CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761210Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

FDA review was conducted in conjunction with other regulatory authorities under Project ORBIS. While the application review is completed by the FDA, the application is still under review at the other regulatory agencies (Brazilian Health Regulatory Agency {Agência Nacional de Vigilância Sanitária; ANVISA} and Medicines and Healthcare products Regulatory Agency).

Disclaimer: In this document, the sections labeled as "Data" and "the Applicant's Position" are completed by the Applicant, which do not necessarily reflect the positions of the FDA or the other Regulatory Authorities.

Application Type	BLA
Application Number	761210
Priority or Standard	Priority
Submit Date	November 24, 2020
Received Date	November 24, 2020
PDUFA Goal Date	July 23, 2021
Division/Office	DO2/OOD
Review Completion Date	May 20, 2021
Established Name	Amivantamab-vmjw
(Proposed) Trade Name	RYBREVANT
Pharmacologic Class	Bispecific EGF receptor-directed and MET receptor-directed antibody
Code name	JNJ-61186372
Applicant	Janssen Biotech, Inc.
Formulation	350 mg/7mL (50 mg/mL) solution in a single-dose vial
Dosing Regimen	Patient baseline body weight < 80 kg: 1050 mg IV once weekly for 4 weeks, then every 2 weeks thereafter. For the initial dose, administer as a split infusion in Week 1 on Days 1 and 2 Patient baseline body weight ≥ 80 kg: 1400 mg IV once weekly for 4 weeks, then every 2 weeks thereafter. For the initial dose, administer as a split infusion in Week 1 on Days 1 and 2
Applicant Proposed Indication	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.
Recommendation on Regulatory Action	Approval
Recommended Indication	Treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

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Glossary

ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AR	accumulation ratio
AST	aspartate aminotransferase
AUC	area under concentration-time curve
BICR	Blinded Independent Central Review
BLA	Biologics License Application
BTD	Breakthrough Therapy Designation
C1D1	Cycle 1, Day 1
C1D2	Cycle 1, Day 2
C2D1	Cycle 1, Day 1
C4D1	Cycle 4, Day 1
CBR	clinical benefit rate
cEGFR	common epidermal growth factor receptor
CFR	Code of Federal Regulations
CI	confidence interval
CL	clearance
C_{max}	maximum observed serum concentration
CNS	central nervous system
COVID-19	Coronavirus Disease 19
CR	complete response
CrCl	creatinine clearance
CSR	clinical study report
ctDNA	circulating tumor deoxyribose nucleic acid
C_{trough}	trough serum concentration
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EHR	electronic health record
EOI	end of infusion
E-R	exposure-response
Exon 20ins	Exon 20 insertion mutations
FDA	Food and Drug Administration
GCP	good clinical practice
GLP	good laboratory practice
GMR	geometric mean ratio
ICH	International Conference on Harmonization
IgG	immunoglobulin G
ILD	interstitial lung disease

IRR	infusion-related reaction
IV	intravenous
kD	kilodalton
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no-observed-adverse-effect level
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NE	not estimable
NSCLC	non-small cell lung cancer
OECD	Organisation for Economic Cooperation and Development
ORR	overall response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PD-L1	programmed cell death ligand 1
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response
PRO	patient reported outcome
QTcF	corrected QT interval using Fridericia formula
RECIST	Response Criteria in Solid Tumors
REMS	risk evaluation and mitigation strategy
RP2D	recommended Phase 2 dose
RWD	real world data
SAP	statistical analysis plan
SC	subcutaneous
SD	stable disease (standard deviation)
SET	Safety Evaluation Team
SOC	system organ class
SoD	sum of diameters
T_{max}	time to maximum serum concentration
TEAE	treatment emergent adverse event
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
US	United States
USPI	United States prescribing information
V1	volume of distribution in central compartment
WOE	weight of evidence

1 Executive Summary

1.1. Product Introduction

Amivantamab-vmjw (hereafter referred to as amivantamab) is a low-fucose, fully human, IgG1-based bispecific antibody against the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) receptor with an established pharmacological class of bispecific EGF receptor-directed MET receptor-directed antagonist. Amivantamab blocks ligand-induced activation and signaling through EGFR and MET and by targeting immune effector cells to EGFR and MET expressing tumor cells. Amivantamab is not currently approved in the United States or any other part of the world. The proposed dosing regimen for amivantamab is 1050 mg (for patient baseline body weight <80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) intravenously (IV) once weekly for 4 weeks, then every 2 weeks thereafter, with the initial infusion administered as a split infusion in Week 1 on Days 1 and 2. Janssen's proposed indication for amivantamab is "for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy."

1.2. Conclusions on the Substantial Evidence of Effectiveness

The submitted evidence meets the statutory evidentiary standard for accelerated approval. The recommendation for accelerated approval according to 21 CFR 601.40 Subpart E is based on results from patients with advanced NSCLC with epidermal growth factor receptor (EGFR) exon 20 insertion mutations who received amivantamab in a multicenter, nonrandomized, open-label, multi-cohort clinical trial (CHRYSALIS). The efficacy population for this application comprises 81 patients with metastatic NSCLC with EGFR exon 20 insertion mutation previously treated with platinum-based chemotherapy who received amivantamab 1050 mg (for patient baseline body weight <80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) IV once weekly for 4 weeks, then every 2 weeks thereafter. The demonstrated overall response rates (ORR) per blinded independent central review (BICR) of 40% (95% CI 29, 51) with a median duration of response (DOR) of 11.1 months is considered clinically meaningful when considering the intended patient population, patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations and disease progression on or after platinum-based chemotherapy. For NSCLC, ORR may be considered an endpoint reasonably likely to predict clinical benefit when the treatment effect size is large and the responses are durable (Guidance for Industry: Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics). Based on the findings in CHRYSALIS, FDA expects that amivantamab will have, as described in section 505(d) of the Act, "the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

1.3. Benefit-Risk Assessment (BRA)

Benefit-Risk Summary and Assessment

Metastatic non-small cell lung cancer (NSCLC) is a fatal, incurable disease, with a 5-year survival rate of <10%. EGFR exon 20 insertion mutations have been identified as oncogenic drivers in NSCLC and have been reported to be present in approximately 2-3% of cases of advanced NSCLC. In comparison to many other EGFR oncogenic driver mutations, NSCLC with EGFR exon 20 insertion mutations does not respond well to treatment with currently approved EGFR tyrosine kinase inhibitors. Current treatment options for patients with NSCLC harboring EGFR exon 20 insertion mutations whose disease has progressed following platinum-based chemotherapy are the same therapies as those used for patients with NSCLC without a specific driver mutation identified. This includes ramucurimab plus docetaxel (ORR 23%) or single agent chemotherapy (ORR 10-15%), as well as treatment with anti-PD-(L)1 antibody as a single agent for patients who did not receive such treatment as part of first-line therapy (associated with ORR 14-19%). Based on the limited data available for review, there is no indication that patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations have a substantially different response rate when treated with chemotherapy and/or immunotherapy compared to the general population of patients with NSCLC. To date, there is no targeted therapy specifically approved for the treatment of patients with NSCLC with EGFR exon 20 insertion mutations.

Amivantamab is a bispecific antibody directed against EGF and MET receptors. The proposed dosing regimen is 1050 mg (for patient baseline body weight <80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) IV once weekly for 4 weeks, then every 2 weeks thereafter, with the initial infusion administered in two divided doses in Week 1 on Day 1 and Day 2. Janssen's proposed indication for amivantamab is "for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy."

The primary efficacy analysis population for this review comprises 81 patients with metastatic NSCLC with EGFR exon 20 insertion mutation previously treated with platinum-based chemotherapy who received amivantamab 1050 mg (for patient baseline body weight <80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) intravenously (IV) once weekly for 4 weeks, then every 2 weeks thereafter in the multi-cohort clinical trial, CHRYSALIS. The confirmed overall response rate (ORR) assessed by blinded independent central review (BICR) was 40% (95% CI: 29, 51) and the median duration of response (DOR) was 11.1 months (95% CI: 6.9, not estimable [NE]), with 63% of the 32 responders having observed DOR of ≥ 6 months. This response rate, coupled with the durability of responses observed, provides clinical benefit in the intended patient population.

Infusion-related reactions (IRR) occurred in the majority (approximately 65%) of patients treated with amivantamab. Over 90% of IRRs occurred on Day 1 or 2 of the initial Week 1 infusion, with an incidence of IRR 65% with Week 1 Day 1 infusion, 3.4% Week 1 Day 2, 0.4% Week 2, and 1.1% with subsequent infusions. IRRs were mostly Grades 1-2, with 2.2% of reported IRRs Grade 3 and 0.4% Grade 4. To address this issue, product labeling will include clear instructions regarding split dosing for initial administration, premedication, and management of IRR with interruption of infusion and reduction in infusion rate or permanent discontinuation based on severity.

In the indicated population, the most common (≥20%) adverse reactions were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. Permanent discontinuation of amivantamab due to adverse reactions occurred in 11% of patients; the most frequent (≥1%) adverse reactions leading to permanent discontinuation were pneumonia, IRR, pneumonitis/interstitial lung disease (ILD), dyspnea, pleural effusion, and rash. Fatal adverse reactions occurred in 3 patients (2.3%), with two fatal events of pneumonia and one event of sudden death. Safety issues identified as significant and serious during the BLA review were IRR, ILD/pneumonitis, dermatologic adverse reactions, and ocular toxicity. These safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during BLA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). Amivantamab appears to have an acceptable safety profile when assessed in the context of a life-threatening disease.

A supplemental premarket application (sPMA) for a plasma-based companion diagnostic test (Guardant360® CDx) was submitted by Guardant Health Inc. for contemporaneous review with this BLA. (b) (4) (b) (4) (b) (4) Janssen has agreed to a post-marketing commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a tissue-based in vitro diagnostic device to detect EGFR exon 20 insertion mutation for identifying patients who may benefit from amivantamab.

The submitted evidence meets the statutory evidentiary standard for accelerated approval. Amivantamab has a favorable benefit-risk profile in the indicated population based on the observed response rate and durable responses in a patient population with a life-threatening disease and an unmet medical need. Given the relatively limited duration of follow-up and the number of patients in the primary efficacy analysis population for this application, the current data are considered adequate to support accelerated approval rather than regular approval. Results

from the ongoing trial entitled, "A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer" may be used to verify the clinical benefit of amivantamab in patients with advanced NSCLC with EGFR exon 20 insertion mutations. Submission of additional data from CHRYSALIS will be requested as a post-marketing commitment to further characterize and provide a more precise estimation of BICR-assessed ORR and DOR with amivantamab in patients with advanced NSCLC with EGFR exon 20 insertion mutations previously treated with platinum-based chemotherapy.

Accelerated approval for amivantamab will be granted for the following indication: "For the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy."

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Lung cancer is the leading cause of cancer death in the U.S., with 80 to 85% of all lung cancer cases identified as non-small cell lung cancer (NSCLC). • Epidermal growth factor receptor (EGFR) exon 20 insertion mutations have been identified as an oncogenic driver in NSCLC and have been reported to be present in approximately 2-3% of cases of advanced NSCLC. • The 5-year survival rate for patients with metastatic NSCLC is <10%. There is no randomized trial data available regarding survival specifically for patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations. • Based on the limited data available for review, there is no indication	Advanced NSCLC with EGFR exon 20 insertion mutations is a life-threatening disease with poor survival. NSCLC with EGFR exon 20 insertion mutations is a rare subset of NSCLC.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	that patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations have a substantially different response rate when treated with chemotherapy and/or immunotherapy compared to the general population of patients with NSCLC.	
Current Treatment Options	• There is no targeted therapy approved specifically for the treatment of patients with NSCLC with EGFR exon 20 insertion mutatiions. • In comparison to many other EGFR oncogenic driver mutations, NSCLC with EGFR exon 20 insertion mutations does not respond well to treatment with currently approved EGFR tyrosine kinase inhibitors. • Current treatment options for patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations are the same as those used for NSCLC without a specific driver mutation identified. • For patients with progression of disease following platinum-based chemotherapy, treatment options include chemotherapy (single agent or docetaxel in combination with ramucirumab), associated with ORR 6-23% with median durations of response in the range of 4 to 9 months or single agent anti-PD-(L)1 antibody if not received in the first-line setting, associated with ORR 14-20% with median durations of response in the range of 16 to 17 months.	There is an unmet medical need for patients with metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. This conclusion is based on observed response rates, durations of response, and overall survival reported for therapies currently used in clinical practice for the treatment of this patient population.
Benefit	• The primary efficacy data supporting this BLA are from 81 patients with NSCLC with EGFR exon 20 insertion mutations and disease progression following platinum-based chemotherapy who received amivantamab in a multicenter, nonrandomized, open-label, multi-	The submitted evidence meets the statutory evidentiary standard for accelerated approval. The observed ORR, along with the observed duration of responses, are clinically meaningful

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	cohort clinical trial (CHRYSALIS). • Confirmed ORR per BICR was 40% (95% CI 29, 51) with median DOR of 11.1 months (95% CI 6.9, not estimable). • Given the relatively limited duration of follow-up and the number of patients in the primary efficacy analysis population for this application, the current data are considered adequate to support accelerated approval rather than regular approval. • A limitation of single arm trials is the potential for known and unknown patient selection bias. • Information submitted by the Applicant utilizing data from Flatiron Health reported 9.4% of patients with NSCLC with EGFR exon 20 insertion mutations were Black or African American. In the primary efficacy population of the CHRYSALIS study, 2.3% of patients were Black or African American.	when considering the intented patient population. Results from the ongoing trial entitled, "A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer" may be used to verify the clinical benefit of amivantamab in patients with advanced NSCLC with EGFR exon 20 insertion mutations. Submission of these results has been requested as a post-marketing requirement. Submission of additional data from CHRYSALIS will be requested as a post-marketing commitment to further characterize and provide a more precise estimation of BICR-assessed ORR and DOR with amivantamab in patients with advanced NSCLC with EGFR exon 20 insertion mutations previously treated with platinum-based chemotherapy. Based on the demographic and baseline disease characteristics of the patients in the primary analysis population for this application, this population is comparable to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		the overall U.S. target population, with the exception that Black or African American patients were underrepresented. The benefit demonstrated in the CHRYSALIS study is expected to extend to the postmarket setting. A PMC was agreed to for the Applicant to submit clinical trial data to further characterize the safety and efficacy of amivantamab in Black or African American patients with EGFR exon 20 insertion mutated NSCLC.
Risk and Risk Management	• The safety database for this BLA includes 302 patients who were treated with amivantamab at the recommended dose (used to inform Warnings and Precautions section of labeling), including 129 patients with NSCLC with EGFR exon 20 insertion mutations and disease progression following platinum-based chemotherapy (the incidences presented below are for the latter population). The data in this BLA is adequate to assess safety with reference to the overall U.S. target population. • Permanent discontinuation of amivantamab due to adverse reactions occurred in 11% of patients; the most frequent (≥1%) adverse reactions leading to permanent discontinuation were pneumonia, IRR pneumonitis/interstitial lung disease (ILD), dyspnea, pleural effusion, and rash. • Dose reductions of amivantamab due to an adverse reaction occurred	The observed safety profile of amivantamab is acceptable when assessed in the context of the treatment of a life-threatening disease. While infusion-related reactions (IRR) occurred in the majority (approximately 65%) of patients treated with amivantamab, this issue will be addressed by inclusion in product labeling of clear instructions regarding split dosing for initial administration, premedication, and management of IRR with interruption of infusion and reduction in infusion rate or permanent discontinuation based on severity. Although amivantamab can cause severe/serious toxicities, these safety concerns are adequately addressed by information in

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	in 15% of patients. Adverse reactions requiring dose reduction in ≥2% of patients were rash and paronychia. While dose interruptions of amivantamab due to an adverse reaction occurred in 78% of patients, the majority of dose interruptions were due to infusion-related reactions (IRR). • IRR occurred in the majority (approximately 65%) of patients treated with amivantamab. Over 90% of IRRs occurred on Day 1 or 2 of the initial Week 1 infusion, with the incidence of IRR 65% with Week 1 Day 1 infusion, 3.4% Week 1 Day 2, 0.4% Week 2, and 1.1% with subsequent infusions. IRRs were mostly Grades 1-2, with 2.2% of reported IRRs Grade 3 and 0.4% Grade 4. • The most common (≥20%) adverse reactions were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. • Safety issues identified as significant and serious enough to warrant inclusion in the Warnings and Precauations section of labeling for amivantamab are IRR, ILD/pneumonitis, dermatologic adverse reactions, and ocular toxicity. • In a non-randomized, non-comparative study such as CHRYSALIS, a direct comparison of amivantamab-associated toxicity versus toxicity associated with current standard of care therapy is not possible.	the Warnings and Precautions section and Dosage and Administration sections of product labeling. Amivantamab will be administered by oncologists who know how to monitor, identify, and manage such toxicities. There were no significant safety concerns identified during BLA review requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigations Strategy (REMS).

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application, include:				Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as			
			x	Patient reported outcome (PRO)	See Section 8.2, Efficacy Results – Secondary or exploratory COA (PRO) endpoints
			□	Observer reported outcome (ObsRO)	
			□	Clinician reported outcome (ClinRO)	
			□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)			
	□	Patient-focused drug development or other stakeholder meeting summary reports			
	□	Observational survey studies designed to capture patient experience data			
	□	Natural history studies			
	□	Patient preference studies (e.g., submitted studies or scientific publications)			
	□	Other: (Please specify)			
□	Patient experience data that was not submitted in the application, but was considered in this review.				

X

Erin Larkins, M.D.
Cross-Disciplinary Team Leader

2 Therapeutic Context

2.1. Analysis of Condition

The Applicant's Position:

Advanced lung cancer is a serious terminal illness that until recently was associated with a median overall survival (OS) of approximately 1 year. As the leading cause of cancer-related mortality, lung cancer is a major global health concern, with 228,000 new diagnoses annually in the United States (US), 490,000 in the European Union, slightly over 1 million in Asia, and the highest reported incidence rates in Korea and China (Bray 2018; Pakzad 2015; SEER 2020a). Non-small cell lung cancer (NSCLC) accounts for 85% to 90% of lung cancers (Globocan 2012), with 5-year survival rates for NSCLC dependent upon on the stage at diagnosis and ranging from 58.7% for localized cancer to 4.7% for cancer that has spread to distant locations (SEER 2020b).

A significant development in the understanding of NSCLC biology has led to the identification of populations of NSCLC patients with "driver mutations" that result in constitutive activation of pro-growth signaling pathways. The most prevalent of these are mutations that affect the epidermal growth factor receptor (EGFR), which have been identified in approximately 15% of Western patients with NSCLC adenocarcinoma (Pao 2011), but in up to 40% to 50% of Asian patients with NSCLC adenocarcinoma (Jänne 2006). The most commonly occurring EGFR mutations, L858R and Exon 19del, are sensitive to approved EGFR tyrosine kinase inhibitors (TKIs). The use of these targeted agents as front-line therapy for these patients has been associated with improved response rates and duration of disease control, leading to dramatically increased median survivals of 32 to 39 months (Ramalingam 2020).

In up to 10% of EGFR-mutated NSCLC, however, EGFR is activated through one of a group of heterogenous, in-frame base pair insertions in EGFR Exon 20, collectively referred to as Exon 20 insertion mutations (Exon 20ins) (Vyse 2019). The unique protein structure associated with this group of EGFR mutations prevents effective binding by approved EGFR TKIs. Tumors arising from EGFR Exon 20ins mutations, therefore, are associated with primary resistance to currently approved EGFR TKIs, and these patients have correspondingly not benefitted from the significantly improved clinical outcomes associated with these agents in their target populations. As a result, patients with EGFR Exon 20ins NSCLC, despite having tumors with a well-understood tumor biology, do not currently benefit from targeted therapy, and they remain a population with significant unmet medical need.

The FDA's Assessment:

FDA agrees with the Applicant's position. Compared to NSCLC with wild-type EGFR, NSCLC with EGFR exon 20 insertion mutations are found in a higher proportion of women, Asian patients, never smokers, and those with adenocarcinoma histology (Oxnard 2013; Remon 2020). Unlike the more common EGFR mutations; however, there is no clear difference in frequency based on

ethnicity, with NSCLC with EGFR exon 20 insertion mutations accounting for 1.8-2.9% of advanced NSCLC cases across different regions of the world (Remon 2020).

Information submitted by the Applicant utilizing data from Flatiron Health reported that among 181 patients with NSCLC with EGFR exon 20 insertion mutations included in an analysis of the prognostic value of exon 20 insertion mutations, 60.2% were White, 9.4% were Black or African American, 6.1% were Asian; race was reported as Other Race for 12.7% and "not applicable" for 11%. While the proportion of patients with race reported as Hispanic or Latino was only 0.6%, based on the variable of ethnicity 5% of patients were Hispanic. The median age was 67.4 years (range: 39, 84), compared to median age of 60 years reported in the review by Oxnard et al (Oxnard 2013), and 61.3% of patients were female.

2.2. Analysis of Current Treatment Options

The Applicant's Position:

There are currently no approved targeted therapies for the treatment of patients with EGFR Exon 20ins disease and no specific treatment guidelines are given by the American Society of Clinical Oncology or in the NCCN Clinical Practice Guidelines for NSCLC (NCCN 2020) for treatment of this population. As a result, this subgroup of EGFR-mutated NSCLC remains less well-studied in comparison to TKI-sensitive EGFR L858R and Exon 19del disease, with relevant literature limited to exploratory analyses, retrospective analyses, and case-series reporting.

All available data demonstrate, however, that patients with EGFR Exon 20ins NSCLC have not benefitted from the 2 major recent advancements in lung cancer therapy: targeted therapy and immunotherapy. Although sharing a similar tumor biology with other EGFR-mutated disease, tumors characterized by Exon 20ins mutation are resistant to currently approved EGFR TKIs. Given the demonstrated lack of efficacy for these agents, patients with EGFR Exon 20ins NSCLC have been largely excluded from the large, Phase 3 studies of EGFR TKIs.

Multiple early Phase 3 studies in patients with EGFR-mutated NSCLC have demonstrated worse outcomes for agents inhibiting programmed cell death protein-1 (anti-PD1) or its ligand (anti-PD-L1) in terms of progression-free survival (PFS) and OS compared with single-agent docetaxel controls (Borghaei 2015; Herbst 2016; Rittmeyer 2017). As such patients with EGFR-mutated disease have been excluded from subsequent studies of immunotherapies, now front-line standard of care for patients with NSCLC not qualifying for targeted therapies. Consequently, patients with EGFR-mutated NSCLC are excluded from the corresponding front-line regulatory approvals of these immunotherapy agents (Keytruda USPI 2020; Opdivo USPI 2020; Tecentriq USPI 2020).

As a result, front-line treatment for Exon 20ins NSCLC has not changed over the last decade, with platinum-based chemotherapy remaining the standard of care, with an associated 30% overall response rate (ORR) and PFS of approximately 4 months in EGFR-mutated NSCLC (Mok 2017, Wu 2019). Upon progression, treatment options are limited, with EGFR TKIs and immunotherapy agents being ineffective in this disease, and single-agent chemotherapy agents being associated with low ORRs of approximately 10% to 15%, and median PFS of less than 4 months (Borghaei 2015; Hanna 2004). More recently, the combination of ramucirumab and docetaxel

has been approved for use in second-line treatment of NSCLC based upon an absolute 1.5-month improvement in median PFS (4.5 vs 3.0 months) and a 1.4-month improvement in median OS (10.5 vs 9.1 months), compared with docetaxel alone. The combination was also associated with an improved ORR of 23% versus 14% in the docetaxel alone arm (Garon 2014). However, a subsequent analysis of ORR by prespecified histological subgroups demonstrated that subjects with adenocarcinoma (the most common histology observed in EGFR-mutated NSCLC) treated with the ramucirumab and docetaxel combination (n=377) had an ORR of 18.6% vs 15.2% in the docetaxel alone arm (n=348) (Paz-Ares 2017). An examination of electronic health record (EHR) and utilization databases (see Section 8.1.5) suggests that regulatory approval has not led to broad uptake and utilization of the ramucirumab and docetaxel combination in the treatment of patients with NSCLC, whether in EGFR-mutated or wild-type disease. Given the paucity of effective treatment options, the outcomes of patients with Exon 20ins disease has not improved, with median OS remaining at 12.5 months after initiation of second-line therapy (Dersarkissian 2019).

New targeted therapies, therefore, are needed to provide effective EGFR inhibition in patients with Exon 20ins mutation, particularly in patients who have not benefitted from platinum-based chemotherapy, for whom there is no standard of care and who represent a population with unmet medical need. Amivantamab, with its unique mechanism of action, is expected to address this unmet medical need, and represents the first targeted treatment option for patients with EGFR Exon 20ins mutation.

The FDA's Assessment:

FDA agrees with the Applicant's statement that there is currently no targeted therapy approved specifically for the treatment of patients with NSCLC whose tumors harbor EGFR exon 20 insertion mutations, and current treatment options for such patients whose disease has progressed following platinum-based chemotherapy are the same therapies as those used for patients with NSCLC without a specific driver mutation identified. This includes ramucurimab plus docetaxel (ORR 23%) or single agent chemotherapy, as well as treatment with anti-PD-(L)1 antibody as a single agent for patients who did not receive such treatment as part of first-line therapy (associated with ORR 14-19%).

FDA does not agree with the Applicant's characterization of the applicability of anti-PD-(L)1 antibody therapy to patients with NSCLC with EGFR exon 20 insertion mutations. While patients with EGFR mutation-positive NSCLC have been excluded from many first-line studies of anti-PD-(L)1 antibodies, this exclusion was most often specific to the common activating mutations, EGFR exon 19 deletion and exon 21 L858R substitution mutations, and therefore did not preclude enrollment of patients with EGFR exon 20 insertion mutations. While data regarding response to immunotherapy in this specific patient population is limited, there is no clear indication that patients with NSCLC with EGFR exon 20 insertion mutations are less likely to respond to such therapy than patients with wild-type EGFR. Two small retrospective studies suggest that patients with NSCLC with EGFR exon 20 insertion mutations treated with immune checkpoint inhibitors have outcomes similar to wild-type historical controls and superior to those reported for patients with NSCLC harboring the more common EGFR mutations (Negrao 2018; Lau 2021).

Amivantamab would be the first targeted treatment option specifically for patients with locally advanced or metastatic NSCLC patients with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Applicant's Position:

Amivantamab (JNJ-61186372) is not currently registered (or approved) in the US or any other part of the world.

The FDA's Assessment:

FDA agrees with the Applicant.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant's Position:

The Applicant submitted IND 135405 on 20 October 2017 to the US Food and Drug Administration (FDA) to support the investigation of amivantamab in the treatment of advanced or refractory solid malignancies, including lung cancer. The "Study May Proceed" letter for the initial Phase 1 Study 61186372EDI1001 (CHRYSALIS; hereafter referred to as EDI1001) was issued on 20 November 2017.

The Applicant's clinical development program was designed after consultation with health authorities around the world. Key meetings with and documents previously submitted to the US FDA are briefly summarized in Table 1.

On 09 March 2020, the US FDA granted a Breakthrough Therapy Designation for amivantamab for the treatment of patients with metastatic NSCLC with EGFR Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy.

Table 1: Key US FDA Interactions Relevant to Amivantamab

Event	Date	Description
Janssen Response to FDA's 17 May 2018 Clinical and Statistics Advice/Information Request	30 May 2018 (IND 135405; SN 0022)	Following receipt of Study 61186372EDI1001 protocol Amendment 4 adding Part 2 Cohorts C and D, FDA recommended to analyze the primary endpoint in a single arm trial for the final analysis using one of the Frequentist's methods for the purposes of regulatory approval. Janssen agreed.
Type B End of Phase 1 Meeting Preliminary Comments	11 Feb 2019	The FDA provided advice on design aspects of the Study 61186372EDI1001 and confirmed acceptability of the proposed recommended phase 2 dose (RP2D) and comparability strategy for amivantamab. *Meeting cancelled based on satisfactory preliminary comments.*

Event	Date	Description
Type C CMC Meeting Preliminary Comments	16 Oct 2019	The FDA agreed with the comparability and shelf life strategy to support commercial launch of amivantamab. *Meeting cancelled based on satisfactory preliminary comments.*
Breakthrough Therapy Designation (BTD) Granted	09 Mar 2020	BTD was granted 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.
Type B CMC Meeting Preliminary Comments	28 Apr 2020	The FDA agreed with the qualification strategy for future working cell banks and stability data package to support a shelf life claim for commercial drug substance (DS) and drug product (DP). The FDA also agreed to provision of a stability update within 30 days of the BLA submission. *Meeting cancelled based on satisfactory preliminary comments.*
Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting	06 May 2020	The FDA indicated that the proposed efficacy data may allow for a substantive review of a BLA to support the proposed indication and that the proposed safety population and the extent of exposure appears adequate to support the filing of a BLA. Additionally, the proposed clinical pharmacology plan supporting the BLA was considered acceptable. The FDA also provided advice and aligned on design aspects of the proposed Phase 3 confirmatory study including study population, endpoints, statistical analyses, and comparator.
Agreed Initial Pediatric Study Plan (iPSP)	13 May 2020	The FDA agreed with the Applicant's plan to submit a request for a full waiver for amivantamab for all age subsets of the pediatric population.
Applicant Response to DMEPA Comments	10 Jul 2020	The Applicant provided a response to Division of Medical Error and Prevention Analysis (DMEPA) comments (received in the 06 May FDA meeting preliminary comments) regarding risk of medication errors related to single vial packaging configuration. This response was subsequently deemed acceptable (via e-mail on 10 August 2020).
Type C Format and Content Meeting	22 Jul 2020	The FDA recommended Janssen request a clinical pre-BLA meeting once the topline independent review committee results were available and indicated FDA would likely use overall response rate (ORR) data from the 82 patients in the primary efficacy analysis population with a June 2020 data cutoff date in the package insert. Updated efficacy data to be provided at the time of BLA submission (including supportive data in the expanded target population), and associated clinical cutoff date, was also agreed upon, as well as other aspects of the BLA format and content.
Type B pre-BLA CMC Meeting Preliminary Comments	28 Jul 2020	The FDA considered the proposed strategies regarding [redacted] (b) (4) hold time for DS manufacturing, [redacted] (b) (4) Bioburden Testing, Commercial Testing, for parental antibodies, and post translational modification (PTM) reasonable. *Meeting cancelled based on satisfactory preliminary comments.*
Proprietary Name Conditional Acceptance	31 Jul 2020	Conditional acceptance granted for the proposed proprietary name of RYBREVANT.
Type B Nonclinical WRO Written Responses	03 Aug 2020	The FDA indicated that fertility and early embryonic development and prenatal and postnatal development studies are not necessary for the planned BLA submission.
Type B Pre-BLA Meeting	04 Nov 2020	The FDA agreed to the 24 November 2020 BLA submission date (based on 08 June 2020 clinical cutoff) and agreed that an updated efficacy dataset, the Assessment Aid, and addendums to clinical documents (CSR, SCE, CO) and updated proposed label, all reflecting updated efficacy for the primary efficacy population (as by BICR) based on an 08 Oct 2020 cutoff, would be submitted by 31 December 2020. The FDA indicated that with this agreement, the BLA review clock would start at 24 November 2020.

The FDA's Assessment:

FDA agrees with the Applicant's position with the caveat that FDA issued the "Study May Proceed" letter on November 16, 2017 not November 20, 2017.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review division (DO2) and OSI selected five clinical investigators, including one alternate site, as well as the central imagining contract research organization (CRO), (b) (4) were identified for inspection. Inspection of two clinical sites selected for inspection could not be conducted because of the ongoing COVID-19 pandemic, as the ORA inspectors could not travel to the sites 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. Therefore, three clinical investigators (Drs. Eric Haura (Site #US10001), Rachel Sanborn (Site #US10012) and Joshua Sabari (Site #US10009)), as well as the CRO, were selected for clinical inspection using a risk-based approach taking into consideration the total number of subjects enrolled and safety and efficacy parameters.

Dr. Eric Haura (Site #US10001) screened 29 patients (14 in Part 1, 15 in Part 2) and enrolled 15 patients (11 in Part 1, 4 in Part 2) at the site prior to February 17, 2021. Five subjects (3 in Part 1, 2 in Part 2) remain on follow-up and no subjects were on active treatment.This was the first FDA inspection for this investigator. The inspection found no regulatory violations at the site.

Dr. Rachel Sanborn (Site # US10012) screened 30 patients and enrolled 11 patients into the clinical trial prior to February 16, 2021. Of the 11 patients, data from the 8 patients enrolled prior to the data cutoff were included in the BLA. Five of 8 patients 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. 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.

Dr. Joshua Sabari (Site #US10009) screened 38 patients (16 screen failures) and enrolled 22 patients. Four patients remain on study (18 patients off study). This was the first FDA inspection for this investigator. There was no underreporting of adverse events or serious AEs or protocol deviation. In addition, there was no evidence of unreported scans or images. The inspection found no regulatory violations at the site.

The Applicant contracted (b) (4) to perform central imaging services for clinical trial 61186372EDI1001, and (b) (4) was inspected as a data audit and surveillance inspection. This CRO has been previously inspected on December 10, 2014, January 28 and July 24, 2015, June 8, 2017, and September 26, 2019, all classified as no action indicated (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 (BioPac) 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.

Based on the results of these inspections, the clinical trial 61186372EDI1001 overall appears to have been conducted adequately, and the data generated by the inspected clinical investigators and the imaging CRO appear acceptable in support of the BLA.

4.2. Product Quality

See Product Review dated April 23, 2021, Quality Executive Summary dated April 28, 2021 and Quality Executive Summary Addendum dated May 20, 2021.

4.3. Clinical Microbiology

See Drug Substance Microbiology and Facility Review dated May 20, 2021 and Drug Product Microbiology and Facility Review dated April 23, 2021.

4.4. Devices and Companion Diagnostic Issues

Contemporaneously with review of this BLA, the Center for Devices and Radiological Health (CDRH) reviewed a supplemental premarket application (sPMA) for a plasma-based companion diagnostic test, Guardant360® CDx, submitted by Guardant Health, Inc. on November 20, 2020. Please refer to the review by Dr. Banu Saritas-Yildirim for additional information on the companion diagnostic device.

(b) (4)

(b) (4) Janssen has agreed to a post-marketing

commitment (PMC) to provide adequate analytical and clinical validation results from clinical trial data to support labeling of a tissue-based in vitro diagnostic device to detect EGFR exon 20 insertion mutation for identifying patients who may benefit from amivantamab.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The FDA's Assessment:

Amivantamab (JNJ61186372 or CNTO4424) is a low-fucose, fully human, IgG1-based bispecific antibody against the epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) receptor with an established pharmacological class of bispecific EGF receptor-directed MET receptor-directed antagonist. The Applicant designed amivantamab to prevent tumor growth and progression by blocking ligand-induced activation and signaling through EGFR and MET and by targeting of immune effector cells to EGFR and MET expressing tumor cells.

In binding studies, amivantamab bound to human EGFR and MET with K_D values of 1.43 and 0.04 nM, respectively. Amivantamab bound to the extracellular domains (ECD) of human and cynomolgus monkey EGFR and MET with similar EC_{50} values, but not to rat EGFR or rat MET. In addition, amivantamab bound to lung cancer cell lines of various EGFR and MET status with IC_{50} values ranging from 0.9 to 12.1 nM. Binding of amivantamab to EGFR and MET, prevented binding of their ligands, epidermal growth factor (EGF) and human growth factor (HGF), with IC_{50} values of 10 and 30 nM, respectively. Amivantamab inhibited ligand-induced receptor phosphorylation in NSCLC cell lines with both wild type (WT) and mutant EGFR (L858R, T790M) with WT MET with IC_{50} values ranging from 0.49 to 29 nM. In several NSCLC cell lines, amivantamab led to greater inhibition of receptor phosphorylation compared to monovalent anti-EGFR or anti-MET antibodies alone or together. Evaluation of the impact of amivantamab on downstream signaling of Ras/RAF/MEK/ERK and PI3K pathways by measuring ERK and AKT phosphorylation showed that amivantamab inhibited ERK and AKT phosphorylation in cell lines with WT or mutant EGFR and WT MET but showed weak to no inhibition in cell lines with amplified WT MET only.

The proposed indication for amivantamab is for the treatment of patients with metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. Exon 20 insertion mutations affect the intracellular EGFR kinase binding domain leading to conformational changes that often confer resistance to earlier generation kinase inhibitors targeting EGFR. Patients with NSCLC with exon 20 insertion mutations typically have a worse prognosis compared to those with exon 19

deletions/mutations. Janssen evaluated the activity of amivantamab in cells with five distinct exon 20 insertion mutations previously found in patients with NSCLC; V769_D770insASV, D770delinsGY, H773_ V774insH, Y764_V765insHH, and D770_N771ins-SVD. Amivantamab dose-dependently decreased cell survival in Ba/F3 cells engineered to express EGFR with these exon 20 insertion mutations, in contrast to osimertinib or gefitinib which both had limited activity against these cells. In addition, amivantamab dose-dependently decreased EGFR expression and phosphorylation of both EGFR and downstream effectors ERK and AKT. In contrast, incubation with osimertinib and gefitinib decreased phosphorylated EGFR but had no impact on downstream proteins. Further analysis showed that amivantamab led to accumulation of cells in the G1 phase and induction of proapoptotic proteins BIM and cleaved caspase-3 in cells with exon 20 insertion mutations. There were similar results in patient derived cells with exon 20 insertion mutations. Amivantamab also inhibited survival of cell lines with WT EGFR and WT MET as well as those containing mutant EGFR (L858R, T790M/ WT MET in the presence of EGF and HGF to a greater extent compared to clinically available EGFR inhibitors afatinib and erlotinib.

In mice bearing patient derived tumors with exon 20 insertion mutations, administration of intraperitoneal (i.p.) amivantamab twice weekly resulted in significant tumor growth inhibition and complete responses in several animals, as did cetuximab and osimertinib. Erlotinib, however, did not show significant anti-tumor activity in this model. In addition, twice weekly i.p. amivantamab decreased tumor volume in mice bearing tumors from the patient derived cell lines harboring exon 20 insertion mutations, and decreased protein expression and phosphorylation of EGFR and MET in the tumor tissue. Treatment with amivantamab in a patient derived xenograft model with an exon 20 insertion mutation resulted in decreased tumor volume, while treatment with cetuximab or poziotinib, an investigational small molecule inhibitor with activity against exon 20 insertion mutations, only modestly reduced tumor volume. Histopathologic analysis of EGFR, MET, and Ki-67, and terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) staining from tumor sections obtained following amivantamab treatment further confirmed receptor inhibition and engagement of apoptotic machinery in EGFR exon 20 insertion mutation-driven tumors in vivo. Blockade of mouse CD16/CD32 via administration of anti-CD16/CD32 antibodies attenuated the anti-tumor effect of amivantamab in co-treated mice bearing tumors with exon 20 insertion mutations suggesting that the Fc effector activity of amivantamab is partially responsible for its anti-tumor activity. Administration of amivantamab to mice bearing tumors with exon 19 DelE746_A750, T790M, and C797S EGFR mutations led to significant tumor growth inhibition and increased survival; osimertinib and erlotinib had no effect.

Amivantamab induced ADCC activity against NSCLC cell lines with WT or mutant EGFR, WT or amplified MET, including EGFR expressing cells with mutations in KRAS. In addition, amivantamab resulted in dose-dependent ADCC in patient derived cells, DFCI-127 and YU-1163, expressing exon 20 insertion mutations, which was impaired when incubated with an Fc

receptor blocker. The level of amivantamab-mediated ADCC was greater than that of cetuximab in the same exon 20 insertion mutation harboring cell lines. Amivantamab induced trogocytosis (severing pieces of the target cell membrane with or without some cytoplasmic content resulting in transfer of content to the effector) against a NSCLC cell line with EGFR L858R, T790M mutations in the presence of macrophages and monocytes. Amivantamab did not induce CDC in any cell line tested.

Janssen conducted a GLP-compliant 13-week toxicology study in cynomolgus monkeys. Monkeys received intravenous amivantamab once weekly at doses of 0, 60, or 120 mg/kg. Exposures achieved in monkeys at the 120 mg/kg dose level were 5x[1] times higher than the AUC in patients (102954 µg*h/mL) at the once weekly dose for 4 weeks, then every 2 weeks clinical dose of 1050 mg. No mortalities occurred at any dose level. Limited clinical signs of liquid feces occurred on several occasions in females at 120 mg/kg. Amivantamab at all dose levels led to non-dose-dependent decreases in albumin in male and female monkeys and increases in globulin with subsequent effects on albumin/globulin ratios. Non-dose dependent gross pathology findings were limited to the stomach in the 60 and 120 mg/kg treat groups and included multifocal dark red foci with or without depression. These findings correlated with minimal to mild microscopic pathology of mucosal degeneration/erosion and hemorrhage in the stomach. Additional histopathology findings included minimal tubular regeneration and mixed cell infiltration in the kidney and Kupffer cell pigmentation and hypertrophy in the liver.

Janssen did not conduct genetic toxicology studies as they are not appropriate for antibody therapies. In addition, Janssen did not conduct dedicated studies to assess fertility or carcinogenicity as these studies are not necessary to support the development of a drug intended to treat patients with advanced cancer.

Rather than conducting a dedicated embryofetal development study, Janssen provided a weight-of-evidence-based assessment of the potential for amivantamab to cause reproductive and embryofetal toxicity. As a part of this assessment, Janssen provided a literature-based summary of effects of both EGFR and MET deletion on development; GLP-compliant study reports for both rat embryofetal development and fertility and early embryonic studies of lazertinib, a small molecule EGFR inhibitor; and an embryofetal development study in cynomolgus monkeys using zalutumumab, an anti-EGFR monoclonal antibody. Based on data from knockout mice and provided study reports, disruption EGFR and/or MET pathways can cause adverse effects on embryofetal development, postnatal development, and survival. Deletion of EGFR or MET led to defects in placental development in mice increasing embryofetal death. Deletion of MET was embryonic lethal, with observations of major defects

[1] Monkey $AUC_{84\text{-}91d}$ from the 3-month repeat-dose toxicology study was 21935 µg*day/mL. For comparison to the human exposure data, 21935 µg*day/mL x 24 hours/day = 526440 µg*day/mL. Monkey AUC of 526440 µg*day/mL vs. human AUC of 102954 µg*day/mL is 5x higher.

in muscle development, including tongue formation. EGFR knockout mice that make it to birth have underdeveloped lungs leading to an inability to initiate or sustain respiration and progressive neurodegeneration in the frontal cortex, olfactory bulb, and thalamus. Inhibition of EGFR with lazertinib in pregnant rats led to increased post-implantation loss, decreased number of live fetuses, and decreased gravid uterine and fetal weights, but did not lead to any external, visceral, or skeletal malformations.

Based on mechanism of action and the provided data from comparator molecules, a warning for embryofetal toxicity is included in the label for RYBREVANT. Based on mechanism of action and serum half-life, advise females of reproductive potential to use effective contraception during treatment and for 3 months after the final dose of RYBREVANT. In addition, because of the potential for serious adverse reactions from RYBREVANT in breast fed child, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the final dose of RYBREVANT.

5.2. Referenced NDAs, BLAs, DMFs

The Applicant's Position:

There are no referenced New Drug Applications, Biologics License Applications (BLA), or Drug Master Files related to nonclinical pharmacology or toxicology for amivantamab.

The FDA's Assessment:

Not applicable.

5.3. Pharmacology

Primary Pharmacology

The FDA's Assessment:

A. In Vitro Studies

Binding

In Study #DD15319, investigators showed that amivantamab (CNTO4424) bound to the extracellular domain (ECD) of human EGFR and MET receptors with binding affinities (K_{Ds}) of 1.43 and 0.04 nM, respectively, as measured via surface plasmon resonance (SPR) (Table 2). Amivantamab bound to the ECD of human and cynomolgus monkey EGFR and MET with similar EC_{50} values (Table 3), but not to the ECD of rat EGFR or MET (data not included in review). In addition, amivantamab bound to lung cancer cell lines with surface expression of various EGFR proteins (including EGFR with deletion mutations, point mutations, and amplifications) and wild type or amplified levels of MET with EC_{50} values ranging from 0.9 to 12.1 nM (Table 4).

FDA - Table 2: Binding affinity of amivantamab to EGFR and MET receptor

Antibody	K_D (nM)
EGFR ECD binding	
EGFR parental	1.61
Amivantamab	1.43
Cetuximab	0.44
MET parental	-
MET ECD binding	
Amivantamab	0.040
MET Parental	<0.005
MetMab	0.145

Cetuximab served as the positive control for EGFR binding and MetMab served as the positive control for MET binding.

FDA - Table 3: Binding of amivantamab to human and monkey EGFR and MET

Species	Amivantamab	Anti-MET	Anti-EGFR
Human MET ECD	0.27 nM	0.27 nM	-
Cynomolgus MET ECD	0.30 nM	0.27 nM	-
Human EGFR ECD	0.38 nM	-	0.38 nM
Cynomolgus EGFR ECD	0.57	-	0.29 nM

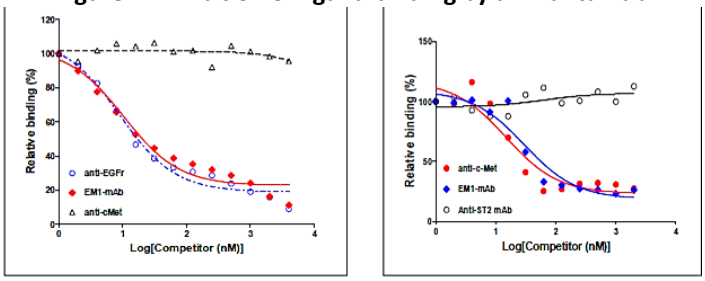
FDA - Table 4: Binding of amivantamab to lung cancer cell lines with various EGFR and MET status

Cell Line	EGFR status	MET status	Amivantamab EC_{50} nM
H292	WT (not AMP)	WT	1.37
SKMES-1	WT (not AMP)	WT	4.37
HCC827	Del (E746, A750)-AMP	WT	1.4
H1975	L858R, T790M (not AMP)	WT	12.1
H3255	L858R-AMP	WT	0.9
H1650	Del (E746, A750)-AMP	WT	4.25
HCC4006	Del (L747, S752)-AMP	WT	1.19
HCC2935	Del (E746, A750) (not AMP)	WT	1.4
H820	Del (E746, A750), T790M	WT-AMP	2.88
H1993	Del (E746, A750), T790M	WT-AMP	2.06

WT – wild type. AMP – amplified. Del – deletion. All cell types are lung cancer cell lines and are KRAS wild type without KRAS amplification.

Investigators confirmed that amivantamab blocked ligand binding (epidermal growth factor [EGF] to EGFR and human growth factor [HGF] to MET) using plate-bound Fc constructs of EGFR and MET incubated with fluorescently labeled human EGF and HGF, with IC_{50} values of 10 and 30 nM, respectively (Figure 1).

Figure 1: Inhibition of ligand binding by amivantamab



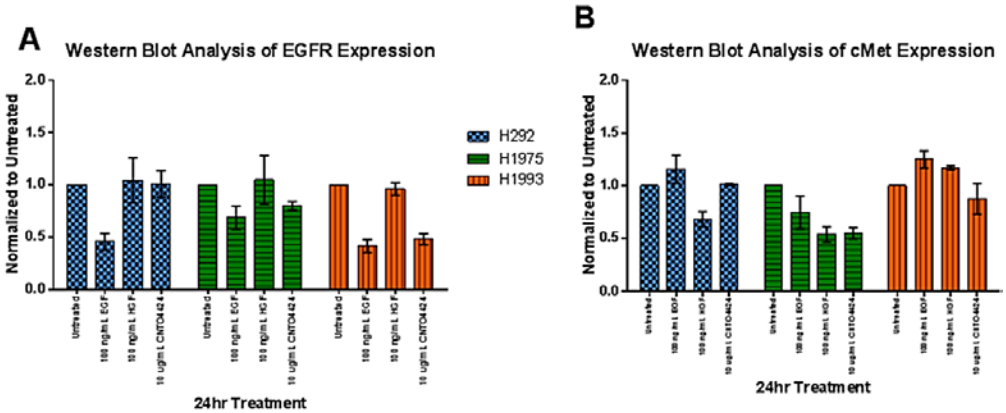
(Excerpted from Study #DD15319)

EM1 = amivantamab. Anti-EGFR and anti-MET = parental antibodies used to make amivantamab. Anti-ST2 = negative isotype control antibody. Panel A is inhibition of EGF binding to EGFR. Panel B is inhibition of HGF binding to MET.

Receptor internalization/degradation

The Applicant assessed the in vitro internalization of EGF and MET receptors upon ligand or antibody binding by immunofluorescent microscopy. Briefly, investigators incubated cells with HGF, EGF, cetuximab, or amivantamab in log dosing increments from 0.1 to 100.0 µg/mL for 2, 24, 48, or 72 hours. EGFR and MET receptor internalization, identified visually as receptor redistribution within the cellular compartments, occurred in H292, H1975, H1993, and A549 cell lines in response to treatment with both cognate ligands but not in response to either amivantamab or cetuximab, even by the 72 hour time-point. Evaluation of EGFR and MET expression in a protein blot indicated that each cognate receptor protein level decreased with ligand treatment in all cell lines except H1993 cells (EGFR exon 19 del/MET amp) treated with HGF. Amivantamab treatment decreased EGFR in H1993 but not H292 (EGFR and MET WT) and only slightly in H1975 (EGFR L858R/T790M; MET WT) cells. Amivantamab decreased MET in H1975, but not in H292 and H1993 cells (Figure 2).

Figure 2: EGFR and MET protein levels after 24 hours of treatment with EGF, HGF, or amivantamab



CNTO4424 = amivantamab.
(Excerpted from Study #DD15319)

Inhibition of cell viability

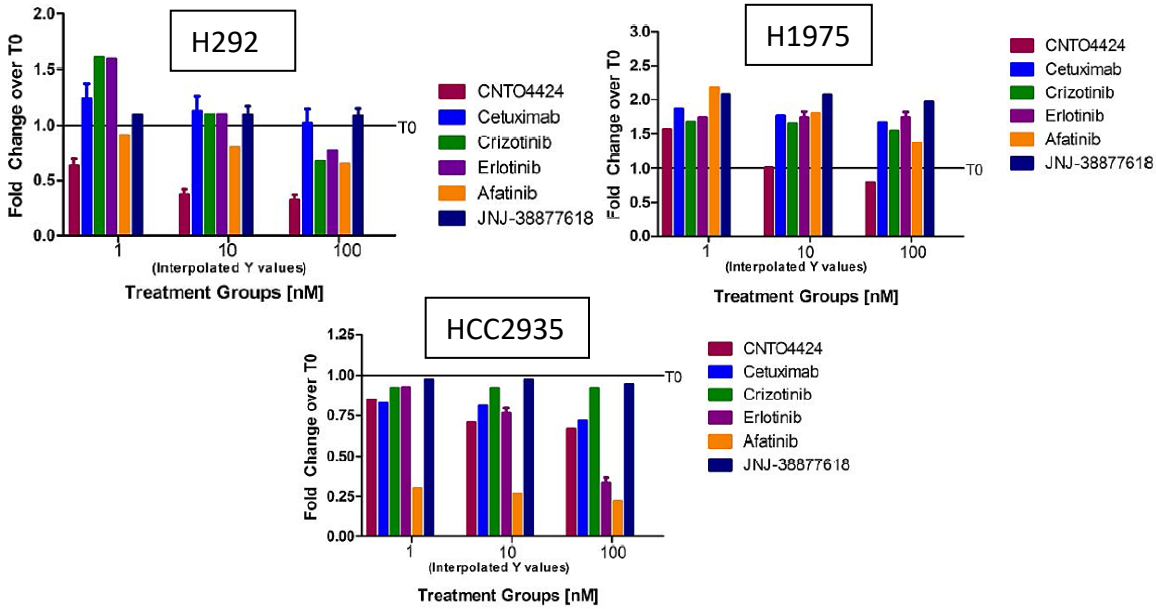
In Study #DD14324, as measured by the CellTiterGlo cell viability assay, amivantamab inhibited survival of cell lines with WT EGFR/ WT MET (H292 and SKMES-1 cells) as well as mutant EGFR (L858R, T790M)/ WT MET (H1975 cells) following incubation for 3 days in the presence of EGF and HGF.

FDA - Table 5: Percent inhibition of cell survival and IC_{50} values for cell lines with WT or mutated EGFR incubated with amivantamab

Cell line	% max inhibition	IC_{50} (nM)
H1975	64	3.5
SKMES-1	87	0.91
H292	81	0.74

Using the same cell survival assay, amivantamab showed greater activity against H292 (EGFR WT) and H1975 (EGFR L858R, T790M) cells compared to approved small molecule EGFR inhibitors afatinib and erlotinib; amivantamab had less robust activity against HCC2935 cells with Del (E746, A750; Figure 3).

Figure 3: Comparison of amivantamab to afatinib and erlotinib in cell survival assays



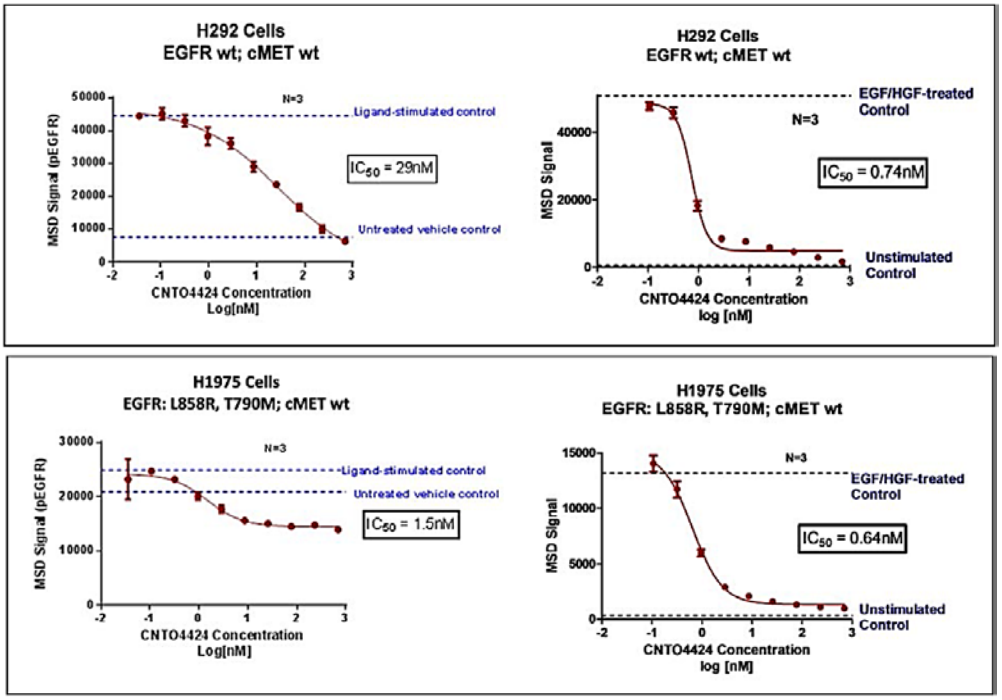
Values are represented as fold change over measurements at time zero (T0).
(Excerpted from Study #DD14324)

Inhibition of receptor phosphorylation

Janssen assessed in vitro inhibition of ligand-induced receptor phosphorylation and inhibition of downstream activation of ERK and AKT by amivantamab in Study #DD14324. Briefly, following a 15-minute incubation with 50 ng/mL EGF or 100 ng/mL HGF in the presence of increasing

concentrations of amivantamab, investigators lysed serum starved H292 (WT/WT) and H1975 (L858R, T790M/WT) lung cancer cells and measured levels of phosphorylated MET (pMET) and phosphorylated EGFR (pEGFR) using Phospho-MET (Tyr1349) Assay Whole Cell Lysate MSD Kit and Phospho-EGFR (Tyr1173) Assay Whole Cell Lysate MSD Kit per the manufacturer's instructions. In H292 and H1975 cells, amivantamab inhibited ligand-induced phosphorylation of EGFR with IC_{50} values of 29 and 1.5 nM, respectively, and ligand-induced phosphorylation of MET with IC_{50} values of 0.74 and 0.64 nM, respectively (Figure 4); absolute inhibition of EGFR signaling was lower in the H1975 cell line bearing the constitutively active EGFR point mutations L858R/T790M . Janssen conducted the same experiment in several other lung cancer cell lines (Table 6).

Figure 4: Inhibition of ligand induced receptor phosphorylation for EGFR (left) and MET (right)



CNTO4424 = amivantamab.
(Excerpted from Study #DD14324)

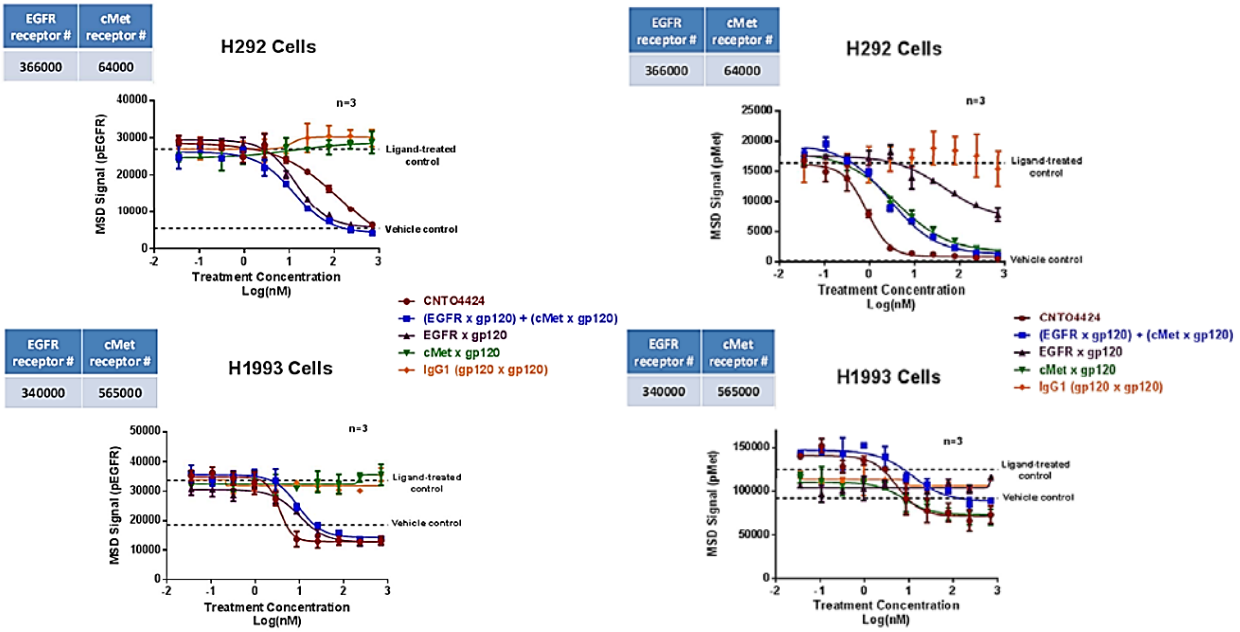
FDA - Table 6: Inhibition of ligand induced phosphorylation of EGFR and MET in several lung cancer cell lines

Cell Line	EGFR status	MET status	pEGFR IC_{50} nM	pMET IC_{50} nM
H292	WT (not AMP)	WT	29	0.74
SKMES-1	WT (not AMP)	WT	NF	0.49
HCC827	Del (E746, A750)-AMP	WT	28	1.4
H1975	L858R, T790M (not AMP)	WT	1.5	0.64
H3255	L858R-AMP	WT	85	1.2
H1650	Del (E746, A750)-AMP	WT	NF	0.86
HCC4006	Del (L747, S752)-AMP	WT	13	1.7
HCC2935	Del (E746, A750) (not AMP)	WT	NF	0.97
H820	Del (E746, A750), T790M	WT-AMP	2.9	3.8
H1993	Del (E746, A750), T790M	WT-AMP	4.2	13

NF= no fit from Excel to determine IC_{50} value.

Study #DD15327 compared the in vitro effects of amivantamab verses control bispecific products comprised of either the EGFR or MET binding arms of (EGFRxgp120 and cMetxgp120) on ligand-induced EGFR and MET phosphorylation in cell lines expressing different EGFR:MET receptor ratios. Investigators serum starved cell lines H292 (ratio = 5.7) and H1993 (ratio = 0.6) overnight and then incubated the cells with serial dilutions of the antibodies in the presence of 100 ng/mL HGF or 50 ng/mL EGF. Amivantamab, the bispecific comparator antibodies, and the mixture of both bispecific comparator antibodies inhibited EGFR and MET phosphorylation in a concentration-dependent manner in both cell lines tested. Amivantamab inhibited EGFR and MET phosphorylation with IC_{50} values of 29 and 0.86 nM in H292 cells and 3.8 and 7.8 nM in H1993 cells, respectively (Figure 5).

Figure 5: Amivantamab inhibited phosphorylation of EGFR (left) and MET receptor (right)

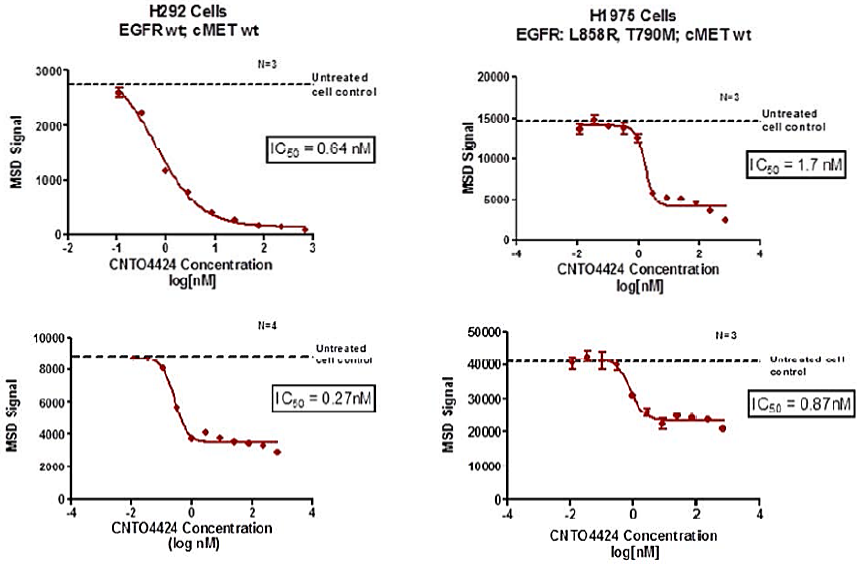


EGFR and MET bispecific x gp120 antibodies contain monovalent EGFR and MET antibodies where the second arm binds gp120 HIV surface glycoprotein which is not present on lung cancer cell lines.
(Excerpted from Study #DD15327)

Inhibition of downstream signaling

Following incubation of cells with the combination of 50 ng/mL EGF and 100 ng/mL HGF, Janssen evaluated the impact of the addition of amivantamab on downstream signaling through the Ras/RAF/MEK/ERK and PI3K pathways by measuring ERK and AKT phosphorylation, respectively. Amivantamab inhibited ERK phosphorylation in cell lines with WT EGFR and WT MET (e.g. H292), and in cell lines with EGFR point mutations (e.g. H1975;Figure 6), but only showed weak inhibition in H820 cells bearing EGFR del (E746, A750)/ T790M mutations, and amplified WT MET. In H1993 and SNU-5 cell lines (MET amplification) amivantamab had no inhibitory activity (Table 7).

Figure 6: Inhibition of pERK (top) and pAKT (bottom) in H292 and H1975 cells by amivantamab



(Excerpted from Study #DD14324)

FDA - Table 7: IC_{50} values for pERK and pAKT inhibition by amivantamab in lung cancer cell lines

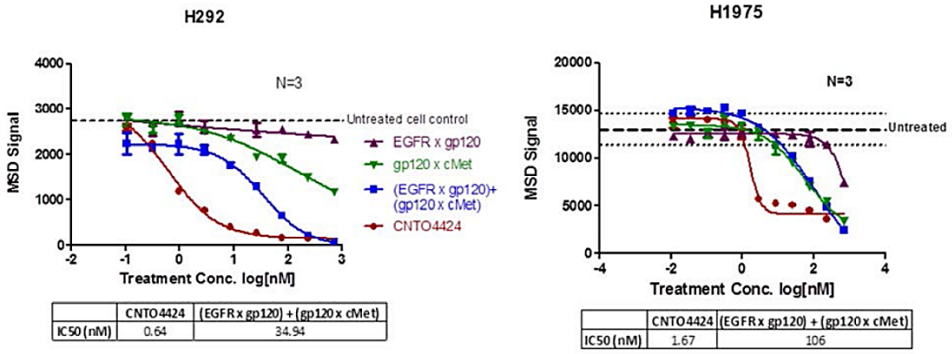
			IC_{50} (nM)		
Cell line	**EGFR status**	**MET status**	**pERK**	**pAKT**	**pAKT**
H292	WT (not AMP)	WT	0.64	0.27	0.3
SKMES-1	WT (not AMP)	WT	0.54	ND	ND
H1975	Del (E746, A750)-AMP	WT	1.7	0.87	0.96
HCC2935	Del (E746, A750) (not AMP)	WT	1.5	0.65	0.85
H3255	L858R-AMP	WT	0.74	0.8	0.71
H820	Del (E746, A750), T790M	WT-AMP	76	22	32
H1650	Del (E746, A750)-AMP	WT	0.53	0.41	0.43
HCC827	Del (E746, A750)-AMP	WT	0.9	0.58	0.58
HCC4006	Del (L747, S752)-AMP	WT	2.5	1.3	1.3
H1993	Del (E746, A750), T790M	WT-AMP	NF	NF	ND
SNU-5	WT (not AMP)	WT-AMP	NF	NF	ND

ND=not determined. NF=no fit.

To evaluate the contribution of inhibition of the individual pathways to the downstream effects of amivantamab on ERK and AKT phosphorylation, investigators incubated H292 cells with EGF and HGF in the presence of monovalent parental antibodies. Treatment with either monovalent antibody alone did not inhibit pERK, whereas the combination of the monovalent antibodies significantly inhibited pERK, suggesting that inhibition of both EGFR and MET was necessary for full inhibition of pERK in this cell line. Amivantamab, however, resulted in increased inhibition of pERK, with a 55-fold increase in potency compared to the combination of monovalent antibodies (IC_{50} values 0.54 nM for amivantamab and 34.94 nM for the combination of

monovalents; Figure 7). In H1975 (EGFR L858R/T790M; WT MET) cells, the monovalent MET antibody inhibited pERK as effectively as the combination of monovalent antibodies, suggesting that pERK is more dependent on MET signaling in this cell line (Figure 7). Again, amivantamab showed 63-fold better potency of pERK inhibition compared to the combination of monovalents in H1975 cells.

Figure 7: Amivantamab leads to greater inhibition of pERK compared to the combination of monovalent EGFR and MET antibodies



	CNTO4424	(EGFR x gp120) + (gp120 x cMet)
IC50 (nM)	0.64	34.94

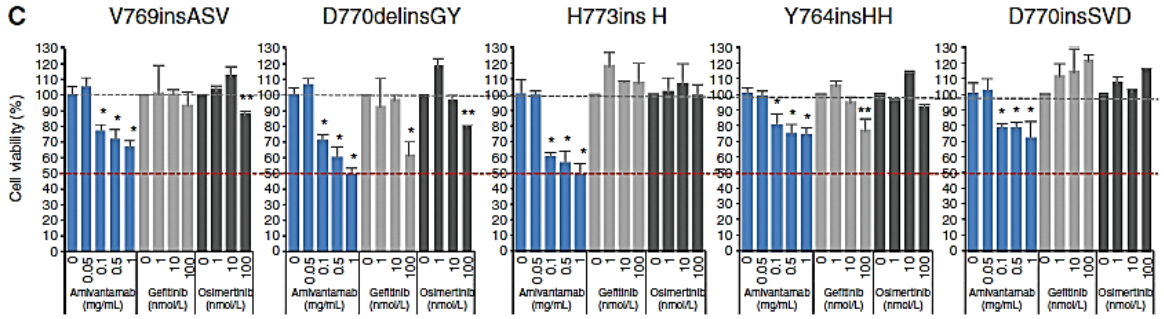
	CNTO4424	(EGFR x gp120) + (gp120 x cMet)
IC50 (nM)	1.67	106

(Excerpted from Study #DD14324)

Activity against cells harboring exon 20 insertion mutations

Janssen published data (Yun J 2020) characterizing the activity of amivantamab in both patient-derived cells and Ba/F3 cells harboring exon 20 insertion mutations. Amivantamab at concentrations ranging from 0.05 – 1 mg/mL dose-dependently decreased cell survival in Ba/F3 cells with five distinct exon 20 insertion mutations that have been observed in patients with NSCLC (V769_D770insASV, D770delinsGY, H773_V774insH, Y764_V765insHH, and D770_N771ins-SVD). In contrast, EGFR TKIs gefitinib and osimertinib showed limited anti-proliferative activity compared to amivantamab (Figure 8) and isotype control antibody had no effect on cell survival (data not shown in review).

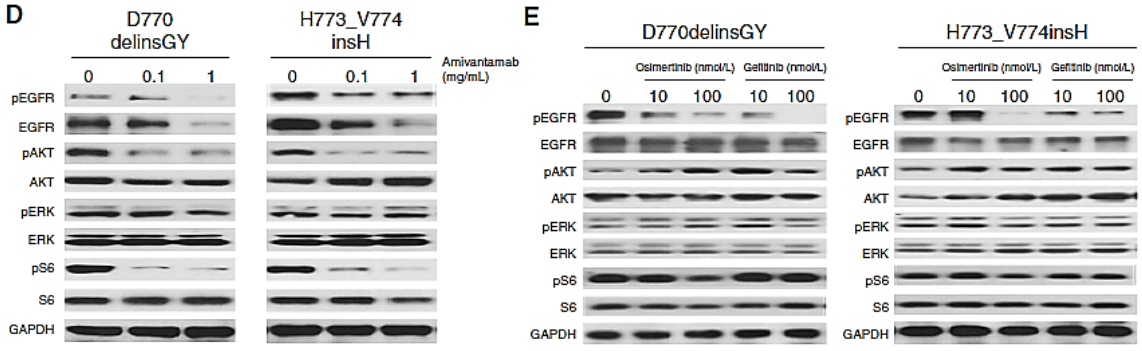
Figure 8: Amivantamab dose-dependently inhibited survival of cells containing exon 20 insertion mutations



(Excerpted from Yun et al., 2020)

To determine the if the mechanism of action (MOA) of amivantamab against cells harboring exon 20 insertion mutations that are resistant to approved EGFR TKIs is similar to that in cells with exon 19 deletions or mutations, investigators conducted immunoblot analysis of total EGFR levels and phosphorylated EGFR and downstream signaling proteins, ERK, AKT, and S6, in Ba/F3 cells expressing the EGFR D770delinsGY or H773_V774insH mutations after a 72 hour incubation with 0, 0.1, or 1 mg/mL amivantamab. Amivantamab dose-dependently decreased EGFR expression in both cell lines with subsequent decreases in phosphorylated EGFR, as well as ERK, and AKT, and slightly decreased phosphorylated S6; however, osimertinib and gefitinib only resulted in decreased phosphorylated EGFR, but not downstream signaling pathway components (Figure 9). Amivantamab had similar results in Ba/F3 cells expressing the V769insASV, Y764 insHH, and D770_N771insSVD mutations (data not shown in review).

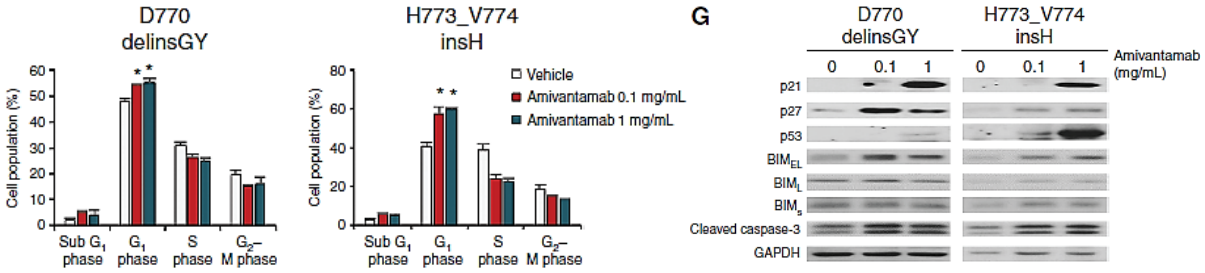
Figure 9: Effect of amivantamab on EGFR and downstream signaling components in cells expressing exon 20 insertion mutations compared to osimertinib and gefitinib



(Excerpted from Yun et al., 2020)

Evaluation of the effect of amivantamab on cell cycle in EGFR D770delinsGY or H773_V774insH expressing cells showed that amivantamab led to an accumulation of cells in G1 phase compared to vehicle treated cells and led to induction of proapoptotic proteins BIM, P53, and cleaved caspase-3 (Figure 10).

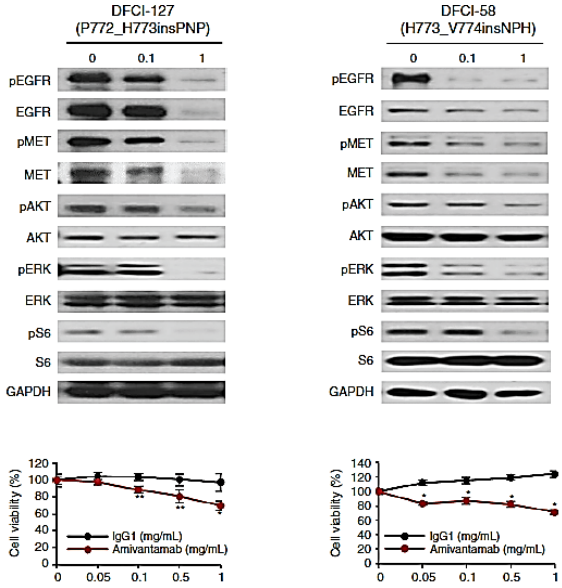
Figure 10: Amivantamab led cell cycle arrest in G1 phase and induction of proapoptotic proteins in cells harboring exon 20 mutations



(Excerpted from Yun et al., 2020)

In patient derived cells (PDCs) harboring P772ins_H773insPNP (DFCI-127 cells) or H773_V774insNPH (DFCI-58 cells) exon 20 insertion mutations, incubation with amivantamab decreased expression of total EGFR and MET levels and inhibited phosphorylation of EGFR, MET, AKT, ERK, and S6. In addition, amivantamab dose-dependently inhibited cell growth and proliferation of the PDCs compared with IgG1 controls (Figure 11).

Figure 11: Amivantamab decreased phosphorylation of EGFR and MET and downstream modulators in patient derived cells with exon 20 insertion mutations



(Excerpted from Yun et al., 2020)

Antibody-mediated toxicity

Amivantamab was designed to have improved effector functions due to low levels of fucosylation. Briefly, investigators incubated PBMCs purified from human blood as effector cells with cancer cell lines mixed at 1:50 target to effector cell ratio with amivantamab, a normal fucose bispecific anti-EGFR/MET antibody, or cetuximab for 2 hours at 37°C. Cell lysis was

measured via fluorescent signal. The Applicant reported no amivantamab-mediated CDC activity against two lung cancer cell lines tested, HCC827 and H3255 (data not shown in study report). Amivantamab was, however, able to mediate ADCC against cell lines with wild-type (WT) or mutant EGFR, WT or amplified MET, and WT or mutant KRAS (Table 8).

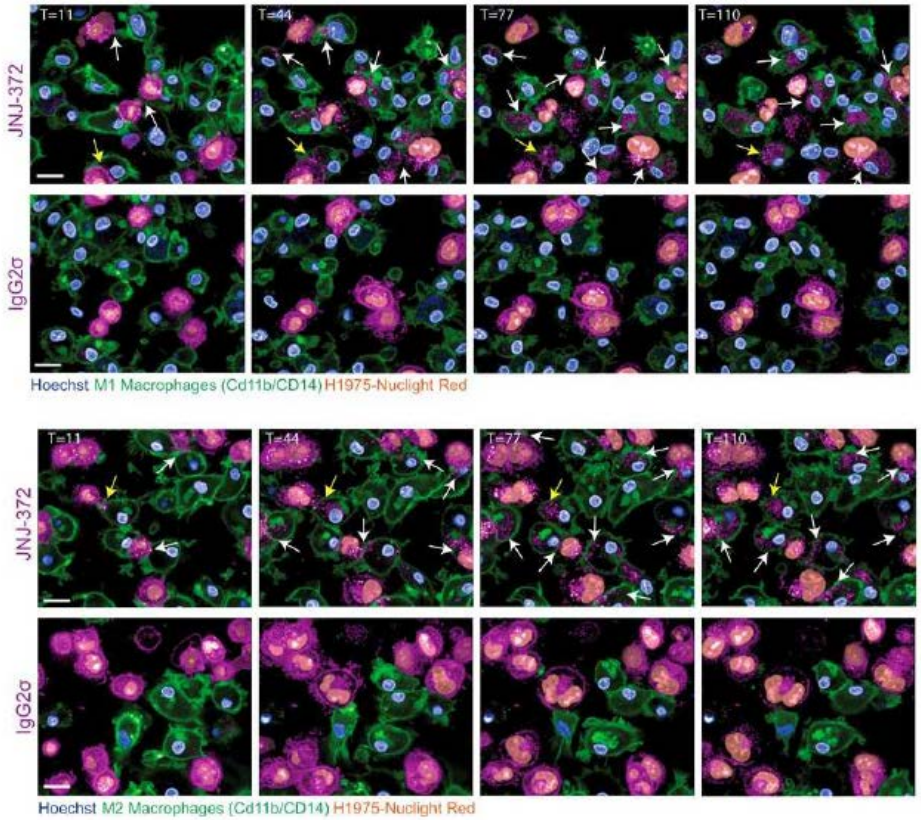
FDA - Table 8: ADCC activity of amivantamab compared to a bispecific with normal fucosylation and cetuximab

Cell line	Values	EGFRxcMet (normal fucose)	Cetuximab	CNTO4424 (low fucose
H1975 L858R T790M EGFR; WT cMet; WT KRAS	Average EC50 (nM)	0.80	0.05	0.06
	Average maximal lysis	18	20	24
HCC-827 Δ (E746 A750) EGFR amp; WT cMet ; WT KRAS	Average EC50 (nM)	0.25	0.05	0.03
	Average maximal lysis	28	28	27
H820 Data Δ (E746 A750) T790M EGFR; WT cMet amp; WT KRAS	Average EC50 (nM)	0.32	0.02	0.02
	Average maximal lysis	37	41	51
H441 Data WT EGFR WT cMet; KRAS G12C	Average EC50 (nM)	N/A	0.07	0.12
	Average maximal lysis	N/A	5	22
H1993 Data WT EGFR WT cMet amp; WT KRAS	Average EC50 (nM)	N/A	N/A	0.01
	Average maximal lysis	N/A	N/A	27
H292 Data WT EGFR; WT cMet; WT KRAS	Average EC50 (nM)	N/A	0.04	0.03
	Average maximal lysis	N/A	12	19

(Excerpted from Study #DD15319)

To determine if amivantamab induced trogocytosis in the presence of M1 or M2 macrophages and monocytes (Study #DD20150) investigators incubated fluorescently labeled H1975 with fluorescently labeled amivantamab, EGFR/MET IgG2 antibodies, or IgG1 isotype control antibodies with fluorescently labeled M1 or M2 macrophages or monocytes. There was increased accumulation of amivantamab within the M1 or M2 cells indicating trogocytosis, while there was no amivantamab accumulation in M1/M2 cells when H1975 cells were treated with the IgG2 antibodies (Figure 12). There were similar results with the use of monocytes as effectors (data not shown in review) indicating trogocytosis. The IgG1 isotype control did not bind H1975 cells.

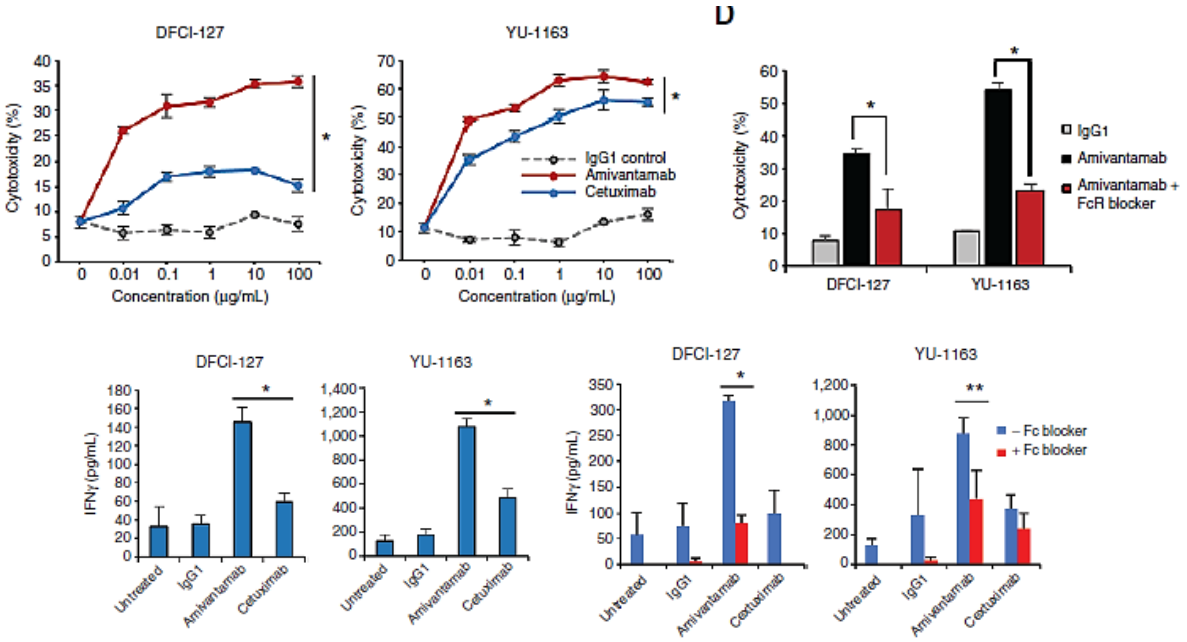
Figure 12: Amivantamab induced trogocytosis of H1975 cells incubated with M1 or M2 macrophages



JNJ-372 = amivantamab.
(Excerpted from Study #DD20150)

In addition to the cell lines listed in Table 8, incubation of PBMCs at a target:effector ratio of 50:1 with amivantamab resulted in dose-dependent ADCC against patient derived cell lines DFCI-127 and YU-1163, both expressing exon 20 insertion mutations. The level of amivantamab-mediated ADCC was greater than that of cetuximab against the same cell lines. Incubation with an Fc receptor blocker impaired amivantamab-mediated ADCC in DFCI-127 and YU-1163 PDCs. In addition, amivantamab increased the secretion of IFNγ compared to cetuximab (Figure 13).

Figure 13: Amivantamab induced ADCC and IFNγ secretion in patient derived cells harboring exon 20 insertion mutation

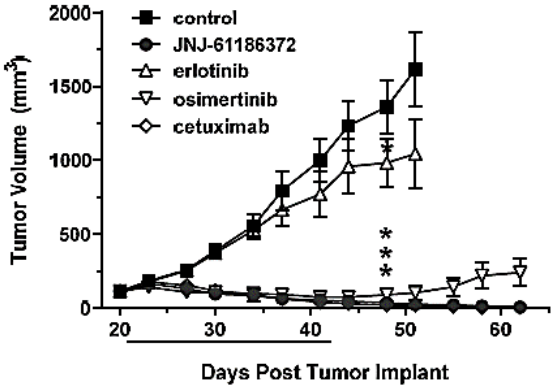


(Excerpted from Yun et al., 2020)

B. In Vivo Studies

In Study #DD20172, investigators treated adult female NMRI nude mice bearing subcutaneous LXFE2478 patient derived tumors which have an exon 20 insertion mutation (M766_A767insASV) with amivantamab, isotype control, or cetuximab all at 10 mg/kg twice weekly intraperitoneally (i.p.) for 3 weeks (Days 21, 24, 28, 31, 35, 38, and 42) or osimertinib and erlotinib dosed orally daily for 3 weeks (Days 21-41) at 30 and 25 mg/kg, respectively, once tumors reached ~111 mm^3 (n=10/group). Amivantamab, osimertinib, and cetuximab significantly inhibited growth of tumors with exon 20 insertion mutations with tumor growth inhibition (TGI) of 106, 102, and 107%, respectively, compared to isotype controls on Day 48. In addition, the groups treated with amivantamab, osimertinib, and cetuximab had 9, 2, and 9 complete responses (CRs), respectively on Day 62 (Figure 14).

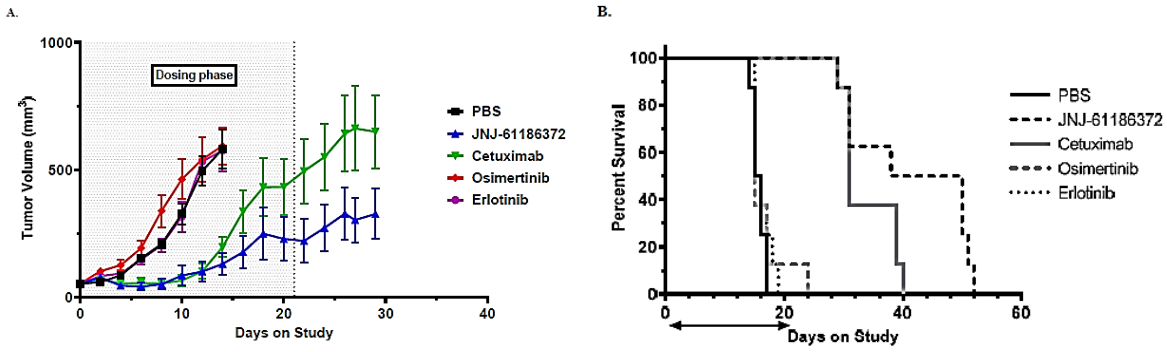
Figure 14: Anti-tumor activity of amivantamab compared to EGFR TKIs and cetuximab in mice bearing patient derived tumors with exon 20 insertion mutations



(Excerpted from Study #DD20172)

In Study #DD17041, investigators evaluated the activity of amivantamab in adult SCID mice bearing Ba/F3 tumors with multiple EGFR mutations including exon 19 DelE746_A750, T790M, and C797S, all of which mirror mutations conferring acquired resistance to EGFR-targeted therapies in the clinical lung cancer setting. Amivantamab or cetuximab (10 mg/kg twice weekly for 3 weeks) led to 77.6 and 66.3% TGI, respectively compared to controls on Day 14 of treatment, while erlotinib and osimertinib at 25 mg/kg/day for 3 weeks did not impact tumor growth. Amivantamab and cetuximab also increased survival of tumor bearing mice to 44 and 31 days respectively, compared to controls at 15.5 days (Figure 15).

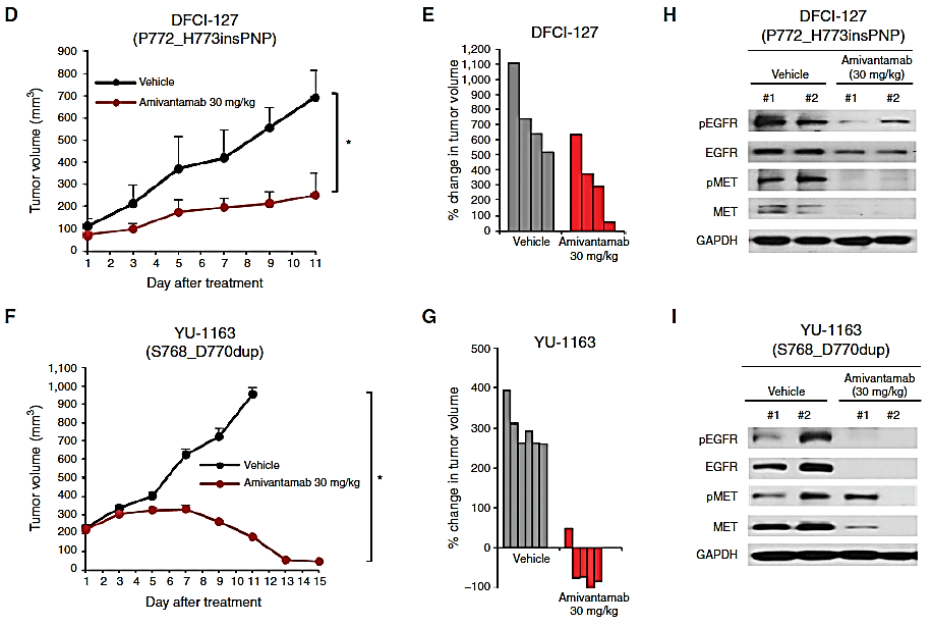
Figure 15: Amivantamab and cetuximab lead to TGI in mice bearing erlotinib and osimertinib-resistant tumors with DelE746_A750, T790M, and C797S EGFR mutations



(Excerpted from Study #DD17041)

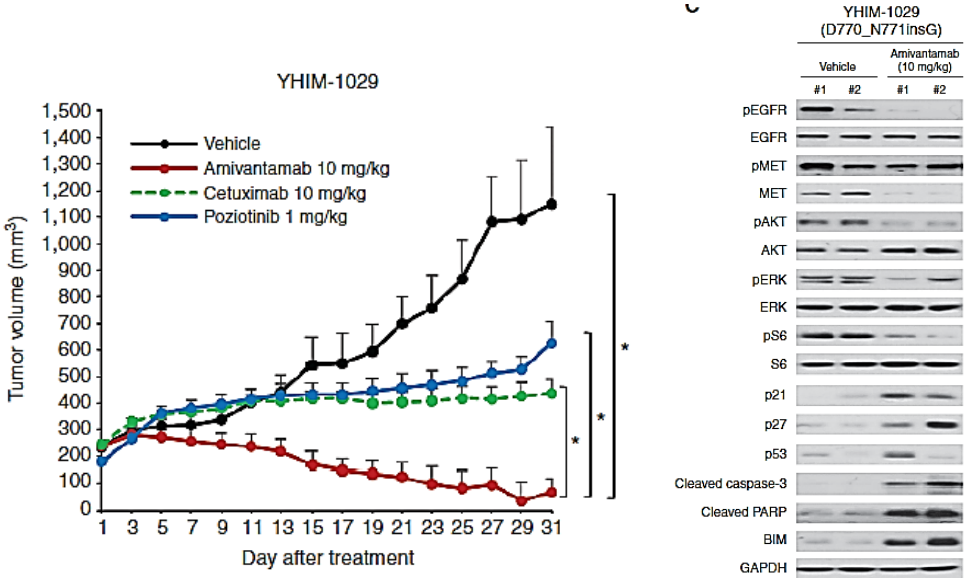
In Yun et al., (2020), compared to vehicle control amivantamab (30 mg/kg; i.p. twice weekly for 15 days) decreased tumor volume in mice bearing tumors from the patient derived cell lines (PDCs) harboring exon 20 insertion mutations P772insPNP (DFCI-127) and S768_D770dup (YU-1163). In addition, amivantamab treatment resulted in decreased protein expression and phosphorylation of EGFR and MET in the tumor tissue taken on Day 15 (Figure 16). There were similar results in mice bearing Ba/F3 tumors overexpressing EGFR with D770delinsGY or H773_V774insH exon 20 insertion mutations (data not shown in review). In addition, treatment with amivantamab in mice implanted with a patient derived xenograft (PDX) with a D770_N771insG exon 20 insertion mutation (YHIM-1029) resulted in decreased tumor volume, while treatment with either cetuximab (10 mg/kg) or poziotinib (1 mg/kg), a small molecule kinase inhibitor with reported activity against exon 20 insertion mutations, led to only modest reductions in tumor volume (Figure 17). Histopathologic analysis of tumor sections obtained following amivantamab or vehicle treatment stained for EGFR, MET, and Ki-67, and terminal deoxynucleotidyl transferase–mediated dUTP nick end labeling (TUNEL) staining further confirmed receptor inhibition and engagement of apoptotic machinery in EGFR exon 20 insertion mutation-driven tumors in vivo (Figure 17, right panel). To determine whether innate immunity in the in vivo models affected the anti-tumor effect of amivantamab, investigators blocked mouse CD16/CD32 via administration of anti-CD16/CD32 antibodies. Treatment with anti-CD16/CD32 antibodies attenuated the anti-tumor effect of amivantamab in co-treated PDX-bearing BALB/c nude mice suggesting that immune cells contribute to the anti-tumor activity of amivantamab (Figure 18).

Figure 16: Amivantamab decreased tumor volume and EGFR and MET expression in mice bearing PDC with exon 20 insertion mutations



(Excerpted from Yun et al., 2020)

Figure 17: Amivantamab decreased tumor volume in exon 20 insertion mutation PDX bearing mice and inhibited activation of downstream effectors



(Excerpted from Yun et al., 2020)

Figure 18: Inhibition of mouse CD16/CD32 decreased the anti-tumor activity of amivantamab in tumor bearing mice

(Excerpted from Yun et al., 2020; supplemental data)

Secondary Pharmacology

The Applicant's Position:

No secondary pharmacology studies have been conducted.

The FDA's Assessment:

FDA confirms that no secondary pharmacology studies were submitted for review and that no additional pharmacology studies are necessary to support the current application.

Safety Pharmacology

The Applicant's Position:

The cynomolgus monkey was selected as the only pharmacologically relevant species for the nonclinical pharmacokinetic (PK) and toxicology assessments of amivantamab based on a comparison of sequence homology, cross-species comparisons of relative target-binding affinities, and functional activity in cell-based assays.

Separate safety pharmacology studies were not conducted with amivantamab; however, the 1-month non-Good Laboratory Practice (GLP) tolerability study, and the 6-week and the 3-month toxicity GLP studies in cynomolgus monkeys incorporated cardiovascular and respiratory assessments as well as observational central nervous system (CNS) assessments (body temperature and clinical signs). [*Source: Mod2.4/Sec2.3, Sec2.4*]

There were no cardiovascular, observational CNS, or respiratory findings associated with intravenous (IV) administration of amivantamab up to 120 mg/kg/week in cynomolgus monkeys.

The FDA's Assessment:

FDA confirms the Applicant's statement and, consistent with the principles discussed in ICH S9, does not expect stand-alone safety pharmacology studies for a drug intended for the treatment of patients with advanced cancer unless there are nonclinical or clinical findings that might suggest a more in-depth analysis is warranted. Review of the 3-month repeat-dose toxicology study in cynomolgus monkeys including analysis of cardiovascular and respiratory toxicity can be found in Section 5.5.1. The repeat-dose study toxicology report does not include detailed neurotoxicological assessments; however, no clinical signs or histopathological findings occurred to indicate neurotoxicity or to trigger a more in-depth assessment.

5.4. ADME/PK

The Applicant's Position:

The nonclinical PK program characterized the linearity, dose proportionality, and immunogenicity of amivantamab in cynomolgus monkeys, the pharmacologically relevant species (see Section 0, Safety Pharmacology). *[Source: Mod2.4/Sec3.1, Sec3.3]*

- The PK of amivantamab was nonlinear at doses lower than 20 mg/kg/week, presumably due to target-mediated drug disposition. In repeat-dose IV toxicity studies with dosing for up to 3 months and in a 2-week subcutaneous (SC) local tolerance study, all cynomolgus monkeys administered amivantamab weekly demonstrated continuous exposure to amivantamab throughout the treatment period.

- At doses ≥20 mg/kg/week, systemic exposure increased generally in a dose-proportional manner, with no apparent sex-related differences and minimal accumulation (approximately 2-fold) in the IV studies. Steady-state concentration was reached at Day 57 in the 3-month toxicity study.
- Among the 67 cynomolgus monkeys dosed with amivantamab in the IV single-dose, 1-month, 6-week, and 3-month studies, 17 tested positive for the presence of anti-drug antibodies (ADA). Five of the 17 ADA-positive animals exhibited a faster concentration decrease compared with other animals in the same dose group. In the 3-month study, all 16 amivantamab-treated animals were ADA-negative; however, potential interference of ADA by residual drug was not excluded in all the ADA-negative animals in all studies.
- Conventional distribution, metabolism, and excretion studies were not conducted for amivantamab since it is a immunoglobulin G (IgG)-based monoclonal antibody (mAb) with a molecular weight of approximately 148,000 Daltons (kD).

The FDA's Assessment:

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td>Absorption</td><td></td></tr>
<tr><td>Study #cp2014pk-032: Pharmacokinetic Analysis of CNTO4424 in Study CP2014PK-032 "PK/PD Study of MAB-M1D03-14 in Cynomolgus Monkeys"</td><td>
• C_{max} increased in a linear fashion after IV administration
• AUC increased with an increase in dose in a non-linear fashion
• Anti-drug antibodies (ADA) occurred in 9/12 monkeys
o ADA development did not affect exposure
• Exposure was similar between males and females, thus data was combined
CNTO 4424 in plasma after single IV injection
<table>
<tr><th>Dose
Number of animals</th><th>3 mg/kg (n=3)</th><th>10 mg/kg (n=4)</th><th>30 mg/kg (n=4)</th></tr>
<tr><td>C_{max} (µg/mL)</td><td>57.55</td><td>212.39</td><td>603.14</td></tr>
<tr><td>AUC_{inf} (day*µg/mL)</td><td>150.57</td><td>791.42</td><td>3324.79</td></tr>
<tr><td>$T_{1/2}$ (day)</td><td>1.88</td><td>3.26</td><td>3.93</td></tr>
</table>
</td></tr>
<tr><td>Distribution</td><td>Not conducted.</td></tr>
<tr><td>Metabolism</td><td>Not conducted.</td></tr>
<tr><td>Excretion</td><td>Not conducted.</td></tr>
<tr><td>TK data from general toxicology studies</td><td>TK data from long-term studies was incorporated in review of general toxicology studies in section 5.5.1</td></tr>
</table>

Type of Study	Major Findings
TK data from reproductive toxicology studies	Reproductive toxicology studies were not conducted.

5.5. Toxicology

The nonclinical safety testing strategy for amivantamab was developed in accordance with the International Council for Harmonisation (ICH) S2(R1), M3(R2), S3A, S5(R3), S6(R1), S7A, and S9 guidelines. All nonclinical studies were conducted in accordance with best scientific principles. Pivotal nonclinical studies were conducted in conformance with GLP; 21 Code of Federal Regulations (CFR), Part 58 and/or the principles of Organisation for Economic Co-operation and Development (OECD) GLP in countries that are part of the OECD Mutual Acceptance of Data process. The cynomolgus monkey is considered the pharmacologically relevant species for the toxicology program of amivantamab (see Section 0, Safety Pharmacology).

5.5.1. General Toxicology

The Applicant's Position:

Amivantamab was well tolerated in cynomolgus monkeys when administered IV once weekly for up to 13 weeks, at dose levels up to 120 mg/kg/week in GLP and non-GLP studies. Treatment-related findings were limited to occasional minor facial skin lesions in the non-GLP study, transaminase elevations in the 1-month and 6-week studies, and decreases in the weight of adrenal gland in males in the 6-week GLP study. Additional clinical pathology findings in all 3 studies included mildly increased neutrophil and white blood cell counts and decreased albumin with decreased albumin:globulin ratios. All findings were reversible. *[Source: Mod2.4/Sec4.1]*

In the 3-month toxicity GLP study, minimal to mild histopathological changes were seen in the kidney (tubular regeneration with associated interstitial mixed cell infiltrates) and liver (Kupffer cell hypertrophy and cytoplasmic pigment, likely related to amivantamab clearance) at ≥60 mg/kg/week. Kidney changes were suggestive of prior injury that is in the state of repair.

The no-observed-adverse-effect level (NOAEL) in the toxicology studies was 120 mg/kg/week (highest tested dose) for the 6-week and 3-month toxicity GLP studies. Serum exposure at the NOAEL was at least 6.1-fold higher for the maximum observed serum concentration (C_{max}) and at least 5.3-fold higher for area under the concentration-time curve (AUC) compared with human exposure. Moreover, findings in cynolmogus monkeys that were also reported in clinical studies with amivantamab were limited to non-adverse, non-dose-dependent and/or transient changes in alanine aminotransferase (ALT), aspartate aminotransferase (AST), or albumin that likely related to modulation of MET. *[Source:Mod2.4/Tab7]*

No evidence of immunotoxicity in cynomolgus monkeys was observed following IV weekly dosing in any of the above toxicity studies. *[Source: Mod2.4/Sec4.5.1*] While ADAs were detected in a number in a number of animals in the toxicology studies, the relationship between immunogenicity in animals and humans is not well established, and results in animals are not expected to be predictive of the human immunogenic response (Bugelski 2004).

Amivantamab was well tolerated at IV injection sites in cynomolgus monkeys when administered at weekly doses up to 120 mg/kg for up to 13 weeks in the above repeat-dose toxicity studies. In addition, an SC local tolerance GLP study showed that amivantamab was well tolerated at injection sites in cynomolgus monkeys administered as 2 weekly doses of 125 mg/kg (2.5 mL dose volume) with or without rHuPH20 (2,000 U/mL). *[Source: Mod2.4/Sec4.4]*

The FDA's Assessment (all data entered by FDA):

Study title/ number: tox14008 - JNJ-61186372 (EGFR x cMET): A GLP 3-Month Intravenous Study in Cynomolgus Monkeys

Key Study Findings

- Intravenous administration of JNJ-61186372 up to 120 mg/kg once weekly did not cause mortalities
- 120 mg/kg led to liquid feces in 2 of 4 females between Weeks 6 and 9
- Minor decreased albumin and increased globulin occurred in all dose groups
- Target organs included liver, kidney, and stomach

Conducting laboratory and location: Contract Organization
GLP compliance: Yes

Methods

Dose and frequency of dosing:	0, 60, 120 mg/kg once weekly for 3 months
Route of administration:	Intravenous; slow bolus injection
Formulation/Vehicle:	D5W (5% dextrose injection, USP)
Species/Strain:	Cynomolgus monkey
Number/Sex/Group:	4/sex/group
Age:	2-3 years
Satellite groups/ unique design:	None
Deviation from study protocol affecting interpretation of results:	None

Parameters	Major findings
Mortality	None.
Clinical Signs	***120 mg/kg*** • 2/4 females displayed non- adverse liquid feces o Days 39, 45, 56, 64, and 65 • No other associated clinical signs or issues due to liquid feces
Body Weights	None.
Ophthalmoscopy	None.
Hematology	None.
Clinical Chemistry	***All dose levels at all time points*** • Decreased albumin – Males ↓6-11%; Females ↓10-19% vs. controls • Increased globulin – Males ↑7-15%; Females ↑6-23% vs. controls Changes in male monkeys were not dose-dependent; changes in female monkeys were dose-dependent for both albumin and globulin.
Urinalysis	None.
Gross Pathology	**Stomach findings** • **60 mg/kg** 4/4 males and 1/4 females; **120 mg/kg** 1/4 males o multifocal dark red foci with or without depression correlated microscopic findings of mucosal degeneration/erosion and hemorrhage • Relatedness to test article is unclear
Organ Weights	None.
Histopathology **Adequate battery:** Yes	See table below.

Dose (mg/kg/day)		0 mg/kg		60 mg/kg		120 mg/kg	
Sex		M	F	M	F	M	F
# animals		4	4	4	4	4	4
Kidney							
Regeneration, tubular	Minimal	-	-	2	4	2	2
Infiltration, mixed cell, interstitial	Minimal	-	-	-	-	2	-
Liver							
Pigmented, Kupffer cell sinusoid with Kupffer cell hypertrophy	Minimal	-	-	2	3	1	3
	Mild	-	-	1	1	2	1
Stomach							
Hemorrhage, acute, mucosal multifocal, lamina propria	Minimal	-	-	1	-	-	-
	Mild	-	-	2	1	1	-
Degeneration/regeneration; epithelial, mucosal, multifocal, glandular	Minimal	-	-	1	1	1	1

Toxicokinetics

- Exposure between sexes was similar, thus values were combined
- Exposure increased in approximately dose-proportionally
- All animals tested negative for anti-drug antibodies
- JNJ-61186372 accumulated by Day 57

Dose (mg/kg)	60	120
Day 1		
Cmax (µg/mL)	1469	2701
$AUC_{0\text{-}7d}$ (µg*day/mL)	4836	9429
Day 85		
Cmax (µg/mL)	2609	11337
$AUC_{84\text{-}91d}$ (µg*day/mL)	5232	21935
R (accumulation)	2.35	2.33

Dr. Stephanie Aungst reviewed the 6-week GLP-compliant repeat dose toxicology study in cynomolgus monkeys dosed with JNJ-61186372 at 0, 20, 60, and 120 mg/kg/week at the time of original IND submission; little to no toxicity occurred in this study. Mortality, clinical signs, body weight, feed consumption, ophthalmoscopy, ECG, urinalysis, and gross pathology were all unremarkable. Slight increases in neutrophils occurred in males and females on Day 2 but returned to baseline by Day 30. Slight decreases in adrenal weights occurred across all doses with no dose-dependence or histological correlates. Histological findings were limited to minimal lymphocytic infiltrates in the eye, salivary gland, kidney, sciatic nerve, pancreas, and liver, and were limited to 1 out of 3 animals in any dose group, with no dose dependency, and never more than one animal. In addition, mild mixed cell infiltrates were present in the liver and lung. Exposure to JNJ61186372 increased in a dose-dependent manner with mild accumulation noted by Day 29 and no differences in exposure between sexes.

5.5.2. Genetic Toxicology

The Applicant's Position:

Genotoxicity studies have not been conducted with amivantamab. As indicated in the ICH S6(R1) guidance, genotoxicity studies, routinely conducted for pharmaceuticals, are not appropriate for biotechnology-derived pharmaceuticals such as mAbs.

The FDA's Assessment:

FDA agrees.

5.5.3. Carcinogenicity

The Applicant's Position:

Carcinogenicity studies have not been conducted with amivantamab. As indicated in the ICH S9 guidance, carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

The FDA's Assessment:
FDA agrees.

5.5.4. Reproductive and Developmental Toxicology

The Applicant's Position:

As indicated in the FDA's Written Response to a meeting request to discuss the proposed assessment for reproductive toxicity/embryo fetal development toxicity (*03 August 2020*), fertility and early embryonic development and prenatal and postnatal development studies are not necessary for the submission of a BLA for the proposed indication.

No adverse effects on reproductive organs and tissues were observed in repeat-dose toxicity studies with weekly IV dosing of amivantamab up to 120 mg/kg for up to 3 months. In accordance with ICH S5(R3) and S6 and the US FDA guidance for Oncology, a weight of evidence (WOE) based on literature and proprietary data for developmental toxicity studies on EGFR and MET compounds of other companies has been provided in Module 4.3 "Assessment for Reproductive Toxicity/EFD Toxicity of Amivantamab" to provide information on pregnancy risk. The WOE for reproductive toxicity and embryo-fetal development describes that disruption of the EGFR and MET pathways are likely to impair development of the placenta, lung, skin, heart, and nervous system, resulting in adverse effects on embryo-fetal development, postnatal development, and survival. This is based on data from knockout mice and developmental toxicity studies with small molecule agents. Developmental toxicity studies conducted in non-human primates show that that blockade of MET signaling also caused embryo lethality and abortions. *[Source: Mod2.4/Sec4.1]*

The FDA's Assessment:
The Applicant did not conduct reproductive and developmental toxicology studies, including embryofetal development studies, with the clinical candidate, amivantamab, to support the submission of the BLA. Based on binding and functional pharmacology data, the cynomolgus monkey is the only relevant species for evaluation of the toxicity of amivantamab. After discussion between the FDA and Janssen a weight-of-evidence based assessment of the potential for amivantamab to cause reproductive and embryofetal toxicity was provided.

EGFR and MET during embryonic development

EGFR is detected early in embryonic development of the rat brain starting around embryonic day 16 (E16), within germinal zones suggesting EGFR influences cellular proliferation in the CNS. In vitro data indicate that EGFR can induce the proliferation of both neuronal and glial precursor cells (Kornblum, et al. 1997). In mouse embryonic development, EGFR is expressed in the trophectoderm of blastocysts, which is the first epithelium that develops in mammalian embryos, and then in several tissues and organs at mid-gestation including embryonic brain (frontal cortex, striatum, hippocampus, cerebellum), kidney, skin, heart, gut, lung, and liver (Dardik, Smith and Shultz 1992) (Wiley, et al. 1992). MET is found during early development and organogenesis in endothelial cells of liver, kidney, lung, and skin (Birchmeier 1998). The HGF/MET receptor signaling is involved in myocardial development with transcripts for both the ligand and receptor co-expressed in mouse cardiomyocytes starting at E7.5. Transcripts for HGF and the MET receptor are detectable prior to beating of cardiac tissue and persist as ventricles and atria form during organogenesis (Rapplolee, Lyer and Patel 1996). In addition, there is expression of both EGFR and MET in the human placenta (Wakeling, et al. 1998) (Uehara, et al. 1995).

Developmental issues observed with EGFR knockout (KO) mice can involve placental development or postnatal skin, lung, and brain defects. Investigation of EGFR KO in multiple mouse strains (129/Sv, C57BL/6, CBA, MF1, C3H) indicated that KO mice died at different stages of development depending on their genetic background. EGFR KO mice of all backgrounds investigated showed placental and lung phenotypes during embryogenesis, and development of progressive postnatal neurodegeneration. In 129/Sv mice, EGFR KO embryos died by day 11.5 of gestation (E11.5), whereas other KO mice in other genetic backgrounds can survive until birth (C57BL/6) or up to postnatal day 20 (P20) (MF1). Death in utero likely resulted from a defect in placental development, specifically in the spongiotrophoblasts, an epithelial cell layer of the placenta that acts as a structural support for placental development (M. a. Sibilia 1995). At birth, EGFR KO mice had immaturely developed lungs leading to inability to initiate or sustain respiration with approximately 60% of mice dying by postnatal Day 5. EGFR KO mice from the C3H and MFI strains displayed severe growth-retardation and exhibited eye defects (born with open eyes) and hair defects (failure to develop a hairy coat). Progressive neurodegeneration started around postnatal Day 4 in the frontal cortex, olfactory bulb, and thalamus, and was characterized by increased cellular apoptosis with little to no viable neurons by PD6-8.

Knock out of MET in mice is embryonic lethal and results in severe defects in placental development and absence of specific muscle groups. In c-MET KO mouse embryos there is a complete absence of the muscle groups that derive from migrating cells, specifically limb muscle, diaphragm, and the tip of the tongue. Histological evaluation of E15.5 MET KO embryos showed a complete absence of myotubes in the limbs, shoulders, and diaphragm, and a reduction in the overall size of the tongue. Detailed analysis revealed a reduction in the number of myotubes in the intrinsic tongue muscle, particularly at the tip. In contrast, axial muscles

such as intercostal and ventral or dorsal body wall muscles or other head muscles such as the extrinsic muscle of the tongue, masseter, and ocular muscles formed as expected (Bladt, et al. 1995) (Birchmeier 1998). Knock out of MET or its ligand HGF is embryonic lethal between E13 and E16.5 due to severe defects in placental development. HGF KO mice showed altered placentas, specifically, decreased labyrinthine trophoblasts cells, which is a layer of specialized epithelium that sits between the maternal blood and fetal blood vessels and is homologous to the floating chorionic villi in human placenta, resulting in failure of continued organogenesis of the placenta (Uehara, et al. 1995).

FDA - Table 9: Viability of embryos from HGF heterozygous mating

Embryonic Age	# of litters	# per genotype of live embryos		
		+/+	+/-	-/-
8.5-9.5	15	37	64	37
10.5-11.5	8	24	26	23
12.5	4	12	16	10
13.5	5	12	24	8 (1)[a]
14.5	4	7	18	3 (8) [a]
15.5	3	9	13	3 (4) [a]
16.5-17.5	6	11	27	0 (12) [a]
W3*	11	21	40	0

*Three weeks postnatal. [a] number of dead homozygous embryos. Data from (Uehara, et al. 1995).

Effects of EGFR or MET inhibitors in embryonic development

Developmental toxicity studies conducted with other EGFR or MET pathway inhibitors demonstrate the detrimental effects these compounds have on pregnancy and embryofetal development. Janssen submitted a US GLP-compliant study report (#8383617) for the small molecule EGFR inhibiter lazertinib in an embryofetal development study in rats. Investigators administered lazertinib orally once daily at 0, 7.5, 30, or 60 mg/kg/day to pregnant rats starting on gestational day (GD) 6 through GD17. Pregnancy rates were 100, 100, 95, or 100% for 0, 7.5, 30, or 60 mg/kg/day, respectively. Lazertinib led to increased post-implantation loss and lower gravid uterine and fetal weights (11.9 and 7.9%, respectively) at 60 mg/kg/day, but not at 7.5 or 30 mg/kg/day. No lazertinib-related fetal external, visceral, or skeletal variations or malformations occurred at any dose tested. In an additional US GLP-compliant study report (#8383615) submitted by Janssen, investigators evaluated the effects of lazertinib in a fertility and early embryonic development study. in rats given lazertinib orally at 0, 7.5, 15, or 30 mg/kg/day starting when rats were 12 weeks old, 2 weeks prior to paring with a mate. While there were no clear effects on ability to conceive, treatment with lazertinib resulted in

increased post-implantation loss and decreased numbers of live fetuses in females administered 30 mg/kg/day. Though these studies cannot provide relevant exposure comparisons and are confounded by potential off-target effects of a small molecule EGFR inhibitor, they do suggest that, consistent with literature describing defects in EGFR knockout animals, that inhibition of EGFR during early pregnancy or during organogenesis can lead to embryolethality.

Janssen also submitted an OECD GLP-compliant embryofetal development study report (#2148-011) in cynomolgus monkeys using the monoclonal anti-EGFR antibody zalutumumab (HuMax-EGFr). Investigators administered intravenous zalutumumab to pregnant cynomolgus monkeys from GD 20 to 50 once weekly for a total of 5 administrations. The incidence of prenatal loss was 0, 16.7, 25, and 0% in 0, 2, 6, and 20 mg/kg groups, respectively. The study report cites a 22% prenatal loss as historical control and concludes administration of zalutumumab had no effect on prenatal loss. No effects on maternal skin, fetal body weights, fetal body measurements, or placental weights among the live fetuses occurred at any dose level. No external, visceral, and skeletal defects related to zalutumumab occurred. Zalutumumab was measurable in maternal monkeys; however, no antibody was found in cord blood samples. The lack of embryo-fetal development findings may be due to the limitations of achieving sufficient fetal exposure during specific times of organogenesis.

Based on the weight of evidence (WOE) report and literature cited indicating the impact of inhibition of EGFR or MET on pregnancy and fetal development including disruption of placental development, and pathology findings in lung, skin, and nervous system, amivantamab would have detrimental effects on embryofetal development.

5.5.5. Other Toxicology Studies

The Applicant's Position:

In the in vitro tissue cross-reactivity studies (non-GLP: monkey and human; GLP: human), amivantamab membrane staining was observed in the epithelium of multiple tissues, including peripheral nerve sheath cells of both monkey and human, and in human placental decidual cells, which is consistent with expected expression of EGFR and MET. In vitro, amivantamab was compatible with human blood and serum at concentrations up to 25 mg/mL. Additionally, in an in vitro assay using human blood, the cytokine release profile for amivantamab was similar to that of the negative control, indicating a low risk for cytokine release syndrome. *[Source: Mod2.4/Sec4.5.3, Sec4.5.4, Sec4.5.5]*

The FDA's Assessment:

Janssen conducted a local tolerance subcutaneous study using 2 weekly doses of JNJ-61186372 at 125 mg/kg with and without recombinant human hyaluronidase (rHuPH20; 2000 U/mL) or vehicle (10 mM Histidine, 8.5% (w/v) Sucrose, 1 mg/mL L-methionine, 0.06% Polysorbate 80, 20 µg/mL EDTA, pH 5.7) in male cynomolgus monkeys (n=4/group). All monkeys survived to terminal euthanasia. Clinical signs related to JNJ-61186372 were limited to 1-2 occurrences of liquid feces in both treatment groups and brown mucoidal material in the group receiving JNJ-61186372 alone. There were no JNJ-61186372-related dose site observations, body weight changes, gross, or microscopic findings observed in any animal. All animals in the 2 JNJ-61186372 treatment groups had quantifiable drug concentrations throughout Days 1-12.

FDA - Table 10: TK parameters in monkeys dosed subcutaneously with JNJ-61186372 with or without rHuPH20

Dose (mg/kg)	JNJ only	JNJ+ rHuPH20
Day 1		
Cmax (µg/mL)	1018	1589
$AUC_{0\text{-}7d}$ (µg*day/mL)	5854	8019
Day 8		
Cmax (µg/mL)	1693	2022
$AUC_{7\text{-}11d}$ (µg*day/mL)	6116	7116

In vitro cross-reactivity studies using monkey and human tissues showed amivantamab staining on membrane of epithelium in multiple tissues consistent with expression of EGFR and MET. A cytokine release assay using immobilized amivantamab indicated that amivantamab is unlikely to induce cytokine release. Evaluation of human serum compatibility indicated that amivantamab is compatible with human serum as no precipitation or relevant hemolysis occurred up to concentrations of 25 mg/mL. Full study reports were reviewed in detail under the IND at the time of original submission.

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Stephanie Aungst, Ph.D.
Primary Reviewer

Emily Wearne, Ph.D.
Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

The FDA's Assessment:

The Applicant seeks approval of amivantamab for the treatment of patients with metastatic NSCLC with EGFR exon 20 insertion mutation who have progressed on or after platinum-based chemotherapy. The proposed amivantamab dosing regimen is based on a body weight (BW) cut-off of 80 kg: 1050 mg for patients with BW <80 kg and 1400 mg for patients with BW ≥80 kg, administered by intravenous infusion once weekly (QW) for 4 weeks and every 2 weeks (Q2W) thereafter. Patients will receive split doses in Week 1, with 350 mg on Day 1, and the remaining dose [700 mg for BW< 80 kg, and 1050 for BW ≥80 kg] on Day 2 to minimize the risk of infusion-related reactions (IRRs).

The Clinical Pharmacology section of the BLA includes the assessment of observed pharmacokinetics (PK) and pharmacodynamics (PD) data, population PK analysis, and exposure-response analyses for efficacy and safety.

The proposed dosing regimen (1050 mg for patients with BW <80 kg and 1400 mg for patients with BW ≥80 kg, QW for 4 weeks and Q2W thereafter) demonstrated efficacy and safety in patients with metastatic NSCLC with EGFR exon 20 insertion mutation in Study EDI1001. No apparent exposure-response relationships were observed for efficacy (overall response rate, ORR) and select adverse events of interests (IRR, nausea, and constipation).

Amivantamab volume of distribution and clearance increase with the increase in body weight. Amivatamab exposure at a given dose was approximately 30-40% lower in patients with BW ≥80 kg compared to patients with BW < 80 kg. Comparable amivatamab exposure was observed between the dose of 1050 mg in patients with BW < 80 kg and the dose of 1400 mg in patients with BW ≥80 kg, which was confirmed by the population PK analysis. There was no clinically meaningful effect of age (32-87 years), sex, race (Asian, n=217; White, n=108; others, n=37), creatinine clearance (Clcr, 29-276 mL/min), or mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN, or total bilirubin ≤ 1.5 times ULN and any AST) on the exposure of amivantamab. No dose adjustments are necessary for patients with mild hepatic impairment and for patients with mild to moderate renal impairment (CLcr 30 to <90 mL/min). The immunogenicity incidence (1%) of amivantamab was a low.

A total of 25 unique EGFR exon 20 insertion variants occurring at 8 different amino acid positions (referred as subtypes) were identified in ctDNA samples of patients comprising the primary efficacy population (N=81). Although treatment responses were observed across subgroups of patients with different EGFR exon 20 insertion subtypes, small sample sizes preclude a definitive conclusion regarding variability in treatment response by insertion subtype.

Recommendations

The proposed RYBREVANT dosing regimen of 1050 mg for patients with body weight (BW) < 80 kg and 1400 mg for patients with BW ≥80 kg, administered intravenously once weekly for 4 weeks and every 2 weeks thereafter, is acceptable. From a Clinical Pharmacology standpoint, the BLA is approvable provided the Applicant and the FDA reach an agreement regarding the labeling language.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Data:

The amivantamab PK, immunogenicity, and pharmacodynamic (PD) data were obtained from subjects with advanced NSCLC treated with amivantamab monotherapy in Study EDI1001 (as of the PK data cutoff date of 31 March 2020). *[Source: Mod2.7.2/Sec2.1, Sec3.1.1]*

Characterization of amivantamab PK (see also Section 6.3.1) showed that PK parameters increased in a dose-proportional manner over a dose range from 350 to 1750 mg. Amivantamab concentration accumulated quickly during the first cycle of weekly dosing, gradually decreasing in subsequent cycles during every 2-week dosing to reach steady state by Cycle 4 (end of Cycle 3). The mean accumulation ratio (AR) of amivantamab was approximately 2.9 after weekly dosing and 2.4 after steady-state (dosing every 2 weeks) based on AUC. The PK of amivantamab following IV administration was adequately described by a 2-compartment model with linear elimination with body weight included as a covariate of clearance and volume of distribution using standard allometric coefficients. The mean (standard deviation [SD]) population PK model-estimated total volume of distribution and nonspecific linear clearance were 5.13 (1.78) L and 360 (144) mL/day, respectively. The estimated clearance was close to the clearance of nonspecific endogenous IgG and increased with increasing body weight. The model-derived mean (SD) half-life of amivantamab associated with linear clearance was 11.3 (4.53) days.

The Applicant's Position:

Amivantamab exhibited linear PK between the dose range of 350 mg and 1750 mg. The observed amivantamab serum concentration-time data were adequately described by a 2-compartment linear population PK model. The mean (SD) population PK model-estimated total volume of distribution and nonspecific linear clearance of amivantamab were 5.13 (1.78) L and 360 (144) mL/day, respectively. Based on the posthoc estimates of the population PK model, mean (SD) half-life of amivantamab associated with linear elimination was 11.3 (4.53) days.

The FDA's Assessment:

FDA agrees with the Applicant's position on the PK characteristics of amivantamab.

6.2.2. General Dosing and Therapeutic Individualization

6.2.2.1. General Dosing

Data:

[Source: Mod2.7.2/Sec1.3.3, Sec3.4]

Weight-based dose adjustment for amivantamab was supported by population PK modeling and simulation analysis, which indicated that tiered weight-based dosing resulted in lower variances in PK parameters when compared with flat dosing without weight adjustment.

The recommended Phase 2 dose (RP2D) for amivantamab was established based on an overall assessment of preliminary PK, PD, safety, and efficacy data from the Phase 1, first-in-human Study EDI1001 obtained from a total of 83 subjects: 46 subjects treated in Part 1 (28 subjects from Korea treated at 140 mg [n=2], 350 mg [n=3], 700 mg [n=9], 1050 mg [n=7], and 1400 mg [n=8], and 18 subjects from the US treated at 1050 mg [n=10] and 1400 mg [n=8]) and 37 subjects treated in Part 2 (all from Korea, treated at 1050 mg). Results of these preliminary overall assessments of the data led to a RP2D with a weight adjustment of the amivantamab dose for subjects ≥80 kg (*11 Feb 2019, End-of-Phase 1 meeting*).

Additional data from the 362 subjects comprising the All Treated safety population, including 114 subjects with EGFR Exon 20ins NSCLC, who had received prior chemotherapy and were treated at the amivantamab RP2D, were collected and analyzed to provide supportive evidence for the proposed RP2D.

Amivantamab was generally well tolerated up to the 1750 mg dose, with no identifiable maximum tolerated dose, and only a single adverse event (AE) meeting criteria for dose-limiting toxicity (DLT) (1050 mg cohort in US; post-DLT evaluation period).

Overall, PK parameters were approximately 30% to 40% lower in subjects who weighed ≥80 kg compared with those who weighed <80 kg at the same dose. Similar amivantamab exposures were achieved in subjects with a body weight ≥80 kg who received 1400 mg and subjects with a body weight <80 kg who received 1050 mg. The population PK model simulations confirmed this observation, indicating that dose adjustment using a body weight cutoff of 80 kg provides adequate exposure coverage for both body weight groups for subjects with NSCLC to be treated with amivantamab.

Pharmacodynamic assessments indicated that saturation of circulating free EGFR started to occur at 350 mg, which corresponds with saturation of the nonlinear component of the clearance, indicating total body engagement of EGFR, and is consistent with the manifestation of on-target toxicities of rash (including dermatitis acneiform). Complete saturation of soluble free MET was achieved at all dose levels. Complete and sustainable saturation of circulating targets throughout the dosing period appears to be achieved at dose levels ≥700 mg, doses at which evidence of clinical benefit was observed.

The exposure-response (E-R) assessments for the primary efficacy endpoint of confirmed ORR (investigator assessment) indicated a favorable treatment effect over the range of the RP2D regimen investigated in Study EDI1001 (1050 and 1400 mg once weekly for 4 weeks and every 2 weeks thereafter for body weight <80 and ≥80 kg, respectively). E-R analyses on the secondary efficacy endpoint of clinical benefit rate (CBR) showed similar responses across the amivantamab concentration range. Furthermore, the E-R analysis of safety between amivantamab exposure and select treatment-emergent adverse events (TEAEs) of clinical interest and those with an incidence of >20% showed no apparent relationship for TEAEs of infusion-related reactions [IRR], nausea, or constipation at the studied amivantamab concentration range in Study EDI1001. Occurrence rates of rash (Grade 1 or 2), paronychia, and hypoalbuminemia increased slightly with an increase in amivantamab exposure, which were likely related to the mechanism of action of EGFR and MET inhibition.

The Applicant's Position:

The appropriate recommended dose of amivantamab is based on body weight; the selected RP2D for amivantamab is 1050 mg for subjects <80 kg body weight (at baseline) or 1400 mg for subjects ≥80 kg body weight (at baseline), administered as an IV infusion once weekly for 4 weeks, then every 2 weeks thereafter. The first dose for Cycle 1 is split over 2 days to better minimize the risk of IRRs, with the first infusion of 350 mg on Day 1 and 700 mg (body weight <80 kg) or 1050 mg (body weight ≥80 kg) on Day 2. Weekly dosing of amivantamab (induction phase) enables faster attainment of therapeutic concentrations.

This regimen was selected based on the benefit/risk ratio observed in the Phase 1 clinical study EDI1001, where a range of doses were tested. The RP2D using body weight cutoff of 80 kg provided adequate exposure coverage for all body weight groups for subjects with EGFR Exon 20ins NSCLC to be treated with amivantamab. Target engagement of circulating soluble serum EGFR and soluble serum MET with amivantamab was achieved at doses of ≥350 mg, while complete soluble target saturation throughout the dosing period up to Cycle 4 was attained at doses of ≥700 mg, doses at which evidence of clinical benefit was observed. The E-R analyses demonstrated a favorable therapeutic efficacy at the current amivantamab RP2D regimen for subjects with EGFR Exon 20ins NSCLC. The E-R analysis for safety indicated a favorable safety profile with a slight increase in the incidence of rash (Grade 1 or 2), paronychia, and hypoalbuminemia with increased exposure of amivantamab at the RP2D. Overall, the clinical efficacy and safety as well as the exposure analyses support the recommended dose and regimen of 1050 and 1400 mg once weekly for 4 weeks and every 2 weeks thereafter for subjects with a body weight <80 kg and ≥80 kg, respectively.

The FDA's Assessment:

FDA concurs with the Applicant's position on pharmacokinetic and pharmacodynamic studies and exposure-response analyses for dose selection. No maximum tolerated dose was achieved up to 1750 mg of amivantamab. Similar amivantamab exposures were achieved for patients with body weight < 80 kg at dose of 1050 mg and patients with body weight ≥ 80 kg at dose of 1400 mg

based on the population PK analysis. Overall response rate (ORR) for patients with EGFR Exon 20ins NSCLC was favorable at the current amivantamab RP2D regimen. No apparent exporsure-response relationship was observed for efficacy. The incidence rates of paronychia, hypoalbuminemia and rash (any grade) were slightly increased with amivantamab exposures and no significant exposure-response relationships were identified for IRR, nausea and constipation.

6.2.2.2. Therapeutic Individualization

Data:

[Source: Mod2.7.2/Sec3.2.2, Sec3.2.3]

Based on the individual population PK parameters, the AUC for the dosing interval at steady state ($AUC_{0\text{-}14\ days,ss}$) and end-of-infusion (EOI) concentration at steady state ($C_{eoi,ss}$) were generated, assuming all subjects received the scheduled doses according to the RP2D (ie, 1050 or 1400 mg once weekly for 4 weeks and every 2 weeks thereafter for subjects with a body weight <80 and ≥80 kg, respectively).

The covariates of interest tested for inclusion in the population PK model included age, sex, race, baseline serum albumin, baseline creatinine clearance (CrCl), presence of hepatic dysfunction at baseline, baseline Eastern Cooperative Oncology Group (ECOG) performance status, and prior chemotherapy status. Baseline body weight was included as a covariate of clearance (CL) and volume of distribution in the central compartment (V1) using standard allometric coefficients (0.75 for CL and 1 for V1). A comparison of amivantamab steady-state exposure parameters was conducted in specific subpopulations using forest plots, ie, by presenting the estimated geometric mean ratio (GMR) and its 90% confidence interval (CI) for the exposure metrics of interest and for a given covariate stratum relative to the reference stratum and adjusting for the other covariates based on the final population PK model. Continuous covariates were first categorized as being either below or above the median value across subjects (except for body weight where the value of 80 kg was used).

The forest plots of $AUC_{0\text{-}14\ days,ss}$ and $C_{eoi,ss}$ showed that none of the estimated GMR CI limits were entirely outside the 80% to 125% range except $AUC_{0\text{-}14\ days,ss}$ in females versus males (GMR: 1.34; 90% CI: 1.26, 1.42). This was expected since sex was deemed a statistically significant covariate of CL in the covariate search. This confirms that for all covariates except sex, amivantamab exposures were similar across different strata of the covariate when adjusted for the effect of other covariates (see also Section 6.3.1).

The Applicant's Position:

Dose individualization is recommended for amivantamab on the basis of body weight; population PK modeling and simulation analyses supported dose adjustment using a body weight cutoff of 80 kg. No dose adjustment is necessary for sex, age, race, patients with mild to moderately decreased renal function, patients with mild hepatic impairment, or other explored intrinsic factors.

Despite a statistically significant effect of sex on exposure, subgroup analyses suggests that the ORR in men and women were similar for the primary efficacy population (see Section 8.1.2, Efficacy Results – Primary Endpoint), indicating no clinically meaningful difference. Given the large molecular mass of amivantamab (~148 kD), its clearance is not anticipated to be affected by decreased renal function. Based on population PK analyses, renal function (mild to moderate impairment) had no statistically significant nor clinically relevant effect on exposure of amivantamab. Changes in hepatic function are unlikely to have any effect on the elimination of amivantamab as IgG1 molecules such as amivantamab are not metabolized through hepatic pathways. Based on population PK analyses, hepatic function (mild impairment) had no statistically significant or clinically relevant effect on exposure of amivantamab.

Based on population PK analyses, no dosage adjustment is necessary for patients with mild or moderate renal impairment or mild hepatic impairment as reflected in the proposed US prescribing information (USPI). No formal studies of amivantamab in subjects with hepatic or renal impairment have been conducted, and this is reflected in the proposed USPI.

The FDA's Assessment:

FDA concurs with the Applicant's position on lack of clinically meaningful effect of age (32-87 years), sex, race (Asian, n=217; White, n=108; others, n=37), mild to moderate renal impairment (creatinine clearance 30 to <90 mL/min), and mild hepatic impairment (total bilirubin ≤ULN and AST>ULN, or total bilirubin ≤1.5 x ULN and any AST) on amivantamab PK. Ten African-American patients with NSCLC were evaluated for PK. Amivantamab exposures appear comparable across different race subgroups. No dose adjustments are recommended for age, sex, race, mild to moderate renal impairment and mild hepatic impairment.

6.2.2.3. Outstanding Issues

Data and Applicant's Position:

Not applicable.

The FDA's Assessment:

There are no outstanding issues.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Data:

The clinical pharmacology of amivantamab has been studied in subjects with advanced NSCLC who received amivantamab by IV infusion once weekly for 4 weeks and every 2 weeks thereafter in a 28-day cycle. Levels of serum amivantamab, serum circulating targets and

anti-amivamntamab antibodies were measured using validated methods to evaluate PK, PD and immunogenicity.

Pharmacokinetics

[Source: Mod2.7.2/Sec2.1]

The PK analyses were based on serum amivantamab concentrations of samples obtained from subjects treated with amivantamab in Parts 1 and 2 of Study EDI1001. In Part 1, serum samples were collected in successive sampling following the first dose on Cycle 1 Day 1 (C1D1) or Cycle 1 Day 2 (C1D2) (for split doses) and following the fifth dose on Cycle 2 Day 1 (C2D1). Additionally, predose and EOI samples were collected after each dose. In Part 2, successive samples were collected in 6 subjects after the dose on Cycle 4 Day 1 (C4D1).

- After the first dose of amivantamab, mean AUC during a dosing interval of 168 hours ($AUC_{0\text{-}168h}$) increased in a dose-proportional manner at doses ≥350 mg. Following the fifth dose of the weekly dose regimen on C2D1, mean C_{max}, trough concentration (C_{trough}), and AUC during an every-2-week dosing interval of 336 hours (AUC_{τ}) increased in a dose-proportional manner at doses ≥350 mg.
- The mean (SD) ARs for $AUC_{0\text{-}168h}$ (C2D1/C1D1) after the induction period of once-weekly dosing in Cycle 1 at 1050 mg (body weight <80 kg) and 1400 mg (body weight ≥80 kg) were 2.88 (0.68) and 3.03 (0.82), respectively. Due to every-2-week dosing during subsequent cycles, the mean (SD) AR of amivantamab declined to 2.44 (0.54) at steady state, achieved by C4D1 (AR after the 9th dose: $AUC_{0\text{-}168h}$ [C4D1/C1D1]). Overall, amivantamab weekly dosing enables faster attainment of therapeutic concentrations.
- Median time to C_{max} (T_{max}) values reported from the start of the infusion were related in most cases to the samples collected either at the EOI or 2 hours after EOI.
- Overall, PK parameters, when compared within the same dose level, were approximately 30% to 40% lower in subjects weighing ≥80 kg compared with subjects weighing <80 kg. Overall, similar exposures of amivantamab were achieved in subjects who received 1400 mg and weighed ≥80 kg and those who received 1050 mg and weighed <80 kg.

Population Pharmacokinetics and Exposure-Response Analyses

[Source: Mod2.7.2/Sec3.1, Sec3.2]

- The observed amivantamab serum concentration-time data were adequately described by a 2-compartment linear population PK model.
- The mean (SD) population PK model-estimated total volume of distribution and nonspecific linear CL of amivantamab were 5.13 (1.78) L and 360 (144) mL/day, respectively. Based on the post hoc estimates of the population PK model, mean (SD) half-life of amivantamab associated with linear elimination was 11.3 (4.53) days.

- Similar amivantamab exposures were observed for subjects with body weight <80 kg and ≥80 kg at the RP2D regimen (ie, 1050 and 1400 mg once weekly for 4 weeks and every 2 weeks thereafter for subjects with a baseline body weight <80 and ≥80 kg, respectively). This suggests that the RP2D using a body weight cutoff of 80 kg provides adequate exposure coverage for all body weight groups of patients with EGFR Exon 20ins NSCLC to be treated with amivantamab.
- During the covariate selection process, none of the investigated subject demographic and baseline characteristics (age, sex, race, CrCl [to categorize renal function], hepatic impairment, albumin, ECOG status, and prior chemotherapy) was statistically significant except sex. Amivantamab clearance was 24% higher in men than in women (correspondingly, the AUC for the dosing interval at steady state [$AUC_{0\text{-}14\ days,ss}$] was 24% higher in women than in men based on population PK typical parameter values).
- Based on the individual exposure parameters $AUC_{0\text{-}14\ days,ss}$ and EOI concentration at steady state ($C_{eoi,ss}$) of the current subject population generated according to the RP2D regimen, the 90% CIs for the estimated GMRs of $AUC_{0\text{-}14\ days,ss}$ and $C_{eoi,ss}$ across different strata within specific covariates overlapped with the range of 80% to 125% except $AUC_{0\text{-}14\ days,ss}$, which was 34% higher in women (90% CI: 26%, 42%) than in men.
- Although lower amivantamab systemic exposures were observed in men, subgroup analyses for the primary efficacy population suggests that the ORR in men and women was similar (45.5% in men and 35.4% in women) and consistent with that in the total efficacy population (see Figure 22). In the context of the E-R relationship, none of the investigated subject demographic and baseline characteristics had a clinically meaningful effect on the amivantamab systemic exposure.
- The relationship between amivantamab exposure and efficacy endpoints of ORR and CBR suggests favorable therapeutic efficacy at the current amivantamab RP2D regimen for subjects with EGFR Exon 20ins NSCLC. No apparent E-R relationship was observed for other efficacy endpoints including PFS, OS, and duration of response (DOR), although DOR appeared to improve with increased amivantamab exposure. A clear conclusion could not be drawn due to the small number of subjects and events in the analysis dataset (see also Section 6.3.2.1).
- There was no apparent E-R relationship between common TEAEs of IRR, nausea or constipation, and exposure was within the studied amivantamab concentration range. Incidence rates of rash, paronychia, and hypoalbuminemia increased slightly with increased exposure. TEAEs of rash were primarily Grade 1 or 2, with no correlation of Grade 3 or higher events with exposure. Overall, E-R analysis for safety indicated a favorable safety profile with increased exposure of amivantamab at the RP2D.

Drug Interactions

No formal clinical drug-drug interaction studies were performed, and no interactions with concomitant medications are expected.

Pharmacodynamics

[Source: Mod2.7.2/Sec1.3.7, Sec2.2]

To assess target engagement of amivantamab with its soluble targets EGFR and MET, serial serum samples were obtained at the time interval of PK sampling of subjects in Parts 1 and 2. Additional predose and EOI serum samples were collected for each amivantamab dose up to C4D1. The results of the serum analyses of free soluble EGFR and MET were summarized for subjects treated in Part 1. Engagement of amivantamab with soluble EGFR and MET targets was inferred by measuring free soluble EGFR and MET.

- Saturation (depletion of targets) of circulating free EGFR and MET started to occur at a dose of 350 mg for EGFR and 140 mg for MET after a single dose, consistent with the manifestation of on-target toxicities of rash (including dermatitis acneiform) for EGFR and hypoalbuminemia and peripheral edema for MET.
- Complete and sustained saturation of both circulating targets (EGFR and MET) throughout the dosing period for all subjects appears to be reliably achieved at dose levels ≥700 mg, where evidence of clinical benefit was observed.

Immunogenicity

[Source: Mod2.7.2/Sec1.3.6, Sec2.3]

A validated sensitive, drug- and target-tolerant electrochemiluminescent immunoassay method on the Meso Scale Discovery platform was used to assess the antibodies to amivantamab in human serum samples. The immunogenicity analysis population in Study EDI1001 consisted of 286 subjects (66 in Part 1 and 220 in Part 2) who had at least 1 postdose sample. The immunogenicity-evaluable population included subjects who received ≥1 dose of amivantamab and had ≥1 analyzed immunogenicity sample after receiving amivantamab.

Among the 286 subjects who received amivantamab and had appropriate samples, only 3 (1.0%) subjects were considered positive for antibodies to amivantamab postdose all with low titers (maximum of 1:40).

Overall, the incidence of antibodies to amivantamab was low with all positive subjects having low titers. There was no evidence to suggest that positive ADA status had an impact on amivantamab exposure, safety, or efficacy. The small number of subjects in each antibody titer level group of precludes drawing a definitive conclusion regarding the impact of antibody titer levels on exposure, safety, or efficacy.

Due to the low risk for immunogenicity and the low incidence of samples positive for antibodies to amivantamab, neutralizing antibodies were not evaluated at this time.

The Applicant's Position:

Amivantamab exhibited linear PK between the dose range of 350 mg and 1750 mg with an estimated half-life of amivantamab associated with linear elimination of 11.3 (4.53) days. Overall, PK parameters, when compared within the same dose level, were approximately 30% to 40% lower in subjects weighing ≥80 kg compared with subjects weighing <80 kg, suggesting the need for dose adjustment for body weight ≥ 80 kg to achieve equivalent exposures.

Complete and sustained saturation of both circulating targets (EGFR and MET) throughout the dosing period for all subjects appears to be achieved at dose levels ≥700 mg, suggesting total body target engagement at doses where evidence of clinical benefit was observed.

The E-R analyses demonstrated a favorable therapeutic efficacy at the current amivantamab RP2D (1050 mg for patients <80 kg body weight [at baseline] or 1400 mg for patients ≥80 kg body weight [at baseline]) regimen for subjects with EGFR Exon 20ins NSCLC. Furthermore, the E-R analysis for safety indicated a favorable safety profile with a slight increase in the incidence of rash (Grade 1 or 2), paronychia, and hypoalbuminemia with increased exposure of amivantamab.

The incidence of antibodies to amivantamab was low with all positive subjects having low titers. There was no evidence to suggest that positive ADA status had an impact on amivantamab exposure, safety, or efficacy. The small number of subjects in each antibody titer level group of precludes drawing a definitive conclusion regarding the impact of antibody titer levels on exposure, safety, or efficacy.

Overall, amivantamab administered by IV infusion at 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for Cycle 1 and every 2 weeks beginning at Cycle 2 for 28-day cycles, demonstrates a favorable benefit-risk profile for NSCLC patients with Exon 20ins mutation.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the proposed amivantamab dosing regimen based on a body weight cut-off of 80 mg: 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for Cycle 1 and every 2 weeks thereafter. The proposed doses based on 80 kg body weight cut-off provide comparable amivantamab exposures.

FDA concurs with the Applicant's postion on the lack of clinically meaningful effect of age, sex, race and mild-to-moderate renal impairment (creatinine clearance 30 to <90 mL/min), and mild hepatic impairment (total bilirubin ≤ULN and AST>ULN, or total bilirubin ≤1.5 x ULN and any AST) on the PK of amivantamab, and the low incidence (1%) of immunogenicity.

6.3.2. Clinical Pharmacology Questions

6.3.2.1 Does the clinical pharmacology program provide supportive evidence of effectiveness?

The clinical pharmacology program provides supportive evidence of amivantamab effectiveness in patients with metastatic NSCLC with EGFR Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy.

Data:

[Source: Mod2.7.2/Sec3.3.1]

To support the clinical efficacy observed with amivantamab dosed at the RP2D (1050 and 1400 mg once weekly for 4 weeks and every 2 weeks thereafter for subjects with a body weight <80 and ≥80 kg, respectively), E-R relationships for efficacy were evaluated in the primary and supportive efficacy populations with EGFR Exon 20ins mutation NSCLC treated at RP2D and non-RP2D doses. The relationship between exposure and the primary efficacy endpoint of ORR was investigated using individual exposure metrics generated based on the final population PK model and actual dosing information. Other efficacy endpoints (CBR, DOR, PFS) were also explored. Binary variable response (ORR and CBR) was evaluated by plotting and logistic regression. Time-to-event variables (DOR and PFS) were evaluated by Kaplan-Meier plot stratified by exposure group.

A correlation between ORR and amivantamab exposure was not evident, although a slight trend of ORR increase with increase of amivantamab $C_{trough.max}$ was observed in subjects with EGFR Exon 20ins NSCLC. This trend should be interpreted in the context of the wide 95% CI band of the estimated ORR at varying amivantamab $C_{trough.max}$.

ECOG was a statistically significant covariate in the E-R analysis of ORR using $C_{trough.max}$. Subjects with a baseline ECOG of 0 appeared to have a higher probability of response compared with subjects with an ECOG of 1 or 2. This covariate effect could partially explain the higher ORR observed in subjects at the RP2D of 1400 mg (45.5%) compared with the RP2D of 1050 mg (34.1%) despite similar exposure.

The E-R relationship for other efficacy endpoints including CBR, PFS, OS, and DOR was evaluated across amivantamab exposure metrics ($C_{trough.max}$ and $C_{trough.1st}$). In general, no apparent E-R relationship was observed for CBR, PFS, and OS. Although DOR appeared to improve with the increase of amivantamab $C_{trough.max}$, a clear conclusion could not be drawn due to the small number of subjects and events in the analysis dataset.

The Applicant's Position:

The E-R analyses for efficacy demonstrated a favorable therapeutic efficacy at the current amivantamab RP2D regimen (ie, 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for Cycle 1 and every 2 weeks beginning at Cycle 2 for 28-day cycles).

The FDA's Assessment:

FDA agrees with the Applicant's position in that the RP2D regimen (i.e., 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for 4 weeks and every 2 weeks thereafter) demonstrated robust efficacy results. No apparent E-R relationships were observed for efficacy. As indicated by the Applicant, the results of the E-R analysis showed that the observed ORR for patients with body weight ≥80 kg at RP2D was higher than patients with body weight <80 kg at RP2D which might be due to the higher proportion of ECOG performance status (PS) 0 patients with body weight ≥80 kg. While for all patients with body weight <80 kg, amivantamab systemic exposure was higher at the non-RP2D of 1400 mg compared to the RP2D of 1050 mg and the proportions of ECOG PS 0 patients were similar in both groups (RP2D: 25.6% vs non-RP2D: 20.0%), the observed ORR in patients at the non-RP2D of 1400 mg was numerically higher (42.9% [95% CI: 28.0, 59.1%]) than that at the RP2D of 1050 mg (34.1% [95% CI: 24.8, 44.9%]). The reason for this observed difference in ORR is inconclusive; it might be due to the higher exposure of amivantamab or the variability of ORR associated with the small number of patients in the non-RP2D dose group.

6.3.2.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Amivantamab administered by IV infusion at a dose of 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for the first 4 weeks and every 2 weeks thereafter on a 28-day cycle, is appropriate for patients with metastatic NSCLC with Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy.

Data: [See also Section 6.3.1]

[Source: Mod2.7.2/Sec3.4]

- Amivantamab was generally well tolerated up to 1750 mg, with no identifiable maximum tolerated dose, and only a single AE meeting criteria for DLT (Grade 3 myalgia in a single subject in the 1050 mg cohort in US during post-DLT evaluation period).
- Similar amivantamab exposures were achieved in subjects with a body weight ≥80 kg who received 1400 mg and subjects with a body weight <80 kg who received 1050 mg. The population PK model simulations confirmed this observation, indicating that dose adjustment using a body weight cutoff of 80 kg provides adequate exposure coverage for all body weight groups for subjects with NSCLC to be treated with amivantamab.
- Saturation of circulating free EGFR started to occur at 350 mg, which corresponds with saturation of the nonlinear component of the clearance, indicating total body engagement of EGFR, and is consistent with the manifestation of on-target toxicities of rash (including dermatitis acneiform). Complete saturation of soluble free MET was achieved at all dose levels consistent with the manifestation of on-target toxicities of hypoalbuminemia and peripheral edema. Complete saturation of circulating targets throughout the dosing period appears to be reliably achieved at dose levels ≥700 mg, doses at which evidence of clinical

benefit was observed. The final E-R models for ORR indicated a favorable treatment effect over the range of the RP2D regimen investigated in Study EDI1001 (1050 and 1400 mg once weekly for 4 weeks and every 2 weeks thereafter for body weights of <80 and ≥80 kg, respectively).

- The E-R analyses on the efficacy endpoint CBR showed similar responses across the amivantamab concentration range.
- No apparent relationship between amivantamab exposure and common TEAEs of IRR, nausea, and constipation was identified at the studied amivantamab concentration range in Study EDI1001. Occurrence rates of rash, paronychia, and hypoalbuminemia increased slightly with the increase of amivantamab $C_{eoi.max}$, which were likely related to the mechanism of action of EGFR and MET inhibition.

The Applicant's Position:

Amivantamab administered by IV infusion at a dose of 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for the first 4 weeks and every 2 weeks thereafter on a 28-day cycle, is appropriate for patients with metastatic NSCLC with Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy, with the weekly dosing in the first cycle enabling faster attainment of therapeutic concentrations. Population PK analysis confirmed the PK equivalency of 1050 mg and 1400 mg dosing in subjects weighing <80 kg and ≥80 kg, respectively. At the current amivantamab RP2D regimen a favorable therapeutic efficacy was demonstrated. Furthermore, a favorable safety profile was demonstrated with a slight increase in the incidence of rash (Grade 1 or 2), paronychia, and hypoalbuminemia with increased exposure of amivantamab at the RP2D and a manageable safety profile consistent with already approved EGFR or MET targeted agents, or other biologic therapies for NSCLC patients with EGFR mutations.

The FDA's Assessment:

FDA concurs with the Applicant's position. Based on the population PK analysis, similar amivantamab exposures were achieved for patients with body weight < 80 kg receiving dose of 1050 mg and patients with body weight ≥ 80 kg receiving dose of 1400 mg at the RP2D dosing regimen. ORR for patients with EGFR Exon 20ins NSCLC was favorable at the current amivantamab RP2D regimen. Although for patients with body weight < 80 kg, higher ORR was achieved at dose of 1400 mg than at dose of 1050 mg, the result was inconclusive due to the limited number of patients receiving dose of 1400 mg. The incidence rates of paronychia, hypoalbuminemia and rash (any grade) were slightly increased with higher amivantamab exposures. No significant exposure-response relationships were identified for IRR, nausea and constipation.

6.3.2.3 Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

Amivantamab administered by IV infusion at the RP2D of 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for the first 4 weeks and every 2 weeks thereafter on a 28-day cycle, is appropriate for the subpopulations analyzed based on intrinsic patient factors (see Section 6.2.2.2 for details regarding these subpopulations).

Data:

A comparison of amivantamab steady-state exposure parameters was conducted in specific subpopulations using forest plots, ie, by presenting the estimated GMR and its 90% CI for the exposure metrics of interest and for a given covariate stratum relative to the reference stratum and adjusting for the other covariates based on the final population PK model. Continuous covariates were first categorized as being either below or above the median value across subjects (except for body weight where the value of 80 kg was used).

Please refer to Section 6.2.2.2. for additional details.

The Applicant's Position:

For all covariates (body weight, age, race, hepatic impairment, renal impairment, and other factors [baseline ECOG status, albumin, and prior chemotherapy]) except sex, amivantamab exposures were similar across different strata of the covariate when adjusted for the effect of other covariates.

Despite statistically significant effect of sex on exposure (ie, lower amivantamab systemic exposures were observed in men), the efficacy analysis suggests that the ORR rates in men and women were similar and consistent to that in the primary efficacy population, indicating the exposure difference between men and women is not clinically meaningful.

No dose adjustment is necessary based on age or race, or in patients with mild to moderately decreased renal function or those with mild hepatic impairment. Given the large molecular mass of amivantamab (~148 kD), its clearance is not anticipated to be affected by decreased renal function. Based on population PK analyses, renal function (mild to moderately decreased) had no statistically significant nor clinically relevant effect on exposure of amivantamab. Changes in hepatic function are unlikely to have any effect on the elimination of amivantamab since IgG1 molecules such as amivantamab are not metabolized through hepatic pathways. Based on population PK analyses, hepatic function (mild impairment) had no statistically significant nor clinically relevant effect on exposure of amivantamab.

The FDA's Assessment:

FDA agrees with the Applicant's position. Although sex was a significant covariate in the population PK analysis, with female patients exhibiting a 34% increase in amivantamab exposures

compared to male patients, the efficacy was similar and safety was comparable between female and male patients. Also, while creatinine clearance was not a significant covariate, a 26% increase in amivantamab exposure was observed in patients with moderate renal impairment (creatinine clearance 30 to <60 mL/min) compared to patients with normal renal function. This increase in exposure may be explained by the lower body weights and higher proportion of female patients in the moderate renal impairment subgroup compared to the normal renal function group, as the population PK analysis indicated that a decrease in body weight decreases clearance (irrespective of sex) and female patients have lower clearance compared to male patients (irrespective of body weight). With regards to safety, patients with moderate renal impairment had a higher incidence of serious adverse events and dose interruptions due to AEs (other than IRR) compared to patients with normal renal function when renal function was classified either by creatinine clearance or estimated GFR (eGFR). However, no apparent exposure-response relationship was observed for safety. The observation of potential for increase in toxicity in moderate renal impairment may be partly explained by the higher proportion of patients who were ≥65 years old in the moderate renal impairment group, as higher incidence of serious adverse events and dose interruptions due to AEs (other than IRR) were observed in age ≥65 years old group compared to age <65 years old group. Nonetheless, dose interruption strategy was used to manage AEs in the study and recommended in the labeling. No dose adjustment is recommended for moderate renal impairment.

EGFR exon 20 insertion subtypes and treatment response. FDA explored the association of EGFR exon 20 insertion subtypes and treatment response in 81 patients comprising the primary efficacy population in Study EDI1001. The presence of EGFR exon 20 insertions for enrollment was determined by local testing performed on tissue or blood samples, utilizing PCR or NGS, and was centrally confirmed following enrollment in 63 patients (77.8%) using a plasma-based NGS assay (ctDNA). The remaining 18 patients (22.2%) had central ctDNA analyses in which exon 20 insertions were not detected. Local test results for these 18 patients are listed under Table 11 (footnote).

The central ctDNA analysis (N=63) revealed a total of 25 unique exon 20 insertion variants clustered at 8 different residues (referred as subtypes) and exhibiting variability in insertion length and sequence. Most variants (72%) ocurred only once. The two most common insertions were A767_V769dup (23.5%) and S768_D770dup (16.0%). Consistent with the literature, most insertions were positioned in the loop that immediately follows the C-helix (A767 - C775), except for A763_Y764insFQEA, which occurs in the C-helix and is reported to be sensitive to EGFR TKIs (Remon et al., 2020, Vyse 2019; Oxnard 2013) (Table 11). Of note, two patients had EGFR T790M and S768I mutations (one each) co-occurring with EGFR exon 20 insertions (Table 11).

Although small numbers preclude the assessment of variability in treatment response by insertion variant and subtype, responses (CR or PR) were observed across all EGFR exon 20 insertion subtypes except for V769, which only occurred in one patient based on ctDNA results.

However, a patient with a V769 insertion subtype based on local test results (unkown status based on central ctDNA) achieved a CR.

FDA - Table 11: Tumor response by EGFR exon 20 insertion subtype in the efficacy population in study EDI1001(N=81).

Exon 20 insertion Subtype	Exon 20 insertion variant	Number of Patients	Tumor Response n (ORR)
A763	A763_Y764insFQEA	1	1 (100%)
A767	A767_V769dup	19	11 (57.9%)
S768	S768_D770dup	13	6 (46.2%)
V769	V769_P772dup	1	0 (0%)
D770	D770_N771insG	1	2 (22.2%)
	D770_N771insGF	2	
	D770_N771insKD	1	
	D770_N771insY	1	
	D770_P772dup	1	
	D770delinsGY	3	
N771	N771_H773dup	3	2 (22.2%)
	N771_P772insH	1	
	N771_P772insT	1	
	N771_P772insV	1	
	N771delinsGF	1	
	N771delinsGY	1	
	N771delinsKG	1	
P772	P772_H773dup	1	1 (33.3%)
	P772_H773insDNP	1	
	P772_H773insPNP	1	
H773	H773_V774dup	1	2 (25.0%)
	H773_V774insAH	2	
	H773_V774insNPH	1	
	H773dup	3	
	H773delinsNPT	1	
Unknown*	not available	18	7 (38.9%)
Total		81	32 (39.5%)

Source: Reviewer's table. Distribution of exon 20 insertions as determined by central ctDNA analysis- primary efficacy population; ORR: Overall response rate by BICR (8 Oct 2020 Cutoff); Co-occurring EGFR mutations included T790M (in one patient with A767 subtype) and S768I (in one patient with unknown insertion based on central test, S768_V769delinsIL based on local test). Other uncommon or uncharacterized EGFR mutations are not listed. *Unknown status (N=18):

no insertion detected by central ctDNA analysis. Of these, the exon 20 insertion variant was identified by local NGS for 11 patients, as follows: A767_V769dup (N=3), S768_V769delinsIL (N=1), V769_D770insGVV (N=1), D770_N771insGD (N=1), N771_H773dup (N=1), P772_H773dup (N=1), H773_V774insNPH (N=1), H773_V774insPH (N=1), H773dup (N=1). For the remaining 7 patients, local PCR tests detected exon 20 insertions but did not identify the specific variants or additional mutations (Response to 11 February 2021 FDA Information Request). Responses (CR or PR) were observed in patients with the following local test results: A767_V769dup (N=1), H773_V774insPH (N=1), V769_D770insGVV (N=1), S768_V769delinsIL (N=1), and not identified (N=3).

6.3.2.4 Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Data:

Not Applicable.

The Applicant's Position:

Amivantamab is intended for IV administration; therefore, food-drug interactions are not expected.

As an IgG1 antibody, renal excretion and hepatic enzyme mediated metabolism of intact amivantamab are unlikely to represent major elimination routes, nor are drug-metabolizing enzymes expected to affect the elimination of amivantamab. As amivantamab binds to the extracellular domains of EGFR and MET with high specificity, it is not anticipated to alter the activity of drug-metabolizing enzymes. Hence, no drug-drug interactions with concomitant medications are expected.

The FDA's Assessment:

FDA concurs with the Applicant's position.

X	X
Sriram Subramaniam, PhD Primary Reviewer OCP/DCPI	Hong Zhao, PhD Team Leader OCP/DCPII
X	X
Yangbing Li, PhD Primary Reviewer OCP/DPM	Jiang Liu, PhD Team Leader OCP/DPM
X	X
Jielin Sun, PhD Primary Reviewer OCP/DTPM	Rosane Charlab Orbach, PhD Team Leader OCP/DTPM

7 Sources of Clinical Data

7.1. Table of Clinical Studies

Data:

An overview of the clinical study supporting the efficacy and safety of amivantamab for the treatment of patients with metastatic NSCLC with EGFR Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy is presented in Table 12.

Table 12: Listing of Clinical Trial Relevant to this BLA for Amivantamab

In addition to being administered as monotherapy in Study EDI1001, amivantamab was also administered in combination with the investigational third-generation EGFR TKI lazertinib (Part 1 and Part 2 cohorts) and in combination with standard of care carboplatin and pemetrexed (Part 1 only). Information for these combination therapy cohorts is not presented in the table below, as data from combination treatment are not included in this submission. The full Study EDI1001 protocol is provided as an appendix to the clinical study report (CSR).

Study Type						
Study ID EudraCT Number NCT Number First Patient First Visit / Completion date (day Month year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objectives	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Study Endpoints
5.3.5.2 Efficacy and Safety Uncontrolled Clinical Studies						
61186372EDI1001 2018-003908-38 NCT02609776 27 May 2016 Ongoing	Australia, Canada, China, France, Japan, Republic of Korea, Spain, Taiwan, UK, US 53	Phase 1 First-in-human, open-label, 2-part, dose escalation and dose expansion, multicenter study Men and women ≥18 years of age with histologically or cytologically confirmed advanced NSCLC **Part 1: Monotherapy Dose Escalations** Determine the MTD, if one existed, and the RP2D for subjects with NSCLC treated with amivantamab	Planned: Part 1: up to 120; Part 2: approx. 460 Enrolled: Part 1: 77 Part 2: 285 Treated: Part 1: 77 Part 2: 285	JNJ-61186372: 50 mg/mL solution for infusion (IV) The study will be conducted in 2 parts: **Part 1 (Dose Escalation):** Subject will receive JNJ-61186372 at the starting dose of 140 mg once a week for the first 4 weeks during the 28-day cycle, then every other week during subsequent cycles. Dose escalation will progress at 140, 350, 700, 1050, 1400, and 1750 mg.	Part 1: 77 Part 2: 285 (08 Jun 2020 cutoff)	**Primary** Part 1: • Dose Limiting Toxicity (DLT) PK, PD Safety

Study Type						
Study ID EudraCT Number NCT Number First Patient First Visit / Completion date (day Month year) Study Status	Country(ies): Number of Centers	Phase Study Description/Design, Study Population, Primary Objectives	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Study Endpoints
		Part 2: Monotherapy Dose Expansion Determine the safety, tolerability, and anti-tumor activity of amivantamab monotherapy at the RP2D Estimate the anti-tumor activity of amivantamab at the RP2D in selected populations of subjects with documented EGFR or MET mutation(s) who have progressed after treatment with standard of care		**Part 2 (Dose Expansion):** Subject will receive JNJ-61186372 at the RP2D regimen determined in Part 1 once weekly for the first 4 weeks (ie, Cycle 1) and once every 2 weeks in all subsequent 28-day cycles. Treatment was to be administered until disease progression, unacceptable toxicity, or withdrawal of consent.		<u>Part 2</u>: Efficacy: Confirmed ORR according to RECIST v1.1. Safety

KEY: Approx.=approximately; EGFR=endothelial growth factor receptor; IV=intravenous; MET=hepatocyte growth factor receptor gene; MTD=maximum tolerated dose; N/A=Not applicable; NSCLC=non-small cell lung cancer; RP2D=recommended Phase 2 dose; UK=United Kingdom; US=United States.
Note: number of countries and sites represent number at which at least 1 subject was treated with amivantamab monotherapy as of 08 June 2020 cutoff.

The FDA's Assessment:

FDA agrees with the Applicant's listing of one clinical trial relevant to this BLA.

The efficacy analyses supporting this marketing application are based on data using a clinical cut-off date of October 8, 2020 for 4 patients from Part 1; 4 patients from Cohort A, and 73 patients from Cohort D, for a total of 81 patients with NSCLC with exon 20 insertion mutations who had received prior platinum-based chemotherapy, were treated at the recommended dose of either 1050 mg (patient baseline body weight <80kg) or 1400 mg (patient baseline body weight ≥80 kg), and who underwent at least three post-baseline disease assessments or discontinued treatment for any reason, including disease progression/death, as of the June 8, 2020 clinical cuf off date.

8 Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The Applicant's Position:

The primary evidence of efficacy and safety for amivantamab as monotherapy for the treatment of patients with metastatic NSCLC with EGFR Exon 20ins mutation, whose disease has progressed on or after platinum-based chemotherapy is based on data from Part 1 and Part 2 of ongoing Phase 1 Study EDI1001, with the efficacy data presented reflecting a clinical cutoff date of 08 October 2020 (08 June 2020 for safety; Day 120 safety update to be provided in early 2021 will use an 08 October 2020 clinical cutoff).

Patients with EGFR Exon 20ins NSCLC have been relatively understudied, and these patients are excluded from the majority of Phase 3 studies of EGFR TKIs and immunotherapies. To provide clinical context to the efficacy of amivantamab observed in Study EDI1001 in subjects with EGFR Exon 20ins NSCLC, the BLA also includes (1) data from a retrospective cohort study of real-world data (RWD) conducted by the Applicant, Study 61186372NSC1002 (hereafter referred to as Study NSC1002), to evaluate the unmet needs and treatment patterns for patients with EGFR Exon 20ins-mutated NSCLC and (2) an analysis of 5 RWD datasets to provide insights on commonly-used second-line regimens for EGFR Exon 20ins NSCLC (including ramucirumab-docetaxel combination). These evaluations utilized EHR and claims reimbursement data. Data from Study NSC1002 and the RWD analysis of treatment patterns provide an important context for interpreting the efficacy data for amivantamab in the target indication. Data from Study NSC1002 are described further in Section 8.1.5.

In addition, an ongoing Phase 3 study (61186372NSC3001) was recently initiated to confirm clinical benefit by evaluating the efficacy and safety of the combination of amivantamab and carboplatin-pemetrexed chemotherapy as compared with carboplatin-pemetrexed chemotherapy alone, in the first-line treatment of patients with EGFR Exon 20ins NSCLC. This confirmatory study design was previously discussed and aligned with FDA (*06 May 2020*). No data

from the ongoing Phase 3 study are available for inclusion in the BLA (primary analysis planned for the second quarter of 2022).

It is the Applicant's position that the current efficacy and safety data from Study EDI1001 demonstrate that amivantamab, if approved, would provide a significant improvement over available therapies for patients with metastatic NSCLC with EGFR Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy. Therefore, the Applicant believes this BLA qualifies for Priority Review Designation.

The FDA's Assessment:

The Applicant submitted the 120 Day safety update on February 19, 2021. With the exception of the first paragraph, the above statements by the Applicant are not relevant to this subsection of the review.

8.1.1. Study 61186372EDI1001

Study EDI1001 was conducted and reported in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with ICH Good Clinical Practice (GCP) guidelines, applicable regulatory requirements, and in compliance with the respective protocol.

Trial Design

The Applicant's Description:

[Source: Mod5.3.5.2/61186372EDI1001/Sec3 and protocol provided in Mod5.3.5.2/61186372EDI1001/App1]

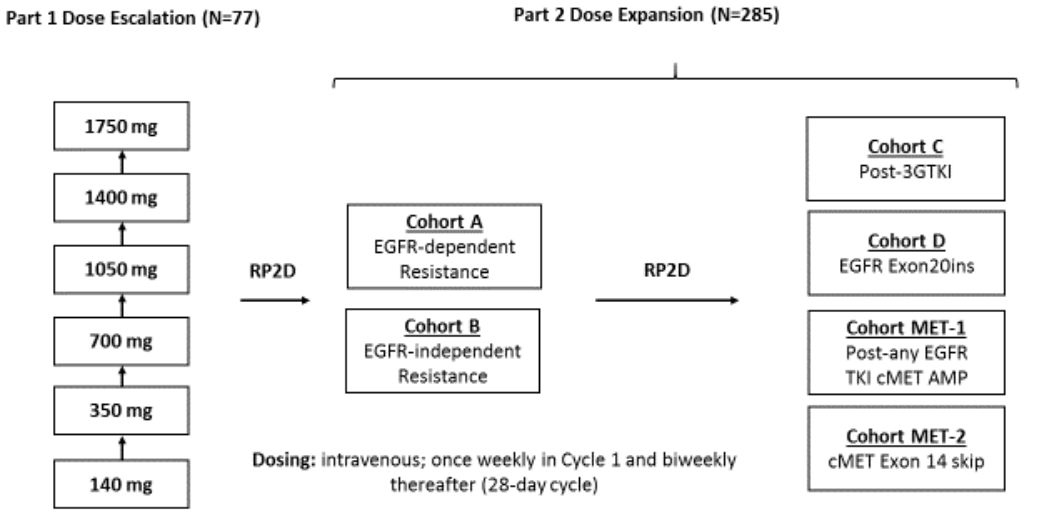
Basic study design*:* Advice on critical aspects of the EDI1001 study design was provided by FDA. As a first-in-human study, EDI1001 included a dose escalation phase with standard 3+3 design (Part 1) to determine the maximum tolerated dose (if one exists) and the RP2D of amivantamab monotherapy in subjects with advanced NSCLC, as well as a dose expansion phase (Part 2) to better characterize the safety and PK of amivantamab monotherapy at the RP2D and to explore its clinical activity within molecularly-defined tumor subgroups. Based upon early efficacy signals observed during dose escalation, and in response to evolving standard of care as a result of osimertinib global regulatory approvals, the Part 2 cohort expansion was modified through an amendment to allow assessment of the efficacy and safety of amivantamab monotherapy in EGFR-mutated NSCLC cohorts characterized by Exon 20ins mutations, third-generation TKI resistance mutations, and MET amplification or mutations (Figure 19).

A single-arm, open-label study design is typical of early phase studies in advanced, refractory cancers with high unmet medical need, requiring new and innovative therapies. This study design can adequately characterize anti-tumor activity demonstrated by a robust response rate and duration of response. A more comprehensive characterization of efficacy, defined by time-to-event endpoints such as PFS and OS, requires subsequent randomized studies utilizing a standard-of-care control arm. While the lack of a direct comparator may limit the overall assessment of the benefit-risk profile for amivantamab, there is no clear global standard of care

regimen for patients with metastatic NSCLC with EGFR Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy (see Section 2.2).

In addition to the evaluation of efficacy, this type of study design, together with enrollment of a sufficient number of subjects, can adequately characterize the safety profile of a new agent.

Figure 19: Design of Study 61186372EDI1001: Monotherapy Cohorts



EGFR=epidermal growth factor receptor; Exon 20 ins=Exon 20 insertion mutation; TKI=tyrosine kinase inhibitor
Cohorts A and B in Part 2 were closed to enrollment upon opening of subsequent cohorts.
Note: RP2D (recommended phase 2 dose) of 1050 mg for weight <80 kg and 1400 mg for weight ≥80 kg was added after initial RP2D determination.

Based on early activity of amivantamab, Study EDI1001 is also investigating amivantamab in combination with the investigational EGFR TKI lazertinib (in Parts 1 and 2) and in combination with carboplatin and pemetrexed (in Part 1 only); however information about and data from these combination therapy cohorts are not within scope of, or presented in, this BLA submission.

***Trial location*:** 53 sites across 10 countries (Australia, Canada, China, France, Japan, Republic of Korea, Spain, Taiwan, US, and United Kingdom) treated a total of 362 subjects (77 in Part 1 and 285 in Part 2) (as of an 08 June 2020 cutoff).

Choice of control group: Not applicable as this was a single-arm study. Furthermore, there is no clear global standard of care for patients with metastatic NSCLC with EGFR Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy (see Section 2.2).

Diagnostic criteria: No molecular eligibility criteria were required for enrollment in Part 1. EGFR Exon 20ins mutation status for Part 2 eligibility was determined by local testing; however, mutation status was also confirmed via central laboratory testing following enrollment. Central laboratory plasma-based and tissue-based diagnostics were utilized in bridging studies to compare to the local testing. The plasma-based diagnostic test, Guardant360® CDx, is proposed as a companion diagnostic (via sPMA P200010/S001) to be approved concurrently with the

amivantamab BLA. (b) (6)

(b) (6)

Key inclusion and exclusion criteria: The eligibility criteria for the study are appropriate for the population under investigation.

- Key inclusion criteria: Subjects 18 years of age or older with histologically or cytogically confirmed diagnosis of advanced NSCLC, with evaluable disease (Part 1) or measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Part 2), with an ECOG performance status of 0 or 1. Specifically for Cohort D of Part 2, inclusion criteria required the presence of previously-diagnosed activating EGFR Exon 20ins not previously treated with a TKI having known activity in Exon 20ins disease (eg, poziotinib). Subjects in this cohort must have progressed after, been ineligible for, or have refused standard-of-care platinum-based chemotherapy.

  While 53% of all subjects treated in Study EDI1001 had mild or moderate renal impairment and 10% had mild hepatic impairment, subjects with moderate or severe hepatic or severe renal impairment were not represented due to eligibility requirements (see Section 8.2.8). Based on population PK analyses, no dosage adjustment is necessary for patients with renal or hepatic impairment (see Section 6.2.2.2).

  Key exclusion criteria: Subjects with untreated brain metastases, subjects with a history of interstitial lung disease (ILD) requiring prolonged immunosuppressive therapy, and subjects with a history of a malignant disease other than NSCLC within 3 years before Screening (excluding squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the Applicant's medical monitor, was considered cured, or with minimal risk of recurrence within a year from Screening).

Dose Selection: The amivantamab monotherapy doses administered in Part 1 were 140 mg, 350 mg, 700 mg, 1050 mg, 1400 mg, and 1750 mg. After identifying body weight as a primary covariate explaining interindividual PK variability, the recommended RP2D was determined to be 1050 mg for subjects weighing <80 kg, and 1400 mg for subjects weighing ≥80 kg. This RP2D was agreed upon with the FDA at the End-of-Phase 1 meeting. See Section 6.2.2.1 for additional discussion of RP2D selection.

***Study treatments*:** Amivantamab was supplied in either 3 or 7 mL vials of 50 mg/mL for dilution for IV infusion (minimum infusion time ≥60 minutes). It was administered once weekly for the first 4 weeks (ie, Cycle 1) and once every 2 weeks thereafter during subsequent 28-day cycles. Once weekly dosing in Cycle 1 was implemented to accelerate achievement of therapeutic concentrations of amivantamab. Preclinical extrapolation-based human PK simulations indicated that average concentrations after an induction phase of 4 weekly doses at 140 mg or higher may reach the therapeutic concentration range within the first 4 weeks. To mitigate the risk of IRRs,

the first dose of Cycle 1 was split over 2 days (350 mg administered on C1D1 and remainder of dose administered on C1D2), required steroid premedication, and was administered using an accelerated infusion strategy. Thus, study drug administration occurred on Days 1, 2, 8, 15, and 22 of Cycle 1, and on Days 1 and 15 of each subsequent 28-day cycle.

Assignment to treatment: Randomization was not applicable; the assignment of a subject to a particular Part 2 cohort was based on specific molecular eligibility requirements.

Dose modification, dose discontinuation: Specific rules for dose modifications and discontinuation are outlined in the study protocol and summarized in the EDI1001 CSR for the management and prevention of IRRs, rash, and other safety issues (elevated transaminase levels, pulmonary toxicity, and other toxicities).

- Amivantamab infusion was to be interrupted at first sign of an IRR of any grade in order to preempt worsening severity of IRR symptoms and then resumed at 50% of previous rate following recovery of symptoms. Permanent discontinuation of amivantamab was to be considered for Grade 3 or 4 IRRs depending on symptom severity.
- Treatment-related toxicities could be managed through either dose interruption and/or dose reduction. Amivantamab dosing was to be interrupted in the event of Grade 3 or 4 toxicity and then resumed at a reduced dose following recovery for interruptions of >7 days; permanent discontinuation of amivantamab was to be considered for subjects whose dose had been withheld due to toxicity for >28 days and for subjects with Grade 4 toxicity whose treatment was interrupted for >7 to ≤28 days.
- For rash, investigators were to consider (in addition to prophylactic and reactive treatment regimen) reducing the dose for Grade 2 events and interrupting treatment for Grade 3 events (or Grade 2 events that did not resolve after 2 weeks) until the event improved. In the event that the rash event(s) worsened or did not improve after 2 weeks, treatment discontinuation was recommended.
- Amivantamab was to be permanently discontinued in the event of development of ILD or pneumonitis (see Section 8.2.6, ILD).

Administrative structure: In addition to the investigator assessment, scans were centrally collected for independent determination of response (using RECIST v1.1 criteria) by Blinded Independent Central Review (BICR), utilizing a 2-reader with adjudication paradigm (see also Study Endpoints).

Safety data obtained during Study EDI1001 were reviewed on a routine basis by a Safety Evaluation Team (SET), consisting of participating principal investigators, the Applicant's medical monitor and clinical pharmacologist, and the Applicant's safety management team chair. Among the SET's responsibilities were the recommendation of modification(s) to the study drug dose, schedule, and/or regimen in the dose escalation phase (Part 1); the RP2D regimen(s) to be

investigated in the dose expansion phase (Part 2); and continued enrollment or termination of cohorts in the dose expansion phase (Part 2).

***Procedures and schedule**:* The Time and Events Schedule provided in Table 13 detail the planned frequency and timing of screening, safety, and efficacy measurements during Part 1 and Part 2 of Study EDI1001. The general timing of PK, immunogenicity, and pharmacodynamic measurements are described in Section 6.3.1.

Concurrent medications: Throughout the study, investigators were allowed to prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed as prohibited therapies. All medications (excluding study treatment and prior antineoplastic treatments), blood transfusions, surgeries and procedures (including physical therapy) administered within 30 days prior to the first dose administration of amivantamab through 30 days after the last dose of amivantamab were recorded in the case report form. Required prophylactic and predose medications were to be administered to all subjects as per the protocol to prevent or lessen the severity of IRRs, rash (see Section 8.2.6, Rash), and nausea (antiemetics). For IRRs, prophylactic treatment included the following:

- Mandatory antihistamine and paracetamol (IV or oral) prior to each scheduled infusion and mandatory pre-infusion administration of IV glucocorticoid on C1D1 and C1D2 (optional for other doses)
- Optional pre-infusion administration of histamine H2 antagonist and/or antiemetic

Concomitant medications administered were representative of those routinely prescribed for subjects with locally advanced or metastatic NSCLC and/or for other illnesses commonly encountered in populations of a similar age. [*Source: Mod5.3.5.2/ 61186372EDI1001/Sec5.1.3.2*]

Treatment compliance: Study drug administration was performed by study site staff and documented in source documents and the case report form.

Subject completion, discontinuation, or withdrawal: Subjects were considered to have completed the study when they were no longer being followed. Subject completion could occur for the following reasons: death, lost to follow-up, or withdrawal of consent to remain in the study. Subjects were withdrawn from treatment due to documented clinical or radiographic disease progression, unacceptable toxicity, withdrawal of consent, pregnancy, use of non-protocol systemic anti-cancer therapy, or investigator decision. Following treatment discontinuation, subjects were followed for overall survival and subsequent anti-cancer therapy until they died, withdrew consent, were lost to follow-up, or the end of study, whichever occurred first. The end of study was to occur 6 months after the last subject on study treatment completed therapy with amivantamab and had at least 6 months of follow-up.

- No subject enrolled as of the 08 June 2020 cutoff was replaced in this study.

Table 13: Time and Events Schedule for Study Assessments/Procedures (61186372EDI1001)

Study Period	**Screening[a]**	**Treatment (28 days/cycle)**											**End of Treatment**	**Post-treatment Follow-Up[e]**
		Cycle 1					**Cycle 2**		**Cycle 3 (and all odd cycles thereafter)**		**Cycle 4 (and all even cycles thereafter)**		**30 Days After Last Dose**	**Q3 months**
Calendar Week		**1**	**1**	**2**	**3**	**4**	**5**	**7**	**9**	**11**	**13**	**15**	--	
Cycle Day		**1**	**2**	**8**	**15**	**22**	**1**	**15**	**1**	**15**	**1**	**15**	--	
Study Day		**1**	**2**	**8**	**15**	**22**	**29**	**43**	**57**	**71**	**85**	**99**	--	
STUDY PROCEDURES														
Study Drug Administration														
JNJ-61186372 dosing[b]		X	X	X	X	X	X	X	X	X	X	X		
Safety Assessments														
Adverse events	Continuous													
Clinical labs[c]	X	X		X	X	X	X	X	X	X	X	X	X	
12-lead electrocardiogram	X	X					X		As clinically indicated					
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X		X	X	X	X	X	X	X	X	X	X	
Efficacy Assessments														
Disease assessment/Tumor response evaluation	X	X[d]												
Survival														X
Subsequent anticancer therapy														X

[a] Includes informed consent (prescreening), evaluation of inclusion and exclusion criteria, demography and disease characteristics, medical history, CT/MRI imaging of chest and any other disease location, and ECOG performance status.

[b] Treatment cycles are 28 days in duration. In Cycle 1, JNJ-61186372 is administered on Days 1, 2 (for doses >350 mg), 8, 15, and 22 of a 28-day cycle. In all subsequent cycles, JNJ-61186372 is administered once every other week on Days 1 and 15 of a 28-day cycle.

[c] Includes hematology, clinical chemistry at all visits as indicated; urine or serum pregnancy tests required at Screening and within 24 hours of first dose and as clinically indicated thereafter for women of childbearing potential; coagulation, serology, and urinalysis at Screening visit only.

[d] CT, MRI, and other imaging/examination (if applicable) performed of all active disease sites documented at Screening, at 6 (+1) weeks, and then every 6 ($\pm$1) weeks relative to Cycle 1 Day 1; repeat CNS imaging may be performed as clinically indicated during the Treatment Period. The same methodology was to be used throughout the study. For subjects who discontinued treatment prior to disease progression, radiological assessments were to continue as per the protocol schedule until disease progression was documented or a new cancer therapy was initiated.

[e] Data were to be collected every 3 months until the end of study, unless the subject died, was lost to follow-up, or had withdrawn consent.

The FDA's Assessment:

FDA agrees with the Applicant's description and rationale for the study design for cohorts receiving amivantamab as a single agent, with the following clarifications. Starting with Protocol Amendment 4 (dated March 9, 2018), in order to "mitigate the risk of IRR", the protocol was modified to administer the initial dose as a split infusion on Week 1 Days 1 and 2 and to require infusion of amivantamab via a peripheral vein for all Cycle 1 doses, with infusion via central line allowed for subsequent dosing starting with the Cycle 2 Day 1 dose. Protocol amendment 4 was instituted after 31 patients had received amivantamab on study.

Study Endpoints

The Applicant's Description:

Given the single-arm nature of Study EDI1001, the primary evaluation of antitumor activity utilized the endpoint of confirmed ORR using RECIST v1.1 (Eisenhauer 2009), defined as the proportion of subjects who achieved a confirmed complete response (CR) or partial response (PR). There was agreement with FDA (*Type B Initial Comprehensive Multidisciplinary Breakthrough Therapy Meeting [06 May 2020]*) concerning the appropriateness of confirmed ORR as an acceptable endpoint for accelerated approval pending review of the data. Response assessments were performed every 6 (±1) weeks, which was considered adequate time to observe a significant change in tumor measurements. Responses were confirmed with repeat scans at least 4 weeks after initial documentation of response as required by RECIST version 1.1 criteria.

Tumor responses were assessed by the investigator. Given the potential bias that may be present in investigator assessment, response was independently determined by a central vendor utilizing a 2-reader with adjudication paradigm per the blinded independent central review charter (BICR). Briefly, tumor images from each imaging timepoint for a subject was reviewed in chronological order by 2 different radiologists. Cases for which the best response (adjudication variable #1) or date for first response (adjudication variable #2) were discordant between the 2 independent readers were adjudicated to a third independent radiologist. Following the radiographic review (and adjudication, if necessary), an independent oncologist incorporated applicable clinical data to determine an overall response assessment. *[Source: Mod5.3.5.2/61186372EDI1001/Blinded Independent Central Review Charter]*

The primary endpoint of confirmed ORR was supported by the additional key secondary endpoints of DOR and CBR:

- DOR was defined as the time from first documentation of a PR or CR to the date of first documented evidence of disease progression or death due to any cause, whichever occurred first, for subjects who achieved a confirmed best overall response of CR or PR.
- CBR was defined as the proportion of subjects achieving a best overall response of confirmed CR, confirmed PR, or durable SD (duration of at least 11 weeks) as defined by RECIST v1.1.

Tumor response rate (ORR) and DOR are standard efficacy endpoints in clinical investigations of new NSCLC therapies. Moreover, the primary endpoint of ORR (per RECIST), in conjunction with the DOR endpoint, has been recognized by the FDA as acceptable endpoints reasonably likely to predict clinical benefit in single-arm studies in settings of unmet medical need in support of accelerated approval. The ORR, together with DOR, allow for evaluation of anti-tumor activity, and enable assessment of the potential clinical benefit of amivantamab in the target population.

Additional secondary efficacy endpoints analyzed for this submission include the time-to-event endpoints of PFS and OS to further characterize the treatment effect. Standard definitions were used to calculate PFS and OS; PFS was defined as the interval from the first dosing date to the first date of disease progression or death due to any cause (whichever occurred first), while OS was defined as the interval from the first dosing date to the date of the subject's death from any cause. Time-to-event endpoints (PFS and OS) are difficult to interpret in single-arm studies without a control arm and are analyzed in a descriptive manner for this BLA.

The FDA's Assessment:

FDA agrees with the Applicant's description. The major efficacy outcome measure for this marketing application was confirmed ORR according to RECIST v1.1 as evaluated by BICR, with DOR a key additional efficacy outcome measure. FDA considers CBR an exploratory endpoint.

Statistical Analysis Plan and Amendments:

The Applicant's Description:

The Study EDI1001 Statistical Analysis Plan (SAP) was finalized and submitted to FDA on 21 August 2019. The study SAP reflected FDA advice (*17 May 2018*) and changes in the protocol (via protocol amendments) such as addition of or expansion of Part 2 cohorts beyond 100 subjects and corresponding adjustments to the statistical plan (sample size and efficacy analysis). A separate SAP, specific to the analyses presented in this BLA submission, was subsequently created based on the agreement with FDA (*22 July 2020 Format & Content Meeting*) regarding the definition of the primary efficacy population. This document was finalized prior to the database lock, and is included in the BLA.

The BLA includes efficacy results for the primary and supportive populations of subjects with EGFR Exon 20ins NSCLC treated with amivantamab monotherapy in either Part 1 or Part 2 (see Section 8.1.2 for definitions) with a clinical cutoff date of 08 October 2020. The clinical cutoff date for the primary efficacy population (N=81) analysis, as well as the efficacy analysis for the expanded target population of all Exon 20ins subjects treated at the RP2D and having received previous treatment with platinum-based chemotherapy (N=114), is 08 October 2020. For the supportive efficacy populations (no prior chemotherapy and non-RP2D), the clinical cutoff date is 08 June 2020.

The BLA submission includes safety results based on the all treated analysis set, ie, subjects who received at least 1 dose of amivantamab monotherapy with a clinical cutoff date of 08 June 2020.

These clinical cutoffs for efficacy and safety analyses were based on agreement with the FDA at the 04 November 2020 pre-BLA meeting.

No data imputation was applied for missing efficacy or safety evaluations , except in instances of partial dates for AE onset or end date, concomitant therapies (start or end date), prior diagnosis date, prior anti-tumor therapies (start or end date), and subsequent anti-tumor therapy (start date), where missing or partial dates were imputed as detailed in the SAP.

Efficacy Analyses: The ORR and its 95% 2-sided exact CI were reported based on both BICR-reported tumor assessment and investigator assessment. The CBR and its associated 95% 2-sided exact CI were calculated. The DOR, PFS, and OS were evaluated using Kaplan-Meier methods, and the median value and corresponding 95% CI for each are provided.

Subgroup analyses: The ORR (and exact 95% CI) as per BICR and investigator assessments was analyzed using the methods described above for the following prespecified subgroups of the Exon 20ins efficacy populations treated at the amivantamab RP2D: age (<65 vs ≥65 years; <75 vs ≥75 years), sex (male vs female), race (Asian vs non-Asian), baseline ECOG (0 vs 1-2), history of smoking (yes vs no), and prior immunotherapy (yes vs no). In addition, the activity of amivantamab as a function of key Exon 20ins variants (based on circulating tumor deoxyribose nucleic acid [ctDNA] analysis of pretreatment samples) was also performed.

Interim analyses: Not applicable.

Safety Analyses: See Section 8.2.3.

The FDA's Assessment:

FDA's assessment of efficacy is based on the results in patients enrolled on Study 61186372EDI1001 in the dose escalation stage (part 1) and cohort D of the dose expansion stage (part 2). Cohort D enrolled patients with NSCLC harboring EGFR exon 20 insertion mutations who were previously treated with platinum-based chemotherapy or were ineligible for or refused platinum-based chemotherapy. The primary efficacy population for this BLA is limited to patients treated at the recommended dose who had disease progression on or after platinum-based chemotherapy. The study design assumed an ORR in Cohort D greater than 25%. A non-binding interim futility analysis was planned based on approximately 30 response evaluable patients, with a futility criterion of observing 5 or less responses among those 30 patients. The primary analysis of ORR was planned at 12 weeks after the start of treatment for the last enrolled patient or at end of the study, whichever occurred first. The end of the study will occur once all patients treated with amivantamab have ≥ 6 months of follow-up or have discontinued from the study. Although not mentioned in the Applicant's description above, the SAP for Study EDI1001 describes formal hypothesis tests for each cohort. FDA does not consider inferential procedures in the evaluation of single arm study results. Instead, the efficacy evaluation is based on the magnitude of response rate and adequate duration of response of the primary analysis population, as described above.

Protocol Amendments

The Applicant's Description:

There were 9 global amendments to the original protocol dated 15 October 2015, all of which are fully described in the study protocol. Key amendments are summarized in Table 14. The Applicant does not believe that any of the amendments impacted the integrity of the study or the interpretation of the results.

Table 14: Key Changes Implemented with Global Protocol Amendments to 61186372EDI1001

Amendment Number (Date)	Key Changes	Main Rationale for Amendment
Amendment 2 (12 Dec 2016)	• To specify which ECG parameters are to be collected and analyzed. • To update the guidance on pre- and post-infusion medication, including requirement for pre-infusion use of IV corticosteroids for all doses.	The overall reason for the amendment is to add guidance for bone scintigraphy and screening brain MRI, clarify the protocol requirement for CT of the neck, specify which ECG parameters will be collected and analyzed, update guidance on pre- and post-infusion medications, provide guidance on follow-up of bone metastases, clarify timeframe for pre-dose vital sign collection, specify that laboratory data should be available and reviewed by the investigator prior to each dose, and to correct a typographical error in Inclusion Criterion 7.
Amendment 3 (31 May 2017)	• Based upon preliminary data suggesting an early tumor response in a subject with an EGFR mutation treated in the 700 mg cohort of Part 1, the protocol amendment was implemented to: • To permit continued dose escalation in Part 1. • To reclassify overall response rate and clinical benefit rate as primary endpoints for Part 2 and to include overall survival as an secondary endpoint. • To allow for more than one RP2D regimen to be explored in Part 2 and to investigate the RP2D regimen(s) in Part 2 prior to completion of Part 1. • To collect information related to survival status and subsequent anti-cancer therapy (including best response to treatment) at 3-month intervals in the Follow-up Period until the end of study, unless the subject died, was lost to follow-up, or had withdrawn consent. • To require disease assessments until radiological progression was confirmed or new anti-cancer therapy began, whichever came first.	Preliminary data suggest an early tumor response in a subject with an EGFR mutation treated in the 700 mg cohort in Part 1 of the current study. A more comprehensive examination of JNJ-61186372 within this population is warranted, and suggests that characterization of the tumor biology both prior to and after treatment with JNJ-61186372 is important to understand the observed efficacy and development of resistance in subjects treated with JNJ-61186372. The treatment landscape for subjects with EGFR mutation continues to evolve. Targeted therapy may improve clinical endpoints in subgroups of subjects with certain molecular features. For this reason, in Part 2 of this study, subjects will be enrolled in 1 of 2 cohorts according to molecular markers of interest. Tumor tissue samples will be required at study entry (screening) and after progression to evaluate biomarkers that may be predictive of drug-clinical response relationship and mechanisms of resistance; circulating DNA will be required for cohort assignment. The Part 2 study population size has been

Table 14: Key Changes Implemented with Global Protocol Amendments to 61186372EDI1001

Amendment Number (Date)	Key Changes	Main Rationale for Amendment
		increased from 20 up to approximately 60 subjects in order to sufficiently evaluate the study objectives and endpoints. Additionally, as clinical benefit has been observed in this study, the objectives now focus on objective response rate and clinical benefit.
Amendment 4 (9 Mar 2018)	• Clarified the efficacy analyses. • Mandated that the first dose of amivantamab in Cycle 1 be administered over 2 days to reduce the risk of infusion-related reactions that appear to occur mainly following the first dose. • Provided instructions to address situations where (a) study treatment was delayed due to toxicity and (b) the subject was unable to have imaging performed with contrast. • Provided instructions regarding biopsy and blood sample collection for pharmacodynamic and biomarker determinations.	The treatment landscape for subjects with epidermal growth factor receptor (EGFR) mutation continues to evolve. Targeted therapy may improve clinical endpoints in subgroups of subjects with certain molecular features. The optimal dose of JNJ-61186372 that results in the most favorable risk/benefit has not yet been determined, and preliminary data from this ongoing study show a manageable toxicity profile. As a result, the SET has declared 1400 mg dose safe, and further escalation was recommended. These results have been added to the protocol and provide the rationale to continue dose escalation. In Part 2 of this study, 2 additional cohorts have been added which reflect clinical populations with unmet medical need, based upon molecular characterization of EGFR mutation and prior anti-cancer therapy. The Part 2 study population size has been increased from 60 to approximately 120 subjects initially enrolled (with potential to expand to 260 maximum) in order to sufficiently evaluate the study objectives and endpoints.
Amendment 5 (6 Sep 2018)	• Require disease assessments to be made every 6 (±1) weeks during Parts 1 and 2. • Revise sampling for infusion-related reactions and biomarkers to simplify and align with other clinical practices. • Changed requirement for pre-infusion IV corticosteroid administration to Cycle 1, Day 1 and Day 2 only.	The overall reason for the amendment is to enact the SET decision to limit eligible subjects for Cohort C to those with a demonstrable EGFR or cMET mutation conferring resistance to treatment with previous TKI. This decision was based on interim analysis of data from 25 subjects treated with JNJ-61186372 after progressing during previous treatment with third generation TKIs, which suggested superior efficacy outcomes if EGFR or cMET-mediated resistance to prior EGFR TKI therapy was demonstrated prior to initiation of JNJ-61186372 therapy.
Amendment 7 (19 Aug 2019)	• "Confirmation of Investigator assessed ORR and DOR can be performed through Independent	The unique mechanism of action of JNJ-61186372 (targeting the extracellular

Table 14: Key Changes Implemented with Global Protocol Amendments to 61186372EDI1001

Amendment Number (Date)	Key Changes	Main Rationale for Amendment
	Review Committee (IRC) if indicated", in Section 8.5 Efficacy Analysis. • Stopping criteria for early termination revised to be based on a null hypothesis (ORR ≤15%) and enrollment for the cohort may be terminated for futility by the SET, in Section 8.4 Interim Monitoring for Futility. • SAP additionally submitted.	domains of EGFR and cMET) suggests potential to also improve clinical outcomes through combination with EGFR TKIs, which target intracellular domains. JNJ-61186372 monotherapy has demonstrated clinical activity against emergence of EGFR (eg, C797S) and cMet (eg, amplification) TKI resistance mutations post third generation TKI. The rationale for the combination of JNJ-61186372 with third generation EGFR-specific TKIs, lazertinib is to prevent or delay the emergence of resistance, thereby prolonging disease control and has the potential to more potently inhibit the EGFR pathway and induce deeper and prolonged responses than either agent alone. Eleven subjects have been enrolled with JNJ-61186372 in combination with lazertinib at 700 mg/240 mg dose and at 1050 mg/240 mg dose, respectively, in South Korea. No DLT has been observed at either dose level. This amendment is intended to expand the combination cohort in all countries to evaluate the safety and PK of JNJ-61186372 in combination with lazertinib and to evaluate anti-tumor activity of the combination in subjects who have progressed on osimertinib (third generation TKI).
Amendment 8 (27 Jan 2020)	• Expansion of Part 2 cohorts beyond 100 subjects to further characterize study treatment activity within cohort subpopulations and to ensure adequate subject representation with the minimum number of prior therapies for each cohort, and adjust the statistical plan (sample size and efficacy analysis) accordingly. • Further definition of cohorts in Part 2 regarding the number of prior therapies allowed. • Clarification of toxicity management and restart of dosing following a delay for toxicity. • Clarification of eligibility testing and allowance of local testing.	The overall reasons for the amendment are to 1) allow expansion of cohorts beyond 100 subjects to further characterize study treatment activity within cohort subpopulations, and to ensure adequate representation of subjects with the minimum number of prior therapies for each cohort, and adjust the statistical plan (sample size and efficacy analysis) accordingly, 2) allow for additional Part 1 cohorts to explore new dosing schedules, routes of administration, or batches of JNJ-61186372 drug product, and provide new alternate dosing schedules, 3) further define cohorts as to the number of prior therapies allowed, and 4) modify inclusion criteria to allow enrollment of treatment naïve subjects into Part 1 combination dose escalation. Additional minor clarifications and modifications to study conduct are also made.

Table 14: Key Changes Implemented with Global Protocol Amendments to 61186372EDI1001

Amendment Number (Date)	Key Changes	Main Rationale for Amendment
Amendment 9 (30 April 2020)	Additional guidance was provided regarding the investigation of any change in respiratory status or non-oncogenic change in pulmonary radiographic appearance to rule out early interstitial lung disease (ILD) or pneumonitis, for subjects in any treatment Cohort	The rationale for inclusion of this additional guidance is to ensure early identification of and optimal management of ILD or pneumonitis
COVID-19 Appendix (30 Apr 2020)	Provided options for study-related management in the event of disruption to the conduct of the study due to the Coronavirus Disease 2019 (COVID-19) pandemic.	

The FDA's Assessment:

FDA agrees with Applicant's above global protocol amendments table, with the exception that information regarding Amendment 6 (May 29, 2019) is not included in the Applicant's table. Amendment 6 was implemented to add two cohorts investigating amivantamab in patients with tumors harboring MET amplification or mutation (MET-1 and MET-2 cohorts) to Part 2 of the trial.

8.1.2. Study Results

Compliance with Good Clinical Practices

Data:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and applicable regulatory requirements. The study protocol and amendments were reviewed by an Independent Ethics Committee or Institutional Review Board. Subjects or their legally acceptable representatives provided their written consent to participate in the study after having been informed about the nature and purpose of the study, participation/termination conditions, and risks and benefits of treatment.

The Applicant's Position:

This study was conducted in accordance with the CFR governing the protection of human subjects (21 CFR part 50), Institutional Review Boards (21 CFR part 56), and the obligation of clinical investigators to GCP (21 CFR 312.50 to 312.70).

The FDA's Assessment:

FDA agrees with the Applicant's position.

Financial Disclosure

Data:

All the 660 principal investigators and subinvestigators participating in Study 61186372EDI1001 were assessed for financial disclosures as defined in 21 CFR Part 54, and none had disclosable financial interests. Further details of financial disclosure are provided in Section 20.2.

The Applicant's Position:
The Applicant has adequately assessed clinical investigators for any financial interest/arrangements and no disclosable financial interests were found.

The FDA's Assessment:

FDA agrees with the Applicant's position. Janssen has adequately disclosed any financial interest/arrangements with the clinical investigators in accordance with the Guidance for Industry. Details of financial disclosure are presented in Section 20.2.

Patient Disposition

Data:

A total of 362 subjects with advanced or metastatic NSCLC received at least 1 dose of amivantamab monotherapy in Part 1 or Part 2 (08 June 2020 cutoff). Of these, 187 had locally-documented EGFR Exon 20ins-mutated disease. In this BLA submission, the primary population of interest is the subgroup of subjects with EGFR Exon 20ins NSCLC treated with amivantamab at the RP2D and whose disease had progressed on or after platinum-based chemotherapy (ie, had metastases within 12 months from last platinum-based chemotherapy use). This Exon 20ins + prior chemotherapy at RP2D population consisted of 114 subjects, of whom 81 consecutively-treated subjects received their first dose of amivantamab monotherapy on or before 05 February 2020. These 81 subjects comprise the primary efficacy population for this BLA. The majority of these subjects were enrolled in Part 2 Cohort D (n=73) which was limited to subjects with EGFR Exon 20ins mutation; an additional 4 subjects were enrolled in Part 2 Cohort A and 4 subjects were enrolled during Part 1 (see Figure 20 for cohort description).

Efficacy results for the Exon 20ins + prior chemotherapy at RP2D primary efficacy population (N=81) as of a clinical cutoff date of 08 October 2020 are reported in detail in an addendum to the CSR and form the basis of the efficacy findings reported in the proposed USPI. Additionally, these results are summarized in this document.

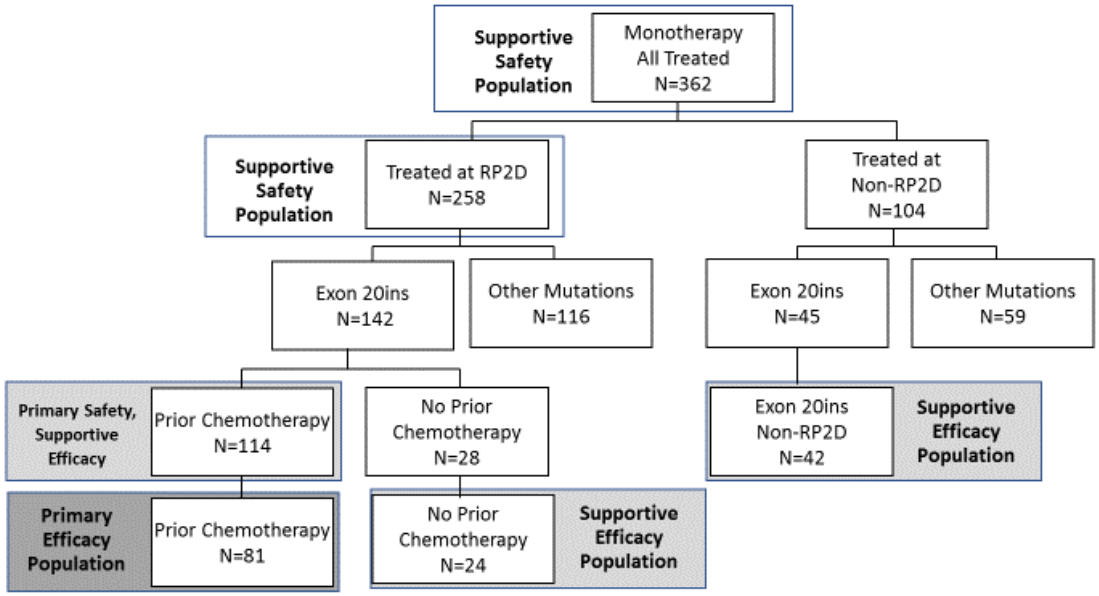
Supportive efficacy data for the following Exon 20ins populations are also summarized in the BLA and briefly discussed in this document: *[Source: Mod2.7.3/Sec1.3, Mod5.3.5.2/61186372EDI1001Addendum/Sec1]*

- Expanded Exon 20ins + prior chemotherapy at RP2D population (N=114): subjects in the Exon 20ins + prior chemotherapy at RP2D population who had received their first dose of amivantamab monotherapy on or before 04 June 2020. This population includes the

81 subjects in the primary efficacy population described above and an additional 33 subjects that were enrolled after 05 February 2020. Efficacy data for these 114 subjects were analyzed as of the 08 October 2020 cutoff. [Of note, this population is also the primary safety population (see Section 8.2.1)].

- Exon 20ins + no prior chemotherapy at RP2D population (N=24): subjects with Exon 20ins NSCLC who had not been treated with platinum-based chemotherapy within 12 months of the diagnosis of metastatic NSCLC and who received their first dose of amivantamab monotherapy at the RP2D on or before 05 February 2020. Efficacy data for this population were analyzed as of the 08 June 2020 cutoff.
- Exon 20ins at Non-RP2D population (N=42): subjects with Exon 20ins NSCLC received their first dose of amivantamab monotherapy at a dose other than the RP2D on or before 05 February 2020. Efficacy data for this population were analyzed as of the 08 June 2020 cutoff.

Figure 20: Study EDI1001 Populations



As of the 08 October 2020 clinical cutoff date, the median follow-up for the 81 subjects comprising the Exon 20ins + prior chemotherapy at RP2D primary efficacy population was 9.7 months (range: 1.08-29.27). *[Source: Mod2.7.3/SCEAddendum/Sec2.1]*

The Applicant's Position:

The primary efficacy population submitted in this BLA was previously aligned with the FDA (*06 May 2020 Type B meeting*). Further, the FDA agreed at the Pre-BLA meeting on 04 November 2020 that efficacy results as of the 08 October 2020 cutoff for the primary efficacy population of

81 subjects would form the basis of the BLA review concerning the benefit of amivantamab in the intended population, and that these results should be presented in this document, the proposed USPI, and in addenda to the CSR, Summary of Clinical Efficacy, and Clinical Overview.

The FDA's Assessment:
FDA agrees with the Applicant's position. FDA's analysis was based on the primary efficacy population which includes 81 patients previously treated with chemotherapy with NSCLC harboring EGFR exon 20 insertion mutations who were treated at the recommended dosages on or before February 5, 2020. The corresponding data cut-off date is October 8, 2020.

Protocol Violations/Deviations

Data:

Major protocol deviations related to study drug administration, study eligibility criteria, and other key study design features were identified through the initial clinical cutoff (08 June 2020) and data are reported in the CSR. Rates of such deviations were low for all study populations identified in the SAP. None of these deviations led to exclusion of data from the efficacy and safety analyses.

Major protocol deviations were identified for 9 of the 81 subjects (11.1%) comprising the Exon 20ins + prior chemotherapy at RP2D primary efficacy population. The major protocol deviations identified for individual subjects were examined in detail, and consisted mainly of exclusionary concurrent conditions (including untreated brain metastases) (3 subjects), a single dose of study drug administered inconsistent with protocol guidelines (2 subjects), and failure to adjust study drug administration following the occurrence of an IRR (2 subjects). All major deviations are described in the CSR. *[Source: Mod5.3.5.2/61186372EDI1001/AttTSIDEV01-E20, Sec5.1.4]*

Data for protocol deviations related to the Coronavirus Disease-19 (COVID-19) pandemic were collected for all treated subjects during the study; all of these deviations were minor and most were related to either missed procedures/visits or visits and/or assessments being performed remotely. None of these minor deviations led to exclusion of data from the efficacy and safety analyses.

The Applicant's Position:

The few major protocol deviations identified in the primary efficacy population were typical of those observed in clinical studies, and did not lead to the exclusion of data from the analyses or impact the interpretation of the results.

The FDA's Assessment:

FDA agrees with the Applicant's analysis of the protocol deviations categorized as "major" and "minor". The following table, abstracted from the clinical study report for clinical trial 61186372EDI1001, summarizes important major protocol deviations observed. FDA agrees with

the Applicant that the reported protocol deviations are not expected to impact the interpretability of the study results.

None of the reported major protocol deviations were COVID-19 related. In the primary efficacy population, there were 48 minor protocol deviations reported in 26 patients. Most were related to either missed procedures/visits or visits and/or assessments performed remotely.

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Subjects with major protocol deviations	12 (10.5%)	25 (9.7%)	38 (10.5%)
Entered but did not satisfy criteria	6 (5.3%)	10 (3.9%)	14 (3.9%)
Received wrong treatment or incorrect dose	3 (2.6%)	7 (2.7%)	11 (3.0%)
Other	6 (5.3%)	12 (4.7%)	19 (5.2%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Note: Subjects may appear in more than one category.
[TSIDEV01.RTF] [JNJ-61186372\EDI1001\DBR_CSR_E20INS\RE_CSR_E20INS\PROD\TSIDEV01.SAS] 14AUG2020, 11:58

Abstracted from the Study EDI1001 Clinical Study Report

Table of Demographic Characteristics

Data:

The 81 subjects in the Exon 20ins + prior chemotherapy at RP2D primary efficacy population had a median age of 62 years (range: 42 to 84), with 8.6% being ≥75 years of age; more than half were female (59.3%), and 49.4% were Asian and 37.0% were White. With the exception of race, which was missing for 9 subjects in the primary efficacy population, key demographic characteristic data were available for each of the 81 subjects. *[Source: Mod2.7.3/Tab4]* A table summarizing demographic characteristics for the Exon 20ins + prior chemotherapy at RP2D safety population (N=114), which includes the 81 subjects in the primary efficacy population, is provided in Table 19.

The Applicant's Position:

The primary (n=81) and expanded (N=114) populations treated in Study EDI1001 are representative of the intended patient population, individuals with metastatic NSCLC with EGFR Exon 20ins whose disease has progressed on or after platinum-based chemotherapy.

The FDA's Assessment:

FDA agrees with the Applicant's description of patient demographics based on the primary population of 81 patients. There were 33 patients (41%) who were aged 65 years or older.

Other Baseline Characteristics (eg, disease characteristics, important concomitant drugs)

Data:

The Exon 20ins + prior chemotherapy at RP2D primary efficacy population predominantly had Stage IV disease (75.3%) at initial diagnosis, with 22.2% having a history of prior brain metastases and 42.0% having bone metastases. Consistent with the known biology of EGFR-mutated NSCLC, 53.1% did not have a smoking history. Among these 81 subjects, insertions in Exon 20 were observed at 8 different residues (based on central ctDNA analysis), the most common of which were A767 (23.5%), S768 (16.0%), D770 (11.1%), and N771 (11.1%). For 18 subjects (22.2%), the Exon 20ins mutation variation was not specified by ctDNA analysis. The median time from the diagnosis of metastatic disease to the first dose of amivantamab was 14.2 months (range: 0.69-116.40). *[Source: Mod2.7.3/Tab5]*

The 81 subjects in the Exon 20ins + prior chemotherapy at RP2D efficacy population were heavily pretreated, having received a median of 2 lines of prior therapy. By definition, all had received prior platinum-based chemotherapy. In addition, 45.7% of subjects in this population had received prior immunotherapy, and 24.7% had received prior TKI therapy (8.6%, 7.4%, and 7.4% for first-, second-, and third-generation EGFR-TKI, respectively). *[Source: Mod2.7.3/Sec2.3.1.3]*

A table summarizing baseline lung cancer characteristics for the Exon 20ins + prior chemotherapy at RP2D safety population (N=114), which includes the 81 subjects in the primary efficacy population, is provided in Table 20.

Demographic and lung cancer characteristics for the other study populations identified in the SAP are presented in the CSR. *[Source: Mod5.3.5.2/61186372EDI1001/Sec5.1.2]* (see also Section 8.2.2, Relevant characteristics of safety population).

The Applicant's Position:

Baseline disease characteristics for the primary efficacy population were representative of the intended patient population: elderly (median age of 62 years), predominantly female (59.3%), ECOG of 0 or 1, and with more than half having no prior smoking history (Midha 2015; Passaro 2020). Moreover, the characteristics of the primary efficacy population for Study EDI1001 were similar to those in studies evaluating subjects with advanced EGFR-mutant NSCLC after progression on first-line therapy (Mok 2017; Soria 2015). Furthermore, disease characteristics of the primary efficacy population were consistent with results seen among 181 subjects with EGFR Exon 20ins NSCLC evaluated in the RWD retrospective cohort to evaluate the unmet needs and treatment patterns for EGFR Exon 20ins-mutated NSCLC (Study NSC1002, see Section 8.1.5). *[Source: Mod2.5/Tab12]* In addition, genetic characterization showed that amivantamab activity was assessed in subjects with diverse Exon 20ins mutations. Thus, the clinical activity seen for amivantamab in Study EDI1001 are believed to be generalizable to the EGFR Exon 20ins NSCLC patient population that will be encountered in clinical practice.

The FDA's Assessment:

FDA agrees with the Applicant's description, with the following clarification. One patient had received both first and third generation EGFR TKIs. A total of 19 (23%) patients had received prior TKI therapy (9% for first generation, 7% each for second and third generations, and 1.2%

for Exon 20 EGFR TKIs). In addition, among the 81 patients in the primary analysis population, 74% had baseline body weight <80 kg; 95% had adenocarcinoma; 67% had ECOG PS of 1; 53% never smoked; and all patients had metastatic disease at time of study entry. As noted by the Applicant, the median number of prior therapies was 2 (range: 1 to 7).

With regards to sex, smoking status, and histology, the baseline characteristics of patients enrolled EDI1001 are representative of the disease characteristics reported in the literature (Oxnard 2013, Remon 2020) and in the Flatiron data submitted by the Applicant. While the median age of 62 years (range: 36, 84) for patients in Study EDI1001 is lower than that reported in the submitted Flatiron data (median age 67.4 years [range: 39, 84]), , it is similar to the median age of 60 years reported by by Oxnard et al.

The proportion of Asian pateints in Study EDI1001 is high (55%), most likely due to the fact that the study was initiated in South Korea prior to expanding to clinical sites globally. As detailed in Section 2.1 of this review, information submitted by the Applicant utilizing data from Flatiron Health reported 9.4% of patients with NSCLC with EGFR exon 20 insertion mutations were Black or African American. In the primary efficacy population of the CHRYSALIS study, 2.3% of patients were Black or African American. A PMC was agreed to for the Applicant clinical trial data from to further characterize the safety and efficacy of amivantamab in Black or African American patients with EGFR exon 20 insertion mutated NSCLC.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Data and Applicant's Position:

Amivantamab was administered by qualified healthcare professionals in the clinical setting, and administrations were recorded in the source document, accurately documenting dose and treatment compliance. Subjects in the primary efficacy population were dosed consistent with intended RP2D regimen: 1050 mg for subjects with baseline body weight <80 kg or 1400 mg for subjects with baseline body weight ≥80 kg body weight, administered as an IV infusion once weekly for 4 weeks, then every 2 weeks thereafter for a 28-day cycle. The median relative dose intensity for the 81 subjects in the Exon 20ins + prior chemotherapy at RP2D primary efficacy population was 100%, indicating that subjects generally received study treatment as planned. *[Mod2.7.3/Sec2.3.1.4]*

Concomitant medications, along with dose modifications, were predominantly used for the management of comorbidities and toxicity (see Section 8.2.6 as well as Section 8.2.5).

Rescue medications: Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position based on the review of the Applicant's analysis presented in study EDI1001 CSR and the data contained in the safety update. The specific permitted concomitant medications prior and post amivantamab infusion can be found in Section

8.1.1 concurrent medications. The Applicant's reference to dose modifications is not relevant to this section.

Efficacy Results – Primary Endpoint (Including Sensitivity Analyses)

Data

The ORR based on BICR and investigator assessments are summarized for the Exon 20ins + prior chemotherapy at RP2D primary efficacy population (N=81) in Table 15. As of the 08 October 2020 cutoff, the median follow-up for these 81 subjects was 9.7 months (range: 1.08-29.27). *[Source: Mod2.7.3Addendum/Sec2.1]*

Table 15: Summary of Best Overall Response Based on RECIST v1.1 (as of 8 Oct 2020 Cutoff) in Subjects With Measurable Disease at Baseline and First Dose On or Before 05 Feb 2020 – Investigator and BICR; Efficacy Evaluable at RP2D with Exon 20 Insertion and Prior Chemotherapy Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	Exon 20 Ins (RP2D) + Prior Chemotherapy	
	Investigator Assessment	BICR Assessment
Analysis set: Efficacy evaluable at RP2D with Exon 20 insertion in monotherapy (JNJ-61186372)	81	81
Best overall response		
Complete response (CR)	0	3 (3.7%)
Partial response (PR)	29 (35.8%)	29 (35.8%)
Stable disease (SD)	39 (48.1%)	39 (48.1%)
Progressive disease (PD)	12 (14.8%)	8 (9.9%)
Not evaluable/unknown	1 (1.2%)	2 (2.5%)
Overall response rate (Confirmed CR + Confirmed PR)	29 (35.8%)	32 (39.5%)
95% CI	(25.4%, 47.2%)	(28.8%, 51.0%)
Clinical benefit rate [a] (Confirmed CR + Confirmed PR + SD)	59 (72.8%)	60 (74.1%)
95% CI	(61.8%, 82.1%)	(63.1%, 83.2%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Note: Percentages are calculated using the number of subjects with measurable disease at baseline as the denominator.
[a] Clinical benefit rate (CBR) is defined as the percentage of subjects achieving confirmed complete or partial response, or durable stable disease (duration of at least 11 weeks).

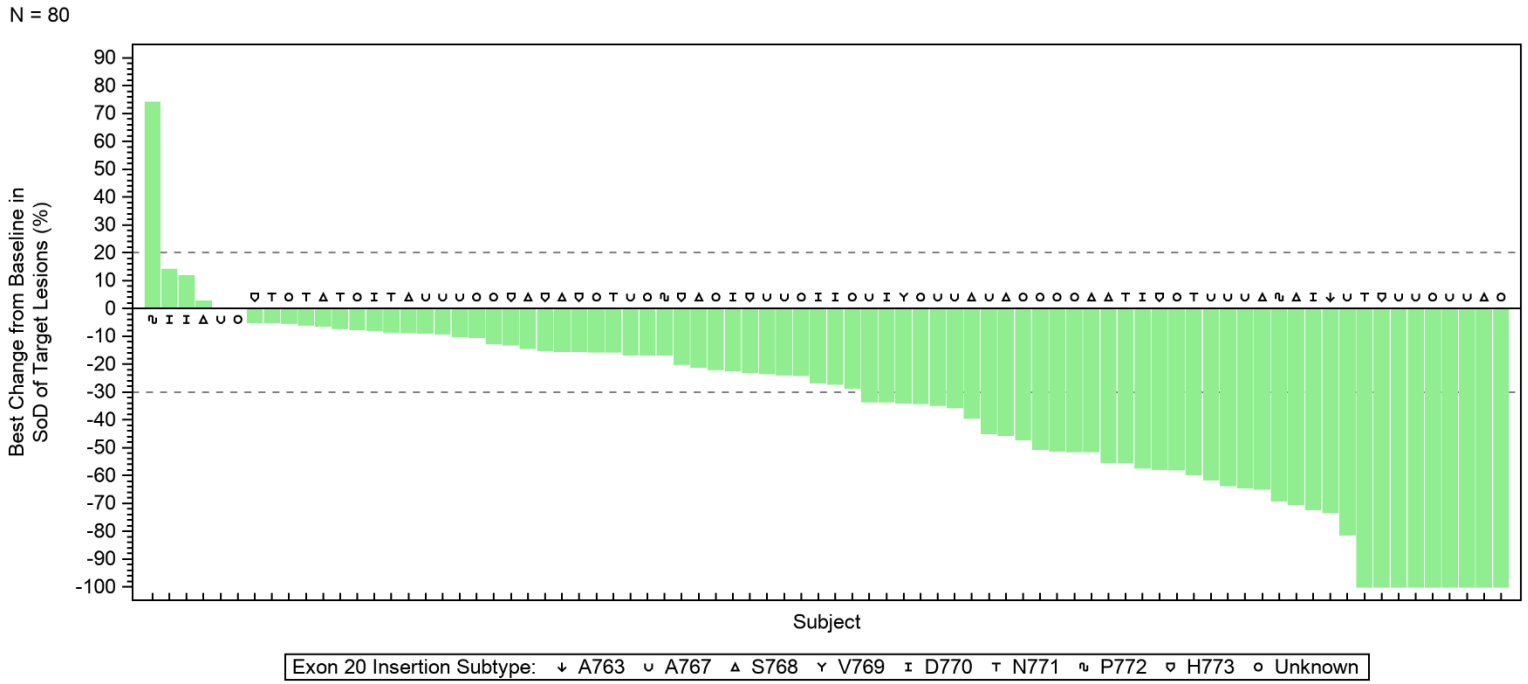
Source: Mod2.7.3/SCEAddendum/Tab1

A waterfall plot reflecting the best percentage change in target lesion sum of diameters (SoD) in the primary efficacy population is presented as a function of Exon 20ins mutation variation in Figure 21 (BICR assessment). The anti-tumor activity observed with amivantamab in the Exon 20ins + prior chemotherapy at RP2D primary efficacy population appeared independent of mutation variation.

Subgroup analyses of confirmed ORR in the primary Exon 20ins + prior chemotherapy at RP2D efficacy population (N=81) demonstrated that clinical activity of amivantamab monotherapy at

the RP2D was observed across all clinically relevant subgroups defined above (see Figure 22 for forest plot based on BICR-assessed ORR).

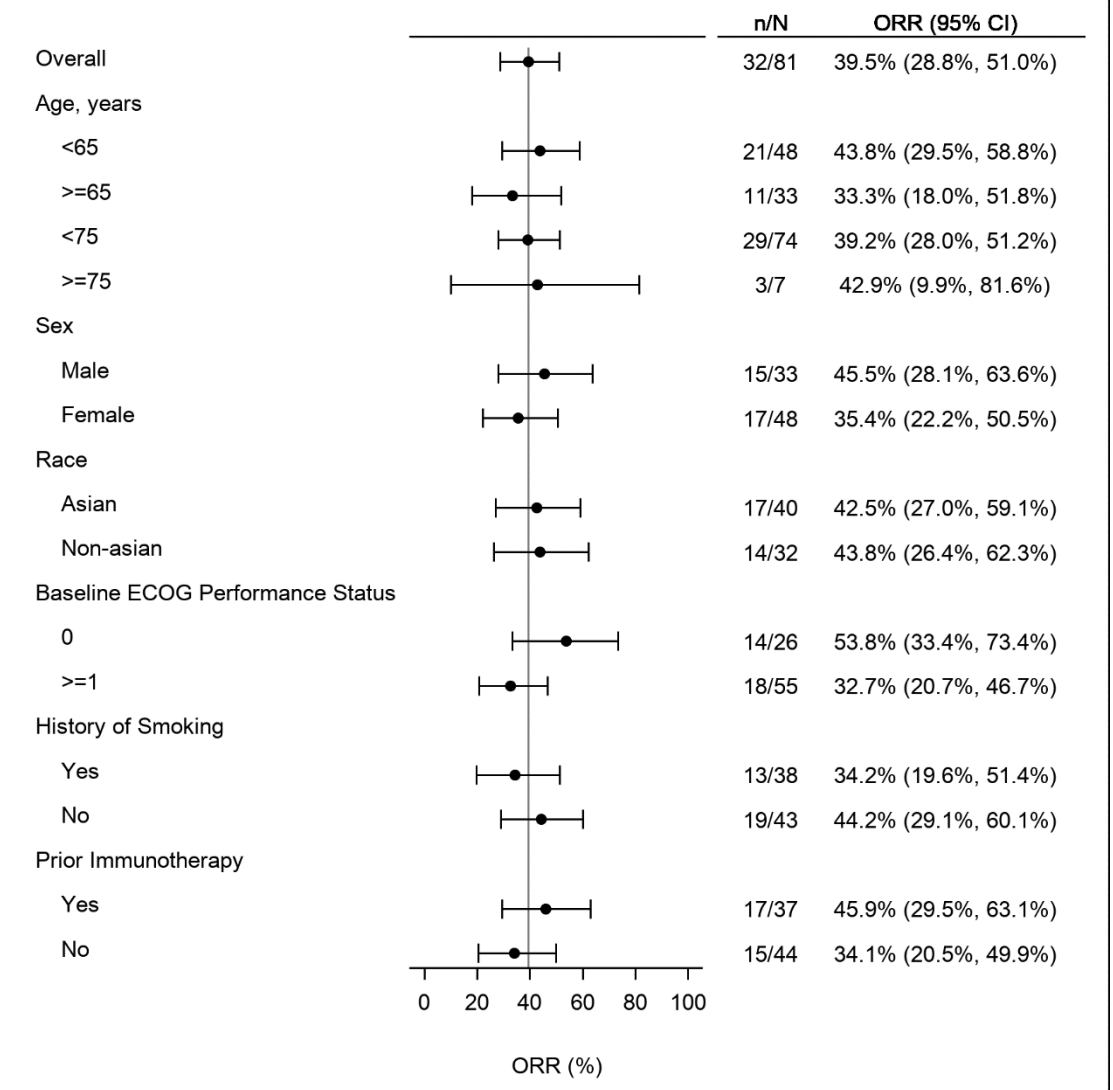
Figure 21: Waterfall Plot of Best Percentage Change from Baseline in Sum of Diameters (SoD) of Target Lesions (as of 08 Oct 2020 Cutoff) Based on Subjects With Measurable Disease at Baseline and First Dose On or Before 05FEB2020 – BICR; Efficacy Evaluable at RP2D with Exon 20 Insertion and Prior Chemotherapy Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)



RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: SoD = Sum of Diameters
The source of Exon 20 Insertion subtype is central Guardant data.

Source: Mod5.3.5.2/61186372EDI1001Addendum/AttGEFRSWF02-E20PC

Figure 22: Forest Plot of Overall Response Rate Based on RECIST v1.1 (as of 08 Oct 2020 Cutoff) in Subjects With Measurable Disease at Baseline by Subgroups with First Dose On or Before 05 Feb 2020 - BICR; Efficacy Evaluable at RP2D with Exon 20 Insertion and Prior Chemotherapy Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)



RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: n = Confirmed CR + Confirmed PR
Note: If race was not reported, then that subject is excluded from the race subgroup.

Source: Mod2.7.3/SCEAddendum/Fig2

The Applicant's Position:

Analyses of efficacy data available as of the 08 October 2020 clinical cutoff demonstrated that treatment at the amivantamab RP2D resulted in robust anti-tumor activity in subjects with

Exon 20ins NSCLC whose disease had progressed on or after platinum-based chemotherapy, a population for which there are no approved targeted therapies or clear standard of care.

- An ORR of 39.5% (95% CI: 28.8%, 51.0%) based on BICR assessment was observed. An additional 28 subjects in this population achieved a BICR-assessed best response of SD for at least 11 weeks, contributing to an overall CBR of 74.1% (95% CI: 63.1%, 83.2%).
- Consistent with the importance of the EGFR pathway in this disease, amivantamab monotherapy at the RP2D delivered consistent clinical benefit across all clinically relevant subgroups. In addition, anti-tumor activity of amivantamab was observed across all variants of EGFR Exon 20ins mutations enrolled, consistent with a mechanism of action that bypasses the steric hindrance surrounding the active site.

The FDA's Assessment:

In general, FDA agrees with the Applicant's description of the results for the primary efficacy endpoint of ORR. However, FDA considers the analyses related to CBR to be exploratory and did not verify the results.

The following table provides FDA's exploratory analyses of clinically relevant subgroups. Overall the results across subgroups are consistent with the primary analysis in the overall population, with no obvious outliers among subgroups with sufficient sample size.

FDA - Table 16: Exploratory Analysis of ORR by Clinical and Demographic Subgroups

Characteristics	Responders	Response Rate (95% CI)
Age		
≥ 65 (n = 33)	11	33 (18, 52)
< 65 (n = 48)	21	44 (29, 59)
Sex		
Female (n = 48)	17	35 (22, 51)
Male (n = 33)	15	45 (28, 64)
Race		
White (n = 30)	13	43 (25, 63)
Black or African American (n = 2)	1	50 (1, 99)
Asian (n = 40)	17	42 (27, 59)
Other (n = 9)	1	11 (0, 48)
Prior Systemic Therapy		
Immunotherapy (n = 37)	17	46 (29, 63)
No prior immunotherapy (n=44)	15	34 (21, 50)
EGFR TKI (n = 18)	9	50 (26, 74)

Data Quality and Integrity

Data:

See also Section 8.1.2, Compliance with GCP.

Beginning in 2020, protocol-specific contingency measures were implemented in response to the COVID-19 pandemic to assure the safety of EDI1001 participants, maintain compliance with GCP, and minimize risks to study integrity. A COVID-19 Protocol Appendix was developed and submitted to Health Authorities and trial sites in all countries involved in the study (see Table 14). A review of all available information indicated that there was minimal impact of COVID-19 on the integrity of the study and study data, assessment of subject safety, and adequacy of data completeness or quality. *[Source: Mod5.3.5.2/61186372EDI1001/Sec3.10.1]*

The Applicant's Position:

It is the Applicant's position that there are no issues related to data quality and integrity.

The FDA's Assessment:

FDA did not identify any issues related to data quality and integrity of the datasets submitted to support the BLA.

Efficacy Results – Secondary and other relevant endpoints

Data:

Duration of response (DOR) was considered the key secondary endpoint for this study. The DOR based on BICR and investigator response assessments are summarized for the 81 subjects comprising the Exon 20ins + prior chemotherapy at RP2D primary efficacy population in Table 17. All of the 32 (100%) BICR-assessed responders had at least 6 months of follow-up from onset of response, or had discontinued treatment as of the 08 October 2020 clinical cutoff.

Table 17: Summary of Duration of Response in Responders with First Dose On or Before 05 Feb 2020 (as of 08 Oct 2020 Cutoff) - Investigator and BICR; Efficacy Evaluable at RP2D with Exon 20 Insertion and Prior Chemotherapy Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	Exon 20 Ins (RP2D) + Prior Chemotherapy	
	Investigator Assessment	BICR Assessment
Analysis set: Efficacy evaluable at RP2D with Exon 20 insertion in monotherapy (JNJ-61186372)	81	81
Responders	29	32
Event	17 (58.6%)	14 (43.8%)
Censored	12 (41.4%)	18 (56.3%)
Duration of response (months)		
25th percentile (95% CI)	5.16 (4.07, 8.31)	5.55 (4.17, 10.84)
Median (95% CI)	11.20 (6.34, 13.14)	11.14 (6.90, NE)
75th percentile (95% CI)	13.14 (11.20, NE)	21.65 (11.14, NE)
Range	(3.2, 16.1)	(1.3+, 21.7)
Duration of response >=6 months	19 (65.5%)	20 (62.5%)
Duration of study treatment (months)[a]		
N	29	32
Mean (SD)	11.37 (5.051)	11.02 (5.374)
Median	10.15	10.10
Range	(3.3, 23.9)	(2.8, 23.9)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg..
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: CI = confidence interval, NE = not estimable, + = censored observation
Quartiles and 95% CIs are estimated with Kaplan-Meier method.
[a] Treatment duration is defined as the duration from the date of the first dose of study drug to the date of last dose of study drug+1 divided by 30.4375.

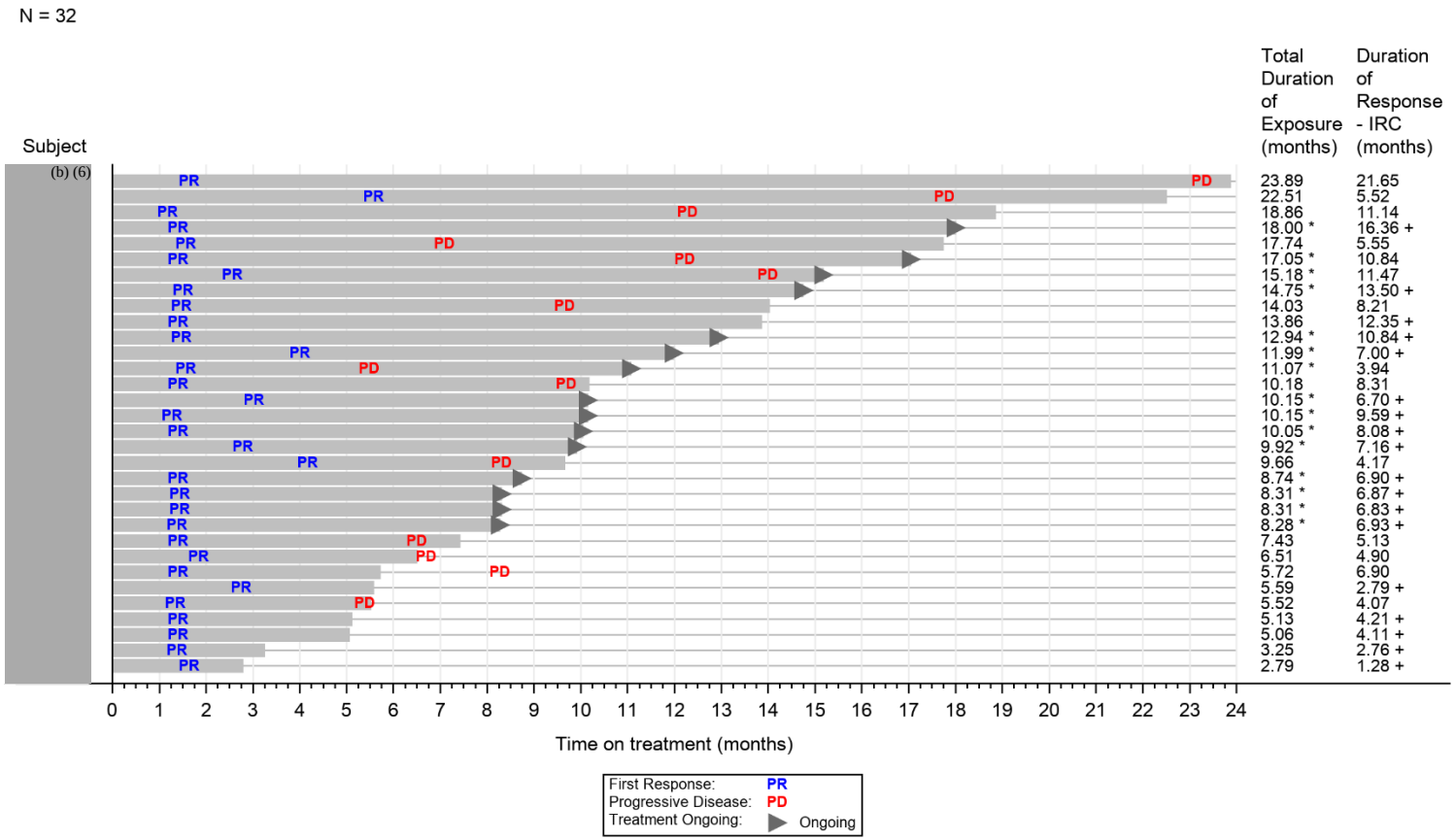
Source: Mod2.7.3/SCEAddendum/Tab2

Of the 32 responders based on BICR assessment, 20 (62.5%) had a DOR of ≥6 months, including 13 who were reported as having ongoing responses at the clinical cutoff. *[Source: Mod2.7.3/SCEAddendum/Sec2.1.2]*

- The remaining 12 BICR-assessed responders had a DOR <6 months. Of these, 5 subjects had an ongoing response by BICR but had discontinued treatment based on investigator assessment, and no new data are forthcoming. None of the remaining 7 subjects had an ongoing response based on BICR.

A swimplot of the DOR for individual responders based on BICR assessment is shown in Figure 23.

Figure 23: Duration of Response in Responders with First Dose On or Before 05 Feb 2020 (as of 08 Oct 2020 Cutoff) BICR Committee; Efficacy Evaluable at RP2D with Exon 20 Insertion and Prior Chemotherapy Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)



Subjects with first dose on or before 05FEB2020 are included.
RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: * = treatment is still ongoing, + = response is still ongoing

Source: Mod2.7.3/SCEAddendum/Fig1

With a median follow up of 9.7 months, the median PFS based on BICR response assessment for the Exon 20ins + prior chemotherapy at RP2D primary efficacy population was 8.28 months (95% CI: 6.51, 10.87). The 6-month and 12-month PFS rates for this population (BICR assessment) using the 08 October 2020 cutoff were 63% (95% CI: 51%, 73%) and 36% (95% CI: 23%, 49%), respectively. *[Mod2.7.3/SCEAddendum/Tab3]*

In the primary efficacy population, with 71.6% of subjects censored, the median OS was 22.77 months (95% CI: 14.59, not estimable). The estimated 12-month survival rate was 75% (95% CI: 62%, 84%), while the estimated 18-month survival rate was 63% (95% CI: 46%, 76%). *[Mod2.7.3/SCEAddendum/Sec2.1.4]*

Supportive Efficacy Results

Supportive efficacy results as of the 08 October 2020 clinical cutoff for 114 subjects in the Exon 20ins + prior chemotherapy at RP2D population who had received their first dose of amivantamab monotherapy on or before 04 June 2020 were consistent with those observed in the primary efficacy population (N=81) (Table 18). The median duration of follow-up for these subjects was 8.3 months (range: 0.23, 29.27). *[Mod2.7.3/SCEAddendum/Sec2.2]*

Table 18: Supportive Clinical Outcomes (as of 8 Oct 2020 Cutoff) in Subjects with First Dose On or Before 04Jun 2020 - Investigator and BICR; Efficacy Evaluable at RP2D with Exon 20 Insertion and Prior Chemotherapy Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	Investigator Assessment	BICR Assessment
Analysis set: Efficacy evaluable at RP2D with Exon 20 insertion in monotherapy (JNJ-61186372)	114	114
Confirmed ORR (95% CI)	35.1% (26.4%, 44.6%)	39.5% (30.4%, 49.1%)
Median DOR(95% CI), months	11.20 (6.34, 13.14)	10.84 (5.55, NE)
CBR (95% CI)	75.4% (66.5%, 83.0%)	72.8% (63.7%, 80.7%)
Median PFS (95% CI), months	7.16 (5.55, 8.84)	6.87 (5.49, 9.66)
Median OS (95% CI), months	22.77 (95% CI: 14.59, NE)	

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
CI=confidence interval; NE=not estimable
BICR = blinded independent central review; CBR = confirmed complete response + partial response + stable disease for ≥11 weeks; NE = not estimable; ORR = confirmed complete or partial response.

Source: Mod2.7.3/SCEAddendum/Tab4

In addition, supportive efficacy results (presented in the CSR) for subjects with Exon 20ins NSCLC who received no prior chemotherapy and were treated at the RP2D (N=24) and subjects with Exon 20ins NSCLC who were treated at a non-RP2D dose (N=42) (as of 06 June 2020 cutoff) were consistent with those for the primary efficacy population.

The Applicant's Position:

The duration of response data as of the 08 October 2020 cutoff demonstrate that the clinical activity of amivantamab in the Exon 20ins NSCLC is durable. With a median treatment duration among responders of 10.1 months, the median DOR among the 32 subjects with a confirmed CR

or PR identified through BICR assessment was 11.1 months (95% CI: 6.90, NE), with the response ongoing for 65% (13/20) of responders having a DOR of ≥6 months at the time of the clinical cutoff.

The clinical activity (demonstrated by the CBR) together with the durability of this activity contributed to the median PFS of 8.28 months (BICR assessment) and the OS of 22.77 months observed for the primary efficacy population. The demonstrated durability of response seen with amivantamab corroborates the clinical relevance of amivantamab as an effective targeted treatment option in this difficult-to-treat population for which limited viable therapies are available. Moreover, efficacy results for 3 supportive Exon 20ins NSCLC subject groups remained consistent with those observed in the primary efficacy population, providing further evidence of the activity seen for amivantamab.

The FDA's Assessment:

FDA agrees with the Applicant's description of DOR as assessed by BICR. FDA considers time-to-event endpoints to be uninterpretable in a single arm study; therefore, statistical analyses of PFS and OS were considered descriptive and were not verified.

Dose/Dose Response

Data:

The RP2D for amivantamab was established based on the totality of PK, PD, safety, and efficacy data obtained in the dose escalation (Part 1) and dose expansion (Part 2) phases of Study EDI1001. Pharmacokinetic and PD data, including population PK and E-R analyses, are described and summarized in Sections 6.2.2.1., 6.3.2.1. and 6.3.2.2.

While exposure in subjects treated at the higher non-RP2D dose was shown to be ~30% to 40% higher than that observed for the population dosed at the RP2D, the increased exposure observed with non-RP2D did not lead to a proportional increase in response (among subjects dosed with 1400 mg: ORR of 42.3% at Non-RP2D [<80 kg, n=26] vs 47.6% at RP2D [≥80 kg, n=21]). *[Source: Mod2.7.3/Sec4]*

The Applicant's Position:

The exposure-efficacy analyses confirmed the PK equivalency of 1050 mg and 1400 mg dosing in subjects weighing <80 kg and ≥80 kg, respectively, and demonstrated a favorable therapeutic efficacy at the current amivantamab RP2D regimen (ie, 1050 mg for body weight <80 kg and 1400 mg for body weight ≥80 kg, once weekly for Cycle 1 and every 2 weeks beginning at Cycle 2 for 28-day cycles).

The FDA's Assessment:

Please refer to FDA's assessment comments in Section 6.3.2

Durability of Response

Data and Applicant's Position:

See discussion of DOR above under Secondary and other relevant endpoints.

The FDA's Assessment:

FDA agrees.

Persistence of Effect

Data and Applicant's Position:

As with all anti-cancer therapies treating advanced or metastatic disease, subjects in Study EDI1001 received amivantamab therapy until there was loss of clinical benefit as assessed clinically or by radiographic evaluation.

The FDA's Assessment:

See discussion of DOR above under Secondary and other relevant endpoints.

Efficacy Results – Secondary or exploratory COA (PRO) endpoints

Data and Applicant's Position:

Due to the limited time period that patient-reported outcome (PRO) assessments were included as part of the EDI1001 evaluations prior to the clinical cutoff for the BLA, the data from these assessments are not sufficiently mature for informing the efficacy of amivantamab at this time.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Additional Analyses Conducted on the Individual Trial

Data and Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees.

8.1.3. Integrated Review of Effectiveness

Data and Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees.

8.1.4. Assessment of Efficacy Across Trials

Data and Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees.

8.1.5. Integrated Assessment of Effectiveness

Data:

As patients with EGFR Exon 20ins NSCLC have been relatively understudied, the natural history, treatment patterns, and outcomes for these patients have not been well characterized. In addition, a direct comparison of outcomes in patients with Exon 20ins mutations and those with as common EGFR (cEGFR) mutations (Exon-19 deletions or L858R substitutions) utilizing real-world data sources has not yet been performed. Therefore, the BLA contains results of RWD evaluations and analyses to further elucidate the prognosis, commonly utilized treatment regimens, and associated outcomes in the subset of patients with EGFR Exon 20ins mutation NSCLC. This included:

- The protocol-driven, retrospective cohort Study NSC1002 conducted in adult patients ≥18 years with a diagnosis of advanced NSCLC between 01 January 2011 and 31 May 2020 using the Advanced NSCLC Flatiron Core Registry EHR-derived deidentified database (a nationwide longitudinal, demographically and geographically diverse database with data from more than 280 cancer clinics including more than 2.4 million US cancer patients).
- Evaluation of 5 different RWD datasets to provide insights on commonly used regimens in second-line settings in EGFR Exon 20ins mutation NSCLC, and to specifically evaluate the use of ramucirumab-docetaxel (approved for second-line treatment in NSCLC) in this population.

[Source: These analyses are described in detail in a report contained in Mod5.3.5.4, Evaluation of the Unmet Needs and Treatment Patterns, and are summarized in Module 2.5, Section 6]

Data from these real-world sources highlight the unmet medical need of Exon 20ins patients with NSCLC who have progressed following first-line platinum-based chemotherapy. Moreover, these data provide a context for assessment of the clinical benefit of amivantamab monotherapy in the patient population seen in open-label Study EDI1001 presented in the BLA. The key findings from these Applicant-conducted evaluations were:

- Direct comparison of TKI efficacy in the Exon 20ins and cEGFR NSCLC populations showed a clear difference in efficacy, with a significantly reduced median real-world (rw)PFS in the Exon 20ins population.
- Patients with Exon 20ins NSCLC had a shorter median survival than those with cEGFR mutations, and a significantly increased risk of death compared with those with cEGFR mutations.
- No clear standard of care for Exon 20ins NSCLC after first-line therapy failure exists, with relatively equal utilization of chemotherapy, TKI therapy, and immunotherapy in the second-line setting.
- Second-line treatment outcomes (after front-line platinum-based chemotherapy) are poor, with a median overall rwPFS estimate of <4 months.
- The ramucirumab and docetaxel combination is not widely utilized in the second-line treatment of EGFR mutated NSCLC as evidenced by multiple real-world datasets.

The Applicant's Position:

Amivantamab is a first-in-class, low-fucose, human IgG1-based EGFR-MET bispecific antibody with a novel mechanism of action that enables simultaneous inhibition of EGFR and MET driver mutations, and recruitment of immune cells for antitumor activity. This mechanism of action, which relies on binding to the wild-type extracellular domain of each receptor, enables amivantamab to inhibit EGFR and MET pathway signaling independent of the nature of activating and/or resistance mutations. Based on early clinical activity observed during the dose escalation phase of Study EDI1001, the protocol was amended to allow exploration of amivantamab monotherapy activity across 4 separate NSCLC populations whose disease is characterized by either EGFR and/or MET activating mutations, but for whom there is recognized unmet medical need. Among these populations, unmet need is greatest for those patients with EGFR Exon 20ins NSCLC, as there is currently no approved TKI therapy demonstrated to be effective for this population. The unmet need in the EGFR Exon 20ins NSCLC population was illustrated by the RWD analyses provided in the BLA showing a lack of effective targeted therapies and no clear standard of care for this patient group. Data presented in the literature show low ORRs (10% to 15%) and a median PFS of <4 months for second-line treatment options in EGFR-mutated NSCLC, and the Applicant's RWD analyses support these findings. Moreover, data for the combination of ramucirumab and docetaxel (approved for use in second-line treatment of NSCLC) show a median PFS of 4.5 months overall and an ORR of <20% for patients with adenocarcinoma (see Section 2.2).

In this clinical context, the observed efficacy of amivantamab from Study EDI1001 demonstrates that amivantamab meets an urgent unmet medical need by providing robust and durable anti-tumor responses in subjects with Exon 20ins NSCLC whose disease had progressed on or after platinum based chemotherapy.

With a median follow-up of 9.7 months, amivantamab monotherapy was associated with a confirmed ORR of 39.5% based on blinded independent adjudicated review and a median DOR of 11.1 months in this patient population. Additional subjects in the primary efficacy population experienced prolonged disease control, reflected in a CBR of 74.1%, leading to an estimated median PFS of 8.3 months. The treatment effect of amivantamab was observed across all clinically relevant subgroups and, consistent with its mechanism of action, anti-tumor activity was observed across all tumor Exon 20ins mutation variants treated.

Thus, it is the Applicant's position that the current efficacy and safety data from Study EDI1001 demonstrate that amivantamab, if approved, would provide a significant improvement over available therapies for patients with metastatic NSCLC with EGFR Exon 20ins mutation whose disease has progressed on or after platinum-based chemotherapy.

The FDA's Assessment:

Given limitations of the RWD submitted by the Applicant, the findings are not conclusive. While there may be no clear standard of care or patients with NSCLC harboring EGFR exon 20 insertion mutations, current treatment option for these patients whose disease has progressed following platinum-based chemotherapy are the same therapies as those used for patients with NSCLC without a specific driver mutation-identified as discussed in section 2.2 of this review. FDA agrees that this is a patient population with unmet medical need given outcomes with currently available therapy. FDA agrees the results from Study EDI1001 show preliminary evidence of clinically meaningful and durable antitumor response with amivantamab in patients with advanced NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

Progression-free survival results are not interpretable in a single-arm study, and FDA considers clinical benefit rate exploratory endpoints. Therefore, these endpoints did not influence our regulatory decision.

8.2. Review of Safety

8.2.1. Safety Review Approach

Applicant's Position:

The safety profile for amivantamab monotherapy comes from data from ongoing Phase 1 Study EDI1001 through a clinical cutoff date of 08 June 2020. *[Source: Module 2.7.4]*

The primary safety population consists of 114 subjects with Exon 20ins NSCLC who had been previously treated with platinum-based chemotherapy and received at least 1 dose of

amivantamab at the RP2D (Exon 20ins + prior chemotherapy at RP2D safety population). This population is a subset of the total safety database (All Treated safety population) of 362 subjects who received at least 1 amivantamab monotherapy dose (at any dose) in Study EDI1001 by the clinical cutoff. The discussion of safety findings in this document centers on those for these 2 populations. Safety information in the proposed USPI for amivantamab also reflects these populations.

Safety data from 258 subjects (irrespective of mutation status or prior chemotherapy) who received at least 1 dose of amivantamab monotherapy at the RP2D (All Treated at RP2D) is presented in the BLA and in the tables presented in this document. This population is inclusive of the 114 subjects in the Exon 20ins + prior chemotherapy at RP2D primary safety population, and is also a subset of the All Treated safety population. The overall TEAE and safety profile of amivantamab monotherapy for the Exon 20ins + prior chemotherapy at RP2D safety population was consistent with those observed for the All Treated and All Treated at RP2D populations.

See Figure 20 for a graphic depiction of the safety populations for Study EDI1001.

At the BLA Format & Content meeting on 22 July 2020, FDA indicated that the proposed safety populations may allow for a substantive review of a BLA to support the proposed indication for amivantamab. The proposed safety populations were described in detail in the briefing document provided in advance of the pre-BLA meeting.

Safety was evaluated through AE monitoring, clinical laboratory tests, vital sign measurements, 12-lead electrocardiograms (ECGs), and physical examinations. A targeted evaluation that involved analysis of all relevant safety information was performed for IRRs as well as for events consistent with the mechanism of action of amivantamab in inhibiting of EGFR and MET pathways, including rash (grouped term), ILD/pneumonitis, peripheral edema (grouped term), paronychia, diarrhea, and eye disorders (including keratitis). Known laboratory changes associated with EGFR and MET signaling (serum albumin and hepatic transaminases) were also evaluated.

The FDA's Assessment:

FDA's clinical safety assessment of amivantamab is based on data from the ongoing clinical trial, Study 61186372EDI1001 (CHRYSALIS). FDA's analyses and assessment of safety are based on data from the 120-day safety update in which the Applicant included data for the following safety analysis populations: the primary safety population of 129 patients with NSCLC with EGFR exon 20 insertion mutations previously treated with platinum-based chemotherapy who received at least one dose of amivantamab at the recommended doses (1050 mg for patient body weight <80kg; 1400 mg for patient body weight ≥80kg); 302 patients (irrespective of mutation status or prior chemotherapy) who received at least one dose of amivantamab as a single agent at the recommended doses; and 411 patients (irrespective of mutation status or dose) who received at least one dose of amivanatamb as a single agent. The data cutoff (October 8, 2020) for the 120-

day safety update provides 4 additional months of follow-up for patients who were included in the initial data cutoff (June 8, 2020) for safety analyses in the initial BLA submission.

The safety population used to inform the Warnings and Precautions section (Section 5) of the USPI comprises 302 patients treated with amivantamab as a single agent at the recommended dose of amivantamab (1050 mg for baseline body weight<80kg; 1400 mg for baseline body weight ≥80kg IV) once weekly for the first 4weeks , then every two weeks, thereafter. These 302 patients include the 258 patients described in the Applicant's position above plus an additional 44 patients with a clinical cutoff date of October 8, 2020 that was provided in the Applicant's 120-day safety update.

The population used to inform the Adverse Reactions section (Section 6) of the USPI is based on 129 patients with NSCLC with EGFR exon 20 insertion mutations previously treated with prior chemotherapy who received ≥1 dose of amivantamab at the recommended dose.

The FDA analyses and assessment are based on the Applicant's 120-day safety update unless otherwise noted. The Applicant's additional analyses in the All treated patients (n=411) are not included in labeling and were not verified by the FDA.

The FDA Grouped Terms (GT) used in this review are listed below:

Abdominal Pain (GT) includes: Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, and Epigastric discomfort.
Cough (GT) includes: Cough, Productive cough, and Upper-airway cough syndrome.
Diarrhea (GT) includes: Colitis, and Diarrhea.
Dizziness (GT) includes: Dizziness, Dizziness exertional, Dizziness postural, and Vertigo.
Dyspnea (GT) includes: Dyspnea, and Dyspnea exertional.
Edema (GT) includes: Eye edema, Eyelid edema, Face edema, Generalised edema, Lip edema, Localised edema, edema, and edema peripheral, and Periorbital edema.
Fatigue (GT) includes: Asthenia, and Fatigue.
Headache (GT) includes: Headache, Migraine, and Migraine with aura.
Hemorrhage (GT) includes: Epistaxis, Gingival bleeding, Hematuria, Hemoptysis, Hemorrhage, Mouth hemorrhage, and Mucosal hemorrhage.
Hypotension (GT) includes: Hypotension, and Orthostatic hypotension.
Musculoskeletal Pain (GT) includes: Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, and Spinal pain.
Neuropathy Peripheral (GT) includes: Hypoaesthesia, Neuralgia, Neuropathy peripheral, Paraesthesia, Peripheral motor neuropathy, and Peripheral sensory neuropathy.
Pneumonia (GT) includes: Atypical pneumonia, Lower respiratory tract infection, Pneumonia, Pneumonia aspiration, and pulmonary sepsis.

Rash (GT) includes: Acne, Dermatitis, Dermatitis acneiform, Eczema, Eczema asteatotic, Erythema multiforme, Palmar-plantar erythrodysaesthesia syndrome, Perineal rash, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin exfoliation, and Toxic epidermal necrolysis.

Stomatitis (GT) includes: Aphthous ulcer, Cheilitis, Glossitis, Mouth ulceration, Mucosal inflammation, Pharyngeal inflammation, and Stomatitis.

The FDA safety review included review and analysis of the clinical study report (CSR), the Applicant's risk:benefit assessment, case report forms, selected narratives, the integrated summary of safety (ISS), the summary of clinical safety (SCS), and the primary datasets submitted by the Applicant. The reviewers analyzed key safety datasets using several safety analysis queries and MedDRA-based Adverse Events Diagnostics tool. Subgroup analyses were performed as necessary to further characterize the safety profile of amivantamab and additional analyses were performed for specific safety issues.

8.2.2. Review of the Safety Database

Data:

The median duration of study treatment for the 114 subjects in the Exon 20ins + prior chemotherapy at RP2D safety population was 3.7 months and the median number of treatment cycles per subject was 5 (maximum, 27). The maximum duration of treatment was 23.9 months, and 29 subjects (25.4%) were exposed to amivantamab for at least 6 months. The majority of the 114 subjects treated with the RP2D in this safety population (92 subjects, 80.7%) had a body weight of <80 kg (ie, received the 1050 mg dose); 22 subjects (19.3%) had a body weight ≥80 kg (ie, treated at the 1400 mg dose) *[Source: Mod2.7.4/Tab 3; Mod5.3.5.2/61186372EDI1001/AttTSIDEM01-E20PCS-DL]* As discussed in Section 8.2.8, the safety profile for amivantamab did not differ as a function of body weight/dose.

Exposure was similar for the All Treated (N=362) safety population (of which the primary safety population of 114 subjects is a subset). The median duration of treatment among all 362 treated subjects was 3.7 months (maximum, 29.7), the median number of treatment cycles was 5 (maximum, 33), and 29.0% (n=105) had been treated for ≥6 months. Among the 362 subjects in this safety population, 258 were treated with the amivantamab RP2D regimen; non-RP2D amivantamab doses received in the remaining 104 subjects were 140 mg (n=3), 350 mg (n=3), 700 mg (n=17), 1050 mg (body weight ≥80 kg; n=5), 1400 mg (body weight <80 kg; n=70), and 1750 (n=6).

The median follow-up (through the 08 June 2020 clinical cutoff) was 5.1 months (maximum, 29.27) and 6.6 months (maximum, 33.61) for the Exon 20ins + prior chemotherapy at RP2D and All Treated populations, respectively. *[Source: Mod5.3.5.2/61185372EDI1001/AttTSIDUR01]*

The Applicant's Position:

The safety experience of 114 subjects in the target indication population of Exon 20ins NSCLC patients (with prior platinum-based chemotherapy treated at RP2D), together with data from 362 subjects treated with any dose of amivantamab, is sufficient to allow adequate characterization of the safety profile of amivantamab.

The FDA's Assessment:

The following results were provided in the Applicant's 120 safety day update. The median follow-up for the **All Treated at RP2D population (n=302)** was 7.6 months, and the median follow-up for the **Exon 20ins + prior chemotherapy at RP2D population (n=129)** was 7.9 months.

All Treated at RP2D (n=302): The median duration of treatment was 4.2 months, with a maximum of 33.8 months. The median number of treatment cycles was 5, and the maximum number of cycles was 36; 36% of patients were still on study treatment; 36% had been treated for 6 months or longer and the median relative dose intensity was 100%.

Exon 20ins + prior chemotherapy at RP2D (n=129): The median duration of treatment increased by approximately 2 months to 5.6 months, with a maximum of 23.9 months. The median number of treatment cycles was 7, and the maximum number of cycles was 27. The median number of cycles of treatment increased slightly as of the new cut off, from 5 cycles to 7 cycles and 44% of this population were still on study treatment. In addition, 44% had been treated for 6 months or longer. The median relative dose intensity in the Exon 20ins + prior chemotherapy population was 100%

FDA agrees with the Applicant's position that the overall exposure duration was sufficient to assess the safety of amivanatamab. Results are presented below for the safety populations assessed by FDA.

FDA - Table 19: Summary of exposure, safety population

Exposure	Analysis population	
	E20 ins mutations prior chemotherapy N = 129 n (%)	**RP2D N = 302 n (%)**
Cumulative Actual Trt Dose - JNJ-61186372 (mg) (DSCMJJA)		
Mean (SD)	17053.1 (12139.1)	15824.9 (13163.9)
Median (Range)	14700 (70–58800)	12170.2 (37.8–76650)
Cumulative Planned Trt Dose - JNJ-61186372 (mg) (DSCMJJP)		
Mean (SD)	17086.4 (12128.5)	15910.6 (13152.1)
Median (Range)	14700 (350–58800)	12600 (350–76650)

Exposure	Analysis population	
	E20 ins mutations prior chemotherapy N = 129 n (%)	**RP2D N = 302 n (%)**
Max No. of JNJ-61186372 Treatment Cycles (MAXCYCL)		
Mean (SD)	7.4 (5.3)	6.9 (6.1)
Median (Range)	7 (1–27)	5 (1–36)
Total JNJ-61186372 Admins Received (TNMDSJJ)		
Mean (SD)	15.6 (10.4)	14.7 (12.1)
Median (Range)	14 (1–52)	12 (1–73)
Relative Dose Intensity JNJ-61186372 (%) (TRTCPJJ)		
Mean (SD)	99.1 (7.1)	97.8 (10.1)
Median (Range)	100 (20–100)	100 (10.8–100)
Treatment duration (months)		
≥ 6 months	57 (44.2)	108 (35.8)
≥ 12 months	15 (11.6)	36 (11.9)

Source: adsl.xpt, adexsum.xpt

Relevant characteristics of the safety population

Data:

Demographic and baseline lung cancer characteristics for the 114 subjects comprising the Exon 20ins + prior chemotherapy at RP2D primary safety population were typical of the intended patient population, ie, subjects with locally advanced or metastatic NSCLC with EGFR Exon 20ins after platinum-based chemotherapy (Table 19 and Table 20).

Furthermore, demographic and baseline lung cancer characteristics of the larger All Treated safety population were consistent with those for the primary safety population.

Table 20: Summary of Demographics and Baseline Characteristics; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Age, years			
N	114	258	362
Mean (SD)	61.7 (9.99)	61.8 (10.62)	61.9 (10.92)
Median	62.0	62.5	63.0
Range	(36; 84)	(32; 87)	(32; 87)
<65	67 (58.8%)	155 (60.1%)	215 (59.4%)
>=65	47 (41.2%)	103 (39.9%)	147 (40.6%)
<75	105 (92.1%)	229 (88.8%)	319 (88.1%)
>=75	9 (7.9%)	29 (11.2%)	43 (11.9%)
Sex			
Female	70 (61.4%)	159 (61.6%)	227 (62.7%)
Male	44 (38.6%)	99 (38.4%)	135 (37.3%)
Race			
Asian	59 (51.8%)	152 (58.9%)	217 (59.9%)
Black or African American	3 (2.6%)	8 (3.1%)	10 (2.8%)
White	42 (36.8%)	81 (31.4%)	115 (31.8%)
Not reported	10 (8.8%)	17 (6.6%)	20 (5.5%)
Weight, kg			
N	114	258	362
Mean (SD)	64.82 (15.841)	64.16 (16.536)	63.04 (15.395)
Median	62.05	60.30	59.90
Range	(35.4; 115.0)	(35.4; 140.3)	(35.4; 140.3)

RP2D (recommended Phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Note: N's for each parameter reflect non-missing values.

Source: Mod2.7.4/Tab4

Table 21: Summary of Lung Cancer Baseline Clinical Disease Characteristics; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D + Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Initial diagnosis NSCLC subtype			
Adenocarcinoma	109 (95.6%)	250 (96.9%)	351 (97.0%)
Large cell carcinoma	0	0	0
Squamous cell carcinoma	3 (2.6%)	5 (1.9%)	8 (2.2%)
Other	2 (1.8%)	3 (1.2%)	3 (0.8%)
Cancer stage at initial diagnosis			
0	0	0	1 (0.3%)
IA	7 (6.1%)	10 (3.9%)	14 (3.9%)
IB	1 (0.9%)	10 (3.9%)	13 (3.6%)
IIA	2 (1.8%)	2 (0.8%)	5 (1.4%)
IIB	4 (3.5%)	6 (2.3%)	11 (3.0%)
IIIA	6 (5.3%)	13 (5.0%)	20 (5.5%)
IIIB	4 (3.5%)	8 (3.1%)	13 (3.6%)
IV	90 (78.9%)	209 (81.0%)	285 (78.7%)
Location of metastasis [a]			
Bone	50 (43.9%)	111 (43.0%)	154 (42.5%)
Liver	12 (10.5%)	44 (17.1%)	61 (16.9%)
Brain	29 (25.4%)	66 (25.6%)	93 (25.7%)
Lymph Node	62 (54.4%)	143 (55.4%)	195 (53.9%)
Adrenal Gland	6 (5.3%)	19 (7.4%)	28 (7.7%)
Other	62 (54.4%)	130 (50.4%)	188 (51.9%)
Time from initial diagnosis of cancer to first dose (months)			
N	114	258	362
Mean (SD)	22.332 (19.9695)	31.884 (31.2176)	34.044 (31.1529)
Median	17.478	23.934	25.265
Range	(1.45; 130.10)	(0.89; 172.68)	(0.89; 172.68)
Number of prior lines of therapy			
N	114	258	362
Mean (SD)	2.1 (1.31)	2.3 (1.86)	2.5 (2.01)
Median	2.0	2.0	2.0
Range	(1; 7)	(0; 14)	(0; 14)
ECOG performance status			
0	33 (28.9%)	72 (27.9%)	97 (26.8%)
1	80 (70.2%)	185 (71.7%)	264 (72.9%)
2	1 (0.9%)	1 (0.4%)	1 (0.3%)
History of smoking			
Yes	49 (43.0%)	104 (40.3%)	141 (39.0%)
No	65 (57.0%)	154 (59.7%)	221 (61.0%)

RP2D (recommended Phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: NSCLC = non-small cell lung cancer, ECOG = Eastern Cooperative Oncology Group
[a] Subjects can be counted in more than one category.

Source: Mod2.7.4/Tab5

The Applicant's Position:

Overall, subjects enrolled into Study EDI1001 had demographic and baseline disease characteristics representative of subjects with advanced, pre-treated EGFR-mutated metastatic NSCLC (see also Section 8.1.2), with a median of 2 prior lines of therapy, including chemotherapy, and the majority of subjects reported as having an ECOG performance status of 1 (70.2%). These characteristics were generally consistent across safety populations for Study EDI1001.

The FDA's Assessment:

FDA agrees with the Applicant's position in general but notes the high proportion of Asian patients and the low proportion of Black or African American patients enrolled in the clinical trial. See FDA's Assessment in Section 8.1.2 following the Applicant's presentation of Other Baseline Characteristics for details.

At the time of the Applicant's 120-day safety update, 49 additional patients had enrolled in the clinical trial since the June 8, 2020 clinical cutoff date. The demographic and baseline disease characteristics remained consistent at the updated cut off date of October 8, 2020. Demographic characteristics of the updated safety populations are presented in the table below, along with proportion of patients with weight <80 kg and ≥80 kg (given differential dosing based on weight).

FDA - Table 22: Demographic Characteristics, Safety population

	RP2D	
	Exon 20 Ins Prior Chemotherapy	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	129	302
Age, years		
Median	62	62
Range	(36, 84)	(32, 87)
Pooled Age Group 1 (AGEGR1)		
<65	76 (59%)	183 (61%)
>=65	53 (41%)	119 (39%)
Pooled Age Group 2 (AGEGR2)		
<75	118 (91%)	268 (89%)
>=75	11 (9%)	34 (11%)
Sex (SEX)		
Female	79 (61%)	189 (63%)
Male	50 (39%)	113 (37%)
Race (RACE)		
Asian	71 (55)	180 (60%)
White	45 (35%)	94 (31%)
Black or African American	3 (2.3%)	9 (3%)
*	10 (8%)	19 (6%)
Weight, kg		
<80 kg	106 (82%)	255 (84%)
>= 80 kg	23 (18%)	47 (16%)

Source: adsl.xpt
* Values are blank.

Among the 129 patients with EGFR exon 20 insertion mutations who were previously treated with platinum-based chemotherapy (n=129), 100% had metastatic disease at study entry.

Adequacy of the safety database

Data and Applicant's Position:

The safety database of all subjects treated with amivantamab monotherapy at any dose in Study EDI1001 as of the clinical cutoff of 08 June 2020 (N=362), which includes 114 subjects with Exon 20ins NSCLC who had progressed on or after platinum chemotherapy and were treated with the amivantamab RP2D regimen proposed for clinical use, is considered by the Applicant to be adequate to assess the safety of amivantamab monotherapy in the treatment of subjects with advanced NSCLC, to provide guidance regarding management of toxicities, and for an assessment of the benefit-risk profile of amivantamab in the target population. In addition, the number of subjects treated (N=362) allows for characterization of less common toxicities associated with EGFR therapy, including pneumonitis.

The FDA's Assessment:

FDA agrees with the Applicant's position regarding the adequacy of the safety database with the caveat that the safety database evaluated by FDA consisted of 129 amivantamab-treated patients with NSCLC with EGFR exon 20 insertion mutations previously treated with platinum-based chemotherapy and the safety population of 302 patients treated at the recommended doses of amivantamab.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Data:

The study centers/clinical sites for Study EDI1001 were monitored by clinical research associates following study-specific monitoring plans for consistency. The data were reviewed by the Applicant's Data Management personnel in accordance with the prespecified Data Management Plan. The Applicant assigned physicians responsible for conducting an ongoing clinical review. All available data as of the clinical cutoff date were included in the safety assessment presented in the BLA.

See also Section 8.1.2, Data Quality and Integrity, for information related to data integrity/quality related to COVID-19 pandemic. As related to safety assessments, there were no issues related to the timelines for AE reporting and central review of safety data through the clinical cutoff demonstrated no meaningful changes in the AE rate after the emergence of the COVID-19 pandemic. *[Mod5.3.5.2/61186372EDI1001/Sec3.10.1]*

The Applicant's Position:

There were no issues regarding data quality identified by the Applicant; thus the Applicant does not anticipate any issues with the safety review or the quality of the overall submission that would affect the FDA's ability to perform the review.

The FDA's Assessment:

FDA agrees with the Applicant's position. The data submitted was organized and adequate to perform a complete review of the safety of amivantamab. Overall, FDA agrees that there were no significant data quality or reporting issues identified during the review of this BLA. FDA did issue several information requests during the review cycle to obtain clarification and additional information regarding safety data included in the BLA.

Categorization of Adverse Events

Data:

All AEs whether serious or non-serious, were reported from the time a signed and dated informed consent form was obtained until 30 days after the last dose of study treatment, until the subject withdrew consent for study participation, or until the subject started subsequent anti-cancer therapy, whichever occurred first. Subjects who discontinued the study drug due to drug-related

toxicity were to be continually monitored for this toxicity until the toxicity resolved to Grade ≤1 or baseline, stabilized, or was deemed irreversible, the subject died, or subsequent anti-cancer therapy was started, whichever occurred first. Adverse events occurring >30 days following the last dose of study drug (and their resolution) were also to be reported if the investigator considered them related to study drug.

Toxicity in Study EDI1001 was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. All AEs were coded using Medical Dictionary of Regulatory Activities (MedDRA), Version 23.0, to ensure consistency. The AE summaries (frequency counts and percentages) were presented by system organ class (SOC) and/or preferred term, and by maximum grades, except where otherwise noted. Subjects with multiple episodes were counted only once per event.

For all reported AEs, the investigator provided his/her opinion regarding the relationship of the event to study treatment in accord with definitions provided in the protocol (not related, doubtful, possible, probable, very likely).

Summaries of reported AEs in the BLA are based on TEAEs, defined as those with an onset after start of the first study drug through 30 days after the last study drug (or the day prior to start of subsequent therapy, whichever was earlier) or that worsened after the first dose of study drug.

Adverse events of clinical importance were selected based on the expected safety profile of amivantamab which took into account the safety profile of other compounds known to affect EGFR or MET signaling pathways.

Information on all deaths occurring at any time during the study, including the Treatment and Follow-up periods, was collected and analyzed.

As agreed with FDA via the 22 July 2020 Type B Format and Content Meeting, subject narratives are provided for the following AEs occurring in EDI1001: deaths within 30 days of the last dose of study treatment, discontinuation of study drug due to an AE(s), serious AEs, AEs of clinical importance as follows: Grade 3 or 4 IRRs, Grade 3 or 4 rash (grouped term), Grade 3 or 4 peripheral edema (grouped term), and any grade ILD (grouped term). These narratives are provided as an attachment to the CSR.

The Applicant's Position:

The recording, coding, and categorization of AEs for Study EDI1001 is considered by the Applicant to be reasonable and appropriate, and is consistent with typical clinical development practices for oncology agents.

The FDA's Assessment:

FDA agrees with the Applicant's position. For purposes of the FDA review of safety, incidences of adverse events were analyzed without consideration of relatedness, given the safety data supporting this BLA is from a nonrandomized, non-comparative study.

Routine Clinical Tests

Data:

In addition to monitoring for AEs, safety evaluations in Study EDI1001 included clinical laboratory data (hematology, clinical chemistry), vital signs (temperature, pulse rate, blood pressure, respiratory rate, pulse oximetry), 12-lead ECGs, and physical examinations. The schedule of evaluations for these safety measures is presented in Table 13~~Table 114~~. Hematology and clinical chemistry data were from local laboratories, and laboratory data were classified into CTC grades according to the NCI CTCAE v4.03 (where applicable).

For hematology and clinical chemistry parameters, changes from baseline by visit, the worst on-treatment toxicity grade, and shifts from baseline to worst value on study (from treatment start to 30 days after last dose or the start of subsequent anti-cancer therapy, whichever was later) were analyzed.

The Applicant's Position:

The assessment methods and time points for collection and analysis of safety measures other than AEs were appropriate for the disease and indication investigated in the Study EDI1001.

The FDA's Assessment:

FDA agrees with the Applicant's position and that the Applicant's schedule of assessments in Study 61186372EDI1001 was adequate to monitor and assess the safety of amivantamab.

8.2.4. Safety Results

Deaths

Data:

Overall survival is a secondary efficacy endpoint in Study EDI1001, and survival data continues to be collected on all subjects including after discontinuation of amivantamab. In all cases of subject death, regardless of timing, the cause of death was separately reported. For all deaths that occurred during the Treatment Period (up through 30 days after last dose), specific information regarding the cause of death was required to be reported as a Grade 5 TEAE. Thus, subject deaths due to progressive disease, if occurring on treatment or within 30 days of the last dose, were also separately reported as an AE having an outcome of death, per protocol.

Table 22 presents a summary of deaths that occurred at any time during the study (including within 30 days of the last dose of study drug) through the 08 June 2020 clinical cutoff. Table 23 summarizes the TEAEs with an outcome of death (Grade 5).

Table 23: Summary of Deaths During Study; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Deaths during study	16 (14.0%)	65 (25.2%)	93 (25.7%)
Progressive disease	11 (9.6%)	52 (20.2%)	74 (20.4%)
Adverse event	4 (3.5%)	9 (3.5%)	11 (3.0%)
Other	1 (0.9%)	4 (1.6%)	8 (2.2%)
Deaths during treatment	8 (7.0%)	14 (5.4%)	17 (4.7%)
Adverse event	4 (3.5%)	7 (2.7%)	9 (2.5%)
Progressive disease	4 (3.5%)	7 (2.7%)	7 (1.9%)
Other	0	0	1 (0.3%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Note: Deaths during treatment are presented for subjects who died within 30 days of last study drug dose.

Source: Mod2.7.4/Tab13

Table 24: Number of Subjects With Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Subjects with 1 or more AEs leading to Death	8 (7.0%)	13 (5.0%)[a]	16 (4.4%)
System organ class			
Preferred term			
Infections and infestations	3 (2.6%)	6 (2.3%)	7 (1.9%)
Pneumonia	1 (0.9%)	3 (1.2%)	4 (1.1%)
Adenovirus infection	1 (0.9%)	1 (0.4%)	1 (0.3%)
Pulmonary sepsis	1 (0.9%)	1 (0.4%)	1 (0.3%)
Sepsis	0	1 (0.4%)	1 (0.3%)
Respiratory, thoracic and mediastinal disorders	3 (2.6%)	5 (1.9%)	6 (1.7%)
Respiratory failure	1 (0.9%)	3 (1.2%)	4 (1.1%)
Dyspnoea	2 (1.8%)	2 (0.8%)	2 (0.6%)
Cardiac disorders	1 (0.9%)	1 (0.4%)	2 (0.6%)
Cardio-respiratory distress	1 (0.9%)	1 (0.4%)	1 (0.3%)
Cardiac arrest	0	0	1 (0.3%)
General disorders and administration site conditions	1 (0.9%)	1 (0.4%)	1 (0.3%)
Sudden death	1 (0.9%)	1 (0.4%)	1 (0.3%)

Table 24: Number of Subjects With Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event
Note: AEs leading to death are based on AE outcome of Fatal. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 23.0.
[a] For 1 subject who died due to progressive disease within 30 days of last dose, the death was not reported as a Grade 5 TEAE.

Source: Mod2.7.4/Tab14

Progressive disease was the most common cause of death across the safety populations analyzed.

No death in any of the safety populations was reported as related to amivantamab monotherapy by the investigator. Infections and respiratory events were the most common TEAEs leading to death in all safety populations.

The Applicant's Position:

TEAEs leading to death were infrequent in all safety populations, and were typical of a predominantly elderly population with underlying malignancy and comorbidities. There were no amivantamab-related deaths in either the primary safety population of 114 Exon 20ins subjects treated at the RP2D who had progressed on or after prior platinum-based chemotherapy or in the expanded clinical experience of 362 subjects treated with any dose of amivantamab.

The FDA's Assessment:

In the Applicant's 120-day update (data cutoff of October 8, 2020), the Applicant indicated that for the **All Treated (n=411) population**, there were 4 new Grade 5 events reported between the June 8, 2020 and October 8, 2020 data cut-off for patients who died within 30 days of the last dose of amivantamab, for a total of 20 patients (4.9%) with a Grade 5 TEAE (Table 24). These 4 new events were reported as pneumonia (2 events), atypical pneumonia (1 event), and pneumonia aspiration (1 event), which were all reported as unrelated to amivantamab.

In the **All Treated at RP2D (n=302)**: All 4 new Grade 5 events occurring in the interim safety period were reported in patients in this safety population.

- Subject (b) (6): For 1 subject in the All Treated at RP2D population whose death due to progressive disease occurred within 30 days of the last dose of amivantamab, a Grade 5 AE was not reported by the investigator. This subject had an ongoing event of facial paralysis (Grade 1) due to leptomeningeal metastasis at the time of death. For this reason, the number of patients with Grade 5 TEAEs is fewer than the number of deaths on treatment for the All Treated at RP2D and All Treated populations. This information was reported in the SCS submitted with the initial BLA submission.

Exon 20ins + prior chemotherapy at RP2D (n=129): One new Grade 5 event occurred within this population (pneumonia aspiration).

Table 25: Number of Subjects With Treatment-Emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D+ Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	129	302	411
Subjects with 1 or more AEs leading to Death	9 (7.0%)	17 (5.6%)	20 (4.9%)
System organ class Preferred term			
Infections and infestations	3 (2.3%)	9 (3.0%)	10 (2.4%)
Pneumonia	1 (0.8%)	5 (1.7%)	6 (1.5%)
Adenovirus infection	1 (0.8%)	1 (0.3%)	1 (0.2%)
Atypical pneumonia	0	1 (0.3%)	1 (0.2%)
Pulmonary sepsis	1 (0.8%)	1 (0.3%)	1 (0.2%)
Sepsis	0	1 (0.3%)	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	4(3.1%)	6 (2.0%)	7 (1.7%)
Respiratory failure	1 (0.8%)	3 (1.0%)	4 (1.0%)
Dyspnoea	2 (1.6%)	2 (0.7%)	2 (0.5%)
Pneumonia aspiration	1 (0.8%)	1 (0.3%)	1 (0.2%)
Cardiac disorders	1 (0.8%)	1 (0.3%)	2 (0.5%)
Cardio-respiratory distress	1 (0.8%)	1 (0.3%)	1 (0.2%)
Cardiac arrest	0	0	1 (0.2%)
General disorders and administration site conditions	3 (2.6%)	1 (0.3%)	1 (0.2%)
Sudden death	1 (0.8%)	1 (0.3%)	1 (0.2%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event
Note: AEs leading to death are based on AE outcome of Fatal. Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 23.0.
[TSFAE02F.RTF] [JNJ-61186372\EDI1001\DBR_120D_E20INS\RE_120D_E20INS\PROD\TSFAE20F.SAS] 12DEC2020, 16:48
Source: Attachment TSFAE02F

FDA - Table 26: Causes of Death in Safety Population in clinical trial 61186372EDI1001

	Analysis population	
	E20 ins mutations prior chemotherapy	**RP2D**
	N = 129 n (%)	**N=302 n(%)**
Total Deaths	27 (21)	86 (28)
Progressive disease	20 (16)	67 (22)
Adverse event	5 (3.9)	13 (4.3)
Other	2 (1.6)	6 (2)
Within 30 days after last dose	9 (7)	18 (6)
Post 30 days of last dose	18 (14)	68 (23)

Source: adsl.xpt

In the safety population (n=302) there were 6 patients with "other" noted as cause of death in the above table. All six deaths occurred more than 30 days after last dose of amivantamab. In two patients (b) (6) the cause of death is unknown, two patients (b) (6) (b) (6) cause of death reported as suicide, one patient (b) (6) died due to massive hemoptysis, and one patient (b) (6) died of pneumonitis related to subsequent chemotherapy.

Patient narratives for deaths were reviewed in detail and narratives for deaths due to adverse events are summarized below. In Section 6 of USPI, which presents safety data for the indicated patient population (n=129), pneumonia (n=2) and sudden death (n=1) will be listed as fatal adverse reactions since based on the FDA review of the narratives, the possible contribution of amivantamab to the fatal event of pneumonia cannot be ruled out (see details below).

The FDA - Table 26 below provides a listing of the deaths due to AE occurring within 30 days of the last amivanatamab dose that FDA considers appropriate for inclusion in labeling as fatal adverse reactions. Summaries of the most relevant information from the narratives for these events are provided below the table.

FDA - Table 27: Original BLA and 120-Day Update: Death due to AE within 30 Days of Last Amivantamab Dose

Patient ID	Total days of treatment	Study day of death	Days from last dose to death	Primary cause of death	Original BLA or 120 Day Update
(b) (6)	685	700	16	Pneumonia	Original
	226	235	10	Pulmonary sepsis	Original
	99	110	12	Sudden death	Original

Death due to AEs are any AE tox grade (AETOXGRN)=5, AEs with an outcome (AEOUT) = fatal or death with no corresponding tox grade =5, and AE ends in death (AESDTH)=Y within 30 days of last dose of drug (may include AEs that begin within 30 days within last dose of drug and become fatal shortly after e.g. AE starts 25 days after last dose of study drug and becomes fatal 32 days after last dose of study drug).
Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AEOUT.

Pneumonia

- Patient (b) (6): A 57 year old female patient with NSCLC with metastasis to lung. Patient received a total of 25 cycles of amivantamab and on Day 541, disease progression was reported. Patient continued with amivantamab therapy.

  On Day 694, patient complained of dyspnea and symptoms worsened on D698 and patient went to the ER. X-ray showed severe pneumonia and serious adverse event of grade 3 pneumonia was reported.

  Day 699, patient was moved to another hospital with an ICU and treated with piperacillin/tazobactam. Amivantamab therapy was interrupted due to pneumonia.

  On Day 700, patient died due to worsening of pneumonia (serious adverse event of grade 5) and disease progression.

Reviewer comments: The cause of death was reported as pneumonia, and the possible contribution of amivantamab to the fatal event of pneumonia cannot be ruled out.

Pulmonary sepsis

- Patient (b) (6): A 73 year old female patient with NSCLC with metastasis to bone and lymph node. Day 226 grade 1 dyspnea and worsening of thoracic pain was reported. On Day 232 serious adverse event grade 3 respiratory tract infection and patient hospitalized with symptoms of dyspnea, bronchospasm, productive cough, and impaired general status. Blood tests showed increased leukocytosis. Treatment with oxygen therapy and broad spectrum antibiotics (unspecified) did not improve with treatment. Day 235 patient died due to serious adverse event grade 5 pulmonary sepsis. Last dose of amivantamab received was reported on Day 226.

Reviewer comments: FDA considers pulmonary sepsis under the pneumonia (GT). The possible contribution of amivantamab to the fatal event of pulmonary sepsis cannot be ruled out.

Sudden death

- Patient (b) (6): A 53 year old female patient with NSCLC with metastasis to pleura and peritoneum. Day 110 patient started feeling bad during dining, 30 minutes later she lost consciousness and died. Grade 5 serious adverse event of sudden death was reported. The last dose of amivantamab received was Day 99.

Reviewer comments: As cause of death is unknown, the possible contribution of amivantamab to this death cannot be ruled out..

The table below provides a listing of the deaths due to AE occurring within 30 days of last amivanatamab dose that FDA considered unlikely to be related to amivantamab. Summaries of the most relevant information from the narratives for these events are provided below the table.

FDA - Table 28: Original BLA and 120-Day Update: Death due to AE within 30 Days of Last Amivantamab Dose					
Patient ID	Total days of treatment	Study day of death	Days from last dose to death	Primary cause of death	Original BLA or 120 Day Update
(b) (6)	57	60	4	Cardio-respiratory distress	Original
	254	263	10	Dyspnea	Original
	7	20	14	Pneumonia	Original
	423	450	28	Pneumonia	120 Day Update
	15	32	18	Pneumonia	Original
	226	248	23	Pneumonia	120 Day Update
	22	25	4	Pneumonia aspiration	120 Day Update
	15	37	23	Dyspnea	Original
	23	53	31	Respiratory failure	Original
	23	46	24	Respiratory failure	Original
	15	33	19	Respiratory failure	Original
	2	7	6	Adenovirus infection	Original
	8	28	21	Sepsis	Original
	42	64	23	Atypical pneumonia	120 Day Update

Death due to AEs are any AE tox grade (AETOXGRN)=5, AEs with an outcome (AEOUT) = fatal or death with no corresponding tox grade =5, and AE ends in death (AESDTH)=Y within 30 days of last dose of drug (may include AEs that begin within 30 days within last dose of drug and become fatal shortly after e.g. AE starts 25 days after last dose of study drug and becomes fatal 32 days after last dose of study drug).
Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AEOUT.

Cardio-respiratory distress

- Patient (b) (6): A 74 year old female patient with NSCLC with metastasis to the bone and brain. On December26, 2019, CT scan showed appearance of alveolar consolidation in the anterolateral segment of the left lower lobe, with air bronchogram, broad pleural base which could suggest a superimposed infectious process; equivocal progression of the diffuse military nodular pulmonary lesions, with blurred outlines today and ground-glass patches on the periphery. On Day 60, serious adverse event of grade 5 cardio-respiratory distress was reported and patient was managed by EMS. Patient had generalized cyanosis and non-invasive ventilation was attempted during transport. Patient died on same day. The last dose of amivantamab was received on Day 57.

Dyspnea

- Patient (b) (6): A 48 year old female patient with NSCLC with metastasis to the lymph node. On Day 98 asthenia was reported and on Day 241 serious adverse event of grade 2 dyspnea reported. On Day 254, patient was admitted to the hospital for administrative reason and received amivantamab therapy along with 4 to 6 liters of oxygen therapy. On Day 259, patient was transferred to another hospital closer to her home for continuous oxygen therapy and on Day 263, patient died due to grade 5 worsening of dyspnea. Due to privacy regulations, other details regarding the patient's death was not available. The last dose of amivantamab was received on Day 254.

- Patient (b) (6): A 45 year old female patient with NSCLC with metastasis to bone, liver, brain, and lymph node. On Day 8, patient was hospitalized with serious adverse event of grade 2 muscular weakness (both leg motor weakness) without pain. MRI with contrast showed bone

metastasis in cervicothoracic spines, pathological compression fracture in C7 and C5; myelopathy at T5 level with suspicious epidural extension of metastasis and indeterminate clinically significant lesions in T11 and L3.

On Day 17, patient underwent thoracic laminectomy and screw fixation. Patient was treated with dexamethasone for muscular weakness and oxycodone, granisetron, tramadol, pregabalin, and paracetamol for musculoskeletal pain. After surgery, patient complained of dyspnea and tachycardia. On the same day, a serious adverse event of grade 3 pleural effusion was reported and chest x-ray revealed right pleural effusion had increased.

On Day 18, pigtail catheter insertion performed with 1000 cc drainage and symptoms improved.

On Day 24, disease progression was reported and amivantamab treatment was permanently discontinued on Day 25 due to disease progression confirmed by CT scan. The last dose of amivantamab the patient received was on Day 15.

Pneumonia

- Patient (b) (6): A 76 year old female patient with NSCLC with metastasis to brain. On Day 12, serious adverse event of grade 3 pneumonia reported and patient was hospitalized with symptom of worsened dyspnea. Chest CT scan showed newly developed multifocal patchy ground glass opacity in left lung, probably pneumonia, remarkable changes in extent of right perihilar peribronchovascular infiltration in the right lungs were noted. Impression was pneumonia in the left lung, neutrophil count 21.10x10^3/µL, neutrophil percentage 93.9%, WBC 22.48x10^3/µL, sputum culture showed normal respiratory tract microbiota and UA negative but showed WBC 1+ and epithelial 3+. Patient treated with antibotics, oxygen, and methylprednisolone for pneumonia. On Day 13, lab test results neutrophil count 24.08 x10^3/µL; neutrophil percentage 96.2%, WBC 25.03 x10^3/µL and negative acid fast bacillus culture and viral PCR test. Chest x-ray showed aggravation of pulmonary edema. On Day 14, patient refused further treatment and on Day 20 patient died of grade 5 pneumonia. The last dose of amivantamab patient received was on Day 7.

- Patient (b) (6): A 78 year old male patient with NSCLC with metastasis to lymph node and other (pleural effusion). On Day 56, grade 1 dermatitis acneiform reported and on Day 72, the dermatitis acneiform worsened. Patient was treated with antibiotics, topical steroid, and methylprednisolone and dermatitis acneiform improved on grade 1 on Day 87.

On Day 428, serious adverse event of grade 3 femoral neck fracture reported and patient hospitalized. On Day 434, patient underwent percutaneous catheter drainage (right) insertion due to pleural effusion. On Day 440, grade 2 pneumonia, grade 2 pneumothorax and grade 2 pulmonary edema reported. On Day 442, chest x-ray results showed newly developed pneumothorax (right), lung cancer in the right lower lung, right malignant effusion and pulmonary metastases in both the lungs. On Day 450, patient's oxygen saturation was 85.8, partial pressure of carbon dioxide was 156.8, partial pressure of oxygen was 81.7, and pH was 6.977. Grade 5 pneumonia reported and patient died. The last dose of amivantamab received by patient was on Day 423.

- Patient (b) (6): A 71 year old male patient with NSCLC with meastatic pleural effusion. OnDay-13 grade 3 pneumonia reported and treated with meropenem and on Day 1 pneumonia reported as grade 1 and resolved on Day 3. This patient is a protocol violation and did not meet exclusionary criteria of infection On Day 21, serious adverse event of grade 4 pneumonia reported and patient's symptoms included fever (a day prior) and dyspnea. On Day 22, grade 1 pulmonary embolism reported and patient was hospitalized. Chest CT scan confirmed pneumonia and showed right lung haziness aggravation with malignant pleural effusion; increased extent of diffuse consolidation in left lingual, left lower lobe and diffuse ground-glass opacification/opacity (GGO) in right upper and right lower lobe; patchy consolidation in right middle lobe, right lower lobe; multiple tiny ill-defined nodules in both lungs; left pleural effusion with diffuse pleural thickening, a focal filing defect in left lower pulmonary artery. Chest x-ray showed aggravated states of haziness in right middle lung field and RLLF (right lower lung field; and left pleural effusion. Sputum culture for bacteria and gram stain showed many gram-positive rods, few yeast, white blood cells 25, and epithelial cells 1-2. On Day 22, clinical progression of disease reported. The Day 26 lab values lymphocytes 5.8%, high WBC (13.36x103/µL), sputum culture: WBC above 25. On Day 32, grade 5 pneumonia reported and patient had low lymphocytes and high WBC (31.06x103/µL) and patient died. The last dose of amivantamab patient received was on Day 15.

- Patient (b) (6): A 83 year old female patient with NSCLC with metastasis to pleural nodule. On Day 16, grade 1 pneumothorax reported and resolved on Day 83. On Day 43, grade 2 pneumonia reported and resolved on Day 51.

On Day 141, grade 2 dyspnea reported and on Day 142 grade 2 pleural effusion reported and confirmed by chest CT scan. Clinical and radiological disease progression reported. On Day 143, patient hospitalized and serious adverse event of grade 3 pleural effusion reported. Percutaneous catheter placed to facilitate drainage of the pleural effusion. On Day 149, pleurodesis performed for pleural effusion and cytology test of the pleural fluids confirmed metastatic carcinoma. On Day 232, grade 2 pneumothorax and serious adverse event of grade 3 pneumonia reported and patient was hospitalized. Chest CT showed suspected pneumonia. Chlamydia pneumoniae IgM test was negative, while the IgG test was positive. On Day 232 to Day 245, percutaneous catheter drainage for pleural effusion. On Day 233, sputum culture showed rare yeast, few gram positive/negative rods and few gram-positive cocci. On Day 237, CT pulmonary angiography for deep vein thrombosis, reported as G2 and treated with anticoagulant. On Day 242 oxygen saturation was 80-83%. On Day 248, grade 5 pneumonia reported and patient died. The last dose of amivantamab patient received was on Day 226.

Pneumonia aspiration

- Patient (b) (6): A 58 year old female patient with NSCLC with metastasis to the pleura. On Day 10, grade 1 pyrexia reported and patient was treated with vancomycin and piperacillin/tazobactam. Amivantamab treatment was interrupted and restarted on Day 22. The patient's leukocyte values were within normal range on Days 15 and 22. On Day 23, a serious adverse event of grade 4 pneumonia aspiration was reported; the patient's body temperature was more than 38^{o}C and drop in oxygen saturation, hypotension and tachycardia. Treatment

included ceftriaxone and metronidazole. On Day 25, pneumonia aspiration worsened (grade 5) and the patient died. The last dose of amivantamab received was Day 22.

Respiratory Failure

- Patient (b) (6): A 50 year old female patient with NSCLC with metastasis to bone, liver, bilateral military lung nodularity (likely peritoneal) and bilateral retina. On Day 7, grade 2 pleural effusion reported and on Day 11, grade 2 pneumothorax reported and chest drainage performed. On Day 13, serious adverse event of grade 2 dyspnea reported and patient was hospitalized the next day. CT pulmonary angiogram showed hydropneumothorax, no pulmonary embolism, and ground glass shadowing, possibly secondary to infection or disease related. On Day 15, repeat chest x-ray showed persisting pneumothorax, related to the disease. On Day 18 grade 1 pyrexia reported due to chest infection. On Day 26, serious adverse event of grade 3 hypoxia reported and patient hospitalized. CT scan of chest/abdomen/pelvis showed changes suggesting lymphangitis, bilateral pleural effusions, and extensive lung nodularity. Patient treated with antibiotics and dexamethasone and discharged from hospital on Day 27. On Day 52, patient died due to serious adverse event of grade 5 respiratory failure and disease progression. The last dose of amivantamab patient received was on Day 23.

- Patient (b) (6): A 56 year old female patient with NSCLC with metastasis to brain. On Day 9, serious adverse event of grade 2 dehydration reported and patient hospitalized. Patient mentioned dysphagia with liquids and solids for the past 1 to 2 weeks; patient also reported generalized weakness, lightheadedness with positional changes and weight loss. On Day 15, patient had placement of percutaneous gastrostomy tube. On Day 25, serious adverse event of grade 3 pneumonia aspiration reported and on Day 29, disease progression was reported. On Day 46, serious adverse event of grade 5 respiratory failure reported and the patient died due to progressive disease and respiratory failure. The last dose of amivantamab patient received was on Day 23.

- Patient (b) (6): A 67 year old female patient with NSCLC with metastasis to lungs. On Day 15, grade 2 pneumonia aspiration reported; chest CT showed number of innumerable pulmonary nodules throughout the lungs consistent with pulmonary metastatic disease, stable malignant right pleural effusion, patchy area of consolidation within the right lower lobe, slightly worse compared to prior exam, concerning for a combination of atelectasis versus aspiration pneumonia. Patient was treated with oxygen and antibotics. On Day 18, grade 3 hypoxia reported; patient complaints of dyspnea over the past week and fever of 38C were noted. Patient also tachypneic and required higher oxygen requirements to 15L non-rebreather. In ER, patient was positive for productive cough, SOB, fatigue, and weakness. Chest x-ray showed diffuse nodular opacities consistent with metastatic disease along with areas of consolidation in the right middle lobe, and small right malignant pleural effusion. On Day 19, disease progression reported and grade 3 respiratory failure and grade 3 pulmonary embolism reported. Chest x-ray showed no pneumothorax, volume loss on right consistent with right lower lobectomy, diffuse nodular opacities were consistent with diffuse metastatic disease, areas of consolidation in the right middle lobed represented areas of atelectasis/aspiration and a small right malignant pleural

effusion. CT scan showed filling defect in the left upper lobe pulmonary artery at table position -206 and -208 with surrounding ground glass seen on lung windows, that represented a tiny subsegmental pulmonary embolism, interval development of ground glass in the lingula which could represent sequela of developing infarct, stable malignant right pleural effusion with unchanged nodules throughout both lungs consistent with known metastatic disease, consolidation in the lung bases "may be secondary" to metastatic disease with superimposed aspiration or pneumonia in the appropriate clinical setting. On Day 21, a peripheral catheter was placed. Amivantamab therapy interrupted and patient treated with anticoagulants for pulmonary embolism, antibiotics, and methylprednisolone for respiratory failure.

On Day 26, pneumonia aspiration resolved and on Day 31, patient was discharged to home hospice in poor condition with 10 to 15 liters oxygen requirement. On Day 31 disease progression noted. The last dose of amivantamab patient received was on Day 15.

Adenovirus infection

- Patient (b) (6): A 65 year old male patient NSCLC with with metastasis to bone and brain. On Day 6, patient had asthenia and episode of hypotension; patient hospitalized due to hypotension accompanied by tachycardia and low oxygen saturation at 50%. Specific CT results showed pneumonia, mild amount of bilateral pleural fluid, lung parenchyma and cystic image stability, diffuse parenchymal involvement in both hemithorax, with areas of increased density in ground glad and presence of consolidation foci, all compatible with infection. PCR was positive for adenovirus and negative for coronavirus and grade 3 serious adverse event of adenovirus infection was reported. On Day 7,serious adverse event of grade 5 adenovirus infection worsened and patient died. The last dose of amivantamab patient received was on Day 2.

Sepsis

- Patient (b) (6): A 78 year old male patient with NSCLC with metastasis to bone, liver, brain and adrenal gland. On Day 14, serious adverse event of grade 4 pneumonia and grade 4 sepsis and patient was hospitalized. Chest CT scan showed a slight increase in the size of mass in right lower lung and increase in size of multiple small nodules in both lungs; progressive disease and atypical pneumonia were ruled out. Diffuse ground glass opacities in both lungs, a small right pleural effusion, and pulmonary emphysema in both lungs. Chest x-ray showed mass-like consolidation in right lower lung field, ground glass opacity and nodular infiltration in both lungs.

C-reactive protein 16.52 mg/dl, WBC 15290x10^3/µL, absolute neutrophil count 11.16x10^3/µL, negative acid fast stain, no presence of Mycoplasma pneumonaie, Chlamydia pneumoniae, Legionella pneumoniae, Bordetella pertussis, or Bordetella parapertussis; negative urine smear gram stain; negative Streptococcus pneumonia; smear gram stain of transtracheal aspirate showed white blood cell 1 to 2, epithelial cell 0 to 1, grade 6 (acceptable), no bacteria; culture stain of transtracheal aspirate showed normal flora; urine culture showed no growth; and viral polymerase chain reaction test was positive for Flu A-H3 (count: 38.58). Patient treated with antibiotics and methylprednisolone, and with other therapies.

On Day 21, blood culture revealed gram positive cocci, Staphylococcus aureus and Staphylococcus epidermidis, methicillin resistant Staphylococcus Aureus (MRSA). On Day 28, serious adverse event of grade 5 sepsis worsened and patient died due to the events of pneumonia and sepsis. The last dose of amivantamab patient received was on Day 8.

Atypical Pneumonia

- Patient (b) (6): A 48 year old female patient with NSCLC with metastasis to the bone. On Day 47, CT scan of chest showed interval development of the left upper and bilateral lower lobe central and peripheral ground-glass opacities. On Day 49, serious adverse event of grade 3 atypical pneumonia and grade 3 hypoxia were reported and patient was hospitalized. Patient was febrile with oxygen saturation of 76% on exertion and 88% on rest in room air. On an unspecified date, Mycoplasma pneumoniae was found to be positive. On Day 49, chest CT with IV contrast showed pulmonary embolism, new hazy ground glass density throughout the mid/upper left lung, presumed pneumonitis, and patchy areas of dense consolidation in lower lungs suspicious for multifocal bilateral pneumonia. Chest x-ray findings were suggestive of multilobar pneumonia/pneumonitis, and the hazy/ground glass opacities were thought to perhaps represent asymmetric pulmonary edema, hemorrhage, or drug toxicity; COVID-19 tests were negative. On Day 50, 1,3-beta-d-glucan test was positive and a sputum culture with Gram stain test on the same day showed evidence of Candidiasis. Patient treated with antibiotics for atypical pneumonia, and methylprednisolone, levosalbutamol and dexamethasone for hypoxia. On Day 56, serious adverse event of grade 4 atypical pneumonia worsened and patient was transferred to ICU. On Day 56, patient was intubated and next day, sputum culture showed presence of few gran-positive cocci. On Day 64, serious adverse event of grade 5 atypical pneumonia worsened and patient died. The last dose of amivantamab patient received was on Day 42.

Serious Adverse Events

Data:

Serious TEAEs (including fatal events) by MedDRA SOC and preferred term (reported at a frequency of ≥1% in the All Treated population) are summarized for the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations in Table 28.

Table 29: Number of Subjects With Treatment-emergent Serious Adverse Events of at Least 1% in the All Treated Population by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D+ Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Subjects with 1 or more SAEs	34 (29.8%)	79 (30.6%)	102 (28.2%)
System organ class Preferred term			
Respiratory, thoracic and mediastinal disorders	9 (7.9%)	24 (9.3%)	31 (8.6%)
Dyspnoea	2 (1.8%)	9 (3.5%)	11 (3.0%)
Pulmonary embolism	3 (2.6%)	5 (1.9%)	5 (1.4%)
Pleural effusion	2 (1.8%)	3 (1.2%)	4 (1.1%)
Pneumothorax	0	3 (1.2%)	4 (1.1%)
Respiratory failure	1 (0.9%)	3 (1.2%)	4 (1.1%)
Pneumonitis	1 (0.9%)	2 (0.8%)	4 (1.1%)
Infections and infestations	8 (7.0%)	19 (7.4%)	22 (6.1%)
Pneumonia	1 (0.9%)	9 (3.5%)	12 (3.3%)
Musculoskeletal and connective tissue disorders	6 (5.3%)	10 (3.9%)	13 (3.6%)
Back pain	3 (2.6%)	5 (1.9%)	6 (1.7%)
Injury, poisoning and procedural complications	3 (2.6%)	6 (2.3%)	9 (2.5%)
Infusion related reaction	2 (1.8%)	4 (1.6%)	6 (1.7%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: SAE = serious adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 23.0.

Source: Mod5.3.5.2/61186372EDI1001/AttTSFAE04A

In the Exon 20ins + prior chemotherapy at RP2D safety population (N=114), *[Source: Mod2.7.4/Sec2.1.3.1]*

- Most serious TEAEs occurred in 1 or 2 subjects each.
- The only serious TEAEs reported in >2 subjects each were assessed as unrelated by the investigator (back pain and pulmonary embolism).
- There were no Grade 4 serious TEAEs.
- Serious TEAEs assessed as related to amivantamab by the investigator were reported in 10 subjects (8.8%). These events included IRR and diarrhea, both reported in 2 subjects each (1.8%), and single reports each of cellulitis, infected dermal cyst, ILD, pneumonitis, atrial flutter, rash, and toxic epidermal necrolysis.

The frequency of serious TEAEs (total and considered related to study drug [5.5%]) in the All Treated safety population (N=362) was consistent with those reported for the Exon 20ins + prior chemotherapy at RP2D safety population. Infusion-related reactions (6 subjects, 1.7%), pneumonitis (3 subjects, 0.8%), and diarrhea (2 subjects, 0.6%) were the only serious TEAEs assessed as related by the investigator that were reported in 2 or more subjects in the All Treated safety population.

The Applicant's Position:

While serious TEAEs occurred in approximately 30% of subjects in the Exon 20ins + prior chemotherapy and All Treated safety populations, there was no clear safety pattern regarding serious events. The majority of individual serious TEAEs occurred with less than 2% frequency and the types of serious TEAEs were consistent across the populations. The most frequent serious TEAEs in the All Treated safety population were dyspnea (3.0%) and pneumonia (3.3%), which are considered consistent with the underlying disease.

The FDA's Assessment:

In the Applicant's 120 day update (data cutoff of October 8, 2020), the Applicant provided the table below (Table 29).

Table 30: TSFAE04A Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	129	302	411
Subjects with 1 or more SAEs	39 (30.2%)	93 (30.8%)	121 (29.4%)
System organ class Preferred term			
Respiratory, thoracic and mediastinal disorders	14 (10.9%)	30 (9.9%)	39 (9.5%)
Dyspnoea	3 (2.3%)	10 (3.3%)	14 (3.4%)
Pulmonary embolism	4 (3.1%)	6 (2.0%)	6 (1.5%)
Pleural effusion	2 (1.6%)	4 (1.3%)	6 (1.5%)
Pneumonitis	3 (2.3%)	4 (1.3%)	6 (1.5%)
Pneumothorax	1 (0.8%)	4 (1.3%)	5 (1.2%)
Respiratory failure	1 (0.8%)	3 (1.0%)	4 (1.0%)
Pneumonia aspiration	1 (0.8%)	2 (0.7%)	2 (0.5%)
Pulmonary oedema	1 (0.8%)	2 (0.7%)	2 (0.5%)
Chronic obstructive pulmonary disease	0	1 (0.3%)	1 (0.2%)
Hypoxia	0	1 (0.3%)	1 (0.2%)
Interstitial lung disease	1 (0.8%)	1 (0.3%)	1 (0.2%)
Haemoptysis	0	0	1 (0.2%)
Infections and infestations	9 (7.0%)	24 (7.9%)	27 (6.6%)
Pneumonia	2 (1.6%)	13 (4.3%)	16 (3.9%)
Respiratory tract infection	2 (1.6%)	3 (1.0%)	3 (0.7%)
Cellulitis	2 (1.6%)	2 (0.7%)	2 (0.5%)
Sepsis	1 (0.8%)	2 (0.7%)	2 (0.5%)

	RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	129	302	411
Adenovirus infection	1 (0.8%)	1 (0.3%)	1 (0.2%)
Atypical pneumonia	0	1 (0.3%)	1 (0.2%)
Device related infection	1 (0.8%)	1 (0.3%)	1 (0.2%)
Impetigo	0	1 (0.3%)	1 (0.2%)
Infected dermal cyst	1 (0.8%)	1 (0.3%)	1 (0.2%)
Kidney infection	0	1 (0.3%)	1 (0.2%)
Lymph gland infection	0	1 (0.3%)	1 (0.2%)
Pulmonary sepsis	1 (0.8%)	1 (0.3%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	7 (5.4%)	12 (4.0%)	16 (3.9%)
Back pain	3 (2.3%)	5 (1.7%)	6 (1.5%)
Muscular weakness	3 (2.3%)	3 (1.0%)	4 (1.0%)
Arthralgia	1 (0.8%)	2 (0.7%)	4 (1.0%)
Myalgia	0	1 (0.3%)	1 (0.2%)
Neck pain	0	1 (0.3%)	1 (0.2%)
Pain in extremity	0	0	1 (0.2%)
Injury, poisoning and procedural complications	5 (3.9%)	9 (3.0%)	12 (2.9%)
Infusion related reaction	2 (1.6%)	4 (1.3%)	6 (1.5%)
Thoracic vertebral fracture	2 (1.6%)	2 (0.7%)	2 (0.5%)
Ankle fracture	0	1 (0.3%)	1 (0.2%)
Femoral neck fracture	0	1 (0.3%)	1 (0.2%)
Spinal compression fracture	1 (0.8%)	1 (0.3%)	2 (0.5%)
Cardiac disorders	4 (3.1%)	7 (2.3%)	9 (2.2%)
Atrial fibrillation	1 (0.8%)	2 (0.7%)	2 (0.5%)
Pericardial effusion	0	2 (0.7%)	3 (0.7%)
Acute coronary syndrome	1 (0.8%)	1 (0.3%)	1 (0.2%)
Atrial flutter	1 (0.8%)	1 (0.3%)	1 (0.2%)
Cardio-respiratory distress	1 (0.8%)	1 (0.3%)	1 (0.2%)
Cardiac arrest	0	0	1 (0.2%)
Gastrointestinal disorders	4 (3.1%)	7 (2.3%)	10 (2.4%)
Diarrhoea	2 (1.6%)	2 (0.7%)	2 (0.5%)
Abdominal pain	1 (0.8%)	1 (0.3%)	1 (0.2%)
Abdominal pain upper	0	1 (0.3%)	1 (0.2%)
Ascites	0	1 (0.3%)	1 (0.2%)
Ileus	1 (0.8%)	1 (0.3%)	1 (0.2%)
Mesenteric artery thrombosis	0	1 (0.3%)	1 (0.2%)
Gastritis	0	0	1 (0.2%)
Nausea	0	0	1 (0.2%)
Vomiting	0	0	2 (0.5%)
Nervous system disorders	1 (0.8%)	7 (2.3%)	13 (3.2%)
Headache	0	2 (0.7%)	2 (0.5%)
Ataxia	1 (0.8%)	1 (0.3%)	1 (0.2%)
Central nervous system haemorrhage	0	1 (0.3%)	1 (0.2%)
Cervicobrachial syndrome	0	1 (0.3%)	1 (0.2%)
Neuropathy peripheral	0	1 (0.3%)	1 (0.2%)
Peripheral sensory neuropathy	0	1 (0.3%)	1 (0.2%)
Brain oedema	0	0	1 (0.2%)
Cerebrovascular accident	0	0	1 (0.2%)
Depressed level of consciousness	0	0	1 (0.2%)
Seizure	0	0	2 (0.5%)
Spinal cord compression	0	0	1 (0.2%)

	RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	129	302	411
Psychiatric disorders	1 (0.8%)	4 (1.3%)	4 (1.0%)
Mental status changes	1 (0.8%)	2 (0.7%)	2 (0.5%)
Confusional state	0	1 (0.3%)	1 (0.2%)
Mental disorder	0	1 (0.3%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	3 (1.0%)	6 (1.5%)
Breast cancer	0	1 (0.3%)	1 (0.2%)
Metastases to central nervous system	0	1 (0.3%)	1 (0.2%)
Tumour pain	0	1 (0.3%)	2 (0.5%)
Basal cell carcinoma	0	0	1 (0.2%)
Neoplasm skin	0	0	1 (0.2%)
Skin and subcutaneous tissue disorders	2 (1.6%)	3 (1.0%)	3 (0.7%)
Rash	2 (1.6%)	2 (0.7%)	2 (0.5%)
Dermatitis acneiform	0	1 (0.3%)	1 (0.2%)
Toxic epidermal necrolysis	1 (0.8%)	1 (0.3%)	1 (0.2%)
Metabolism and nutrition disorders	0	2 (0.7%)	3 (0.7%)
Dehydration	0	1 (0.3%)	1 (0.2%)
Hypoglycaemia	0	1 (0.3%)	1 (0.2%)
Decreased appetite	0	0	1 (0.2%)
Renal and urinary disorders	1 (0.8%)	2 (0.7%)	2 (0.5%)
Renal vein thrombosis	1 (0.8%)	1 (0.3%)	1 (0.2%)
Ureterolithiasis	0	1 (0.3%)	1 (0.2%)
Vascular disorders	1 (0.8%)	2 (0.7%)	4 (1.0%)
Hypotension	0	1 (0.3%)	2 (0.5%)
Peripheral embolism	1 (0.8%)	1 (0.3%)	1 (0.2%)
Embolism	0	0	1 (0.2%)
General disorders and administration site conditions	1 (0.8%)	1 (0.3%)	5 (1.2%)
Sudden death	1 (0.8%)	1 (0.3%)	1 (0.2%)
Fatigue	0	0	2 (0.5%)
Gait disturbance	0	0	1 (0.2%)
Pain	0	0	1 (0.2%)
Hepatobiliary disorders	0	1 (0.3%)	1 (0.2%)
Cholelithiasis	0	1 (0.3%)	1 (0.2%)
Investigations	0	1 (0.3%)	1 (0.2%)
Alanine aminotransferase increased	0	1 (0.3%)	1 (0.2%)
Reproductive system and breast disorders	0	1 (0.3%)	1 (0.2%)
Pelvic pain	0	1 (0.3%)	1 (0.2%)
Eye disorders	0	0	1 (0.2%)
Vision blurred	0	0	1 (0.2%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: SAE = serious adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 23.0.

[TSFAE04A.RTF] [JNJ-61186372\EDI1001\DBR_120D_E20INS\RE_120D_E20INS\PROD\TSFAE04A.SAS] 14DEC2020, 16:54

The incidence and nature of SAEs occurring after the interim safety period was consistent with the safety profile reported in the BLA. There were 14 new SAE terms and 38 new events reported

during the safety follow up. Most serious TEAEs occurred with less than 2% frequency and the types of serious TEAEs were consistent across analysis populations. The all treated patients (n=411) had a similar safety profile when compared to the recommended dosages of amivantamab and the patients with exon 20 insertion mutations previously treated with platinum-based chemotherapy.

FDA completed additional analyses of serious events based on the Applicant's 120-day update and regardless of the assessment of relatedness to amivantamab. The table below presents the overall incidence of serious adverse events (SAE) and SAE occurring in ≥2% of patients.

FDA - Table 31: Serious Adverse Events occurring in ≥2% of patients

	Analysis population			
	E20 ins mutations prior chemotherapy N = 129		RP2D N = 302	
	Grade 1-5 (%)	Grade 3-4 (%)	Grade 1-5 (%)	Grade 3-4 (%)
Total patients with at least one SAE	30	14	31	18
Pulmonary embolism	3.1	2.3	2	1.7
Dyspnea (GT)	3.1	1.6	3.6	2.6
Pneumonitis (GT)	3.1	0.8	1.7	0.7
Musculoskeletal Pain (GT)	3.1	0	3	1.3
Muscular weakness	2.3	0.8	1	0.3
Pneumonia (GT)	2.3	0	5	2

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AESER.
Dyspnea (GT) includes: Dyspnea.
Musculoskeletal Pain (GT) includes: Arthralgia, Back pain, Myalgia, and Neck pain.
Pneumonia (GT) includes: Atypical pneumonia, Pneumonia, and Pneumonia aspiration.
Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.

FDA does not agree with the Applicant's statement "There were no Grade 4 serious TEAEs" as there was one grade 4 serious TEAE infusion-related reaction and one case of toxic epidermal necrolysis (TEN), which was reported as a grade 3 but should be classified grade 4 as there is no grade 3 for TEN in CTCAE v4.03.

Dropouts and/or Discontinuations Due to Adverse Effects

Data:

TEAEs leading to discontinuation of study drug are summarized by MedDRA SOC and preferred term for the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations in Table 31. For 5 subjects (4.4%) in the Exon 20ins + prior chemotherapy at RP2D safety population, the TEAEs leading to discontinuation were assessed by the investigator as related to study drug (IRR in 2 subjects [1.8%] and 1 subject each [0.9%] for dermatitis acneiform, toxic epidermal necrolysis, and paronychia). In the All Treated safety population, TEAEs leading to discontinuation assessed as related to study drug by the investigator were reported for 4.7% of subjects. [*Source: Mod2.7.4/Sec2.1.4.3.1*]

Table 32: Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Agent by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Subjects with 1 or more AEs leading to discontinuation of study agent	11 (9.6%)	17 (6.6%)	29 (8.0%)
System organ class Preferred term			
Infections and infestations	4 (3.5%)	7 (2.7%)	10 (2.8%)
Pneumonia	1 (0.9%)	3 (1.2%)	6 (1.7%)
Paronychia	1 (0.9%)	2 (0.8%)	2 (0.6%)
Adenovirus infection	1 (0.9%)	1 (0.4%)	1 (0.3%)
Pulmonary sepsis	1 (0.9%)	1 (0.4%)	1 (0.3%)
Respiratory tract infection	1 (0.9%)	1 (0.4%)	1 (0.3%)
Sepsis	0	1 (0.4%)	1 (0.3%)
Injury, poisoning and procedural complications	2 (1.8%)	4 (1.6%)	8 (2.2%)
Infusion related reaction	2 (1.8%)	4 (1.6%)	8 (2.2%)
Respiratory, thoracic and mediastinal disorders	2 (1.8%)	2 (0.8%)	3 (0.8%)
Pleural effusion	2 (1.8%)	2 (0.8%)	2 (0.6%)
Pneumonitis	0	0	1 (0.3%)
Skin and subcutaneous tissue disorders	2 (1.8%)	2 (0.8%)	2 (0.6%)
Dermatitis acneiform	1 (0.9%)	1 (0.4%)	1 (0.3%)
Toxic epidermal necrolysis	1 (0.9%)	1 (0.4%)	1 (0.3%)
Musculoskeletal and connective tissue disorders	1 (0.9%)	1 (0.4%)	3 (0.8%)
Muscular weakness	1 (0.9%)	1 (0.4%)	1 (0.3%)
Musculoskeletal chest pain	0	0	1 (0.3%)
Myalgia	0	0	1 (0.3%)
Nervous system disorders	0	1 (0.4%)	2 (0.6%)
Central nervous system haemorrhage	0	1 (0.4%)	1 (0.3%)

Table 32: Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Agent by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Akathisia	0	0	1 (0.3%)
Gastrointestinal disorders	0	0	1 (0.3%)
Stomatitis	0	0	1 (0.3%)
General disorders and administration site conditions	0	0	1 (0.3%)
Asthenia	0	0	1 (0.3%)
Vascular disorders	0	0	1 (0.3%)
Hypotension	0	0	1 (0.3%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 23.0.

Source: Mod2.7.4/Tab15

The Applicant's Position:

TEAEs leading to treatment discontinuation occurred at low rates of <10% across the safety populations, and the incidence of specific TEAEs leading to discontinuation were generally <1%.

The FDA's Assessment:

In the Applicant's 120-day update, the below table was provided.

The incidence and nature of TEAE leading to treatment discontinuation was consistent across the updated safety population and the BLA safety population in the initial BLA submission.

Table 33: TSFAE02E: Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Agent by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Analysis set: All treated in monotherapy (JNJ-61186372)	129	302	411
Subjects with 1 or more AEs leading to discontinuation of study agent	14 (10.9%)	22 (7.3%)	35 (8.5%)
System organ class			
Preferred term			
Infections and infestations	5 (3.9%)	9 (3.0%)	12 (2.9%)
Pneumonia	2 (1.6%)	4 (1.3%)	7 (1.7%)
Paronychia	1 (0.8%)	2 (0.7%)	2 (0.5%)
Sepsis	1 (0.8%)	2 (0.7%)	2 (0.5%)
Adenovirus infection	1 (0.8%)	1 (0.3%)	1 (0.2%)
Atypical pneumonia	0	1 (0.3%)	1 (0.2%)
Pulmonary sepsis	1 (0.8%)	1 (0.3%)	1 (0.2%)
Respiratory tract infection	1 (0.8%)	1 (0.3%)	1 (0.2%)

Table 33: TSFAE02E: Number of Subjects With Treatment-emergent Adverse Events Leading to Discontinuation of Study Agent by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated
	Exon 20 Ins Prior Chemotherapy	Total	(RP2D + Non-RP2D)
Analysis set: All treated in monotherapy (JNJ-61186372)	129	302	411
Respiratory, thoracic and mediastinal disorders	5 (3.9%)	6 (2.0%)	7 (1.7%)
Pneumonitis	2 (1.6%)	3 (1.0%)	4 (1.0%)
Pleural effusion	2 (1.6%)	2 (0.7%)	2 (0.5%)
Pneumonia aspiration	1 (0.8%)	1 (0.3%)	1 (0.2%)
Pulmonary embolism	1 (0.8%)	1 (0.3%)	1 (0.2%)
Injury, poisoning and procedural complications	3 (2.3%)	5 (1.7%)	9 (2.2%)
Infusion related reaction	2 (1.6%)	4 (1.3%)	8 (1.9%)
Skin laceration	1 (0.8%)	1 (0.3%)	1 (0.2%)
Skin and subcutaneous tissue disorders	2 (1.6%)	2 (0.7%)	2 (0.5%)
Dermatitis acneiform	1 (0.8%)	1 (0.3%)	1 (0.2%)
Toxic epidermal necrolysis	1 (0.8%)	1 (0.3%)	1 (0.2%)
Gastrointestinal disorders	1 (0.8%)	1 (0.3%)	2 (0.5%)
Stomatitis	1 (0.8%)	1 (0.3%)	2 (0.5%)
Musculoskeletal and connective tissue disorders	1 (0.8%)	1 (0.3%)	3 (0.7%)
Muscular weakness	1 (0.8%)	1 (0.3%)	1 (0.2%)
Musculoskeletal chest pain	0	0	1 (0.2%)
Myalgia	0	0	1 (0.2%)
Nervous system disorders	0	1 (0.3%)	3 (0.7%)
Central nervous system haemorrhage	0	1 (0.3%)	1 (0.2%)
Akathisia	0	0	1 (0.2%)
Spinal cord compression	0	0	1 (0.2%)
Eye disorders	0	0	1 (0.2%)
Vision blurred	0	0	1 (0.2%)
General disorders and administration site conditions	0	0	1 (0.2%)
Asthenia	0	0	1 (0.2%)
Vascular disorders	0	0	1 (0.2%)
Hypotension	0	0	1 (0.2%)

RP2D (recommended Phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 23.0.

[TSFAE02E.RTF] [JNJ-61186372\EDI1001\DBR_120D_E20INS\RE_120D_E20INS\PROD\TSFAE02E.SAS] 14DEC2020, 16:47
Source: Attachment TSFAE02E

The FDA's Assessment:

The table below presents the adverse reactions leading to amivantamab discontinuation in ≥1% of patients.

FDA - Table 34: **Adverse Events leading to treatment discontinuation in ≥1 %**

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Total patients with at least one AE leading to treatment discontinuation	14(11)	5 (3.9)	22 (7)	9 (3)
Pneumonia (GT)	3 (2.3)	0	6 (2)	1 (0.3)
Infusion related reaction	2 (1.6)	2 (1.6)	4 (1.3)	4 (1.3)
Dyspnea (GT)	2 (1.6)	1 (0.8)	2 (0.7)	1 (0.3)
Pleural effusion	2 (1.6)	1 (0.8)	2 (0.7)	1 (0.3)
Rash (GT)	2 (1.6)	1 (0.8)	2 (0.7)	1 (0.3)
Pneumonitis (GT)	2 (1.6)	1 (0.8)	2 (0.7)	1 (0.3)

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AEACN = 'DRUG WITHDRAWN'.
Note: Custom grouped terms are designated by '(GT)'.
Dyspnea (GT) includes: Dyspnea.
Pneumonia (GT) includes: Atypical pneumonia, Pneumonia, and Pneumonia aspiration.
Pneumonitis (GT) includes: Pneumonitis.
Rash (GT) includes: Dermatitis acneiform, and Toxic epidermal necrolysis.

The Applicant indicated “TEAEs leading to discontinuation were assessed by the investigator as related to study drug.” When assessing data from a single arm clinical trial, FDA considers treatment-emergent adverse events regardless of investigator or Applicant assessment of relatedness to study drug.

Dose Interruption/Reduction Due to Adverse Effects

Data:

Drug Interruption Due to Adverse Events

A total of 40 subjects (35.1%) in the Exon 20ins + prior chemotherapy at RP2D safety population had a TEAE (other than IRR) that had an action taken of "drug interrupted. Those TEAEs that led to dose interruption in more than 2 subjects in this population were dermatitis acneiform (4 subjects, 3.5% [all related]), asthenia (4 subjects, 3.5% [all unrelated]), pyrexia (3 subjects, 2.6% [all unrelated]), and diarrhea (3 subjects, 2.6% [related in 2 subjects]). The type and relative frequencies of TEAEs leading to drug interruption were consistent for the All Treated safety population (29.8% having TEAE resulting in drug interruption). *[Source: Mod2.7.4/Sec2.1.4.1.1]*

A total of 70 subjects (61.4%) in the Exon 20ins + prior chemotherapy at RP2D safety population had a TEAE that resulted in infusion modification (59.4% in All Treated safety population), with IRRs being the most frequent event leading to infusion modification. A discussion of IRRs, including the timing and management of IRRs by cycle, is provided in Section 8.2.6.

Dose Reduction

Fifteen subjects (13.2%) in the Exon 20ins + prior chemotherapy at RP2D safety population had a TEAE that resulted in a reduction of the amivantamab dose (all assessed by investigator as related), with those in the skin and subcutaneous tissue disorders SOC being the most commonly reported TEAEs with this action taken (11 subjects, 9.6%). Rash events and their management are discussed in more detail in Section 8.2.6. Other TEAEs leading to dose reduction in this population were paronychia, cellulitis, neutropenia, and pneumonitis (1 subject [0.9%] each). The type and relative frequencies of TEAEs leading to dose reduction were consistent for the All Treated safety population (overall rate of TEAEs leading to dose reduction, 11.9%). *[Source: Mod2.7.4/Sec2.1.4.1.1]*

The Applicant's Position:

As described in Section 8.1.1, the protocol for Study EDI1001 provided specific guidance on the modification of study drug infusion (including dose interruption and dose reduction) for the management of toxicity. Toxicity was effectively managed through these approaches, with low rates of treatment discontinuation due to TEAEs (<10% overall, <5% reported as related).

TEAEs that led to drug interruption occurred in 30% to 35% of subjects in each of the safety populations, while dose reduction due to TEAEs occurred in 10% to 13% of subjects. The median relative dose intensity for amivantamab in each of the safety populations was 100%, indicating that subjects generally received study treatment as planned. [*Source: (Mod5.3.5.2/61186372EDI1001/AttTSIEX02]*

Consistent with protocol guidance on the modification of study drug infusion (including dose interruption and dose reduction) for the management of toxicity (Section 8.1.1), skin and subcutaneous tissue disorders were the most common TEAEs leading to dose reduction in all

safety analysis populations. Discussions of treatment modification for rash TEAEs (grouped term) and modification of an ongoing infusion due to a TEAE (almost exclusively due to IRRs and predominantly occurring in the first infusion) are presented in Section 8.2.6.

The FDA's Assessment:

In the Applicant's 120-day update, the Applicant presented treatment-emergent AEs leading to drug interruption separately for IRR and for AEs other than IRR that had an action taken of "drug interrupted" and reflected either an interruption of an ongoing infusion or interruption of amivantamab administration (eg, skipped infusion).

For FDA's analyses below, which were used to inform labeling, assessment of both IRR and TEAE other than IRR were both evaluated, with additional analyses performed for adverse reactions commonly associated with infusion-related reactions to determine incidence of such events occurring outside of an IRR.

FDA - Table 35: Adverse events ≥ 5 % leading to treatment interruption

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Total patients with at least one AE leading to treatment interruption	100 (78)	25 (19)	232 (77)	61 (20)
Infusion related reaction	76 (59)	1 (0.8)	185 (61)	2 (0.7)
Dyspnea (GT)	27 (21)	1 (0.8)	67 (22)	1 (0.3)
Chills	24 (19)	0	69 (23)	0
Nausea	21 (16)	0	58 (19)	0
Flushing	20 (16)	0	47 (16)	0
Rash (GT)	15 (12)	3 (2.3)	29 (10)	7 (2.3)
Vomiting (GT)	14 (11)	0	35 (12)	0
Chest discomfort	13 (10)	0	33 (11)	0
Pyrexia (GT)	12 (9)	0	23 (8)	1 (0.3)
Hypotension (GT)	9 (7)	1 (0.8)	18 (6)	1 (0.3)
Fatigue (GT)	8 (6)	2 (1.6)	9 (3)	2 (0.7)
Diarrhea (GT)	7 (5)	3 (2.3)	7 (2.3)	3 (1)

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AEACN = 'DRUG INTERRUPTED'.
Note: Custom grouped terms are designated by '(GT)'.
Diarrhea (GT) includes: Diarrhea.
Dyspnea (GT) includes: Dyspnea.
Fatigue (GT) includes: Asthenia, and Fatigue.
Hypotension (GT) includes: Hypotension, and Orthostatic hypotension.
Pyrexia (GT) includes: Pyrexia.
Rash (GT) includes: Dermatitis acneiform, Rash, Rash erythematous, Rash maculo-papular, and Rash pustular.
Vomiting (GT) includes: Vomiting.

FDA evaluated adverse reactions commonly associated with IRR, including chills, pyrexia, hypotension, chest discomfort/chest pain, and flushing to determine the incidence of these adverse reactions outside of the setting of IRR. The below tables provide the results TEAEs and dose interruptions, which were used to inform product labeling. For other adverse reactions which might be associated with IRR but have a significant incidence outside of the setting of IRR (making distinction as part of IRR vs concurrent but separate AR more difficult to assess), such as nausea, vomiting, diarrhea, dyspnea, rash, and pruritis, the incidence used to inform labeling was based on overall incidence (i.e., not excluding events occurring concurrently with an IRR).

FDA - Table 36: Non-IRR* TEAEs occurring in ≥ 10% of safety population

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Any TEAE	30 (23)	2 (1.6)	61 (20)	4 (1.3)
General disorders and administration site conditions				
Pyrexia	17 (13)	0	29 (10)	0
Chills	3 (2.3)	0	8 (2.6)	0
Chest discomfort	2 (1.6)	0	6 (2)	0
Vascular disorders				
Hypotension	8 (6)	2 (1.6)	22 (7)	4 (1.3)
Flushing	5 (3.9)	0	8 (2.6)	0

* Non-IRR TEAEs identified with AEINFRCT = 'N'

FDA - Table 37: Non-IRR TEAEs leading to dose interruption

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 n (%)	Grade 3-5 n (%)	Grade 1-5 n (%)	Grade 3-5 n (%)
Any TEAE	5 (3.9)	0	5 (1.7)	0
Pyrexia	4 (3.1)	0	4 (1.3)	0
Flushing	1 (0.8)	0	1 (0.3)	0

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AEINFRCT, AEACN = 'DRUG INTERRUPTED', INFINFL = 'Y'

The following table lists the overall incidence of adverse reactions leading to dose reductions and adverse reactions leading to dose reduction in ≥ 2% of patients.

FDA - Table 38: Adverse events≥ 2 % leading to dose reduction 120 day update

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Any TEAE	19 (15)	3 (2.3)	33 (11)	3 (1)
Rash (GT)	8 (6)	0	13 (4.3)	0
Paronychia	3 (2.3)	1 (0.8)	7 (2.3)	1 (0.3)

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AEACN = 'DOSE REDUCED'.
Note: Custom grouped terms are designated by '(GT)'.
Rash (GT) includes: Dermatitis acneiform, Rash, and Rash maculo-papular.

The table below presents adverse events leading to either dose reduction or dose interruption.

FDA - Table 39: Adverse events≥ 2 % leading to treatment modification (dose reduction or dose interruption) 120 day update

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Any TEAE	102 (79.1)	27 (20.9)	236 (78.1)	63 (20.9)
Infusion related reaction	76 (58.9)	1 (0.8)	185 (61.3)	2 (0.7)
Dyspnea (GT)	27 (20.9)	0	67 (22.2)	1 (0.3)
Chills	24 (18.6)	0	69 (22.8)	0
Rash (GT)	19 (14.7)	3 (2.3)	36 (11.9)	7 (2.3)
Nausea	21 (16.3)	0	58 (19.2)	0
Flushing	20 (15.5)	0	47 (15.6)	0
Vomiting (GT)	14 (10.9)	0	35 (11.6)	0
Chest discomfort	13 (10.1)	0	33 (10.9)	0
Pyrexia (GT)	12 (9.3)	0	23 (7.6)	1 (0.3)
Hypotension (GT)	9 (7)	1 (0.8)	18 (6)	1 (0.3)
Fatigue (GT)	9 (7)	2 (1.6)	11 (3.6)	2 (0.7)
Paronychia	6 (4.7)	2 (1.6)	13 (4.3)	3 (1)
Diarrhea (GT)	7 (5.4)	3 (2.3)	7 (2.3)	3 (1)
Headache (GT)	6 (4.7)	0	10 (3.3)	2 (0.7)
Musculoskeletal Pain (GT)	6 (4.7)	0	12 (4)	1 (0.3)
Hypoxia	6 (4.7)	1 (0.8)	16 (5.3)	2 (0.7)
Stomatitis (GT)	4 (3.1)	1 (0.8)	6 (2)	1 (0.3)
Pneumonia (GT)	3 (2.3)	1 (0.8)	9 (3)	7 (2.3)
Cough (GT)	5 (3.9)	0	14 (4.6)	0

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 n (%)	Grade 3-4 n (%)	Grade 1-5 n (%)	Grade 3-4 n (%)
Oxygen saturation decreased	3 (2.3)	0	9 (3)	0
Alanine aminotransferase increased	3 (2.3)	1 (0.8)	6 (2)	3 (1)
Dizziness (GT)	4 (3.1)	1 (0.8)	6 (2)	1 (0.3)
Tachycardia	4 (3.1)	0	9 (3)	0
Ocular hyperaemia	4 (3.1)	0	7 (2.3)	0
Feeling hot	4 (3.1)	0	6 (2)	0
Pneumonitis (GT)	4 (3.1)	0	6 (2)	0
Hot flush	3 (2.3)	0	5 (1.7)	0
Hyperhidrosis	2 (1.6)	0	6 (2)	0
Neutropenia	3 (2.3)	3 (2.3)	5 (1.7)	3 (1)
Abdominal Pain (GT)	3 (2.3)	1 (0.8)	7 (2.3)	1 (0.3)
Edema (GT)	3 (2.3)	1 (0.8)	6 (2)	1 (0.3)
Sinus tachycardia	3 (2.3)	0	9 (3)	0
Bronchospasm	3 (2.3)	0	4 (1.3)	0
Hypertension (GT)	3 (2.3)	0	17 (5.6)	3 (1)
Pruritus	3 (2.3)	0	10 (3.3)	0
Lacrimation increased	3 (2.3)	0	3 (1)	0

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN, AEACN = 'DOSE REDUCED' or 'DRUG INTERRUPTED'.
Note: Custom grouped terms are designated by '(GT)'.
Abdominal Pain (GT) includes: Abdominal discomfort, Abdominal pain, and Abdominal pain upper.
Cough (GT) includes: Cough, and Upper-airway cough syndrome.
Diarrhoea (GT) includes: Diarrhoea.
Dizziness (GT) includes: Dizziness, and Vertigo.
Dyspnoea (GT) includes: Dyspnoea.
Fatigue (GT) includes: Asthenia, and Fatigue.
Haemorrhage (GT) includes: Gingival bleeding, Haematuria, and Rectal haemorrhage.
Headache (GT) includes: Headache.
Hypertension (GT) includes: Blood pressure increased, and Hypertension.
Hypotension (GT) includes: Hypotension, and Orthostatic hypotension.
Musculoskeletal Pain (GT) includes: Arthralgia, Back pain, Neck pain, and Non-cardiac chest pain.
Neuropathy Peripheral (GT) includes: Hypoaesthesia, Neuropathy peripheral, and Paraesthesia.
Oedema (GT) includes: Eyelid oedema, Face oedema, Lip oedema, and Oedema peripheral.
Pneumonia (GT) includes: Atypical pneumonia, and Pneumonia.
Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis.
Pyrexia (GT) includes: Pyrexia.
Rash (GT) includes: Dermatitis acneiform, Rash, Rash erythematous, Rash maculo-papular, and Rash pustular.
Stomatitis (GT) includes: Mucosal inflammation, and Stomatitis.
Vomiting (GT) includes: Vomiting.

Significant Adverse Events

Data:

For the purpose of this section, severe TEAEs (Grade 3 or higher) are considered to be significant. All reported Grade 3 or higher TEAEs (reported at frequency ≥1% in All Treated safety population) are presented for the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated populations in Table 39.

Table 40: Number of Subjects With Grade 3 or Higher Treatment-emergent Adverse Events (Frequency ≥1% in All Treated Population) by Preferred Term; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D + Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Subjects with 1 or more grade >=3 AEs	40 (35.1%)	101 (39.1%)	139 (38.4%)
Preferred term			
Dyspnoea	2 (1.8%)	11 (4.3%)	14 (3.9%)
Hyponatraemia	3 (2.6%)	8 (3.1%)	9 (2.5%)
Pneumonia	2 (1.8%)	8 (3.1%)	13 (3.6%)
Hypokalaemia	6 (5.3%)	7 (2.7%)	7 (1.9%)
Pulmonary embolism	4 (3.5%)	7 (2.7%)	9 (2.5%)
Infusion related reaction	3 (2.6%)	6 (2.3%)	9 (2.5%)
Diarrhoea	4 (3.5%)	5 (1.9%)	6 (1.7%)
Gamma-glutamyltransferase increased	1 (0.9%)	5 (1.9%)	6 (1.7%)
Neutropenia	4 (3.5%)	5 (1.9%)	6 (1.7%)
Hypoalbuminaemia	3 (2.6%)	4 (1.6%)	5 (1.4%)
Hypoxia	1 (0.9%)	4 (1.6%)	4 (1.1%)
Pleural effusion	1 (0.9%)	4 (1.6%)	5 (1.4%)
Alanine aminotransferase increased	1 (0.9%)	3 (1.2%)	4 (1.1%)
Hypophosphataemia	1 (0.9%)	3 (1.2%)	5 (1.4%)
Hypotension	2 (1.8%)	3 (1.2%)	4 (1.1%)
Paronychia	1 (0.9%)	3 (1.2%)	5 (1.4%)
Respiratory failure	1 (0.9%)	3 (1.2%)	4 (1.1%)
Dermatitis acneiform	1 (0.9%)	2 (0.8%)	5 (1.4%)
Fatigue	2 (1.8%)	2 (0.8%)	4 (1.1%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. Adverse events are coded using MedDRA Version 23.0. Toxicity Grade is based on NCI common toxicity criteria, version 4.03.

Source: Mod5.3.5.2/61186372EDI1001/AttTSFAE08A1

In the Exon 20ins + prior chemotherapy at RP2D safety population:

- Two subjects (1.8%) had Grade 4 TEAEs (hypokalemia and neutropenia). *[Source: Mod2.7.4/Sec2.1.1.2.1]*

- Grade 3 or higher TEAEs reported by the investigator as related to study drug were experienced by 18 subjects (15.8%), with IRR (2.6%), neutropenia (2.6%), hypoalbuminemia (1.8%), acne (1.8%), and diarrhea (1.8%) being those related Grade 3 or higher TEAEs reported in more than 1 subject in this population. *[Source: Mod5.3.5.2/61186372EDI1001/Sec5.4.2.3]*

In the All Treated safety population:

- Twelve subjects (3.3%) had Grade 4 events (IRR, pneumonia, dyspnea, pulmonary embolism, hypokalemia, hyperkalemia, brain edema, ALT increased, lipase increased, and neutropenia each reported in 1 subject, and hyperglycemia reported in 2 subjects).
- Grade 3 or higher TEAEs assessed by the investigator as related to amivantamab were experienced by 14.6% of subjects, with those reported in at least 1% of subjects being IRR (2.5%), paronychia and dermatitis acneiform (each in 1.4% of subjects), and diarrhea and neutropenia (each in 1.1% of subjects).

The Applicant's Position:

There was no consistent pattern of TEAEs of Grade 3 or higher severity, with the majority of these events being reported for 1 or 2 subjects each in the Exon 20ins + prior chemotherapy at RP2D population. Hypokalemia was the only Grade 3 or higher TEAE reported in >5% of subjects in this population (6 subjects, 5.3%), and did not result in treatment discontinuation for any subject. Few subjects in each safety population had a Grade 4 TEAE.

The FDA's Assessment:

In the Applicant's safety update, the Applicant presented Grade 3 or higher TEAEs assessed by the investigator as related to amivantamab. As the clinical trial is a non-randomized, non-comparative, single study, FDA does not consider this appropriate. FDA performed analyses of treatment-emergent adverse events regardless of attribution to study drug (FDA - Table 40). Please refer to Section 8.2.5 for treatment-emergent laboratory abnormalities.

FDA - Table 41: Grade 3-4 Treatment Emergent Adverse Events (TEAE) occurring in in ≥ 1% of safety population in any arm

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 3 n (%)	Grade 4 n (%)	Grade 3 n (%)	Grade 4 n (%)
Any TEAE	41 (32)	3 (2.3)	104 (34)	7 (2.3)
Paronychia	4 (3.1)	0	6 (2)	0
Respiratory tract infection	2 (1.6)	0	3 (1)	0
Pneumonia (GT)	1 (0.8)	0	6 (2)	1 (0.3)
Pulmonary embolism	6 (4.7)	0	9 (3)	1 (0.3)
Dyspnea (GT)	3 (2.3)	0	13 (4.3)	0
Hypoxia	2 (1.6)	0	6 (2)	0
Pleural effusion	1 (0.8)	0	5 (1.7)	0
Rash (GT)	3 (2.3)	0	8 (2.6)	0
Acne	2 (1.6)	0	2 (0.7)	0
Diarrhea (GT)	4 (3.1)	0	5 (1.7)	0
Abdominal Pain (GT)	1 (0.8)	0	3 (1)	0
Fatigue (GT)	3 (2.3)	0	3 (1)	0
Edema (GT)	1 (0.8)	0	3 (1)	0
Headache (GT)	1 (0.8)	0	3 (1)	0
Hypotension (GT)	3 (2.3)	0	5 (1.7)	1 (0.3)
Hypertension (GT)	2 (1.6)	0	8 (2.6)	0
Infusion related reaction	4 (3.1)	0	6 (2)	1 (0.3)
Musculoskeletal pain (GT)	0	0	5 (1.7)	0

For this table, acne presented separately from rash but included in grouped term of rash for purposes of labeling

8.2.5. Treatment Emergent Adverse Events and Adverse Reactions

Data:

In the Exon 20ins + prior chemotherapy at RP2D safety population, the most frequently reported TEAEs (ie, frequency ≥20%) included IRRs (65.8%), constipation (23.7%), and the on-target EGFR inhibition events of dermatitis acneiform (45.6%) and rash (36.8%), paronychia (44.7%), and stomatitis (21.1%), and with the on-target MET inhibition event of hypoalbuminemia (27.2%). Other TEAEs associated with EGFR inhibition, such as dry skin (15.8%) and diarrhea (12.3%) or MET inhibition such as peripheral edema (18.4%), were also observed in at least 10% of subjects in this population. The types and relative frequencies of TEAEs in the All Treated population were consistent with those reported for the Exon 20ins + prior chemotherapy at RP2D population. *[Source: Mod2.7.4/Tab8]*

Safety data were reviewed by the Applicant's medical experts using the definition of adverse drug reactions (ADRs) from the ICH E6 guideline. Specifically, ADRs were evaluated according to the following considerations:

- TEAEs reported in ≥10% of subjects were considered to have met the ADR threshold.

- TEAEs reported in >1% of subjects were evaluated in the context of a potential plausible biological or pharmacological association with amivantamab, or as medically significant events with a high probability that they could be associated with amivantamab regardless of frequency.
- All serious TEAEs, including all fatal events, were reviewed.
- TEAEs by severity were reviewed for safety trends.
- TEAEs that led to dose modification were reviewed for safety trends.
- All laboratory parameters were reviewed. Note: No laboratory parameters had an incidence of Grade 3 or 4 values ≥10%.

Similar medical concepts were grouped by MedDRA preferred terms.

Table 42 presents the ADRs identified for amivantamab in the Exon 20ins + prior chemotherapy at RP2D safety population (N=114), which is the population used to define ADRs in the USPI for amivantamab.

Table 42: Incidence of Treatment-emergent Adverse Drug Reactions (ADRs) by System Organ Class, Preferred Term, and Toxicity Grade; All Treated at RP2D with Exon 20 Insertion and Prior Chemo Analysis Set in Monotherapy(JNJ-61186372) (Study 61186372EDI1001)

		Exon 20 Ins Prior Chemotherapy(RP2D) (N=114)	
MedDRA System Organ Class (SOC)	Adverse Drug Reaction	All Grades (%)	Grade 3-4 (%)
Skin and subcutaneous tissue disorders	Rash[a]	86	4
	Dry skin[b]	24	0
	Pruritus	17	0
Injury, poisoning and procedural complications	Infusion related reaction	66	3
Gastrointestinal disorders	Constipation	24	0
	Stomatitis[c]	24	0
	Nausea	19	0
	Diarrhoea	12	4
	Vomiting	11	0
Infections and infestations	Paronychia[d]	45	1
General disorders and administration site conditions	Fatigue[e]	30	3
	Oedema peripheral[f]	22	0
Metabolism and nutrition disorders	Hypoalbuminaemia[g]	30	3
	Decreased appetite	14	0
Investigations	Alanine aminotransferase increased	15	1
Musculoskeletal and connective tissue disorders	Myalgia	12	0
Eye disorders	Eye disorder[h]	11	0
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[i]	4	0

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Adverse events were coded using MedDRA version 23.0. In MedDRA version 23.0 the preferred term of "Blood albumin decreased" is coded to the system organ class of "Investigations". In this analysis, it has been coded to the system organ class of "Metabolism and nutrition disorders".
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
[a] includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Perineal rash, Pustule, Rash, Rash maculo-papular, Rash papular, Rash vesicular, Skin exfoliation, Skin lesion, Toxic epidermal necrolysis
[b] includes Dry skin, Eczema, Eczema asteatotic, Skin fissures, Xeroderma
[c] includes Aphthous ulcer, Mouth ulceration, Stomatitis
[d] includes Nail bed infection, Paronychia
[e] includes Asthenia, Fatigue
[f] includes Generalised oedema, Oedema peripheral, Peripheral swelling
[g] includes Blood albumin decreased, Hypoalbuminaemia
[h] includes Blepharitis, Conjunctival hyperaemia, Corneal irritation, Dry eye, Eye pruritus, Growth of eyelashes, Keratitis, Ocular hyperaemia, Uveitis, Vision blurred, Visual acuity reduced, Visual impairment
[i] includes Interstitial lung disease, Pneumonitis
Frequency Grouping: Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing frequency.

Source: Mod5.3.5.3/ISS/AttTSFADR01B-E20

In the Exon 20ins + prior chemotherapy at RP2D population (N=114) represented in the proposed USPI:

- Serious adverse reactions occurred in 6% of subjects who received amivantamab. Serious adverse reactions in >1% of subjects included diarrhea, ILD, and IRR. *[Source: Mod5.3.5.3/ISS/AttTSFADR06-E20]* No fatal adverse reactions occurred.
- Treatment discontinuation of amivantamab due to an adverse reaction occurred in 4% of subjects. The most frequent adverse reactions leading to treatment discontinuation were IRR and rash. *[Source: Mod5.3.5.3/ISS/AttTSFADR03-E20]*
- Dose interruptions due to an adverse reaction occurred in 70% of subjects who received amivantamab. Adverse reactions requiring dose interruption in >2% of subjects included IRRs, rash, fatigue, diarrhea, and ILD. *[Source: Mod5.3.5.3/ISS/AttTSFADR07-E20]*
- Dose reductions due to an adverse reaction occurred in 11% of subjects who received amivantamab. Adverse reactions requiring dose reductions in >2% of subjects included rash. *[Source: Mod5.3.5.3/ISS/AttTSFADR04-E20]*

The Applicant's Position:

The most common adverse reactions (frequency ≥20%) for amivantamab monotherapy at the proposed RP2D were rash, IRR, paronychia, fatigue, hypoalbuminemia, constipation, dry skin, stomatitis, and peripheral edema.

Overall the ADRs were manageable and consistent with EGFR and MET inhibition by amivantamab, and only infrequently prevented subjects from continuing therapy.

The FDA's Assessment:

Results in the Applicant's safety update were similar to those reported in the initial BLA submission. The table below presents treatment-emergent adverse reactions, confirmed by FDA analysis, as presented in Section 6 Adverse Reactions section of the labeling. As discussed above, FDA evaluated adverse reactions commonly associated with IRR, including chills, pyrexia, hypotension, chest discomfort/chest pain, and flushing to determine the incidence of these adverse reactions outside of the setting of IRR. For other adverse reactions which might be associated with IRR but have a significant incidence outside of the setting of IRR (making distinction as part of IRR vs concurrent but separate AR more difficult to assess), such as nausea, vomiting, diarrhea, dyspnea, rash, and pruritis, the incidence used to inform labeling was based on overall incidence (i.e., not excluding events occurring concurrently with an IRR).

FDA - Table 43: Incidence of Treatment-emergent Adverse Reactions (ADRs)

Adverse Reaction	amivantamab (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash[a]	84	3.9
Pruritis	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue[b]	33	2.3
Edema[c]	27	0.8
Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[d]	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea[e]	37	2.3
Cough[f]	25	0
Pneumonia[g]	10	0.8
Gastrointestinal disorders		
Nausea	36	0
Stomatitis[h]	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain[i]	11	0.8
Vascular disorders		
Hemorrhage[j]	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy[k]	13	0
Dizziness	12	0.8
Headache[l]	10	0.8

[a] Rash: acne, dermatitis, dermatitis acneiform, eczema, eczema asteatotic, palmar-plantar erythrodysesthesia syndrome, perineal rash, rash, rash erythematous, rash maculo-papular, rash papular, rash vesicular, skin exfoliation, toxic epidermal necrolysis

[b] Fatigue: asthenia, fatigue

[c] Edema: eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, peripheral swelling

[d] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[e] Dyspnea: dyspnea, dyspnea exertional

[f] Cough: cough, productive cough, upper airway cough síndrome

[g] Pneumonia: atypical pneumonia, lower respiratory tract infection, pneumonia, pneumonia aspiration, pulmonary sepsis

[h] Stomatitis: aphthous ulcer, cheilitis, glossitis, mouth ulceration, mucosal inflammation, pharyngeal inflammation, stomatitis

[i] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, and epigastric discomfort

[j] Hemorrhage: epistaxis, gingival bleeding, hematuria, hemoptysis, hemorrhage, mouth hemorrhage, mucosal hemorrhage

[k] Peripheral neuropathy: hypoaesthesia, neuralgia, paraesthesia, peripheral sensory neuropathy

[l] Headache: headache, migraine

Given the 19% incidence of reported for the grouped term of hemorrhage in the analysis above, FDA conducted additional analyses to further assess this finding (using a broader grouped term for hemorrhage). Hemorrhage was not found to be associated with thrombocytopenia, and using the grouped term above all events were grade 1-2 with no serious adverse events of hemorrhage. Given these findings and the fact that the majority of events were due to epistaxis and gingival bleeding, this was considered not to rise to the level of a severe or serious adverse reaction that would require inclusion in Warnings and Precautions. See Section 20.5 in the Appendix for details of the analysis.

In the larger safety population of 302 patients, the most common (≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema, cough, fatigue, stomatitis, constipation, vomiting and pruritis.

Laboratory Findings

Data:

In the Exon 20ins + prior chemotherapy at RP2D and All Treated safety populations:

- Grade 3 hematology laboratory abnormalities during the study were infrequent (generally <1.5%) except for low lymphocyte counts where Grade 3 abnormalities were observed for approximately 10% of subjects. Only isolated occurrences of Grade 4 hematology laboratory abnormalities were evident during treatment with amivantamab in all study populations. *[Source: Mod2.7.4/Tab20; Mod5.3.5.2/61186372EDI1001/Tab36]*
- Grade 3 clinical chemistry laboratory abnormalities during the study were also infrequent, generally reported in <5% of subjects. Grade 3 hypophosphatemia (6.3%) was the only clinical chemistry abnormality observed in >5% of subjects in the Exon 20ins + prior chemotherapy at RP2D safety population.
- For most subjects in the Exon 20ins + prior chemotherapy at RP2D population, the worst on treatment Grade 3 abnormality represented a shift from a Grade 0 or Grade 1 value at baseline.
- Only isolated occurrences of Grade 4 hematology or clinical chemistry laboratory abnormalities were evident during treatment with amivantamab in all study populations.

Hypoalbuminemia and elevated hepatic transaminases were evaluated in detail based on the pharmacologic profile for amivantamab.

Hypoalbuminemia

Hypoalbuminemia is a suspected consequence of MET inhibition on hepatocyte protein synthesis (Ishii 1995). When albumin levels are decreased, there is a decrease in osmotic pressure and peripheral edema may result from a shift of the fluid into the interstitial spaces (Gatta 2012).

Serum albumin levels over time on treatment in all safety populations showed an expected decrease in albumin levels over the first 2 treatment cycles of approximately 7 to 8 g/L; thereafter, albumin levels tended to stabilize for the remainder of the time on treatment.

Of note, the reporting rate of Grade 3 TEAEs of hypoalbuminemia was low (5 subjects, 1.4%) among the 362 subjects treated in Study EDI1001, and none of these TEAEs were considered serious or resulted in treatment discontinuation. There were no Grade 4 TEAEs of hypoalbuminemia as of the clinical cutoff. *[Source: Mod5.3.5.2/61186372EDI1001/Sec 5.4.5.2]*

Hepatoxicity (Increased Aminotransferases)

EGFR and MET signaling play complex and important roles in the maintenance of hepatic liver repair and regeneration (Komposch 2016). Aminotransferase elevations, including rare reports of hepatic failure with fatal outcomes, have been observed with the small-molecule EGFR TKIs (Giotrif SmPC 2020; Iressa SmPC 2019; Tagrisso USPI 2020; Tarceva SmPC 2016).

In a 6-week toxicity GLP study of amivantamab in cynomolgus monkeys, findings included non-adverse transient increases in ALT and minimal increases in AST without histopathological correlates in the liver. *[Source: Mod2.4/Sec4.2.2]*

For most subjects treated in Study EDI1001, the worst toxicity grade on treatment for hepatic transaminase values was Grade 0 or 1, with Grade 3 values for ALT or AST seen in <2% of treated subjects. There was a single 1 Grade 4 ALT and AST increase among the 362 treated subjects. *[Source: Mod2.7.4/Tab20]*

Subjects in the All Treated safety population (N=362) meeting various components of the criteria for potential drug-induced hepatotoxicity (ie, ALT or AST ≥3 times upper limit of normal [ULN] and total bilirubin ≥2 times ULN) were identified and examined. While elevations of ALT and AST (largely transient) were observed in the All Treated safety population during Study EDI1001, there have been no confirmed cases of drug-induced liver injury (or subjects meeting Hy's law criteria) with amivantamab and the reporting rate of Grade 3 or higher TEAEs of ALT increased or AST increased was low (1.1% and 0.6%, respectively). No TEAEs of ALT increased or AST increased led to discontinuation of study treatment (see Table 31). *[Source: Mod2.7.4/Tab9, Sec3.2.2]*

The Applicant's Position:

Treatment with amivantamab monotherapy was not associated with hematologic toxicity.

An expected decrease in serum albumin levels that stabilized after Cycle 2 was observed in subjects receiving amivantamab.

While increased aminotransferases have been observed with amivantamab use, elevations were transient, no clinical sequelae were observed, and no cases of drug-induced liver injury were confirmed.

Hypoalbuminemia and ALT increased are identified ADRs in the proposed amivantamab USPI.

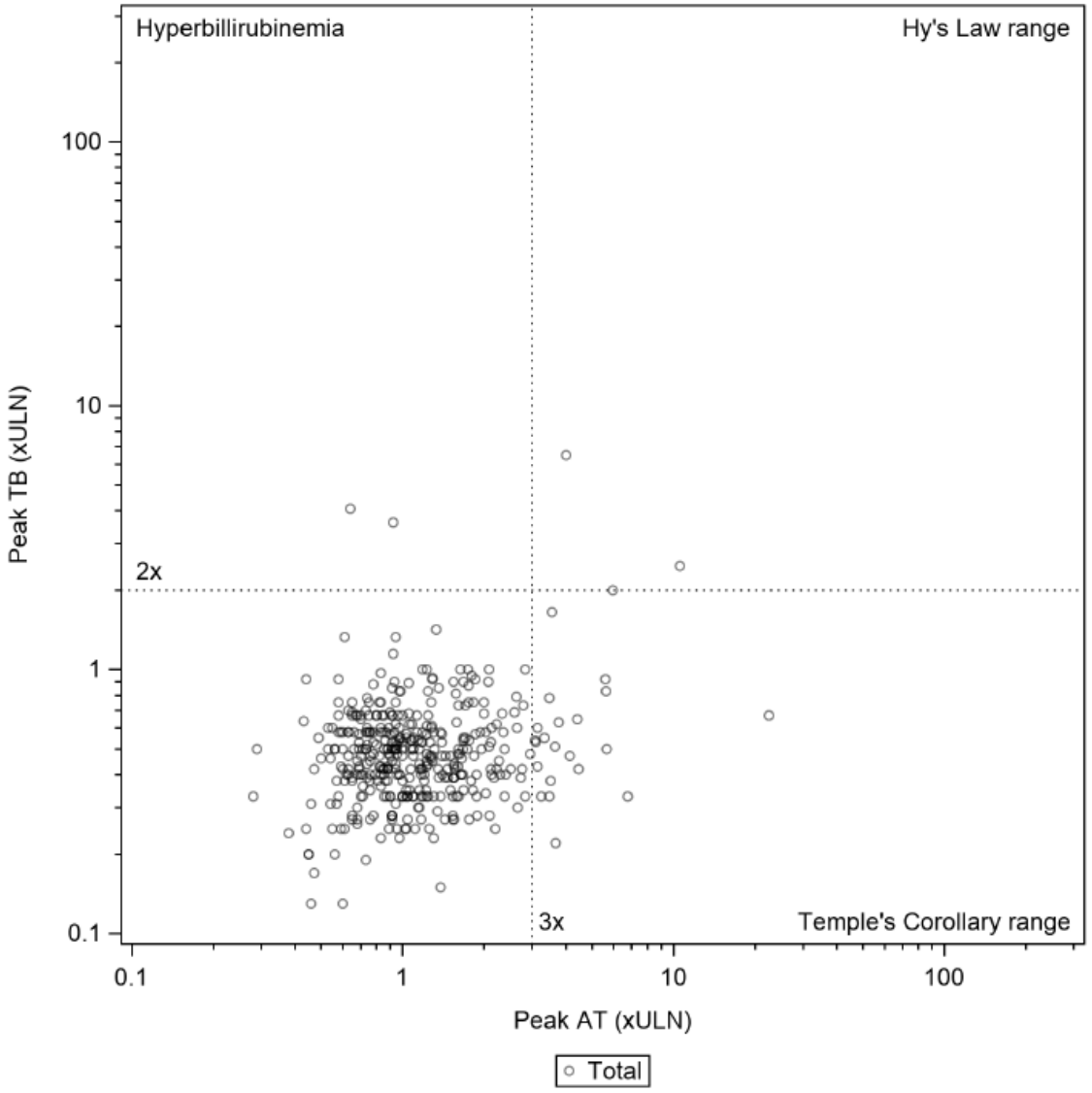
The FDA's Assessment:

In the Applicant's 120 day update, the below information was provided.

Hepatotoxicity

All Treated (n=411): Elevations of ALT and AST were observed (including one Grade 4 ALT increase, however, there have been no confirmed cases of drug-induced liver injury (or subjects meeting Hy's law criteria) with amivantamab.

Figure 24: Evaluation of Drug-induced Serious Hepatoxicity (eDISH); All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)



RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Key: Peak TB=Peak Total Bilirubin, Peak AT=Maximum of (ALT, AST)
[GSFLAB03.RTF] [JNJ-61186372\EDI1001\DBR_120D_E20INS\RE_120D_E20INS\PROD\GSFLAB03.SAS] 14DEC2020, 17:12

FDA agrees with Applicant's position regarding hepatoxicity. Laboratory abnormalities were analyzed by FDA using the laboratory datasets. The table below summarizes laboratory abnormalities worsening from baseline that occurred in ≥20% of patients who received amivantamab in the safety populations.

FDA - Table 44: Select Laboratory Abnormalities (>20%) That Worsened from Baseline in Patients who received amivantamab, Safety Population

Laboratory Abnormality	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 (%)	Grade 3-4 (%)	Grade 1-5 (%)	Grade 3-4 (%)
Chemistry				
Decreased albumin (G/L)	79	8	81	4.7
Increased glucose (Mmol/L)	56	4	54	4.7
Increased alkaline phosphatase (U/L)	53	4.8	52	3.1
Increased creatinine (Umol/L)	46	0	45	0
Increased alanine aminotransferase (U/L)	38	1.6	34	1.4
Decreased phosphate (Mmol/L)	33	8	27	6
Increased aspartate aminotransferase (U/L)	33	0	31	0.7
Decreased magnesium (Mmol/L)	27	0	24	0.3
Increased gamma glutamyl transferase (U/L)	27	4	25	4.4
Decreased sodium (Mmol/L)	27	4	26	4.1
Decreased potassium (Mmol/L)	26	6	22	3.1
Hematology				
Decreased lymphocytes (x10e9/L)	36	8	33	7

Denominator for laboratory analyses are based on patients with a baseline and at least one on-study value. Patients must have had at least one grade worsening on study to be counted in analyses and only worst grade will be included in the analyses.
The denominator used to calculate the rate was based on 126 patients for the n=129 population and the rate varied from 294 or 295 patients for the n=302 population.

Vital Signs

Data:

Changes from baseline in vital sign parameters were summarized over time (through Cycle 4, Day 15) for the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations in the CSR. *[Source: Mod5.3.5.3/61186372EDI1001/AttTSFVIT01]*

The Applicant's Position:

Mean and median changes in vital signs were typically small and not clinically meaningful for any of the safety populations.

The FDA's Assessment:

FDA agrees with the Applicant's position. FDA reviewed the Applicant's submitted Summary of Clinical Safety, clinical study report, and the 120 day safety update. Vital sign assessments were made pre-dose of amivantamab infusion and every 30 minutes thereafter.

Electrocardiograms

Data:

In Study EDI1001, single and triplicate ECGs were conducted to evaluate the effects of amivantamab on 12-lead ECGs (QT, QTcF, PR, QRS, and heart rate). Changes from baseline to Cycle 2, Day 1 (pre-infusion and post-infusion) in each measured ECG parameter (heart rate; PR, QRS, RR, QT, QTcF intervals; QRS axis) were summarized descriptively for the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated populations in the CSR. Within each safety population, approximately 65% of subjects with baseline ECG data had corresponding ECG data for the C2D1 predose timepoint and approximately 12% to 16% of subjects had corresponding ECG data for the C2D1 postdose timepoint (time of amivantamab C_{max}). Mean and median changes from baseline in all safety populations were not considered clinically meaningful. *[Source: Mod5.3.5.2/61186372EDI1001/Sec5.4.7]*

The Applicant's Position:

Based on review of the data, there is no evidence that amivantamab affects ECG parameters, and as discussed below, there is no safety signal for QT prolongation.

The FDA's Assessment:

FDA agrees with the Applicant's position.

QT Interval

Data:

Based on the maximum QTcF value for each subject, categorical distributions of the actual and change from baseline values for the QTcF interval over time were evaluated according to ICH E14, guideline categories. In the All Treated safety population, only 3 [1.0%] subject had an increase in QTcF >60 msec, and no subject had a maximum QTcF interval of >500 msec. *[Mod5.3.5.2/61186372EDI1001/Sec5.4.7]*

The Applicant's Position:

As an antibody, amivantamab is too large to directly inhibit the human ether-à-go-go-related gene channel and is highly specific to the extracellular epitope of the transmembrane EGFR and MET proteins; therefore, it is unlikely to directly impact cardiac repolarization.

The lack of outlier repolarization findings across Study EDI1001 (ie, no QTcF >500 msec) and a biologic mechanism for amivantamab to impact QTcF, suggests there is no safety signal for QT prolongation with amivantamab.

The FDA's Assessment:

FDA agrees with the Applicant's position.

Immunogenicity

Data:

A review of data regarding immunogenicity, including an assessment of the impact of antibody titer levels on PK parameters, or the clinical efficacy or safety of amivantamab, is presented and summarized in Section 6.3.1.

The Applicant's Position:

Overall, incidence of antibodies to amivantamab was low, with all the positive subjects having low titers suggesting a low immunogenicity risk for amivantamab.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.6. Analysis of Submission-Specific Safety Issues

Targeted reviews of the following specific AEs for amivantamab were done: IRRs, rash, ILD, peripheral edema, paronychia, diarrhea, and eye disorders, as described in Section 8.2.1.

8.2.5.1. Infusion-related Reaction

The Applicant's Description:
Systemic IRRs have been observed with protein therapeutics, but the mechanisms inducing the reactions are varied (Cáceres 2019; Matucci 2016). The exact pathophysiology of amivantamab IRRs is currently unknown. However, the clinical characteristics of these events, and translational studies utilizing serum samples drawn from a subset of subjects prior to, during, and at the conclusion of amivantamab administration have been able to exclude cytokine release syndrome, complement activation, tumor lysis syndrome, and mast cell degranulation as causative factors of amivantamab-related IRRs. Lastly, the low recurrence rate of IRRs after the initial amivantamab infusion suggests that a role of pre-formed IgEs or other immunoglobulins is inconsistent with the IRRs associated with amivantamab.

As described in Section 8.1.1, several modifications were made to the EDI1001 protocol in order to minimize the occurrence and mitigate the severity of IRRs. These included the splitting the first dose in Cycle 1 over Days 1 and 2; the requirement for prophylactic pre-infusion medication administration; interruption of infusion at first sign of an IRR (of any grade) and resuming infusion at 50% of previous rate following recovery of symptoms for Grade 1 to 3 events; administration

of supportive post-infusion medications (eg, additional glucocorticoids, antihistamine, antipyretics) as clinically indicated; interruption of infusion for Grade 3 or 4 IRRs; and consideration of permanent discontinuation of amivantamab based on severity of symptoms. During the study, supplemental information on IRR symptoms was collected to better characterize these events; IRR symptom information was separate from AE reporting.

Data:

A summary of key characteristics of IRRs reported in Study EDI1001 in the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations is provided in Table 47. *[Source: Mod2.7.4/Sec2.1.5.1]*

IRRs have been observed at all amivantamab dose levels (starting dose of 140 mg to 1,750 mg). *[Source: Mod5.3.5.2/61186372EDI1001/AttTSFAE03A-P1]* Across all subjects treated with amivantamab monotherapy in Study EDI1001 (N=362), the majority of reported IRRs were Grade 1 or Grade 2 in severity and only 1 subject (0.3%) had a Grade 4 IRR. The single Grade 4 IRR resolved within an hour following stopping the amivantamab infusion and providing supportive treatment; study treatment was discontinued for this event. The preponderance of Grade 2 events reflected the recommendation that an interruption of amivantamab infusion be considered even for Grade 1 IRRs, and in instances where the infusion was interrupted, the severity was, by definition, Grade 2 (Grade 2 IRR: 'Therapy or infusion interruption indicated but responds promptly to symptomatic treatment').

The most frequent symptoms associated with an IRR (≥10% in the All Treated safety population were chills (22.4%), nausea (22.1%), dyspnea (20.4%), flushing (17.7%), chest discomfort (12.7%), and vomiting (10.8%). Few reported IRRs were assessed as serious or resulted in discontinuation of study treatment. The types and relative distribution of IRR symptoms were consistent for the Exon 20ins + prior chemotherapy and All Treated at RP2D safety populations.

Table 45: Summary of Treatment-emergent Adverse Events of Clinical Importance – Infusion-related Reaction; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D + Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Infusion Related Reaction			
Number (%) with any grade IRR	75 (65.8%)	167 (64.7%)	233 (64.4%)
Number (%) with maximum severity IRR			
Grade 1	9 (7.9%)	21 (8.1%)	33 (9.1%)
Grade 2	63 (55.3%)	140 (54.3%)	191 (52.8%)
Grade 3	3 (2.6%)	5 (1.9%)	8 (2.2%)
Grade 4	0	1 (0.4%)	1 (0.3%)
Grade 5	0	0	0
Number (%) with serious IRR	2 (1.8%)	4 (1.6%)	6 (1.7%)
Number (%) with IRR leading to discontinuation	2 (1.8%)	4 (1.6%)	8 (2.2%)
Time to first onset (min)			
Median	45.00	44.00	44.00
Range	(10.0; 613772.0)	(7.0; 613772.0)	(0.0; 613772.0)

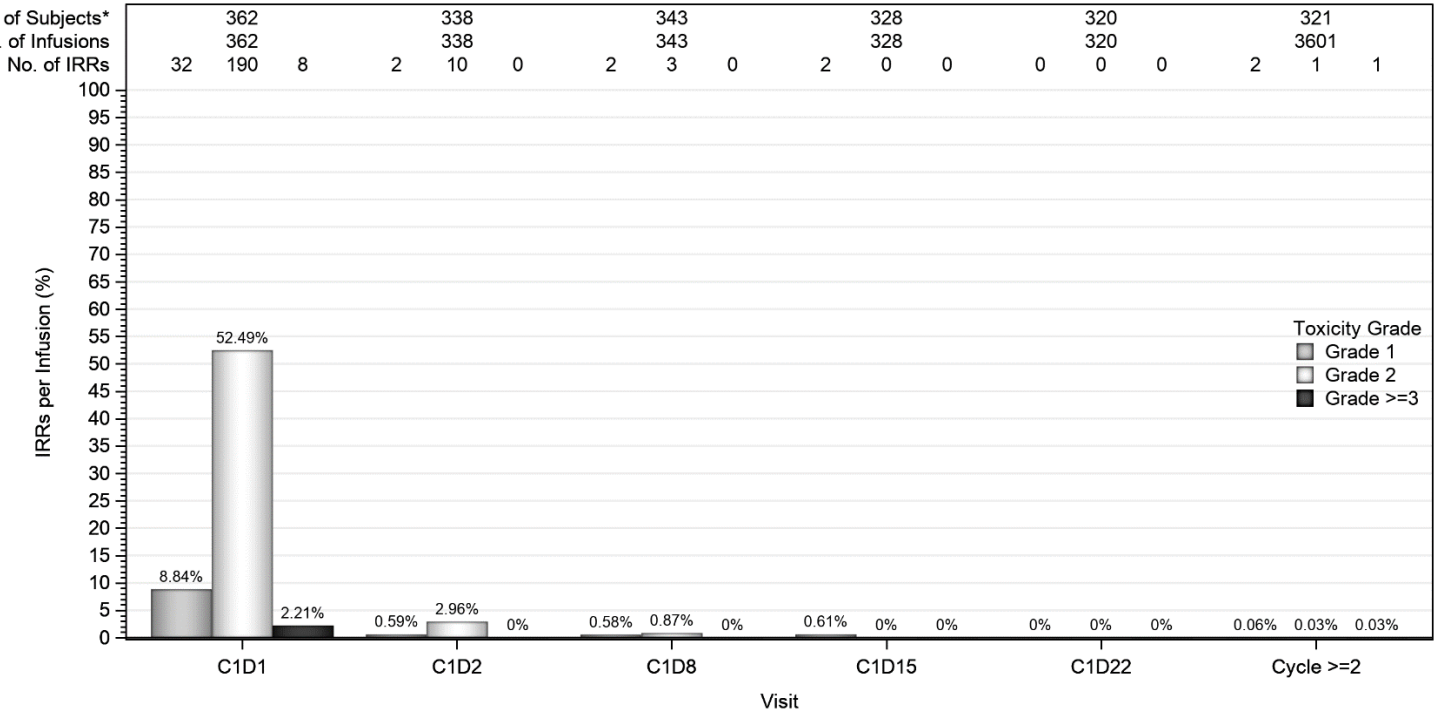
RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the total column for that adverse event. Adverse events are coded using MedDRA Version 23.0. Toxicity Grade is based on NCI common toxicity criteria, version 4.03.

Source: Mod5.3.5.2/61186372EDI1001/AttTSFAE03CPART1OF2, AttTSFAE03CPART2OF2, AttTSFAE03E, AttTSFAE05CPART1OF2, AttTSFAE05CPART2OF2, AttTSFAE03TT

Time Course for IRRs

The median time to first onset of a reported IRR was 44.0 minutes in the All Treated safety population. The IRR occurrence by toxicity grade and dose is presented for the All Treated safety population in Figure 25. Most of IRRs occurring with the first infusion was also seen for the Exon 20ins + prior chemotherapy and All Treated at RP2D safety populations.

Figure 25: Bar Chart of Infusion Related Reactions (IRR) per Study Drug Infusion by Toxicity Grade; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)



RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Key: IRR = Infusion Related Reaction
* Number of subjects that received study drug infusion during that cycle/day.
Note: Infusion Related Reactions are counted only once per visit (Cycle 1 Day 1 and Cycle 1 Day 2 are counted as separate infusion visits) per subject. The event experienced by the subject with the worst toxicity is used.

Source: Mod2.7.4/Fig3

Management of IRRs

In addition to the use of split dosing of the first dose (Cycle 1) over Days 1 and 2, IRRs were prophylactically managed via administration of select drugs prior to the scheduled amivantamab infusion. Post-infusion medications could have been prescribed and continued for up to 48 hours after infusion of study drug if clinically indicated for the management of IRRs or other infusion-related symptoms; these included IV or oral glucocorticoids, antihistamines, antipyretics (paracetamol), opiates (meperidine), and antiemetics.

The experience regarding IRR management was consistent for the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations. In the All Treated safety population (N=362): *[Source: Mod2.7.4/Sec2.1.5.1]*

- Pre-infusion systemic corticosteroid use was reported for 99.2% for the C1D1 infusion and 99.7% of subjects for the C1D2. Pre-infusion administration of a systemic corticosteroid was required in 48.5% of subjects with infusions administered on Cycle 1, Day 8, and between ~30% to 40% of subjects with infusions administered thereafter.
- Consistent with protocol guidelines, pre-infusion antihistamine and paracetamol was reported for all or almost all (≥99%) subjects for each infusion.
- Histamine H2 receptor antagonists were administered pre-infusion to approximately 50% to 60% of subjects at each scheduled dose, while the frequency of pre-infusion antiemetics/antinauseant administration was low, and declined from approximately 15% for C1D1 and C1D2 infusions to ~10% from Cycle 3, Day 1.

Most IRRs were managed with a modification of the ongoing infusion and, in accordance with protocol recommendations, few required post-infusion treatment. In the All Treated safety population:

- 59.4% of subjects had an IRR during the Treatment period that resulted in modification of an ongoing infusion. Characterization of these modifications indicated that almost all occurred during the C1D1 infusion. For each subsequent infusions, 3% or fewer subjects in this population required a modification due to an IRR.
- Modifications to the C1D1 infusion consisted of an interruption of the infusion and a subsequent reduction in the infusion rate, consistent with protocol guidelines. Fewer than 15% of subjects aborted the C1D1 infusion due to an IRR.

Post-infusion medication use to manage IRRs/symptoms was uncommon in the All Treated safety population, with post-infusion administration of systemic antihistamines, systemic corticosteroids, and paracetamol reported for 5.2%, 3.9%, and 2.5% of subjects, respectively. Other types of post-infusion medications were used by ≤2.5% of subjects in this population.

The Applicant's Position:

Systemic IRRs, including severe reactions, have been observed with protein therapeutics. The available clinical experience indicates that the majority of treated subjects experienced an IRR associated with

amivantamab infusion, with >90% of IRRs occurring on Day 1 of the first infusion of Cycle 1. Most IRRs were mild to moderate in severity, transient, and managed by amivantamab interruption, additional steroids, and antihistamines. Few IRRs required post-infusion treatment or resulted in treatment discontinuation.

The proposed USPI for amivantamab provides specific guidance in the Dosage and Administration and Warnings and Precautions sections to minimize and manage the risk of IRRs. As stated in the Warnings and Precautions section, patients should be treated with amivantamab in a setting with appropriate medical support necessary to treat IRRs.

The FDA's Assessment:

The Applicant provided the below information in the safety update.

All Treated (n=411): In the All Treated population, most subjects experienced IRR at Grade 2 (53.3%), the majority of events were Grade 2 IRR, and the predominance of this severity of events was consistent with the recommendation that an interruption of amivantamab infusion be considered for any symptoms of IRR (including Grade 1 severity) to preempt worsening of IRR symptoms. In these instances where the infusion was interrupted, the severity was, by definition, a Grade 2 (Grade 2 IRR: 'Therapy or infusion interruption indicated but responds promptly to symptomatic treatment'.

Nine subjects (2.2%) experienced a Grade 3 IRR, and 1 subject (0.2%) a Grade 4 IRR. The proportion of subjects with IRRs that were serious was ≤2% (in any analysis set).

Of the 9 subjects who experienced Grade 3 IRR, 7 subjects experienced the IRR on Day 1 of treatment and 4 of these events were classed as serious. All events resolved following treatment, but amivantamab was discontinued in 6 cases, interrupted in 2 cases and not changed in 1 case.

All Treated at RP2D (n=302): The overall occurrence and pattern of reported IRRs for the All Treated at RP2D population was consistent with that reported for the All Treated population.

- The overall frequency of IRR events was 65.9% for the All Treated at RP2D population, with 2.0 % of subjects having an IRR event of worst Grade 3 severity.
- The proportion of subjects with IRRs that were serious was (1.3 %, for All Treated at RP2D population),

Exon 20ins + prior chemotherapy at RP2D (n=129): The overall occurrence and pattern of reported IRRs for the Exon 20ins + prior chemotherapy at RP2D populations was consistent with that reported for the All Treated population.

- The overall frequency of IRR events was 64.3% for the Exon 20ins + prior chemotherapy at RP2D population, with 3.1% of subjects having an IRR event of worst Grade 3 severity.
- The proportion of subjects in these populations with IRRs that were serious was 1.6%, for the Exon 20ins + prior chemotherapy at RP2D population.

All Treated at RP2D (n=302) and **Exon 20ins + prior chemotherapy at RP2D (n=129)**: The median time to first onset of a reported IRR was 43.0 minutes (range: 7.0; 613772.0) for the All Treated at RP2D

population and 45.0 minutes (range: 10.0- 613772) for the Exon 20ins + prior chemotherapy at RP2D population.

All Treated (n=411): In the All Treated population the incidence of IRRs occurring on Cycle 1, Day 1 was 65%, with few IRRs occurring with subsequent infusions. Moreover, all but 1 of the few Grade 3 IRR events occurred with the Cycle 1, Day 1 infusion.

- The overall rates of IRRs per infusion (regardless of toxicity grade) were 65% for Cycle 1, Day 1; 4% for Cycle 1, Day 2; just over 1% for Cycle 1, Day 8; just under 1% for Cycle 1, Day 15; 0% for Cycle 1, Day 22; and 0.1% for Cycle 2 onwards.

All Treated at RP2D (n=302): Among subjects treated with the amivantamab RP2D (including subjects with Exon 20ins + prior chemotherapy at RP2D), 93% (197 of 212) of the reported IRRs occurred on Cycle 1, Day 1, with few IRRs occurring with subsequent infusions All but 1 of the few Grade 3 IRR events occurred with the Cycle 1, Day 1 infusion.

- The overall rates of IRRs per infusion (regardless of toxicity grade) were 65.23% for Cycle 1, Day 1; 3.39% for Cycle 1, Day 2; 0.35% for Cycle 1, Day 8; 1.12% for Cycle 1, Day 15; 0% for Cycle 1, Day 22; and 0.03% for Cycle 2 onwards.

FDA performed the analysis for IRR in the context of treatment emergent adverse events. Discontinuations due to IRR occurred 1.3% of the 302 patients in the safety population used to inform Warnings & Precautions section of labeling.

FDA evaluated the onset of infusion-related reactions in the safety populations in the table below. The median time to onset of IRR was 1 hour (range: 0.1-18 hours).

FDA - Table 46: Time to Infusion Related Reaction Onset

IRR time to onset (hr) (CTTONHR)	Analysis population	
	E20 ins mutations prior chemotherapy N = 129 n (%)	RP2D N = 302 n (%)
Mean (SD)	1.1 (1.9)	0.9 (1.3)
Median (Range)	0.8 (0.1-18.5)	0.7 (0.1-18.5)

The Applicant provided the below table in the safety update.

Table 47: TSFAE10A Number of Subjects with Treatment Emergent Symptoms of Infusion Related Reactions by System Organ Class and Preferred Terms; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	Analysis population	
	E20 ins mutations prior chemotherapy (N=129)	RP2D (N=302)
	N (%)	N (%)
Subjects with 1 or more symptoms of IRR	83 (64.3)	199 (65.9)
General disorders and administration site conditions	46 (35.7)	115 (38.1)
Chills	24 (18.6)	71 (23.5)
Chest discomfort	15 (11.6)	36 (11.9)
Pyrexia	11 (8.5)	23 (7.6)
Feeling hot	4 (3.1)	6 (2.0)
Non-cardiac chest pain	3 (2.3)	6 (2.0)
Malaise	2 (1.6)	3 (1.0)
Chest pain	0	2 (0.7)
Face oedema	0	1 (0.3)
Pain	1 (0.8)	1 (0.3)
Peripheral swelling	1 (0.8)	1 (0.3)
Thirst	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	39 (30.2)	94 (31.1)
Dyspnoea	29 (22.5)	65 (21.5)
Hypoxia	6 (4.7)	17 (5.6)
Cough	8 (6.2)	16 (5.3)
Wheezing	3 (2.3)	7 (2.3)
Bronchospasm	3 (2.3)	5 (1.7)
Tachypnoea	0	4 (1.3)
Dysphonia	1 (0.8)	2 (0.7)
Laryngeal inflammation	1 (0.8)	1 (0.3)
Oropharyngeal pain	0	1 (0.3)
Pleuritic pain	1 (0.8)	1 (0.3)
Upper airway cough syndrome	0	1 (0.3)
Oropharyngeal discomfort	0	0
Respiratory disorder	0	0
Sneezing	0	0
Throat irritation	0	0
Vascular disorders	39 (30.2)	84 (27.8)
Flushing	25 (19.4)	55 (18.2)
Hypotension	10 (7.8)	20 (6.6)
Hypertension	3 (2.3)	12 (4.0)
Hot flush	3 (2.3)	5 (1.7)
Pallor	2 (1.6)	2 (0.7)
Hyperaemia	1 (0.8)	1 (0.3)
Gastrointestinal disorders	31 (24.0)	80 (26.5)
Nausea	22 (17.1)	59 (19.5)
Vomiting	13 (10.1)	35 (11.6)
Abdominal pain	1 (0.8)	4 (1.3)
Diarrhoea	3 (2.3)	3 (1.0)
Dyspepsia	0	2 (0.7)
Abdominal discomfort	1 (0.8)	1 (0.3)

	Analysis population	
	E20 ins mutations prior chemotherapy (N=129)	RP2D (N=302)
	N (%)	N (%)
Abdominal pain upper	0	1 (0.3)
Abdominal rigidity	1 (0.8)	1 (0.3)
Dysphagia	0	1 (0.3)
Lip oedema	1 (0.8)	1 (0.3)
Lip swelling	0	1 (0.3)
Skin and subcutaneous tissue disorders	15 (11.6)	36 (11.9)
Pruritus	4 (3.1)	12 (4.0)
Rash	7 (5.4)	10 (3.3)
Hyperhidrosis	2 (1.6)	7 (2.3)
Erythema	2 (1.6)	4 (1.3)
Cold sweat	1 (0.8)	2 (0.7)
Rash erythematous	0	1 (0.3)
Rash macular	0	1 (0.3)
Rash maculo-papular	0	1 (0.3)
Skin discolouration	1 (0.8)	1 (0.3)
Urticaria	0	1 (0.3)
Cardiac disorders	8 (6.2)	23 (7.6)
Tachycardia	4 (3.1)	10 (3.3)
Sinus tachycardia	3 (2.3)	9 (3.0)
Palpitations	1 (0.8)	4 (1.3)
Bradycardia	1 (0.8)	1 (0.3)
Nervous system disorders	10 (7.8)	18 (6.0)
Headache	6 (4.7)	8 (2.6)
Dizziness	3 (2.3)	5 (1.7)
Paraesthesia	0	2 (0.7)
Dizziness postural	0	1 (0.3)
Hypoaesthesia	0	1 (0.3)
Lethargy	1 (0.8)	1 (0.3)
Loss of consciousness	0	1 (0.3)
Tremor	0	1 (0.3)
Investigations	4 (3.1)	16 (5.3)
Oxygen saturation decreased	3 (2.3)	10 (3.3)
Blood pressure increased	1 (0.8)	5 (1.7)
Hear rate increased	0	2 (0.7)
Electrocardiogram ST segment elevation	0	1 (0.3)
Eye disorders	9 (7.0)	14 (4.6)
Ocular hyperaemia	3 (2.3)	6 (2.0)
Lacrimation increased	3 (2.3)	3 (1.0)
Conjunctival hyperaemia	0	1 (0.3)
Eye pruritus	0	1 (0.3)
Eyelid oedema	1 (0.8)	1 (0.3)
Swelling of eyelid	1 (0.8)	1 (0.3)
Vision blurred	1 (0.8)	1 (0.3)
Musculoskeletal and connective tissue disorders	2 (1.6)	4 (1.3)
Back pain	2 (1.6)	4 (1.3)
Psychiatric disorders	1 (0.8)	3 (1.0)

	Analysis population	
	E20 ins mutations prior chemotherapy (N=129)	**RP2D (N=302)**
	N (%)	**N (%)**
Anxiety	1 (0.8)	2 (0.7)
Hallucination	0	1 (0.3)
Immune system disorders	0	0
Hypersensitivity	0	0
Infections and infestations	0	0
Erythema induratum	0	0

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg. Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: IRR = infusion related reaction
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event.
Adverse events are coded using MedDRA Version 23.0.
[TSFAE10A.RTF] [JNJ-61186372\EDI1001\DBR_120D_E20INS\RE_120D_E20INS\PROD\TSFAE10A.SAS] 14DEC2020, 16:56

The results in the above table were not independently verified by FDA.

In response to an information request from FDA requesting additional information regarding the onset on infusion-related reactions, the Applicant provided the table below (submitted May 4, 2021).

Table 48: TSFAE03F_LABEL-RP2D-FDA10: Time to Onset of Infusion Related Reaction; All Treated at RP2D Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	All treated at RP2D Event Onset Time		
	Total	1st Infusion[a]	Subsequent Infusion
Analysis set: All Treated at RP2D in Monotherapy (JNJ-61186372)	302		
Total number of subjects with infusion related reactions	199	198 (99.5%)	5 (2.5%)
Total number of infusion related reactions	273	268 (98.2%)	5 (1.8%)
Total number of grade 1-2 infusion related reactions	266 (97.4%)*	262 (98.5%)	4 (1.5%)
Total number of grade 3 or higher infusion related reactions	7(2.6%)*	6 (85.7%)	1 (14.3%)
Total number of grade 3 infusion related reactions	6 (2.2%)*	5 (83.3%)	1 (16.7%)
Total number of grade 4 infusion related reactions	1 (0.4%)*	1 (100.0)%	0
Time to onset of infusion related reactions (minutes)			
N	273	268	5
Mean (SD)	87.5 (108.98)	83.6 (90.26)	295.8 (456.72)
Median	60.0	59.5	130.0
Range	(7; 1108)	(7; 1071)	(42; 1108)

[a] Infusion related reactions occurred between C1D1 infusion start and C1D8 infusion start.
* Percentages are calculated with the number of total infusion related reactions as denominator.
Note: Percentages of the number of infusion related reactions in each event onset subgroup are calculated with the number of total column in each group as denominator.
Note: Time to onset of infusion related reactions in minutes are calculated as the start of the infusion related reaction minus the start of the last infusion which is prior to this event.

[TSFAE03F_LABEL-RP2D-FDA10.RTF] [JNJ-61186372\EDI1001\DBR_120D_E20INS\RE_HA_RESPONSE\PROD\TSFAE03F_LABEL-FDA10.SAS] 28APR2021, 14:05

Based on review of the information provided by the Applicant and FDA's review of the data, the following information regarding IRR is included in the Warnings and Precautions section of the label (based on n=302):

IRR occurred in 66% of patients treated with amivantamab. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62% and 1.3% of patients permanently discontinued amivantamab due to IRR.

8.2.5.2. Rash (Grouped Term)

Applicant's Description:
EGFR is expressed in the sebaceous and eccrine glands, and hair follicles of the epidermis (Lacouture 2018; Melosky 2009), and EGFR inhibition disrupts epidermal integrity and induces an associated cytokine reaction leading to leukocyte chemotaxis and infiltration to these EGFR-receptor rich areas (Gravalos 2019). Thus, rash and other dermatologic side effects are frequently reported with EGFR TKIs (Beech 2018; Lynch 2007).

Management guidelines for rash were incorporated into the study protocol, including recommendations for prophylactic measures including avoidance of sun exposure, use of broad spectrum topical sunscreen, and thick alcohol-free emollient creams, as well as treatment approaches as indicated below: *[Source: Mod5.3.5.2/61186372EDI1001/Sec5.4.3.4.2]*

Protocol-specified treatment options for rash AEs were:

- Topical corticosteroids (eg, hydrocortisone 2.5% cream), topical clindamycin (1% gel) or systemic antibiotics (doxycycline 100 mg twice daily or minocycline 100 mg twice daily)
- For pruritic lesions: cool compresses and oral antihistamine agents
- For paronychia: antiseptic soaks and local potent corticosteroids in addition to oral antibiotics; a dermatology or surgery consultation recommended in the event of no improvement
- For fissuring: Monsel's solution (ferric subsulfate solution), silver nitrate, or zinc oxide cream
- For desquamation: thick emollients and mild soap
- For infected lesions: bacterial and fungal culturing followed by the appropriate culture-driven systemic or topical antibiotics

In addition to the treatment options recommended above, the protocol specified a step-wise approach for management of rash. In brief, for rash, investigators were to consider (in addition to prophylactic and reactive treatment regimen) reducing the dose for Grade 2 events and to interrupt treatment for Grade 3 events (or Grade 2 events that did not resolve after 2 weeks) until the event improved to Grade ≤1. In the event that the rash event(s) worsened or did not improve after 2 weeks, treatment discontinuation was recommended.

Data:

A summary of key characteristics of rash TEAEs (grouped term) reported in Study EDI1001 in the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations is provided in Table 52. The pattern of rash TEAEs was consistent across the safety populations. *[Source: Mod2.7.4/Sec2.1.5.2; Mod2.5/Sec5.2.3.2]*

Among all subjects treated with amivantamab (N=362), rash events (grouped term) were the most common category of TEAEs reported (76.5%), with dermatitis acneiform (35.9%), and rash (35.9%) being the most frequent specific events observed. Characteristics of these events for the All Treated safety population are as follows:

- Among the 277 subjects in this population with a rash TEAE, 146 (52.7%) had more than 1 rash TEAE as of the clinical cutoff date, with 25.6% of subjects having 3 or more rash TEAEs.
- Rash TEAEs were mostly of Grade 1 or 2 severity and non-serious.
- Rash TEAEs typically occurred within the first treatment cycle, with the median time to first onset of event being 14.0 days.

- For 25.6% of subjects with a rash TEAE (grouped term), the TEAE(s) resolved on treatment, with the median time to resolution of all reported rash events being 89 days (range: 2-737).

The single serious rash TEAE reported through the clinical cutoff occurred in a subject in the Exon 20ins + prior chemotherapy at RP2D safety population. This event (toxic epidermal necrolysis) presented in a subject with a medical history of Grade 3 rash on immunotherapy (nivolumab) who started study treatment with an ongoing Grade 1 rash (verbatim: papulo-erythematous lesions under nivolumab). The pre-existing rash worsened on study (Day 29), required hospitalization (initial hospitalization on Day 37), after which time amivantamab was discontinued (last dose on Day 23). Following medical management, the event resolved on Day 107.

Table 49: Summary of Treatment-emergent Adverse Events of Clinical Importance – Rash [Grouped Term]; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D + Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Rash TEAE (grouped term)[a]			
Number (%) with any grade rash TEAE	98 (86.0%)	202 (78.3%)	277 (76.5%)
Number (%) with maximum severity rash TEAE			
Grade 1	43 (37.7%)	101 (39.1%)	140 (38.7%)
Grade 2	51 (44.7%)	94 (36.4%)	126 (34.8%)
Grade 3	4 (3.5%)	7 (2.7%)	11 (3.0%)
Grade 4	0	0	0
Grade 5	0	0	0
Number (%) with serious rash TEAE	1 (0.9%)	1 (0.4%)	1 (0.3%)
Number (%) with rash TEAE leading to discontinuation	2 (1.8%)	2 (0.8%)	2 (0.6%)
Time to first onset (days)			
Median	11.00	14.00	14.00
Range	(1.0; 99.0)	(1.0; 276.0)	(1.0; 276.0)
Number (%) with rash TEAE leading to dose interruption[b]	9 (9.2%)	17 (8.4%)	19 (6.9%)
Number (%) with rash TEAE leading to dose reduction[b]	11 (11.2%)	15 (7.4%)	26 (9.4%)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: TEAE = treatment-emergent adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the total column for that adverse event. Adverse events are coded using MedDRA Version 23.0. Toxicity Grade is based on NCI common toxicity criteria, version 4.03.
[a] Rash TEAE medical concept consist of preferred terms: dermatitis acneiform, rash, rash maculo-papuler, acne, folliculitis, skin lesion, erthyema, rash erythematous, rash popular, dermatitis, erythema multiforme, perineal rash, pustule, rash macular, rash pruritus, rash pustular, rash vesicular, skin exfoliation, toxic epidermal necrolysis, macule
[b] Percentages are based on the number of subjects with one or more treatment-emergent rash AEs of clinical importance.

Source: Mod5.3.5.2/61186372EDI1001/AttTSFAE03CPART1OF2, AttTSFAE03CPART2OF2, AttTSFAE03E, AttTSFAE05CPART1OF2, AttTSFAE05CPART2OF2, AttTSFAE03TT, AttTSFAE03X2PART1OF2, Att TSFAE03X2PART2OF2

Management of Rash TEAEs

As indicated above, rash was an anticipated AE for EDI1001 and management guidelines for rash were incorporated into the study protocol.

Among the 277 subjects in All Treated population with a rash TEAE (grouped term), the most frequent treatment for the rash event was antibacterials for systemic use (70.4%) eg, tetracyclines (58.8%). Corticosteroids for systemic use were administered to 48.4% of subjects, eg, glucocorticoids.

In the All Treated population, dose reduction, dose interruption, and treatment discontinuation to manage a rash TEAE was undertaken in 9.4%, 6.9%, and 0.6%, respectively (Table 52).

The experience regarding rash event treatment and management in the Exon 20ins + prior chemotherapy at RP2D and All Treated at RP2D populations was consistent with that described for the All Treated population.

The Applicant's Position:

The rash-related data in Study EDI1001 is consistent with the EGFR inhibitor class of therapeutics, and is familiar to health care providers who treat NSCLC. While rash was the most common category of TEAEs, most cases were Grade 1 or 2 in severity and non-serious. Rash TEAEs were successfully managed by dose interruption or dose reduction and antibacterial and steroid treatment; very few of these TEAEs (<1%) required discontinuation of amivantamab treatment.

The proposed USPI for amivantamab provides specific guidance in the Warnings and Precautions section to minimize and manage the risk of skin (b) (4) reactions, including rash, and rash is a listed ADR.

The FDA's Assessment:

In the Applicant's 120 day update, the below information was provided.

All Treated (n=411): Rash events (grouped term) were the most common category of TEAEs reported in All Treated population (73.0%), with dermatitis acneiform (35.3%), and rash (34.3%), being the most frequent specific events observed.

Among the 300 subjects in this population with a rash TEAE, 162 (54.0%) had more than 1 rash TEAE as of the clinical cutoff date, with 27.7% of subjects having 3 or more rash TEAEs.

In general, rash events were of Grade 1 or 2 severity and non-serious. The initial reported rash TEAE was Grade 1 (233 of 300, 77.7%) or Grade 2 (66 of 300, 22.0%) in all subjects.

- In the 120 day safety update follow up period, there were 23 subjects who reported initial rash-related events.
- Among the 300 subjects in the All Treated population with a rash event (grouped term), the maximum severity was Grade 1 in 152 subjects (37.0%) and Grade 2 in 133 subjects (32.4%). Fifteen subjects (3.6%) had a Grade 3 rash event (dermatitis acneiform [6 subjects], rash [6 subjects] acne [2 subjects], and toxic epidermal necrolysis and rash pustular [each for 1 subject]).
    - All of the 21 Grade 3 rash events in 15 subjects were related to study treatment; 4 were rated as serious and required hospitalization. Treatment was provided in all cases. Thirteen events led to dose interruption, 4 events led to dose reduction, only one event of toxic epidermal necrolysis caused discontinuation from treatment. This event is described in the SCS submitted with the BLA. One event is not recovered/not resolved, 3 events are recovering/resolving, 4 events are recovering with sequelae.

All Treated at RP2D (n=302) and **Exon 20ins + prior chemotherapy at RP2D (n=129)**: The overall occurrence and pattern of rash events (grouped term) for the All Treated at RP2D and Exon 20ins + prior chemotherapy at RP2D populations were consistent with that reported for the All Treated population.

- The overall frequency of rash events was 73.5% and 82.2% for the All Treated at RP2D and Exon 20ins + prior chemotherapy at RP2D populations, with 3.3% and 3.9% of subjects, respectively, having a worst grade rash event of Grade 3 severity

FDA agrees with the Applicant's position that the clinical trial protocol included a suggested algorithm for management of rash in patients receiving amivantamab. The rash management guidelines included both proactive and reactive rash management. The below table presents FDA's analysis of the rash events reported in the clinical trial.

FDA - Table 50: Treatment-emergent Adverse Events (TEAE) occurring in ≥10% of safety population

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 (%)	Grade 3-4 (%)	Grade 1-5 (%)	Grade 3-4 (%)
Skin and subcutaneous tissue disorders				
Rash (GT)	109 (84)	5 (3.9)	225 (74)	10 (3.3)

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN.
Rash-SP (GT) includes: Acne, Dermatitis, Dermatitis acneiform, Eczema, Eczema asteatotic, Palmar-plantar erythrodysaesthesia syndrome, Perineal rash, Rash, Rash erythematous, Rash maculo-papular, Rash papular, Rash vesicular, Skin exfoliation, and Toxic epidermal necrolysis.

In the safety population of 302 patients, the median time to onset of rash (GT) was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients treated with amivantamab, and amivantamab was permanently discontinued due to rash in 0.7% of patients.

Toxic epidermal necrolysis

Toxic epidermal necrolysis was reported in one patient. Patient (b) (6) is a 61 year old female NSCLC with metastasis to lymph node and parenchyma of lower right lung lobe. Patient received 1050 mg of amivantamab and on Day 16, a grade 2 adverse event of rash was reported. The patient had roseoliform eruption of the trunk, thighs, and appearance of oral erosions. On Day 29, the rash worsened in severity to grade 3 and grade 2 pruritus was reported. Amivantamab therapy was interrupted due to rash. Patient continued with doxycycline therapy and on Day 37, the rash worsened and patient was hospitalized. The rash was covering more than 30% of the body surface and was composed of erythematous, popular, crusted elements with erosive areas on the outer thighs, right breast, and lips. Amivantamab treatment interrupted and patient continued with doxycycline therapy and corticosteroids. On Day 48, SAE of Grade 3 toxic epidermal necrolysis (TEN) with involvement of approximately 50% of the body surface area was reported and subject was hospitalized. Day 49 biopsy of skin lesion confirmed epidermal necrolysis. Amivanatmab treatment

discontinued on Day 50 and the last dose received was Day 23. TEN resolved on Day 107 and patient was discharged from the hospital.

The Warnings and Precautions section of the label will include dermatologic adverse reactions. FDA's review of nail reactions (paronychia) is located in Section 8.5.5.4. Section 17 of the label will provide guidance to patients to limit sun exposure, wear protective clothing, and use a broad-spectrum UVA/UVB sunscreen while on amivantamab therapy (b) (4) as these were the specific instructions provided to patients enrolled in the clinical trial.

8.5.5.3. Interstitial Lung Disease (Grouped Term)

The Applicant's Description:
Interstitial lung disease (ILD) and ILD-like AEs have been associated with EGFR TKI use at an incidence on average between 1% and 4% (Endo 2006; Min 2011; Shi 2014; Suh 2018). While the mechanism of action is not clear, it is thought that EGFR inhibition may lead to injury of the endothelium of alveolar capillaries and pneumocytes, thus, leading to the recruitment of inflammatory cells and subsequent pulmonary damage (He 2019; Min 2011).

Based on this class effect, the monitoring and management for pulmonary toxicity was incorporated into the EDI1001 protocol initially for the combination with lazertinib, but was then subsequently instituted for all subjects. Study treatment was to be withheld upon the diagnosis of suspected ILD/pneumonitis and steroid treatment was to be initiated (implemented in Amendment 9 [30 April 2020] to the protocol). Upon confirmation of ILD, discontinuation of amivantamab was recommended. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD have not been studied.

Data:

A summary of key characteristics of ILD TEAEs (grouped term) reported in Study EDI1001 in the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations is provided in Table 54. The pattern of these events was consistent across the safety populations. *[Source: Mod2.7.4/Sec2.1.5.3; Mod2.5/Sec5.2.3.3]*

Table 51: Summary of Treatment-emergent Adverse Events of Clinical Importance – Interstitial Lung Disease; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D + Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Interstitial Lung Disease (grouped term)			
No. (%) with any grade ILD TEAEs	5 (4.4%)	7 (2.7%)	10 (2.8%)
Pneumonitis	4 (3.5%)	6 (2.3%)	9 (2.5%)
Interstitial lung disease	1 (0.9%)	1 (0.4%)	1 (0.3%)
No. (%) with maximum severity ILD TEAEs			
Grade 1	2 (1.8%)	2 (0.8%)	2 (0.6%)
Grade 2	3 (2.6%)	4 (1.6%)	6 (1.7%)
Grade 3	0	1 (0.4%)	2 (0.6%)
Grade 4	0	0	0
Grade 5	0	0	0
No. (%) with serious ILD TEAEs	2 (1.8%)	3 (1.2%)	5 (1.4%)
No. (%) with ILD TEAE leading to discontinuation	0	0	1 (0.3%)
Time to first onset (days)			
Median	44.00	55.00	56.00
Range	(42.0; 57.0)	(42.0; 128.0)	(12.0; 322.0)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the total column for that adverse event. Adverse events are coded using MedDRA Version 23.0. Toxicity Grade is based on NCI common toxicity criteria, version 4.03.

Source: Mod5.3.5.2/61186372EDI1001/AttTSFAE03CPART1OF2, AttTSFAE03CPART2OF2, AttTSFAE03E, AttTSFAE05CPART1OF2, AttTSFAE05CPART2OF2, AttTSFAE03TT

In the All Treated safety population, 10 subjects (2.8%) had treatment-emergent ILD TEAEs, including 9 subjects with pneumonitis. All but 2 of these events were Grade 1 or 2 in severity, and none were Grade 4. The 5 serious ILD TEAEs (grouped term) in the All Treated safety population included 4 events of pneumonitis and 1 event of ILD.

All ILD TEAEs received treatment, most commonly with glucocorticoids such as prednisolone. The action with regards to amivantamab therapy was varied (no change, dose interrupted, dose reduced). Only 1 ILD TEAE (pneumonitis, non-serious, Grade 2) led to treatment discontinuation of amivantamab therapy. *[Source: Mod2.7.4/Sec2.1.5.3]*

The Applicant's Position:

As anticipated based on its mechanism of action, cases of ILD and ILD-like adverse reactions were reported at a low rate (<3%) with amivantamab, within the expected incidence rate for other EGFR

TKIs. The majority of the events were managed with interruption of amivantamab treatment and initiation of steroids.

The proposed USPI for amivantamab provides specific guidance in the Warnings and Precautions sections to minimize and manage the risk of ILD reactions, and ILD is a listed ADR.

The FDA's Assessment:

In the Applicant's 120 day update, the below information was provided.

ILD (grouped term) occurred in 3.2% of the All Treated population, 3.3% of the All Treated at RP2D population and 4.7% of the Exon 20ins + prior chemotherapy at RP2D treated population.

All Treated (n=411): Thirteen subjects (3.2%) in the All Treated population had treatment-emergent ILD events: 1 subject (0.2%) with interstitial lung disease and 12 subjects (2.9%) with pneumonitis. Overall, 10 of 13 ILD events were Grade 1 or 2 severity.

All Treated at RP2D (n=302) and **Exon 20ins + prior chemotherapy at RP2D (n=129)**: The overall occurrence and pattern of ILD TEAEs for the All Treated at RP2D and Exon 20ins + prior chemotherapy at RP2D populations were consistent with that reported for All Treated populations. Interstitial lung disease or pneumonitis were reported in 4.7% of 129 subjects.

FDA agrees with the Applicant's position; see the table below for FDA's analysis of pneumonitis.

Pneumonitis occurred in 3.3% of patients in the n=302 population with 0.7% of patients experiencing Grade 3 pneumonitis. Three patients (1%) discontinued amivantamab due to pneumonitis. The Warnings and Precautions section of the label will include instructions to monitor patients for new or worsening symptoms indicative of ILD/pneumonitis, withhold treatment when ILD/pneumonitis is suspected, and permanently discontinue amivantamab if ILD/pneumonitis is confirmed.

FDA - Table 52: Treatment-emergent adverse event - Pneumonitis (GT)

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 (%)	Grade 3-4 (%)	Grade 1-5 (%)	Grade 3-4 (%)
Pneumonitis (GT)	6 (4.7%)	1 (0.8%)	10 (3.3%)	2 (0.7%)
Pneumonitis	5 (3.9%)	1 (0.8%)	9 (3%)	2 (0.7%)
Interstitial lung disease	1 (0.8%)	0	1 (0.3%)	0

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN.
Pneumonitis (GT) includes: Interstitial lung disease, and Pneumonitis

8.5.5.4. Peripheral Edema (Grouped Term)

Applicant's Description:
Peripheral edema has been identified as a class effect with MET TKIs (Parikh 2014; Puccini 2019; Salgia 2014; Spigel 2017). For this reason, peripheral edema was considered an AE of clinical importance with

amivantamab. No specific guidelines were included in the protocol concerning the prophylaxis or management of peripheral edema events.

Hypoalbuminemia, another event that has been identified as a class effect with MET TKIs, may be a potential contributor to the event of peripheral edema. Inhibition of hepatocyte growth factor, the ligand that activates the MET receptor (Ishii 1995), can result in decreased serum albumin based on role of MET in stimulation of protein synthesis in liver. As albumin is the predominant protein regulating osmotic pressure, a decrease in albumin levels can lead to reduced osmotic pressure and peripheral edema may result from a shift of fluid into the interstitial spaces (Gatta 2012). Consistent with amivantamab's on-target MET activity, subjects in this study have demonstrated a decline in serum albumin levels as described above under Clinical Laboratory data.

Data:

A summary of key characteristics of peripheral edema TEAEs (grouped term) reported in Study EDI1001 in the Exon 20ins + prior chemotherapy at RP2D, All Treated at RP2D, and All Treated safety populations is provided in Table 56. The pattern of these events was consistent across the safety populations. *[Source: Mod2.7.4/Sec2.1.5.4; Mod2.5/Sec5.2.3.4]*

Table 53: Summary of Treatment-emergent Adverse Events of Clinical Importance – Peripheral Edema; All Treated Analysis Set in Monotherapy (JNJ-61186372) (Study 61186372EDI1001)

	RP2D		All Treated (RP2D + Non-RP2D)
	Exon 20 Ins Prior Chemotherapy	Total	
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Peripheral Edema TEAEs (grouped term)[a]			
No. (%) with any grade Peripheral edema TEAE	22 (19.3%)	52 (20.2%)	70 (19.3%)
No. (%) with maximum severity Peripheral edema TEAE			
Grade 1	20 (17.5%)	42 (16.3%)	59 (16.3%)
Grade 2	2 (1.8%)	8 (3.1%)	9 (2.5%)
Grade 3	0	2 (0.8%)	2 (0.6%)
Grade 4	0	0	0
Grade 5	0	0	0
No. (%) with serious Peripheral edema TEAE	0	0	0
No. (%) with Peripheral edema TEAE leading to discontinuation	0	0	0
Time to first onset (days)			
Median	55.00	70.00	71.00
Range	(14.0; 588.0)	(1.0; 588.0)	(1.0; 588.0)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: AE = adverse event
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. The event experienced by the subject with the worst toxicity is used. If a subject has missing toxicity for a specific adverse event, the subject is only counted in the total column for that adverse event. Adverse events are coded using MedDRA Version 23.0. Toxicity Grade is based on NCI common toxicity criteria, version 4.03.
[a] Peripheral edema TEAE medical concept consist of preferred terms of edema peripheral, edema, and generalized edema.

Source: Mod5.3.5.2/61186372EDI1001/AttTSFAE03CPART1OF2, AttTSFAE03CPART2OF2, AttTSFAE03E, AttTSFAE05CPART1OF2, AttTSFAE05CPART2OF2, AttTSFAE03TT

In the All Treated safety population, almost all peripheral edema TEAEs (grouped term) were Grade 1, none were Grade 3 or higher, and all were non-serious. Additional characteristics of the pattern of peripheral edema TEAEs in the All Treated safety population are as follows:

- Twenty-four (34.3%) of the 70 subjects in the All Treated safety population with a peripheral edema TEAE had a reported TEAE of hypoalbuminemia within 30 days prior to the onset of peripheral edema.
- For 18 (25.7%) of the 70 subjects with a peripheral edema TEAE, the event resolved by the clinical cutoff, and the median time to resolution was 39.0 days (range: 1 to 293).
- No subject in this population had a peripheral edema TEAE that resulted in study drug discontinuation; for 1 subject each with a peripheral edema TEAE (1.4%), the event resulted in dose reduction or drug interruption. [*Source: Mod2.7.3/Sec2.1.5.4]*

Similar results were seen for the Exon 20ins + prior chemotherapy at RP2D and All Treated at RP2D safety populations.

Peripheral edema TEAEs (grouped term) in this study were most commonly managed by concomitant use of diuretic medications. Eighteen (25.7%) of the 70 subjects in the All Treated safety population with a peripheral edema TEAE received diuretic treatment for their event.

The Applicant's Position:

The clinical experience regarding peripheral edema TEAEs in Study EDI1001 is consistent with the class of MET inhibitors. All of the reported events of peripheral edema were Grade 1 or 2 in severity and non-serious, and were managed with concomitant therapy (ie, diuretics) and generally did not result in amivantamab treatment modification. Peripheral edema is a listed ADR in the proposed amivantamab USPI.

The FDA's Assessment:

See the table below for FDA's evaluation of edema (GT) based on the 120-day safety update.

FDA - Table 54: Treatment emergent adverse event - Edema (GT) safety population

	Analysis population			
	E20 ins mutations prior chemotherapy (N=129)		RP2D (N=302)	
	Grade 1-5 (%)	Grade 3-4 (%)	Grade 1-5 (%)	Grade 3-4 (%)
Edema (GT)	32 (25%)	1 (0.8%)	70 (23%)	3 (1%)
Edema peripheral	27 (21%)	1 (0.8%)	60 (20%)	3 (1%)
Face edema	2 (1.6%)	1 (0.8%)	6 (2%)	1 (0.3%)
Eyelid edema	2 (1.6%)	0	2 (0.7%)	0
Periorbital edema	2 (1.6%)	0	2 (0.7%)	0
Generalised edema	2 (1.6%)	0	4 (1.3%)	0
Edema	1 (0.8%)	0	2 (0.7%)	0
Lip edema	1 (0.8%)	0	1 (0.3%)	0
Eye edema	0	0	1 (0.3%)	0
Localised edema	0	0	2 (0.7%)	0

Source: adae.xpt, adsl.xpt. Variables used: USUBJID, APOP, TRTEMFL, AEDECOD, AEBODSYS, AETOXGRN.
Edema (GT) includes: eye edema, eyelid edema, face edema, generalized edema, lip edema, localized edema, edema, edema peripheral, and periorbital edema.

In the safety population of 129 patients, edema led to interruption of amivantamab dosing in 2.3% of patients and dose reduction in 0.8% of patients.

8.5.5.4. Additional EGFR-Mediated Adverse Reactions

Data:

Evaluation of 3 additional adverse reactions known to be associated with EGFR inhibition were included in the Summary of Clinical Safety for this BLA: paronychia (represented by single preferred

term), diarrhea (represented by single preferred term), and eye disorders (represented by MedDRA SOC). For these events, results are described below for the All Treated safety population; similar findings were seen for the Exon 20ins + prior chemotherapy at RP2D and All Treated at RP2D populations. *[Source: Mod2.7.4/Sec 2.1.6]*

- Paronychia: In the All Treated safety population, paronychia was reported in 39.2% of subjects, with most events being of Grade 1 or 2 severity (5 subjects [1.4%] with Grade 3 paronychia). All reported events of paronychia were non-serious, and treatment was discontinued in <1% of subjects (2 subjects) for this TEAE.
- Diarrhea: In the All Treated safety population, diarrhea occurred in 10.5% of subjects, with most events being of Grade 1 or 2 severity (6 subjects [1.6%] with Grade 3 diarrhea). Two subjects experienced events of serious diarrhea for which they were hospitalized and amivantamab was interrupted. Study treatment was not discontinued for any subject due to diarrhea.
- Eye Disorders: Eye disorders occurred in 11.0% of the All Treated population, with dry eye (3.3%), vision blurred (1.7%), and eye pruritis (1.4%) being the most frequently reported preferred terms. Keratitis occurred at a frequency of 0.6%, with 1 event considered related to amivantamab by the investigator and which led to amivantamab dose interruption. Study treatment was not discontinued for any subject due to an eye disorder TEAE.

The Applicant's Position:

Paronychia, diarrhea, and eye disorders are listed ADRs in the proposed USPI. In addition, specific guidances are included in the Warnings and Precautions section to minimize and manage the risk of eye disorders and (b) (4) paronychia.

The available clinical experience indicates that these 3 adverse reactions, which are known to be associated with EGFR inhibition, are mostly Grade 1 and 2 in severity, are generally non-serious, and typically do not result in discontinuation of amivantamab treatment.

The FDA's Assessment:

In the Applicant's 120 day update, in the **All treated (n=411):** Paronychia occurred in 39.9%; 40.4% and 49.6% in the **All treated at RP2D (n=302)** and **Exon 20ins + prior chemotherapy at RP2D (n=129)**, respectively.

Diarrhea occurred in 10.9% of the All Treated (n=411); 10.9% and 14.7% in the All Treated at RP2D (n=302) and Exon 20ins_+ prior chemotherapy at RP2D (n=129).

Eye disorders occurred in 11.9% of the All Treated (n=411); 13.2% and 14.0% in the All Treated at RP2D (n=302) and Exon 20ins + prior chemotherapy at RP2D (n=129).

The following information is based on FDA's assesement of paronychia and diarrhea in the indicated population (n=129). The incidence of paronychia was 50% all grades and 3.1% grade 3. Paronychia results in dose interruption in 3.1% of patients and dose reduction in 2.3%. Paronychia did not rise to the level of a Warnings and Precautions in the labeling as this event is a manageable toxicity.

Paronychia is listed in both Section 6 Adverse Reactions and Section 17 Patient Counseling Information in the amivantamab product labeling.

The incidence of diarrhea was 16% all grades and 3.1% grade 3. Diarrhea resulted in dose interruption in 5% of patients; no patient had dose reduction for diarrhea. Two patients (b) (6) (b) (6) experienced serious diarrhea for which they were hospitalized. One of these patients (b) (6) (b) (6) experienced ongoing diarrhea at the end of study. In both patients, amivantamab dosing was interrupted. Diarrhea is listed in Section 6 Adverse Reactions in the amivantamab product labeling.

FDA assessed ocular toxicity in the larger safety population of 302 patients. Ocular toxicity occurred in 13.2% of patients. The most common events (≥1%) include dry eye (3%), vision blurred (1.7%), eye pruritus (1.3%), and visual impairment (1%). Keratitis was reported in 0.7% of patients and uveitis was reported in 0.3% (one patient). Patients may experience dry eye symptoms, conjunctival redness, blurred vision, ocular itching, periocular edema, and uveitis. The potential consequences of untreated keratitis or uveitis can include loss of vision, and therefore, ocular toxicity is included in the Warnings and Precautions section of the label.

8.2.7. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with Applicant's position.

8.2.8. Safety Analyses by Demographic Subgroups

Data:

Separate analyses of TEAEs are included in this BLA to evaluate potential differences in the safety profile for amivantamab monotherapy among subgroups defined by intrinsic factors of age (<65 vs ≥65, <75 vs ≥75), sex (male vs female), race (Asian vs Non-Asian), baseline body weight (<80 vs ≥80 kg), presence of renal impairment at baseline (normal, mild, moderate), and presence of hepatic impairment at baseline (normal, mild, moderate). Safety in these special populations is evaluated for the All Treated safety population (N=362), except for body weight, which is evaluated for the All Treated at RP2D safety population (N=258).

Data for these subgroup analyses of the amivantamab safety profile are summarized in:

- Module 2.7.4, Table 23 for the overall TEAE profile as a function of age, sex, and race for the All Treated safety population. [see *Mod5.3.5.2/61186372EDI1001/AttTSFAE03S1*, *AttTSFAE03S3*, and *AttTSFAE03S4* for TEAEs of clinical importance]
- Module 5.3.3.2/61186372EDI1001, Attachment TSFAE01-RP2D-DL for the overall TEAE profile as a function of baseline body weight/RP2D dose for the All Treated at RP2D safety population

- Module 2.7.4, Table 24 for the overall TEAE profile as a function of baseline renal impairment for the All Treated safety population. The proportions of subjects with mild (estimated glomerular filtration rate [eGFR]: 60 to <90 mL/min/1.73m^2) or moderate (eGFR: 30 to <60 mL/min/1.73m^2) renal impairment at baseline were 43.1% and 9.9%, respectively.
- Module 2.7.4, Table 25 for the overall TEAE profile as a function of baseline hepatic impairment (for the All Treated safety population. The number of subjects with mild hepatic impairment (total bilirubin ≤ULN and AST >ULN) or (ULN < total bilirubin ≤1.5× ULN) was 37 (10.2%) at baseline.

Key findings of these subgroup analyses were as follows: *[Source: Mod2.7.4/Sec5.1]*

- Age: The overall tolerability profile of amivantamab was generally consistent for subjects aged <65 years and those ≥65 years, with the possible exception of a higher frequency (difference >10%) of TEAEs leading to dose interruption among the older subjects. Interpretation of potential differences in safety profiles between subjects <75 years of age and those 75 years or older is difficult given the fact that more than 85% of the safety population were <75 years of age.
- Sex: The overall tolerability profile of amivantamab was generally consistent for men and women, with the possible exception of a higher rate (difference >10%) of TEAEs leading to dose interruption for women and of rash TEAEs (grouped term) for men.
- Race: The overall tolerability profile of amivantamab was generally consistent with respect to overall incidence of TEAEs, serious TEAEs, TEAEs leading to discontinuation or death, and TEAEs of clinical importance (ILD, peripheral edema) for Asian and non-Asian subjects; higher frequencies (difference >10%) for Grade 3 or higher TEAEs, TEAEs of IRR and rash (grouped term), TEAEs leading to dose reduction, dose interruption, or infusion modification were apparent among non-Asian subjects.
- Body weight: The overall tolerability profile of amivantamab was generally consistent for subjects with a baseline body weight of <80 kg (treated with 1050 mg dose) and those weighing ≥80 kg (treated with 1400 mg dose), with the possible exception of higher rates (difference >10%) of TEAEs leading to dose reduction or infusion modification in the ≥80 kg subgroup, and higher rates of TEAEs leading to dose interruption in the <80 kg subgroup.
- Renal impairment: The overall tolerability profile of amivantamab was consistent for subjects with normal and mild renal impairment; among the small subgroup of subjects (n=36) with moderate renal impairment, apparently higher rates of Grade 3 or higher TEAEs and serious TEAEs were observed compared with subjects having normal or mild renal impairment. Interpretation of these latter differences is difficult given the small number of subjects.
- Hepatic impairment: Of the 362 subjects in the All Treated population, 325 (89.8%) had normal baseline hepatic function (total bilirubin ≤ULN and AST ≤ULN). Thus, interpretation of the differences in safety profiles for amivantamab as a function of baseline hepatic function is difficult. Nevertheless, there were no apparent differences in any TEAE endpoint between subjects with normal hepatic function and those with mild hepatic impairment (difference in frequency <10%).

The Applicant's Position:

Although some differences were observed in the frequency of certain TEAE categories in subgroups defined by age, sex, race, or baseline body weight, none suggested that administration of amivantamab was associated with a clinically meaningful increased risk in any of the subgroups evaluated. Moreover, the overall safety profile for amivantamab as a function of baseline renal or hepatic function did not suggest that any dosage adjustment was necessary for patients with mild or moderate renal impairment or for those with mild hepatic impairment.

The FDA's Assessment:

In the Applicant's 120 day update, the below information was provided.

Age

- There was no apparent difference in the overall frequency of TEAEs, related TEAEs, Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to dose reduction, infusion modification, discontinuation, or death as a function of age for this population (difference in frequency <10%).
- There was a higher frequency (difference >10%) of TEAEs leading to dose interruption among the ≥65 years subgroup compared with the <65 years subgroup.
- The most frequent TEAE in both age subgroups was rash, which was reported at a similar rate among subjects <65 years (73.9%) and among those ≥65 years (71.7%).
- The other TEAEs of clinical importance also had a less than 10% difference between the age groups (<65 years and ≥65 years), though peripheral edema was just under a 10% difference.
- Individual common TEAEs (>20% in either age subgroup) generally occurred at similar frequencies (difference <10%) for subjects aged <65 or ≥65 years (rash, paronychia, dermatitis acneiform, hypoalbuminemia, nausea, constipation, fatigue, stomatitis, dyspnea, peripheral edema, IRR, and pruritus).

Overall, the TEAEs profile among subjects <65 years and those ≥65 years was consistent.

In the safety population of 129 patients, 41% were 65 years of age or older and 9% were 75 years of age or older. FDA agrees with the Applicant's presentation of the data.

Sex

- There was a higher frequency of Grade 3 or higher TEAEs among women (42.7% with women and 36.4% with men), although the frequency of related Grade 3 or higher TEAEs was similar for both sexes.
- Of the 20 subjects who had a TEAE resulting in death, 15 were women. None of the events leading to death was related to amivantamab.

- TEAEs leading to dose reduction (any event as well as related events), infusion modification, or treatment discontinuation occurred at similar rates for men and women, although TEAEs leading to dose interruption were slightly higher in women (34.6% in women and 26.5% in men).
- There were no clinically relevant differences for this population between the sexes in the frequencies of the TEAEs of clinical importance categories.
- Individual common TEAEs (>20% in either sex subgroup) generally occurred at similar frequencies (difference <10%) for men and women (peripheral edema, IRR, rash, paronychia, hypoalbuminemia, stomatitis, nausea, and constipation). The frequency of the common TEAEs of dermatitis acneiform was higher in men (42.4% in men and 31.2% in women).

In addition, no major difference in TEAEs was observed between males and females when comparing subsets within the RP2D dose (1050 mg for <80 kg and 1400 mg for ≥80 kg).

In general, FDA agrees with the Applicant except for the Applicant's statement, "None of the events leading to death was related to amivantamab." See FDA's Assessment regarding deaths earlier in this review.

Race

Race was reported for 94.6% of subjects; 60.0% of the population was Asian.

There was no apparent difference in the overall frequency of TEAEs, related TEAEs, serious TEAEs, or TEAEs leading to discontinuation or death as a function of race for the All Treated population (difference in frequency <10%).

Within the All Treated population, IRRs and on-target events of paronychia, dermatitisacneiform, rash, and hypoalbuminemia were among the most frequently reported TEAEs for both the Asian and non-Asian subgroups. The frequencies of IRRs and dermatitis acneiform were higher (difference of >10%) for the non-Asian subgroup, while the frequency of paronychia and rash were higher for the Asian subgroup.

Importantly, the differences in the All Treated comparison of Asian and non-Asian populations may also reflect differences in study conduct and enrolled population, as the initial Part 1 Dose Escalation (NSCLC) and initial Part 2 Cohorts A and B were conducted in Korea, prior to the global expansion of the study, and opening of Cohorts C, D, MET-1, and MET-2.

Correspondingly, when the Asian and non-Asian analysis is limited to the more uniform Exon 20ins + prior chemotherapy at RP2D, these differences in race-specific safety profiles were not observed (Table 21). The rates of EGFR and MET toxicities were also similar between Asians and non-Asians.

In addition, no major difference in TEAEs was observed between Asians and non-Asians when comparing subsets within the RP2D dose (1050 mg for <80kg and 1400 mg for ≥80kg).

In general, FDA agrees with the Applicant.

Weight

The overall tolerability profile was generally consistent for the two RP2D amivantamab doses administered (1050 mg and 1400 mg), with the possible exception of higher rates of TEAEs leading to dose reduction or infusion modification at the 1400 mg dose level, and higher rates of TEAEs leading to dose interruption at the 1050 mg dose level.

FDA notes that in the safety population of 302 patients, 84% had baseline body weight <80 kg and 16% had baseline body weight ≥80 kg and in the safety population of 129 patients, 82% had baseline body weight <80 kg and 18% had baseline body weight ≥80 kg which may not accurately reflect the US population.

For renal and hepatic impairment subgroup analysis, please see the clinical pharmacology review in Section 6.2.2.2.

8.2.9. Specific Safety Studies/Clinical Trials

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees with the Applicant's position.

8.2.10. Additional Safety Explorations

The FDA's Assessment:

Not applicable.

8.2.11. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

The Applicant's Position:

Not applicable as amivantamab is not yet marketed in any region.

The FDA's Assessment:

FDA agrees.

Expectations on Safety in the Postmarket Setting

Data and Applicant's Position:

Not Applicable.

The FDA's Assessment:

The review teams determined that a REMS is not required to ensure safe and effective use of amivantamab. Amivantamab will be prescribed by oncologists who are trained on how to monitor, diagnosis, and manage serious adverse reactions caused by anti-neoplastic drugs in accordance with

FDA-approved labeling. Additionally, standard practice in oncology dictates informed consent prior to prescribing or administering anti-neoplastic drugs.

8.2.12. Integrated Assessment of Safety

Data:

Safety data presented in this BLA are derived from a single ongoing study of amivantamab, Study EDI1001, and thus there was no integration with other Applicant-conducted clinical trial data.

The Applicant's Position:

With a safety experience of 114 subjects in the target indication population of Exon 20ins NSCLC patients (with prior platinum-based chemotherapy treated at RP2D), 258 subjects treated with amivantamab at the RP2D, and 362 subjects treated with any dose of amivantamab, the Applicant considers the safety profile of amivantamab to be well characterized. Among the most frequently experienced TEAEs are those anticipated with on-target EGFR and MET inhibition, providing further evidence of effective pathway inhibition by amivantamab. The proposed USPI provides guidance to physicians regarding the identification and management of risks associated with amivantamab treatment, which are consistent with other approved agents in the class of EGFR and MET inhibitors and are familiar to health care providers who treat NSCLC.

The FDA's Assessment:

The primary safety database analyzed by the FDA for this BLA was from the 120-day safety update and includes 411 patients treated with any dose of amivantamab. The primary safety populations analyzed by FDA included 302 patients treated with amivantamab (1050 mg for patient baseline body weight <80 kg or 1400 mg for patient baseline body weight ≥80 kg) and the subgroup of 129 patients with NSCLC harboring exon 20 insertion mutations previously treated with platinum-based chemotherapy. Among the 129 patients with NSCLC harboring exon 20 insertion mutations treated with prior platinum-based chemotherapy, discontinuation of amivantamab due to adverse reactions occurred in 11% of patients and dose reduction due to adverse reactions occurred in 15% of patients. While 78% of patients had amivantamab dosing interrupted for an adverse reaction, the majority of dose interruptions were related to infusion-related reactions (IRR). Over 90% of IRRs occurred on Day 1 or 2 of the initial Week 1 infusion, with the incidence of IRR 65% with Week 1 Day 1 infusion, 3.4% Week 1 Day 2, 0.4% Week 2, and 1.1% with subsequent infusions. IRRs were mostly Grades 1-2, with 2.2% of reported IRRs Grade 3 and 0.4% Grade 4. The most common adverse reactions (incidence ≥20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting.

Safety issues identified as significant and serious during the BLA review were IRR, ILD/pneumonitis, dermatologic adverse reactions, and ocular toxicity. These safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. There were no significant safety concerns identified during BLA review

requiring risk management beyond labeling or warranting consideration for Risk Evaluation and Mitigation Strategy (REMS). Amivantamab appears to have an acceptable safety profile when assessed in the context of a life-threatening disease.

9 SUMMARY AND CONCLUSIONS

9.1. Statistical Issues

The FDA's Assessment:

There were no major statistical issues in the review of this BLA. However, the single-arm design of the main trial supporting efficacy limits the interpretation of time-to-event endpoints, such as PFS and OS, given the absence of an active control or comparison to the natural history of disease.

9.2. Conclusions and Recommendations

The FDA's Assessment:

Based on the data from Study EDI1001, for patients with NSCLC harboring EGFR exon 20 insertion mutations with disease progression following platinum-based chemotherapy, amivantamab demonstrated a clinically meaningful overall response rate and duration of response. The ORR per RECIST v1.1 as assessed by BICR was 40% (95% CI: 29, 51), with a median duration of response of 11.1 months (95% CI: 6.9, not evaluable).

Available therapy for this patient population is the same as that for patients without a specific driver mutation and progression of disease following platinum-based chemotherapy, and includes chemotherapy (single agent or docetaxel in combination with ramicurimab), associated with ORR 6-23% with median durations of responses in the range of 4 to 9 months, or single agent anti-PD(L)-1 antibody if not received in the first-line setting, associated with ORR 14-20% with median durations of response in the range of 16 to 17 months. When considered in this context, the ORR along with the durability of responses observed with amivantamab provide clinical benefit in patients with advanced NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

Given the relatively limited duration of follow-up and the number of patients in the primary efficacy analysis population for this application, the current data are considered adequate to support accelerated approval rather than regular approval. Results from the ongoing trial entitled, "A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer" may be used to verify the clinical benefit of amivantamab in patients with advanced NSCLC with EGFR exon 20 insertion mutations. Submission of additional data from CHRYSALIS will be requested as a post-marketing commitment to further characterize and provide a more precise estimation of BICR-assessed ORR and DOR with

amivantamab in patients with advanced NSCLC with EGFR exon 20 insertion mutations previously treated with platinum-based chemotherapy.

The safety populations used to inform labeling included 302 patients with NSCLC treated with amivantamab at the recommended dose and the subgroup of 129 patients with NSCLC with exon 20 insertion mutations and disease progression on or after platinum-based chemotherapy. The most common adverse events were rash, infusion-related reactions (IRR), paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. Serious adverse reactions occurred in 30% of patients. Permanent discontinuation due to an adverse reaction occurred in 11% of patients.

While 78% of patients had amivantamab dosing interrupted for an adverse reaction, the majority of dose interruptions were related to infusion-related reactions (IRR). IRR occurred in the majority (approximately 65%) of patients treated with amivantamab. Over 90% of IRRs occurred on Day 1 or 2 of the initial Week 1 infusion; IRRs were mostly Grades 1-2, with 2.2% of reported IRRs Grade 3 and 0.4% Grade 4. To address this issue, product labeling will include clear instructions regarding split dosing for initial administration, premedication, and management of IRR with interruption of infusion and reduction in infusion rate or permanent discontinuation based on severity. Safety issues identified as significant and serious during the BLA review were IRR, ILD/pneumonitis, dermatologic adverse reactions, and ocular toxicity. These safety concerns are adequately addressed by information in the Warnings and Precautions section and the dose modification recommendations included in product labeling. The safety profile of amivantamab is acceptable when assessed in the context of clinical benefit observed and the life-threatening nature of metastatic NSCLC.

The submitted evidence meets the statutory evidentiary standard for accelerated approval and provides preliminary evidence of the effectiveness of amivantamab as a single agent in patients with advanced NSCLC with exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy. The reviewers recommend granting accelerated approval of amivantamab for the following indication: “RYBREVANT is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.”

X	X
Somak Chatterjee, Ph.D. Primary Statistical Reviewer	Pallavi Mishra-Kalyani, Ph.D. Statistical Team Leader
Katie Chon, PharmD. Primary Clinical Reviewer	Erin Larkins, M.D. Clinical Team Leader

10 Advisory Committee Meeting and Other External Consultations

The FDA's Assessment:

The Division did not refer this application to an advisory committee because the application did not raise significant public health questions on the role of amivantamab in the proposed indication. The application also did not raise significant safety or efficacy issues.

11 Pediatrics

The Applicant's Position:

The FDA agreed on 13 May 2020 to the Applicant's initial Pediatric Study Plan (plan to request waiver for requirement for pediatric assessments for amivantamab for all pediatric age groups) because studies would be impossible or highly impracticable (Ref ID: 4608034). A request for full pediatric waiver consistent with the agreed iPSP is provided in Module 1.9 of the BLA.

The FDA's Assessment:

FDA issued an "Agreed Initial Pediatric Study Plan-Agreement" letter on June 10, 2020, in response to the Applicant's initial pediatric study plan requesting a full waiver.

12 Labeling Recommendations

Data:

This is an original application. Please see annotated label in Module 1.14.1.2 for proposed USPI.

The Applicant's Position:

Not Applicable.

The FDA's Assessment of the Prescribing Information:

Summary of Significant Laeling Changes		
Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
INDICATIONS AND USAGE	No age range specified.	Clarified that the indicated population is adult patients.
DOSAGE AND ADMINISTRATION – Patient Selection	(b) (4)	Specified that patients should be selected based on EGFR

Summary of Significant Laeling Changes		
Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
	(b) (4)	exon 20 insertion mutations. Link to FDA-approved tests.
DOSAGE AND ADMINISTRATION – Recommended Dosage	Recommended Dosage Table.	Clarified that initial dose to be split in Week 1 Day 1 and Day 2. Administer premedications before infusion.
DOSAGE AND ADMINISTRATION – Dosage Modification for Adverse Reactions	Text instructions for skin, (b) (4) and interstitial lung disease (ILD) were provided.	Constructed three column-dosage modification table for management of adverse reactions (ARs), providing details for the management of infusion-related reactions (IRRs), ILD/pneumonitis, Dermatologic and Other ARs. Removed (b) (4) as management is covered under Other ARs.
WARNINGS AND PRECAUTIONS	Text describing IRRs, ILD, (b) (4) (b) (4) and Embryo-Fetal Toxicity.	Edited and revised content to identify the incidence and severity of serious adverse reactions and clarified mitigation strategies. Revised title (b) (4) (b) (4) to Dermatologic Adverse Reactions and (b) (4) (b) (4) to Ocular Toxicity.
ADVERSE REACTIONS	Description of CHRYSALIS trial and reporting of observed adverse reactions.	Revisions to this section were made in accordance with the FDA Guidance: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format and in a format consistent with recently approved oncology labeling.

Summary of Significant Laeling Changes		
Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		Tables for adverse reactions were revised to include appropriate safety group terms.
USE IN SPECIFIC POPULATIONS	Statement that there is no human or animal data to assess the risk in pregnancy.	8.1: Revised based on 21CFR 201.57(c)(9)(i) to include the lack of human and animal data and required background risk statement and in a format that is consistent with recently approved oncology labeling. Although there is no animal data, a description of the mechanism of action's effect on pregnant mice is included. 8.2: Revised in accordance with the format used in recently approved oncology labeling. 8.6 Renal Impairment and 8.7 Hepatic Impairment were removed because there were no clinically significant data/recommendations to present.
DESCRIPTION	Description of Amivantimab.	Revised to include the established pharmacologic class consistent with 21 CFR 201.57(c)(12).
CLINICAL PHARMACOLOGY	Mechanism of Action description, effect on albumin, list of exposure parameters.	12.1 Mechanism of Action: Revised to describe the mechanism of action for the approved indication. 12.2 Pharmacodynamics: Removed the proposed text

Summary of Significant Laeling Changes		
Section	Applicant's Proposed Labeling	FDA's Proposed Labeling
		and included a statement stating that the exposure response relationship and time course of pharmacodynamic response for safety and effectiveness have not been fully characterized as required by 21 CFR 201.57(c)(13)(i)(B). 12.3 Pharmacokinetics: FDA edited text removing unnecessary list of exposure parameters. Removed unnecessary text describing no meaningful differences on pharmacokinetics of Amivantimab based on sex.
CLINICAL STUDIES		Included details on the determination of EGFR Exon 20 insertion mutations in the efficacy population. Revised description of clinical trial for clarity and brevity in accordance with best labeling practices.
PATIENT COUNSELING INFORMATION		Revised text for clarity and brevity in accordance with best labeling practices.

13 Risk Evaluation and Mitigation Strategies (REMS)

The Applicant is not proposing a Risk Evaluation and Mitigation Strategy (REMS) for amivantamab and considers the USPI to serve as the primary risk minimization tool for the management for all adverse reactions. More specifically, IRR and ILD can be sufficiently managed by the dosage and administration and warnings and precautions sections of the proposed USPI. Other approved IV therapies with established IRRs, including EGFR inhibitors, address the IRR management through the labels without associated REMS. Interstitial lung disease is a well-established ADR within the TKI class and there are no REMS for ILD management for the other approved EGFR and MET inhibitors. Lastly, health care providers will administer amivantamab in a health care environment and these health care providers are familiar with the early recognition of symptoms and management of IRRs and ILD. No additional risk minimization and mitigation measures outside of the USPI and the standard fair balanced communications are planned.

The FDA's Assessment:

The clinical review team determined that a risk evaluation and mitigation strategy (REMS) was not required to ensure safe and effective use of amivantamab for the indicated population. Recommendations for the safe and effective use of amivantamab are made in labeling and a patient package insert. There are no additional risk management strategies required beyond the recommended labeling. Although amivantamab is associated with a high incidence of infusion-related reactions and can cause severe/serious toxicity, it will be prescribed by oncologists who, by training, understand how to monitor and manage such toxicities.

14 Postmarketing Requirements and Commitment

The FDA's Assessment:

The Applicant has agreed to the following postmarketing requirement (PMR) and postmarketing commitments (PMC):

Clinical PMR:

Submit the final report, including datasets for progression free survival, overall response rate, duration of response, and overall survival from a randomized clinical trial to verify and confirm the clinical benefit of amivantamab-vmjw for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. This could be from the ongoing clinical trial entitled, "A Randomized, Open-label Phase 3 Study of Combination Amivantamab and Carboplatin-Pemetrexed Therapy, Compared With Carboplatin-Pemetrexed, in Patients With EGFR Exon 20ins Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer."

Final Protocol Submission:	07/2020
Trial Completion:	08/2022
Final Report Submission:	02/2023

Clinical PMC #1:

Submit the final results, including datasets for overall response rate and duration of response, from CHRYSALIS titled " A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of Amivantamab, a Human Bispecific EGFR and cMet Antibody, in Participants with Advanced Non-Small Cell Lung Cancer" to further characterize the clinical benefit of amivantamab-vmjw for the treatment of patients with NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy to provide a more precise estimation of the blinded independent central review-assessed overall response rate and duration of response after all responders in the relevant patient population (approximately 128 patients) have been followed for at least 6 months from the date of initial response (or until disease progression, whichever comes first). These results may inform product labeling.

Final Report Submission:	10/2021

Clinical PMC #2:

Submit a final report containing data from clinical trials enrolling a sufficient representation of Black or African American patients that is reflective of the US population of patients with EGFR exon 20 insertion mutated NSCLC to further characterize the safety and efficacy of amivantamab-vmjw in Black or African American patients with EGFR exon 20 insertion mutated NSCLC.

Draft Analysis Plan Submission: 10/2022

Final Analysis Plan Submission: 01/2023

Final Report Submission: 04/2023

Clinical PMC#3:

Submit a summary of the final report of an analytical and clinical validation study, using clinical trial data, that is adequate to support labeling of a tissue-based in vitro diagnostic device that demonstrates the device is essential to the safe and effective use of amivantamab-vmjw for patients diagnosed with NSCLC with EGFR exon 20 insertion mutations. The results of the validation study may inform product labeling.

Final Report Submission: 08/2021

15 Division Director (DHOT) (NME ONLY)

X

John Leighton, Ph.D.

16 Division Director (OCP)

X

Nam Atiqur Rahman, Ph.D.

17 Division Director (OB)

X

Shenghui Tang, Ph.D.

18 Division Director (Clinical)

X

Harpreet Singh, M.D.

19 Office Director (or designated signatory authority)

This application was reviewed by the Oncology Center of Excellence (OCE) per the OCE Intercenter Agreement. My signature below represents an approval recommendation for the clinical portion of this application under the OCE.

X

Julia Beaver, M.D.

20 Appendices

20.1. References

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20.2. Financial Disclosure

The Applicant's Position:

As noted in Section 8.1.2, the Applicant has adequately assessed clinical investigators for any financial interest/arrangements as defined in 21 CFR Part 54 and no disclosable financial interests were found.

The FDA's Assessment:

FDA agrees with Applicant's position. None of the clinical investigator have disclosable financial interests and the Applicant selected the "NO" boxes and indicated "Not applicable" in the below table.

Covered Clinical Study (Name and/or Number):* 61186372EDI1001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 660		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator in study: N/A Applicant of covered study: N/A		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☒ Not applicable
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☒ Not applicable
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☒ Not applicable

*The table above should be filled by the applicant, and confirmed/edited by the FDA.

20.3. Nonclinical Pharmacology/Toxicology

The Applicant's Position:

Not applicable.

The FDA's Assessment:

FDA agrees.

20.4. OCP Appendices (Technical documents supporting OCP recommendations)

20.4.1. Bioanalytical Method Validation and In-Study Performance

The electrochemiluminescent immunoassay (ECLIA) method on the Meso Scale Discovery (MSD) platform was initially validated at the Janssen Biologics Development Sciences Laboratory (Spring House, PA, USA) to determine concentrations of amivantamab in human serum between 0.32 to 40.96 µg/mL. This method was transferred to (b) (4) and a full validation was performed.

Briefly, a master mix solution consisting of Biotin- huEGFR-Fc Fusion protein and SulfoTag- cMET Fc Fusion protein was added to calibration standards, quality controls (QC), and study samples. The mixture was then transferred to Streptavidin-coated MSD assay plate. Amivantamab present in human serum samples was captured by the formation of a complex between Biotin- huEGFR-Fc and SulfoTag- cMET-Fc Fusion proteins. Unbound material was removed by plate washing, MSD read buffer was added, and the bound complexes were detected by electrochemiluminescence on the MSD plate reader. Amivantamab concentrations were determined by interpolation from the standard curve using a 5 parameter logistic auto-Estimate regression with 1/y2 weighting. Refer to Table Y for assay parameters during method validation.

Table Y: Validation for Project 2329-15411

Analyte	Amivantamab
Assay	ECLIA method on the Meso Scale Discovery (MSD) platform
Matrix	Human serum
Standard Curve (µg/mL)	0.32 to 40.96: 8 calibrators. Anchor points 0.16 and 101.6
Standard performance	Accuracy 0.1 to 1.8%, and Precision 3.1 to 5.2 % CV
Minimum required dilution (MRD)	40
QC levels (µg/mL)	0.32 (LLOQ), 0.96 (Low), 4 (Mid), 32 (High), and 40.96 (ULOQ)
Selectivity	10 lots of Normal human serum and 10 human serum samples from cancer unspiked and spiked at LLOQ and HQC: ≥80% Blanks < LLOQ, and 80% of LLOQ with accuracy of ± 25% and CV ≤ 25%, and HQC with accuracy of ± 20% and %CV ≤ 20%

Specificity	Blank serum samples and LLOQ and ULOQ spiked with 200 and 500 ng/mL of anti-EGFR monoclonal antibody or anti-cMET monoclonal antibody: Blank serum samples <LLOQ and Accuracy of LLOQ and ULOQ within 25%
ADA Interference	Blank serum samples and LLOQ and ULOQ spiked with 200 and 500 ng/mL of anti-human Fc monoclonal antibody: Blanks <LLOQ and LLOQ and ULOQ with accuracy of within 25%
Target Interference	EGFR and cMET were spiked to Blank serum, LLOQ, and ULOQ samples at molar ratios of 10:1, 1:1, 0.1:1, 0.01:1, 0.001:1, and 0:1 (EGFR/cMET: amivantamab): Blanks <LLOQ and LLOQ and ULOQ with accuracy of within 25%
Hemolysis	Hemolyzed (~1000 mg/dL Hb) and lipemic (triglyceride levels 300-350 mg/dL) human serum samples were tested unspiked (naïve) and spiked at the LLOQ and HQC levels: Blanks <LLOQ and ULOQ within ± 25% and CV ≤ 25% and HQC within ± 20% and %CV ≤ 20%
QC performance: Intra-assay accuracy Intra-assay (%CV)	 -0.2 % to -11.8% 2.0% to 9.2%
Inter-assay accuracy Inter-assay (%CV)	-5.0% to -6.8% 4.5% to 8%
Stock soln	129 days at -20C: -0.1 to -1.2%, and 6 hours at room temperature (WL):-0.1 to 0.3%
Dilution linearity	1000 µg/mL diluted with dilution factor of 1 to 5000 (before MRD): In range at dilution factor of 40-1000 (before MRD) or 1600-40000 (including MRD)
Parallelism	5 incurred samples >ULOQ: diluted at MRD, >ULOQ, 3 dilutions within range, and one <LLOQ: %CV of the 5 samples ≤10%
Bench-top	72 hours at room temperature: -2.2% to 14.4% (Project CP2015V-077)
Freeze/Thaw Stability	Up to 6 cycles: -10.7% to 1.5%
Refrigerated Stability	48 hours at 5°C: -11.6% to 3.3%
Long-term Stability	4 weeks at -20°C: -2.8% to -8.0% (Project CP2015V-077)
	1824 days at -70°C:-2.2% to 5.2% (Project CP2015V-077)
Whole blood Stability	24 hour at room temperature: -4.8% to 19.5% (Project CP2015V-077)
Cross-Validation	30 individual incurred samples from study EDI1001 and 30 QC samples analyzed (all blinded): 80% of incurred samples and 80% of QCs were within 20% between Janssen and (b) (4)

The Applicant provided interim bioanalytical reports for analysis of samples in Study EDI1001. Refer to Table Z for the in-study performance.

Table Z: Amivantamab Assay Performance in Study EDI1001

Parameters	61186372EDI1001	61186372EDI1001C
Acceptable Plates	56 (3 rejected)	370 (54 rejecetd)
Matrix	Serum	
Dilution factor	40 and 1600	
Standard curve concentrations (µg/mL)*	0.32 to 40.96: 8 calibrators Anchor points 0.16 and 101.6	
QCs (µg/mL)*	0.96, 4, & 32	
QC Performance:**		
Inter-assay accuracy	0.96 µg/mL: 97.9% 4 µg/ml: 97.8% 32 µg/ml: 99.7%	0.96 µg/ml: 100.8% 4 µg/ml: 101.2% 32 µg/ml: 103.6%
Inter-assay precision (CV)	0.96 µg/ml: 12.0% 4 µg/ml: 5.9% 32 µg/ml: 6.3%	0.96 µg/ml: 9.9% 4 µg/ml: 10.8% 32 µg/ml: 7.9%
Reassays	2.4% (16 of 661)	1.1% (104 of 9107)

*the units in the titles of Tables 3 and 4 in Reports 61186372EDI1001 and 61186372EDI1001C incorrectly states the as ng/mL instead of µg/mL
**Including all values

20.4.2. Population PK Analysis

The Applicant conducted a population PK analysis to characterize the PK of amivantamab, identify covariate factors that could affect amivantamab disposition and compare the individual exposure estimates for subsequent exposure-response analysis. Data was collected from subjects with NSCLC who received IV amivantamab as monotherapy in Study of EDI1001. Study EDI1001 included subjects with EGFR Exon 20ins NSCLC treated at the RP2D or non-RP2D and subjects with NSCLC who do not harbor the EGFR Exon 20ins mutation.
The population PK analysis dataset was summarized in Table 59 by study parts and subject groups. There were 8756 rich and sparse serum concentration samples from 362 subjects with advanced NSCLC on Study EDI10001.

Table 55: Summary of subjects and PK observations included in the analysis dataset.

Study Part	Subject Group[a]	Number of Subjects	Number of Obs.	Number of Missing Obs.	Number of BQL Obs.	Number of Non-BQL Obs.	Number of Available Obs.
Part 1	E20 w/ prior chem	5	329	0	0	329	329
Part 1	E20 w/o prior chem	1	47	0	0	47	47
Part 1	E20-NR	8	253	0	0	253	253
Part 1	Non-E20	63	1920	0	0	1920	1920
Part 2	E20 w/ prior chem	96	1995	0	0	1995	1995
Part 2	E20 w/o prior chem	25	349	0	0	349	349
Part 2	E20-NR	34	876	0	0	876	876
Part 2	E20-others	18	0	0	0	0	0
Part 2	Non-E20	112	2987	0	0	2987	2987
All study parts	All subject groups	362	8756	0	0	8756	8756

BQL=below the quantification limit; Obs=observations.
[a] E20: subjects with EGFR Exon 20ins NSCLC treated at the RP2D;
E20-NR: subjects with EGFR Exon 20ins NSCLC treated at the non-RP2D;
E20-others: subjects with EGFR Exon 20ins NSCLC who are excluded from both E20 and E20-NR groups (ie, efficacy not evaluable); and
Non-E20: subjects with NSCLC who do not harbor the EGFR Exon 20ins mutation.
Note: RP2D regimen: 1050 mg for subjects <80 kg body weight (at baseline) or 1400 mg for subjects ≥80 kg body weight (at baseline), administered as an IV infusion once weekly for 4 weeks, then every 2 weeks thereafter.

Source: Applicant's Population PK and E-R Report, Page 23, Table 5.

The primary population of the subjects were Asian (217, 59.9%) and White (108, 29.8%), while 10 (2.8%) blacks patients were involved in the study. The median age of all subjects was 63 years old (range: 32-87), 62.7% were females and the median body weight was 59.9 kg (range: 35.4-140 kg). The median value of the calculated creatinine clearance and albumin were 76.3 mL/min (range: 28.8-276) and 40 g/L (range: 2.8, 51). The majority (325; 89.8%) of the 362 cancer participants were of normal liver function and 37 (10.2%) were of mild hepatic dysfunction based on NCI hepatic impairment classification. No patients with moderate or severe hepatic function were involved in the analysis. The majority of the 362 patients had normal (106; 29.3%), mildly impaired (164; 45.3%) renal function, 90 (24.9%) had moderate renal impairment, 2 (0.6%) had severe renal impairment function. The majority of the patients were ECOG Grade 0 (97, 26.8%) or Grade 1 (264, 72.9%) at baseline. The baseline covariates for population PK analysis were summarized in Table 60.

Table 56: Summary of demographics and baseline covariates in the analysis dataset.

Variable	Labels	Value
N		362
ECOG at Baseline, n (%)	Grade 0	97 (26.8)
	Grade 1	264 (72.9)
	Grade 2	1 (0.3)
	Grade 3	0
	Grade 4	0
	Grade 5	0
	Missing	0
Hepatic function[a], n (%)	Normal	325 (89.8)
	Mild dysfunction	37 (10.2)
	Moderate dysfunction	0
	Severe dysfunction	0
	Missing	0
Indicator for Japanese country, n (%)	Not Japanese	337 (93.1)
	Japanese	25 (6.9)
	Missing	0
Prior chemotherapy, n (%)	E20 without prior chemotherapy	39 (10.8)
	E20 with prior chemotherapy	148 (40.9)
	Other subjects	175 (48.3)
	Missing	0
Race/Ethnicity, n (%)	White, not Hispanic or Latino, or ethnicity unknown	108 (29.8)
	Black, of African heritage or African American	10 (2.8)
	White, Hispanic or Latino	7 (1.9)
	Asian	217 (59.9)
	Native Hawaiian or Other Pacific Islander:	0
	American Indian or Alaskan Native	0
	Other	20 (5.5)
	Missing	0
Sex, n (%)	Male	135 (37.3)
	Female	227 (62.7)
	Missing	0
Age (years)	Mean (SD)	61.9 (10.9)
	Median	63.0
	Range	(32.0; 87.0)
	N Missing (%)	0
Albumin (g/L)	Mean (SD)	39.1 (5.25)
	Median	40.0
	Range	(2.80; 51.0)
	N Missing (%)	0
Creatinine clearance, calculated (mL/min)	Mean (SD)	79.6 (28.8)
	Median	76.3
	Range	(28.8; 276)
	N Missing (%)	0
Free soluble MET (ng/mL)	Mean (SD)	99.6 (71.0)
	Median	90.7
	Range	(2.11; 867)
	N Missing (%)	80 (22.1)
Free soluble EGFR (ng/mL)	Mean (SD)	39.2 (11.9)
	Median	36.8
	Range	(6.46; 79.1)
	N Missing (%)	44 (12.2)
Total soluble MET (ng/mL)	Mean (SD)	166 (112)
	Median	131
	Range	(58.6; 1182)
	N Missing (%)	40 (11)
Total soluble EGFR (ng/mL)	Mean (SD)	41.1 (13.0)
	Median	40.1
	Range	(18.0; 87.2)
	N Missing (%)	40 (11)
Weight (kg)	Mean (SD)	63.0 (15.4)
	Median	59.9
	Range	(35.4; 140)
	N Missing (%)	0

Source: Applicant's Population PK and E-R Report, Page 24-25, Table 7.

The population PK analysis was conducted via nonlinear mixed-effects modeling with the NONMEM software, version 7.3 using first-order conditional estimation with INTERACTION option (FOCE+I). Data management, exploratory analyses, diagnostic graphics, and post-processing of the data and NONMEM outputs were performed using statistical software R (version 3.4.1 or later). The plasma concentrations of amivantamab data were described by a two-compartment disposition model with linear clearance. Several covariates including age, weight, serum albumin, creatinine clearance (CRCL), sex, race, hepatic function, ECOG and prior chemotherapy were tested for parameters in the population PK model.

The final population PK parameters for amivantamab are presented in Table 61. The final PK model was parameterized in terms of CL/F, V1/F, Q/F, and V2/F. Estimated fixed and random effect parameters were estimated with good precision (%RSE < 25%). Random effects related to IIV appeared to be approximately zero-centered and normally distributed and had correlation coefficients <30% in absolute value. The magnitude of the interindividual variability was moderate for CL/F, V1/F and V2/F. Residual variability was moderate.

Table 57: Parameter estimates of final population PK model

Parameter	Estimate	Standard Error	RSE%	Estimate (%)[a]	Shrinkage (%)[b]
CL (L/h)[c]	0.012	0.000	2	-	-
V1 (L)[c]	2.410	0.051	2	-	-
Q (L/h)[c]	0.300	0.023	8	-	-
V2 (L)[c]	2.330	0.092	4	-	-
Weight on CL (unitless)[d]	0.75 (fixed)	-	-	-	-
Weight on V1 (unitless)[e]	1 (fixed)	-	-	-	-
Sex on CL (unitless)[d]	0.237	0.050	21	-	-
IIV CL	0.098	0.009	9	32	8
IIV V1	0.054	0.006	12	24	17
IIV V2	0.313	0.038	12	61	20
Residual error	0.082	0.001	2	29	-

Q=intercompartmental clearance; V2=volume of distribution in the peripheral compartment.

[a] Estimates in relative percentage scale for IIV and residual error, calculated as 100×sqrt(exp(var)-1), where var represents the variance estimate for log-normally distributed random effects and residual error as returned by NONMEM.

[b] Subjects who did not have observations and hence had estimated random effects (ETA's) equal to 0 were removed from shrinkage calculation.

[c] Typical parameter values.

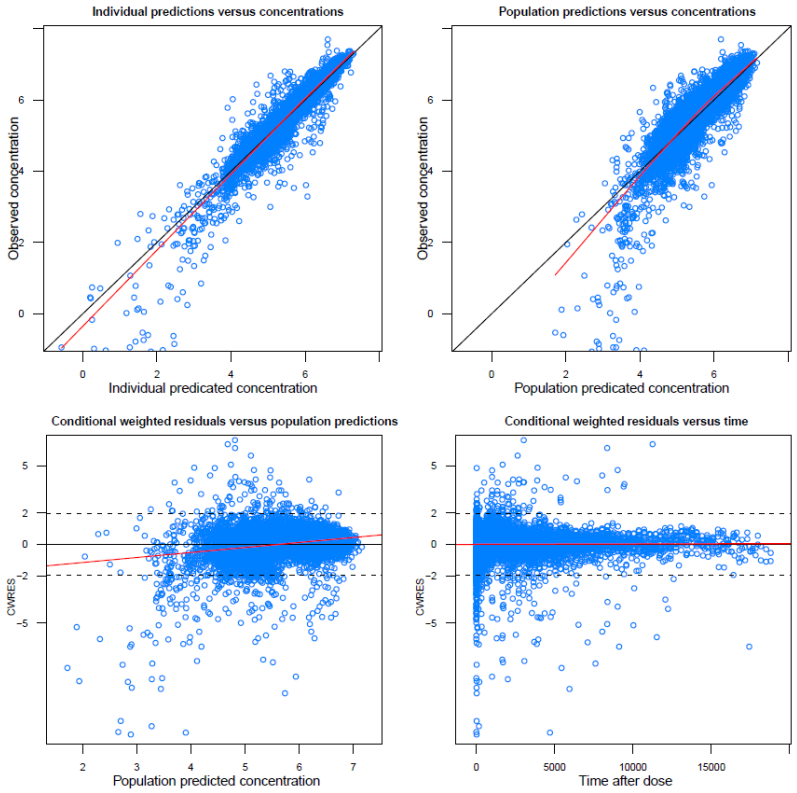
[d] Weight and sex effects on the typical value of CL were modeled as follows: $TVCL=\theta_{CL}\times(WT/WT_{med})^{\theta_{wt,CL}}\times(1+\theta_{sex}\times sex)$, where TV stands for "typical value," θ_{CL} is the clearance value in a typical subject with weight (WT) equal to WT_{med}, $\theta_{wt,CL}$ is the allometric coefficient for clearance (fixed to 0.75), *sex* is an indicator variable for female (*sex*=0; reference category) or male (*sex*=1) subjects, and θ_{sex} is the multiplicative term for male sex effect on TVCL.

[e] Weight effect on the typical value of V1 was modeled as follows: $TVV1=\theta_{V1}\times(WT/WT_{med})^{\theta_{wt,V1}}$, where TV stands for "typical value", θ_{V1} is the central volume of distribution value in a typical subject with weight (WT) equal to WT_{med}, and $\theta_{wt,V1}$ is the allometric coefficient for the central volume of distribution (fixed to 1).

Source: Applicant's Population PK and E-R Report, Page 39, Table 13.

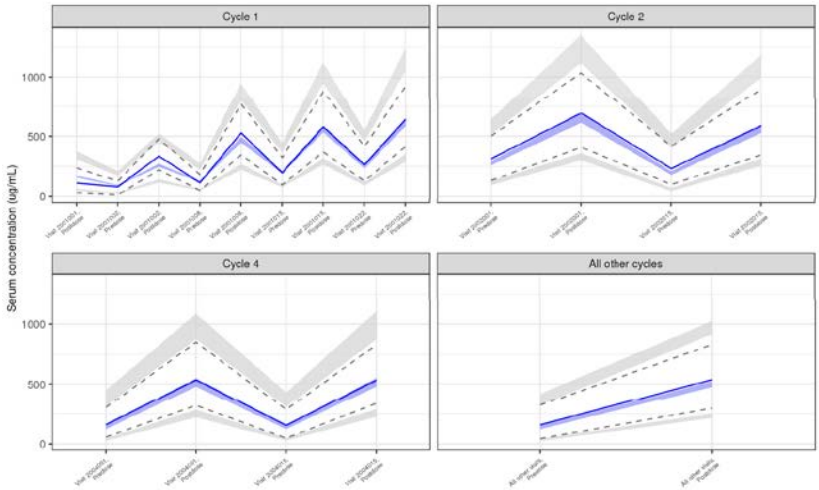
The diagnostic plots for the final PK model are shown in Figure 26. The VPC (visual predictive check) plots of pre-dose and post-dose concentrations across cycles for the final population PK model are shown in Figure 27. VPC plots for final population PK model in Figure 28 and Figure 29 are stratified by dose group and RP2D status. The population PK model appeared to adequately capture the central tendency and the variability of the data, with only a minor overestimation of the variability, as attested by the general agreement between the observed 5th, 50th, and 95th percentiles of the data and the respective 95% CIs obtained from the simulation. No apparent bias were observed in the overall model fit for the data.

Figure 26: Goodness of fit plots for the final population PK model



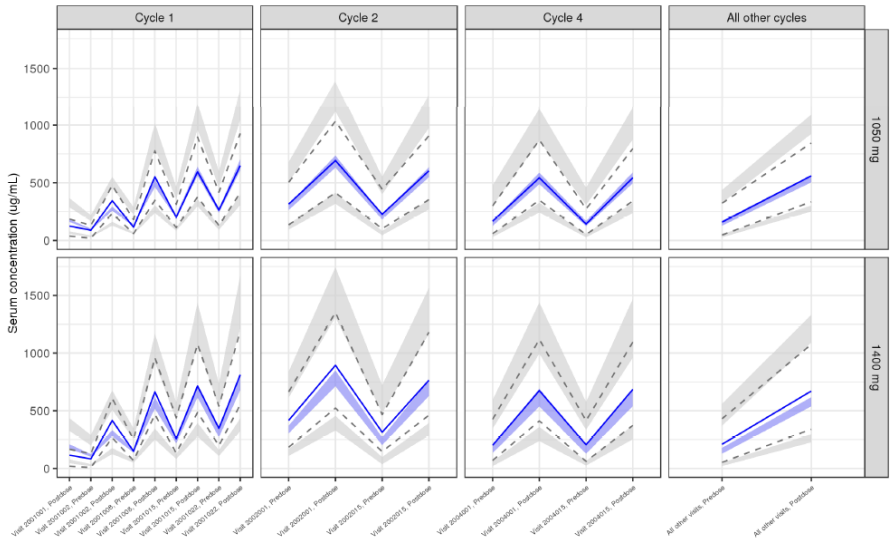
Source: Reviewer's analysis

Figure 27: VPC plots for the final population PK model



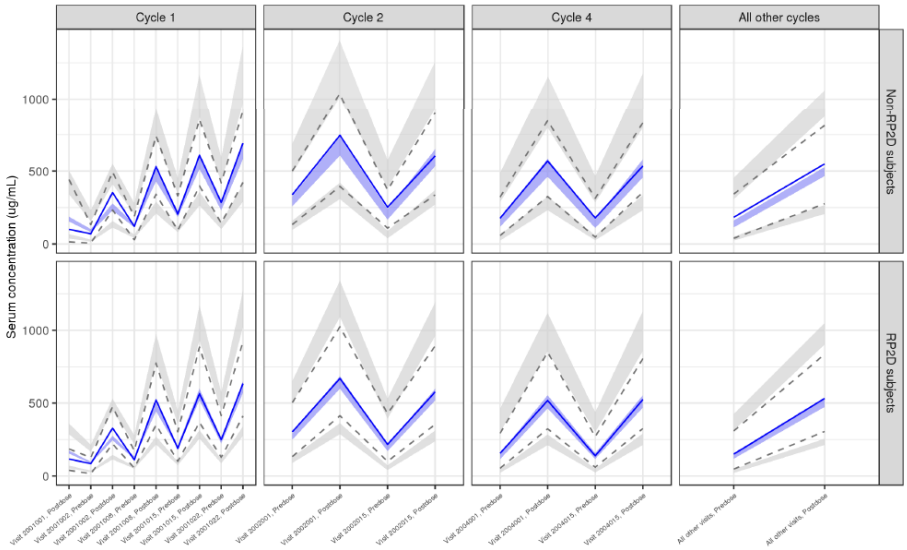
Source: Applicant's Population PK and E-R Report, Page 41, Figure 5.

Figure 28: VPC plots stratified by dose group for the final population PK model.



Source: Applicant's Population PK and E-R Report, Page 175, Figure 62.

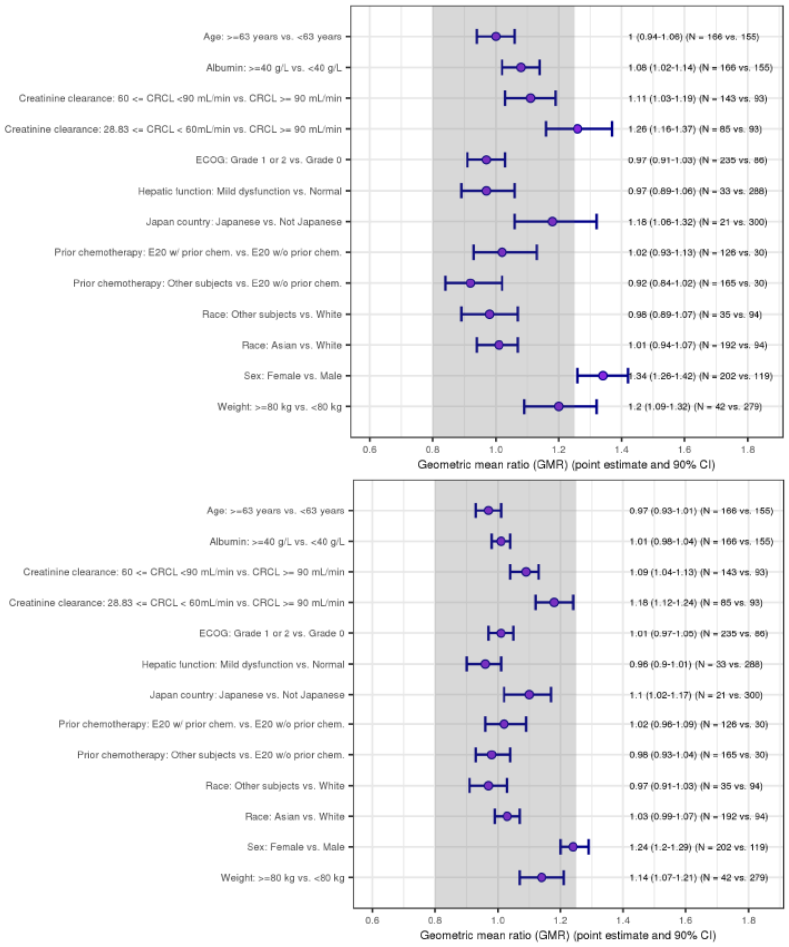
Figure 29: VPC plots stratified by RP2D status for the final population PK model.



Source: Applicant's Population PK and E-R Report, Page 175, Figure 63.

Empirical Bayes estimates of the PK parameters were generated from the final PK model for individual participant and forest plots of amivantamab exposures based on the RP2D dosing regimen were shown in Figure 30. None of the estimated GMR CI limits were entirely outside the 80% to 125% range except $AUC_{0\text{-}14\ days,ss}$ in women vs men.

Figure 30: Forest plot of $AUC_{0\text{-}14days,ss}$ and $C_{eoi,ss}$ based on the RP2D regimen



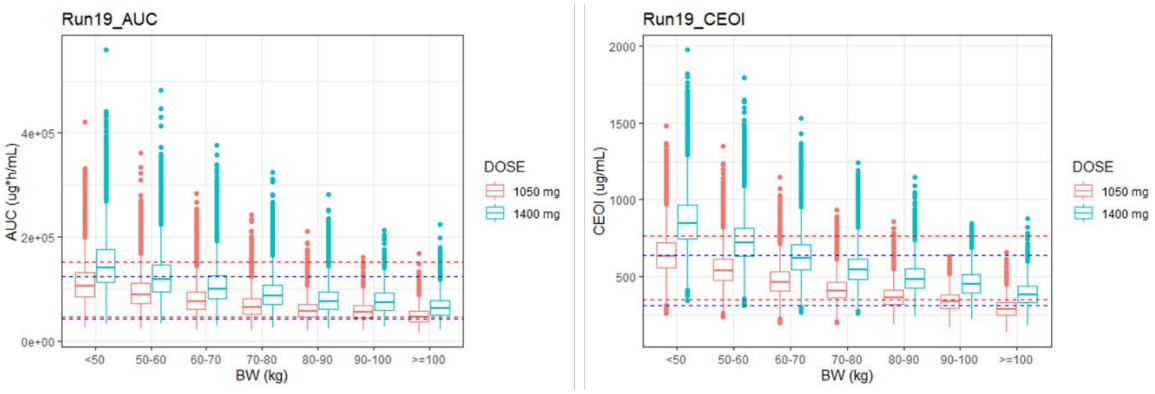
chem=chemotherapy; E20=exon 20 insertion mutation.
Note: RP2D regimen: 1050 mg for subjects <80 kg body weight (at baseline) or 1400 mg for subjects ≥80 kg body weight (at baseline), administered as an IV infusion once weekly for 4 weeks, then every 2 weeks thereafter.

Source: Applicant's Population PK and E-R Report, Page 46-7, Figure 8-9.

Reviewer's comments:

The population PK model developed by the Applicant was verified by the reviewer. The model appears to be reasonable in general because there was a good agreement between observations and predictions. Simulation based on the final population PK model showed that similar amivantamab exposures were achieved for subjects with body weight < 80 kg and ≥ 80 kg at the RP2D dosing regimen.(Figure 31) In the Applicant's model, gender was identified to be a significant covariate for clearance, which amivantamab clearance was about 24% higher in men than women.

Figure 31: Simulated amivantamab exposure for subjects in body weighted groups at RP2D.



Source: Reviewer's analysis

20.4.3. Exposure-Response Efficacy Analysis

The relationships of the exposures of amivantamab ($C_{eoi,1st}$ and $C_{eoi,amx}$) and the efficacy endpoints (ORR, CBR, PFS, OS and DoR) were explored in subjects with EGFR Exon 20 insertion mutation NSCLC . Binary variable responses (ORR and CBR) were evaluated by plotting and logistic regression. Time-to-event variable responses (DOR, PFS and OS) were evaluated by KM plot stratified by exposure groups.

The relationship of ORR and exposure of amivantamab was described by logistic regression analysis with E_{max} relationship. Covariates including age, weight, sex, race (Asian vs White), baseline ECOG (1 or 2 vs 0), and prior chemotherapy (yes vs no) were tested in the logistic regression, and ECOG was identified to be a statistically significant covariate in the E-R analysis of ORR using $C_{trough.max}$. The parameter estimates of the final model was shown in Table 62. The covariate effect could partially explain the higher ORR observed in patients at the RP2D of 1400 mg (45.5%) compare with RP2D of 1050 mg (34.1%) despite similar exposure. (Figure 32)

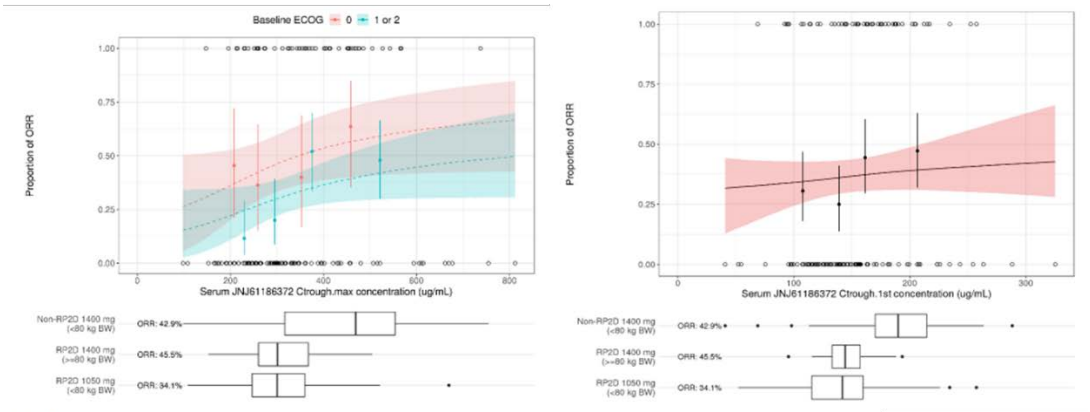
Table 58: Parameter estimates in final model with $C_{trough.max}$

Parameter	Estimate	90% Credible Interval	Neff	$\hat{R}$
E_{max}	3.51	(0.16, 8.87)	2873.52	1
EC_{50} (μg/mL)	372.00	(116.00, 2360.00)	2890.00	1
γ (Hill factor in E_{max} model)	1.83	(0.40, 5.57)	3144.73	1
α (intercept in logistic regression)	-1.54	(-4.88, -0.04)	2717.13	1
Baseline ECOG (1 or 2 vs 0)	-0.71	(-1.36, -0.05)	6005.84	1

EC_{50}=half maximal effective concentration; Neff=number of effective independent posterior samples from 4 Markov Chains.
Note: $\hat{R}$ is a MCMC convergence diagnostic statistics.

Source: Applicant's Population PK and E-R Report, Page 53, Table 20.

Figure 32: ORR vs $C_{trough.max}$ (left) and $C_{trough.1st}$ (right) in subjects with EGFR Exon 20 Insertion Mutation NSCLC.

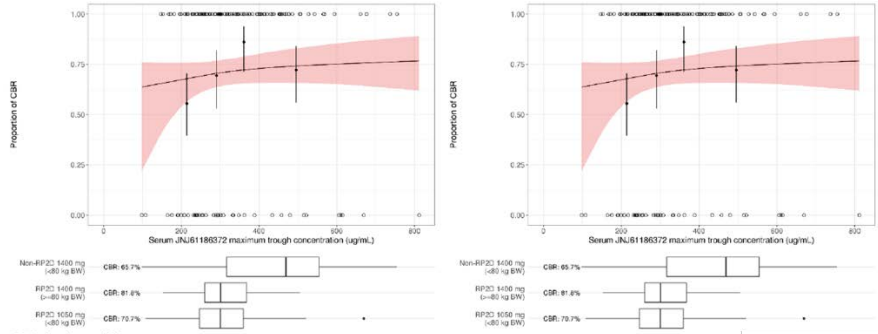


BW=body weight.
Notes: N=144.
The line represents model fitting with E_{max} relationship between logit-transformed probability of response and amivantamab $C_{trough.max}$. Solid points are observed ORR and the associated 95% CI in groups defined by quartiles of amivantamab $C_{trough.max}$. Open circles at horizontal lines of 0 and 1 on the Y-axis are predicted individual amivantamab $C_{trough.max}$ corresponding to nonresponse and response, respectively. The horizontal boxplots summarize amivantamab $C_{trough.max}$ in each dosing group with the observed ORR shown for the respective group. Subjects who received the first amivantamab dose on or before 05 February 2020 and had evaluable amivantamab PK were included in the analysis.

Source: Applicant's Population PK and E-R Report, Page 54, Figure 13.

The relationships between amivantamab exposures ($C_{trough.max}$ and $C_{trough.1st}$) with CBR were explored by logistic regression analysis with Emax relationship for subjects with EGFR Exon 20ins NSCLC at both the RP2D and non-RP2D of amivantamab in Study EDI1001. No significant relationships between CBR and amivantamab exposures were identified and relationships were flat in general. (Figure 33)

Figure 33: CBR vs $C_{trough.max}$ (left) and $C_{trough.1st}$ (right) in subjects with EGFR Exon 20 Insertion Mutation NSCLC.



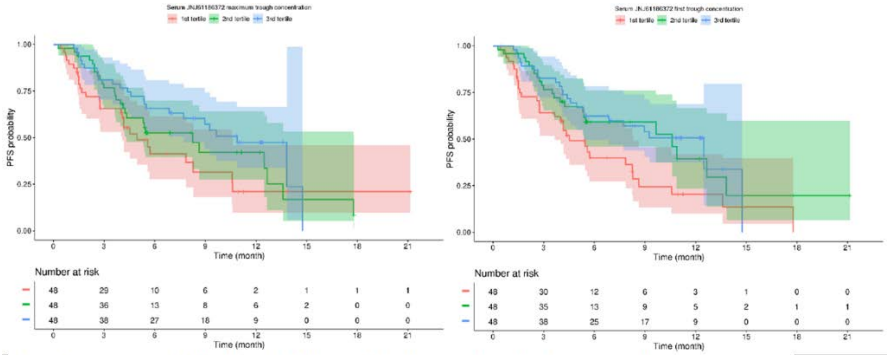
BW=body weight.
Note: Line and shaded area represent median and 95% CI of CBR from model fitting (E_{max} relationship between logit-transformed probability of response and amivantamab exposure metrics). Solid points are observed CBR and the associated 95% CI in groups defined by quartiles of amivantamab exposure metrics. Open circles at horizontal lines of 0 and 1 on the Y-axis are predicted individual amivantamab exposure metrics corresponding to nonbenefit and benefit, respectively. The horizontal boxplots summarize amivantamab exposure metrics in each dosing group with the observed CBR shown for the respective group. Subjects who received the first amivantamab dose on or before 05 February 2020 and had evaluable amivantamab PK were included in the analysis.

Source: Applicant's Population PK and E-R Report, Page 56, Figure 14.

The KM plots for PFS, OS, and DOR stratified by amivantamab exposures are shown in Figure 34, Figure 35 and Figure 36. Although PFS appeared to improve when amivantamab exposures increased,

the significant overlapping suggested a flat exposure relationship. And no significant difference was identified in OS and DOR. The results of E-R relationships for efficacy are inconclusive due to the limited number of patients and events in the current analysis dataset.

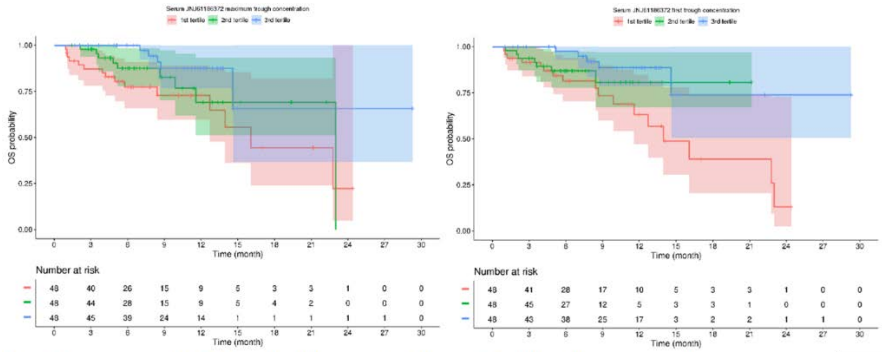
Figure 34: PFS stratified by tertiles of $C_{trough.max}$ (left) and $C_{trough.1st}$ (right) in subjects with EGFR Exon 20 Insertion Mutation NSCLC.



Note: Line represents K-M plots (shaded area: 95% CI) for each tertile of amivantamab exposure metrics.

Source: Applicant's Population PK and E-R Report, Page 57, Figure 15.

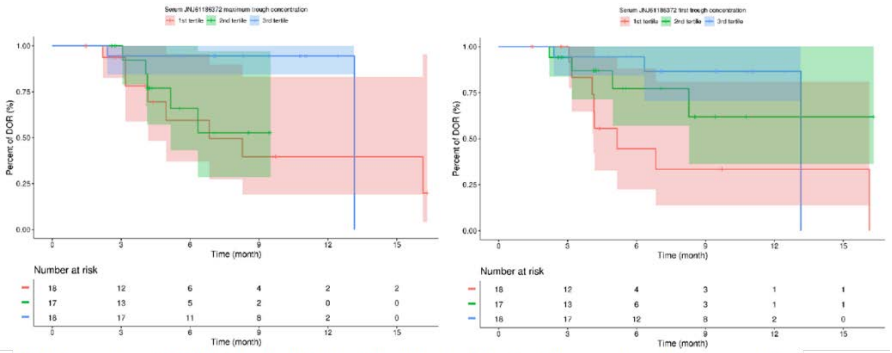
Figure 35: OS stratified by tertiles of $C_{trough.max}$ (left) and $C_{trough.1st}$ (right) in subjects with EGFR Exon 20 Insertion Mutation NSCLC.



Note: Line represents K-M plots (shaded area: 95% CI) for each tertile of the amivantamab exposure metric.

Source: Applicant's Population PK and E-R Report, Page 58, Figure 16.

Figure 36: DOR stratified by tertiles of $C_{trough.max}$ (left) and $C_{trough.1st}$ (right) in subjects with EGFR Exon 20 Insertion Mutation NSCLC.



Note: Line represents K-M plots (shaded area: 95% CI) for each tertile of the amivantamab exposure metric.

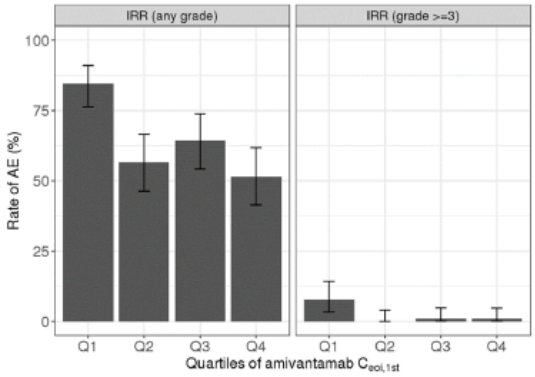
Source: Applicant's Population PK and E-R Report, Page 59, Figure 17.

Reviewer's Comments:
Although the exposures of amivantamab in subjects with body weight <80 kg at RP2D of 1050 mg were similar to that in subjects with body weight ≥80 kg at RP2D of 1400 mg, the observed ORR for subjects with body weight ≥80 kg was higher than subjects with body weight <80 kg. The observed difference in ORR might be caused by the higher proportion of ECOG 0 subjects with body weight ≥80 kg at RP2D.
While for all patients with body weight <80 kg, amivantamab systemic exposure was higher at the non-RP2D of 1400 mg than at the RP2D of 1050 mg and the proportion of ECOG 0 subjects was similar in both groups (RP2D: 25.6% vs non-RP2D: 20.0%). In these patients, the observed ORR in subjects with body weight <80 kg at the non-RP2D of 1400 mg was numerically higher (42.9% [95% CI: 28.0, 59.1%]) than that at the RP2D of 1050 mg (34.1% [95% CI: 24.8, 44.9%]). The observed difference in ORR might be due to the higher exposure of amivantamab or the variability of ORR associated with the small number of subjects in non-RP2D dose groups, deemed it inconclusive.

20.4.4. Exposure-Response Safety Analysis

The relationships between selected adverse event (AE) responses (IRR, rash, paronychia, hypoalbuminemia, nausea, constipation) and amivantamab exposures ($C_{eoi.max}$ and $C_{eoi.1st}$) were analysized by plots. There was no apparent exposure-response relationship between the selected AEs and amivantamab exposures except the incidence rates of rash, paronychia, and hypoalbuminemia slightly increased with the increase of $C_{eoi.max}$. (Figure 37 and Figure 38)

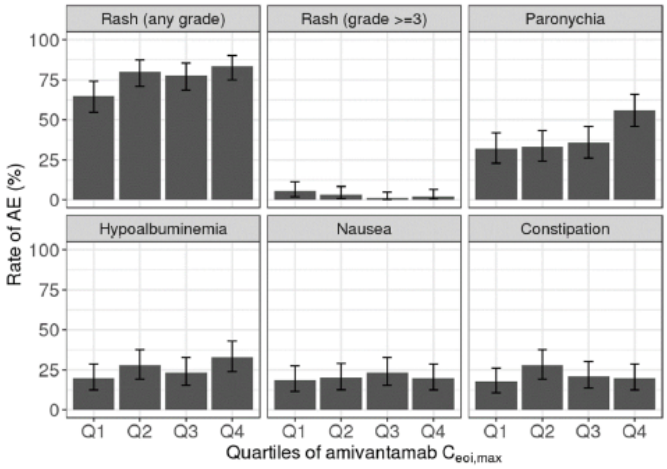
Figure 37: Comparison of IRR Rates (%) Across Predicted Amivantamab $C_{eoi.1st}$.



Note: Q1 to Q4 refer to Quartile 1 to 4 for amivantamab $C_{eoi.1st}$ respectively. Vertical bars and lines represent the AE rate and the associated 95% CI, respectively.

Source: Applicant's Population PK and E-R Report, Page 61, Figure 18.

Figure 38: Comparison of Other AE Rates (%) Across Predicted Amivantamab $C_{eoi.max}$.

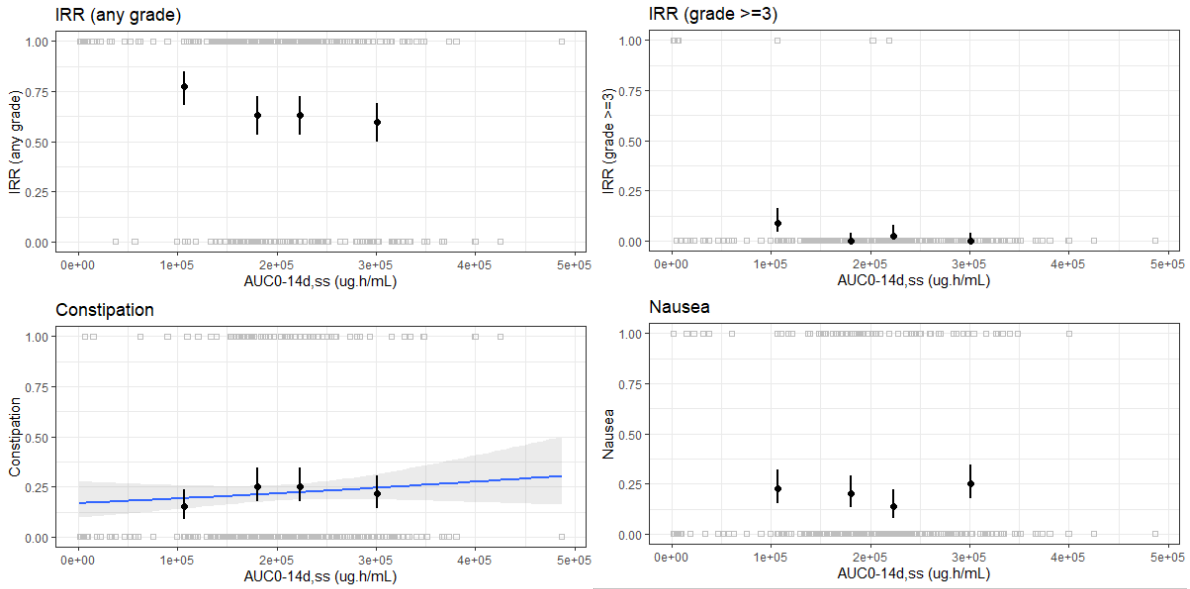


Note: Q1 to Q4 refer to Quartile 1 to 4 for amivantamab $C_{eoi.max}$ respectively. Vertical bars and lines represent the AE rate and the associated 95% CI, respectively.

Source: Applicant's Population PK and E-R Report, Page 61, Figure 19.

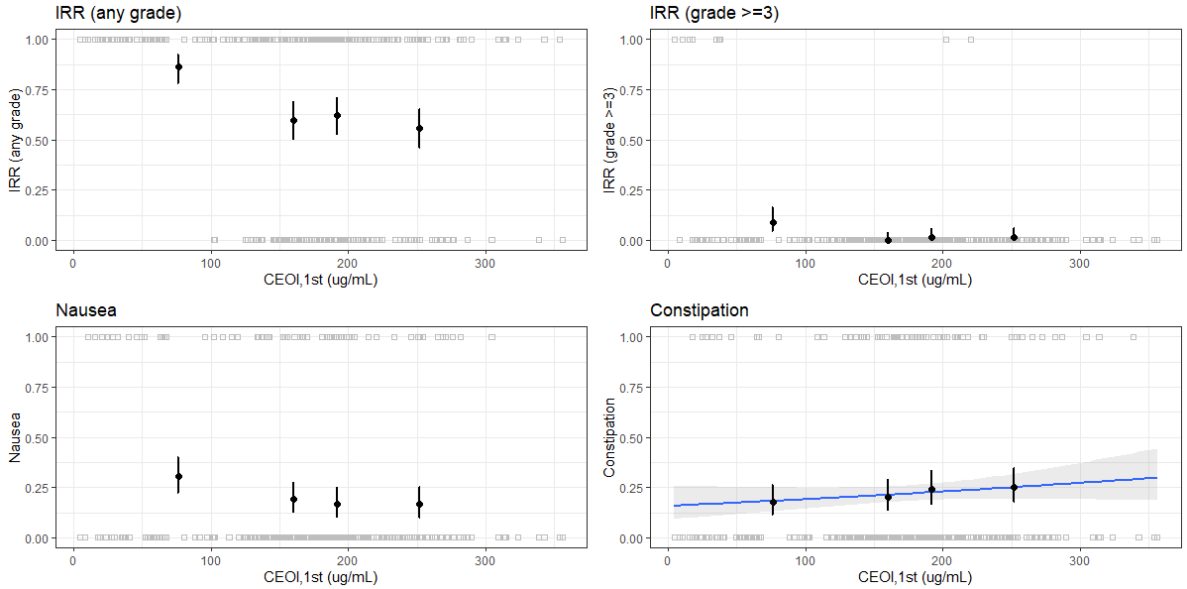
Reviewer's comments:
The results of ER safety analysis for the selected AEs were checked by the reviewer. The reviewer conducted ER analysis for selected AEs with amivantamab exposures ($AUC_{0\text{-}14day,\ ss}$, $C_{eoi,1st}$ and $C_{eoi,max}$). The results are shown in Figure 39, Figure 40 and Figure 41. No significant ER relationships were identified for selected AEs (IRR, nausea, constipation) in the analysis.

Figure 39: Comparison of Selected AE Rates (%) Across Predicted Amivantamab $AUC_{0\text{-}14days,ss}$



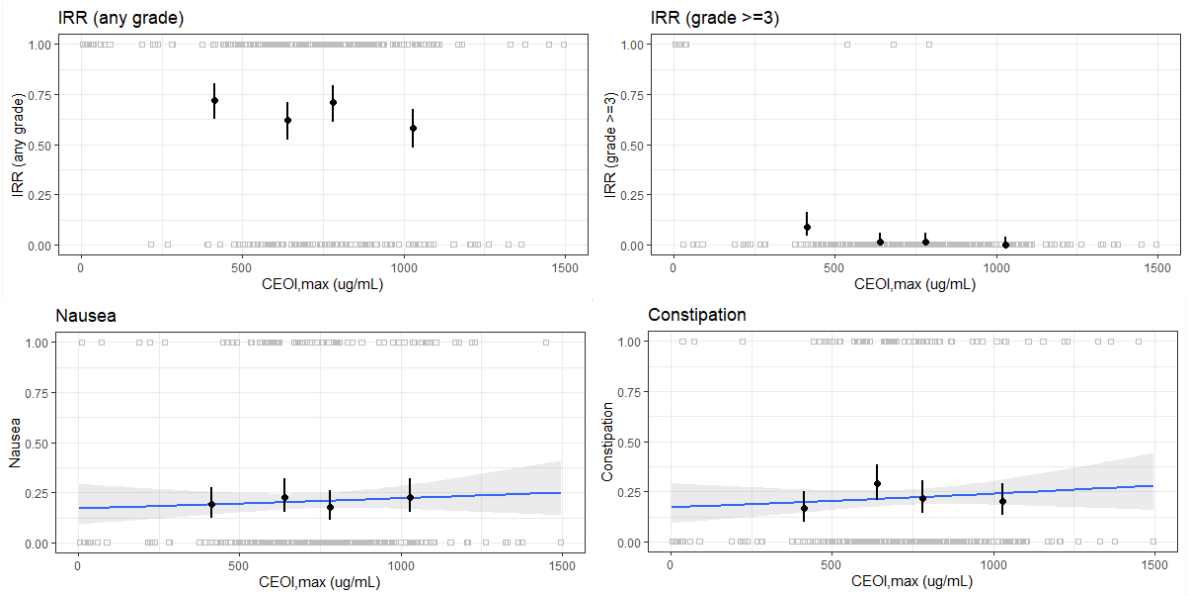
Source: Reviewer's analysis

Figure 40: Comparison of Selected AE Rates (%) Across Predicted Amivantamab $C_{eoi.1st}$



Source: Reviewer's analysis

Figure 41: Comparison of Selected AE Rates (%) Across Predicted Amivantamab $C_{eoi, max}$



Source: Reviewer's analysis

20.5. Additional Safety Analyses Conducted by FDA

The FDA's Assessments:

Hemorrhage

FDA performed an additional safety analysis on hemorrhage (GT) includes: Anal hemorrhage, Central nervous system hemorrhage, Dysfunctional uterine bleeding, Epistaxis, Gingival bleeding, Hematuria, Hemoptysis, Hemorrhage, Hemorrhoidal hemorrhage, Lip hemorrhage, Mouth hemorrhage, Mucosal hemorrhage, Rectal hemorrhage, and Vaginal hemorrhage; reported in both safety populations (n=129 exon 20 insertion mutations with prior chemotherapy and n=302 recommended doses) to evaluate a potential safety signal. Analysis was performed evaluating thrombocytopenia occurring at the same time as the hemorrhage event. There were a total of 36% of patient who had either reported hemorrhage or thrombocytopenia (labs) at some point in the clinical trial in the NSCLC with exon 20 insertion mutation with prior chemotherapy population and 29% in the larger safety population. There were 2.3% and 1.7% of patients who had hemorrhage reported concurrently with thrombocytopenia in these two populations, respectively. Based on this data, there is no clear correlation between hemorrhage and thrombocytopenia.

Among the broader safety population (n=302) evaluated using the more inclusive grouped term for hemorrhage, one event of Grade 3 hemorrhage (also the only hemorrhage event classified as a serious adverse event) was reported. This was an event of CNS hemorrhage in a patient with brain metastases. Based on the narrative for this event, it appears this bleeding was not considered clinically significant

as during hospitalization for this event the patient was treated with enoxaparin. All other events were grade 1-2, with the majority of events due to epistaxis and gingival bleeding.

Based on these additional analyses, this was considered not to rise to the level of a severe or serious adverse reaction that would require inclusion in Warnings and Precautions.

FDA - Table 59: Hemorrhage and Thrombocytopenia, Safety Population

Hemorrhage and Thrombocytopenia, Safety Population, BLA 761210, CHRYSALIS, amivantamab

	Analysis population	
	E20 ins PCM N = 129 n (%)	**RP2D N = 302 n (%)**
Patients with Hemorrhage (Hem)		
Total (either Hemorrhage or Thrombocytopenia)	46 (36)	89 (29)
Y	29 (22)	60 (20)
N	17 (13)	29 (10)
Patients with Thrombocytopenia (Throm)		
Total (either Hemorrhage or Thrombocytopenia)	46 (36)	89 (29)
N	25 (19)	53 (18)
Y	21 (16)	36 (12)
Patients with Hemorrhage but not Thrombocytopenia (Hem no Throm)		
Total (either Hemorrhage or Thrombocytopenia)	46 (36)	89 (29)
Y	25 (19)	53 (18)
N	21 (16)	36 (12)
Patients with Thrombocytopenia but not Hemorrhage (Throm no Hem)		
Total (either Hemorrhage or Thrombocytopenia)	46 (36)	89 (29)
N	29 (22)	60 (20)
Y	17 (13)	29 (10)
Patients with Hemorrhage and concurrent Thrombocytopenia (conthrom)		
Total (either Hemorrhage or Thrombocytopenia)	46 (36)	89 (29)
N/A	42 (33)	82 (27)
THROM CONCURRENT WITH HEM	3 (2.3)	5 (1.7)
THROM NOT CONCURRENT WITH HEM	1 (0.8)	2 (0.7)

Source: adsl.xpt
Thrombocytopenia is defined to be concurrent with hemorrhage if at least one positive labs collection date fell within the hemorrhage window.

COVID-19

The Applicant included COVID-19 flags in the dataset. See Section 8.1.2 under Protocol Violations/Deviations where COVID-19 flags were used for minor deviations reported in the clinical trial. In addition, in the ADAE dataset, there was one patient (b) (6) flagged with a COVID-19 related TEAE reported in the Exon 20 Ins prior chemotherapy (n=129) group. The non-serious, Grade 1 COVID-19 related event was reported in a 72 year old male; amivantamab therapy was interrupted until the patient recovered.

See Protocol Violations/Deviations in Section 8.1.2 of this review for details regarding COVID-19 related protocol deviations, all of which were classified as minor protocol deviations.

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Nonclinical Reviewer	Stephanie Aungst	OOD/DHOT	Section 5	X Authored X Approved
	Signature: Stephanie L. Aungst -S Digitally signed by Stephanie L. Aungst -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001570045, cn=Stephanie L. Aungst -S Date: 2021.05.13 07:55:56 -04'00'			
Nonclinical Team Leader	Emily Wearne	OOD/DHOT	Section 5	X Authored X Approved
	Signature: Emily F. Wearne -S Digitally signed by Emily F. Wearne -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001296929, cn=Emily F. Wearne -S Date: 2021.05.13 08:24:52 -04'00'			
Nonclinical Team Division Director	John Leighton	OOD/DHOT	Section 5	___ Authored X Approved
	Signature: John K. Leighton -S Digitally signed by John K Leighton S DN: c=US, o=U S Government, ou=HHS, ou=FDA, ou=People, 0 9 2342 19200300 100 1 1=1300085260, cn=John K Leighton S Date: 2021 05 13 08:39:56 04'00'			
Clinical Pharmacology Reviewer	Sriram Subramaniam	OCP/DCPI	Sections 6 & 20.4	X Authored _ Approved
	Signature: Sriram Subramaniam -S Digitally signed by Sriram Subramaniam -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300115066, cn=Sriram Subramaniam -S Date: 2021.05.19 09:06:11 -04'00'			
Clinical Pharmacology Team Leader	Hong Zhao	OCP/DCPII	Sections 6 & 20.4	X Authored X Approved
	Signature: Hong Zhao -S Digitally signed by Hong Zhao -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hong Zhao -S, 0.9.2342.19200300.100.1.1=1300136450 Date: 2021.05.13 08:45:22 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED / APPROVED
Clinical Pharmacology Division Director	Nam Atiqur Rahman Stacy Shord signs as Proxy	OCP/DCPII	Sections 6 & 20.4	___ Authored X Approved
	Signature: Stacy Shord -S Digitally signed by Stacy Shord -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Stacy Shord -S, 0.9.2342.19200300.100.1.1=2000356537 Date: 2021.05.13 08:50:18 -04'00'			
Pharmacometrics Reviewer	Yangbing Li	OCP/DPM	Sections 6 & 20.4	X Authored ___ Approved
	Signature: Yangbing Li -S (Affiliate) Digita ly signed by Yangbing Li S (Affiliate) DN: c=US o=U S Government ou=HHS ou=FDA ou=People 0 9 2342 19200300 100 1 1=2002587726 cn=Yangbing Li S (Affiliate) Date: 2021 05 12 17:11 54 04'00'			
Pharmacometrics Team Leader	Jiang Liu	OCP/DPM	Sections 6 & 20.4	X Authored X Approved
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Genomics Reviewer	Jielin Sun	OCP/DTPM	Section 6	X Authored ___ Approved
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Genomics Team Leader	Rosane Charlab Orbach	OCP/DTPM	Section 6	X Authored X Approved
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Clinical Reviewer	Katie Chon	OOD/DO2	Sections 2, 3, 4, 8 & 20	X Authored ___ Approved
	Signature: Katie Chon -S Digitally signed by Katie Chon -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Katie Chon -S, 0.9.2342.19200300.100.1.1=2001297729 Date: 2021.05.18 19:49:53 -04'00'			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Team Leader and CDTL	Erin Larkins	OOD/DO2	Sections: All	X Authored X Approved
	Signature: Erin A. Larkins -S5 Digitally signed by Erin A. Larkins -S5 Date: 2021.05.19 15:22:15 -04'00'			
Statistical Reviewer	Somak Chatterjee	OB/DV	Section 8	X Authored ___ Approved
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Statistical Team Leader	Pallavi Mishra-Kalyani	OB/DV	Section 8	X Authored X Approved
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Division Director (OB)	Shenghui Tang	OB/DV	Section 8	___ Authored X Approved
	Signature: Shenghui Tang -S Digitally signed by Shenghui Tang -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Shenghui Tang -S, 0.9.2342.19200300.100.1.1=1300224175 Date: 2021.05.18 08:22:47 -04'00'			
Safety Analyst	Peter Schotland	OOD	Sections 8 & 20	X Authored ___ Approved
	Signature: Peter A. Schotland -S Digitally signed by Peter A. Schotland -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2001366044, cn=Peter A. Schotland -S Date: 2021.05.19 16:04:24 -04'00'			

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/s/

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