. No Form FDA 483 was issued to (b) (4) at the conclusion of the inspection.

{See appended electronic signature page}

Lee Pai-Scherf, MD
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Karen Bleich, M.D.
Team Leader,
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
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Good Clinical Practice Assessment Branch
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CC:

Central Doc. Rm.
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Review Division /Medical Team Leader/Erin Larkins, MD
Review Division /Project Manager/Sharon Sickafuse
Review Division/Clinical Reviewer/Katie Chon
OSI/Office Director/Dave Burrow
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Consult Memorandum

U.S. FOOD & DRUG ADMINISTRATION

Date	4/14/2021
To	Katie Chon, Clinical Reviewer, CDER/ORO/DRO-OD; Erin Larkins, Clinical Team Lead, CDER/OND/OOD/DOII; Sharon Sickafuse, Regulatory Project Manager, CDER/OND/ORO/DROOD
From	Banu Saritas-Yildirim, Ph.D., Scientific Reviewer, CDRH/OHT7/DMGP/MPCB RamaKamesh Bikkavilli, Ph.D., Scientific Reviewer, CDRH/OHT7/DMGP/MPCB
Through	Soma Ghosh, Ph.D., Branch Chief, CDRH/OHT7/DMGP/MGB Reena Philip, Ph.D., Director, CDRH/OHT7/DMGP
Subject	CDER consult request for BLA 761210
ICC Number	ICC2100017
ICCR Number	ICCR# 00051412, ICCR# 00051479
BLA Number	761210
Drug Name	RYBREVANT™ (amivantamab)
Drug Sponsor	Janssen Biotech., Inc.
Device Name	Guardant360® CDx
Device Sponsor	Guardant Health, Inc.
Analytes Detected	EGFR Exon 20 insertions
Related Submissions	Q200694, P200010, ICC2000977, ICC2000978, ICCR00035996
Protocol Title	**Janssen EDI1001 (61186372EDI1001 or CHRYSALIS):** A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific *EGFR* and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer

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Rama Kamesh Bikkavilli -S
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I. SUMMARY

CDER is currently reviewing BLA 761210 from Janssen Biotech., Inc. that seeks approval for RYBREVANT™ (amivantamab) as monotherapy for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) having an in-frame base pair insertion mutation in *EGFR* Exon 20 whose disease has progressed on or after platinum-based chemotherapy. CDRH received two supplemental premarket approval (sPMA) applications for the detection of *EGFR* Exon 20 insertion mutations in patients with NSCLC who may benefit from treatment with amivantamab. The (b) (4) (b) (4) plasma-based Guardant360 CDx test was submitted by Guardant Health, Inc. (P200010/S001) on November 20, 2020. (b) (4) seek contemporaneous approvals as companion diagnostic (CDx) devices for amivantamab. However, CDER should note that while Guardant360 CDx is expected to be co-approved with the drug, due to COVID-19 related delays, (b) (4)

(b) (4). CDRH recommends CDER to consider including a PMC to the drug for the tissue-based CDx device.

During the course of BLA and sPMA review, the CDRH reviewers provided feedback to drug labeling and attended relevant CDER meetings. The following section is a summary of the sPMA review for CDER's consideration.

II. Guardant360® CDx – PROPOSED DEVICE INTENDED USE

Guardant360® CDx is a qualitative next generation sequencing-based in vitro diagnostic device that uses targeted high throughput hybridization-based capture technology for detection of single nucleotide variants (SNVs), insertions and deletions (indels) in 55 genes, copy number amplifications (CNAs) in two (2) genes, and fusions in four (4) genes. Guardant360 CDx utilizes circulating cell-free DNA (cfDNA) from plasma of peripheral whole blood collected in Streck Cell-Free DNA Blood Collection Tubes (BCTs). The test is intended to be used as a companion diagnostic to identify non-small cell lung cancer (NSCLC) patients who may benefit from treatment with the targeted therapy listed in Table 1 in accordance with the approved therapeutic product labeling.

Table 1. Companion Diagnostic Indications

Indication	Biomarker	Therapy
Non-small cell lung cancer (NSCLC)	*EGFR* exon 19 deletions, L858R, and T790M*	TAGRISSO® (osimertinib)
	EGFR exon 20 insertions	RYBREVANT™ (amivantamab)

A negative result from a plasma specimen does not assure that the patient's tumor is negative for genomic findings. NSCLC patients who are negative for the biomarkers listed in **Table 1** should be reflexed to tissue biopsy testing for Table 1 biomarkers using an FDA approved tumor tissue test, if feasible.

*The efficacy of TAGRISSO® (osimertinib) has not been established in the *EGFR* T790M plasma-positive, tissue-negative or unknown population and clinical data for T790M plasma-positive patients are limited; therefore, testing using plasma specimens is most appropriate for consideration in patients from whom a tumor biopsy cannot be obtained.

Additionally, the test is intended to provide tumor mutation profiling to be used by qualified health care professionals in accordance with professional guidelines in oncology for cancer patients with any solid malignant neoplasm. The test is for use with patients previously diagnosed with cancer and in conjunction with other laboratory and clinical findings.

Genomic findings other than those listed in **Table 1** are not prescriptive or conclusive for labeled use of any specific therapeutic product.

Guardant360 CDx is a single-site assay performed at Guardant Health, Inc.

REVIEWER NOTE: While the device clinical validation was based on the variants identified in the Janssen clinical study, Guardant Health used additional variants for analytical validation of Guardant360 CDx; and therefore, the device is aimed to detect *de novo EGFR* Exon 20 insertion mutations.

III. P200010/S001 GUARDANT360® CDx REVIEW SUMMARY

The Janssen EDI1001 trial enrolled NSCLC patients with *EGFR* Exon 20 insertions as determined by prospective local testing using tissue or plasma samples. Of the 81-efficacy population used to support the current BLA application, only 5 subjects were enrolled using a plasma-based assay while the rest was based on tissue-based assays. The local tests included various technologies including NGS and PCR tests. The Sponsor banked all available biomarker positive tissue and plasma samples for CDx co-development.

Upon completion of the study, FDA-approved Guardant360® CDx was used to retrospectively re-test all available clinical plasma samples. To support the sPMA application, Guardant Health, Inc. submitted a PMA supplement to CDRH that included analytical and clinical validation data supporting the proposed intended use of the Guardant360® CDx test. Since Guardant360® CDx was not the clinical trial assay and, in fact, majority of the subjects were enrolled based on tissue testing, a bridging study was needed to demonstrate the clinical effectiveness of the device to aid in the selection of NSCLC patients with *EGFR* Exon 20 insertions for the amivantamab therapy.

Diagnostic study patient population included all biomarker-positive patients enrolled in the primary clinical efficacy population for the Janssen EDI1001 study, biomarker-negative patients enrolled in Guardant Health's Noninvasive vs. Invasive Lung Evaluation (NILE) clinical study from PMA P200010 (for sensitivity analysis), and subjects failed screening for the Janssen study. Since the Janssen EDI1001 primary therapy registration population consisted primarily of subjects positive for *EGFR* Exon 20 insertions by local tissue testing, additional subjects were required to evaluate the tissue-negative portion of the Guardant360 CDx-positive intended use population. Therefore, screen fail subjects from the clinical study tested with both Guardant360 CDx and tissue central testing as well as clinical sample data generated from subjects enrolled in the NILE study were used.

Demographics and baseline clinical characteristics of subjects enrolled in the Janssen EDI1001 clinical study were similar to the diagnostic study populations including those for the biomarker negative samples from the NILE study.

The primary therapy registration population included 81 patients from the Janssen EDI1001 clinical study. Of these, 78 (96.3%) met the diagnostic study inclusion criteria and were included. Sixty-two (62) patients (76.5%) had an *EGFR* Exon 20 insertion detected result by Guardant360 CDx and were included in the efficacy analysis set, while 16 (19.8%) had an *EGFR* exon 20 insertion not detected result by Guardant360 CDx, 3 (3.7%) did not have plasma samples for testing, and 0 (0%) failed testing.

The Objective Response Rate (ORR) observed in the primary objective analysis set (gCEAS) by blinded independent central review (BICR) was 38.7% (95% CI 26.6% – 51.9%). The lower limit of the 95% CI of 26.6% establishes statistically significant amivantamab efficacy relative to the size-adjusted benchmark ORR of 14% (unadjusted benchmark 15%) from the Janssen EDI1001 clinical study in the Guardant360 CDx-positive, tissue-positive portion of the intended use population and satisfies the prespecified efficacy acceptance criterion. The gCEAS ORR point estimate was also similar to the full analysis set (FAS) ORR of 39.5% (95% CI 28.8% – 51.0%) (**Table 2**). The Sponsor also provided ORR analysis by Investigator Assessment, which yielded similar results as FAS from the Janssen EDI1001 (data not included in memo).

Table 2: Summary of ORR in the Guardant diagnostic study (gCEAS) and Full Analysis Set (FAS) from the Janssen EDI1001 by BICR

	gCEAS	FAS
Analysis set: Efficacy	62	81
Best overall response N		
	62	81
Complete response (CR)	2 (3.2%)	3 (3.7%)
Partial response (PR)	22 (35.5%)	29 (35.8%)
Stable disease (SD)	29 (46.8%)	39 (48.1%)
Progressive disease (PD)	7 (11.3%)	8 (9.9%)
Not evaluable/unknown	2 (3.2%)	2 (2.5%)
Overall response rate (Confirmed CR + Confirmed PR)	24 (38.7%)	32 (39.5%)
95% CI	(26.6%, 51.9%)	(28.8%, 51.0%)
Clinical benefit rate a (Confirmed CR + Confirmed PR + SD)	43 (69.4%)	60 (74.1%)
95% CI	(56.3%, 80.4%)	(63.1%, 83.2%)

In order to compare the clinical performance of Guardant360 CDx to that of clinical trial assays (i.e. local tests), a concordance analysis was performed between clinical trial assays used for enrollment and Guardant360 CDx. The results showed that Guardant360 CDx demonstrates high negative percent agreement (NPA) (100%, 95% CI 97.7% – 100%) and relatively high positive percent agreement (PPA) (80.8%, 95% CI 72.2% – 87.2%) and overall percent agreement (OPA) (92.5%, 95% CI 88.8% – 95.1%) relative to clinical trial assay testing.

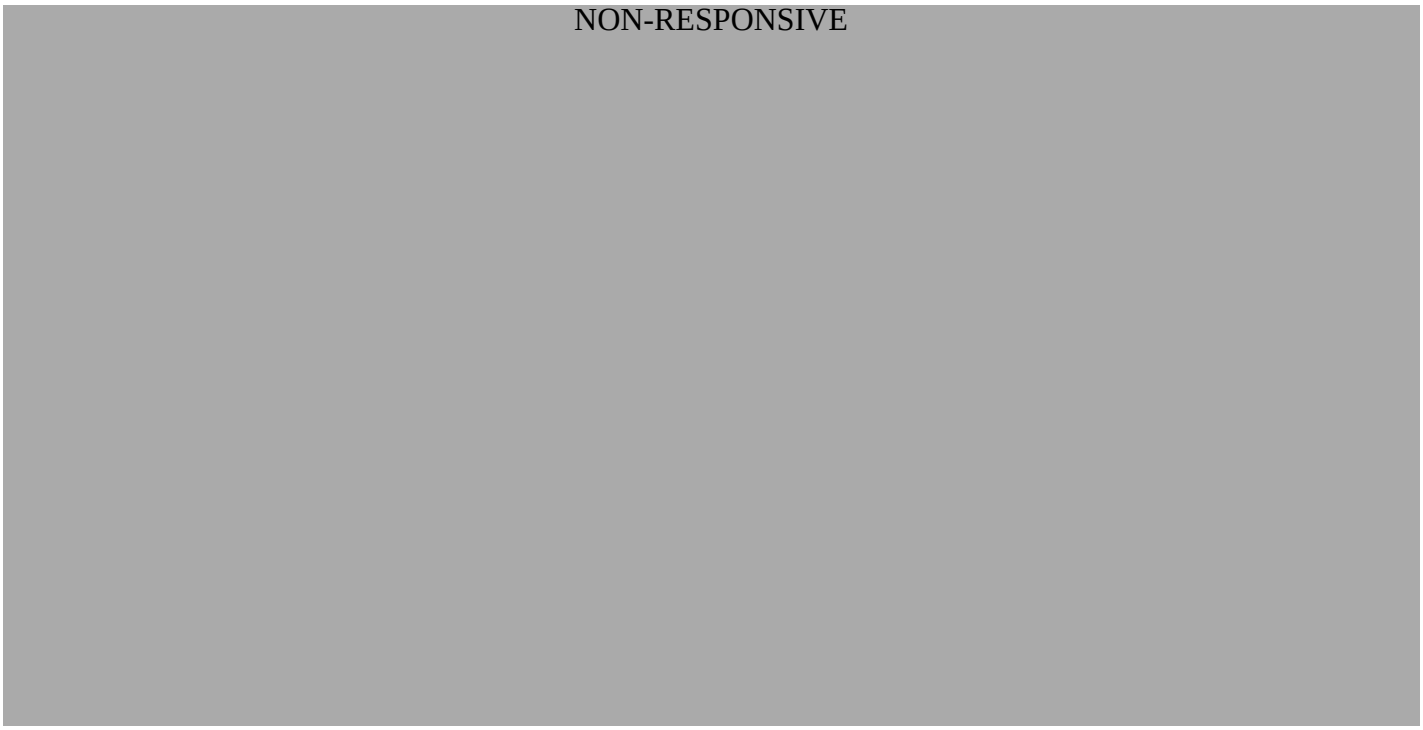
The Sponsor performed a sensitivity analysis to demonstrate efficacy across the entire Guardant360 CDx intended use population using BICR ORR, which demonstrated robustness to the contribution of the unrepresented Guardant360 CDx-positive, tissue-negative subjects and estimated that ORRs for the overall Guardant360 CDx intended use population are similar to those observed for both the gCEAS and FAS due to the low observed prevalence (0%) of the Guardant360 CDx-positive, tissue-negative population. In the diagnostic study, only 3.7% of samples were missing; thus, imputation was not conducted.

In addition to clinical validation results, Guardant Health provided analytical validation data including limit of detection, accuracy, and precision, to support addition of *EGFR* exon 20 insertion variants to the device's intended use. These study results were acceptable in general. However, since the sponsor was not able to provide adequate validation for longer insertion variants (12 bp), given the low prevalence of these variants, it was determined that a limit of detection confirmation study for long insertions will be provided in the postmarket setting.

In conclusion, CDRH considers the supplemental PMA for Guardant360 CDx approvable as a companion diagnostic device for RYBREVANT™ (amivantamab) monotherapy to select NSCLC patients with *EGFR* Exon 20 insertions mutations.

If there are any questions regarding the Guardant360 CDx test, please contact Banu Saritas-Yildirim, Ph.D. by phone at (301) 796 9613 or by email at Banu.Saritas@fda.hhs.gov

NON-RESPONSIVE


NON-RESPONSIVE

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/s/

SHARON K SICKAFUSE
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HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

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

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

Date of This Review:	March 24, 2021
Requesting Office or Division:	Division of Oncology 2 (DO2)
Application Type and Number:	BLA 761210
Product Type:	Single-ingredient
Drug Constituent Name and Strength	Rybrevant[a] (amivantamab-xxxx[b]) injection, 350 mg/7 mL (50 mg/mL)
Rx or OTC:	Rx
Applicant/Sponsor Name:	Janssen Biotech, Inc.
Submission Date:	11/24/2021, 2/8/2021, 2/10/2021, 2/16/2021
OSE RCM #:	2020-2485; 2020-2615
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader (Acting):	Colleen Little, PharmD
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate/Deputy Director:	Chi-Ming (Alice) Tu, PharmD

[a] The proposed proprietary name Rybrevant was found conditionally acceptable on February 2, 2021.

[b] The nonproprietary name suffix for this BLA has not been designated yet. Therefore, the suffix placeholder '-xxxx' is used throughout this review.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761210 for Rybrevant (amivantamab-xxxx) injection. The proposed product is not a combination product.

1.1 PRODUCT DESCRIPTION

Rybrevant is indicated for the treatment of patients with metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 20 insertion mutation, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. Rybrevant is an injection supplied in a 350 mg/7 mL vial. The intended doses of Rybrevant are 1,050 mg and 1,400 mg, which require three or four vials, respectively, to complete a single dose. Rybrevant injection must be further diluted in 250 mL of diluent prior to intravenous infusion. The intended users of the proposed product are healthcare professionals (specifically pharmacists, pharmacy technicians, and oncology nurses) in an outpatient infusion center or hospital setting (See Appendix A).

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

In a May 6, 2020 Type B pre-IND meeting under IND 135405, the Agency noted that the Applicant's intended product strength of 350 mg/7 mL was incongruent with the intended dosing and administration.[c] The Agency also noted concern for medication errors related to calculation, preparation, and administration of a dose given the requirement of three or four vials to achieve one dose.

In response to the Agency's medication error concerns, the Applicant completed HF validation testing. The Applicant did not submit their HF validation study protocol for Agency review prior to commencing the study. On November 24, 2020, the Applicant submitted the results of a HF study under BLA 761210, which is the subject of this review.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A

[c] Korsah, K. Type B pre-IND Meeting Minutes for IND 135405. Silver Spring (MD): FDA, CDER, OND, DO2 (US); 11 MAY 2020. Available from: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80562bc2&_afrRedirect=108533161848 5816

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

3 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, use errors (failures/close calls/use difficulties) observed, and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	• Pharmacist/pharmacy technician user group, n = 16 • Nurse user group, n = 15
Training	None
Test Environment	For the pharmacist user group, the test room simulated a pharmacy setting in which a shelf displayed five product cartons and cartons of other oncology products (see Figure 1).  Figure 1. Refrigerator Presentation

	For the nurse user group, the test room simulated a clinical setting.
Sequence of Study	Pharmacist/pharmacy technician user group: • Use Scenario 1 (product selection): The pharmacist/pharmacy technician was given a mock prescription for amivantamab 1050 mg or 1400 mg. The pharmacist/pharmacy technician then selected the correct number of product cartons from a refrigerator (see Figure 1 above) based on the mock prescription*. For example, for the 1050 mg dose, the user needed to select three 350 mg/7 mL vials and for the 1400 mg dose, the user needed to select four 350 mg/7 mL vials. The pharmacist/pharmacy technician was then asked to confirm the product name and weight-based dose according to the mock prescription. • Use Scenario 2 (labeling comprehension): The pharmacist/pharmacy technician was asked to answer label comprehension questions based on information found on the carton, vial, and prescribing information (PI). Nurse user group: • Use scenario 1 (product selection): The nurse was given product cartons with the correct corresponding mock prescription*. They determined whether they had been supplied with the correct product (e.g. correct number of vials) and whether the weight-based dose was correct. • Use scenario 2 (labeling comprehension): The nurse was asked to answer label comprehension questions based on information found on the carton, vial, and PI. *The mock prescription contained the name of the drug, dose, and information about patient such as name, date of birth, and weight.

3.2 RESULTS AND ANALYSES

The HF validation study showed use errors (e.g. failures, difficulties, and close calls) with three critical tasks; however, our assessment of these use errors finds the residual risk is acceptable. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis, and Applicant's proposed risk mitigation strategy to determine acceptability. Subsequently, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable for the critical tasks below; thus, we find no recommendations to

further address the use errors or mitigations are necessary at this time to address the use errors related to the following use tasks.

- Determine the number of drug product vials needed per the prescribed dose.
- Withdraw and then discard a volume of either 5% dextrose solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of amivantamab to be added.
- If an interruption is longer than 7 days, restart amivantamab at a reduced dose as outlined in Table 4 of the PI.

3.3 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 3: Identified Issues and Recommendations for Division of Division of Oncology 2			
	Identified Issue	Rationale for Concern	Recommendation
Highlights of Prescribing Information			
1.	The Highlights of the Prescribing Information does not inform users that the proposed product has complex dosing and administration requirements.	There should be a statement under Dosage and Administration heading in Highlights of PI to alert the health care provider that additional important information is in the FPI.	Consider revising Highlights to include the statement “See Full Prescribing Information for instructions on dilution, preparation, and administration of injection”.
Full Prescribing Information			
1.	Section 2 Dosage and Administration does not specify whether the prescribers should use actual body weight or adjusted body weight for dose calculation. For example, Table 1 Recommended Dose states “Body Weight of Patient at Baseline”.	In the human factors validation study, there was subjective feedback from one participant which noted confusion with determining which weight to use for dosing. The participant asked whether the body weight is actual or adjusted and suggested including “actual body weight" or "do not use adjusted body weight" in the PI. Confusion regarding the correct weight to use for weight-based dosing might result in wrong dose errors.	Consider specifying whether the baseline body weight used for dose calculation should be actual body weight or adjusted body weight.

Table 4: Identified Issues and Recommendations for Janssen Biotech, Inc. (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Container Label			
1.	The route of administration statement can be improved for clarity and to reduce clutter.	Unclear or cluttered route of administration and preparation information might result in wrong technique in drug usage process errors.	Revise the "For Intravenous Infusion Only….Dilute Before Use" statements on the principal display panel (PDP) to read "Dilute before intravenous infusion". We recommend this condensed statement to reduce clutter on the PDP and to minimize the risk of administering the drug as an intravenous bolus.
2.	You propose the expiration date format "YYYY-MM-DD"; however, it is unclear whether you intend to use numerical or alphabetic characters to represent the month.	When alphabetic characters are used to represent the month in the expiration date format "YYYY-MM-DD", user confusion regarding product storage might result in deteriorated drug product errors leading to patient harm and compromised care (e.g., confusion over whether "MA" represents March or May).	Ensure that the expiration date appears in YYYY-MMM-DD if alphabetical characters are used to represent the month. See Draft Guidance for Industry: Product Identifiers under the Drug Supply Chain Security Act - Questions and Answers (September 2018).
Carton Labeling			
1.	Refer to container label recommendations #1 and revise carton labeling accordingly.		

2.	(b) (4)

[d] Error-Prone Abbreviations, Symbols, and Dose Designation: ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2021 JAN 28]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

4 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrate that representative users can use the product, as designed, safely and effectively. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 3 for the Division and Table 4 for the Applicant. We ask that the Division convey Table 4 in its entirety to the Applicant so that recommendations are implemented prior to approval of this BLA 761210.

4.1 RECOMMENDATIONS FOR JANSSEN BIOTECH, INC.

We found the results of your human factors (HF) validation study acceptable. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations for this BLA 761210.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Rybrevant that Janssen Biotech, Inc. submitted on February 16, 2021.

<table>
<tr><th colspan="2">Table 5. Relevant Product Information</th></tr>
<tr><td>Initial Approval Date</td><td>N/A</td></tr>
<tr><td>Therapeutic Drug Class or New Drug Class</td><td>fully human EGFR and cMET bispecific antibody</td></tr>
<tr><td>Active Ingredient (Drug or Biologic)</td><td>amivantamab-xxxx</td></tr>
<tr><td>Indication</td><td>treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutation, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy</td></tr>
<tr><td>Route of Administration</td><td>Intravenous infusion</td></tr>
<tr><td>Dosage Form</td><td>injection</td></tr>
<tr><td>Strength</td><td>350 mg/7 mL (50 mg/mL)</td></tr>
<tr><td>Dose and Frequency</td><td>The recommended dose is provided in Table 1. The product is administered intravenously once weekly for 4 weeks, then every 2 weeks thereafter (see Table 3).

Table 1: Recommended Dose

<table><tr><th>Body Weight of Patient at Baseline*</th><th>Recommended Dose</th><th>Number of 350 mg/7 mL Vials</th></tr><tr><td>Less than 80 kg</td><td>1050 mg</td><td>3</td></tr><tr><td>Greater than or equal to 80 kg</td><td>1400 mg</td><td>4</td></tr></table>*Dose adjustments not required for subsequent body weight changes.

Administer infusion intravenously according to the infusion rates in Table 3. Due to the frequency of infusion-related reactions (IRRs) at the first dose, infusion via a peripheral vein at Week 1 and Week 2 should be considered to minimize drug exposure in the event of an IRR; infusion via central line may be administered for subsequent weeks. It is recommended for the first dose to be diluted as close to</td></tr>
</table>

administration as possible to allow for maximal flexibility in IRR management.

Table 2: Infusion Rates for 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. Preparation TRADENAME solution must be diluted and prepared for intravenous infusion [redacted] 1. Determine the dose required (either 1050 mg or 1400 mg) and number of TRADENAME vials needed based on patient's baseline weight. Each vial of TRADENAME contains 350 mg of amivantamab. 2. Check that the TRADENAME solution is colorless to pale yellow. Do not use if discoloration or visible particles are present. 3. Withdraw and then discard a volume of either 5% dextrose solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of TRADENAME to be added (i.e., discard 7 mL diluent from the infusion bag for each TRADENAME vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE). 4. Withdraw 7 mL of TRADENAME from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a [redacted] overfill to ensure sufficient extractable volume. Discard any unused portion left in the vial. 5. Gently invert the bag to mix the solution. Do not shake. 6. Visually inspect the diluted solution before administration. Do not use if discoloration or visible particles are observed. 7. Diluted solutions should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) [redacted]. Administration 1. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE. 2. Do not infuse TRADENAME concomitantly in the same intravenous line with other agents.

	(b) (4)
How Supplied	TRADENAME (amivantamab) injection is supplied as a colorless to pale yellow preservative-free solution for intravenous infusion in a single-(b) (4) vial individually packed in a carton (NDC 57894-501-01).
Storage	Store in a refrigerator at 2°C to 8°C (36°F to 46°F). Do not freeze. Protect from light.
Container Closure/Device Constituent	(b) (4)
Intended Users	Healthcare professionals (specifically pharmacists, pharm techs, and oncology nurses)
Intended Use Environment	Outpatient infusion center, hospital

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On February 2, 2021, we searched the L:drive and AIMS using the terms, amivantamab and IND 135405, to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search did identify any previous relevant reviews.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessed in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessed in EDR via:
\\CDSESUB1\evsprod\bla761210\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\2l-e20-nsclc\5354-other-stud-rep\urra\label-compr-dose-diff-hf.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On February 1, 2021, we sent an Information Request (IR) to the Applicant to request clarification regarding the HF validation study results report. The Applicant responded on February 8, 2021 and submitted an updated HF results report on February 10, 2021. See EDR links:

- February 8, 2021 submission: \\CDSESUB1\evsprod\bla761210\0017\m1\us\cover.pdf
- February 10, 2021 submission: \\CDSESUB1\evsprod\bla761210\0019\m1\us\cover.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

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

- Container label received on 11/24/2020
- Carton labeling received on 11/24/2020
- Prescribing Information (Image not shown) received on 2/16/2021
    - \\CDSESUB1\evsprod\bla761210\0020\m1\us\draft-labeling-text.pdf

F.2 Label and Labeling Images

Container label

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

Carton labeling

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

/s/

EBONY A WHALEY
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COLLEEN L LITTLE
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LOLITA G WHITE
03/29/2021 01:47:48 PM

CHI-MING TU
03/29/2021 07:37:19 PM

Medical Officer's Review of BLA 761210
Ophthalmology Consultant

BLA 761210		Submission:	10/27/2020
IND 135405		Review completed:	2/14/2021

Name:	Amivantamab (JNJ-61186372)
Sponsor:	Janssen Biotech, Inc
Requested Indication:	Advanced non-small cell lung cancer (NSCLC)

Requested: Evaluate the TEAE - eye disorders and provide an opinion regarding if information regarding ophthalmologic AEs should be included in the USPI and, if so, provide recommendations for labeling. Data are from the ongoing study 61186372EDI1001 (CHRYSALIS). The clinical study report is located in m5.3.5.2.

Background: The CHRYSALIS Phase 1 study (61186372EDI1001, hereafter referred to as EDI1001), is an ongoing, first-in-human investigation of amivantamab in advanced non-small cell lung cancer (NSCLC). This open-label, multicenter study includes both a dose escalation phase (Part 1 -subjects with advanced NSCLC) and a dose expansion phase (Part 2 - subjects with advanced epidermal growth factor receptor [EGFR] mutation or MET mutation NSCLC after standard of care therapy). The results of this study through a clinical cutoff of 08 June 2020 have been previously summarized in the clinical study report (CSR) dated 27 October 2020.

The primary population of interest for this CSR Addendum of Study EDI1001 is the primary efficacy population of 81 subjects with locally-documented EGFR-mediated NSCLC having an in-frame base pair insertion in EGFR Exon 20 (i.e., Exon 20ins) who were treated with the recommended Phase 2 amivantamab monotherapy regimen (RP2D) by 05 February 2020. These 81 consecutively-treated subjects had undergone at least 3 post-baseline disease assessments or discontinued treatment for any reason, including disease progression/death, prior to the clinical cutoff of 08 June 2020.

A study report addendum contains efficacy data in the 114 subjects with the Exon 20ins NSCLC who had received prior chemotherapy, were treated at the RP2D, and who underwent at least 3 post-baseline disease assessments or discontinued treatment for any reason, including disease progression/death, as of the 08 October 2020 clinical cutoff. This population of 114 subjects had each initiated amivantamab therapy by 04 June 2020, is inclusive of the 81 subjects in the primary efficacy population with a longer follow-up described above, and correlates with the primary 114-subject safety population (as defined by the 08 June 2020 cutoff) described in the CSR. The median follow-up in this population (as of 08 October 2020) was 8.3 months.

A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer

TSFAE02A: Number of Subjects with Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

		Recommended Phase 2 Dose (RP2D)		Non-RP2D	
	Total	Exon 20 Ins Prior Chemotherapy	Total	Exon 20 Ins	Total
All treated in monotherapy (JNJ-61186372)	362	114	258	45	104
Eye disorders	40 (11%)	15 (13.2%)	32 (12.4%)	6 (13.3%)	8 (7.7%)
Dry eye*	12 (3%)	4 (3.5%)	9 (3.5%)	2 (4.4%)	3 (2.9%)
Vision blurred	6 (1.7%)	1 (0.9%)	6 (2.3%)		
Eye pruritus	5 (1.4%)	2 (1.8%)	3 (1.2%)	2 (4.4%)	2 (1.9%)
Conjunctival hyperaemia	2 (0.6%)	2 (1.8%)	2 (0.8%)		
Growth of eyelashes	2 (0.6%)	1 (0.9%)	2 (0.8%)		
Conjunctivitis	6 (1.7%)	2 (1.8%)	6 (2.3%)		
Eyelid ptosis	2 (0.6%)	1 (0.9%)	1 (0.4%)	1 (2.2%)	1 (1.0%)
Keratitis*	2 (0.6%)	2 (1.8%)	2 (0.8%)		
Ocular hyperaemia	2 (0.6%)	2 (1.8%)	2 (0.8%)		
Conjunctivitis bacterial	2 (0.6%)	1 (0.9%)	1 (0.4%)	1 (2.2%)	1 (1.0%)
Visual acuity reduced	2 (0.6%)	1 (0.9%)	2 (0.8%)		
Visual impairment	3 (0.8%)	1 (0.9%)	2 (0.8%)	1 (2.2%)	1 (1.0%)
Blepharitis	1 (0.3%)	1 (0.9%)	1 (0.4%)		
Corneal irritation*	1 (0.3%)	1 (0.9%)	1 (0.4%)		
Diplopia	1 (0.3%)	0	1 (0.4%)		
Eye disorder	1 (0.3%)	0	1 (0.4%)		
Eye oedema	1 (0.3%)	0	1 (0.4%)		
Eye pain	1 (0.3%)	1 (0.9%)	1 (0.4%)		
Eyelid oedema	1 (0.3%)	1 (0.9%)	1 (0.4%)		
Noninfective conjunctivitis	1 (0.3%)	0	1 (0.4%)		
Periorbital oedema	1 (0.3%)	1 (0.9%)	1 (0.4%)		
Periorbital swelling	1 (0.3%)	1 (0.9%)	1 (0.4%)		
Pinguecula	1 (0.3%)	0	1 (0.4%)		
Trichomegaly	1 (0.3%)	0	1 (0.4%)		
Uveitis	1 (0.3%)	1 (0.9%)	1 (0.4%)		
Vitreous detachment	1 (0.3%)	0	1 (0.4%)		
Eye inflammation	1 (0.3%)	0	0	1 (2.2%)	1 (1.0%)
Eyelash thickening	1 (0.3%)	0	0	1 (2.2%)	1 (1.0%)
Eyelid disorder	1 (0.3%)	0	0	0	1 (1.0%)
Lacrimation increased*	3 (0.8%)	0	0	1 (2.2%)	3 (2.9%)
Macular degeneration	1 (0.3%)	0	0	1 (2.2%)	1 (1.0%)
Punctate keratitis*	1 (0.3%)	0	0	1 (2.2%)	1 (1.0%)

*Dry eye, keratitis, corneal irritation, lacrimation increased, and punctate keratitis are all likely to be manifestations of dry eye.

TSFAE02A-P1: Number of Subjects with Treatment-emergent Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set in Part 1 (Dose Escalation) of Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	140 mg	350 mg	700 mg	1050 mg	1400 mg	1750 mg	RP2D	Total
Treated in Part 1	3	3	14	25	26	6	30	77
Eye disorders	0	0	0	3 (12%)	4 (15%)	1 (17%)	6 (20%)	8 (10%)
Dry eye	0	0	0	2 (8%)	1 (4%)	0	3 (10%)	3 (4%)
Vision blurred	0	0	0	0	2 (8%)	0	2 (7%)	2 (2.6%)
Conjunctival hyperaemia	0	0	0	1 (4%)	0	0	1 (3%)	1 (1.3%)
Eye disorder	0	0	0	1 (4%)	0	0	1 (3%)	1 (1.3%)
Eye pruritus	0	0	0	1 (4%)	0	0	1 (3%)	1 (1.3%)
Eyelash thickening	0	0	0	0	0	1 (17%)	0	1 (1.3%)
Eyelid disorder	0	0	0	0	1 (4%)	0	0	1 (1.3%)
Growth of eyelashes	0	0	0	0	1 (4%)	0	1 (3%)	1 (1.3%)
Keratitis	0	0	0	1 (4%)	0	0	1 (3%)	1 (1.3%)
Lacrimation increased	0	0	0	0	1 (4%)	0	0	1 (1.3%)
Visual impairment	0	0	0	0	0	1 (17%)	0	1 (1.3%)

Reviewer's Comments: *Ocular events were not reported until doses exceeded 700 mg.*

Ocular Adverse Events Reported in AE.dat

USUBJID	17	11	9	7	6	4	4	2	1	1	1	1	1	1	1
(b) (6)	DRY EYES														
								Left eye ptosis							
					Eyelid edema										
									pingueculum						
			Blurred vision												
		Conj hyperemia													
				Itching											
	CORNEAL IRRITATION														
										blepharitis					
					puffy eyelids										
		Red eyes													
		Red eyes													
		Red eyes													
	DRY EYES														
					palpebral edema										
		ocular erythema	Reduced visual acuity												
											vitreous detachment				
	PUNCTATA KERATITIS			left eye itch											
		Conjunctivitis			periocular edema										
	DRY EYE and watering														
												CONJUCTIVAL PHLYCTENULE			
		CONJUNCTIVAL HYPEREMIA													
								RIGHT PTOSIS							
													MACULAR DEGENERATION		
	EYE DRYNESS			eye itchi	PERIORBITAL S	LENGTHED EYELASHES									
	DRY EYE														
	DRY EYE														
						THICKENING	VISION PROBLEMS								
			BLURRY VISION												
	DRY EYES			ITCHY EYES											
				ITCHING - EYES											
				EYES ITCHING			EYE DISORDER: FEELING CROSSED EYED								
	WATERING EYES						NS DISORDERS: HEAVINESS OF EYELIDS								
			BLURRED VISION			EYELASHES INCREASE GROWTH (SKIN-SUBQ TISSUE DSO)									
	DRY EYE	BILATERAL CONJUNCTIVAL INJECTION													
	DRY EYES	BLOODSHOT EYES													
			BLURRY VISION												
			BLURRED VISION												
						TRICHOMEGALY OF EYELASH									
	DRY EYES			ITCHY EYES											
					PERIORBITAL EDEMA										
	WATERY EYES														
	WATERY EYES	RED EYES													
	DRY EYE						EYE INFLAMMATION								
			BLURRED VISION												
														DIPLOPIA	
	DRY EYE	LEFT EYE REDNES	BLURRED VISION												UVEITIS LEFT EYE
			VISION CHANGES												

Reviewer's Comments: *There were a total of 48 reported ocular adverse events in Study 61186372EDI1001. Seventeen (5%) were consistent with dry eye syndrome, 11 (3%) were conjunctival redness, 9 (2%) blurred vision, 7 (2%) ocular itching, and 6 (2%) ocular lid or periocular edema. There was one case of uveitis. Other reported events were consistent with common ocular events unrelated to drug treatment. The percentages listed are based on 362 patients having been treated. Considering that no ocular events occurred in patients treated with doses below 1050 mg, the percentages of reported ocular adverse events in the future are likely to be higher.*

Summary Comments:

1. Ocular adverse events were reported in Study 61186372EDI1001. The most common reported ocular events were consistent with the product causing dry eye symptoms.

2. It is recommended that if approved, labeling for amivantamab include the potential for patients to experience dry eye symptoms, conjunctival redness, blurred vision, ocular itching, periocular edema, and uveitis.

3. Although only one case of uveitis has been reported, the potential consequences of untreated uveitis can include loss of vision, and therefore it is recommended this adverse event be labeled.

4. Grading of ocular adverse events is potentially misleading and is not recommended.

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Supervisory Medical Officer, Ophthalmology

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/s/

WILEY A CHAMBERS
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