14 October 2021
EMA/629045/2021
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Rybrevant

International non-proprietary name: amivantamab

Procedure No. EMEA/H/C/005454/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ADCC	antibody-dependent cellular cytotoxicity
AdjHR	adjusted hazard ratio
ADR	Adverse drug reaction
AE	adverse event
AGHC	Aglycosylated heavy chain
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATR FT-IR	attenuated total reflection Fourier transform infra-red microscopy
AUC	Area under concentration-time curve
BICR	Blinded Independent Central Review
CBR	clinical benefit rate
CCIT	Container closure integrity test
cEGFR	common epidermal growth factor receptor
CHO	Chinese hamster ovary
CI	confidence interval
cIEF	Capillary isoelectric focusing
CL	Clearance
cMET	c-mesenchymal-epithelial transition factor
CO	Clinical Overview
CR	complete response
CrCL	creatinine clearance
cSDS	Capillary sodium dodecyl sulfate gel electrophoresis
CSR	clinical study report
CQA	Critical quality attribute
CPP	Critical process parameter
DCO	Data cut-off
DNA	deoxyribose nucleic acid
DoE	Design of experiments
DOR	duration of response
ECD	Extracellular domain
ECG	electrocardiogram
ECLIA	electrochemoilumenscent immunoassay
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
EHR	electronic health record
E-R	Exposure-response
Exon 19del	Exon 19 deletions
Exon 20ins	Exon 20 insertion mutations
Fab	antigen-binding fragment
FDA	Food and Drug Administration

FOIA	Freedom of Information Act
GGT	gamma-glutamyl transferase
GMR	Geometric mean ratio
HC	heavy chains
HCP	Host cell protein
HMWS	High molecular weight species
HR	hazard ratio
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IgG1	immunoglobulin G1
ILD	interstitial lung disease
INV	investigator (assessment)
IPC	In-process control
IRC	Independent Review Committee
IRR	infusion-related reaction
IV	Intravenous
K-M	Kaplan-Meier
LC	Light chani
LO	Light obscuration
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Affairs
MAD	maximum administered dose
MCB	Master cell bank
MDI	microflow digital imaging
MET	mesenchymal-epidermal transition
MMV	mouse minute virus
MSD	Meso Scale Discovery
MTD	maximum tolerated dose
NCA	Non-compartmental analysis
nCPP	non-critical process parameter
NE	not estimable
NSCLC	non-small cell lung cancer
OFV	Objective function value
ORR	overall response rate
OS	overall survival
PAR	Proven acceptable range
PD-1	programmed cell death protein-1
PD-L1	programmed cell death ligand 1
PDE	Permitted daily exposure
PFS	progression-free survival
PK	Pharmacokinetic
PPI	Posterior predictive interval
PPK	Population pharmacokinetics
PR	partial response
PRV	pseudorabies virus
PTM	Post transitional modifications
QbD	Quality by design
RECIST	Response Criteria in Solid Tumors

REO	reovirus type 3
RP2D	recommended Phase 2 dose
RSM	reduced scale model
RWD	real-world data
rwOS	real-world overall survival
rwPFS	real-world progression-free survival
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	stable disease
SD	standard deviation
SEM-EDX	Scanning electron microscopy with energy-dispersive X-ray spectroscopy
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SoD	sum of diameter
TEAE	treatment-emergent adverse event
TEM	transmission electron microscopy
TKI	tyrosine kinase inhibitor
TMDD	Target mediated drug disposition
TTF	time to treatment failure
UF/DF	ultrafiltration/diafiltration
ULN	upper limit of normal
US	United States
VPC	Visual predictive check
WCB	Working cell bank
XMuLV	xenotropic murine leukemia virus

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 23 December 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Rybrevant, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 September 2019.

The applicant applied for the following indication:

Rybrevant as monotherapy is indicated for treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7of Regulation (EC) No 1901/2006, the application included an EMA Decision (P/0289/2019) on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation and accelerated assessment

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14-a of Regulation (EC) No 726/2004.

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active Substance status

The applicant requested the active substance amivantamab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Scientific advice

The applicant did not receive Scientific advice on the development relevant for the indication subject to the present application.

1.7. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Filip Josephson Co-Rapporteur: Johanna Lähteenvuo

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Brigitte Keller-Stanislawski

The application was received by the EMA on	23 December 2020
The procedure started on	21 January 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 April 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 April 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 May 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 July
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 August 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	02 September 2021
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	16 September 2021
The applicant submitted the responses to the CHMP List of Outstanding	21 September 2021

Issues on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	29 September 2021
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	N/A
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positiveopinion for granting a marketing authorisation to RYBREVANT on	14 October 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant is seeking a Marketing Authorisation for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based chemotherapy.

The inclusion criteria of the pivotal study required histologically or cytologically confirmed NSCLC that was metastatic or unresectable. Thus, the term locally advanced is used in the meaning unresectable.

2.1.2. Epidemiology

Advanced NSCLC is a serious, almost invariably terminal illness. 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, 490,000 in the European Union, and slightly over 1 million in Asia, with the highest reported incidence rates in Korea and China (SEER 2020a, Bray 2018, Pakzad 2015). NSCLC accounts for 85% to 90% of lung cancers (Globocan 2012), with 5 year survival rates for NSCLC depending upon on the stage at diagnosis, ranging from 58.7% for localized cancer to 4.7% for cancer that has spread to distant locations (SEER 2020b).

2.1.3. Biologic features

Recent developments include the identification of populations of NSCLC patients with "driver mutations" that result in constitutive activation of pro-growth signalling pathways. The most prevalent of these are mutations affecting EGFR in approximately 15% of Western patients with NSCLC adenocarcinoma (Pao 2011), and 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 TKIs, and the use of these targeted agents in the front-line therapy of these patients has been associated with improved response rates and duration of disease control, leading to dramatically increased median OS 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 EGFR Exon 20ins (Vyse 2019). The unique protein structure associated with this group of EGFR mutations prevents effective binding by approved EGFR TKIs. Tumours arising from EGFR Exon 20ins, 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 tumours with well-understood tumour biology, do not currently benefit from targeted therapy, and they remain a population with significant unmet medical need.

2.1.4. Clinical presentation, diagnosis and prognosis

Lung cancer is often insidious, producing no symptoms until the disease is well advanced. In approximately 7-10% of cases, lung cancer is diagnosed in asymptomatic patients when a chest radiograph performed for other reasons reveals the disease. At initial diagnosis, 20% of patients have localized disease, 25% of patients have regional metastasis, and 55% of patients have distant spread of disease (Tan 2021).

Signs and symptoms of lung cancers may be due to the primary tumour, locoregional spread, metastatic disease, or ectopic hormone production. Cough is reported to be the most common presenting symptom of lung cancer. Other respiratory symptoms include dyspnoea, chest pain, and haemoptysis (Tan 2021).

2.1.5. Management

Several EGFR TKIs, including erlotinib, dacomitinib, and osimertinib, have been approved for use in the front-line therapy of NSCLC based on Phase 3 studies that exclusively enrolled patients with EGFR Exon 19del and L858R mutations. These studies have resulted in significantly improved patient outcomes, with improved response rates, prolonged disease control, and an improved median OS of 32 to 39 months (Ramalingam 2020).

In contrast to EGFR L858R or Exon 19del disease, tumours arising from EGFR Exon 20ins are known to be insensitive to currently approved EGFR TKI treatments. As a result, there are no approved therapies specifically for the treatment of patients with Exon 20ins disease and no specific treatment guidelines are given by the American Society of Clinical Oncology (ASCO) or the European Society for Medical Oncology (ESMO) for treatment of this population.

In the absence of effective targeted therapies, the current standard of care for newly diagnosed patients with EGFR Exon 20ins NSCLC remains platinum-based chemotherapy (Wu 2019). Although the platinum-based chemotherapy regimen has not been extensively studied prospectively in EGFR Exon 20ins disease, the similar underlying biology and available evidence from retrospective studies suggest equivalent efficacy to patients with TKI-sensitive EGFR-mutant NSCLC, with an approximate ORR of 30% and median PFS of approximately 4 months (Mok 2017, Wu 2019).

As patients with EGFR Exon 20ins NSCLC have been excluded from the majority of Phase 3 studies of EGFR TKIs, this population has been relatively understudied in clinical studies, and published reports often have been based on retrospective analyses or case series/reports. Available evidence demonstrates that after progression on platinum-based chemotherapy, there is no predominant standard of care for EGFR Exon 20ins NSCLC. Single-agent chemotherapy is commonly used in NSCLC patients but is associated with relatively low ORR (8%-12%) and median PFS (2 3 months) in randomized Phase 3 studies (Borghaei 2015, Hanna 2004). These agents can be associated with

toxicities such as anaemia, neutropenia, nausea, vomiting, diarrhoea, or peripheral neuropathy, all of which may prevent patients from deriving clinical benefit due to dose modification and/or interruption and additionally may detrimentally impact patient well being and health-related quality of life, with little associated clinical benefit.

Single-agent immunotherapy with agents inhibiting programmed cell death protein-1 (anti-PD-1) or its ligand (anti-PD-L1), have also been approved for use in NSCLC in the second-line setting. However, these agents have repeatedly demonstrated worse PFS and OS outcomes than single agent docetaxel and platinum-based chemotherapy in subjects with EGFR mutated disease, as compared with EGFR wild-type disease (Borghaei 2015, Herbst 2016, Rittmeyer 2017). As a result, patients with EGFR-mutated NSCLC have been excluded from frontline immunotherapy Phase 3 studies, and the resulting frontline indications for approved anti-PD-1/anti-PD-L1 agents in metastatic NSCLC have specifically excluded patients with EGFR-mutated disease, including patients with EGFR Exon 20ins (Opdivo Summary of Product Characteristics [SmPC] 2020, Tecentriq SmPC 2020).

The combination of ramucirumab and docetaxel has been more recently approved for use in second-line treatment of NSCLC, based upon a 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), as 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 treated with the ramucirumab and docetaxel combination (n=377) had a non-significant increase in ORR of 18.6% vs 15.2% in the docetaxel alone arm (n=348) (Paz-Ares 2017). Subjects in the ramucirumab and docetaxel group, however, experienced higher rates of stomatitis (23% vs 13%), bleeding or haemorrhage (29% vs 15%), hypertension (11% vs 5%), and peripheral oedema (16% vs 8%) compared with subjects in the docetaxel alone arm (Garon 2014).

Nintedanib in combination with docetaxel has also been approved in the European Union in patients who have received any prior chemotherapy based on a modest improvement of 1.2 months PFS over treatment with docetaxel (4.0 months vs 2.8 months) and an objective response rate of 4.7% versus 3.6% (Nintedanib SmPC 2020). However, in the 1199.13 pivotal study, treatment with the nintedanib and docetaxel combination was associated with a reported overall incidence of adverse events (AEs) leading to discontinuation of 22.7% of subjects (nintedanib EPAR: 002569/0000). Subjects in the nintedanib and docetaxel group experienced higher rates of hepatic failure, non-gastrointestinal perforations, and neutropenia. The rates of sepsis (1.3%) and febrile neutropenia (7.5%) were increased under treatment with nintedanib and docetaxel as compared to docetaxel alone. The most commonly observed Grade 3 or higher TEAEs were liver enzymes elevations, decreased white blood cells and neutrophils, diarrhoea, vomiting, nausea, and neutropenia. Analysis of the Ipsos Healthcare database using European EHRs identified that despite approval of the nintedanib and docetaxel combination, there is limited utilization in the European Union.

In summary, these data outline the lack of benefit in patients with EGFR Exon 20ins despite recent advancements in treatment of NSCLC. Although EGFR TKIs have significantly improved outcomes in patients with EGFR Exon 19del or L858R mutations, patients with EGFR Exon 20ins NSCLC have not benefitted, despite the similar underlying biology of their tumours. With no effective targeted therapies and demonstrated low responses to anti-PD-1/PD-L1 agents, patients with EGFR Exon 20ins NSCLC have limited treatment options and overall outcomes remain very poor. Recently published real-world data (RWD) analyses of Exon 20ins disease treatments have confirmed the relatively poor outcomes in both first-line and second-line settings with TKI, immunotherapy, and chemotherapy (median duration of treatment of 3.5 months), and a reported median OS of 16.2 months (Dersarkissian 2019).

New targeted therapies, therefore, are needed to provide effective EGFR inhibition in patients with Exon 20ins, specifically 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.

For further discussion on available therapies and their effect size, please refer to the B/R section.

2.2. About the product

Rybrevant (amivantamab) is an EGFR and MET receptor bispecific antibody. The pharmacotherapeutic group was not yet assigned. Three potential mechanisms of action for amivantamab to inhibit tumours with aberrant EGFR and MET signalling are proposed: 1) inhibition of ligand-dependent signalling, 2) downregulation of EGFR and MET levels from cell surface, and 3) initiation of antibody-dependent cellular cytotoxicity (ADCC) and/or antibody-dependent cellular trogocytosis (ADCT) mechanisms.

The proposed dose is 1050 mg for patients <80 kg body weight (at baseline) or 1400 mg for patients ≥80 kg body weight (at baseline), administered as an intravenous (IV) infusion once weekly for 4 weeks, then every 2 weeks thereafter. The first Cycle 1 dose is split over 2 days 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.

The CHMP adopted a positive opinion for use of Rybrevant in the following indication:

Rybrevant as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.

Treatment with Rybrevant should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Rybrevant should be administered by a healthcare professional with access to appropriate medical support to manage infusion-related reactions (IRRs) if they occur.

Before initiation of Rybrevant therapy, EGFR Exon 20 insertion mutation-positive status must be established using a validated test method.

Posology

Premedications should be administered to reduce the risk of IRRs with Rybrevant (see below "Recommended concomitant medicinal products").

The recommended dose of Rybrevant is provided in Table 1, and the dosing schedule is provided in Table 2.

Table 1. Recommended dose of Rybrevant

Body weight of patient (at baseline*)	**Recommended dose**	**Number of vials**
Less than 80 kg	1,050 mg	3
Greater than or equal to 80 kg	1,400 mg	4

* Dose adjustments not required for subsequent body weight changes

Table 2. Dosing schedule for Rybrevant

Weeks	**Schedule**
Weeks 1 to 4	Weekly (total of 4 doses)
Week 5 onwards	Every 2 weeks starting at Week 5

Duration of treatment

It is recommended that patients are treated with Rybrevant until disease progression or unacceptable toxicity.

Missed dose

If a planned dose is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

Dose modifications

Dosing should be interrupted for Grade 3 or 4 adverse reactions until the adverse reaction resolves to ≤ Grade 1 or baseline. If an interruption is 7 days or less, restart at the current dose. If an interruption is longer than 7 days, it is recommended restarting at a reduced dose as presented in Table 3. See also specific dose modifications for specific adverse reactions below (Table 3).

Table 3. Recommended dose modifications for adverse reactions

Body weight (at baseline)	**Initial dose**	**1st dose modification**	**2nd dose modification**	**3rd dose modification**
Less than 80 kg	1,050 mg	700 mg	350 mg	Discontinue Rybrevant
Greater than or equal to 80 kg	1,400 mg	1,050 mg	700 mg	

Recommended concomitant medicinal products

Prior to infusion (Week 1, Days 1 and 2), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs (see Table 4.). For subsequent doses, antihistamines and antipyretics are required to be administered. Antiemetics should be administered as needed.

Table 4. Dosing schedule of premedications

Premedication	**Dose**	**Route of administration**	**Recommended dosing window prior to Rybrevant administration**
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Paracetamol/Acetaminophen (650 to 1,000 mg)	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (10 mg) or Methylprednisolone (40 mg) or equivalent	Intravenous	45 to 60 minutes

* Required at all doses.

‡ Required at initial dose (Week 1, Days 1 and 2); optional for subsequent doses.

2.3. Type of Application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the uncontrolled design of the pivotal trial and the uncertainties on the impact of amivantamab on PFS.

The applicant requested consideration of its application for a Conditional Marketing Authorisation in

accordance with Article 14-a of Regulation (EC) No 726/2004, based on the following criteria:

- The benefit-risk balance is positive.

Amivantamab is a new and novel targeted agent for the treatment of subjects with NSCLC and EGFR Exon 20ins mutations. The initial MAA is based on data from a Phase 1 single arm study EDI1001. The current efficacy and safety, albeit with the limitations of a single-arm study, demonstrates that amivantamab delivers a substantially increased clinical benefit over available therapies for EGFR Exon 20ins patients. The observed efficacy demonstrates significant benefit in a patient population that has no standard of care after the failure of platinum-based chemotherapy and has not benefitted from targeted therapy and immunotherapy. A favourable safety profile has been demonstrated, with clinically manageable side effects.

- It is likely that the applicant will be able to provide comprehensive data.

The ongoing Phase 3 study (Study 61186372NSC3001) is 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 and will be used to fulfil specific obligations associated with a conditional authorization.

- Unmet medical needs will be addressed.

NSCLC with EGFR Exon 20ins is distinguished by de novo resistance to currently approved EGFR TKIs, including third generation TKIs such as osimertinib. Whereas the median OS for patients with common EGFR mutations has increased to 38.6 months with the introduction of osimertinib as a first line treatment for locally advanced or metastatic patients, this has not translated to a benefit for patients with Exon 20ins mutations and whose median OS is still limited to approximately 16 months at the same stage of the disease. Amivantamab is anticipated to address a major public health interest by providing an effective treatment option for patients with NSCLC and Exon 20ins mutations, who have failed platinum-based chemotherapy.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.

The Company considers a delay to gather this comparative data would be disproportionate from a public health perspective, as amivantamab addresses a major unmet medical need, which outweighs the risks due to the need for further data. Amivantamab is distinct from approved agents for EGFR-mutated NSCLC and delivers a major therapeutic innovation as a first in class EGFR/MET bispecific Ab. The robust and durable anti-tumour activity of amivantamab observed in subjects with EGFR Exon 20ins NSCLC after failure of platinum-based chemotherapy provides a benefit for this distinct molecular subtype of the disease that clearly has poorer prognosis and worse treatment outcomes compared with patients without these aberrations. The overall safety profile of amivantamab is favourable, and treatment is expected to prolong PFS and OS without introducing significant new toxicities or risks for patients with Exon 20ins mutations. Once approved, amivantamab is expected to rapidly emerge as a standard of care for the treatment of Exon 20 ins mutation NSCLC after the failure of platinum-based chemotherapy. Amivantamab will be a highly valued treatment option for clinicians and would be utilized despite the fact that no comparative Phase 3 data are available.

2.4. Quality aspects

2.4.1. Introduction

Amivantamab, the active substance contained in Rybrevant, is a fully human Immunoglobulin G1 (IgG1) based bispecific antibody directed against the epidermal growth factor receptor (EGFR) and mesenchymal epidermal transition receptor (MET), produced by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Rybrevant is presented as a concentrate for solution for infusion in a Type I glass vial containing 350 mg of amivantamab in 7 mL (strength 350 mg). The pack size contains one vial.

Amivantamab is formulated with the following compendial excipients: L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80, L-methionine, EDTA disodium salt dihydrate and water for injections.

2.4.2. Active Substance

2.4.2.1. General information

Amivantamab is a fully human low-fucose IgG1 bispecific antibody that binds to the extracellular domains of EGF and MET receptors and disrupts EGFR and MET signalling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumour growth and progression. The presence of EGFR and MET on the surface of tumour cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

Amivantamab consists of 2 heavy chains (HC) and 2 light chains (LC) which are linked together via non-covalent heavy-heavy and heavy-light interactions, as well as covalent heavy-heavy and heavy-light disulfide bonds. Disulfide bond pairings have been determined experimentally by peptide mapping and follow the expected topology for a human IgG1 antibody.

Amivantamab is produced by cultivation of recombinant CHO cells and has a molecular mass of 148209 Da for the major glycoform. It is prepared by controlled reduction and oxidation of the parental JNJ-55986736 (also referred to as CNTO 4005 or anti-EGFR) and JNJ-55944083 (also referred to as CNTO 9541 or anti-MET) monospecific antibodies (MAbs) resulting in an exchange of the Fab arms. The Fab arm exchange is facilitated by amino acid substitutions in the CH_3 domains at positions K411R of the parental JNJ-55944083 HC and F413L of the parental JNJ-55986736 HC, to enable preferential refolding of the heterodimer.

The information in this section is considered sufficient. No concerns are raised.

2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

The manufacturing process of amivantamab active substance encompasses the manufacture of two separate parental MAb intermediates (concentrated protein A eluates), a Fab arm exchange to produce the bispecific antibody, further purification steps, formulation, and filtration to active substance fill.

The two parental MAb intermediates are manufactured at Biogen Inc., 5000 Davis Drive, Research Triangle Park, NC 27709, USA (Stages 1 to 5). Amivantamab active substance is manufactured by Janssen Sciences Ireland UC, Barnahely, Ringaskiddy, Co. Cork, Ireland (JSI) (Stages 6 to 14). Manufacturing operations, including release and stability testing, are performed in house at Janssen, and by contract manufacturers. The name, address, and responsibilities of each manufacturer involved in the manufacture, storage, and testing of the intermediates and the active substance is available in the dossier. Appropriate GMP certification and manufacturing authorisations are provided.

For each parental MAb concentrated protein A eluate, the manufacturing process encompasses cell culture, harvest, capture, concentration and filling into bottles. Maximum time in the preculture seed train and maximum production bioreactor duration are identified. Harvest samples are tested for adventitious agents (viruses, bioburden, and mycoplasma) and IgG concentration. The intermediates are.

The manufacturing process of the bispecific antibody encompass thawing and mixture of the two parental MAbs, reduction and oxidation to enable Fab arm exchange, purification by chromatography steps, viral inactivation and virus filtration, formulation, and 0.2 um filtration to final fill.

The manufacturing process and process controls are summarised in flow charts and process parameters are tabulated, including limits and criticality assignments. Limits for in-process controls (IPCs) are provided. The purpose of each step is clearly stated, and a detailed description is provided. Operating sequences, resin and filter materials, buffers, flow rates, transmembrane pressure, membrane cut-off, and collection of fractions are provided for the chromatography steps and the filtration steps. Representative chromatograms are provided for each chromatography step and the scale of the columns are provided. The level of detail is considered sufficient.

All media used for the cell culture process are chemically defined and free of animal-derived components. In-process pool hold times and hold conditions are sufficiently described for each step.

Reprocessing is allowed and described in sufficient detail and supported by validation data (see below).

In summary, the description of the proposed manufacturing processes (parental MAbs and active substance) is acceptable.

Control of materials

Detailed descriptions of raw materials and consumables such as resins, filters, and single-use bags are presented. Specifications with acceptance criteria and short descriptions of test methods are provided for non-compendial raw materials. Animal-derived and human-derived components were used during cell development. No animal-derived or human-derived material was used during manufacture of the master cell banks (MCBs) and the WCBs, and no such material is used during manufacture of the active substance. The information regarding raw material is considered sufficient.

The two parental MAbs are expressed in a variant adapted to growth in chemically defined media and subjected to selection to enable expression of low-fucose recombinant proteins. The human sequences for anti-EGFR and anti-MET, respectively, originates from hybridoma technology (mice were immunised with a human epidermoid carcinoma cell line + soluble human EGFR, or CHO-S cells expressing human

MET). The information regarding the host cell and the origin of the nucleotide sequences coding for the two parental antibodies have been sufficiently described.

A sequence variant (due to a point mutation) was detected in the anti-MET LC. It exists in the MCB, the WCB and the end-of-production cell bank (EPCB) at levels close to the limit of detection. Based on the totality of information regarding the sequence variant throughout the dossier, it is considered well controlled at low levels. This is acceptable.

The MCBs and WCBs were manufactured and tested according to ICH Q5A, Q5B and Q5D guidelines. The analytical test package is extensive, and the virus testing is sufficiently justified by detailed description of cell line development history. Certificate of analysis are provided for both MCBs and both WCBs and further test results regarding identity testing, sequencing, and cell bank stability testing are provided.

The cell banks are stored in vapour phase over liquid nitrogen. This is supported.

WCB vials are shipped to the Biogen site on an as needed basis and stored in validated cryogenic freezers in the vapour phase over liquid nitrogen.

The limit of *in vitro* cell age was evaluated by manufacture and testing of an extended end of production cell bank for each parental MAb. Cells were withdrawn in the production bioreactor, and further cultivated beyond the normal total manufacturing time. This is considered appropriate as it is shown that there is no additional cell growth in the production bioreactor . The test package and the results, including testing for viruses, support sufficient stability through the length of the proposed cell cultivation process.

Preparation of future WCBs is sufficiently described and protocols are included.

Control of critical steps and intermediates

Process parameters were categorised as non-critical (non-CPPs) and critical (CPPs) by assessing their impact on critical quality attributes (CQAs). The CPPs are a subset of process parameters that have the greatest potential to influence CQAs. Based on information in 3.2.S.2.6, a proven acceptable range (PAR) is defined as in ICH Q8. According to the descriptions for CPPs (3.2.S.2.2) and CQAs (3.2.P.2.3), it can be concluded that these terms also are defined in line with ICH Q8.

IPCs, including microbial controls (bioburden, endotoxin, mycoplasma, *in vitro* adventitious virus), and limits are presented in a condensed format. Justifications are provided for the IPCs in the parental MAb intermediates and active substance manufacturing processes.

All manufacturing process stages during the production of the parental MAb intermediates and amivantamab active substance are considered equally critical. IPCs can have one of three different types of limits: acceptance criterion, action limit, or pre-defined instruction. An action limit is a condition that, when exceeded, requires immediate response, investigation and correction. Exceeded acceptance criteria will also be investigated before decision regarding batch disposition. Specifically, if the acceptance criteria for mycoplasma or *in vitro* adventitious virus testing are exceeded, and the out-of-specification result is confirmed after investigation, the failed batch will be rejected. The Applicant states that an excursion from a CPP or non-CPP PAR triggers a deviation and results in an investigation and impact assessment which must be resolved prior to batch release. This is acceptable. The assignment of the limit types to the IPCs is supported.

The Applicant states that this list of IPCs and the associated acceptance criteria, action limits, and predefined instructions may evolve as the level of process understanding increases during the product's lifecycle. This is expected as part of process lifecycle management. As a general comment,

the Applicant is reminded that a change to a process parameter listed in section 3.2.S.2.2 or a change to an IPC listed in 3.2.S.2.4 should be subject to a variation application.

Intermediate specifications

The specifications for concentrated protein A eluates for both parental MAb intermediates include tests for general characteristics (pH-Ph. Eur), identity (Dot blot), quantity (A280), charge heterogeneity (cIEF), purity (SE-HPLC), reduced cSDS, non-reduced cSDS) and microbial contaminants (bioburden/endotoxins Ph. Eur.).

Justification of specifications for the parental MAb intermediates (concentrated protein A eluates)

Justifications are provided and the proposed commercial parental MAb specifications are considered acceptable. The specifications were derived from compendial guidelines, product and process knowledge, prior experience with other MAb products, and statistical analysis of release and stability data primarily from a clinical subset of batches. Parts of the overall strategy to set specifications are supported. A clear explanation is provided regarding the batches used for the clinical trial.

The Applicant proposes to set acceptance criteria for the parental MAbs separately from active substance and finished product since amivantamab is a bispecific molecule and different to the parental MAbs. Many attributes of the bispecific molecule are derived from the attributes of the parental MAbs. Thus, the link from the finished product specification to the active substance specification is considered to continue also to the parental MAb intermediate specifications, at least for some attributes.

Data from structure-function studies and other characterisation studies support the proposed acceptance criteria which are considered approvable. The proposed limits for quantity are rather wide but still considered acceptable as the starting point for manufacture of the bispecific antibody is based on a weight ratio of anti-EGFR to anti-MET.

Intermediate batch analysis

Batch release results for concentrated protein A eluate intermediate lots are provided. The data is presented without the specifications in place at the time for manufacture, however historical specifications are provided. This is acceptable.

For the anti-EGFR parental MAb (JNJ-55986736) concentrated protein A eluate, batch analyses are provided in the dossier.

For the anti-MET parental MAb (JNJ-55944083) concentrated protein A eluate, batch analyses are provided in the dossier.

The release data is consistent for most attributes through all batches for the respective intermediates. It is noted that there is a difference, although the results fall within the currently proposed intermediate specifications.

The submitted intermediate batch data from the different process versions could be concluded to support a consistent manufacture of both intermediates.

Overall, the proposed controls of critical steps and intermediates are considered acceptable.

Process validation

An extensive set of studies for process validation is presented, along with descriptions of methods and tools. Four consecutive batches each for the parental MAb intermediates, and five consecutive batches of active substance were included. The parental MAb intermediate batches were started from a single WCB vial each. For two of the five active substance process validation batches, parental MAb intermediate material from more than one batch was included.

The process validation of the manufacturing steps for active substance is adequately described and reported.

Process validation commercial scale results are scattered throughout the dossier; however clear cross-references are given: the approach and results from CPPs/non-CPPs and selected IPCs are available in S.2.5. Process validation release results for the parental MAb intermediates are available in 3.2.S.2.4. Process validation release results for the active substance are available in 3.2.S.4.4 and the acceptance criteria in 3.2.S.4.1.

Except for a few deviations, the results for parameters, IPCs (the select group with acceptance criteria only, because batch data for IPCs with action limits and predetermined actions are available in 3.2.S.2.6) and attributes for the parental MAbs and active substance are well aligned within rather narrow intervals. The deviations were acceptably investigated and handled.

During commercial scale process validation, extended sampling and testing were performed beyond routine release and in-process testing. Such samples were used for further characterisation according to a predetermined protocol without acceptance criteria. This approach is endorsed, and it is agreed that the results support consistent parental MAb intermediate and active substance quality and process performance.

The approach to demonstrate clearance of impurities is endorsed (reduced-scale spiking studies and clearance data from commercial scale process validation batches). The criticality of impurities is further discussed and assessed in the manufacturing development section. It is agreed that residual amounts do not have to be included batch testing for routine manufacture. Although commercial scale process validation data and reduced-scale spiking data demonstrates consistent low levels , this is a relevant safety attribute and is therefore included in the active substance specification.

Information provided regarding extractables and leachables is considered sufficient. The extractable risk assessment strategy and the performed studies are supported. Details are provided in technical reports. Based on the information provided, it is agreed that the use of the specified polymeric product contact materials for the manufacturing process poses minimal risk to patient safety.

The hold times study approach for biochemical and microbial stability is considered acceptable (scale, containers/vessels, sampling, test panel). Thus, the biochemical hold times and hold conditions can be considered validated.

Small-scale data support the proposed reuse of chromatography resins and UFDF membranes. Continued verification of resin lifetime limits is performed during commercial manufacturing by testing for certain attributes (including microbial controls) at regular intervals, as detailed in the dossier. The strategy seems approvable. The ultrafiltration membrane lifetime verification program for the JSI site can also be considered suitable.

A potential need for reprocessing is foreseen. Reprocessing for each of these stages will also be verified at the commercial scale on the first batch that requires reprocessing. Validation protocols were submitted. The protocols contain information regarding the circumstances for execution, the testing and the acceptance criteria. The content and the level of detail is considered approvable.

It is clearly stated that reprocessing may be performed once and must be completed within the hold times specified for the step. This is acknowledged.

Analytical methods used during process validation studies were validated as appropriate for intended use. The analytical method validations are provided. The level of information is considered sufficient, no concerns are raised.

The information provided regarding shipping validation is sufficient. Furthermore, a strategy for alternate shipping systems, suppliers or methods is presented with the goal to ensure that any alternate systems meet the same requirements for quality and protection as the current systems. It is stated that the health authority will be notified of any changes in insulated shipping as appropriate. The presented strategy for introduction of alternate shipping systems seems scientifically sound. The Applicant is reminded that future changes to the registered shipping system should be subject to variation.

The outlined ongoing process verification program (trending and analysis to ensure that the process remains in its validated state) is endorsed.

Overall, it is agreed that the results support the conclusion that the commercial manufacturing processes for parental MAb intermediates and active substance can be considered validated.

Manufacturing process development

Process development history

Three different versions of the active substance manufacturing process have been used during clinical development:. The changes between the process versions are clearly outlined and comparability studies are submitted. One batch was used in the clinical trial included with this submission.

For active substance, the major changes were manufacturing site for the parental MAbs, scale, cultivation media and feeds, pH and parental MAb ratio for the Fab arm exchange step, protein A resin, hydrophobic interaction chromatography (HIC) resin, virus filter, and formulation. The major changes were scale (all steps) and cultivation valine supplementation (anti-Met parental MAb).

An extensive number of active substance batches is available for all scales; however not all of them were included in the comparability study.

QbD elements such as risk assessments and designs of experiments (DoE) were included during process development; however the proposed active substance manufacturing process does not contain any multivariate elements of process control.

Process development studies and reduced-scale model qualification

An extensive process development program is submitted, including justifications for all stages of the proposed active substance manufacturing process which consists of a traditional set of PARs, and in some cases operational ranges (ORs) (a minimal level of variation around the target setpoint).

Univariate and multivariate development studies were performed to identify PARs for process parameters. For multivariate/DoE studies, model designs are described, statistical significance evaluated (p-values are mentioned in the narrative), and practical significance/insignificance concluded. The strategy is supported, and the outcome is considered appropriate. The evaluated ranges are not wide (PARs are in many cases close to or equal the evaluated range) and the variations in attribute levels are small.

The reduced scale models (RSM) used for many development studies were appropriately qualified. The approach and conclusions are supported and it is agreed that the RSMs can be considered qualified.

The approach to the impurity criticality evaluation, encompassing process related impurities, is considered scientifically sound. The summary of results and the conclusions are supported. In the end, no process-related impurities were identified as CQAs.

In summary, the process development program is considered appropriate and supportive of the proposed manufacturing process.

Process control strategy development

Consistent process performance and control of the CQAs are managed by an integrated control strategy encompassing release specifications for raw materials and consumables, CPP limits, in-process testing, and release and stability specifications for intermediates and active substance. This is supported. The integrated control of each CQA is also described in sufficient detail.

CPPs are identified by an initial evaluation of presumptive process parameters followed by process development studies. Observed or assumed impact levels are combined with the degree of knowledge uncertainty to give the final criticality assignment: CPP, non-CPP or potential CPP (pCPPs). Parameters still identified as pCPPs will require further investigation but is currently controlled as CPPs. This is endorsed. The Applicant is reminded that changes to the registered CPPs will require a post-approval variation application. The overall approach to CPP identification is supported and the presentation with criticality summary tables for each step is appreciated. The proposed process parameter criticality assignment is approvable.

The microbial control strategies at Biogen (parental MAbs) and JSI (active substance) are described in detail. Preparation and control to minimise risks for microbial contamination of facilities, equipment, and materials are considered sufficient.

Comparability

Comparability for both active substance and finished product is described in section 3.2.S.2.6. Three different comparability studies are presented:

The comparability studies encompass comparison to the clinical release specifications, characterisation testing, stability studies, forced degradation rates (temperature, light).

The aspects considered and the panel of tests included in the comparability exercise are considered sufficient and in compliance with ICH Q5E. Individual batch results are presented in tables, chromatograms, electropherograms, and spectra (sufficient resolution and peaks identified), and conclusions are clearly stated.

Release testing did meet clinical specification criteria, but the fact that process versions fulfil specifications does not automatically render them comparable, as potential trends within ranges are not evaluated and clinical specifications tend to be rather generous. Comparability limits are presented as mean ± 3 standard deviations or prediction intervals, which is a measure of process capability rather than of comparability. The statistical models as such were described in the original application but the use in the comparability exercise is not sufficiently justified. Therefore, the assessment of the comparability studies is based on post-change results in relation to the historical pre-change min-max intervals.

Based on the results from study 1, it is agreed that the finished product derived from the pre-clinical toxicology and clinical processes can be considered comparable.

For study 2, it can be concluded that there are obvious shifts in active substance and finished product. In comparison of the single post-change batch to other batches in S.4.4 (Batch analyses), these changes seem consistent over the range.

are considered acceptable and part of the targeted improvement and optimisation of the 2000 L process. It is also agreed that for the batch tested, binding to receptors is highly similar, thus the biological function seems comparable.

For study 3, it can be concluded that there are obvious shifts in active substance and finished product.

The Applicant states that the would not impact safety based on the dose used in the toxicology study. The relevance of the toxicity study to the safety in humans is considered limited, as already discussed during the procedure. However, it is agreed that could be concluded as not scientifically meaningful because that difference only had a small impact. It is also agreed that the slight decrease in purity could be considered of no practical importance.

The same comments apply to the results from finished product from pre-change and post-change active substance.

There were no new peaks or variants detected in any of the comparability studies. For some attributes, batches fall outside the historical min-max interval and slight shifts are visible between scales. Based on the discussion of these differences and results from structure function studies and other data, it is agreed that the detected differences do not have any practical impact to the biological function of the product.

batches fall outside the statistical intervals. Thus, throughout the development, increase for each change. However, it is agreed that there seem to be no practical impact to the biological function, based on binding studies and ADCC. The relevance of data from a six times higher dose in toxicology studies is still considered limited.

In summary, for some attributes there are differences between scales but they are acceptably justified. Product from the commercial process version, , could be considered comparable to product from the earlier versions used in the clinical trial.

Quality management system

A quality management system is established and briefly described. As it relates mainly to GMP it is outside the scope of this assessment; however, a comment is warranted. The Applicant states that section 3.2.S.2.6 is not considered to be a commitment for future routine commercial manufacturing. Even though sections 3.2.S.2.1, 3.2.S.2.2, 3.2.S.2.3 and 3.2.S.2.4 describe the active substance manufacturing process to be registered, the Applicant is reminded that all parts of the MAA are considered equally binding. It is noted that all changes to CPPs, non-CPPs, and IPCs will be assessed and managed through the internal change control system and reported via a post-approval variation application in accordance with regional regulations and guidance. This is expected and supported.

Characterisation

Elucidation of structure

Amivantamab is a fully human bispecific antibody (IgG1) that binds EGFR and MET, and also exhibit Fc effector functions like ADCC. It is manufactured from two parental monoclonal antibodies by a controlled Fab arm exchange (reduction followed by oxidation). Specific mutations on each parental monoclonal antibody guides the Fab arm exchange to a resulting heterodimer rather than the original homodimers. The host CHO cell line is engineered to express protein with low fucose content to increase the ADCC function.

A comprehensive physicochemical and biological characterisation of the amivantamab molecule is presented. In general, the results show that amivantamab has the covalent structure, post-translational modifications, and other characteristics of a typical monospecific human IgG1 antibody derived from CHO cells. Studies of primary, secondary and higher order structure, various physicochemical properties, carbohydrate structure, heterogeneity pattern, biological functions, degradation pathways, purities and impurities were included.

An extensive panel of state-of-the-art and orthogonal tests were applied. Characterisation methods and preparations of variants for characterisation studies are sufficiently described. All peaks are

characterised and identified to a sufficient level of detail, and relevant chromatograms, peptide maps, spectra, electropherograms, and thermograms are provided.

Active substance, was used for the major part of the testing. This is found acceptable.

Experimentally confirmed extinction coefficients are presented.

This conclusion is considered reasonable.

It was demonstrated that HMWS consist mainly of dimers.

Amivantamab contains N-linked glycosylation at positions EGFR HC Asn305 and MET HC Asn299.

The proposed mechanisms of action include inhibition of EGFR and MET signalling functions, Fc mediated ADCC, and Fc mediated trogocytosis (target cell receptor degradation). Based on product-specific published data, the Applicant claims that that the ADCC activity of amivantamab is primarily driven by the EGFR arm (an active Fc is of course also required). This is acknowledged. The biological function of amivantamab was characterised by the following methods:

Representative dose-response curves are provided for these *in vitro* binding assays and for the other biological function assays as well.

The two EGFR ADCC assays were compared by analyses of forced degradation samples. It is agreed that similar results were obtained.

The two MET binding assays were compared by analyses of samples from forced degradation and samples from active substance and finished product stability testing. It is agreed that the methods show similar results on the forced degradation samples.

Extensive forced degradation studies were performed to determine the criticality of post-translational modification quality attributes (PTM CQAs), including identification of the most suitable analytical methods for characterisation and control of these PTM CQAs. Correlation between PTM CQAs and receptor binding is demonstrated.

The probability that the PTM CQAs would impact product quality was defined as lowest, low or medium based on the results. The criteria for these definitions are further described in the dossier and considered appropriate. Glycated variants are not identified as PTM CQAs since they do not affect any binding. It is agreed that the levels normally present in the active substance have no negative impact to efficacy.

Impurities

Active substance product-related and process-related impurities, respectively, are listed together with the analytical methods for control. The main degradation routes are described and characterised. HMWS are present mainly as dimers, as already mentioned. Impurity criticality is discussed and clearance is demonstrated.

Microorganisms, adventitious viruses, endotoxins, exotoxins (non-endotoxin pyrogens) and mycoplasma are considered contaminants. Regarding the issue of nitrosamines, the Applicant concludes that as amivantamab active substance is a biological medicinal product with no chemically synthesised components, no meaningful exposure to the nitrosating agents is expected and the active substance presents a remote risk of nitrosamine impurities.

Sufficient information is provided regarding impurities.

In summary, the submitted information regarding characterisation of the active substance is acceptable and demonstrates a solid product understanding.

2.4.2.3. Specification

Specifications

The specification for active substance includes control of general characteristics (colour of solution, pH by Ph.Eur.), identity (Dot blot), quantity (A280), charge heterogeneity (cIEF), purity (SE-HPLC, reduced cSDS, non-reduced cSDS), and impurities (HI-HPLC, residual HCP), potency (EGFR ADCC Bioassay, cMET Binding), post translational modifications (MAM Peptide map), carbohydrate structure (HILIC), and microbial contaminants (bioburden and endotoxins by Ph. Eur.).

Active substance release and stability (end-of-shelf life) specifications are presented. The proposed stability specification acceptance criteria are the same as the release limits as no significant trends were found during stability testing. This is supported.

The specifications were derived from compendial guidelines, product and process knowledge, prior experience with other monoclonal antibody products, and statistical analysis of release and stability data primarily from a clinical subset of batches. These active substance specifications are also aligned with the finished product specifications. The proposed list of attributes to test for is considered suitable and the justifications for omitting from routine testing are acceptable.

The statistical methods used for setting specifications are described.

The justification for active substance acceptance criteria for the carbohydrate structure (specifically afucosylation) and EGFR HC Met260/cMET HC oxidation is considered scientifically sound, based on the presented structure function relationships and calculations from batches used in the pivotal clinical trial (61186372EDI1001). Acceptance criteria for purity and potency are aligned with the acceptable finished product specification. This is supported.

The proposed active substance specification is considered approvable.

Analytical procedures

A majority of the analytical procedures described for amivantamab are used for testing of both active substance and finished product. The procedures used for testing of both active substance and finished product and corresponding validations are described in sections 3.2.P.5.2 and 3.2.P.5.3, respectively.

Two non-compendial analytical procedures are specific for the testing of active substance, Oligosaccharide mapping by hydrophilic interaction liquid chromatography (HILIC) and Quantitation of residual homodimer using hydrophobic interaction high performance liquid chromatography (HI-HPLC). The non-compendial analytical procedures are generally described with a sufficient level of detail.

Validation reports were provided for the three non-compendial methods, Oligosaccharide Mapping, HI-HPLC, and host cell protein assay, demonstrating suitability for the intended use.

Batch analysis

Batch release results for manufacturing versions of the active substance lots are provided:.

Batch results are generally consistent within process versions, especially for the versions. For all batches included, tests and results are listed but acceptance criteria are missing (it is noted that historical specifications are provided in section 3.2.S.2.6). The submitted batch data support a conclusion regarding consistent manufacture of the active substance.

Reference standard

Information on preparation, qualification, storage and intended use are provided for the reference materials. A two-tiered reference material system is applied. The current primary and working

reference materials were prepared from active substance batches manufactured using the manufacturing process. The reference standards are tested and characterised using an extensive panel of analytical methods and data is provided in the dossier. Acceptance criteria for potency are tighter compared to the proposed commercial active substance release specification. This is supported.

Primary and working reference material are stored. The reference material is assessed annually for stability. This is considered appropriate. The selection, preparation, qualification and re-qualification of future reference materials have been described in sufficient detail, including specifications and characterisation testing. Information of historical reference materials have been provided.

In summary, the reference material system is considered acceptable.

Container closure system

The intermediate and active substance container closure consists of a bottle with closure. The bottle is single use and pre-sterilised (gamma irradiated). Technical drawings of the container closure system are provided.

A brief overview is provided regarding the active substance container closure material. Adherence to specifications is demonstrated.

Container closure integrity is considered demonstrated. It is agreed that the described studies show that the integrity is maintained during freezing, storage, thawing, and shipping of materials.

The approach described for assessment of extractables/leachables from the active substance container closure system is found adequate. The Applicant concludes that the level of the most abundant potential leachable is below the ICH M7 safety threshold, based on the dosing of the finished product, and that extraction studies indicate that there are no individual or cumulative levels of potential leachables of safety concern to patients. These conclusions are supported.

In conclusion, the container closure system could be considered sufficiently described and found suitable for its intended use (storage of concentrated protein A eluate intermediates and active

2.4.2.4. Stability

This section covers stability studies for the concentrated protein A eluate intermediates (anti-EGFR and anti-MET) and the active substance. Additional data was submitted during the procedure, although no concern was raised to the originally proposed shelf lives.

The subjects covered by the description of the stability studies (including freeze-thaw, recommended, accelerated and stressed conditions) and the stability data are appropriate, in compliance with ICH Q1A(R2) and Q5C, and the chosen analytical methods appear adequately stability indicating.

The container closure material is representative to the intermediates and active substance container closure, except for the volume. This is endorsed.

The proposed commercial shelf life for amivantamab active substance and the two concentrated protein A eluate intermediates is at the recommended long-term storage condition.

The Applicant concludes that the test results for all concentrated protein A eluate intermediates and active substance batches stored at the recommended long-term storage condition meet the acceptance criteria. The Applicant also concludes that the stability indicating attributes shows no apparent changes at the long-term storage condition as evaluated by statistical trend calculations (confidence interval 95%) and only very limited changes during accelerated and stressed conditions. This conclusion is

supported. It is also agreed that results from the forced degradation study confirm the product-related impurities reported under normal conditions, as outlined in 3.2.S.2.6.

It is noted that the active substance levels of HMWS appear to be very stable also at accelerated and stressed conditions.

The concentrated protein A eluate intermediate shelf-life claims are based on data

The active substance shelf life claim is based on data.

In summary, test results met the acceptance criteria and the stability indicating attributes shows no apparent changes during the recommended long-term storage conditions. Thus, the submitted data support shelf life at the recommended long-term storage conditions.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the finished product

The finished product is a concentrate for solution for infusion filled in clear Type I glass vials with butyl rubber stoppers and aluminium flip-off caps. It contains no preservative and is intended for single use only. The solution is colourless to pale yellow, with a pH of 5.7 and an osmolality of approximately 310 mOsm/kg.

Besides the active ingredient, amivantamab, the composition comprises only compendial components typically used for formulating monoclonal antibodies and is acceptable.

No formula overages are included.

Pharmaceutical development

An acceptable overview of the development of the formulation development is provided, including satisfactory data supporting the composition proposed for the commercial finished product.

Two different finished product formulations have been used during development. The final commercial finished product contains 50 mg/mL amivantamab in 10 mM histidine, 8.5% (w/v) sucrose, 1 mg/mL methionine, 20 µg/mL EDTA, 0.06% (w/v) polysorbate 80, pH 5.7 stored at 2-8°C.

The rationale used to select the final composition has been described in the dossier. The type and concentration of each excipient in the finished product were selected based on formulation screening, stability, and stress studies. Based on these studies, methionine and EDTA were added as stabilisers in the commercial formulation to minimise aggregation and oxidation. The robustness of the formulation composition was demonstrated by a robustness DoE study at concentrations of components at above and below the target concentrations.

Three different manufacturing processes for finished product have been used during development. as the finished product manufacturing processes were named in accordance with the corresponding active substance process scale. The manufacturing process changes performed during development have mainly been related to site changes and scale up. There is no complete overview of the process development provided in this section, instead, much of the relevant information is given in section S.2.6 Comparability. The different finished product process versions have been described in sufficient detail with respect to changes to the finished product manufacturing process.

Comparability for both active substance and finished product is described in section 3.2.S.2.6 and it can be concluded that finished product used in the clinical development can be considered representative of the commercial product.

The development of the control strategy is generally well explained and acceptable justification has been provided. The CQA identification process and criticality assessment are well described, and sufficient justification was presented. The CPPs are listed and sufficiently justified.

A section providing the development history of analytical procedures is presented.

The development of the primary container closure system is sufficiently described. The safety of the materials of construction was established in accordance with the relevant standards. Extractables studies have been performed and leachables studies are ongoing. The results obtained so far do not indicate any toxicological concern.

The information related to microbiological attributes is found acceptable. Container closure integrity is being monitored by blue dye ingress testing as part of the ongoing stability study.

Compatibility of diluted finished product with IV bags and administration sets of polypropylene, polyethylene, polyolefin, polyurethane, polybutadiene and polyvinylchloride contact materials has been demonstrated. During administration, use of an in-line filter is required based on the visible and subvisible particulate results, and this is appropriately reflected in the SmPC.

2.4.3.2. Manufacture of the product and process controls

Manufacture and process controls

The finished product is manufactured at Cilag AG, Schaffhausen, Switzerland, while Janssen Biologics B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands is responsible for batch release into the EU.

The commercial finished product manufacturing process is referred to as in other sections of the dossier.

The finished product manufacturing process is summarised in a flow chart and detailed in a written narrative. The manufacturing process consists of active substance thawing, compounding (pooling by pre-filtration and mixing), sterile filtration, aseptic filling, stoppering, and capping. The finished product vials are then optically inspected before secondary packaging and stored at 2-8°C. The manufacturing process is described in sufficient detail.

No reprocessing has been described in the dossier.

A summary of process parameters and corresponding PARs is presented. There are four CPPs identified:. The CPPs as well as all PARs have been acceptably justified by data presented in section 3.2.P.2.3. Hold times were acceptably justified by validation data presented in section 3.2.P.3.5 and all applied hold times have been listed in a separate table in the manufacturing description.

The batch numbering system is described in Section 3.2.P.5.4 Batch analyses.

The information provided in this section of the dossier is sufficiently detailed.

All IPC limits are applied as acceptance criteria. The proposed limits are acceptably justified by data presented in section 3.2.P.2.3. The bioburden limit applied before sterile filtration is in accordance with guideline requirements.

There are no intermediates isolated in the finished product manufacturing process.

Process validation

The process validation followed a traditional approach and covered four consecutive production scale batches. The validation was run at set points while the ranges of process parameters were challenged during the manufacturing process development described in 3.2.P.2.3. This approach is found acceptable. The results of IPCs and process characterisation samples met their predefined acceptance criteria, and all CPPs were controlled within their predefined ranges. All release results met finished product release specifications, and all process validation batches demonstrated consistent quality profiles, demonstrating that the finished product can be consistently manufactured within predefined processing parameters.

The presented filter validation comprises membrane compatibility, bacterial retention validation, and air diffusion and bubble point determination. Membrane extractables/leachables were also evaluated. The results demonstrate that the membrane is chemically compatible and suitable for use during finished product manufacture.

Media fills are described, and re-qualification is performed twice per year.

Shipping qualification and transportation studies were performed and support the transportation during commercial distribution.

In conclusion, the process validation data are acceptable.

2.4.3.3. Product specification

Specifications

The specification proposed for amivantamab finished product includes control of appearance, colour of solution (Ph. Eur.), pH (Ph. Eur.), extractable volume (Ph. Eur.), osmolality (Ph. Eur.), turbidity (Ph. Eur), polysorbate 80 content, visible particles (Ph. Eur.), subvisible particles (Ph.Eur.), identity (dot blot), quantity (A280), charge heterogeneity (cIEF), purity (SE-HPLC, reduced cSDS, non-reduced cSDS)and impurities, potency (EGFR ADCC Bioassay, cMET Binding), post translational modifications (MAM Peptide map), and microbial contaminants (sterility Ph. Eur.), Endotoxins (Ph. Eur.) and container closure integrity.

The proposed finished product release and end of shelf life specifications are found acceptable with respect to proposed test parameters. Sterility is tested at release only, while for stability the test for container closure integrity is performed to confirm sterility. This is acceptable.

The Applicant states that the used process ensured that the proposed finished product specifications were aligned with the clinical exposure levels of the CQAs, and this can be agreed to.

Batches used as the basis to set specifications are listed. The batches are referred to either as the "Total manufacturing experience" comprising finished product batches manufactured from active substance or the "Clinical data subset". It is clearly stated which finished product batches were used in the pivotal study submitted with this MAA, and the selection of batches for the "Clinical data subset" has been acceptably justified. It has been confirmed that finished product of the proposed commercial manufacturing process has been used in the clinic.

The statistical methods used for setting specifications are described. The justification and data provided by the Applicant are considered acceptable.

The acceptance criteria proposed for colour, pH, extractable volume, osmolality, turbidity, polysorbate 80, particles (visible foreign, and sub-visible), identity, quantity, potency (MET), charge variants (cIEF), purity (cSDS reduced and non-reduced), and post transitional modifications (Asp99

isomerisation by multi-attribute method (MAM) peptide mapping), endotoxin, sterility, and container closure integrity have been sufficiently justified and are approvable.

For visible translucent particlesGiven that an in-line filter will be used during patient administration by infusion, the proposed limit is found approvable.

The acceptance criteria for potency by EGFR ADCC are proposed based on clinical experience rather than on the wider range obtained by calculation of predictive intervals and are found acceptable.

In conclusion, the finished product specification is approvable.

Analytical procedures

The following tests are performed in accordance with Ph. Eur.: Colour of Solution (Ph. Eur. 2.2.2), Extractable volume (Ph. Eur. 2.9.17), Osmolality (Ph. Eur. 2.2.35), Particulate matter (sub-visible) (Ph. Eur. 2.9.19), Particulate matter (visible foreign) (Ph. Eur. 2.9.20), Bacterial endotoxins (Ph. Eur. 2.6.14), Sterility (Ph. Eur. 2.6.1), Turbidity (Ph. Eur. 2.2.1), and pH (Ph. Eur. 2.2.3).

The non-compendial analytical procedures used for both active substance and finished product are described in this section and are described with a sufficient level of detail.

Validation reports for all non-compendial test methods were provided. The reports are comprehensive and demonstrate suitability of the methods proposed for routine testing. Suitability of the compendial methods for endotoxin and sterility was verified as appropriate.

Batch analysis

Batch analyses data has been provided for the four process validation batches, which are also included as stability batches, manufactured using the proposed commercial process and at commercial scale. All data complies with the proposed finished product specifications.

In addition, batch analyses data is also included for development batches.

In conclusion, the batch analyses data demonstrates acceptable batch-to-batch consistency and reproducibility of the manufacturing process proposed for the finished product.

Reference standard

The reference standard system described in the dossier is used for testing of both finished product and active substance.

Characterisation of impurities

A majority of the product-related impurities for finished product are the same as for active substance, except for translucent particles that are applicable specifically to the finished product. Visible and subvisible translucent particles were monitored and the results indicate that the translucent particles are mainly composed of protein. No significant increase of translucent subvisible or visible particles was demonstrated upon storage at long-term, accelerated or stressed conditions, or after freeze-thaw, light exposure or shipping/transportation. Translucent particles will be controlled by the proposed finished product specification.

A comprehensive risk evaluation report regarding the potential presence of nitrosamines in the finished product was provided. The following components of the finished product were assessed to determine if the risk of nitrosating conditions or the presence of nitrosamines exist in the finished product: active substance manufacturing, raw materials, excipients and water, finished product manufacturing and primary packaging. By evaluating the production process, product components and packaging the Applicant concludes there is no risk of nitrosamine impurities in the finished product. The conclusion is endorsed, and thus the outcome of the nitrosamine risk evaluation is considered acceptable.

An elemental impurity risk assessment in accordance with ICH Q3D was performed, taking into account potential contributions from the active substance, excipients, processing water, manufacturing equipment and container closure system. Analytical screening using inductively coupled plasma-mass-spectrometry (ICP-MS) was also performed. Control threshold concentrations based on parenteral permitted daily exposures (PDEs) and maximum daily finished product intake were calculated for all elemental impurities. The Applicant concluded that none of the elemental impurities assessed are expected to exceed their corresponding control thresholds in the finished product and that the levels of the elemental impurities in the finished product do not exceed the permitted levels. The conclusion is endorsed, and thus the outcome of the elemental risk assessment is considered acceptable.

Container closure system

The container closure system used for finished product is a 8 mL Type 1 glass vial closed with a fluoropolymer coated 20-mm stopper and a 20-mm aluminum seal with a flip-off cap. For the primary packaging materials acceptable specifications, critical dimensions and drawings are provided in the dossier.

The information provided in this section is found acceptable. The materials in contact with the product comply with Ph. Eur. The glass vial complies with Ph. Eur. 3.2.1 "Glass Containers for Pharmaceutical use" and the rubber stopper complies with Ph. Eur, 3.2.9 "Rubber closures for containers for aqueous parenteral preparations, for parenteral use".

The sterilisation of the vials and stoppers is described in section P.3.5. The vials are washed and sterilised/depyrogenated on site prior to finished product manufacture at Cilag AG using a dry heat depyrogenation tunnel. The stoppers are provided by the supplier as prewashed and ready-to-sterilise. The stoppers are sterilised onsite at Cilag AG by a closure processor system using a fractionated vacuum method alternating with steam injections (moist heat). The information provided on sterilisation of the vials and stoppers is considered sufficient. The aluminum crimp seals with a flip-off cap are supplied ready to use by the vendors, i.e., pre-washed but not sterilised. Given that the stoppered vials are capped in a Grade C environment this is acceptable.

The photostability testing (P.8.1) indicates that the finished product is sensitive to light, however it was demonstrated that the secondary packaging provides sufficient protection. A precautionary statement that the product should be stored in the carton has been included in the SmPC.

2.4.3.4. Stability of the product

The proposed shelf life is 24 months at 2°C-8°C, protected from light.

The stability studies are being performed in accordance with ICH guidelines. The Applicant considers all primary stability batches to be representative of the commercial manufacturing process, and this can be agreed, as comparability between the scales has been demonstrated.

The stability testing was performed according to the proposed specifications and comprise the following parameters: bioactivity (EGFR ADCC bioassay, MET binding), purity by cSDS (reduced and non-reduced), purity by SE-HPLC (main component, HMWS), charge heterogeneity by cIEF, quantity, pH, colour of solution, turbidity, particulate matter (sub-visible and visible translucent MDI), peptide mapping and container closure integrity testing (CCIT). The analytical procedures are identical to those described in section P.5.2. The stability-indicating properties of the analytical procedures were demonstrated during method validation.

The finished product stability studies were conducted using product packaging representative of the commercial product packaging described in section 3.2.P.7.

clinical batches have currently reached the 24 months' time point, while batches have reached the 18 months' time point and batches the 12 months' time point. For the process validation batches, batches have reached the 12 months' time point and batch the 9 months' time point.

At the long-term conditions (5±3°C) all results for all parameters are within the specifications.

At accelerated and stressed conditions more pronounced changes were observed over time,

A photostability study was conducted in accordance with ICH Q1B. The results show that the finished product is sensitive to light however the commercial secondary packaging will provide adequate light protection. This has been properly addressed in the SmPC.

The Applicant commits to continue the ongoing stability studies up to 36 months according to the testing schedule presented.

Based on the presented stability data, the proposed shelf life of 24 months at 2°C-8°C, protected from light is approvable.

Based on the results obtained in the compatibility and microbial challenge studies, an in-use storage time of 10 hours at 20-25°C after dilution in 5% dextrose or saline is proposed for the finished product. This is acceptable.

2.4.3.5. Adventitious agents

No animal-derived or human-derived material was used during manufacture of the MCBs and the WCBs, and no such material is used during manufacture of the active substance. Foetal bovine serum and advanced DMEM/F12 (Dulbecco's Modified Eagle Medium/Nutrient Mixture F-12) including human plasma-derived transferrin and bovine serum albumin were used during single cell cloning of the development cell banks (used for manufacture of the MCBs). Human recombinant insulin expressed in yeast was also used. Early use of rabbit serum (non-TSE relevant) is also mentioned. EDQM certificates of suitability are provided for the sera, and certificates of origin are available for the human plasma-derived transferrin including collection and testing. A TSE statement is provided in annex 5.12 to the application form, and the animal-derived sera and human transferrin are appropriately listed. The information provided regarding animal- and human-derived materials is considered sufficient and together with the testing of the cell banks, the unprocessed bulk and the validation of virus clearance during active substance manufacturing, it is concluded that the risk for presence/transmission of TSE is very low.

In accordance with ICH Q5D the cell substrates, MCB and WCB used for manufacturing of amivantamab were assessed for sterility and mycoplasma at Charles River Laboratories. The MCB and WCB cell banks were determined to be sterile and tested negative for mycoplasma. Control of mycoplasma, bioburden and endotoxin is further managed through routine in-process testing. The viral testing was performed in compliance with ICH Q5A (R1) at the appropriate levels. The general approach, the testing, and the results are acceptable. Routine testing for adventitious virus using four cell lines was proposeded to be a 14-day assay, considering the overall viral safety approach, this is acceptable.

Virus clearance studies have been performed. Both RT-PCR and infectivity assays have been used.

In general, for all virus studies the lowest clearance data for runs has been summarised as a conservative measure. The principles of removal/inactivation of virus are orthogonal. The summary of results provided in section 3.2.A.2 discusses the relevant controls and design of virus clearance studies, although further details are requested. This is found acceptable.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The dossier is of good quality.

Characterisation of amivantamab was performed using an extensive panel of appropriate methods.

A science- and risk-based approach with QbD elements was used for process development and process characterisation, supporting the proposed manufacturing process control strategy and demonstrating a solid process understanding. The active substance and finished product manufacturing processes and process controls are appropriately described, and the processes are appropriately validated.

Three versions of the manufacturing process are presented. Changes are clearly described for manufacture of the parental monoclonal antibodies and the active substance, as well as the finished product process. There are differences between scales for some attributes but they are acceptably justified. Product from the commercial process version, can be considered comparable to product from the earlier versions used in the clinical trial.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Rybrevant is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Rybrevant is considered approvable from the quality point of view.

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

Amivantamab is a first-in-class, low fucose human bispecific immunoglobulin (Ig) G1 based antibody, directed against the EGF and MET receptors.

Amivantamab is produced in an engineered Chinese hamster ovary (CHO) cell line where low levels of fucose are incorporated into carbohydrate chains attached to the antibodies. One antigen-binding fragment (Fab) arm binds epidermal growth factor receptor (EGFR) and the other binds the mesenchymalepithelial transition factor (cMet), also known as hepatocyte growth factor (HGF) receptor. Amivantamab acts by blocking ligand binding and prevents receptor activation by inhibition of phosphorylation followed by downregulation and trogocytocis. This is mediated by Fc-domain interaction with immune cells and the interaction is simplified by low fucosylation of antibodies. The presence of EGFR and cMet on the surface of tumour cells allows amivantamab to bind and target the cells for destruction by immune effector cells through Antibody-dependent cellular cytotoxicity (ADCC) and/or Antibody-dependent cellular trogocytosis (ADCT) mechanisms.

Amivantamab is indicated for treatment of patients with metastatic non-small cell lung cancer (NSCLC) when the NSCLC has progressed on, or after platinum-based chemotherapy, i.e. in patients with Exon 20 insertion mutation, and /or resistance to current EGFR therapies including secondary and tertiary mutations in EGFR, and MET amplification or mutation.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The primary pharmacodynamics studies aimed at characterisation of amivantamab binding affinities to human, mouse, rat and cynomolgus monkey EGFR and MET extracellular domains as well as to FcRγ, *in vitro* functional activity in various cancer cell lines, and *in vivo* activity in various xenograft tumour models including tumours with EGFR and MET gene amplifications and EGFR activating mutations and mutations conferring resistance to TKIs.

In vitro studies

Amivantamab blocks the binding of human EGF and HGF to the extra cellular domain (ECD) of human EGFR and MET with an IC50-value of 10 and 30 nM respectively, shown in an ELISA format. Amivantamab displayed a Kd value of 1.43 and 0.04 nM for EGFR and Met respectively, by a surface plasmon resonance kinetic study. In addition, disruption of EGF-induced homodimerization of EGFR and heterodimerization of EGFR:ErBB2 was also confirmed using PathHunter® assays.

Amivantamab inhibited *in vitro* biological activity of EGFR and MET in a dose dependent manner in human lung cancer cell lines including those with EGFR primary activating mutations (L858R or deletions in Exon 19), EGFR gene amplification, the EGFR T790M mutation that confers resistance to EGFR TKIs, and the EGFR T790M mutation accompanied by MET gene amplification as well as cell lines with WT EGFR and WT MET. Amivantamab inhibited ligand-induced formation of phosphorylated pEGFR and pMET in a concentration-dependent manner in all cell lines tested. In addition, assays on downstream key signalling pathways from EGFR and cMet activation were analysed; Ras/RAF/MEK/ERK and PI3K/Akt. Amivantamab inhibited phosphorylation of ERK and AKT in a panel of cell lines including various EGFR mutations and cells with wild-type receptors. No effect was observed in cell lines with

MET amplification (H1993 and SNU-5). Amivantamab was also shown to possess higher activity against ERK and AKT phosphorylation compared to a mixture of monovalent EGF- and MET antibodies.

Amivantamab did not substantially inhibit cell viability in *in vitro* standard 2D assays (except for EGFR wt/cMet wt cell line SKMES-1 and H292 to some extent), but showed better activity in a 3D assay format, inhibiting survival in cell lines with WT EGFR as well as mutant EGFR. Amivantamab inhibited proliferation and promoted apoptosis of tumour cell lines that are mutant for EGFR (H1975) or amplified for MET (SNU-5), which occurred only when tumour cells and amivantamab were co-cultured with human PBMCs.

Moreover, ADCC activity of Amivantamab against a variety of WT or mutant EGFR, WT or amplified cMet, as well as WT or mutant K-RAS cell lines was confirmed in different cell lines. The ADCC response of Amivantamab has also been shown to be dependent on the presence of human PBMC. With addition of human PBMC, Amivantamab induced a concentration-dependent decrease in tumour cell proliferation, with maximum anti-proliferative effect observed at 72 hours (IC50 = 0.005 µg/mL). Amivantamab treatment also resulted in a concentration-dependent increase in apoptosis in the presence of PBMCs (IC50 = 0.0004 µg/mL). In addition, the response is stronger by the low fucose Amivantamab compared to the normal fucose equivalent version. The importance of the Fc region of Amivantamab in activation of immune cells has been demonstrated in several studies by comparing the effect by Amivantamab to its Fc silent version, IgG2-sigma. Thus, these data indicate that the interaction between the Fc region of Amivantamab and the effector immune cells, is an important factor in the mode of action by Amivantamab in the anti-tumoral effect.

The impact of amivantamab Fc interaction on EGFR and cMet protein and phospho-protein levels was evaluated in H1975 cells (*EGFR* mutations L858R/T790M and WT for MET) co-cultured with or without PBMCs. Treatment with amivantamab alone in the absence of PBMCs showed marginal effects on the levels of EGFR, pEGFR, and cMet proteins. In contrast, the presence of PBMCs markedly potentiated amivantamab-mediated downregulation of EGFR, pEGFR, and cMet by 46%, 67%, and 44% respectively. The corresponding figures in the *MET*-amplified cell line model SNU-5, was 79%, 89%, 87%, and 90% in EGFR, pEGFR, cMet, and pMet proteins, respectively, compared to the protein levels in the absence of PBMCs. Co-culture experiments in H1975 tumour cells showed that monocytes and macrophages were required for amivantamab-mediated downregulation of EGFR and cMet proteins. A positive correlation between the percentage of monocytes in the PMBC from the donors and the ability to downregulate EGF, pEGF and cMet was shown, while no correlation was found for T-, B-, or NK-cells. Moreover, confocal microscopic studies visualised labelled Amivantamab localised inside M1 and M2c polarised macrophages, and in monocytes cocultured with H1975 cells suggesting that Amivantamab downmodulates EGFR and c-Met through a trogocytosis mechanism.

In vivo studies

The importance of tumour-associated-macrophages, TAMs, was assessed in a xenograft study using a macrophage-depleting antibody (αCSF1R), showing a decreased tumour growth inhibition by Amivantamab from 72.8% to 38.5% (p=0.014), suggesting that macrophages play a key role in mediating the anti-tumour efficacy of amivantamab *in vivo*.

In the H1975-HGF xenograft model, Amivantamab exhibited a synergistic effect over treatment with the monovalent antibodies, as single treatments or in combination with monovalent antibodies.

Various studies on xenograft models have been performed. The effect was successful (tumour growth inhibition (TGI) >77%) on cancer cells expressing EGFR insertion mutation T790M exon 20 and substitution mutation L858R exon 21 with MET wt receptor in NSCLC, either PDX-derived- or H1975 xenografts with or without human HGF expression. Similarly successful was the treatment on the EGFR deletion mutation (del E746-A750 exon 19) in the NSCLC cell line HCC827, with MET amplification or

MET wt, or with human HGF expression with MET wt. The IC50 value for pEGFR was 1.5 and 29 nM in H1975 and HCC827, respectively, and for pMet between 0.64-2.1 nM and the IC50 for pERK and pAKT was <2 nM for both H1975 and HCC827.

Interestingly, in contrast to H1975, Amivantamab did not show activity on viability in cell lines with MET amplification (SNU-5, H1993) in *in vitro* low attachment cell cultures. *In vivo*, however, Amivantamab inhibited SNU-5 tumours with a TGI of 97% while Amivantamab treatment on H1993 xenografts remained unaffected (TGI%=11, non-significant). This indicates that additional factors (such as immune cells) are required for Amivantamab to inhibit cell viability in some type of tumours as well as other cellular features.

The effect of Amivantamab on PDX xenograft models varied, with the best effect in NSCLC (TGI42-81%) and gastric PDX (TGI 67%) and less effective in colorectal PDX models despite a number of studies (TGI 59% in one PDX model of seven investigated).

2.5.2.2. Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been conducted.

2.5.2.3. Safety pharmacology programme

Safety pharmacology parameters (cardiovascular, respiratory and observational CNS safety pharmacology endpoints) were evaluated in the repeat-dose toxicology studies in cynomolgus monkeys. The applicant did not submit any *in vitro* safety pharmacology studies such as hERG channel testing.

No cardiovascular, respiratory, or observational CNS findings occurred in cynomolgus monkeys administered amivantamab at IV doses up to 120 mg/kg/week for up to 13 doses in the 3-month toxicity study. Non-sedated monkeys had qualitatively normal electrocardiogram (ECG) recordings, no changes in ECG parameters or abnormalities in rhythm or waveform morphology, and no amivantamab-related effects on heart rate or blood pressure, respiration rate, or body temperature. Moreover, there were no amivantamab-related changes noted on veterinary physical examinations or daily cage-side observations or weekly detailed observations. At the highest dose tested, 120 mg/kg/week for the 6-week and 3-month monkey GLP studies, mean Cmax values after the last dose were 5040 and 5232 µg/mL, respectively, corresponding to approximately 6-fold the clinical Cmax.

2.5.2.4. Pharmacodynamic drug interactions

No pharmacodynamics drug interactions studies have been conducted.

2.5.3. Pharmacokinetics

Methods of analysis

Electrochemiluminescent immunoassay (ECLIA) methods on the MesoScale Discovery (MSD®) platform were used for the quantification of amivantamab serum concentrations and for the detection of anti-drug antibodies (ADA) in serum in the single-dose PK, 1-month tolerability, pivotal 6-week and 3-month repeat-dose studies in cynomolgus monkeys. An ECLIA method was also used for quantification of amivantamab serum concentrations in the subcutaneous (SC) local tolerance study in cynomolgus monkeys. Validation reports for the qualified method (CP2014Q-030) and the validated method (CP2015V-005) have been provided.

A validated MSD ECLIA (CP2014V-036) was also used to detect antibodies directed against amivantamab in cynomolgus monkey serum samples obtained in the single-dose PK, 1-month tolerability, pivotal 6-week and 3-month repeat-dose toxicity studies. The ADA assay was validated for cynomolgus monkey serum in terms of naïve sample reactivity, intra-assay and inter-assay precision, sensitivity, specificity, and robustness. The validation was not formally performed in compliance with GLP.

Absorption

The PK and immunogenicity of amivantamab was studied in cynomolgus monkeys following a single IV injection of 3, 10, or 30 mg/kg. The Cmax of amivantamab increased in an approximately dose-proportional manner between 3 and 30 mg/kg, but AUCinf increased in a greater than dose-proportional manner. As the dose level increased from 3 to 10 to 30 mg/kg, clearance values decreased from 19.93 to 12.67 and 9.12 mL/day/kg, respectively, indicating a trend toward saturation of target-mediated drug disposition. There were no differences in PK parameters observed between sexes within each dose group. The distribution volume indicated that amivantamab is mainly located in the plasma compartment.

Nine out of 12 animals (3 from each group) tested positive for ADA. Serum drug concentration-time profiles from ADA-positive animals were similar to the profiles from ADA-negative animals, except for 2 ADA-positive animals that exhibited lower amivantamab concentrations after Day 22.

Distribution

No tissue distribution studies were conducted with amivantamab.

Metabolism

No dedicated metabolism studies were performed for amivantamab.

Excretion

As a monoclonal antibody, no urinary excretion is anticipated due to its molecular size. Therefore, no specific studies to measure excretion amivantamab were performed.

2.5.4. Toxicology

A limited toxicology program has been conducted for amivantamab, largely in accordance with ICH S6 and S9 guidance, to support IV administration for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating EGFR Exon 20 insertion mutations, after failure of platinum-based chemotherapy.

The program included repeat-dose toxicity studies incorporating safety pharmacology endpoints, a weight of evidence for reproductive and developmental toxicity, *in vitro* studies on human blood and serum compatibility, *in vitro* cytokine release in human blood, and SC local tolerance. All pivotal studies were conducted in accordance with GLP.

Species selection for toxicity testing

The cynomolgus monkey was selected as a pharmacologically relevant species for the safety assessment of amivantamab. Amivantamab exhibited a similar binding affinity to cynomolgus monkey and human EGFR and MET, respectively, as well as a similar ability to inhibit phosphorylation of c-MET. However, inhibition of EGF-induced phosphorylation of EGFR was approximately 10-fold lower in cynomolgus monkey lung fibroblasts compared to human lung fibroblasts.

2.5.4.1. Single dose toxicity

No single-dose toxicity studies have been performed with amivantamab. This is agreed. No clinical signs of acute toxicity were observed in cynomolgus monkeys following the first weekly IV dose of up to 120 mg/kg in the repeat-dose toxicity studies.

2.5.4.2. Repeat dose toxicity

The repeat-dose toxicity of amivantamab in cynomolgus monkeys was evaluated in a 4-week tolerability non-GLP study, and 6-week toxicity with 6-week recovery and 13-week toxicity GLP studies. In addition to standard toxicological evaluations, safety pharmacology assessments were incorporated into the study designs. Cardiovascular system safety was evaluated by electrocardiogram (ECG) recordings, blood pressure, and heart rate. Respiratory system safety was evaluated by respiration rate and clinical signs. Central nervous system safety was evaluated by body temperature and clinical signs. There were no apparent safety signals of amivantamab on the cardiovascular system, respiratory system, or central nervous system in cynomolgus monkeys (see further in section 2.5.2.3. Safety pharmacology programme).

Amivantamab was well tolerated when administered IV once weekly at doses up to 120 mg/kg/week for 13 weeks (13 doses). There were no dose-limiting toxicity and no clear target organs of toxicity and the minor findings, all considered non-adverse, are presented below.

Gastrointestinal tract

The were no clear or adverse GI effects noted in amivantamab-treated animals, although a few observations where a relation to treatment cannot be excluded were observed.

In the 13-week study, slight to moderate liquid faeces occurred in some female monkeys at 120 mg/kg/week. As there were no other associated changes in body weights, disturbances in electrolytes, or findings at gross or microscopic pathology, the observation of liquid faeces is considered non-adverse. Given that diarrhoea, or soft or liquid faeces, is a common finding with other mAbs targeting EGFR such as panitumumab (Vectibix) and cetuximab (Erbitux), a relation to amivantamab treatment seems possible. However, it is also noted that non-specific diarrhoea (i.e. not associated with an etiologic agent) is a common background finding in cynomolgus monkeys.

Gross pathology findings of multifocal dark red foci with or without depression were noted in the gastric fundus of the stomach in a few animals (all males and 1 female at 60 mg/kg/week and 1 male at 120 mg/kg/week). The gross findings correlated with microscopic observations of minimal to mild focal to multifocal acute mucosal haemorrhage, and in one animal the dark red focus was also noted to be depressed and correlated microscopically with mucosal degeneration/erosion.

Microscopic pathology findings were observed in the stomach at ≥ 60 mg/kg/week. Minimal mucosal/glandular epithelial degeneration/regeneration was seen in one animal in each group at ≥60 mg/kg/week and included occasional foci of dilated gastric glands that contained rare sloughed necrotic epithelial cells and/or mixed neutrophilic infiltrates; minimal focal mucosal erosion noted in one 60 mg/kg/week group female; and focal epithelial basophilia/regeneration, consistent with a reparative response seen in another 60 mg/kg/week group male. Both findings were associated with acute haemorrhage.

Liver

Slight or minimal ALT and AST elevations were observed in the amivantamab repeat-dose studies. In the 4-week non-GLP tolerability study, minimal elevations in ALT and AST without histopathological liver correlates were observed at 100 mg/kg/week. In the 6-week GLP study, minimal, non-dose

dependent elevations in liver enzymes (ALT at ≥20 mg/kg/week, AST at 20 and 120 mg/kg/week) with no microscopic correlates in the liver were observed. The findings were reversible following a 6-week recovery period.

In the 13-week study, no alterations in liver enzymes were observed but minimal to mild Kupffer cell hypertrophy and cytoplasmic pigment was noted at both dose levels (60 and 120 mg/kg/week) in similar incidence and severity. This finding was considered likely related to test article clearance (Rojko et al., 2014).

Kidney

In the 13-week study, mild to minimal histopathological changes in the kidney were observed at 60 and 120 mg/kg/week without correlative changes in kidney-related clinical pathology parameters. Minimal tubular regeneration was noted at ≥60 mg/kg/week. At 120 mg/kg/week, degenerative/regenerative tubules were associated with minimal interstitial mixed cell infiltrates (with amphophilic material accumulation) in two males. The pathologist interpretation is that the tubule changes were suggestive of prior injury that is in the state of repair.

Haematology

Transient (Day 2 only) and mild increases in neutrophils associated with increases in white blood cell count, as well as decreased eosinophil and lymphocyte counts, occurred only in the 6 week study at 120 mg/kg/week. Minimal decreases in albumin at all doses and increases in globulin, with resultant decreases in the albumin:globulin ratio, in the 6- and 13-week studies at ≥60 mg/kg/week were consistent with a mild acute phase response. These clinical pathology changes had no histopathological correlates and were shown to be reversible after a 6-week recovery period in the 6-week study, although a non-adverse decrease in albumin was noted for 1 female in each recovery group.

2.5.4.3. Genotoxicity

No genotoxicity studies were conducted with amivantamab.

2.5.4.4. Carcinogenicity

No carcinogenicity studies were conducted with amivantamab.

2.5.4.5. Reproductive and developmental toxicity

No developmental or reproductive toxicity studies have been conducted with amivantamab. Regarding developmental toxicity, a weight-of-evidence assessment on potential consequences of disruption of the EGFR and MET pathways has been provided. Data from knockout mice indicate that EGFR and MET have critical roles during embryonic development. While data from knockout models should be interpreted with caution, data from both small molecule and mAbs support the view that disruption of the EGFR and MET pathways are likely to cause adverse effects on embryo-foetal and postnatal development and survival.

2.5.4.6. Local Tolerance

Local tolerance to IV administration of amivantamab was assessed as part of the general repeat-dose toxicity studies in cynomolgus monkeys. In the pivotal GLP 6-week and 3-month toxicity studies, there were no amivantamab-related effects on clinical observations or histopathology evaluation of administration sites following IV doses of up to 120 mg/kg/week for 5 or 13 doses.

A dedicated study was performed to assess local tolerance to SC administration in cynomolgus monkeys. SC administration of amivantamab with and without rHuPH20 was well tolerated at the sites of injection.

2.5.4.7. Other toxicity studies

Antigenicity

The development of ADAs to amivantamab in cynomolgus monkeys was evaluated in the 1-month tolerability study, 6-week toxicity GLP study with a 6-week recovery period, and 3-month toxicity study. Among the 55 cynomolgus monkeys administered weekly IV doses of amivantamab, 8 tested positive for the presence of ADA: 2 of 9 animals in the 1-month tolerability study (1 each in the 30 and 100 mg/kg/week dose groups) and 6 of 30 animals in the 6-week toxicity study (3, 2, and 1 in the 20, 60, and 120 mg/kg/week dose groups, respectively). All 16 animals in the 3-month toxicity study tested ADA negative. Potential interference of ADA by residual drug was not excluded in ADA-negative animals in these studies. It should be noted that immunogenicity studies in animals are not predictive of the human immunogenic response.

Immunotoxicity

Immunotoxicity was evaluated by standard parameters in the repeat-dose studies in cynomolgus monkeys. No amivantamab-related microscopic changes were observed in lymphatic organs (e.g., thymus, mandibular and mesenteric lymph nodes, tonsils, spleen, gut-associated lymphoid tissue). Haematological changes noted only in the 6-week toxicity study (mild increases in neutrophil count and decreases in lymphocyte and eosinophil counts on Day 2 at 120 mg/kg/week), although similar to those associated with physiological stress, were considered potentially treatment-related because they occurred only at the high dose.

Tissue cross-reactivity

In monkey and human *in vitro* tissue cross-reactivity studies, membrane staining was observed in the epithelium of multiple tissues, including peripheral nerve sheath cells and in human placental decidual cells, which is consistent with the expected expression of EGFR and MET.

Cytokine release assay

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.

Serum compatibility and haemolytic potential

Serum compatibility and haemolytic potential of amivantamab were evaluated by incubating graded concentrations (0.025 to 25 mg/mL). There was no evidence of amivantamab induced serum precipitation or haemolysis of human blood.

2.5.5. Ecotoxicity/environmental risk assessment

Amivantamab is a monoclonal antibody and is consequently classified as a protein. According to the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no environmental risk assessment for amivantamab is required.

2.5.6. Discussion on non-clinical aspects

The relevance of selected species in the pharmacological and pivotal toxicological studies has been demonstrated. For the pharmacology efficacy studies, mouse models with human cell xenografts were used, and Amivantamab did not exhibit any interaction with murine c-Met or EGFR in cross-reactivity studies while beneficial properties against human c-Met or EGFR have been shown, which is satisfactory. In addition, a cross-reactivity study with tissues from standard toxicology species using Zalutumumab, a parental antibody of Amivantamab targeting human EGFR was presented. Zalutumumab reacts with tissues from human, cynomolgus monkey and dog but not to mouse, pig, rabbit or rat. Furthermore, the binding affinity of Amivantamab was similar between cynomolgus monkey and human EGFR and Met respectively, and inhibition of HGF-induced phosphorylation of c-Met was comparable between the two species. However, the inhibition of the EGF-induced phosphorylation of EGFR was approximately 10-fold lower in Cynomolgus lung fibroblasts compared to human lung fibroblasts. This may explain the relatively mild toxicity profile observed in the Cynomolgus monkey in comparison to other pharmaceuticals inhibiting EGFR.

Pharmacology

Amivantamab inhibits a broader range of tumour growth, including those driven by aberrant EGFR and/or MET signalling for growth. Amivantamab was shown to possess higher activity against ERK and AKT phosphorylation compared to a mixture of monovalent EGF- and MET antibodies. This may indicate that treatment with bispecific amivantamab could be more efficient than blocking EGFR and MET receptors with two separate entities. A description of the pharmacological function of amivantamab, a bi-specific antibody, was presented with the aim to increase tolerability compared to other EGFR bivalent antibodies due to less avidity via a single binding arm to EGFR in normal tissues.

Safety pharmacology parameters (cardiovascular, respiratory and observational CNS safety pharmacology endpoints) were evaluated in the repeat-dose toxicology studies in cynomolgus monkeys. This approach is in line with the ICH S6(R1) guidance. The applicant did not submit any *in vitro* safety pharmacology studies such as hERG channel testing. This is acceptable considering the nature of the drug product (a monoclonal antibody). In summary, there were no apparent safety signals of amivantamab on the cardiovascular system, respiratory system, or central nervous system in cynomolgus monkeys.

Pharmacokinetics

The pharmacokinetic profile of amivantamab is considered as adequately characterised for the proposed indication. No dedicated distribution, metabolism or excretion studies were performed, and this is considered acceptable and in agreement with the ICH S6(R1) guideline. The metabolic pathways of biotechnology-derived pharmaceuticals are generally understood and include degradation to small peptides and individual amino acids.

Toxicology

Overall, the scope of the amivantamab toxicology program is considered adequate and in agreement with ICH S6 and S9 guidance.

Cynomolgus monkey was selected as a relevant species for safety assessment of amivantamab. This is agreed.

In the repeat-dose toxicity monkey studies, amivantamab was well tolerated when administered IV once weekly at doses up to 120 mg/kg/week for 3 months (13 doses). There were no dose-limiting toxicity or adverse effects expected from inhibition of EFGR and MET such as on-target effects in tissues of epithelial origin were observed with exception of mild effects in the GI tract with unclear

relation to amivantamab-treatment. However, the exposure margin at the highest dose was only about 5-fold the clinical AUC indicating that the high dose levels were not set at an appropriate level. The lower *in vitro* potency on inhibition of phosphorylated EGFR, should also have been taken into consideration in the justification of dose levels. It can be argued that the high dose level employed in the repeat-dose studies, 120 mg/kg/week, represents the highest feasible dose level based on the highest available concentration of amivantamab 50 mg/mL and a dose volume of 2.4 mL/kg. The employed dose volume exceeds the maximum recommended volume of 2 mL/kg IV in cynomolgus monkeys. It is unclear if the concentration of amivantamab in the dose formulation is the highest feasible based on solubility. Taken together, the highest dose level employed in the repeat-dose toxicity studies is not considered fully justified but given that EFGR and MET are rather well characterised targets, and that amivantamab is indicated for treatment of patients with advanced cancer, no further studies are needed.

Non-adverse effects with uncertain relation with amivantamab-treatment include findings in the GI tract in the 13-week study. No GI-related findings were observed in the 6-week monkey study where dose levels of 20, 60 and 120 mg/kg/week were used. In the 13-week monkey study, GI findings including liquid faeces, and gross and microscopic pathology findings were observed in some animals at 60 mg/kg/week and above. The observed GI findings are likely incidental.

Liquid faeces were observed in all 4 females given amivantamab at 120 mg/kg/week, but not in male animals at comparable Cmax and AUC exposures. Given that the finding was observed prior to treatment in 2 females and only transiently in connection with dosing in the remaining 2 females, it is agreed that a relation to amivantamab exposure is weak. As there were no other associated changes in body weights, or disturbances in electrolytes, it is also agreed that the liquid faeces are considered non-adverse.

Microscopically, inflammatory cell infiltration in the stomach lamina propria was observed in most study animals including those in the control group. This is a very common spontaneous finding in cynomolgus monkeys according to literature and is not considered related to amivantamab treatment. Additional microscopic findings include minimal mucosal/glandular epithelial degeneration/regeneration seen in one animal in each group at ≥60 mg/kg/week and included occasional foci of dilated gastric glands that contained rare sloughed necrotic epithelial cells and/or mixed neutrophilic infiltrates; minimal focal mucosal erosion noted in one 60 mg/kg/week group female; and focal epithelial basophilia/regeneration, consistent with a reparative response seen in another 60 mg/kg/week group male. Both findings were associated with acute haemorrhage.

In literature, it is reported that the common spontaneous gastritis sometimes is associated with acute multifocal haemorrhage and erosions especially in the fundic part of the stomach. Thus, the haemorrhage observed in 3 males and 1 female at 60 mg/kg/week, and 1 male at 120 mg/kg/week may also be incidental.

Taken together, given lack of dose-response, and the fact that most microscopic pathology findings are reported as spontaneous lesions in cynomolgus monkeys or were observed also in control monkeys, it is agreed that the findings are likely not related to amivantamab treatment. Nevertheless, GI disorders (i. e. constipation, stomatitis, nausea, diarrhoea and vomiting) are reported as very common adverse reactions in SmPC 4.8 and in general, GI toxicity is considered a class effect of EGFR and MET inhibitors. The risk of GI toxicity in relation to EGFR or MET inhibition and the management of GI toxicity is well known in clinical practice.

No developmental or reproductive toxicity studies have been conducted with amivantamab. An evaluation of fertility is not warranted for biopharmaceuticals intended to treat advanced cancer (refer to Section and 4.6 of the SmPC).

Regarding developmental toxicity, a weight-of-evidence assessment on potential consequences of disruption of the EGFR and MET pathways has been provided. In general, it is agreed that the risk for reproductive and developmental toxicity could be addressed based on published scientific evidence regarding mechanism of action, animal models and class effects. In addition to the EGFR inhibitors referred to by the Applicant, similar findings are reported for panitumumab, reported to cause foetal abortions and/or foetal deaths in cynomolgus monkeys when administered during the period of organogenesis at doses approximately equivalent to the recommended human dose (see Vectibix SmPC). Additionally, for cetuximab, a dose-related increased incidence of abortion was observed in cynomolgus monkeys (see Erbitux SmPC). Taken together, the view that the risks of amivantamab to human development can be communicated appropriately to patients and prescribers based on the existing scientific information without conducting additional developmental animal studies is agreed. The brief description of these findings in SmPC section 5.3 is considered adequate.

Regarding breast-feeding, the risk for achieving plasma levels of the therapeutic antibody that would be sufficiently high to exert any biological activity is negligible based on the low transfer of IgG to human breast milk, the likely loss of biological activity in the low pH of gastric juice and the low uptake of intact IgG through intestinal wall. Regarding the ligands of the amivantamab targets (EGFR and Met receptors), literature reports that EGF and HGF growth factors, among others, are present in human early milk in ng/mL concentrations during the first week post-partum at concentrations much higher that the serum levels in lactating women or in healthy adults (about 100-fold for EGF and about 5-fold for HGF). It is also described that the milk levels were highest in colostrum and decreased in concentration in breast milk throughout lactation. Mainly based on the enrichment in milk, these growth factors are assumed to be important for post-natal development. In particular, it is speculated that EGF and HGF are important gut development and maturation. No data has been provided on whether the targets of amivantamab, EGFR and Met receptors, are expressed in the newborn human gut. In rodents, it is reported that EGF receptors have low expression during milk feeding and delayed expression until weaning (Gallo-Payet N, Pothier P, Hugon JS. Ontogeny of EGF receptors during postnatal development of mouse small intestine. J Pediatr Gastroenterol Nutr 1987). A recommendation regarding breast-feeding is included in section 4.6 of the SmPC.

No genotoxicity or carcinogenicity studies were conducted with amivantamab as these studies are generally inappropriate for a monoclonal Ab, and because carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, the available pharmacological, pharmacokinetics and toxicological data are considered appropriate and sufficient for approval of amivantamab for the treatment of NSCLC patients with EGFR Exon 20 insertions.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 5. Summary of ongoing and planned amivantamab monotherapy and combination studies

	Study Design	Study Population	Number of Planned Subjects	Treatment Regimen	Status
61186372EDI1001 **Pivotal study**	*A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and MET Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer.*	*Part 1: Dose escalation* Subjects with advanced NSCLC *Part 2: Dose expansion* Cohort A: previously treated, EGFR-driven tumour progression. Cohort B: previously treated, EGFR-independent tumour progression. Cohort C: documented EGFR alterations (eg, C797S) mediating resistance to previous treatment with a third-generation TKI. Cohort D: previously diagnosed activating EGFR Exon 20ins mutation, not previously treated with a TKI with known activity in Exon 20ins disease. Cohort MET-1: documented primary EGFR-mutated disease, and documented MET amplification or mutation after progression on any EGFR TKI. Cohort MET-2: documented primary MET Exon 14 skipping mutation NSCLC. No subjects have been enrolled in this cohort as of the clinical cutoff. Cohort E: advanced EGFR-mutated NSCLC characterized by Exon 19del or L858R sensitive activating mutations, progression after first- or second-line treatment with a third-generation TKI.	Part 1: 3+3 MTD design; up to 20 subjects per dose cohort Part 2: ~460 subjects Cohort A: ~40 subjects Cohort B: ~20 subjects Cohorts C, D, MET-1, MET-2: up to 100 subjects	Part 1, monotherapy doses: 140 mg, 350 mg, 700 mg, 1050 mg, 1400 mg, and 1750 mg. The recommended RP2D was determined to be 1050 mg for subjects weighing <80 kg at baseline, and 1400 mg for subjects weighing ≥80 kg at baseline. Amivantamab monotherapy: N=362 (as of 08 June 2020) Amivantamab in combination with lazertinib N=91 (as of 08 June 2020) Amivantamab in combination with carboplatin and pemetrexed Planned: 20	Ongoing Exon 20 Insertion Analysis: 08 Jun 2020; 08 Oct 2020; 30 Mar 2021
73841937NSC1001	*An Open-label Phase 1/1b Study to Evaluate the Safety and Pharmacokinetics of JNJ-73841937 (Lazertinib), a Third-Generation EGFR-TKI, as Monotherapy or in Combinations With JNJ-61186372, a Human Bispecific EGFR and MET Antibody in Participants With Advanced Non-Small Cell Lung Cancer.*	EGFR-mutated NSCLC after treatment with osimertinib and a platinum-based chemotherapy.	120	Amivantamab in combination with lazertinib N=6 (as of 08 June 2020) Lazertinib monotherapy N=12 (as of 08 June 2020)	Ongoing Interim Analysis: 11 Jan 2021 Final Analysis: 28 May 2024

	Study Design	Study Population	Number of Planned Subjects	Treatment Regimen	Status
61186372NSC1003	*An Open-label, Multicentre, Dose Escalation Phase 1b Study to Assess the Safety and Pharmacokinetics of Subcutaneous Delivery of Amivantamab, a Human Bispecific EGFR and MET Antibody for the Treatment of Advanced Solid Malignancies*	Participants with solid malignancy which may derive benefit from EGFR or cMET directed therapy and who have progressed after prior standard of care therapy, be ineligible for, or have refused currently available therapeutic options.	Part 1: 16 Part 2: 60	Part 1: 50 mg/mL SC with/without rHuPH20 Part 2: 160 mg/mL SC with/without rHuPH20	Ongoing Primary Analysis: 4th Q 2021
61186372NSC3001 **Proposed confirmatory study**	*A Randomized, Open-label Phase 3 Study of Combination JNJ-61186372 and Carboplatin-Pemetrexed Therapy, Compared with Carboplatin-Pemetrexed, in Patients with EGFR Exon 20ins-mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer*	Treatment naïve, EGFR Exon 20ins NSCLC Confirmatory study in this population	300	Amivantamab in combination with carboplatin and pemetrexed	Planned Primary Analysis: 05 May 2022
73841937NSC3003	*A Phase 3, Randomized Study of Amivantamab and Lazertinib Combination Therapy Versus Osimertinib Versus Lazertinib as First-Line Treatment in Patients with EGFR-Mutated Locally Advanced or Metastatic Non-Small Cell Lung Cancer*	Treatment naïve, EGFR-mutated NSCLC	1000	Amivantamab in combination with lazertinib	Planned Interim Analysis: 11 Apr 2023 Final Analysis: 15 Dec 2025

EGFR=epidermal growth factor receptor; ins=insertion mutation; MET=mesenchymal-epidermal transition; MTD=maximum tolerated dose; NSCLC=non-small cell lung cancer; rHuPH20=recombinant human hyaluronidase; RP2D=recommended Phase 2 dose; SC=subcutaneous; TKI=tyrosine kinase inhibitor. Pivotal and proposed confirmatory study highlighted in green colour.

2.6.2. Clinical pharmacology

This submission for a conditional marketing authorization includes PK-data from 413 subjects treated with amivantamab as monotherapy in the ongoing Phase 1 Study 61186372EDI1001 (hereafter referred to as EDI1001). No clinical pharmacology studies in healthy volunteers have been provided.

2.6.2.1. Pharmacokinetics

Methods

Quantification of amivantamab in serum

An adequately validated ECLIA assay on the MSD platform was used to analyse total amivantamab concentrations in human serum. Samples were pre-treated with 100 mM acetic acid, dissociating any bound amivantamab from e.g. soluble target or ADAs, then mixed with both biotin-human EGFR and Sulfo-Tag-MET. Amivantamab bound to biotin-human EGFR was captured on streptavidin coated 96-well MSD plate and subsequently detected by the signal generated by the Sulfo-Tag-MET bound to amivantamab.

Detection of anti-drug antibodies (ADA)

A standard multi-tiered approach was developed including screening, confirmatory and titer and characterization assays (bridging ELISA format) to evaluate anti-drug antibodies in accordance with EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1). Human serum samples and controls are first treated with acid, followed by an incubation with biotinylated-amivantamab (bio-amivantamab). Bio-amivantamab-ADA complexes are then captured on NeutraAvidin-coated magnetic particles and washed. The biotin-amivantamab bound antibodies are eluted from the bead complex by a second acid treatment and incubated in the presence of Sulfo-TAG-amivantamab. The samples are added to the wells of the blocked MSD-streptavidin plate and the wells that contain antibody bound to both bio-amivantamab and Sulfo-TAG-amivantamab will generate an ECL signal.

To establish screen and confirmatory assay cut points (CP), 20 normal and 25 non-small cell lung cancer (NSCLC) individual human serum samples were analysed. No statistically significant difference was found between the normal and NSCLC disease population. The assay is acceptably selective and sensitive (screen assay sensitivity is 2 ng/ml). Drug tolerance, defined as the highest drug concentration at which samples remained positive, is reported to be above 400 μg/ml for the middle (MPC 40 ng/ml) and high (HPC 100 ng/ml) positive control samples. For the low positive control (LPC 5 ng/ml) drug tolerance was 100 μg/ml for the screening assay and 50 μg/ml in the confirmatory assay. EGFR target interference is apparent in the screen assay at levels of 31.25 ng/mL and higher when the dimeric form of the target is present but does not impact the confirmatory assay at levels up to 8000 ng/mL EGFR dimeric protein. The monomeric form did not interfere with the assays at levels up to 8000 ng/mL. cMET will cause a false positive result at concentrations above 62.5 ng/ml.

Given the overall low incidence of anti-amivantamab antibodies in the clinical study (3 subjects or 1%) no assay for determining the neutralising potential of ADAs were developed.

Quantification of free and total soluble EGFR and Met in human serum

Sandwich MSD ECLIA methods were developed and qualified to measure engagement of amivantamab with soluble EGFR and MET targets at the different dose levels in study EDI1001.

Non-compartment data analysis (NCA)

Standard non-compartment analysis was performed where rich sampling was applied.

Population pharmacokinetic analysis

A population PK (PPK) analysis was performed using the nonlinear mixed-effects modelling software NONMEM, version 7.3. The FOCEI method was employed for all model runs.

The PPK analysis was based on 13440 rich and sparse serum concentration samples from 413 subjects, with advanced NSCLC receiving IV amivantamab as monotherapy, in Study EDI1001 (Part 1: dose escalation; Part 2: dose expansion). Rich individual serum concentration-time data are shown in Figure 3.

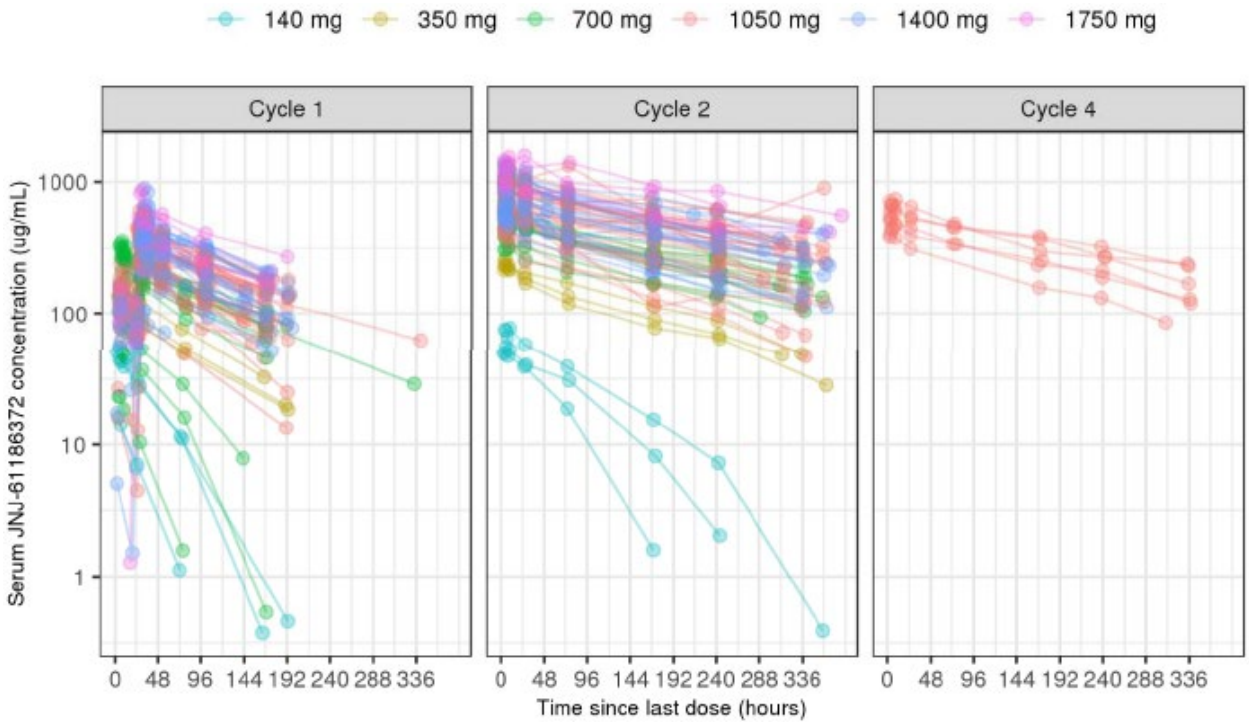


Figure 1. Amivantamab Serum Concentration Profiles in Cycles 1, 2, and 4.

A faster decline was observed for the 140 mg dose group compared with the other dose groups, which is consistent with the notion of amivantamab undergoing target-mediated drug disposition. The PK of amivantamab appeared to be dose-proportional in the dose range of 350 to 1750 mg.

A 2-compartment model significantly improved the model fit compared with a 1-compartment model. A parallel linear and saturable (ie, Michaelis-Menten) clearance mechanism further improved the model fit compared with linear clearance. Body weight was included as covariate on clearance (CL) and central volume of distribution (V1) [allometric scaling with estimated exponents], whereas sex was included on CL [these were the key covariate effects identified for amivantamab PK in the original analysis with a linear clearance model – not reassessed with the parallel linear and saturable clearance model]. Based on the parameter estimates of the updated final PPK model, a 50% increase in body weight (e.g., from 60 to 90 kg) results in a 20% increase in linear clearance (irrespective of sex) and a 31% increase in V1, while males are associated with a 23% higher linear clearance compared with females (irrespective of body weight).

The prediction-corrected VPC (pcVPC) of predose and postdose concentrations, stratified by recommended Phase 2 dose (RP2D) status, for the PPK final model, is shown in Figure 4. Other time points (2, 6, 24, 72, 168, and 240 hours postdose) all had fewer than 100 observations at each cycle and were therefore not included in the plot. Based on the pcVPC plots, the PPK final model appeared to adequately capture the central tendency and the variability of the data.

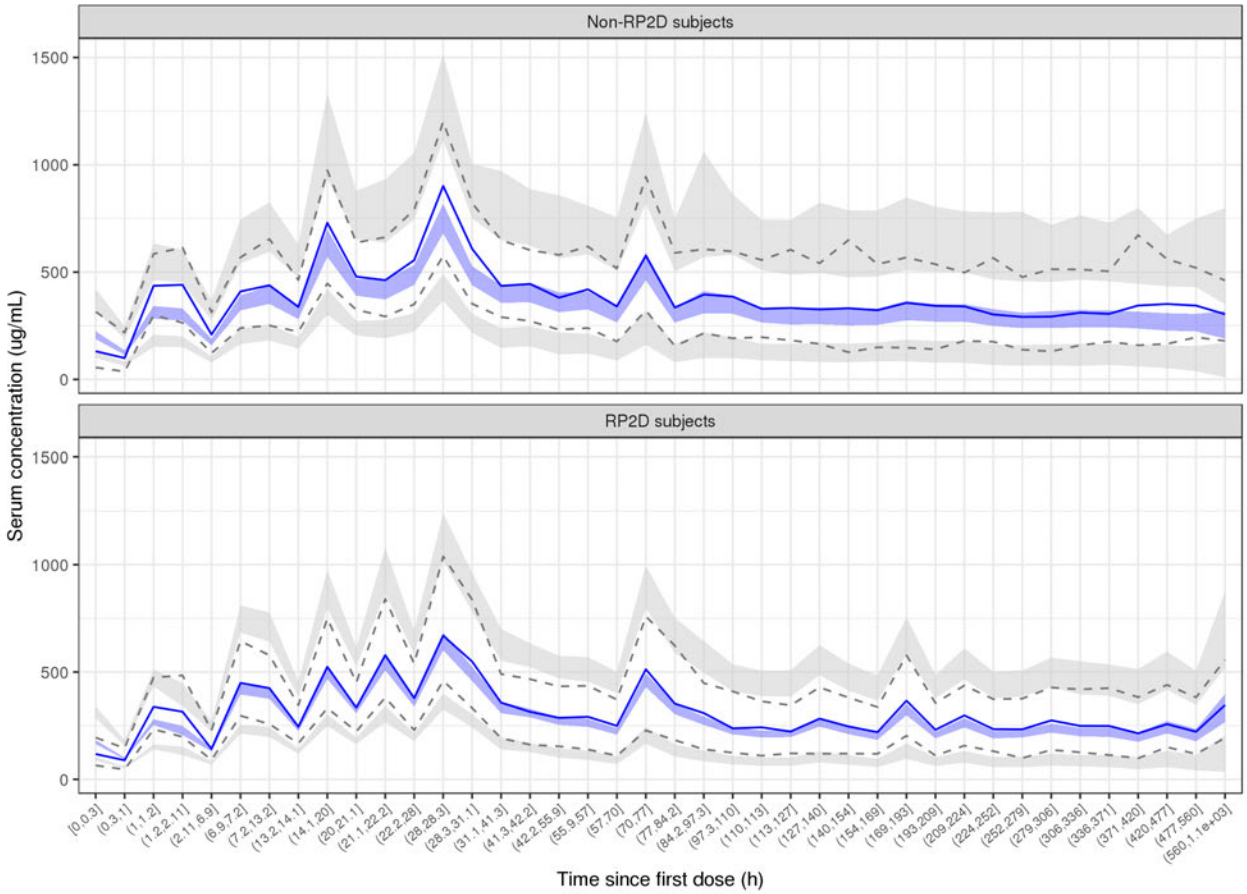


Figure 2. Prediction-Corrected Visual Predictive Check Stratified by RP2D Status (Population Pharmacokinetic Final Model) [The unit is Days, not hours]

The lines represent the median (blue solid line), 5th and 95th percentiles (gray dashed lines) of the prediction-corrected observations plotted versus bins of time since first dose containing approximately equal number of observations. Shaded areas represent the 95% confidence intervals for the median (blue), 5th and 95th percentiles (gray) of the prediction-corrected simulated observations based on 1000 population PK simulations.

The individual amivantamab steady-state exposure parameters ($AUC_{0\text{-}14\ days,ss}$ [AUC over 2 weeks at steady state], $C_{eoi,ss}$ [concentration at end of infusion, e.g. C_{max}, at steady state], and $C_{trough,ss}$ [trough concentration at steady state]), derived from the individual PPK final model parameters and assuming RP2D regimen, are summarized in Table 11. Exposures for body weights <80 kg (resulting from the RP2D of 1050 mg) and ≥80 kg (resulting from the RP2D of 1400 mg) were comparable.

Table 6. Summary of Individual Exposure Parameters at Steady State Based on the RP2D Regimen (Population Pharmacokinetic Final Model)

Parameter	Dose	No. subjects	GeoMean	GeoSD	CV%	Min	5th %	Median	95th %	Max
$AUC_{0\text{-}14d,ss}$ (ug h/mL)	1050 mg	379	80213	1.38	32.7	20435	44893	82299	129100	186574
$AUC_{0\text{-}14d,ss}$ (ug h/mL)	1400 mg	60	83039	1.26	23.6	50578	56972	83899	120710	136884
$C_{eoi,ss}$ (ug/mL)	1050 mg	379	531	1.26	23.3	231	355	537	769	980
$C_{eoi,ss}$ (ug/mL)	1400 mg	60	529	1.17	15.6	351	415	535	689	722
$C_{trough,ss}$ (ug/mL)	1050 mg	379	130	3.09	160	0.00130	55.1	153	276	417
$C_{trough,ss}$ (ug/mL)	1400 mg	60	146	1.45	38.5	63.5	68.8	151	244	278

Parameter	Dose	No. subjects	GeoMean	GeoSD	CV%	Min	5th %	Median	95th %	Max

Key: $AUC_{0\text{-}14d}$= area under the serum concentration-time curve from 0 to 14 days; C_{eoi}=end-of-infusion concentration; C_{trough}=trough concentration; CV%=percentage coefficient of variation; GeoMean: geometric mean; GeoSD: geometric standard deviation; RP2D=recommended phase 2 dose; ss=steady state

Forest plots of $AUC_{0\text{-}14\ days,ss}$, $C_{eoi,ss}$, and $C_{trough,ss}$ (Figure 5 [only figure for $C_{trough,ss}$ included in AR]), presenting the estimated geometric mean ratio (GMR) and 90% CI for one covariate stratum relative to the reference stratum, while adjusting for the other covariates and assuming that each subject received the RP2D regimen, showed that none of the estimated GMR CI limits were entirely outside the 80% to 125% range. This confirms that for all covariates, amivantamab exposures with the RP2D regimen were similar across different strata of the covariate when adjusted for the effect of other covariates.

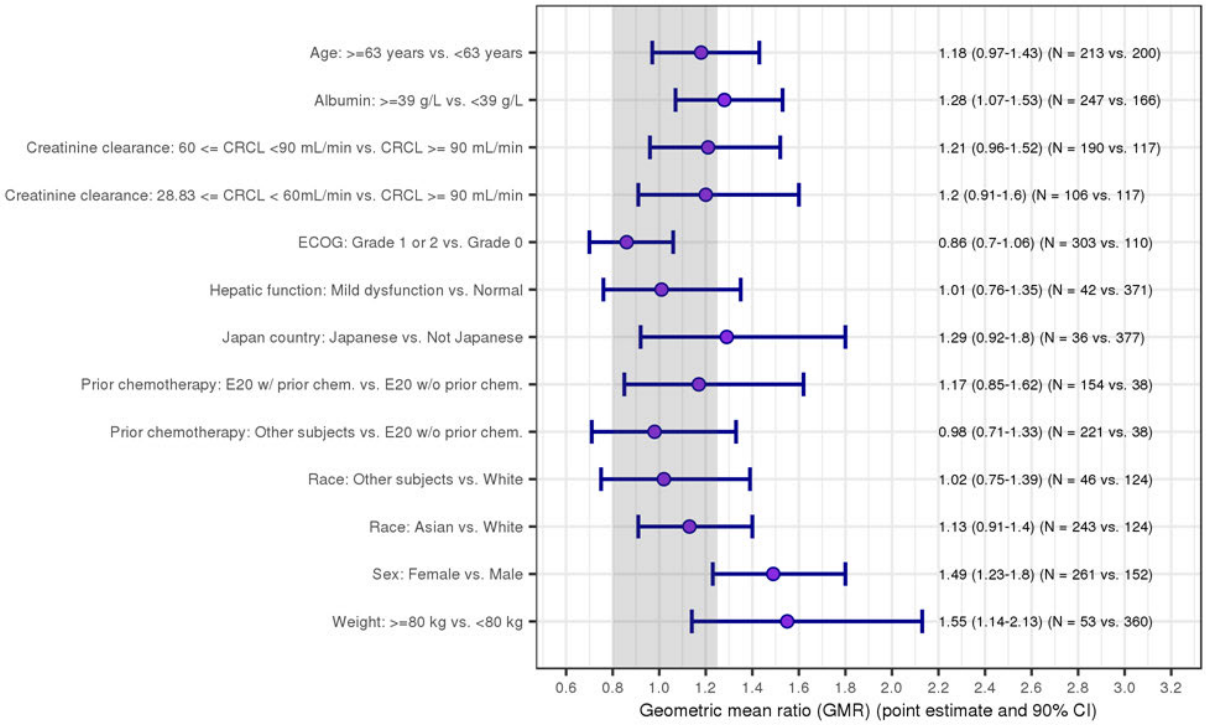


Figure 3. Forest Plot of $C_{trough,ss}$ Based on the RP2D Regimen (Population Pharmacokinetic Final Model)

Absorption

Absorption data are not available since all studies administered amivantamab as an IV infusion and no food effect study was conducted.

Bioequivalence

Clinical Study EDI1001 used 150mg/vial and 350mg/vial formulations of amivantamab for dilution for intravenous administration. The 350mg/vial formulation is identical to the proposed commercial formulation. Further several different batches of amivantamab were used in the clinical trial. A comprehensive overview of the formulation development process along with the formulation development as well as a discussion of the impact of changes implemented throughout development of the drug substance and drug product manufacturing processes are provided in the quality sections of the dossier.

Distribution

Typical IgG1-based mAbs are primarily confined in the vascular system. The geometric mean (CV%) total volume of distribution, based on individual parameter estimates from the PPK model, was 5.37 (20.6%) L. Traditional protein-binding studies using human serum albumin as conducted for small molecules are not applicable to mAbs.

Elimination

The excretion and metabolic pathways of amivantamab has not been investigated. As an IgG1 antibody, the biotransformation of amivantamab is expected to be similar to endogenous IgG (degraded into small peptides and amino acids via catabolic pathways) and subject to similar elimination pathways. For a 148 kDa protein renal excretion is not anticipated.

The PPK model-estimated nonspecific linear clearance of amivantamab was 225 mL/day (with inter-individual variability [CV%] of 25%). The geometric mean (CV%) half-life of amivantamab associated with linear elimination, derived based on individual parameter estimates from the PPK model, was 15.7 (25.5%) days.

Dose proportionality and time dependencies

Dose proportionality

Target-mediated drug disposition was apparent at the lowest dose (140 mg) and in the first cycle also for doses up to 700 mg. Based on $AUC_{0\text{-}168h,}$ C_{max} and C_{trough} dose proportionality was observed in the amivantamab dose range of 350 to 1750 mg. No data from NCA comparing the different doses at steady state (achieved by the ninth infusion) is available.

Time dependency

The increase in C_{trough} during weekly dosing in Cycle 1 demonstrates moderate accumulation of amivantamab. The mean (SD) accumulation ratios (AR)s of amivantamab based on AUC0-168 h (C2D1/C1D1) at 1050 mg (for body weight <80 kg) and 1400 mg (for body weight ≥80 kg) were 2.88 (0.68) and 3.03 (0.82), respectively. The mean (SD) AR of amivantamab at steady state based on AUC0-168h (C4D1/C1D1) at 1050 mg was 2.44 (0.54).

Intra- and inter-individual variability

Inter-individual variability (CV%) in CL, V_{max} (maximum velocity of the Michaelis-Menten elimination process), V1 and V2 was estimated to be 25%, 55%, 25% and 36%, respectively, based on PPK model estimates.

Pharmacokinetics in target population

The PK analyses are based on serum amivantamab concentrations of samples obtained from subjects treated with amivantamab monotherapy in Parts 1 and 2 of Study EDI1001 which is an ongoing, first-in-human, open-label, 2-part Phase1 dose escalation study.

The primary objective of Part 1 was to determine the maximal tolerable dose, if one exists and the recommended phase 2 dose (RP2D). 76 subjects were allocated to amivantamab doses of 140, 350, 700, 1050, 1400, and 1750 mg were administered as IV infusion, once weekly for the first 4 weeks (ie, Cycle 1) and every 2 weeks thereafter in all subsequent 4-week cycles. Rich sampling was applied at day 1 in Cycle 1 and 2 in addition to sparse sampling throughout the study period.

The primary objectives of Part2 (n=285) were to determine the safety, tolerability, and antitumor activity of amivantamab monotherapy at the RP2D which was 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 Cycle 1 dose was split over

2 days to better manage the risk of IRRs. Apart from rich sampling in 6 individuals (dosed 1050 mg) at day 1 in cycle 1,2 and 4 sparse sampling was applied.

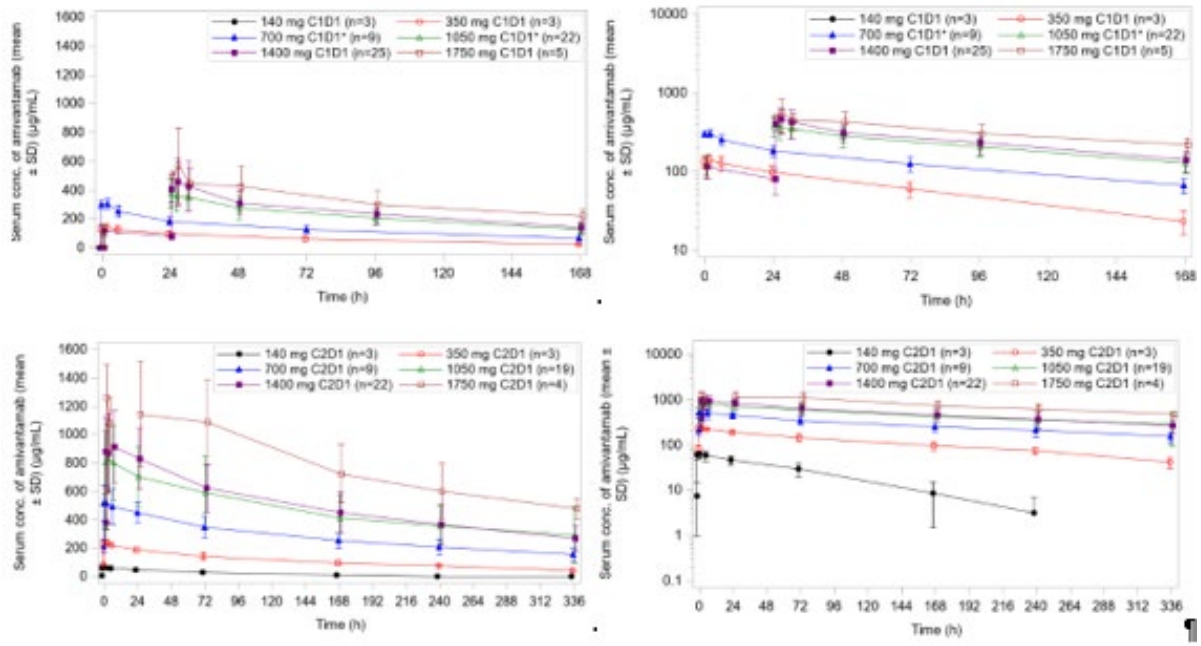


Figure 4. Mean C1D1 (top) and C2D1 (bottom) serum concentration-time curves of amivantamab, linear (left) and semilogarithmic (right) scale. Part 1 study EDI1001

Table 7. Summarized pharmacokinetic parameters of amivantamab at the RP2D

Mean (SD) T_{max}: Median (Range)[a]	Amivantamab Dose (Weight Category) Updated Analysis	
	1050 mg (<80 kg)	1400 mg (≥80 kg)
Cycle 1 Day 1		
n	25[b1]	8
C_{max} (full dose), µg/mL	220	-
C_{max} (split dose), µg/mL	386 (87.4)	337 (74.8)
$AUC_{0\text{-}168h}$, µg.h/mL	33723 (9231)	28062 (5612)
Cycle 1 Day 8		
n	181	34
C_{trough}, µg/mL	126 (51.2)	129 (36.3)
Cycle 1 Day 15		
n	193	35
C_{trough}, µg/mL	213 (74.7)	208 (52.1)
Cycle 1 Day 22		
n	181	36
C_{trough}, µg/mL	279 (77.5)	285 (72.9)
Cycle 2 Day 1		
n	26[c1]	8[d1]
C_{max}, µg/mL	836 (264)	655 (109)
C_{trough}, µg/mL	330 (107)	348 (134)
T_{max}, h	4.08 (2.03-8.33)	5.72 (2.28-25.47)
$AUC_{0\text{-}168h}$, µg.h/mL	94946 (35440)	76946 (14557)
AUC_{τ}, µg.h/mL	154519 (59957)	121017 (28922)
AR $AUC_{0\text{-}168h(C2D1/C1D1)}$	2.88 (0.68)	3.03 (0.82)
Cycle 2 Day 15		
n	161	32
C_{trough}, µg/mL	243 (112)	251 (87.3)
Cycle 3 Day 1		
n	156	29
C_{trough}, µg/mL	209 (83.8)	206 (78.9)
Cycle 3 Day 15		
n	148	26
C_{trough}, µg/mL	193 (91.7)	182 (78.0)
Cycle 4 Day 1		
n	6[e1]	21
C_{max} (full dose), µg/mL	586 (123)	-
T_{max} (full dose), h		-
C_{trough}, µg/mL	185 (93.0)	171 (54.2)
$AUC_{0\text{-}168h}$, µg.h/mL	66385 (15981)	-
AUC_{τ}, µg.h/mL	102954 (27665)	-
AR $AUC_{0\text{-}168h(C4D1/C1D1)}$	2.44 (0.54)	-

[a] If n<3, individual results are displayed.
[b1] n=24 for C_{max} (split dose) and $C_{max,\ dose\ normalized}$ (split dose).
[c1] n=174 for C_{trough} and $C_{trough,\ dose\ normalized}$, n=25 for $AUC_{0\text{-}168h}$, $AUC_{0\text{-}168h,\ dose\ normalized}$, AUC_{τ} and $AUC_{\tau,\ dose\ normalized}$ and n=21 for AR $AUC_{0\text{-}168h(C2D1/C1D1)}$.

After discussions during the procedure, regarding the appropriateness of the body weight cut-off of 80 kg (applied in the RP2D regimen), Table 13 was provided, presenting observed C_{trough} at Cycle 2 Day 1 for four body weight groups (<60 kg, ≥60 and <70 kg, ≥70 and <80 kg, and ≥80 kg).

Table 8. Summary statistics of Individual Observed C_{trough} Cycle 2 Day 1 for Subjects Who Received the RP2D

Weight group	No. subjects	Mean	SD	GeoMean	GeoSD	CV%	Min	5th %	Median	95th %	Max
< 60 kg	136	346	114	325	1.45	38.6	83.9	168	344	536	617
≥ 60 and < 70 kg	57	310	126	275	1.78	63	34.4	72.9	298	499	693
≥ 70 and < 80 kg	38	240	84.4	220	1.66	54.3	19.8	136	229	385	408
≥ 80 kg	44	329	132	306	1.47	40.1	90.8	174	306	573	850

Note: C_{trough} values are in µg/mL units

Special populations

Variations in renal and hepatic function or drug-metabolizing enzymes are not expected to affect the elimination of amivantamab. No dedicated formal intrinsic factor PK studies have been conducted. Demographic factors and the effect of organ dysfunction was investigated in the population PK analysis. Based on this no dose adjustments are proposed for patients with mild or moderate renal impairment or for patients with mild hepatic impairment or based on age, gender and race. Amivantamab was not studied in children and is not intended for use in children.

PK Trials	*Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Study 61186372EDI1001	134/439 (30.52%)	52/439 (11.85%)	3/439 (0.68%)

*≤64: 250/439 (56.9%)

Pharmacokinetic interaction studies

No dedicated drug-drug interaction studies were performed with amivantamab. As an antibody that binds to the ECDs of EGFR and MET with high specificity, amivantamab is also not anticipated to alter the activity of drug-metabolizing enzymes. In addition, amivantamab is not a modulator of cytokines that have known effects on CYPs and transporters.

2.6.2.2. Pharmacodynamics

Mechanism of action

No clinical studies investigating the mechanism of action have been conducted. The information is derived from non-clinical studies.

Amivantamab is an EGFR and MET receptor bispecific antibody. Three potential mechanisms of action for amivantamab to inhibit tumours with aberrant EGFR and MET signalling are proposed: 1) inhibition of ligand-dependent signalling, 2) downregulation of EGFR and MET levels from cell surface, and 3) initiation of ADCC and/or ADCT.

Primary and Secondary pharmacology

An exploratory PD assessment was one of the objectives of the Study EDI1001. Soluble EGFR and MET target engagement was used as a surrogate for evaluating whole body engagement and was assessed by measuring free and total soluble targets. Mean serum concentrations of free EGFR and free MET were highest at baseline and significantly reduced after the EOI on C1D1 and remained at similar levels at all subsequent time points for all dose cohorts with the exception to concentrations of free EGFR at 140 mg dose which tended to return to baseline at the predose time points. Saturation of free soluble EGFR and soluble MET with amivantamab was observed at doses ≥350 mg and ≥140 mg, respectively. Complete saturation (i.e., depletion of free targets) of circulating EGFR throughout the dosing interval was achieved at dose levels ≥700 mg, while the complete saturation of soluble free MET was achieved at all dose levels tested

Exposure-response analysis

The purpose of the analysis was to explore E-R to corroborate and supplement the evidence of efficacy and safety of amivantamab in subjects with NSCLC and to confirm the selected dosing regimen. Efficacy endpoints investigated were ORR (primary endpoint), CBR, DOR, and PFS, and the exposure metrics derived for the E-R analyses of efficacy (generated by simulation using the individual PK parameter estimates and the actual dosing information for each subject) were $C_{trough,1st}$ [trough concentration after the first dose in Cycle 1] and $C_{trough,max}$ [maximum trough concentration – usually corresponding to trough concentration prior to the first dose in Cycle 2]. In the updated analysis, cumulative AUC in Cycle 1 (AUC_{cycle1}) was investigated as exposure used to drive E-R analysis on ORR. Safety analyses (visual exploration) for TEAEs were initially conducted using individual predictions of $C_{eoi,max}$ [maximum concentration at end-of-infusion – usually corresponding to concentration at end-of-infusion after the first dose in Cycle 2], but were also repeated using C_{av} [average amivantamab concentration during treatment, i.e., from the first amivantamab dose to the last PK sampling or dosing time, whichever comes last].

Subject demographic and baseline characteristics of subjects included in the data set for E-R analyses (ie, subjects with EGFR Exon 20ins NSCLC who received the first amivantamab dose on or before 05 February 2020) are summarised in Table 14 [updated table not available].

Table 9. Summary of Subject Demographic and Baseline Characteristics in E-R Analysis for Efficacy

	Non-RP2D			RP2D	
	1050 mg (n=3)	1400 mg[a] (n=35)	1750 mg (n=2)	1050 mg[a] (n=82)	1400 mg (n=22)
Age (year)					
Median	61.0	62.0	63.0	64.5	57.5
Mean (SD)	59.0 (15.1)	60.9 (12.1)	63.0 (12.7)	64.4 (10.8)	57.7 (8.25)
Range	43.0-73.0	38.0-82.0	54.0-72.0	40.0-87.0	44.0-73.0
Baseline body weight (kg)					
Median	97.6	57.5	59.0	59.0	86.9
Mean (SD)	93.7 (11.6)	59.1 (10.5)	59.0 (0.71)	59.6 (9.41)	90.7 (10.3)
Range	80.6-103	39.8-77.3	58.5-59.5	35.4-79.8	80.4-115
Sex, n (%)					
Male	2 (66.7%)	11 (31.4%)	0 (0.0%)	27 (32.9%)	15 (68.2%)
Female	1 (33.3%)	24 (68.6%)	2 (100.0%)	55 (67.1%)	7 (31.8%)
Race, n (%)					
White, not Hispanic or Latino	2 (66.7%)	10 (28.6%)	1 (50.0%)	25 (30.5%)	12 (54.5%)
Black or African American, not Hispanic or Latino	0 (0.0%)	1 (2.9%)	0 (0.0%)	1 (1.2%)	1 (4.5%)
White, Hispanic or Latino	0 (0.0%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	1 (4.5%)
Asian, not Hispanic or Latino	1 (33.3%)	21 (60.0%)	1 (50.0%)	50 (61.0%)	5 (22.7%)
Other	0 (0.0%)	1 (2.9%)	0 (0.0%)	6 (7.3%)	3 (13.6%)
ECOG, n (%)					
0	1 (33.3%)	7 (20.0%)	1 (50.0%)	21 (25.6%)	13 (59.1%)
1	2 (66.7%)	28 (80.0%)	1 (50.0%)	60 (73.2%)	9 (40.9%)
2	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.2%)	0 (0.0%)
Prior chemotherapy, n (%)					
No	0 (0.0%)	10 (28.6%)	0 (0.0%)	23 (28.0%)	1 (4.5%)
Yes	3 (100.0%)	25 (71.4%)	2 (100.0%)	59 (72.0%)	21 (95.5%)

[a] Two subjects at the non-RP2D of 1400 mg and 1 subject at the RP2D of 1050 mg were excluded from E-R analysis due to the lack of derived exposure metrics.

Binary response variables (ORR and CBR) were evaluated by logistic regression, analysed using R version 3.4.1 (The R Project for Statistical Computing, [www.r-project.org]) and Stan (Carpenter 2017), as called by the R package rstan, version 2.19.2. The E-R relationship was described by a sigmoidal E_{max} model. Since there was no placebo information in the current E-R dataset, the covariate effects were added on the baseline probability but not E_{max}. The full covariate model included a set of preselected covariates of clinical interest (age, weight, time from metastatic diagnosis to first dose [months], sex, race [Asian vs non-Asian], baseline ECOG [1 or 2 vs 0], and prior chemotherapy [yes vs no]). Based on the statistical significance criteria (90% credible interval of regression coefficient for a specific covariate excluding zero), the reduced full model was established to keep the statistically significant covariates, which was regarded as the final model.

Time-to-event variables (DOR and PFS) were evaluated by Kaplan-Meier (K-M) plots, stratified by exposure group (tertile of the relevant exposure metrics).

The E-R relationship was explored for selected AEs of clinical interest including infusion-related reactions (IRR) and rash. The AEs were stratified by the appropriate exposure metrics to evaluate whether there is a relationship between the AEs and exposure to amivantamab.

Objective Response rate

In the updated analysis, none of the tested covariates was statistically significant. The relationships between ORR and amivantamab $C_{trough.max}$, and ORR and amivantamab AUC_{cycle1}, indicate a slight trend of ORR increase with increase of amivantamab exposure, approaching E_{max} at the high end of the

concentration range (Figure 7). A correlation between ORR and amivantamab $C_{trough.1st}$ was not evident [figure not included in AR].

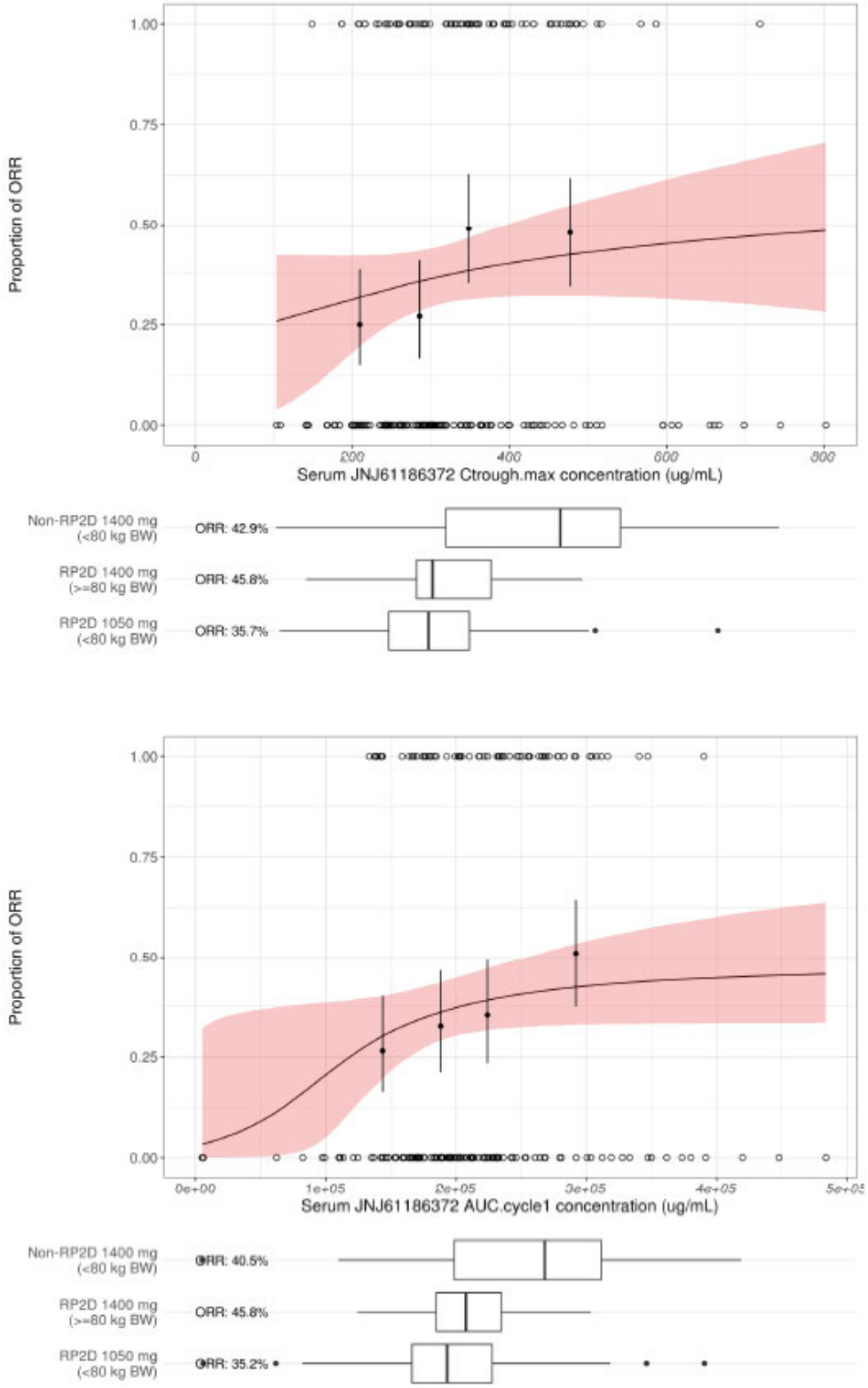


Figure 5. Objective Response Rate as a Function of $C_{trough.max}$ (top) or AUC_{cycle1} (bottom) According to the E_{max} Model in Subjects With EGFR Exon 20 Insertion Mutation NSCLC

The results from the updated analysis were consistent with those in the initial submission. Specifically, the probability of response for subjects with ECOG performance status of 1 or 2 at baseline seemed to be lower than for subjects with ECOG performance status of 0, however, this difference was not statistically significant in the updated E-R efficacy analysis with more subjects in the dataset and exposure predicted based on the parallel linear and saturable clearance PPK model (the proportion of ECOG 0 subjects was higher at the RP2D of 1400 mg than at the RP2D of 1050 mg [59.1% vs 25.6%; Table 14]).

The purpose of the analysis was to explore E-R to corroborate and supplement the evidence of efficacy and safety of amivantamab in subjects with NSCLC and to confirm the selected dosing regimen. Efficacy endpoints investigated were ORR (primary endpoint), CBR, DOR, and PFS, and the exposure metrics derived for the E-R analyses of efficacy (generated by simulation using the individual PK parameter estimates and the actual dosing information for each subject) were $_{Ctrough,}$1st [trough concentration after the first dose in Cycle 1] and $_{Ctrough,}$max [maximum trough concentration – usually corresponding to trough concentration prior to the first dose in Cycle 2]. In the updated analysis, cumulative AUC in Cycle 1 (AUCcycle1) was investigated as exposure used to drive E-R analysis on ORR. Safety analyses (visual exploration) for TEAEs were initially conducted using individual predictions of $_{Ceoi,}$max [maximum concentration at end-of-infusion – usually corresponding to concentration at end-of-infusion after the first dose in Cycle 2], but were also repeated using Cav [average amivantamab concentration during treatment, i.e., from the first amivantamab dose to the last PK sampling or dosing time, whichever comes last].

Subject demographic and baseline characteristics of subjects included in the data set for E-R analyses (ie, subjects with EGFR Exon 20ins NSCLC who received the first amivantamab dose on or before 05 February 2020) are summarised in Table 14 [updated table not available].

Clinical Benefit Rate

Exploratory logistic regression analysis was applied to link logit-transformed probability of CBR to amivantamab $C_{trough.max}$ and $C_{trough.1st}$ with E_{max} relationship. This analysis demonstrated a flat E-R relationship between CBR and the amivantamab exposure metrics at the tested amivantamab doses in Study EDI1001 [figures not included in AR; not repeated in updated analysis].

Progression-Free Survival

Progression-free survival appeared to improve when amivantamab systemic exposure increased. However, a flat E-R relationship could not be ruled out due to significant overlap of 95% CI bands around the K-M curves between subject groups at different tertiles of amivantamab systemic exposure [figures not included in AR; not repeated in updated analysis].

Overall Survival

A definitive conclusion could not be drawn for the E-R relationship between OS and amivantamab exposure metrics due to the limited number of events (ie, death) within the current follow-up period and crossover of K-M plots in the current dataset [figures not included in AR; not repeated in updated analysis].

Duration of Response

A longer DOR appeared to be associated with higher amivantamab exposure. Since the number of subjects was small (n<20 in each tertile of amivantamab exposure metrics), in association with largely overlapping 95% CIs of K-M plots, a definite E-R relationship could not be drawn [figures not included in AR; not repeated in updated analysis].

Selected Adverse Events

No apparent relationship between amivantamab exposure and treatment-emergent adverse events (TEAEs; IRR, nausea, and constipation) was identified at the studied amivantamab concentrations, except a somewhat higher incidence rate of IRRs in subjects in the 1st quartile of $C_{eoi.1st}$ compared with the rate in subjects in the subsequent quartiles; likely due to the lack of risk mitigation strategies for IRR at the beginning of the study. The incidence 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.

2.6.3. Discussion on clinical pharmacology

Amivantamab is a first-in-class, fully human IgG1-based, bispecific antibody which simultaneously targets both the EGFR and MET pathways by binding to the extracellular domain (ECD) of each receptor. The PK-information in this submission is based on a single ongoing study in subjects with advanced non-small cell lung cancer, including subjects with EGFR Exon 20 insertion mutations. No clinical pharmacology studies in healthy volunteers have been provided. A limited number of individuals had dense PK-sampling, especially at steady state, and were included in the non-compartmental analysis (NCA). Typical PK-parameters such as AUC_{inf}, t½ and Cl were not estimated using NCA. The distribution, metabolism, and excretion characteristics of amivantamab are based on population PK model-estimated parameters.

Amivantamab was provided for clinical studies as 150 mg/vial and 350 mg/vial formulations for dilution for IV administration. No BE-study has been provided comparing the different formulations and processes, which is acceptable.

An adequately validated ECLIA assay on the MSD platform was used to analyse total amivantamab concentrations in human serum. Results from within study validation show that the assay performed adequately.

The immunogenicity of amivantamab was evaluated in the clinical study. For this purpose, a standard multi-tiered approach was used, including screening, confirmatory and titer and characterization assays (bridging ELISA format), to evaluate anti-drug antibodies. Overall, the method appears appropriately validated. 25 individuals from the clinical study had samples with amivantamab-concentrations above drug-tolerance limits and have been classified with ADA-status inconclusive. In a worst-case scenario, all of these could be ADA-positive. Therefore, the clinical relevance of this was analysed, i.e. if PK, efficacy or safety is affected in subjects with inconclusive ADA-status. While the available data limited the efficacy analysis, no alarming trends were detected for safety and PK in subjects with inconclusive ADA-status.

Target mediated drug disposition was apparent at the lowest dose of 140 mg and in the first cycle for doses up to 700 mg. However, the nonlinear clearance is saturated at the proposed clinical doses. Dose proportionality was indicated in the dose range of 350 to 1750 mg, though no NCA data was provided comparing the different doses at steady state (achieved by the ninth infusion). After weekly administrations during the first cycle (28 days) the accumulation ratio (AR) for AUC_{1week} is close to 3. The Accumulation ratio at steady state was 2.44. This is based on the PK-data from 6 individuals all in the 1050 mg dose cohort.

In the target population, pharmacokinetic parameters (C_{max}, C_{trough}, AUC_{0-168h} and AUC_{τ}) following IV infusion of amivantamab at 1050 mg and 1400 mg were approximately 30% to 40% lower in those subjects with body weight ≥80 kg compared to those with body weight <80 kg. From the limited NCA-data presented in Table 12, the proposed weight-based dose regime appears to provide similar C_{trough}

for the two weight-groups while there still are some differences in AUC and C_{max}, especially at C2D1. However, Table 13 indicates that subjects with body weight <70 kg, and subjects with body weight ≥80 kg, achieve similar C_{trough} at C2D1, whereas subjects with body weight ≥70 and <80 kg achieve a lower C_{trough}, when dosed according to the RP2D regimen (further discussed below). There are only NCA-data for C_{torugh} available for comparison at steady state. The population PK model has been used to compare the AUC, C_{max} and C_{trough} at steady state for the suggested RP2D body weight-groups (<80 kg receiving 1050 mg and ≥80 kg receiving 1400 mg); however, the covariate model is not considered fully adequate, which hampers the comparison [further discussed below].

The developed population PK model for amivantamab has been used to characterize amivantamab PK in NSCLC subjects, to assess the impact of potential covariate effects, to support the proposed weight-based posology, and to calculate exposure metrics, based on individual parameter estimates, subsequently used in the exposure-response (E-R) analysis. The model was updated to account for the observed nonlinear kinetics (due to TMDD). However, the covariate modelling was not repeated for the updated model, and trends are noted in the goodness-of-fit plots for individual parameter estimates vs. covariates [Figures not included in AR], both for body weight (volume of peripheral compartment) and for sex (volumes of central and peripheral compartments), indicating a suboptimal covariate model. The pcVPCs reveal a minor but consistent under-prediction of the median, especially around C_{max} for the first dose in Cycle 1 and the first dose in Cycle 2. Despite these shortcomings, the model is considered to provide an acceptable prediction at steady state, especially for the RP2D regimen (Figure 4) and hence the current model can be used to provide information on amivantamab's PK (for the RP2D regimen) in section 5.2 of the SmPC.

Subjects in the lower body weight categories (<60 kg, and ≥60 and <70 kg, receiving a dose of 1050 mg) and subjects in the higher body weight category (≥80 kg, receiving a dose of 1400 mg) achieved similar C_{trough}, whereas subjects in the middle body weight category (≥70 and <80 kg, receiving a dose of 1050 mg) achieved a lower C_{trough}. The preclinical target exposure was 110-168 µg/mL (established based on the least sensitive lung adenocarcinoma mouse xenograft model), and hence the majority of subjects – also those with a body weight ≥70 and <80 kg – achieved exposures that are within or above the preclinically established target exposure, when treated according to the RP2D regimen. Furthermore, the objective response rate (ORR) per body weight group, for subjects receiving doses according to RP2D regimen, shows that there is no decrease in ORR with increasing body weight (data not shown) – i.e., there is no indication of under-exposure of subjects weighing ≥70 and <80 kg in terms of ORR. It was therefore concluded that an increase of the exposure, for subjects with a body weight ≥70 and <80 kg (e.g., by lowering the body weight dosing cut-off), is unlikely to result in a clinical benefit (see further assessment under 2.6.5 Clinical efficacy).

No dedicated studies have been conducted to investigate the pharmacokinetics of amivantamab in special populations, which is considered acceptable for a monoclonal antibody.

No drug interaction studies have been performed. The Applicant has provided a sufficient justification that amivantamab is not an immunomodulator hence the absence of interaction studies is acceptable.

Pharmacodynamics and PK/PD

Study EDI1001 involved exploratory PD assessment, which was based on the measurement of free and total soluble EGFR and MET targets. The Applicant was asked to perform target engagement analysis by combining data from subjects treated at RP2D in Part 1 and Part 2. In response to that the applicant provided free EGFR and free MET profiles at RP2D for 53 subjects out of 60. As this analysis represents the majority (~85%) of RP2D population it can be expected that the remaining missing samples would not essentially change the target engagement profile and can be seen as showing the consistent suppression of both free MET and free EGFR serum concentrations at C1D6 and later throughout the therapy.

The purpose of the E-R analysis was to supplement the evidence of efficacy and safety of amivantamab, and support the dose selection in subjects with NSCLC. It is noted that the number of subjects, and the dose range (and hence exposure range) explored, is limited, and this will compromise the validity of the analysis.

2.6.4. Conclusions on clinical pharmacology

The PK-information in this submission is based on a single ongoing study in subjects with advanced non-small cell lung cancer. Mainly sparse sampling and population PK modelling has been applied to characterize the basic ADME of amivantamab. Despite the limitations, the provided clinical pharmacology data are considered sufficient for the approval of amivantamab for the treatment of NSCLC patients with EGFR Exon 20 insertions.

2.6.5. Clinical efficacy

The market authorisation application rests upon data from a selected subset of patients in the Phase 1 study, Protocol 61186372EDI1001 (CHRYSALIS), referred to as Study EDI1001.

Study EDI1001 is an ongoing Phase 1 first-in-human (FIH) open-label study that includes both dose escalation and dose expansion phases, and both monotherapy and combination therapy regimens (Table 10).

The combination regimens include combination with the investigational third-generation epidermal growth factor receptor tyrosine kinase inhibitor lazertinib (Part 1 and Part 2 cohorts), and combination with standard of care carboplatin and pemetrexed (Part 1 only). Further information about, and data from, the amivantamab combination therapy cohorts are not presented in this submission.

The monotherapy cohorts are presented in Table 15.

The study was conducted in compliance with Good Clinical Practice, including the archival of essential documents.

Table 10. Summary of pivotal study – monotherapy cohorts – additional efficacy data cut-off (DCO:30 March 2021)

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)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
5.3.5.2 Efficacy and Safety Uncontrolled Clinical Studies (information provided is limited to amivantamab monotherapy)						
61186372EDI1001 Synopsis 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, openlabel, 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 **Part 2: Monotherapy Dose Expansion** Determine the safety, tolerability, and antitumor activity of amivantamab monotherapy at the RP2D	Planned: Part 1: up to 120; Part 2: approx. 460 Enrolled: Part 1: 80 Part 2: 409 Treated: Part 1: 80 Part 2: 409	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 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.	Part 1: 80 Part 2: 409	Interim CSR 30 October 2020 EDMS-RIM-60626 Module 5.3.5.2 (Updated number based on 30 Mar 2021)

	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 or care	Treamtent was to be administered until disease progression, unacceptable toxicity, or withdrawal of consent

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

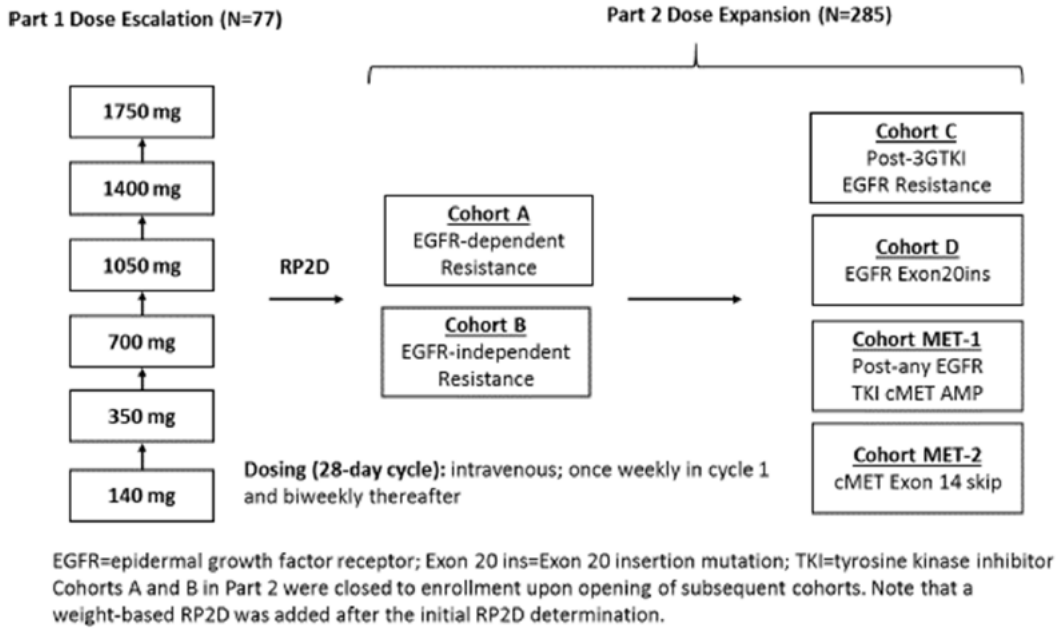
Source: Response to Day 180 LoQ, Question 32, follow-up question. Table 2.

2.6.5.1. Dose response study(ies)

Study EDI1001 (CHRYSALIS) – Part 1 – dose escalation

Study EDI1001 is an ongoing, first-in-human phase 1, open-label, multicentre study of amivantamab as monotherapy being conducted globally in subjects of at least 18 years of age with advanced or metastatic NSCLC.

The study consisted of 2 parts: a dose escalation phase (Part 1, n=77) to determine the RP2D of amivantamab monotherapy in subjects with advanced or metastatic NSCLC; and a dose expansion phase (Part 2, n=285) to better characterize the safety and pharmacokinetics of amivantamab monotherapy at the RP2D and to explore its clinical activity within molecularly-defined tumour subgroups (Figure 8). Part 2 is further described under Main study below.



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 that a weight-based RP2D was added after the initial RP2D determination.

Figure 6. Design of Study 61186372EDI1001: Monotherapy Cohorts
Source: CSR, Figure 1. (SCE, Figure 2)

Part 1 was designed to determine the RP2D of amivantamab monotherapy in subjects with advanced NSCLC based on safety, pharmacokinetic, pharmacodynamic, and anti-tumour activity data.

Part 1 started with a standard 3+3 design. Dose escalation was to stop when the maximum tolerated dose (MTD) or maximum administered dose (MAD) (in case no MTD is determined) was reached.

Study participants

Subjects enrolled to Part 1 were not required to meet any molecular eligibility requirements. However, the majority of subjects (66 of 77; 86%) in Part 1 of Study EDI1001 were previously diagnosed with EGFR-mutated NSCLC.

Primary Objective

Determine the maximum tolerated dose (MTD), if one existed (Part 1 monotherapy dose escalation only), and the RP2D for subjects with NSCLC treated with amivantamab.

Baseline characteristics

Subjects treated in Part 1 had a median age of 63 years (42% ≥ 65 years) and there were more women (64%) than men (36%). Race was 62% Asian, 34% White, and 4% Black/African American. ECOG performance status was 0 in 29% and 1 in 71%. 40% had a history of smoking. 95% of subjects had adenocarcinoma, the median number of lines of prior therapy was 3 (range: 0-10).

Treatments

Amivantamab was administered as an intravenous (IV) infusion once weekly for 4 weeks (Cycle 1) then every 2 weeks thereafter during subsequent cycles.

Doses of 140 mg to 1750 mg were investigated, using the following dose cohorts:

140 mg (n=3), 350 mg (n=3), 700 mg (n=14), 1050 mg (n=25), 1400 mg (n=26), and 1750 mg (n=6). The 1750 mg dose cohort was added after recommendation from the safety evaluation team (SET) for further dose escalation (Amendment 4, March 2018). In total 77 patients were included in Part 1.

Disposition

Of the 77 subjects treated with amivantamab monotherapy in Part 1, 24 (31.2%) remained on study and 11 (14.3%) remained on treatment as of the clinical cut-off. The median duration of follow-up across all treated subjects in Part 1 was 7.6 months (range: 0.07-33.6).

The main reason for discontinuation of treatment was progressive disease. Few subjects discontinued treatment for withdrawal of consent (7.8%). Six subjects (7.8%) were identified on the study disposition page of the CRF as discontinuing treatment due to AEs (pneumonia in 2 subjects, and 1 subject each for IRR and musculoskeletal chest pain, myalgia, paronychia, stomatitis).

Table 11. Study and treatment disposition; All Treated analysis set in Part 1 of Study EDI1001

	140 mg	350 mg	700 mg	1050 mg	1400 mg	1750 mg	Total
Analysis set: All treated in part 1 (dose escalation) of monotherapy (JNJ-61186372)	3	3	14	25	26	6	77
Study Disposition							
Subjects ongoing	0	0	3 (21.4%)	8 (32.0%)	8 (30.8%)	5 (83.3%)	24 (31.2%)
Completed study participation [a]	0	0	3 (21.4%)	10 (40.0%)	12 (46.2%)	1 (16.7%)	26 (33.8%)
Terminated study participation prematurely	3 (100.0%)	3 (100.0%)	8 (57.1%)	7 (28.0%)	6 (23.1%)	0	27 (35.1%)
Withdrawal by subject	0	0	8 (57.1%)	6 (24.0%)	6 (23.1%)	0	20 (26.0%)
Progressive disease	3 (100.0%)	3 (100.0%)	0	0	0	0	6 (7.8%)
Physician decision	0	0	0	1 (4.0%)	0	0	1 (1.3%)
Treatment Disposition							
Subjects ongoing	0	0	1 (7.1%)	5 (20.0%)	2 (7.7%)	3 (50.0%)	11 (14.3%)
Discontinued study treatment	3 (100.0%)	3 (100.0%)	13 (92.9%)	20 (80.0%)	24 (92.3%)	3 (50.0%)	66 (85.7%)
Reason for discontinuation							
Progressive disease	3 (100.0%)	3 (100.0%)	9 (64.3%)	15 (60.0%)	20 (76.9%)	2 (33.3%)	52 (67.5%)
Adverse event	0	0	1 (7.1%)	2 (8.0%)	3 (11.5%)	0	6 (7.8%)
Withdrawal by subject	0	0	3 (21.4%)	2 (8.0%)	0	1 (16.7%)	6 (7.8%)
Physician decision	0	0	0	1 (4.0%)	1 (3.8%)	0	2 (2.6%)

[a] Subject is considered to have completed the study if the subject died prior to the end of study.

Source: CSR, Table 4. (DCO 08 June 2020)

A larger proportion of patients in the highest dose group was ongoing at the data cut-off together with a lower frequency of treatment discontinuation due to progressive disease (PD) (Table 16). It is not clear to which degree this is caused by a later inclusion in the highest dose group. It is also noted that the median duration of study treatment was numerically higher in the (earlier) 1050 mg dose cohort

(5.1 months) compared to the 1400 mg and 1750 mg dose cohorts (3.7 and 4.4 months, respectively). This could similarly potentially be due to different recruitment periods.

Anti-tumour activity

As of the clinical cut-off, 08 June 2020, 76 of the 77 subjects treated in Part 1 were included in the efficacy analysis set for this study phase. One subject in the 1750 mg cohort was not included in the efficacy analysis set for Part 1 as the subject was enrolled <1 month prior to the clinical cut-off date. Furthermore, 1 subject in the 1050 mg cohort did not have measurable disease and therefore, 75 subjects were response evaluable.

Confirmed partial responses (PR) per RECIST v.1.1 were observed for 14 subjects in Part 1; no complete responses (CR) were observed, giving an ORR of 18.7% (95% CI: 10.6%, 29.3%). A best response of durable SD (i.e., SD for at least 11 weeks) was observed for 22 subjects in Part 1, contributing to an overall clinical benefit rate (CBR) of 48.0% (95% CI: 36.3%, 59.8%).

Similar response rates around 20% were observed in the 4 dose cohorts (700-1750 mg) where objective responses were observed (Table 17). Amivantamab doses <700 mg were not associated with a response in Part 1, with no subject in the 140 mg or 350 mg dose cohorts having a confirmed response and 1 subject in the 350 mg cohort having durable SD (Table 17).

Table 12. Summary of Best Overall Response based on RECIST v1.1 in subjects with measurable disease at baseline – Investigator assessment; Efficacy Evaluable analysis set in Part 1 of Study EDI1001

	140 mg	350 mg	700 mg	1050 mg	1400 mg	1750 mg	Total
Analysis set: Efficacy evaluable in part 1 (dose escalation) of monotherapy (JNJ-61186372)	3	3	14	25	26	5	76
Best overall response							
N	3	3	14	24	26	5	75
Complete response (CR)	0	0	0	0	0	0	0
Partial response (PR)	0	0	3 (21.4%)	5 (20.8%)	5 (19.2%)	1 (20.0%)	14 (18.7%)
Stable disease (SD)	0	2 (66.7%)	4 (28.6%)	12 (50.0%)	8 (30.8%)	2 (40.0%)	28 (37.3%)
Progressive disease (PD)	3 (100.0%)	1 (33.3%)	3 (21.4%)	6 (25.0%)	10 (38.5%)	1 (20.0%)	24 (32.0%)
Not evaluable/unknown	0	0	4 (28.6%)	1 (4.2%)	3 (11.5%)	1 (20.0%)	9 (12.0%)
Overall response rate (Confirmed CR + Confirmed PR)	0	0	3 (21.4%)	5 (20.8%)	5 (19.2%)	1 (20.0%)	14 (18.7%)
95% CI	(0.0%, 70.8%)	(0.0%, 70.8%)	(4.7%, 50.8%)	(7.1%, 42.2%)	(6.6%, 39.4%)	(0.5%, 71.6%)	(10.6%, 29.3%)
Clinical benefit rate [a] (Confirmed CR + Confirmed PR + SD)	0	1 (33.3%)	7 (50.0%)	14 (58.3%)	11 (42.3%)	3 (60.0%)	36 (48.0%)
95% CI	(0.0%, 70.8%)	(0.8%, 90.6%)	(23.0%, 77.0%)	(36.6%, 77.9%)	(23.4%, 63.1%)	(14.7%, 94.7%)	(36.3%, 59.8%)

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: CSR, Table 14. (DCO 08 June 2020)

The waterfall plot in Figure 9 shows the maximum percentage change in target lesion size, sum of diameters (SoD), for the 66 subjects in the Part 1 efficacy population with available data. Eighteen (27%) of these subjects had tumour shrinkage of ≥ 30%.

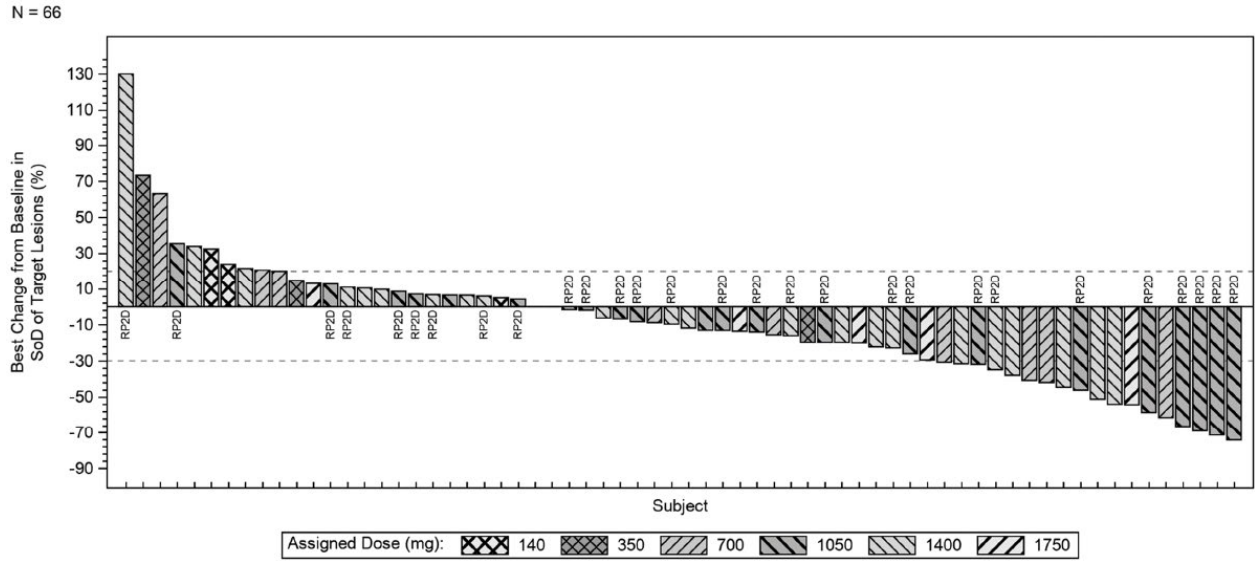


Figure 7. Waterfall plot of Best Percentage Change from Baseline in Sum of Diameters (SoD) – Investigator assessment; Efficacy Evaluable Analysis Set in Part 1 (DCO 08 June 2020)

RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg. Key: SoD = Sum of Diameters.

While keeping in mind the small dose cohorts and the fact that the patients in Part 1 were molecularly unselected, based on the waterfall plot, there is no strong trend for improved efficacy with doses higher than the chosen RP2D of 1050 mg. Responses were observed despite a molecularly unselected population.

Only 66 out of the 75 patients with measurable disease and sufficient follow-up in Part 1 of study were evaluable for tumour response, the other 9 had discontinued therapy prior to their first disease assessment. They were, however, included in the efficacy analyses. Five of the 9 patients discontinued due to AE, and 4 due to withdrawal of consent by the subject.

Dose-limiting Toxicity and Maximum Tolerated Dose

Only one AE meeting the DLT criteria was observed in the 77 patients treated with amivantamab monotherapy as of the clinical cut-off date.

This consisted of a Grade 3 toxicity of myalgia in a US subject in the 1050 mg dose cohort. The myalgia occurred on Day 5, 3 days after receiving the Cycle 1, Day 2 infusion. Treatment with amivantamab was discontinued due to this TEAE, although the subject remained in the study.

Thus, the **MTD** (defined as highest dose level at which <33% of subjects treated at that level experienced a DLT) for amivantamab as monotherapy was not established. The MAD for amivantamab monotherapy in Part 1 was 1750 mg.

The **1050 mg** dose of amivantamab as monotherapy was identified as the **first RP2D** to be explored in Part 2 on the basis of available safety, efficacy, and pharmacokinetic data. Additional analyses of available pharmacokinetic, pharmacodynamic, safety, and efficacy data from subjects treated in Part 1 and Part 2 led to a **modification of the RP2D** for amivantamab as monotherapy to 1050 mg for subjects <80 kg body weight and **1400 mg for subjects ≥80 kg** body weight, at a regimen of once weekly for Cycle 1 and every 2 weeks for Cycle 2 and beyond (28-day cycles). Dosing was split for the first treatment in Cycle 1 to better manage the risk of IRRs; 350 mg was administered on Day 1 and 700 mg (for body weight <80 mg) or 1050 mg (for body weight ≥80 kg) was administered on Day 2.

The input contributing to the final RP2D included among other things population-pharmacokinetic analyses with data from 80 subjects (46 from Part 1; 34 from Part 2) and for exposure-response (E-R) analysis from 63 subjects. This is further described in the PK section.

Furthermore, the **1750 mg cohort** was added to Part 1 with protocol Amendment 4 (March 2018); the first dose of treatment in the 1750 mg cohort given on 29 January 2019.

Results of **additional analyses** conducted in August 2019 which included 32 subjects with **Exon 20ins NSCLC** treated with amivantamab 1050 mg (n=16) or 1400 mg (n=16) upheld the earlier preliminary results and showed a flat exposure response relationship for TEAEs at doses >700 mg and complete soluble target saturation throughout dosing at doses ≥700 mg.

Efficacy data from Part 1 and Part 2 of Study EDI1001 relevant to dosing recommendations

Based on investigator-based response data from patients on RP2D and non-RP2D, the group of patients weighing < 80 kg who received the 1050 mg dose had a numerically lower ORR (35%) than patients who received the 1400 mg dose, weighing < 80 kg (42%) and ≥ 80 kg (45%), respectively. This raised concern that heavier patients in the < 80 kg group might be underdosed. However, based on analyses of patients on RP2D, ORR results showed no trend towards decreased ORRs as a function of increasing weight, within subjects weighing <80kg at RP2D dose (1050 mg).

2.6.5.2. Main study

Study EDI1001 (CHRYSALIS) – Part 2 – dose expansion

Protocol number: 61186372EDI1001

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

See information on Part 1 of the study above. Based on the activity observed in the Part 1 dose escalation, the Part 2 cohort expansion was modified through an amendment to allow assessment of amivantamab activity in 4 different NSCLC patient populations with unmet medical need.

The dose expansion phase (Part 2) of Study EDI1001 currently consists of 6 cohorts investigating the efficacy and safety of treatment with amivantamab monotherapy in subjects with locally advanced or metastatic EGFR-mutated NSCLC (EGFR Exon 20ins, third-generation TKI resistance mutations, and MET amplification or mutations).

The efficacy and safety data for subjects with Exon 20ins NSCLC are analysed according to exposure to prior platinum-based therapy for NSCLC and RP2D treatment status (i.e., subjects receiving 1050 mg dose with a baseline body weight of <80 kg plus subjects receiving 1400 mg dose with a baseline body weight of >80 kg) (Figure 10).

- The primary population of interest includes the 114 subjects with Exon 20ins NSCLC treated at the RP2D who had progressed on or after prior platinum chemotherapy, of which 81 subjects met the criteria for inclusion in the efficacy analysis set, having received their first dose on or before 05 FEB 2020, at the initially submitted data cut-offs, 08 June 2020, and 08 October 2020. This population of **81** subjects is hereafter referred to as the ***initial primary efficacy population***. During the marketing authorisation application procedure, data were provided for a later cut-off, 30 March 2021, for which all **114** subjects fulfilled the criteria for follow-up, having received their first dose on or before 04 June 2020. This population of 114 patients is

hereafter referred to as the ***extended primary efficacy population*** and considered the ***pivotal data set***.

- In addition, supportive efficacy results in subjects with Exon 20ins NSCLC treated at RP2D who had not received prior platinum-containing chemotherapy (N=24), and subjects with Exon 20ins NSCLC treated at Non-RP2D doses (N=42) are briefly summarized.

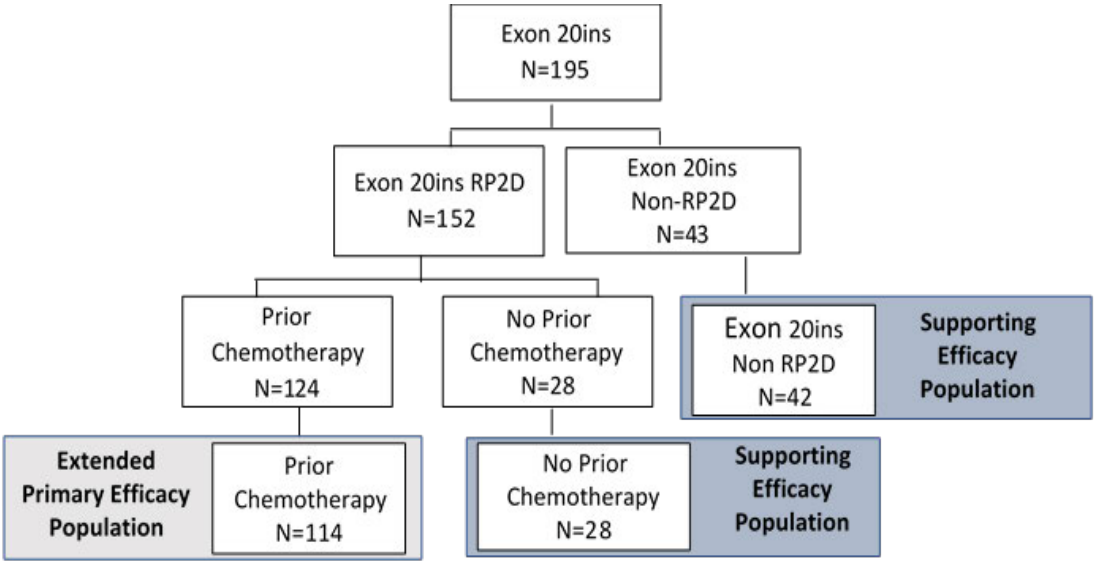


Figure 8. Efficacy Populations in Study 61186372EDI1001, Exon 20ins

Methods

- **Study Participants**

According to protocol amendments several of the key inclusion criteria have been amended more than once during the study.

According to the final eligibility criteria, subjects were required to have histologically or cytologically confirmed NSCLC that was metastatic or unresectable and must have either progressed after prior standard of care therapy for metastatic disease, be ineligible for, or have refused all other currently available therapeutic options.

Performance status of ECOG 0-1 and acceptable organ and bone marrow function according to stipulated laboratory criteria was required. Exclusion criteria concerned uncontrolled brain metastases and history of ILD. See further details below.

Identification of EGFR-mutated disease for the assignment to the key efficacy Cohort D, as well as efficacy-contributing Cohort A, was based on a variety of local test results from archival or biopsy tumour tissue or ctDNA from plasma (see baseline data below).

Key eligibility criteria for inclusion in the study:

- ≥18 years of age.
- Have histologically or cytologically confirmed NSCLC that was metastatic or unresectable. Subjects must have either progressed after prior standard of care therapy (e.g., Cohort C and MET-1: EGFR TKI; Cohort D and MET-2: platinum-based chemotherapy) for metastatic disease, be ineligible for, or have refused all other currently available therapeutic options.

- Treatment with prior chemotherapy, targeted cancer therapy, immunotherapy, or treatment with an investigational anti-cancer agent must have been stopped within 2 weeks or 4 half-lives (whichever was longer) before the first administration of study drug. For agents with long half-lives, the maximum required time since last dose to the start of study drug was 4 weeks. Further, toxicities from previous anti-cancer therapies were to have been resolved to baseline levels or to Grade 1 or less, (except for alopecia [any grade], Grade ≤2 peripheral neuropathy, and Grade <2 hypothyroidism stable on hormone replacement).

- For Part 2 only, have disease with a previously-diagnosed activating EGFR mutation (included both inhibitor sensitive primary mutations such as Exon 19 deletion and L858R [Cohorts C and MET-1], as well as marketed TKI-resistant mutations such as Exon 20ins [Cohorts C, D, and MET-1], or activating MET Exon 14 skipping mutation [Cohort MET-2]). Documentation of primary activating EGFR or MET mutation eligibility by Clinical Laboratory Improvement Amendment-certified laboratory (or equivalent) testing was required. Note: in Part 2, subjects were assigned to cohorts on the basis of tissue or blood sample NGS analysis submitted during Screening, or on the basis of previous local testing.

Specifically:

- Cohorts A and B: Recent progression of EGFR-mutated disease following treatment with a marketed EGFR inhibitor, with the exception for subjects diagnosed with mutations associated with de novo EGFR inhibitor resistance (e.g., Exon 20ins) where only previous treatment with combination platinum-based chemotherapy was required. The inclusion criteria for Cohort A thus allowed inclusion of patients with EGFR T790M+ disease after prior first- or second-generation TKI, or EGFR C797S+ disease after prior third-generation TKI, as well as for patients with EGFR Exon 20ins disease. Identification of EGFR-mutated disease for Cohort A or B assignment was based on local circulating tumour deoxyribose nucleic acid (ctDNA) or tumour NGS.

- Cohort C: Primary EGFR mutated disease, with a documented EGFR alteration (e.g., C797S) mediating resistance to previous treatment with a third generation EGFR TKI (e.g., osimertinib). In the case of primary Exon20ins disease, the documented EGFR alteration could have arisen following treatment with a TKI with known activity against Exon 20ins disease (e.g. poziotinib). Cohort C assignment was based on identification of EGFR resistance mutation (e.g., C797S) by any of the following: central tumour NGS, local NGS, central ctDNA, or local ctDNA.

- Cohort D: EGFR Exon20ins mutation not been previously treated with a TKI with known activity against Exon20ins disease (e.g., poziotinib). Identification of EGFR-mutated disease for Cohort D assignment was based on local test results (tumour or ctDNA).

- Cohort MET-1: Documented primary EGFR mutated disease and documented MET amplification or MET mutation after progression on any EGFR TKI. Subjects in this cohort could have received or have been intolerant to prior platinum-based chemotherapy.MET-1 assignment was based on identification of 3 or more copies of MET as detected by any of the following: local fluorescence in situ hybridization, local tumour NGS; or central tumour NGS.

- Cohort MET-2: Documented primary MET Exon 14 skipping mutation. Identification of MET Exon 14 skipping mutation was detected by any of the following: central tumour NGS, local tumour NGS, local ctDNA, or central ctDNA.

- Have evaluable disease (Part 1) or measurable disease according to Response Criteria in Solid Tumors (RECIST) v1.1 (Part 2).
- Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
- Subject must have organ and bone marrow function as follows:

LABORATORY PARAMETER	VALUE
Hematology	
Hemoglobin	≥10 g/dL
ANC	≥1.5 x 10^9/L
Platelets	≥75 x 10^9/L
Hepatic and Renal	
AST and ALT	≤3 x ULN
Total bilirubin	≤1.5 x ULN; subjects with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits
Serum creatinine	<1.5 x ULN or if available, calculated or measured creatinine clearance * >50 mL/min/1.73 m^2
ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; ULN = upper limit of normal *For Chemotherapy Combination Cohorts, Creatinine clearance must be calculated by Cockroft Gault formula and should be >50 mL/min.	

- A number of criteria ensuring non-pregnant state and pregnancy prevention for women and men.
- Subjects eligible for Part 2 must agree to the pre-treatment tumour biopsy (or submission of equivalent archival material) and a tumour biopsy at the time of disease progression, as well as corresponding blood samples for ctDNA analysis. For subjects in Cohorts C, MET-1, MET-2, and E, equivalent pre-treatment tumour tissue must have been collected after progression on the most recent systemic anti-cancer treatment.

Key exclusion criteria:

- Subjects with untreated brain metastases. Patients with definitively, locally-treated metastases that are clinically stable and asymptomatic for at least 2 weeks and who are off or receiving low-dose corticosteroid treatment (≤10 mg prednisone or equivalent) for at least 2 weeks prior to study treatment are eligible.
- Medical history of interstitial lung disease (ILD), including drug-induced ILD or radiation pneumonitis requiring treatment with prolonged steroids or other immune suppressive agents within the last 2 years.

- **Treatments**

Amivantamab was administered via intravenous (IV) infusion (minimum infusion time ≥ 60 minutes) once weekly for the first 4 weeks (i.e., Cycle 1) and once every 2 weeks (Days 1 and 15 of each cycle) thereafter during subsequent 28-day cycles. To minimize the risk of infusion-related reactions (IRRs), the first dose was split over 2 days (Cycle 1, Days 1 and 2), required steroid premedication, and was administered using an accelerated infusion strategy. The RP2D was determined to be 1050 mg for subjects weighing <80 kg, and 1400 mg for subjects weighing ≥80 kg and this dosage is the basis of the primary efficacy population. Treatment beyond disease progression was allowed for individual patients following approval from the medical monitor. This was also done in a number of patients, as evident in Figure 11.

- **Objectives**

Table 13. Objectives and endpoints, Study EDI1001 (study protocol)

OBJECTIVES	ENDPOINTS
Primary	
Part 1 JNJ-61186372 Monotherapy and Combination Dose Escalations • Determine the maximum tolerated dose (MTD), if one exists (Part 1 monotherapy dose escalation only), and the recommended Phase 2 dose (RP2D)/recommended Phase 2 combination dose (RP2CD) regimen for subjects with NSCLC treated with JNJ-61186372 or JNJ-61186372 and lazertinib, respectively	• Dose Limiting Toxicity (DLT)
• Determine the recommended Phase 2 dosing of JNJ-61186372 when administered on a 21-day cycle (RP2Dq3W), in combination with standard of care carboplatin and pemetrexed	• DLT, JNJ-61186372 C_{trough}, Area Under the Curve (AUC_{tau})
Part 2 (Expansion) • Determine the safety, tolerability, and anti-tumor activity of JNJ-61186372 monotherapy at the RP2D, and of JNJ-61186372 and lazertinib combination therapy at the RP2CD	• Adverse events defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Criteria Version 4.03 in subjects treated at the RP2D regimen of JNJ-61186372 and at the RP2CD regimen of lazertinib combination therapy
• Estimate the anti-tumor activity of JNJ-61186372 at the RP2D, and of JNJ-61186372 and lazertinib combination therapy at the RP2CD in selected populations of subjects with documented EGFR or MET mutation(s) who have progressed after treatment with standard of care	• Overall response rate (ORR), duration of response (DOR), and clinical benefit rate (CBR) as determined by investigator, according to the Response Criteria in Solid Tumors (RECIST) v1.1. Confirmation of investigator-assessed ORR and DOR will be performed through Independent Review Committee (IRC) if indicated
Secondary	
JNJ-61186372 Monotherapy and Combination Dose Escalations • Assess additional measures of clinical benefit with JNJ-61186372 as monotherapy and in combination with lazertinib	• Progression free survival (PFS), overall survival (OS), time to treatment failure (TTF)
• Assess the PK and immunogenicity of JNJ-61186372 as monotherapy and in combination with lazertinib, and in combination with standard of care carboplatin and pemetrexed following multiple dose administrations in subjects with NSCLC	• Serum PK parameters of JNJ-61186372 including but not limited to C_{max}, T_{max}, $AUC_{(t1-t2)}$, AUC_{tau}, C_{trough}, and R; detection of anti-JNJ-61186372 antibodies • Plasma PK parameters of lazertinib including but not limited to C_{max}, T_{max} and C_{trough}

Exploratory	
• Explore the relationship between serum PK and pharmacodynamic (PD) markers (eg, soluble EGFR and cMet) • Explore biomarkers predictive of clinical response and resistance to JNJ-61186372 in blood and tumor tissue	
• Patient-reported outcomes (PRO) measures will be implemented at the start of the expansion cohorts after interim review.	• Patient Global Impression of Severity (PGIS), Patient Global Impression of Change (PGIC), the Non-Small Cell Lung Cancer Symptom Assessment Questionnaire (NSCLC-SAQ), and the EQ-5D-5L.

Source: EDI1001 study protocol, Amendment 9, 30 April 2020

Objectives according to Statistical Analysis Plan (SAP) for Exon20 IA, version 7 (File: "CSR statistical methods"):

Primary Objectives

- Determine the safety, tolerability, and anti-tumour activity of amivantamab monotherapy at the RP2D
- Estimate the anti-tumour activity of amivantamab at the RP2D in selected populations of subjects with documented EGFR or MET mutation(s) who have progressed after treatment

Secondary Objectives

- Assess additional measures of clinical benefit with amivantamab as monotherapy
- Assess the pharmacokinetic and immunogenicity of amivantamab as monotherapy following multiple dose administrations in subjects with NSCLC

Exploratory Objectives

- Explore the relationship between serum pharmacokinetics and pharmacodynamic markers (e.g., soluble EGFR and MET)
- Explore biomarkers predictive of clinical response and resistance to amivantamab in blood and tumour tissue

- **Outcomes/endpoints**

Endpoints according to Statistical Analysis Plan for Exon20 IA, version 7:

Primary endpoint

- Overall response rate (ORR) as per RECIST v.1.1 as evaluated by the investigator. ORR is defined as the proportion of subjects achieved either a confirmed CR or PR based on RECIST v. 1.1. among efficacy evaluable analysis set.
- ORR assessed by IRC will also be analysed.

Secondary endpoints

- Duration of response (DOR) [by investigator assessment] will be analysed for subjects who achieve the confirmed CR or PR. DOR is defined as time from first documentation of a response of PR or CR to the date of first documented evidence of progressive disease or death due to any cause, whichever occurs first. Subjects who are progression free and alive or have unknown status will be censored at last tumour assessment. Subjects who started a

subsequent anti-cancer therapy in the absence of progression will be censored at the last disease assessment before the start of subsequent therapy. DOR assessed by IRC will also be analysed.

- Progression free survival (PFS) [by investigator assessment], defined as the interval between the date of the first dose and the date of disease progression or death due to any cause, whichever occur first. Subjects who are progression-free and alive or have unknown status will be censored at last tumour assessment. Subjects with no post baseline disease assessment will be censored on Day 1. Subjects who started a subsequent anti-cancer therapy in the absence of progression will be censored at the last disease assessment before the start of subsequent therapy. Subjects whose diseases have not progressed and who are still alive at the end of the study or clinical cut-off will be censored at the last adequate disease assessment. PFS assessed by IRC will also be analysed.
- Overall survival (OS), defined as the interval between the date of the first dose and the date of the subject's death from any cause. If the subject is alive or the vital status is unknown, then the subject's data will be censored at the date the subject was last known to be alive. The date of last known alive will be determined by the maximum collection/assessment date from among data domains within the clinical database.
- Clinical benefit rate (CBR), defined as the percentage of subjects achieving complete or partial response, as well as durable stable disease (defined as a duration of at least 11 weeks) as defined by RECIST v1.1.
- Time to Treatment Failure (TTF), defined as the time from the first infusion of the study drug to discontinuation of treatment for any reason, including disease progression, treatment toxicity, death, and will be utilized to capture clinical benefit for patients continuing treatment beyond RECIST v1.1 defined disease progression. Subjects who are treatment failure free or have unknown status will be censored at last tumour assessment. Subjects with no post baseline disease assessment will be censored on Day 1.

- **Sample size**

For Part 1 dose escalation cohorts, 3 to 6 subjects will be treated at each dose level based on the 3 + 3 dose escalation scheme.

For Part 2, the maximum total sample size at a RP2D was set to be approximately 460 subjects. This includes approximately 40 subjects in Cohort A, 20 subjects in Cohort B, and up to 100 subjects each if sufficient efficacy is observed in Cohorts C, D, MET-1, and MET-2 at a RP2D of JNJ-61186372 monotherapy.

For Cohorts C, D, MET-1, and MET-2 in Part 2, within each cohort, a 2-stage design will be employed. The interim analysis will be performed when approximately 30 subjects were enrolled in each cohort and has sufficient data (i.e., post-baseline disease assessment) to be evaluable for response. Future enrolment into each cohort may have been terminated if it is determined during the first stage that the treatment is considered as ineffective as compared to other treatment options and/or not well tolerated. The null hypothesis is that the ORR ≤15%, and the alternative hypothesis is that the ORR ≥30%. With a one-sided alpha of 2.5%, and a power of 87.5%, the total number of subjects needed for each cohort is 86 response-evaluable subjects. Assuming a non-evaluable rate of 15%, approximately 100 subjects will be enrolled within each cohort, although the number of subjects may be expanded beyond 100 subjects (maximum of approximately 150) to further characterize activity for subpopulations within a cohort.

The sample size consideration for the subgroup of Exon 20 insertion mutant NSCLC patients who required to have had previous therapy with a combination platinum-doublet chemotherapy regimen is based on the null hypothesis of ORR ≤12%, and the alternative hypothesis of ORR >25%. To have a power of 80% to reject the null hypothesis with a 1-sided alpha of 0.025, at least 60 subjects will be required to enrol in the subgroup; approximately 100 subjects were targeted for enrolment to characterize the activity of JNJ 61186372 in this population.

- **Randomisation and Blinding (masking)**

This is an open-label, single-arm study. No randomization or blinding of treatment were performed.

- **Statistical methods**

Analysis population

Data reported are summarized separately for the dose escalation phase (Part 1) and for the combined dose escalation and dose expansion phases (Part 1 and Part 2), with a focus on subjects comprising the Exon 20ins + prior chemotherapy at RP2D population.

The efficacy analysis population includes subjects treated with amivantamab monotherapy in the dose expansion phase (Part 2; derived primarily from subjects enrolled in Cohort D and to a lesser extent, Cohort A) as well as those treated in the dose escalation phase (Part 1).

Planned Analyses

Data reflect those available as of the clinical cut-off of 08 June 2020 (31 March 2020 for pharmacokinetic, immunogenicity, pharmacodynamic data) from subjects treated with amivantamab monotherapy.

All efficacy analyses were performed using the efficacy analysis set (also referred to as efficacy evaluable analysis set on tables and listings), which included all subjects who received the first dose of amivantamab as monotherapy on or before 05 February 2020 and were to have undergone at least 3 scheduled post-baseline disease assessments or discontinued treatment for any reason, including disease progression/death, prior to the clinical cut-off.

Efficacy analyses were performed based on the efficacy analysis set for the following populations:

- Exon 20ins + prior chemotherapy at RP2D population: subjects with locally-documented Exon 20ins NSCLC enrolled in Part 1 or Part 2 who were treated with amivantamab monotherapy at a dose consistent with the RP2D (1050 mg for body weight <80 kg and 1400 mg for body weight >80 kg), had received prior platinum chemotherapy and had metastases within 12 months from last platinum-based chemotherapy use.
- Exon 20ins + no prior chemotherapy at RP2D population: subjects with locally-documented Exon 20ins NSCLC enrolled in Part 1 or Part 2 who were treated with amivantamab monotherapy at a dose consistent with the RP2D who had not received platinum-based chemotherapy within 12 months of diagnosis of metastatic NSCLC.
- Exon 20ins at Non-RP2D population: subjects with locally-documented Exon 20ins NSCLC (irrespective of prior chemotherapy) enrolled in Part 1 or Part 2 and treated at amivantamab monotherapy doses other than the RP2D.

The primary efficacy analysis is based on the Exon 20 + prior chemotherapy at RP2D efficacy population.

Primary Efficacy Endpoint

The protocol-specified primary efficacy endpoint was the ORR, defined as the proportion of subjects with a best overall response of a confirmed CR or PR based on RECIST v1.1 criteria (best response as recorded in the CRF from the start of the study drug until disease progression, withdrawal of consent, or start of a subsequent anti-cancer therapy, whichever came first).

The observed overall response rate and its 95% 2-sided exact confidence interval were presented based on efficacy evaluable analysis set: Exon 20ins subjects at RP2D with prior chemotherapy, Exon 20ins subjects at RP2D without prior chemotherapy, Exon 20ins subjects at RP2D, Exon 20ins subjects at non-RP2D, and all subjects in part 1. The summary for all subjects in part 1 will be presented for each dose level and total.

ORR assessed by IRC will also be analyzed similarly for Exon 20ins subjects at RP2D with prior chemotherapy, Exon 20ins subjects at RP2D without prior chemotherapy, Exon 20ins subjects at RP2D.

The null hypothesis would be rejected if the lower bound of 95% two-sided CI of the ORR was above 12% for the Exon 20ins subjects + prior chemotherapy at RP2D efficacy population.

The following *secondary efficacy analyses* were performed to explore the clinical activity of amivantamab:

- Clinical benefit rate (CBR), defined as the percentage 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. The CBR and its 95% 2-sided exact CI, based on investigator and BICR assessments, were calculated.
- Duration of response (DOR) was evaluated using the Kaplan-Meier method. The median DOR and corresponding 95% CI were provided, as was a swim lane plot for responders. The DOR was defined as 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 based on investigator and BICR assessment. Subjects who were progression-free and alive, or who had an unknown status, were censored at the last tumour assessment; subjects who started subsequent anti-cancer therapy in the absence of progression were censored at the last disease assessment before the start of subsequent therapy.
- Progression-free survival (PFS) was evaluated using the Kaplan-Meier method. The median PFS and corresponding 95% CI based on investigator and BICR assessments, as well as the PFS rates at specified timepoints, were provided. The PFS was defined as the time interval from the first dosing date to the first date of disease progression or death due to any cause, whichever occurred first. Subjects who were progression-free and alive, or who had an unknown status, were censored at the last tumour assessment; subjects who started subsequent anti-cancer therapy in the absence of progression were censored at the last disease assessment before the start of subsequent therapy. Subjects with no post-baseline disease assessment were censored on Day 1.
- Overall survival (OS) was evaluated using the Kaplan-Meier method. The median OS and corresponding 95% CI, as well as the OS rate at specified timepoints, were provided. The OS was defined as the time interval from the first dosing date to the date of the subject's death from any cause. Subjects who were alive or whose vital status was unknown were censored at the date the subject was last known to be alive.

- Time to treatment failure (TTF) was evaluated using the Kaplan-Meier method. The median TTF and corresponding 95% CI were provided. The TTF was defined as the time interval from the first dosing date to study drug discontinuation for any reason. Subjects who were treatment failure-free or had an unknown status were censored at last tumour assessment. Subjects with no post-baseline disease assessment were censored on Day 1.
- The best percentage change from baseline in the sum of diameters (SoD) of target lesions was determined for each subject with measurable disease at baseline based on investigator and BICR assessments and summarized using a waterfall plot.

Subgroup Analyses

The ORR (and exact 95% CI) as per investigator assessments was analysed for the following subgroups of the Exon 20ins at RP2D efficacy populations (ie, Exon 20ins + prior chemotherapy at RP2D; Exon 20ins + no prior chemotherapy at RP2D):

- Age: subgroups of <65 versus ≥65 years and <75 versus ≥75 years
- Sex: male versus female
- Race: Asian versus non-Asian (subjects with unknown race were not included in the subgroup analysis)
- Baseline ECOG performance status: 0 versus ≥1
- History of smoking: yes versus no
- Prior immunotherapy: yes versus no
- Key Exon 20ins variants (based on ctDNA analysis of pretreatment samples). The change in SoD for target lesions was also described for these subgroups using a waterfall plot.

Interim Monitoring for Futility

A planned interim monitoring for futility will be carried out separately for Cohorts C, D, MET-1, and MET-2 when there are at least 30 response evaluable subjects in the respective cohort. With 30 subjects evaluable for response within each cohort, if 5 or fewer responses are observed, the null hypothesis (ORR ≤15%) will be accepted and enrolment for the cohort may be terminated for futility by the SET. Otherwise, additional subjects will be enrolled for total 100 subjects in the cohort for the final analysis. This stopping criterion leads to probability of early termination (at least 71.1%) at the interim analysis under the null hypothesis that the ORR is at most 15%.

For Cohorts C, MET-1, and MET-2, the ORR of pre-defined molecular subgroups (EGFR-mediated [eg, C797S mutation], cMet-mediated [eg, degree of cMet amplification, cMet Exon 14 skipping], or other TKI resistance [eg, B-raf]) will be calculated in addition to the ORR for the cohort. Based on the data of these molecular subgroups at the interim monitoring, if the SET determines that any of these molecular subgroups has clinically meaningful ORR (as defined in Section 8.2), that particular molecular subgroup may be expanded to have a total of 100 subjects.

A planned interim monitoring for futility will also be carried out for Cohort E when there are 40 response evaluable subjects in the cohort. With 40 response evaluable subjects, if 11 or fewer responses are observed, the null hypothesis (ORR ≤25%) will be accepted and enrolment for the cohort may be terminated for futility by the SET. Otherwise, additional subjects will be enrolled for a total of 100 subjects in the cohort for the final analysis. This stopping criterion leads to probability of early termination (at least 71.5%) at the interim analysis under the null hypothesis of the ORR ≤25%.

Results

- **Participant flow**

Refer to Figure 10.

The contribution of patients from different cohorts to the pooled primary efficacy population, is shown in the Table 21.

Table 14. Contribution of subjects from different study cohorts to the primary efficacy population

	Total Screened	Screen Failures	<80kg, 1050mg	>80kg, 1400mg	Total N=114	Non-RP2D N=32
Part 1	13	0	4	1	5	8
Part 2, Cohort A	4	0	4	0	4	0
Part 2, Cohort D	183	54	84	21	105	24

Source: Response to Day 180 LoQ, Question 32, Table 16.

Table 15. Treatment Disposition, efficacy evaluable at RP2D with Exon 20 insertion in monotherapy and prior chemotherapy (Study EDI1001, 30 March 2021)

	Exon 20 Ins (RP2D)
	Prior Chemotherapy
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114
Subjects ongoing	31 (27.2%)
Discontinued study treatment	83 (72.8%)
Reason for discontinuation	
Progressive disease	62 (54.4%)
Adverse event	11 (9.6%)
Withdrawal by subject	7 (6.1%)
Death	2 (1.8%)
Physician decision	1 (0.9%)

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.

Table 16. Study Disposition, efficacy evaluable at RP2D with Exon 20 insertion in monotherapy and prior chemotherapy (Study EDI1001, 30 Mar. 2021)

	Exon 20 Ins (RP2D)
	Prior Chemotherapy
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ61186372), first dose on or before 04JUN2020	114
Subjects ongoing	61 (53.5%)
Completed study participation [a]	39 (34.2%)
Terminated study participation prematurely	14 (12.3%)
Reason for termination	
Withdrawal by subject	12 (10.5%)
Lost to follow-up	1 (0.9%)
Progressive disease	1 (0.9%)

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.
[a] A subject is considered to have completed the study if the subject died prior to the end of study.

- **Recruitment**

The first subject in Study EDI1001 consented on 27 May 2016 (Part 1). Cohorts A, B, C, D, MET-1, and E are closed for enrolment. Of these, cohorts C, D, MET-1 and E have patients with treatment still ongoing. The only cohort currently open to enrolment is MET-2 (Figure 8). In addition, 2 cohorts are planned in wild-type EGFR NSCLC. The end of study is planned to occur after the last subject on study treatment completes therapy and has at least 6 months of follow-up.

- **Conduct of the study**

Protocol deviations

Major protocol deviations were reported in 19/114 (16.7%) subjects in the Exon 20ins + prior chemotherapy at RP2D primary efficacy population. None of these deviations led to exclusion of data from the safety or efficacy analyses.

- 6/114 (5.3%) subjects developed withdrawal criteria, but were not withdrawn from study treatment. All 6 subjects had RECIST disease progression and continued on study treatment, prior to obtaining Sponsor approval for treatment beyond progression, as instructed by the protocol.
- 5/114 (4.4%) subjects did not satisfy the protocol-specified eligibility criteria, but were enrolled. Two of these subjects had Screening laboratory criteria out of range and 3 subjects had exclusionary concurrent conditions; 1 subject with untreated brain metastases, 1 subject with an active infection (Gr. 2 mucositis), and 1 subject with uncontrolled pain.
- 1/114 (0.9%) subject received prohibited concomitant treatment of radiotherapy. This subject had RECIST PD reported 24 Oct 2019 and was continuing treatment with amivantamab beyond progression when they received palliative radiotherapy to a non-target lesion from 12 Dec 2019 through 18 Dec 2019, prior to obtaining Sponsor approval, as instructed by the protocol.
- 4/114 (3.53%) subjects received incorrect treatment or incorrect dose. Of these, 3 subjects had deviations concerning a single dose administration inconsistent with protocol guidelines. The remaining deviation related to study treatment involved 1 subject who received amivantamab using a central line during Cycle 1, instead of a peripheral line, as instructed by the protocol.
- Major protocol deviations categorized as 'Other' occurred in 6/114 (5.3%) subjects. This category included deviations for 5 subjects concerning failure to adjust study drug administration following the occurrence of an IRR. Of these 5 subjects, 4 deviations were due to the infusion flow rate not being reduced following an IRR and 1 deviation was due to an infusion not being interrupted at the time of the IRR. All 5 subjects recovered from the IRR and remained on study treatment.
    - The remaining major deviation categorized as 'Other' was failure to obtain pregnancy test within 24 hours of the first infusion in a woman of child-bearing potential (this subject had a negative pregnancy test at Screening and during Treatment Period).

Table 17. Summary of subjects with major protocol deviations; All treated analysis set in monotherapy (DCO 30 March 2021)

	Exon 20 Ins (RP2D)	RP2D	RP2D and Non-RP2D
	Prior Chemotherapy First dose on or before 04JUN2020	Total	Total
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114	380	489
Subjects with major protocol deviations	19 (16.7%)	57 (15.0%)	79 (16.2%)
Developed withdrawal criteria but not withdrawn	6 (5.3%)	13 (3.4%)	20 (4.1%)
Entered but did not satisfy criteria	5 (4.4%)	11 (2.9%)	15 (3.1%)
Received a disallowed concomitant treatment	1 (0.9%)	2 (0.5%)	3 (0.6%)
Received wrong treatment or incorrect dose	4 (3.5%)	20 (5.3%)	26 (5.3%)
Other	6 (5.3%)	19 (5.0%)	26 (5.3%)

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: Subjects may appear in more than one category.

Protocol amendments

Table 18. Protocol amendments, Clinical Protocol 61186372EDI1001 (Study EDI1001)

Protocol Version	Issue Date
Original Protocol	15 October 2015
Amendment 1	14 April 2016
Amendment 2	12 December 2016
Amendment 3	31 May 2017
Amendment 4	9 March 2018
Amendment 5	6 September 2018
Amendment 6	29 May 2019
Amendment 7	19 August 2019
Amendment 8	27 January 2020
Amendment 9	30 April 2020

The overall reasons for the amendments:

Amendment 9 (30 April 2020): This amendment is being instituted to determine the recommended Phase 2 dosing of JNJ-61186372 when administered on a 21-day cycle (RP2Dq3W) in combination with standard of care carboplatin and pemetrexed.

Amendment 8 (27 January 2020):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 enrolment of treatment naïve subjects into Part 1 combination dose escalation. Additional minor clarifications and modifications to study conduct are also made

Amendment 7 (19 August 2019): This amendment is intended to expand the combination cohort in all countries to evaluate the safety and pharmacokinetics (PK) of JNJ-61186372 in combination with lazertinib and to evaluate anti-tumour activity of the combination in subjects who have progressed on osimertinib (third generation TKI)

Amendment 6 (29 May2019): Initiation of two new MET-specific cohorts: Cohort MET-1 and Cohort MET-2, and removing MET as a qualifying mutation for Cohort C. The overall reasons for the amendment are to include the additional cohorts in Part 2 of the study, increase the study population size for Part 2, and include an optional Pre-Screening period.

Amendment 5 (6 September 2018): 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.

Amendment 4 (9 March 2018): 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. The overall study population initially enrolled in Part 2 is increased from 60 up to approximately 120 subjects (40 in Cohort A and 20 in Cohort B), and two cohorts (Cohort C and Cohort D, 30 subjects each with potential to increase to 100 subjects each) based on previously diagnosed EGFR mutation and prior anti-cancer therapy are added to more clearly evaluate clinical endpoints. Due to changing standard of care, and overlapping target populations, Cohort A and B will be closed to further recruitment upon opening of Cohort C and D.

Amendment 3 (31 May 2017): In Part 2 of this study, subjects will be enrolled in one of two cohorts according to molecular markers of interest. Tumour 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 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. Primary objective was expanded to include anti-tumour activity, in addition to previously safety and tolerability. ORR by investigator and CBR were added as primary endpoints.

Amendment 2 (12- Dec-2016): Addition of 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 analysed, 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 1 (14 April 2016): Remove the time interval limitation for triplicate ECG collection, change body temperature location from oral to tympanic, clarify that vital sign measurements during study drug infusion should include a pre-infusion timepoint, update the blood volume required, and make wording corrections.

- **Baseline data**

Table 19. Summary of demographics and baseline characteristics

	Exon 20 Ins (RP2D)
	Prior Chemotherapy
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114
Age, years	
N	114
Mean (SD)	61.7 (9.99)
Median	62.0
Range	(36; 84)
<65	67 (58.8%)
>=65	47 (41.2%)
<75	105 (92.1%)
>=75	9 (7.9%)
Sex	
N	114
Female	70 (61.4%)
Male	44 (38.6%)
Race	
N	114
Asian	59 (51.8%)
Black or African American	3 (2.6%)
White	42 (36.8%)
Not reported	10 (8.8%)
Weight, kg	
N	114
Mean (SD)	64.82 (15.841)
Median	62.05
Range	(35.4; 115.0)
<80kg	92 (80.7%)
>=80kg	22 (19.3%)
Body mass index, kg/m^2	
N	114
Mean (SD)	24.073 (4.7430)
Median	23.455
Range	(14.00; 36.87)
Underweight <18.5	11 (9.6%)
Normal 18.5-<25	65 (57.0%)
Overweight 25-<30	25 (21.9%)
Obese >=30	13 (11.4%)

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.
Note: N's for each parameter reflect non-missing values.

Table 20. Summary of lung cancer baseline clinical disease characteristics

	Exon 20 Ins (RP2D)
	Prior Chemotherapy
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114
Initial diagnosis NSCLC subtype	
N	114
Adenocarcinoma	109 (95.6%)
Large cell carcinoma	0
Squamous cell carcinoma	3 (2.6%)
Other	2 (1.8%)

	Exon 20 Ins (RP2D)
	Prior Chemotherapy
Histology grade at initial diagnosis	
N	114
Moderately differentiated	23 (20.2%)
Poorly differentiated	19 (16.7%)
Well differentiated	7 (6.1%)
Other	64 (56.1%)
Not reported	1 (0.9%)
Cancer stage at initial diagnosis	
N	114
0	0
IA	7 (6.1%)
IB	1 (0.9%)
IIA	2 (1.8%)
IIB	4 (3.5%)
IIIA	6 (5.3%)
IIIB	4 (3.5%)
IV	90 (78.9%)
Location of metastasis [a]	
N	114
Bone	51 (44.7%)
Liver	13 (11.4%)
Brain	29 (25.4%)
Lymph Node	62 (54.4%)
Adrenal Gland	6 (5.3%)
Other	62 (54.4%)
Time from initial diagnosis of cancer to first dose (months)	
N	114
Mean (SD)	22.332 (19.9695)
Median	17.478
Range	(1.45; 130.10)
Time from metastatic disease diagnosis to first dose (months)	
N	114
Mean (SD)	18.264 (15.5470)
Median	15.491
Range	(0.69; 116.40)
Number of prior lines of therapy	
N	114
Mean (SD)	2.1 (1.31)
Median	2.0
Range	(1; 7)
1	48 (42.1%)
2	34 (29.8%)
3	15 (13.2%)
4	9 (7.9%)
5	6 (5.3%)
6	1 (0.9%)
7	1 (0.9%)
ECOG performance status	
N	114
0	33 (28.9%)
1	80 (70.2%)
2	1 (0.9%)
History of smoking	
N	114
Yes	49 (43.0%)
No	65 (57.0%)

	Exon 20 Ins (RP2D)
	Prior Chemotherapy
Exon 20 Insertion Subtype	
N	114
A763	2 (1.8%)
A767	25 (21.9%)
D770	14 (12.3%)
H773	9 (7.9%)
N771	13 (11.4%)
P772	4 (3.5%)
S768	18 (15.8%)
Unknown	27 (23.7%)
V769	2 (1.8%)

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.

Prior systemic therapies

All subjects had received prior platinum-based systemic therapy. In addition, 44% of subjects had received prior immunotherapy, and 20% had received any prior EGFR TKI therapy (Table 28).

Among the 50 patients (44% of the 114 subjects in the pivotal efficacy population) who had received prior treatment with an immune checkpoint inhibitor, 17 (15% of the pivotal efficacy population) received a checkpoint inhibitor as part of a platinum-based chemo-immunotherapy regimen (Data not shown).

Table 21. Prior systemic therapies of special interest in 5% or more of subjects

	Exon 20 Ins (RP2D)
	Prior Chemotherapy
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114
Subjects with one or more prior systemic therapies of special interest	114 (100.0%)
Special interest category Standardized medication name	
Non-platinum-based Chemotherapy	114 (100.0%)
PEMETREXED	69 (60.5%)
PEMETREXED DISODIUM	25 (21.9%)
PACLITAXEL	24 (21.1%)
DOCETAXEL	19 (16.7%)
GEMCITABINE	16 (14.0%)
VINORELBINE TARTRATE	7 (6.1%)
Platinum-based Chemotherapy	114 (100.0%)
CARBOPLATIN	71 (62.3%)
CISPLATIN	63 (55.3%)
Immunotherapy	50 (43.9%)
PEMBROLIZUMAB	22 (19.3%)
NIVOLUMAB	13 (11.4%)
ATEZOLIZUMAB	10 (8.8%)
Any EGFR TKI [a]	23 (20.2%)
OSIMERTINIB	6 (5.3%)
AFATINIB	7 (6.1%)

	Exon 20 Ins (RP2D)
	Prior Chemotherapy

Subjects with first dose on or before 04 June 2020 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.
[a] EGFR TKI includes EGFR TKI (1st Generation), EGFR TKI (2nd Generation), EGFR TKI (3rd Generation) and EGFR TKI (Exon 20 Insertion).

Identification of EGFR Exon 20 insertion mutation

Tumour tissue (93%) and/or plasma (10%) samples for all patients were tested locally to determine EGFR Exon 20 insertion mutation status using next generation sequencing (NGS) in 46% of patients and/or polymerase chain reaction (PCR) in 41% of patients; for 4% of patients, the testing methods were not specified.

As part of the study, both blood and tumour samples were requested from each subject for the clinical validation of 2 companion diagnostic (CDx) tests (ThermoFisher Oncomine Dx Target Test with tissue and Guardant360 CDx with ctDNA). The concordance estimate and 2-sided 95% Wilson CI of the valid Oncomine Dx Target Test (tissue CDx) results to the local testing results within the primary efficacy population is 94.1% (84.1% - 98.0%). The concordance estimate and 2-sided 95% Wilson CI of the valid Guardant360 CDx (ctDNA CDx) test results to the local testing results within the primary efficacy population is 79.1% (70.6% - 85.6%).

- **Numbers analysed**

The application primarily concerns the results in subjects with the Exon 20ins mutation who had had progressed on or after prior platinum-based chemotherapy and who were treated at the RP2D for amivantamab monotherapy. This includes subjects treated with amivantamab monotherapy in the dose expansion phase (Part 2; derived primarily from subjects enrolled in Cohort D and to a lesser extent, Cohort A) as well as those treated in the dose escalation phase (Part 1).

Efficacy analysis set

All efficacy analyses were performed using the efficacy analysis set (also referred to as efficacy evaluable analysis set), which included all subjects who received the first dose of amivantamab as monotherapy on or before 05 February 2020 (an additional cut-off was subsequently used for the pivotal analysis set, 04 June 2020), were to have undergone at least 3 scheduled post-baseline disease assessments or discontinued treatment for any reason, including disease progression/death, prior to the clinical cut-off.

Efficacy analyses were performed based on the efficacy analysis set for the following populations:

- **Exon 20ins + prior chemotherapy at RP2D population**: subjects with locally-documented Exon 20ins NSCLC enrolled in Part 1 or Part 2 who were treated with amivantamab monotherapy at a dose consistent with the RP2D (1050 mg for body weight <80 kg and 1400 mg for body weight >80 kg), had received prior platinum chemotherapy and had metastases within 12 months from last platinum-based chemotherapy use.
- **Exon 20ins + no prior chemotherapy at RP2D population**: subjects with locally-documented Exon 20ins NSCLC enrolled in Part 1 or Part 2 who were treated with amivantamab monotherapy at a dose consistent with the RP2D who had not received platinum-based chemotherapy within 12 months of diagnosis of metastatic NSCLC.

- **Exon 20ins at Non-RP2D population**: subjects with locally-documented Exon 20ins NSCLC (irrespective of prior chemotherapy) enrolled in Part 1 or Part 2 and treated at amivantamab monotherapy doses other than the RP2D.

- **Outcomes and estimation**

The focus of the efficacy assessment will be on the results from the most recent data cut-off, 30 March 2021, and the most extensive data set fulfilling the criteria for the primary efficacy population, provided during the marketing authorisation application procedure. An update was not provided for the supportive efficacy populations (i.e., 24 subjects with Exon 20ins NSCLC treated at RP2D who had not received prior platinum-based chemotherapy and 42 subjects with Exon 20ins NSCLC treated at Non-RP2D doses). Therefore, data from different cut-offs will be presented.

Summary of key efficacy outcomes

Three data cut-offs have been presented for the initial primary 81 efficacy population: 08 June 2020, 08 October 2020, and in responses to questions, 30 March 2021, the latter reflecting an additional 9 months of follow-up from the 08 October 2020 cut-off (Table 29), in total a median follow-up of 14.5 months.

Results were presented for an extended primary efficacy population of 114 subjects, with a first dose on or before 04 June 2020 (Table 30). At the latest data cut-off, representing a median follow-up of 12.5 months, this population fulfilled the follow-up criterion for the primary efficacy population.

Table 22. Summary of efficacy endpoints, initial primary efficacy population (first dose on or before 05 February 2020)– Investigator and BICR (DCO 30 March 2021)

	Investigator Assessment (N=81)	BICR Assessment (N=81)
Overall response rate[a] 95% CI	31 (38.3%) (27.7%, 49.7%)	35 (43.2%) (32.2%, 54.7%)
Complete response	0%	3 (3.7%)
Partial response	31 (38.3%)	32 (39.5%)
Clinical benefit rate 95% CI	59 (72.8%) (61.8%, 82.1%)	59 (72.8%) (61.8%, 82.1%)
Duration of response		
Median (95% CI), months Patients with DOR ≥ 6 months	12.5 (6.5, 16.1) 21 (67.7%)	11.0 (6.9, NE) 21 (60.0%)
Median progression-free survival (95% CI), months	8.3 (5.5, 12.3)	8.3 (5.5, 11.1)
Median overall survival (95% CI), months	22.8 (17.5, NE)	

[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).

PFS event rate, INV: 70%, BICR: 67%. OS event rate: 38%. Median follow-up 14.5 months.

Extended efficacy population

Table 23. Summary of efficacy endpoints, extended primary efficacy population (first dose on or before 04 June 2020)– Investigator and BICR (DCO 30 March 2021)

	Investigator Assessment (N=114)	BICR Assessment (N=114)
Overall response rate[a] (95% CI)	42 (36.8%) (28.0%, 46.4%)	49 (43.0%) (33.7%, 52.6%)
Complete response	0	3 (2.6%)
Partial response	42 (36.8%)	46 (40.4%)
Clinical benefit rate (95% CI)	86 (75.4%) (66.5%, 83.0%)	84 (73.7%) (64.6%, 81.5%)
Duration of Response		
Median (95% CI), months	12.5 (6.5, 16.1)	10.8 (6.9, 15.0)
Subjects with DOR ≥6 months	27 (64.3%)	27 (55.1%)
Median progression-free survival (95% CI), months	6.9 (5.6, 8.6)	6.7 (5.5, 9.7)
Median overall survival (95% CI), months	22.8 (17.5, NE)	

[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).

PFS event rate, INV: 71%, BICR: 70%. OS event rate: 35%. Median follow-up 12.5 months.

Reliability of ORR estimates

The reliability and potential bias of the ORR estimates was a major concern, given the exploratory nature of the pivotal study and was therefore explored in different ways. The ORR estimates have been consistent in all analyses for different data cut-offs and analysis sets of Exon 20ins patients at RP2D provided in the regulatory process to date, providing reassurance in the ORR estimate:

Scientific advice, DCO 30 Oct 2019:	n=39	ORR (INV): 35.9% (95% CI: 21.2%, 52.8%)
1st submission, DCO 08 Jun 2020:	n= 81	ORR (INV) 35.8% (95% CI: 25.4%, 47.2%)
1st submission, DCO 08 Oct 2020:	n= 81	ORR (INV) 35.8% (95% CI: 25.4%, 47.2%)
Responses, DCO 30 March 2021:	n= 81	ORR (INV) 38.3% (95% CI: 27.7%, 49.7%)
Responses, DCO 30 March 2021:	n= 114	ORR (INV) 36.8% (95% CI: 28.0%, 46.4%)
1st submission, DCO 08 Jun 2020:	n= 81	ORR (BICR) 39.5% (95% CI: 28.8%, 51.0%)
1st submission, DCO 08 Oct 2020:	n= 81	ORR (BICR) 39.5% (95% CI: 28.8%, 51.0%)
Responses, DCO 30 March 2021:	n= 81	ORR (BICR) 43.2 % (95% CI: 2.2%, 54.7%)
Responses, DCO 30 March 2021:	n= 114	ORR (BICR) 43.0% (95% CI: 33.7%, 52.6%)

Primary endpoint

The best overall response in the extended primary efficacy population is based on RECIST v1.1 in subjects with Exon 20 insertion and prior chemotherapy with measurable disease at baseline and first dose on or before 04 JUN 2020, who were treated with amivantamab (JNJ-61186372) monotherapy at RP2D in Study 61186372EDI1001.

Table 24. Summary of Best Overall Response – Investigator and BICR (DCO 30 March 2021, extended primary efficacy population)

	Investigator	BICR

Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114	114
Best overall response		
N	114	114
Complete response (CR)	0	3 (2.6%)
Partial response (PR)	42 (36.8%)	46 (40.4%)
Stable disease (SD)	56 (49.1%)	47 (41.2%)
Progressive disease (PD)	14 (12.3%)	15 (13.2%)
Not evaluable/unknown	2 (1.8%)	3 (2.6%)
Overall response rate (Confirmed CR + Confirmed PR)	42 (36.8%)	49 (43.0%)
95% CI	(28.0%, 46.4%)	(33.7%, 52.6%)
Clinical benefit rate [a] (Confirmed CR + Confirmed PR + SD)	86 (75.4%)	84 (73.7%)
95% CI	(66.5%, 83.0%)	(64.6%, 81.5%)

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).
Note: Chinese patients enrolled beyond the initial global cohort enrollment are excluded.

Secondary endpoints

Further details on DOR, Time to response (TTR), PFS and OS are shown below.

Duration of response

Table 25. Summary of Duration of response in responders - Investigator and BICR (DCO 30 March 2021, extended primary efficacy population)

	Investigator	BICR
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114	114
Responders	42	49
Event	21 (50.0%)	27 (55.1%)
Censored	21 (50.0%)	22 (44.9%)
Time to event (months)		
25th percentile (95% CI)	4.96 (4.14, 8.31)	5.13 (4.07, 8.21)
Median (95% CI)	12.45 (6.54, 16.13)	10.84 (6.90, 14.98)
75th percentile (95% CI)	16.13 (12.68, NE)	21.65 (11.04, NE)
Range	(1.1+, 19.0+)	(1.1+, 21.7)
Duration of response >=6 months	27 (64.3%)	27 (55.1%)
Duration of study treatment (months)[a]		
N	42	49
Mean (SD)	12.77 (5.087)	12.13 (5.770)
Median	13.59	13.37
Range	(2.3, 23.9)	(1.7, 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.
Note: Chinese patients enrolled beyond the initial global cohort enrollment are excluded.

Source: Response to Day 120 LoQ, Question 106, Appendix, Table TEFDOR01A-E20PC and Table TEFDOR02A-E20PC.

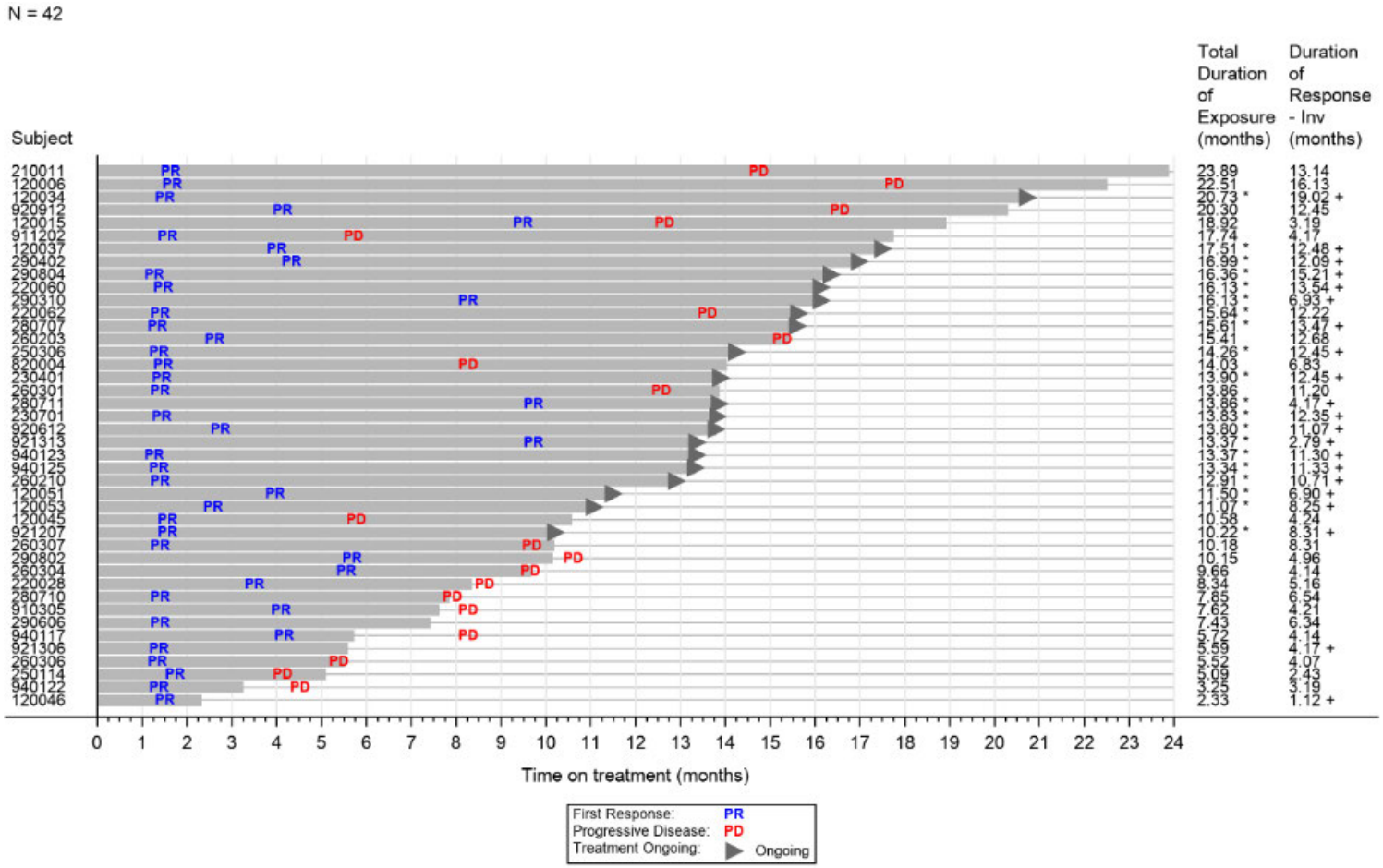


Figure 9. Duration of Response in Responders - BICR; Efficacy Evaluable at RP2D with Exon 20 Insertion and Prior Chemotherapy Analysis Set in Monotherapy (DCO 04 JUN 2020)

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

Time to response

The swimmer plot shows generally early partial responses, the majority occurring before 2 months of treatment (Figure 11). This was confirmed in a requested analysis of time to response. In the 114 subjects in the primary efficacy population, at final cut-off date of 30 March 2021, there were 42 investigator-assessed responders, with a median time to response of 1.6 months (range:1.3 to 9.7 months), which corresponds with the first scheduled post-baseline disease assessment at 6 weeks.

Post-progression continuation of therapy

Among the 114 patients, data from 25 patients who received continued treatment with amivantamab post progression and who had a post-progression disease assessment, showed a duration of post-progression amivantamab treatment of mean 4.5 months, and median 4.2 months. 16% received post-progression therapy for ≥ 6 months.

Progression-free survival

Table 26. Summary of Progression-free survival - Investigator and BICR (DCO 30 March 2021, extended primary efficacy population)

	Investigator	BICR
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114	114
Event	81 (71.1%)	80 (70.2%)
Censored	33 (28.9%)	34 (29.8%)
Time to event (months)		
25th percentile (95% CI)	3.71 (2.60, 4.34)	3.94 (2.66, 4.83)
Median (95% CI)	6.93 (5.55, 8.64)	6.74 (5.45, 9.66)
75th percentile (95% CI)	16.56 (12.58, NE)	12.45 (10.87, NE)
Range	(0.0+, 24.1)	(0.0+, 23.3)
3-month event-free rate (95% CI)	0.77 (0.68, 0.84)	0.78 (0.69, 0.85)
6-month event-free rate (95% CI)	0.55 (0.45, 0.64)	0.55 (0.45, 0.64)
9-month event-free rate (95% CI)	0.39 (0.30, 0.48)	0.41 (0.31, 0.50)
12-month event-free rate (95% CI)	0.35 (0.26, 0.44)	0.29 (0.21, 0.39)
15-month event-free rate (95% CI)	0.28 (0.19, 0.37)	0.22 (0.14, 0.31)
18-month event-free rate (95% CI)	0.18 (0.09, 0.30)	0.14 (0.06, 0.26)
21-month event-free rate (95% CI)	0.18 (0.09, 0.30)	0.14 (0.06, 0.26)
24-month event-free rate (95% CI)	0.18 (0.09, 0.30)	0 (NE, NE)
27-month event-free rate (95% CI)	0 (NE, 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.
Key: CI = confidence interval, NE = not estimable, + = censored observation
Quartiles and 95% CIs are estimated with Kaplan-Meier method.
Note: Chinese patients enrolled beyond the initial global cohort enrollment are excluded.

Source: Response to Day 120 LoQ, Question 106, Appendix, Table TEFPFS01A-E20PC and Table TEFPFS02A-E20PC.

PFS sensitivity analysis

Subjects who started a subsequent anti-cancer therapy in the absence of progression were censored at the last disease assessment before the start of subsequent therapy. In the primary efficacy population (n=114) only 2 patients were censored for this reason. A requested sensitivity analysis showed a

similar median PFS (6.87 months, 95% CI: 5.49, 8.28 months) as in the primary analysis (6.93 months, 95% CI: 5.55, 8.64 months), when the initiation of subsequent anti-cancer therapy was treated as a progression event.

Overall survival

Table 27. Summary of Overall survival (DCO 30 March 2021, extended primary efficacy population)

Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	114
Event	40 (35.1%)
Censored	74 (64.9%)
Time to event (months)	
25th percentile (95% CI)	9.95 (8.48, 14.59)
Median (95% CI)	22.77 (17.48, NE)
75th percentile (95% CI)	NE (23.00, NE)
Range	(0.2, 30.5+)
3-month event-free rate (95% CI)	0.95 (0.89, 0.98)
6-month event-free rate (95% CI)	0.90 (0.83, 0.94)
9-month event-free rate (95% CI)	0.79 (0.70, 0.86)
12-month event-free rate (95% CI)	0.73 (0.63, 0.80)
15-month event-free rate (95% CI)	0.66 (0.55, 0.75)
18-month event-free rate (95% CI)	0.61 (0.49, 0.71)
21-month event-free rate (95% CI)	0.53 (0.39, 0.66)
24-month event-free rate (95% CI)	0.40 (0.21, 0.58)
27-month event-free rate (95% CI)	0.40 (0.21, 0.58)
30-month event-free rate (95% CI)	0.40 (0.21, 0.58)

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.
Note: Chinese patients enrolled beyond the initial global cohort enrollment are excluded.

Source: Response to Day 120 LoQ, Question 106, Appendix, Table TEFOS01A-E20PC.

- **Ancillary analyses**

Subgroup analyses from the pivotal data set

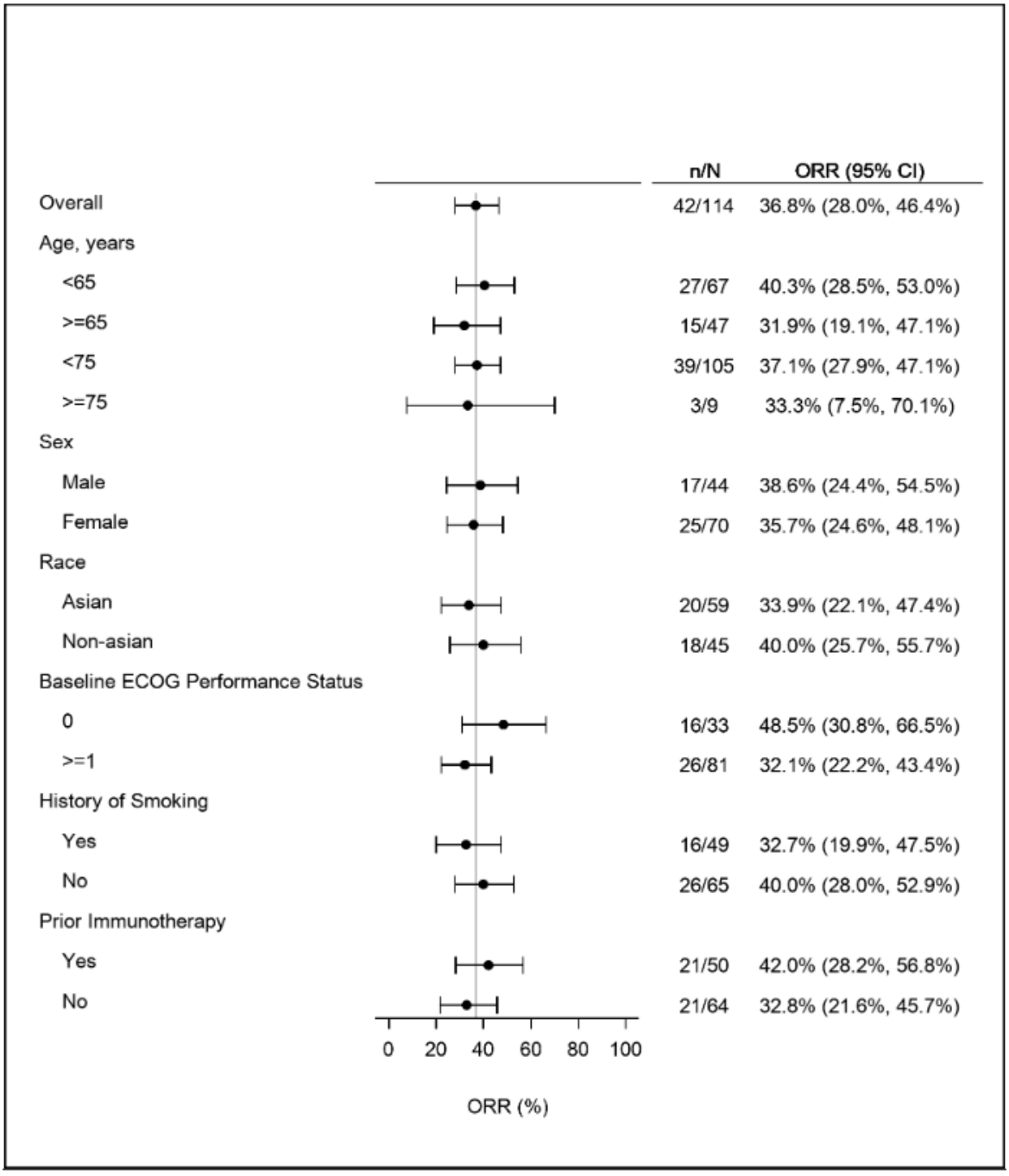


Figure 10. Subgroup forest plot of Overall response rate – Investigator (DCO 30 March 2021)

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 per RECIST 1.1.
Note: If race was not reported, then that subject is excluded from the race subgroup.
DCO 30 March 2021, Subjects with measurable disease at baseline and first dose on or before 04 JUN 2020.

Source: Response to Day 180 LoQ, Question 32, Figure 9.

The ORR by INV is overall consistent across subgroups, ranging from 32% to 48%, compared to the overall ORR of 37% (Figure 12). The ORR by BICR in the same subgroups ranged from 33 to 55%

compared to the overall BICR ORR of 43% (data not shown; Source: Response to Day 180 LoQ, Question 32, Figure 10.)

These subgroups were "pre-planned", to the extent it is meaningful to discuss pre-planning in relation to this exploratory study with many and major protocol changes.

It is noted that activity of amivantamab is present irrespective of prior immunotherapy.

The largest difference is seen for ECOG performance status, with ORR 48% for ECOG 0 and 32% for ECOG 1. The median number of lines of prior therapy was 2, (range 1-7). There was no discernible biologically plausible pattern with regard to number of lines, however (Figure 13).

Prior lines of therapy

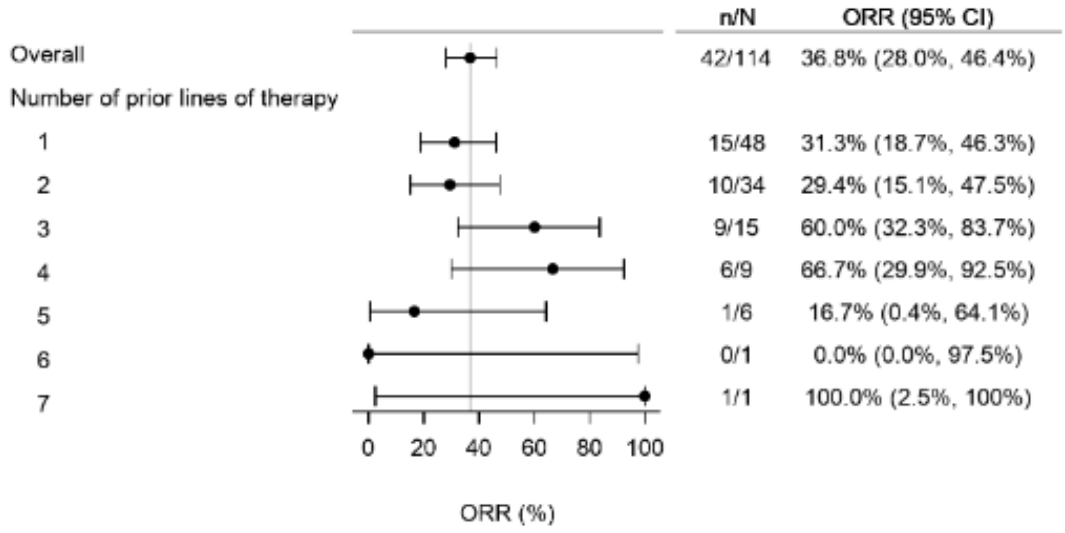


Figure 11. Forest Plot of Overall Response Rate Based by Number of Prior Lines of Therapy

Study 61186372EDI1001, All Treated at RP2D in monotherapy, subjects with Exon 20 insertion and prior chemotherapy, with measurable disease at baseline and first dose on or before 04 June 2020 (n=114), based on RECIST v1.1, Investigator assessments. (Data cut-off date: 08 Oct 2020.)
Source: Response to Day 120 LoQ, Question 113, Figure 19.

Brain metastases

Patients with untreated brain metastases were excluded from study participation. Regular follow-up imaging for new CNS disease was not required by the protocol and intracranial responses were not assessed. Subjects with a prior history of brain/CNS metastases had similar overall response rate (43% vs 39%) and duration of response (16.1 vs. 11.2 months) as those without (Table 35).

Table 28. Best overall response by brain/CNS lesions at baseline (Present, Absent) – Investigator assessment

	Exon 20 Ins (RP2D)	
	Prior Chemotherapy	
	Present	Absent
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	38	76
Responders (ORR)	12 (31.6%)	30 (39.5%)

	Exon 20 Ins (RP2D)	
	Prior Chemotherapy	
	Present	Absent
Best overall response		
Complete response (CR)	0	0
Partial response (PR)	12 (31.6%)	30 (39.5%)
Stable disease (SD)	19 (50.0%)	37 (48.7%)
Progressive disease (PD)	6 (15.8%)	8 (10.5%)
Not evaluable/unknown	1 (2.6%)	1 (1.3%)
Event	5 (41.7%)	16 (53.3%)
Censored	7 (58.3%)	14 (46.7%)
Time to Event (months)		
25th percentile (95% CI)	12.22 (4.14, NE)	4.24 (3.19, 6.83)
Median (95% CI)	16.13 (4.21, NE)	11.20 (5.16, NE)
75th percentile (95% CI)	16.13 (12.68, NE)	NE (12.45, NE)
Range	(4.1, 16.1)	(1.1+, 19.0+)
Duration of response >=6 months	9 (75.0%)	18 (60.0%)
Duration of study treatment (months)[a]		
N	12	30
Mean (SD)	13.75 (4.518)	12.38 (5.319)
Median	14.83	13.36
Range	(5.7, 22.5)	(2.3, 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.
Note: Subjects with brain/CNS lesions present at baseline included subjects that had brain/CNS metastasis history or had brain/CNS lesions as target or non-target lesions at baseline.

Source: Response to Day 180 LoQ, Question 32, follow-up question. Table 7 (BOR), and Advance response to draft 2nd LoOI, Question 4, Table 2 (median DoR).

EGFR Exon 20 insertion mutation subtypes

Responses with amivantamab seem to occur independently of EGFR exon20ins mutation subtypes.

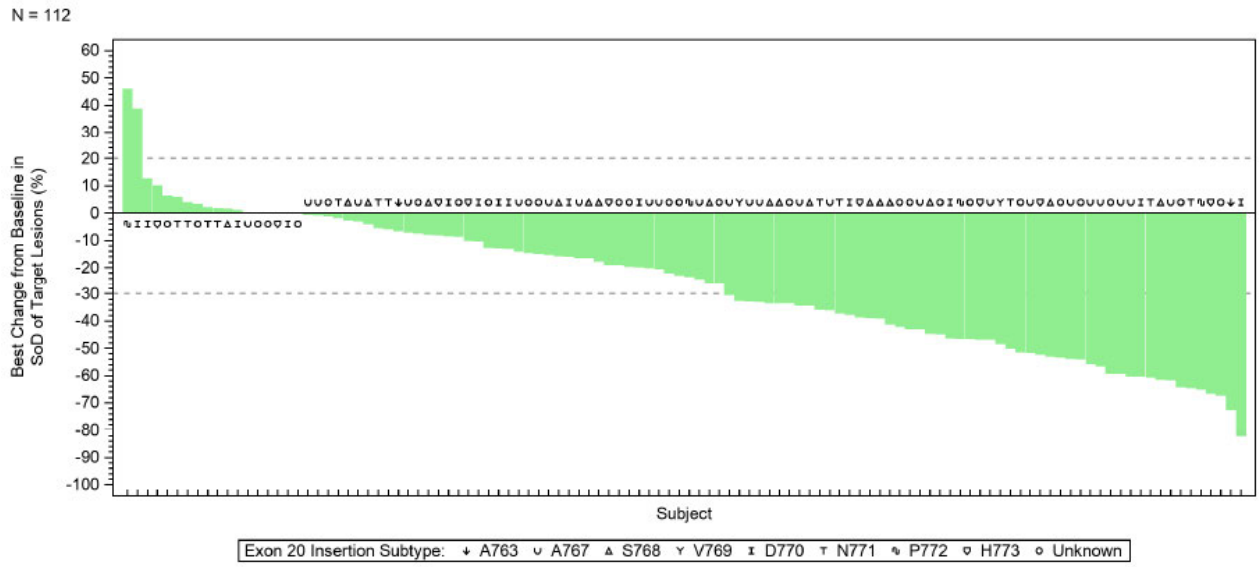


Figure 12. Waterfall plot of Best percentage change from baseline in Sum of diameters (SoD) of target lesions based on subjects with measurable disease at baseline and first dose on or before 04 June 2020 - Investigator (DCO 30 March 2021)

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: Response to Day 180 LoQ, Question 32, Figure 11.

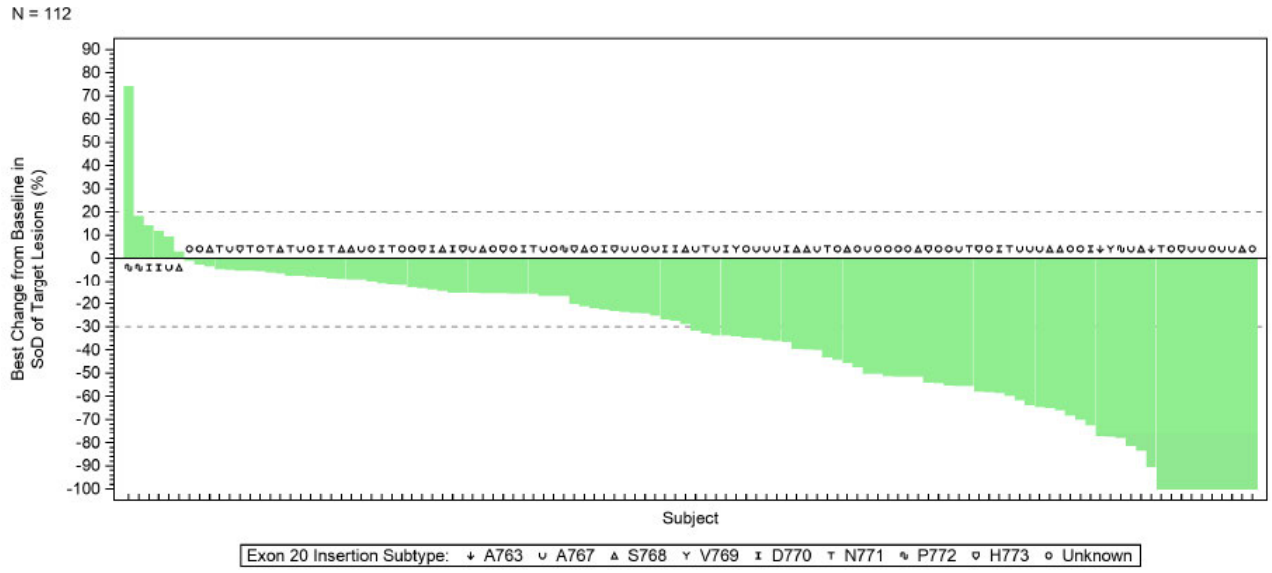


Figure 13. Waterfall plot of Best percentage change from baseline in Sum of diameters (SoD) of target lesions based on subjects with measurable disease at baseline and first dose on or before 04 June 2020 - Independent Review Committee (DCO 30 March 2021)

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: Response to Day 180 LoQ, Question 32, Figure 12.

Age groups

Response rates were largely consistent across age groups.

	Exon 20 Ins (RP2D) Prior Chemotherapy			
	<65 years	65-74 years	75-84 years	>=85 years
Analysis set: All treated at RP2D with Exon 20 insertion and prior chemotherapy in monotherapy (JNJ-61186372)	67	38	9	-
Overall response rate (Confirmed CR + Confirmed PR) 95% CI	27 (40.3%) (28.5%, 53.0%)	12 (31.6%) (17.5%, 48.7%)	3 (33.3%) (7.5%, 70.1%)	-

Source: Response to Day 180 LoQ, Question 32, Table 23.

Other analysis sets from the pivotal study

The ORR in the two supportive data sets from Study EDI1001 (CHRYSALIS) were similar to the pivotal analysis set.

Exon 20ins + no prior chemotherapy at RP2D population

In the 24 subjects with locally- documented Exon 20ins NSCLC enrolled in Part 1 or Part 2 who were treated with amivantamab monotherapy at a dose consistent with the RP2D who had not received platinum-based chemotherapy within 12 months of diagnosis of metastatic NSCLC, the ORR as per the initial DCO 08 June 2020, was 37.5% (95% CI: 18.8%, 59.4%), with 9 patients with PR, no CR. (Source: CSR, table TEFRSP01-E20NR)

Exon 20ins at Non-RP2D population:

In the 42 subjects with locally-documented Exon 20ins NSCLC (irrespective of prior chemotherapy) enrolled in Part 1 or Part 2 and treated at amivantamab monotherapy doses other than the RP2D, the ORR as per the initial DCO 08 June 2020, was 36.6% (95% CI: 22.1%, 53.1%), with 15 patients with PR, no CR. (Source: CSR, table TEFRSP01-E20NR)

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 29. Summary of efficacy for trial 61186372EDI1001

Title: A Phase 1, First-in-Human, Open-Label, Dose Escalation Study of JNJ-61186372, a Human Bispecific EGFR and cMet Antibody, in Subjects with Advanced Non-Small Cell Lung Cancer		
Study identifier	61186372EDI1001 (CHRYSALIS); 2018-003908-38; NCT02609776	
Design	Open-label, first-in-human, dose-escalation, multi-centre	
	Duration of main phase:	Dose-Escalation Phase - Dose escalation through 6 planned dose escalation cohort levels, until MTD reached, or maximum assessed dose is identified.
	Duration of Run-in phase:	Not Applicable
	Duration of Extension phase:	Individual patients meeting eligibility criteria were treated with amivantamab at the RP2D, until disease progression, unacceptable toxicity, or other reason for treatment discontinuation.
Hypothesis	None, uncontrolled study	
Treatments groups	**Part 1 – Dose Escalation**	Six pre-planned Amivantamab dose cohorts from 140mg to 1750mg, administered once weekly for the first 4 weeks and once every 2 weeks thereafter via intravenous infusion, in order to identify the MTD, if one exists, and to identify the RP2D for further exploration in Part 2. (See notes below)
	Cohort 1	140mg dose cohort
	Cohort 2	350mg dose cohort
	Cohort 3	700mg dose cohort
	Cohort 4	1050mg dose cohort
	Cohort 5	1400mg dose cohort

	Cohort 6		1750mg dose cohort
	Part 2 Dose Expansion		Subjects with EGFR or MET-driven NSCLC were enrolled and treated with the RP2D of amivantamab into one of six Part 2 cohorts. Cohort A and B were closed with Amendment 4.
	Part 2 - Cohort A		Amivantamab administered at the RP2D for subjects meeting eligibility criteria for Cohort A, which enrolled subjects who had had progressed after previous EGFR TKI therapy, and had an identified EGFR-based mechanism of resistance. Cohort Closed with Amendment 4.
	Part 2 - Cohort B		Amivantamab administered at the RP2D for subjects meeting eligibility criteria for Cohort B, which enrolled subjects who had had progressed after previous EGFR TKI therapy, and did not have EGFR-based mechanism of resistance. Cohort closed with Amendment 4.
	Part 2 - Cohort C		Amivantamab administered at the RP2D for subjects meeting eligibility criteria for Cohort C, which enrolled subjects who had progressed on prior 3rd generation TKI, and had an identified EGFR-based mechanism of resistance.
	Part 2 - Cohort D		Amivantamab administered at the RP2D for subjects meeting eligibility criteria for Cohort D, which enrolled subjects who had previously diagnosed EGFR Exon20ins disease, and progressed through standard of care therapy.
	Part 2 - Cohort MET-1		Amivantamab administered at the RP2D for subjects meeting eligibility criteria for Cohort MET-1, which enrolled subjects who had progressed on prior EGFR TKI, and had an identified MET-based mechanism of resistance.
	Part 2 - Cohort MET-2		Amivantamab administered at the RP2D for subjects meeting eligibility criteria for Cohort MET-2, which enrolled subjects who had previously diagnosed MET Exon14skip disease, and progressed through standard of care therapy.
Endpoints and definitions	Part 1 – Primary endpoint	Determine the MTD and RP2D	Determine the appropriate dose of amivantamab for further clinical investigation.
	Part 2 – Primary endpoint	ORR	As assessed using RECIST v1.1 criteria.
	Part 2 – Secondary endpoint	CBR	Proportion of subjects achieving a BOR of confirmed CR, PR, or SD (duration of at least 11 weeks) as defined by RECIST v1.1.
	Part 2 – Secondary endpoint	DOR	Time from first documented PR or CR, to documented evidence of disease progression or death due to any cause.
	Part 2 – Secondary endpoint	PFS	Time from first dosing date to the first date of disease progression or death due to any cause.

	Part 2 – Secondary endpoint	OS	Time from first dosing date to the date of death due to any cause.
Data cut-off date	30 March 2021		
Results and Analysis			
Analysis description	**Interim Analysis**		
Analysis population and time point description	Subjects from Part 1 and Part 2 with EGFR Exon 20 insertion and prior platinum-based chemotherapy, treated with monotherapy amivantamab (JNJ-61186372) at RP2D, with first dose on or before 04 June 2020		

Descriptive statistics and estimate variability		**Primary analysis by investigator assessment (INV)**	Sensitivity analysis by blinded independent central review (BICR)
	Treatment group	**Amivantamab**	Amivantamab
	Number of subjects	**114**	114
	ORR (%)	**36.8%**	43.0%
	95% CI	**(28.0%, 46.4%)**	(33.7%, 52.6%)
	Confirmed CR and PR (%)	**CR - 0%** **PR - 36.8%**	CR – 2.6% PR – 40.4%
	CBR (%)	**75.4%**	73.7%
	95% CI	**(66.5%, 83.0%)**	(64.6%, 81.5%)
	Median DOR (months)	**12.5**	10.8
	95% CI	**(6.5, 16.1)**	(6.9, 15.0)
	Patients with DOR ≥6 months (%)	**64.3%**	55.1%
	Median PFS (months)	**6.9**	6.7
	95% CI	**(5.6, 8.6)**	(5.5, 9.7)
	OS (months, median)	**22.8**	
	95% CI	**(17.5, NE)**	

Effect estimate per comparison	Not applicable, uncontrolled study
Notes	The selected RP2D (recommended phase 2 dose) from Part 1 of the study was 1050 mg in patients weighing < 80 kg and 1400 mg for ≥ 80 kg.

2.6.5.3. Clinical studies in special populations

Table 30. Experience in elderly subjects by age brackets

Elderly Subjects	Age <65 years (number/total number)	Age 65-74 years (number/total number)	Age 75-84 years (number/total number)	Age 85+ years (number/total number)	Total
Efficacy Population	67	38	9	-	114
Safety Population	287	146	53	3	489

Source: Response to Day 180 LoQ, Question 32, follow-up question. Table 3.

There is some experience (n= 56) of amivantamab safety in patients aged 75 years or more.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

See "Identification of EGFR Exon 20 insertion mutation" Baseline data.

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

2.6.5.6. Supportive study(ies)

Study NSC1002 – Real-world data (RWD)

As patients with EGFR Exon 20ins NSCLC have been excluded from the majority of Phase 3 studies of EGFR TKIs, this population has been relatively understudied in clinical studies, and published reports have often been based on retrospective analyses or case series/reports. To better understand the prognosis of these patients with EGFR Exon 20ins, as compared with patients with common EGFR (cEGFR) mutations, and to confirm treatment utilization and outcomes with available therapies, a **retrospective cohort study of RWD,** Study 61186372NSC1002 (hereafter referred to as Study NSC1002), was conducted and utilized claims reimbursement data and electronic health records (EHRs) on second-line treatment patterns for advanced NSCLC, including EGFR Exon 20ins NSCLC.

Methods

Study Design and Setting

This retrospective cohort study included patients aged ≥18 years with a diagnosis of advanced NSCLC between 01 January 2011 and 31 May 2020 in the Advanced NSCLC Flatiron 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). Eligible patients were required to have (1) at least 2 documented clinical visits on or after 01 January 2011, (2) structured activity (e.g., office visit, medication fill), (3) started first-line therapy within 90 days of diagnosis, and (4) a positive test result for Exon 20ins or cEGFR mutation on or before the start date of treatment Line 1, Line 2, Line 3, or first TKI line (+28 days) to ensure that treatment was based on the known mutation status.

Data Conventions and Analytic Approach

Derivation of rwOS relies on death information. Due to privacy regulations, only month and year of death are recorded in the data. As a convention, the date of the death is derived as 15th day of the month or last confirmed activity date +1, whichever is later.

Real-world OS and rwPFS endpoints were summarized using Kaplan–Meier survival function estimation for each cohort, including median and quartiles of survival with 95% CIs for each cohort. For assessing the prognosis for Exon 20ins compared with cEGFR mutations, adjusted hazard ratio (HR), its 95% CI, and p-value were calculated using multivariable Cox proportional hazards model, including the covariates of age, time from diagnosis of advanced disease to treatment, time from initial diagnosis to advanced diagnosis, line of therapy, ECOG performance score, smoking history, sex, and practice type. For the Exon 20ins comparison with cEGFR mutations in patients treated with TKIs, the TKI line of therapy was used as strata, in addition to the covariates used in the Cox model for the prognosis assessment.

Results

Among 62,464 patients with advanced NSCLC in the database, EGFR mutations were detected in 4485 patients. These mutations were mostly detected by next-generation sequencing or polymerase chain reaction (69.6%). Of these, 3281 met the inclusion criterion of structured activity within 90 days and starting first-line therapy within 90 days of diagnosis. A total of 3014 patients met all study criteria and had an EGFR mutation detected on or before the start of treatment Line 1 +28 days and so were eligible for the analysis of prognostic value of Exon 20ins versus cEGFR mutations. For Line 2 and Line 3 of therapy, 1744 and 949 patients, respectively, had an EGFR mutation detected on or before the start of that treatment line +28 days. For predictive value of Exon 20ins versus cEGFR mutations for TKI treatment, 2825 patients had an EGFR mutation detected on or before the start of first TKI line of therapy +28 days, and so were eligible for the analysis. Nine patients who had both Exon 20ins as well as cEGFR mutations detected and identified were excluded from all analyses so as not to bias results for either cohort.

Baseline characteristics for the 3014 patients were generally similar between the Exon 20ins and cEGFR mutation cohorts, except for the proportion of men (39% vs 33%, respectively) and history of smoking (54% vs 45%, respectively) (See table below). Subsets of these patients were used for the predictive value of Exon 20ins for TKI treatment and treatment patterns analyses.

Table 31. Baseline characteristics of patients Included in the analysis of prognostic value of Exon 20ins mutations vs cEGFR mutations (Study NSC1002)

	cEGFR Mutations (n=2833)	EGFR Exon 20ins (n=181)	All (n=3014)
Age (years)			
Mean (SD)	68.0 (10.65)	66.0 (10.28)	67.9 (10.63)
Median	69.4	67.4	69.1
Range	(25; 85)	(39; 84)	(25; 85)
Sex, n (%)			
Female	1895 (66.9%)	111 (61.3%)	2006 (66.6%)
Male	938 (33.1%)	70 (38.7%)	1008 (33.4%)
Race, n (%)			
Asian	379 (13.4%)	11 (6.1%)	390 (12.9%)
Black or African American	205 (7.2%)	17 (9.4%)	222 (7.4%)
Hispanic or Latino	6 (0.2%)	1 (0.6%)	7 (0.2%)
NA	305 (10.8%)	20 (11.0%)	325 (10.8%)
Other Race	335 (11.8%)	23 (12.7%)	358 (11.9%)
White	1603 (56.6%)	109 (60.2%)	1712 (56.8%)
Ethnicity, n (%)			
Hispanic	146 (5.2%)	9 (5.0%)	155 (5.1%)
NA	2687 (94.8%)	172 (95.0%)	2859 (94.9%)
ECOG PS score, n (%)			
≤1	1327 (46.8%)	96 (53.0%)	1423 (47.2%)
≥2	292 (10.3%)	13 (7.2%)	305 (10.1%)

	cEGFR Mutations (n=2833)	EGFR Exon 20ins (n=181)	All (n=3014)
Unknown	1214 (42.9%)	72 (39.8%)	1286 (42.7%)
Histology, n (%)			
NSCLC histology NOS	52 (1.8%)	2 (1.1%)	54 (1.8%)
Non-squamous cell carcinoma	2741 (96.8%)	174 (96.1%)	2915 (96.7%)
Squamous cell carcinoma	40 (1.4%)	5 (2.8%)	45 (1.5%)
Group stage at initial diagnosis, n (%)			
Stage I	176 (6.2%)	12 (6.6%)	188 (6.2%)
Stage II	93 (3.3%)	8 (4.4%)	101 (3.4%)
Stage III	178 (6.3%)	11 (6.1%)	189 (6.3%)
Stage IIIB/C	103 (3.6%)	8 (4.4%)	111 (3.7%)
Stage IV	2229 (78.7%)	140 (77.3%)	2369 (78.6%)
Unknown	54 (1.9%)	2 (1.1%)	56 (1.9%)
Smoking status, n (%)			
History of smoking	1271 (44.9%)	97 (53.6%)	1368 (45.4%)
No history of smoking	1550 (54.7%)	84 (46.4%)	1634 (54.2%)
Unknown/Not documented	12 (0.4%)	0	12 (0.4%)
Practice type, n (%)			
Academic	301 (10.6%)	20 (11.0%)	321 (10.7%)
Community	2532 (89.4%)	161 (89.0%)	2693 (89.3%)
Practice type/region, n (%)			
Academic/Unknown	301 (10.6%)	20 (11.0%)	321 (10.7%)
Community/West US	660 (23.3%)	31 (17.1%)	691 (22.9%)
Community/non-West US	1872 (66.1%)	130 (71.8%)	2002 (66.4%)
Time from advanced diagnosis to treatment (months)			
Mean (SD)	1.1 (0.65)	1.1 (0.62)	1.1 (0.64)
Median	1.0	1.1	1.0
Range	(0; 3)	(0; 3)	(0; 3)
Time from initial diagnosis to advanced diagnosis (months)			
Mean (SD)	4.9 (15.24)	6.6 (19.45)	5.0 (15.53)
Median	0.0	0.0	0.0
Range	(0; 192)	(0; 155)	(0; 192)

Exon 20ins=Exon 20 insertion mutation; cEGFR=common epidermal growth factor receptor; ECOG PS=Eastern Cooperative Oncology Group performance status; Exon 20ins=Exon 20 insertion mutations; NA=not applicable; NSCLC=non-small cell lung cancer; NOS=not otherwise specified; SD=standard deviation.

Prognostic Value of Exon 20ins Mutations Versus cEGFR Mutations

The analysis compared outcomes in the first-line setting (Line 1) and included 3014 patients (181 Exon 20ins and 2833 cEGFR mutations). Patients with Exon 20ins had a shorter median survival (16.23 months, 95% CI: 11.04, 19.38) than those with cEGFR mutations (25.49 months, 95% CI: 24.48, 27.04), and a 75% increased risk of death compared with those with cEGFR mutations (adjusted hazard ratio [AdjHR]: 1.75 [95% CI: 1.45, 2.13); p<0.0001 (Figure 16).

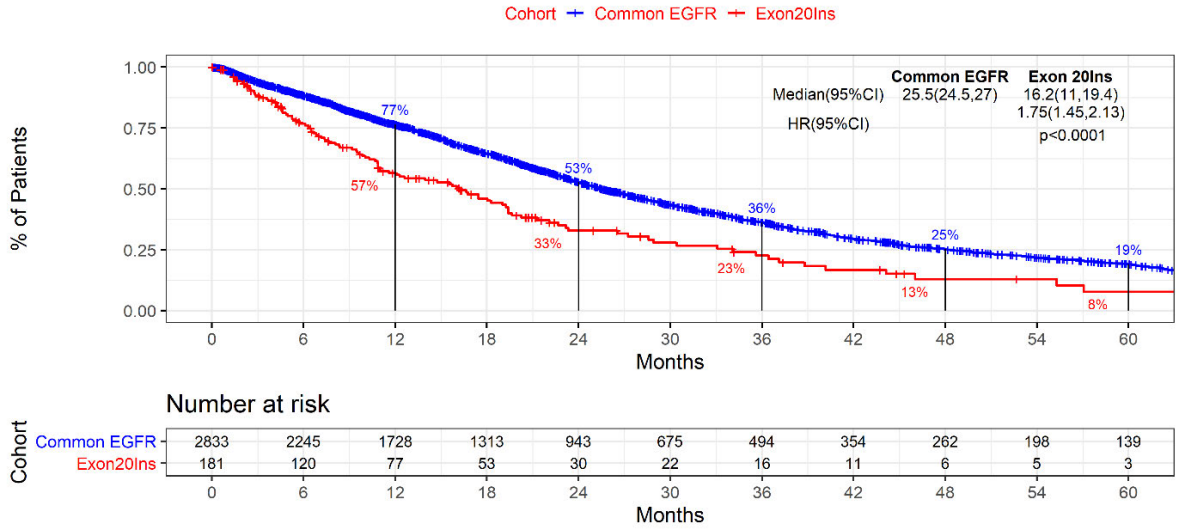


Figure 14. Real-World Overall survival in 1L setting (Study NSC1002)

Exon 20ins=Exon 20 insertion mutation; CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio.

Predictive value of Exon 20ins on EGFR TKI outcomes (Exon 20ins versus cEGFR patients)

This analysis, stratified by the line of TKI treatment, included data from the first use of a TKI in 2825 TKI-treated patients (76 with Exon 20ins and 2749 with cEGFR mutations). Overall, 80.8% initiated TKI as first-line therapy, 15.9% as second-line, and 3.3% at third-line or later.

After a median follow-up of 20.6 months, 59 (79.6%) progression events or deaths were observed in the Exon 20ins cohort and 1793 (65.2%) in the cEGFR mutation cohort. Exon 20ins patients treated with EGFR TKI showed worse outcomes, with a median PFS estimate of 2.86 months (95%CI: 2.14, 3.91) compared with 10.45 (95%CI: 10.05, 10.94) months in cEGFR patients. The Exon 20ins cohort had 169% increased risk of progression or death (AdjHR: 2.7 [95%CI: 2.05, 3.54]; p<0.0001) (Figure 17).

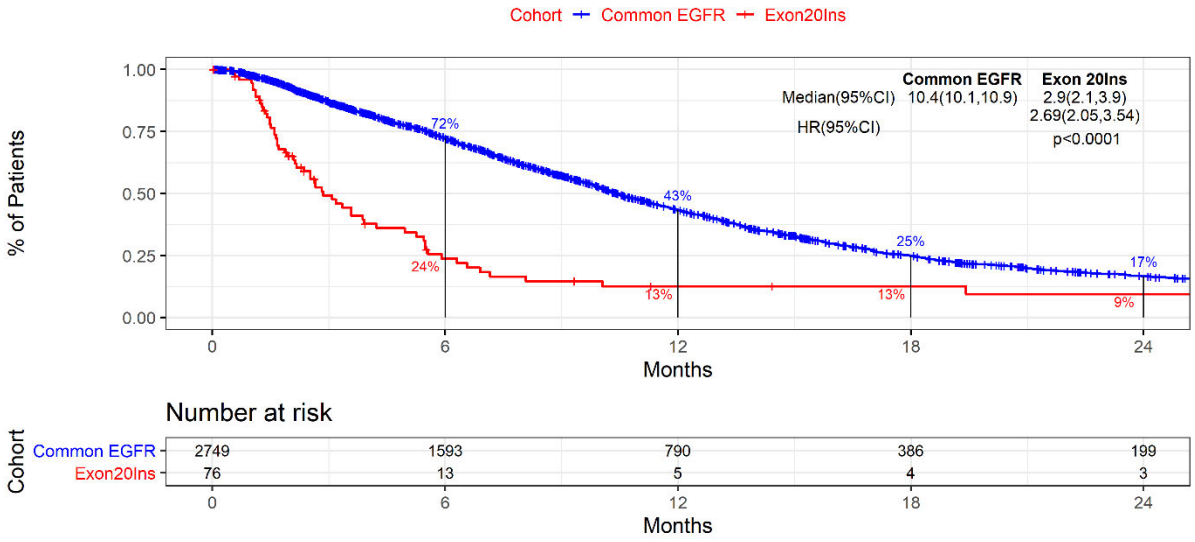


Figure 15. Real-World Progression-free survival on first EGFR TKI treatment (Study NSC1002)

Note: Analysis stratified by TKI line of treatment.
Exon 20ins=Exon 20 insertion mutation; CI=confidence interval; EGFR=epidermal growth factor receptor; HR=hazard ratio; TKI=tyrosine kinase inhibitor.

Treatment Patterns

Treatment patterns in the Exon 20ins patient population for front-line (Line 1), second-line (Line 2), and third-line (Line 3) settings are summarized in the table below.

Platinum-based chemotherapy regimens are the most frequently prescribed front-line regimen (61.3%), followed by TKI monotherapy (21.5%). However, in the second-line setting, there is a more equal utilization of chemotherapy (23.5% platinum-based regimen, 13.0% non-platinum chemotherapy), TKI therapy (21.7%), and immunotherapy (28.7%), indicating no clear standard of care after first-line therapy failure.

Table 32. Treatment patterns of Exon 20ins patients (Study NSC1002)

	Line 1	Line 2	Line 3
Treatment Pattern Detail			
N	181	115	64
1. Platinum-based regimen	111 (61.3%)	27 (23.5%)	14 (21.9%)
a. Platinum doublet	50 (27.6%)	13 (11.3%)	5 (7.8%)
b. Platinum + TKI	1 (0.6%)	0	0
c. Platinum + IO	32 (17.7%)	8 (7.0%)	2 (3.1%)
d. Platinum + IO + TKI	1 (0.6%)	0	0
f. Platinum + TKI + VEGFi	1 (0.6%)	0	0
g. Platinum + IO + VEGFi	1 (0.6%)	0	0
h. Platinum + VEGFi	25 (13.8%)	5 (4.3%)	7 (10.9%)
i. Platinum alone	0	1 (0.9%)	0
2. TKI alone	39 (21.5%)	25 (21.7%)	7 (10.9%)
3. Other TKI Combinations	1 (0.6%)	0	0
4. IO alone	16 (8.8%)	33 (28.7%)	14 (21.9%)
6. VEGFi alone	1 (0.6%)	11 (9.6%)	7 (10.9%)
7. Non-platinum chemo	5 (2.8%)	15 (13.0%)	19 (29.7%)
8. Others	8 (4.4%)	4 (3.5%)	3 (4.7%)

Exon 20ins=Exon 20 insertion mutation; IO=immuno-oncology; TKI=tyrosine kinase inhibitor; VEGFi=vascular endothelial growth factor inhibitor.

Source: CO, Table 13.

Exon 20ins Outcomes by Line of Treatment and Therapy Type

The relative efficacy of chemotherapy, TKI therapy, and immunotherapy in front-line and second-line treatment of Exon 20ins population, in terms of rwPFS and rwOS, is demonstrated in Figure 18 and Figure 19, respectively. Of note, platinum-based chemotherapy is associated with the longest rwPFS, whether administered in the front- or second-line setting and was the most frequently utilized front-line therapy for this population, leading to the longest rwOS outcomes.

After platinum-based chemotherapy, second-line treatment outcomes are very poor (median rwPFS estimates range from 2.3 to 5 months; overall median rwPFS of 3.2 months) across the most commonly prescribed therapies, which were utilized in relatively equivalent frequencies.

Taken together, these data confirm the rationale and use of platinum-based chemotherapy as the front-line standard of care and highlight the lack of effective treatment options in the second-line setting.

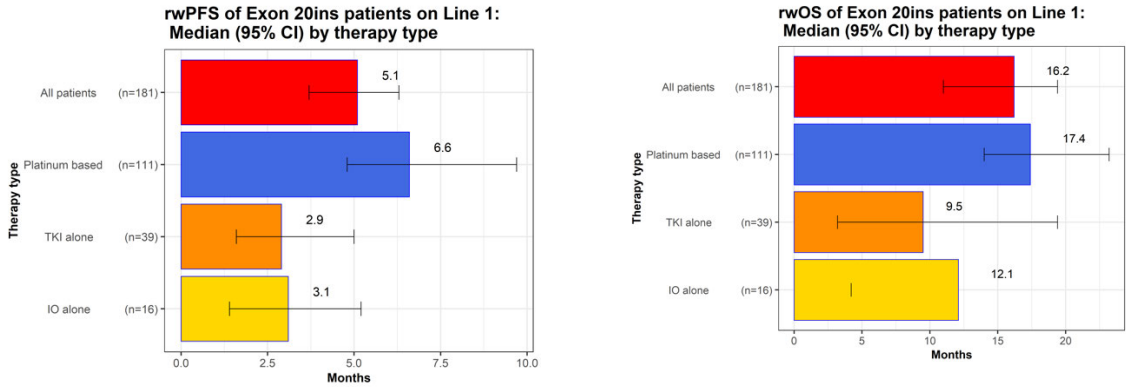


Figure 16. Outcomes of Line 1 treatment by therapy type in patients with Exon 20ins (Study 2NSC1002)

CI=confidence interval; Exon 20ins=Exon 20 insertion mutation; IO= immuno-oncology; TKI= tyrosine kinase inhibitor; VEGFi= vascular endothelial growth factor inhibitor.

Source: CO, Figure 13.

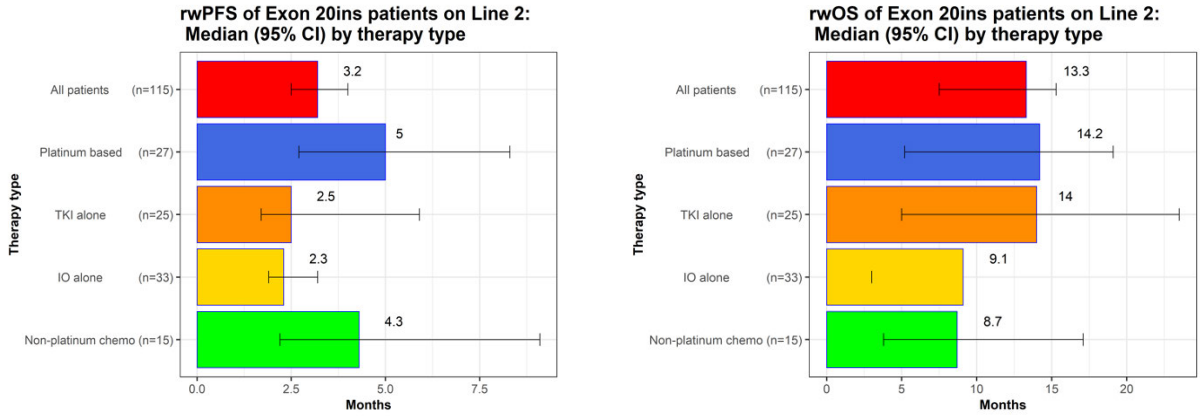


Figure 17. Outcomes of Line 2 treatment by therapy type in patients with Exon 20ins (Study NSC1002)

CI=confidence interval; Exon 20ins=Exon 20 insertion mutation; IO=immuno-oncology; TKI= tyrosine kinase inhibitor; VEGFi= vascular endothelial growth factor inhibitor.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This application rests on preliminary efficacy data, pooled from different parts and cohorts of a single, exploratory, first-in-human (FIH), single-arm trial (SAT), lacking meaningful pre-specification of efficacy hypotheses.

The exploratory character of the pivotal study is noticeable in aspects related to study conduct, for example inconsistencies between the study protocol and the SAP for the present analysis, including major aspects such as the primary endpoint. In line with the exploratory setting, data-driven changes to the protocol have been made repeatedly. Primary and secondary endpoints were changed in protocol amendments during the course of the study. Several efficacy endpoints (ORR, DOR, CBR) were noted as primary endpoints in the last (global) protocol amendment (Amendment 9, 30 April

2020). However, in the last version of the SAP for Exon 20ins IA, (version 7, 9 July 2020), ORR by investigator was listed as the primary endpoint, while it is mentioned that ORR by BICR "will also be analysed". Similarly, for DOR and PFS it is mentioned that BICR assessments "will also be analysed", suggesting that the investigator assessment is the primary analysis. Taken together, the BICR analysis is interpreted to be a sensitivity analysis to the designated primary analysis based on investigator assessments for ORR, DOR and PFS.

These are issues that if observed in a standard confirmatory phase 3 study would raise concerns with regard to study and data integrity and might thus trigger a GCP inspection. In the present setting, however, they are considered to merely reflect the early exploratory phase of drug development.

ORR, according to standardised criteria, is the only acceptable primary efficacy endpoint from this single-arm trial, because objective tumour response is the only of the presented disease outcome measures that directly reflects a drug-effect. This is because malignant tumours only anecdotally shrink spontaneously to the extent required for a partial response. All other efficacy measures tend to reflect to a high degree also the tumour biology, the inherent prognosis of the disease and the patients' performance status and comorbidities. Thus, these are not interpretable with regard to drug-effect in a single-arm study. Measures such as time-to-event outcomes, including PFS and OS, and clinical benefit rate, which includes not only complete and partial response (CR and PR) but also stable disease (SD), are therefore only relevant for contextualisation and not as claims. Duration of response (DOR) is also affected by prognosis but is considered of relevance as a description of the responses and for evaluation of their clinical value.

Statistical issues

Due to the non-randomised/single-arm open-label design, the risk of selection bias cannot be eliminated. Without a concurrent control, the impact of e.g. subject selection on the claimed effect size is difficult to assess. In this context, it is notable that the primary efficacy population was selected from a study in which the efficacy of amivantamab was tested in several biomarker defined populations, among which the present one was selected.

The statistical analysis plan for the interim analysis for Exon 20 insertion mutation patients which this application is based on was dated 9 July 2020. This date is after the date of cut-off for the analysis database. The lack of pre-specification, together with the open-label nature of the study, provides results that can only be interpreted as exploratory and the risk of selection bias is apparent.

In a previous national advice meeting it was suggested to address the likely bias in the estimates due to data-driven selection of cohorts for expansion, by using the latter 40 patients as a separate validation set to confirm the results in the first approximately 40 (39) patients. Normally, the results in the validation set would be used as the primary estimates for approval. An alternative way to assess the evolving ORR estimate over time to is to plot ORR over time based on "step-wise" estimates starting with the first 5 patients and incrementing the population by 5 patients for each estimate. In the same way, a presentation of moving average ORR based on 20 patients with increments of 1 patient was requested, i.e. beginning from the ORR among the first 20 patients initiating treatment (in the efficacy population), followed by the ORR for the set of patients from the 2nd to 21st etc. through to the ORR for the last 20 patients that contribute to the efficacy assessment. These analyses showed a slight decline in estimated ORR assessed by investigators towards the end of the study. The same analysis based on ORR by BICR showed a stable ORR estimate over time.

In response to a request for further information to evaluate the impact of shorter follow-up time and changes in patient characteristics on ORR estimate, the Applicant conducted a logistic regression analysis regressing the probability of response to a range of potentially relevant patient characteristics

and follow-up time. Following stepwise model selection, time from the latest platinum chemotherapy date, bone metastasis, and the duration of follow-up were found to be predictive of response.

Based on these predictive parameters, the predicted ORR for the 43 subjects enrolled after 05 February 2020 was 29.3% that was predicted to raise to 41.4% with an average of 5 month's additional follow-up.

In absence of detailed analysis specifications, it appears that the Applicant's method of adjustment for follow-up duration may not be appropriate since it is based on the correlation of response and follow-up duration among those who were enrolled before 05 February 2020. This correlation cannot be interpreted as causal effect of follow-up duration on the probability of response. On the contrary, long follow-up is a consequence of a good response. Based on the correlation, no predictions can be made about how many additional responses are likely to be observed if these particular patients would be followed up further.

Efficacy data and additional analyses

Dose-finding

The dose-finding Part 1 of Study EDI1001 was performed in a molecularly non-selected patient population with advanced or metastatic NSCLC. However, the majority of subjects (86%) were previously diagnosed with EGFR-mutated NSCLC. This could explain why objective responses were observed at similar frequency around 20% in the 4 dose cohorts (700-1750 mg) where objective responses were observed. However, anti-tumour activity (tumour decrease of -20% from baseline) was observed also in a couple of patients with wild-type EGFR cancers in 350 mg (squamous cell carcinoma) and 1050 mg cohorts (adenocarcinoma), respectively. One may speculate that this could indicate that amivantamab activity is not specific to EGFR or MET mutated tumours but might exert a certain degree of effect regardless of mutational status on the basis of these pathways being important to all tumours.

No MTD was identified at doses up to 1750 mg. A flat dose of 1050 mg was initially selected as the RP2D. However, because patients who weighed ≥ 80 kg had a lower exposure than patients weighing < 80 kg, the dosing was increased in patients ≥ 80 kg in order to achieve similar exposure across groups. A concern was raised, however, based on the efficacy data in Part 2 from patients receiving RP2D and non-RP2D doses, that heavier patients in the < 80 kg group might be underdosed. However, based on analyses of patients on RP2D, ORR results showed no trend towards decreased ORRs as a function of increasing weight, within subjects weighing <80kg at RP2D dose. The selection of RP2D appears reasonably well-founded based on the available data at the time and is supported by the subsequent efficacy data.

Efficacy

The initially presented primary efficacy population consisted of 81 patients pooled from Part 1 and from the Part 2 cohorts A, "EGFR-dependent resistance", and D, "EGFR Exon 20ins". Key criteria for inclusion were Exon 20 insertion and prior chemotherapy, measurable disease at baseline, and treatment with amivantamab monotherapy at RP2D. With regard to follow-up, a first dose on or before 05 February 2020 was required. During the evaluation, the applicant presented a new data cut-off of 30 March 2021, by which also the full 114 population defined as population of interest fulfilled the follow-up criteria for the primary efficacy population, based on a required first dose on or before 04 June 2020. This is referred to as the extended primary efficacy population or the 114 population. In the absence of a pre-planned hypothesis testing analysis population, this extended primary efficacy population is considered the most informative, and thus the pivotal data set for the approval.

Key efficacy results in the pivotal 114-population included the primary endpoint **ORR** by investigator assessments (INV) at 36.8% (95% CI: 28.0%, 46.4%). The ORR sensitivity analysis by BICR showed ORR 43.0% (95% CI: 33.7%, 52.6%).

The median **DOR** was 12.5 months (95% CI: 6.5, 16.1) by INV, and 10.8 months (95% CI: 6.9, 15.0) by BICR. Subjects with DoR ≥ 6 months: 64.3% (INV), 55.1% (BICR).

Median **PFS** was 6.9 months (95% CI: 5.6, 8.6) by INV, and 6.7 months (95% CI: 5.5, 9.7) by BICR.

Median **OS** was 22.8 months (95% CI: 17.5, not estimable).

With regard to claims, due to the single-arm design, among all efficacy endpoints, only ORR can be interpreted in terms of a drug effect. Therefore, only ORR and DOR, as description of the responses, may be presented in the SmPC as claims. OS, PFS and CBR are only presented for descriptive reasons and are excluded as claims of drug effect since highly affected by tumour biology and prognosis, in this case further underscored by the highly exploratory nature of the study. Furthermore, BICR analyses have traditionally been used for non-randomised trials. In order to allow across-product comparison, the BICR results are therefore reflected in a footnote to the efficacy table in the SmPC.

Given the exploratory character of the main study, some of the key issues for the present application concerned the external validity and robustness of the estimate of the primary efficacy outcome. An important issue for the present application concerns the risk of selection bias when a subset of patients from a larger context is selected for market approval, potentially causing an upward bias in the ORR estimate. The ORR for the other monotherapy cohorts were therefore requested and provided. It was notable that the results were better in the chosen primary efficacy population (n=81), with ORR (INV) at 36%, compared with ORRs at 12-14% for Cohorts A, B and MET-1 and 28% for Cohorts C. From this perspective, a potential upward bias is still an uncertainty for the ORR estimate.

Scrutinised from a different perspective, the ORR estimate was found to be very consistent in the three different efficacy data sets available (n=39 at scientific advice, 81, and 144) and by the 4 different DCOs presented, including one in scientific advice. Across these analyses, BICR results (39-43%) were generally somewhat higher than INV results (36-37%).

Analyses to investigate the stability of the ORR estimate showed a numerical decline in estimated ORR assessed by investigator towards the end of the study but a stable estimate for ORR assessed by BICR.

Size of the treatment effect

The reported ORR in second-line patients with NSCLC EFGR Exon20ins is low for an approval based on a single-arm trial. Accepted at face value, the ORR of 37% (95% CI: 28, 46%) would be considered relevant or even "good", however. The DOR of 12 months is furthermore considered a clearly clinically relevant length of time under which disease progression is being delayed and symptoms of disease may potentially be alleviated.

Evidence on EGFR mutated subgroups from the pivotal trials of other drugs, taken together, suggest that ORR in this subpopulation on available treatment alternatives may likely not be more than 20%, and most often less (See AR sections on current management and B/R, respectively).

Subgroups

Subgroup analysis showed activity of amivantamab irrespective of prior immunotherapy, with ORR at 42% and 33% for patients with and without prior immunotherapy, respectively (Figure 12).

Subgroup analysis indicated a possibly relevant difference (16%) in ORR between patients with ECOG performance status 0 and 1, respectively. This could theoretically be affected by line of therapy. No discernible biologically plausible pattern with regard to number of lines were noted, however. ECOG

performance status at baseline was also evaluated as covariate in the E-R analysis for ORR. A trend towards lower probability of response for subjects with ECOG 1 or 2 at baseline, relative to those with ECOG 0, was observed; however, this effect was not statistically significant (for further information, see section 3.3.2 Pharmacodynamics).

Patients with untreated brain metastases were excluded from study participation. Regular follow-up imaging for CNS disease was not required by the protocol and intracranial responses were not assessed. Subjects with a prior history of brain/CNS metastases had similar overall response rate and duration of response as those without.

The Applicant is recommended to submit results from any future data cut-offs from the pivotal Study EDI1001. Considering the maturity of the data submitted from study EDI1001, further analysis are not expected to contribute to the comprehensiveness of the data for Rybrevant.

Supportive studies

In the RWD study, the median OS in the first-line setting was 16.2 months in patients with Exon 20Ins and 25.5 months in patients with common EGFR mutations (cEGFR). This may likely reflect the use of highly potent EGFR-targeted drugs in first-line treatment of cEGFR-positive patients. In addition, it is noted that what would appear to be non-optimal drugs are being used to a non-negligible extent in first-line treatment of Exon 20Ins disease (Table 39). The median PFS on first EGFR TKI was 2.7 months in patients with Exon 20Ins and 10.4 months in patients with common EGFR mutations, consistent with the reported lack of efficacy of approved TKIs in Exon 20Ins disease.

In the RWD study, immunotherapies and non-platinum chemotherapies were mainly used in 2nd and 3rd line treatment of Exon 20Ins disease, alongside platinum-based regimens. Only around 60% of patients with Exon 20Ins disease in the RWD study received a platinum-based chemotherapy regimen as e first-line therapy, which may be the only reasonably active treatment for this subset. The RWD estimations suggest a 2-5-month PFS and 9-14-month OS, in the second-line treatment of NSCLC with EGFR Exon 20ins, using presently approved therapies.

Additional efficacy data needed in the context of a conditional MA

The main limitations in relation to the efficacy of amivantamab are related to the uncontrolled nature of the pivotal study which hampers the assessment of time-dependent endpoints such as PFS and OS. In cases with very high ORRs, the demonstration of such an impact may not be needed. This is not the case with ORR around 35-40%, however. Furthermore, while the ORR has been found stable in multiple DCOs and extensions of the efficacy analysis population to date, the total number of patients is still small (n=114) and a potential selection bias is still a concern.

The Applicant will submit as a specific obligation (SOB) the results of study 61186372NSC3001, a randomized, open-label phase 3 study comparing amivantamab in combination with carboplatin-pemetrexed therapy versus carboplatin-pemetrexed, in advanced or metastatic NSCLC patients with activating EGFR Exon 20 insertion mutations in the first-line setting. Results from this study are intended to provide a comprehensive data package and potentially convert the conditional MA into a full MA.

2.6.7. Conclusions on the clinical efficacy

The number of patients in the pivotal efficacy population is relatively small, with 114 subjects, but the consistence of the ORR estimate across the three consecutively increased efficacy analysis populations available, by four different DCOs, offers sufficient reassurance to allow approval.

Taken together, the reported outcomes of ORR 37% and DOR 12 months are considered compatible with clinical utility for use in the present disease and line of treatment.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

- In order to further confirm the efficacy and safety of amivantamab in the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, the MAH should submit the results of study 61186372NSC3001, a randomized, open-label phase 3 study comparing amivantamab in combination with carboplatin-pemetrexed therapy versus carboplatin-pemetrexed, in advanced or metastatic NSCLC patients with activating EGFR Exon 20 insertion mutations in the first-line setting. The CSR should be submitted by 31 March 2023.

2.6.8. Clinical safety

This MAA is based on a single study, the Phase 1 study EDI1001 (see section on clinical efficacy). Study EDI001 is a single-arm trial, and the safety evaluation must therefore be made without comparator.

The Applicant's Summary of Clinical Safety (SCS) presents safety data primarily from the 362 subjects treated with **amivantamab as monotherapy** in either the dose escalation or dose expansion phases as of **the clinical cut-off date of 08 June 2020**.

During the marketing authorisation application procedure, updated safety data was provided, as of the **clinical cut-off date 30 March, 2021**, which is approximately 10 additional months after the original data cut-off. Unless otherwise specified, the analyses from the updated data cut-off (30 March 2021) are presented below.

2.6.8.1. Patient exposure

Extent and duration of exposure

The safety analysis set included primarily the following subject populations from Study EDI1001 (patient numbers from the updated data cut-off, 30 March 2021):

- **All Treated (n=489)**: In the recently updated safety population with a cutoff of 30 March 2021, 28.8% of the All Treated population remained on treatment with amivantamab and 48.3% were still in the study, the most common reason for treatment discontinuation was still PD (57.7%) (Appendix TSIDS04 and Appendix TSIDS02).
- **All Treated at RP2D (n=380)**: The updated All Treated at RP2D population was similar, with 32.9% of subjects remaining on treatment at the cutoff and 52.4% were still in the study. As with the All Treated population, the most common reason for treatment discontinuation was PD (54.2%) (Appendix TSIDS04 and Appendix TSIDS02).
- **Exon 20ins + prior chemotherapy at RP2D (n=153)**: In the updated safety population 36.6% remained on treatment with amivantamab and 62.1% were still in the study. The percentage of subjects remaining on treatment dropped slightly from that seen with the previous cutoff date (from 57.0% to 36.6%; this reflected the completion of enrolment into this cohort during the interim). The most common reason for discontinuation remained PD (47.7%) (Appendix TSIDS04 and Appendix TSIDS02).

The subject and treatment disposition at the **updated** data cut-off (30 March, 2021) is summarised in Table 40. Treatment duration at data cut-off is summarised in Table 41. A summary of the duration of follow-up is presented in Table 42.

Table 33. Study and Treatment Disposition; All Treated Analysis Set in Monotherapy (data cut-off 30 March, 2021)

	RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	153	380	489
Subjects ongoing	56 (36.6%)	125 (32.9%)	141 (28.8%)
Discontinued study treatment	97 (63.4%)	255 (67.1%)	348 (71.2%)
Reason for discontinuation			
Progressive disease	73 (47.7%)	206 (54.2%)	282 (57.7%)
Adverse event	12 (7.8%)	22 (5.8%)	33 (6.7%)
Withdrawal by subject	7 (4.6%)	12 (3.2%)	17 (3.5%)
Physician decision	2 (1.3%)	9 (2.4%)	9 (1.8%)
Death	3 (2.0%)	6 (1.6%)	7 (1.4%)

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.

Table 34. Summary of Treatment With Study Agent; All Treated Analysis Set in Monotherapy (data cut-off 30 March, 2021)

	RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	153	380	489
Duration of study treatment, months[a]			
N	153	380	489
Mean (SD)	7.283 (5.8124)	6.213 (6.2390)	6.355 (6.5024)
Median	5.552	4.140	4.140
Range	(0.03; 23.89)	(0.03; 39.66)	(0.03; 39.66)
Duration of study treatment, months[a]			
<2	31 (20.3%)	101 (26.6%)	137 (28.0%)
2-<4	26 (17.0%)	88 (23.2%)	107 (21.9%)
4-<6	25 (16.3%)	54 (14.2%)	71 (14.5%)
>=6	71 (46.4%)	137 (36.1%)	174 (35.6%)
Total number of cycles[b]			
N	153	380	489
Mean (SD)	8.5 (6.24)	7.3 (6.74)	7.5 (7.01)
Median	7.0	5.0	5.0
Range	(1; 27)	(1; 43)	(1; 43)

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.
[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.
[b] A subject is considered as treated in a cycle if the subject received any nonzero dose of study agent in that cycle.

Table 35. Summary of Duration of Follow-up; All Treated Analysis Set in Monotherapy

	RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	114	258	362
Duration of follow-up (months)			
N	114	258	362
Mean (SD)	6.533 (5.2671)	7.991 (6.4457)	8.161 (6.1641)
Median	5.076	6.127	6.587
Range	(0.23; 29.27)	(0.23; 33.61)	(0.07; 33.61)

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: Duration of follow-up is the duration of first dosing date to the end of follow-up. The end of follow-up is the date of death for subjects who died. For those who are still alive, the end of follow-up is defined as the maximum date of the study assessment/evaluations and the date of last known to be alive.

Demographics and baseline disease characteristics

Demographic and baseline characteristics were consistent across safety analysis populations.

Prior and concomitant medications

Prior and concomitant medications were as expected for the subject population and were consistent across analysis populations.

Pre- and post-infusion treatment was administered to prevent and treat infusion-related reactions (IRRs). This is further described below.

Other than pre- or post-infusion medications, the most common (≥30%) types of concomitant medications used (ATC Level 4 category) in the All Treated population were systemic glucocorticoids, tetracycline antibiotics, anilide analgesics (eg, paracetamol), natural opioid alkaloids, and proton pump inhibitors.

2.6.8.2. Adverse events

Safety monitoring was the same for both Part1 and Part 2 of study EDI1001, and included evaluation of adverse events (AEs) and laboratory abnormalities (haematology, clinical chemistry), which were graded per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03. Other safety measures include monitoring of vital signs (temperature, pulse rate, blood pressure, respiratory rate, pulse oximetry), ECGs, and physical examinations.

All AEs whether serious or non-serious, were reported from the time a signed and dated ICF 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, stabilised, or was deemed irreversible, the subject died, or subsequent anti-cancer therapy was started, whichever occurred first. Adverse events occurring >30days following the last dose of study drug (and their resolution) were also to be reported if the investigator considered them related to study drug.

Common adverse events

In addition to infusion related reactions (IRR), the safety profile of amivantamab was consistent with EGFR and MET inhibition. The main reported AEs were therefore IRR, dermatitis, paronychia and rash, none of which was dose limiting and were primarily Grade 1 or 2 in severity.

The safety profile of amivantamab monotherapy in the All treated at RP2D population and Exon 20ins + prior chemotherapy at RP2D population are consistent with All Treated population.

Table 43 presents an overall summary of treatment-emergent adverse events (TEAEs) in the safety populations at both data cut-offs. Of the 489 subjects in the All Treated population, all but 2 subjects experienced TEAEs and most subjects (96.3%) had at least 1 TEAE considered by the investigator to be related to amivantamab. A consistent overall safety profile for amivantamab monotherapy was observed among subjects in the All Treated at RP2D population and subjects in the Exon 20ins + prior chemotherapy at RP2D population comparted to the All Treated population. Table 44 summarises the most common TEAEs (listed by **frequency of 10% or higher)** in any of the three safety populations at the data cut-off 30 March, 2021.

Covid-19

There were five COVID-19-related TEAEs reported in the All Treated population, were all non-serious.

Table 36. Overall Summary of Treatment-emergent Adverse Events; All Treated Analysis Set in Monotherapy

	30 March 2021 Cutoff			08 June 2020 Cutoff		
	RP2D			RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All Treated in Monotherapy (JNJ-61186372)	153	380	489	114	258	362
Subjects with 1 or more:						
AEs	153 (100.0%)	378 (99.5%)	487 (99.6%)	113 (99.1%)	257 (99.6%)	361 (99.7%)
Related AEs [a]	150 (98.0%)	365 (96.1%)	471 (96.3%)	112 (98.2%)	247 (95.7%)	348 (96.1%)
AEs leading to death [b]	11 (7.2%)	20 (5.3%)	23 (4.7%)	8 (7.0%)	13 (5.0%)	16 (4.4%)
Related AEs leading to death [a,b]	0	0	0	0	0	0
Serious AEs	44 (28.8%)	111 (29.2%)	141 (28.8%)	34 (29.8%)	79 (30.6%)	102 (28.2%)
Related serious AEs [a]	13 (8.5%)	18 (4.7%)	27 (5.5%)	10 (8.8%)	13 (5.0%)	20 (5.5%)
AEs leading to discontinuation of study agent	18 (11.8%)	26 (6.8%)	39 (8.0%)	11 (9.6%)	17 (6.6%)	29 (8.0%)
Related AEs leading to discontinuation of study agent [a]	8 (5.2%)	12 (3.2%)	21 (4.3%)	5 (4.4%)	8 (3.1%)	17 (4.7%)
AEs leading to dose reduction	22 (14.4%)	39 (10.3%)	59 (12.1%)	15 (13.2%)	26 (10.1%)	43 (11.9%)
Related AEs leading to dose reduction [a]	22 (14.4%)	39 (10.3%)	59 (12.1%)	15 (13.2%)	26 (10.1%)	43 (11.9%)
AEs leading to infusion modification [c]	91 (59.5%)	246 (64.7%)	304 (62.2%)	70 (61.4%)	158 (61.2%)	215 (59.4%)
Related AEs leading to infusion modification [a, c]	90 (58.8%)	243 (63.9%)	301 (61.6%)	69 (60.5%)	156 (60.5%)	213 (58.8%)
AEs leading to dose interruption [d]	55 (35.9%)	129 (33.9%)	155 (31.7%)	40 (35.1%)	88 (34.1%)	108 (29.8%)
Related AEs leading to dose interruption [a, d]	32 (20.9%)	64 (16.8%)	82 (16.8%)	24 (21.1%)	47 (18.2%)	59 (16.3%)
Grade >=3 AEs	64 (41.8%)	155 (40.8%)	199 (40.7%)	40 (35.1%)	101 (39.1%)	139 (38.4%)
Related grade >=3 AEs [a]	30 (19.6%)	58 (15.3%)	78 (16.0%)	18 (15.8%)	36 (14.0%)	53 (14.6%)
Maximum severity of any AE						
Grade 1	4 (2.6%)	21 (5.5%)	24 (4.9%)	1 (0.9%)	12 (4.7%)	14 (3.9%)
Grade 2	85 (55.6%)	202 (53.2%)	264 (54.0%)	72 (63.2%)	144 (55.8%)	208 (57.5%)
Grade 3	49 (32.0%)	126 (33.2%)	164 (33.5%)	31 (27.2%)	83 (32.2%)	115 (31.8%)
Grade 4	4 (2.6%)	9 (2.4%)	12 (2.5%)	1 (0.9%)	5 (1.9%)	8 (2.2%)
Grade 5	11 (7.2%)	20 (5.3%)	23 (4.7%)	8 (7.0%)	13 (5.0%)	16 (4.4%)
COVID-19 related AEs	3 (2.0%)	4 (1.1%)	5 (1.0%)	1 (0.9%)	1 (0.4%)	1 (0.3%)
COVID-19 related serious AEs	0	0	0	0	0	0
COVID-19 related non-serious AEs	3 (2.0%)	4 (1.1%)	5 (1.0%)	1 (0.9%)	1 (0.4%)	1 (0.3%)

a An AE is categorized as related if assessed by the investigator as possibly, probably, or very likely related to study agent.
b AEs leading to death are based on AE outcome of Fatal.
c AEs leading to infusion modification of study agent are based on infusion interrupted, infusion rate decreased, and infusion aborted due to adverse event on the infusion eCRF page.
d Excludes infusion related reactions.

Table 37. Number of Subjects With Treatment- emergent Adverse Events With Frequency of at Least 10% in the RP2D Group by System Organ Class and Preferred Term; All Treated Analysis Set in Monotherapy (data cut-off 30 March, 2021)

	RP2D		
	Exon 20 Ins Prior Chemotherapy	Total	Total
Analysis set: All treated in monotherapy (JNJ-61186372)	153	380	489
Subjects with 1 or more AEs	153 (100.0%)	378 (99.5%)	487 (99.6%)
Skin and subcutaneous tissue disorders	136 (88.9%)	304 (80.0%)	387 (79.1%)
Rash	66 (43.1%)	136 (35.8%)	174 (35.6%)
Dermatitis acneiform	60 (39.2%)	133 (35.0%)	169 (34.6%)
Pruritus	24 (15.7%)	68 (17.9%)	89 (18.2%)
Dry skin	21 (13.7%)	48 (12.6%)	58 (11.9%)
Injury, poisoning and procedural complications	102 (66.7%)	269 (70.8%)	343 (70.1%)
Infusion related reaction	97 (63.4%)	256 (67.4%)	326 (66.7%)
Gastrointestinal disorders	114 (74.5%)	265 (69.7%)	334 (68.3%)
Nausea	38 (24.8%)	88 (23.2%)	110 (22.5%)
Constipation	36 (23.5%)	86 (22.6%)	111 (22.7%)
Stomatitis	34 (22.2%)	77 (20.3%)	96 (19.6%)
Vomiting	21 (13.7%)	46 (12.1%)	57 (11.7%)
Diarrhoea	21 (13.7%)	42 (11.1%)	54 (11.0%)
Infections and infestations	107 (69.9%)	232 (61.1%)	295 (60.3%)
Paronychia	81 (52.9%)	164 (43.2%)	208 (42.5%)
Metabolism and nutrition disorders	92 (60.1%)	209 (55.0%)	262 (53.6%)
Hypoalbuminaemia	60 (39.2%)	115 (30.3%)	149 (30.5%)
Decreased appetite	27 (17.6%)	59 (15.5%)	76 (15.5%)
Hypocalcaemia	16 (10.5%)	38 (10.0%)	53 (10.8%)
Respiratory, thoracic and mediastinal disorders	88 (57.5%)	209 (55.0%)	260 (53.2%)
Dyspnoea	30 (19.6%)	75 (19.7%)	94 (19.2%)
Cough	26 (17.0%)	62 (16.3%)	77 (15.7%)
General disorders and administration site conditions	96 (62.7%)	207 (54.5%)	262 (53.6%)
Oedema peripheral	35 (22.9%)	80 (21.1%)	100 (20.4%)
Fatigue	30 (19.6%)	73 (19.2%)	100 (20.4%)
Pyrexia	26 (17.0%)	41 (10.8%)	46 (9.4%)
Musculoskeletal and connective tissue disorders	73 (47.7%)	166 (43.7%)	208 (42.5%)
Back pain	25 (16.3%)	51 (13.4%)	64 (13.1%)
Myalgia	18 (11.8%)	41 (10.8%)	52 (10.6%)
Investigations	63 (41.2%)	142 (37.4%)	176 (36.0%)
Alanine aminotransferase increased	34 (22.2%)	56 (14.7%)	73 (14.9%)
Aspartate aminotransferase increased	25 (16.3%)	49 (12.9%)	62 (12.7%)
Blood alkaline phosphatase increased	16 (10.5%)	44 (11.6%)	57 (11.7%)
Nervous system disorders	50 (32.7%)	128 (33.7%)	168 (34.4%)
Dizziness	18 (11.8%)	44 (11.6%)	59 (12.1%)
Headache	11 (7.2%)	39 (10.3%)	56 (11.5%)
Blood and lymphatic system disorders	36 (23.5%)	80 (21.1%)	101 (20.7%)
Anaemia	20 (13.1%)	44 (11.6%)	53 (10.8%)

Psychiatric disorders	29 (19.0%)	77 (20.3%)	97 (19.8%)
Insomnia	16 (10.5%)	42 (11.1%)	56 (11.5%)

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.

Adverse Drug Reactions for labelling

The All Treated at RP2D population (n=380) with a data cut-off date of 30 March 2021 was used as basis when considering AEs for inclusion in the label (section 4.8 of the SmPC).

- All TEAEs reported in ≥10% of subjects were considered to have met the ADR threshold, except the PTs that are consistent with signs and/or symptoms of the underlying disease
- 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. One of the 3 criteria listed below was used:
    - TEAEs with ≥10% incidence, or
    - Laboratory abnormalities (≥ 20%) that worsened from baseline and demonstrated consistent up or down trend based on mean values over time, or
    - Had biological plausibility and demonstrated consistent up or down trend based on mean values over time
- Similar medical concepts were grouped by MedDRA PTs.

Table 45 summarizes the adverse drug reactions that occurred in patients receiving amivantamab (section 4.8 of the SmPC).

The data reflects exposure to amivantamab in 380 patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based chemotherapy. Patients received amivantamab 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg). The median exposure to amivantamab was 4.1 months (range: 0.0 to 39.7 months).

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 38. Adverse drug reactions for amivantamab

System organ class Adverse reaction	**Frequency category**	**Any Grade (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders			
Hypoalbuminaemia[a] (see section 5.1)	Very common	31	2*
Decreased appetite		16	0.5*

Hypocalcaemia		10	0.3*
Nervous system disorders			
Dizziness[b]	Very common	13	0.3*
Eye disorders			
Visual impairment[c]	Common	3	0
Growth of eyelashes[d]		1	0
Other eye disorders[e]		6	0
Keratitis	Uncommon	0.5	0
Uveitis		0.3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease[f]	Common	3	0.5*
Gastrointestinal disorders			
Diarrhoea	Very common	11	2*
Stomatitis[g]		24	0.5*
Nausea		23	0.5*
Constipation		23	0
Vomiting		12	0.5*
Abdominal pain[h]	Common	9	0.8*
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	15	2
Aspartate aminotransferase increased		13	1
Blood alkaline phosphatase increased		12	0.5*
Skin and subcutaneous tissue disorders			
Rash[i]	Very common	76	3*
Nail toxicity[j]		47	2*
Dry skin[k]		19	0
Pruritus		18	0
Toxic epidermal necrolysis	Uncommon	0.3	0.3*
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	11	0.3*
General disorders and administration site conditions			
Oedema[l]	Very common	26	0.8*
Fatigue[m]		26	0.8*
Injury, poisoning and procedural complications			
Infusion-related reaction	Very common	67	2

* Grade 3 events only

[a] Hypoalbuminaemia: blood albumin decreased, hypoalbuminaemia

[b] Dizziness: dizziness, dizziness exertional, vertigo

[c] Visual impairment: vision blurred, visual acuity reduced, visual impairment

[d] Growth of eyelashes: growth of eyelashes, trichomegaly

[e] Other eye disorders: blepharitis, conjunctival hyperaemia, corneal irritation, dry eye, episcleritis, eye disorder, eye pruritus, noninfective conjunctivitis, ocular hyperaemia

[f] Interstitial lung disease: interstitial lung disease, pneumonitis

[g] Stomatitis: aphthous ulcer, cheilitis, glossitis, lip ulceration, mouth ulceration, mucosal inflammation, stomatitis

[h] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort, gastrointestinal pain

[i] Rash: acne, dermatitis, dermatitis acneiform, erythema, erythema multiforme, folliculitis, impetigo, palmar-plantar erythrodysaesthesia syndrome, perineal rash, perioral dermatitis, pustule, rash, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pruritic, rash pustular, rash vesicular, skin exfoliation, skin lesion

[j] Nail toxicity: ingrowing nail, nail bed infection, nail cuticle fissure, nail disorder, nail ridging, onychoclasis, onycholysis, paronychia

[k] Dry skin: dry skin, eczema, eczema asteatotic, skin fissures, xeroderma

[l] Oedema: eye oedema, eyelid oedema, face oedema, generalised oedema, localised oedema, oedema, oedema peripheral, periorbital oedema, periorbital swelling, peripheral swelling, swelling face

[m] Fatigue: asthenia, fatigue

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Deaths occurring within the treatment phase (up through 30 days after last dose) and reported as Grade 5 AEs were infrequent in all 3 analysis populations (4.7% in All Treated, 5.3% in All Treated at RP2D, and 7.2% in Exon 20ins + prior chemotherapy at RP2D), there was no trend to the TEAEs leading to death, and all events were reported by the investigator as being unrelated to amivantamab.

Treatment-emergent Serious Adverse Events

A total of 141 (28.8%) subjects in the All Treated population had a serious TEAE (including the fatal events, discussed above). The most common SAEs were pneumonia and dyspnoea . All reported serious events of pneumonia and dyspnoea were assessed as *unrelated* by the investigator.

There were 12 Grade 4 serious TEAEs in this population (dyspnoea, pulmonary embolism, pneumonia, IRR, brain oedema). There were 23 Grade 5 serious TEAEs. As described above, all Grade 5 TEAEs were considered unrelated to amivantamab.

Serious TEAEs in the All Treated population that were suggested as related to amivantamab included IRR, pneumonitis, rash, dermatitis acneiform, diarrhoea, and interstitial lung disease, pulmonary embolism, cellulitis, impetigo, infected dermal cyst, toxic epidermal necrolysis, vomiting, atrial flutter, pericardial effusion, myalgia, conjunctival granuloma, fatigue.

2.6.8.4. Adverse events leading to dose modifications

Dose reductions

Dose reduction due to an AE was made in 12.1% of subjects in the All treated population. Among the 151 subjects in the Exon 20 Ins + Prior Chemotherapy group (target population), treated at the RP2D, dose reductions due to AE were made in 22 subjects (14.4%). TEAEs within the grouped term Rash (See Adverse events of special interest below) were the most common events leading to dose modification in all three safety analysis populations. Of note, the study protocol recommended that investigators consider dose reduction at a Grade 2 AE within the grouped term "Rash".

Dose interruptions

Treatment-emergent AEs leading to drug interruption includes AEs (other than IRRs) 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).

A total of 155 subjects (31.7%) in the All Treated population had a TEAE (other than IRR) that resulted in dose interruption through the clinical cutoff. Dose interruption due to events that were considered related to amivantamab were made in 82 subjects (16.8%).

There were 36 patients (9.5%) who had both a dose interruption and a dose reduction.

Infusion modifications

A total of 304 subjects (62.2%) in the All Treated population had a TEAE that resulted in infusion modification through the clinical cutoff, with the predominant of these TEAEs being IRR (reported for 301 subjects). Almost all IRRs occurred during the Cycle 1, Day 1 infusion.

IRRs are discussed in more detail below.

2.6.8.1. Discontinuation due to adverse events

A total of 39 subjects (8.0%) in the All Treated population had a TEAE leading to treatment discontinuation and in 21 subjects (4.3%), the TEAE was assessed as related to amivantamab, including: IRRs (8 subjects, 1.6%); pneumonitis (3 subjects, 0.6%); paronychia and stomatitis (2 subjects each, 0.4%); and skin laceration, dyspnoea, pulmonary embolism, dermatitis acneiform, toxic epidermal necrolysis, hypoalbuminemia, asthenia, myalgia, and akathisia (1 subject each, 0.2%).

Events considered not related included pneumonia, other infections, pleural effusion, and single events of muscular weakness, musculoskeletal chest pain, CNS haemorrhage and hypotension.

The overall frequencies of TEAEs leading to discontinuation (any event and related events) in the All Treated at RP2D and Exon 20ins + prior chemotherapy at RP2D treated populations were consistent with that reported for the All Treated population.

The incidence and nature of TEAEs leading to treatment discontinuation was also consistent across the updated safety population (30 March 2021) and the MAA safety population (8 June, 2020).

Adverse events of special interest

The Applicant considered the following adverse events as being of specific clinical importance:

- rash (grouped term), class effect of EGFR inhibitors
- IRR, known effect at infusion of antibody treatment
- peripheral oedema (grouped term), class effect of MET inhibitors
- ILD (grouped term), an effect associated with EGFR inhibitors

These events were reported in 76.5%, 64.4%, 19.3%, and 2.8% of subjects in the All Treated population and 86.0%, 65.8%, 19.3%, and 4.4% of subjects in the Exon 20ins + prior chemotherapy at RP2D population, respectively.

In addition, the following additional EGFR-mediated events were specifically discussed:

- Paronychia
- Diarrhoea
- Eye disorders

Infusion-related reactions (IRRs)

IRRs were reported for 67% of subjects in the **All Treated population,** with 2.0% of subjects experiencing events of Grade 3 or higher. Serious IRR events occurred in 6 subjects (1.2%).

In general, these events (characterised predominantly by symptoms of dyspnoea, flushing, chills, nausea, chest discomfort, and vomiting) were of mild or moderate severity, non-serious and not treatment-limiting. There were no Grade 5 events.

In total, 66% of subjects experienced an IRR on Week 1 Day 1, 3.9% of subjects experienced an IRR with the Day 2 infusion, 1.5% of subjects experienced an IRR with the Day 8 infusion, and cumulatively 1.5% with subsequent infusions. The median time to onset was 60 minutes after start of first infusion.

Most IRRs were managed with a modification of the ongoing infusion, and few required post-infusion treatments. The incidence of infusion modifications due to IRR was 62% and 1.6% of subjects permanently discontinued amivantamab due to IRR. No subject had dose reduction due to IRR.

IRRs were prophylactically managed through use of split dosing of the first dose (Cycle 1) over Days 1 and 2 and the administration of select drugs. Furthermore, algorithms were provided to the investigators to assist in the management of any IRRs that did occur during or after infusion.

Rash TEAEs (Grouped Term)

In the **All treated safety population (n=489)**: Rash events (grouped term) were the most common category of TEAEs reported in All Treated population (75.1%), with rash (35.6%) and dermatitis acneiform (34.6%), being the most frequent specific events observed. In general, the majority of the rash events were of Grade 1 or 2 severity and non-serious; 18 (3.7%) subjects experienced an event with the highest grade of Grade 3. Four (0.8%) subjects had serious rash events.

The median time to onset of rash was 14 days.

Rash leading to dose reduction occurred in 1.6% of subjects, and study drug was permanently discontinued due to dermatitis acneiform in 0.2% of subjects. A case of serious toxic epidermal necrolysis (TEN) occurred in 1 subject (0.2%).

Interstitial Lung Disease (Grouped Term)

Thirteen subjects (2.7%) in the **All Treated population** had treatment-emergent ILD events. Three (0.6%) and 7 (1.4%) subjects experienced Grade 3 and serious ILD/pneumonitis events, respectively.

Peripheral Oedema

Peripheral oedema TEAEs (grouped term) were reported for 22% of subjects. Grade 1 was reported in 16% of subjects. Twenty-four (4.9%) subjects experienced an event with the highest grade of Grade 2 and four (0.8%) subjects experienced an event with the highest grade of Grade 3. There were no peripheral oedema SAEs. For almost all events amivantamab dose remained unchanged (there were 2 events where the dose was reduced); no subjects discontinued due to peripheral oedema.

Paronychia

Paronychia occurred in 42.5% (208 subjects) of the All treated population. Most events were Grades 1 or 2, with Grade 3 paronychia occurring in 10 (2.0%) subjects. Paronychia led to discontinuation of study agent in 2 subjects (0.4%). None of the events were serious.

Diarrhoea

Diarrhoea occurred in 11% of the **All Treated population**. Most events were Grade 1 or 2. Seven subjects had Grade 3 events. Two subjects experienced events of serious diarrhoea for which they were hospitalised and amivantamab was interrupted. One of these subjects was experiencing ongoing diarrhoea at the end of study (treatment discontinuation). Both of these subjects were in the Exon 20ins + prior chemotherapy at RP2D population.

Eye Disorders

Eye disorders occurred in 12% of the **All Treated population**. The most frequently reported TEAEs were dry eye (3.3%), vision blurred (1.2%), and eye pruritis (1.2%). Keratitis occurred at a frequency of 0.5% (2 subjects), with one event considered related to amivantamab by the investigator and which led to amivantamab dose interruption. All events were Grade 1-2, except 1 event of vision blurred was Grade 3. Three subjects experienced events of serious eye disorders including retinal artery occlusion,

conjunctival granuloma and vision blurred. One event of vision blurred led to discontinuation of study agent.

2.6.8.2. Laboratory findings

Note: Laboratory findings are reported based on data provided in the original MAA submission (data cut-off 8 June, 2020). The updated data from the cutoff 30 March 2021 were overall in agreement with the originally presented data.

For haematology parameters (haemoglobin, leukocytes, lymphocytes, neutrophils, platelets) and clinical chemistry parameters, the worst on treatment toxicity grades in the All treated population are summarised in Table 46.

Grade 3 haematology laboratory abnormalities during the study were infrequent (<3%) except for low lymphocyte counts, where Grade 3 abnormalities were observed for 34 subjects (9.6%). Of these 34 subjects, 27 had a shift from Grade 0, 1, or 2 at baseline to Grade 3 on treatment. The overall trend was, however, a small increase in mean lymphocyte count from baseline over time. Lymphopenia was reported as AE in 3.6% of the All treated population but was, by the investigator, suggested related to amivantamab in only 1.4%.

Hypoalbuminaemia and increased aminotransferases are further discussed below.

Table 39. Summary of Chemistry and Haematology Worst US NCI-CTCAE Toxicity Grade During Treatment Period (data cut-off 8 June, 2020)

	Total					
		Worst US NCI-CTCAE Toxicity Grade During the Treatment Period				
	N	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Analysis set: All treated in monotherapy (JNJ-61186372)	362					
Chemistry						
Alanine Aminotransferase Increased	354	212 (59.9%)	123 (34.7%)	12 (3.4%)	6 (1.7%)	1 (0.3%)
Alkaline Phosphatase Increased	354	132 (37.3%)	184 (52.0%)	29 (8.2%)	8 (2.3%)	1 (0.3%)
Aspartate Aminotransferase Increased	354	218 (61.6%)	132 (37.3%)	1 (0.3%)	3 (0.8%)	0
Blood Bilirubin Increased	354	347 (98.0%)	3 (0.8%)	3 (0.8%)	1 (0.3%)	0
CPK Increased	352	317 (90.1%)	26 (7.4%)	8 (2.3%)	1 (0.3%)	0
Creatinine Increased	354	156 (44.1%)	194 (54.8%)	4 (1.1%)	0	0
GGT Increased	352	189 (53.7%)	114 (32.4%)	28 (8.0%)	21 (6.0%)	0
Hyperglycemia	354	78 (22.0%)	197 (55.6%)	60 (16.9%)	16 (4.5%)	3 (0.8%)
Hyperkalemia	353	300 (85.0%)	36 (10.2%)	12 (3.4%)	4 (1.1%)	1 (0.3%)
Hypermagnesemia	353	332 (94.1%)	18 (5.1%)	0	3 (0.8%)	0
Hypernatremia	353	329 (93.2%)	24 (6.8%)	0	0	0
Hyperuricemia	353	326 (92.4%)	22 (6.2%)	0	0	5 (1.4%)
Hypoalbuminemia	354	52 (14.7%)	106 (29.9%)	183 (51.7%)	13 (3.7%)	0
Hypoglycemia	354	313 (88.4%)	36 (10.2%)	5 (1.4%)	0	0
Hypokalemia	353	276 (78.2%)	0	70 (19.8%)	6 (1.7%)	1 (0.3%)
Hypomagnesemia	353	243 (68.8%)	105 (29.7%)	4 (1.1%)	1 (0.3%)	0
Hyponatremia	353	229 (64.9%)	112 (31.7%)	0	11 (3.1%)	1 (0.3%)
Hypophosphatemia	354	258 (72.9%)	7 (2.0%)	74 (20.9%)	15 (4.2%)	0
Hematology						
Anemia	354	171 (48.3%)	150 (42.4%)	28 (7.9%)	5 (1.4%)	0
Hemoglobin Increased	354	327 (92.4%)	26 (7.3%)	1 (0.3%)	0	0
Leukocytosis	354	354 (100.0%)	0	0	0	0
Lymphocyte Count Decreased	354	175 (49.4%)	54 (15.3%)	90 (25.4%)	34 (9.6%)	1 (0.3%)
Lymphocyte Count Increased	354	335 (94.6%)	0	19 (5.4%)	0	0
Neutrophil Count Decreased	343	278 (81.0%)	33 (9.6%)	25 (7.3%)	6 (1.7%)	1 (0.3%)
Platelet Count Decreased	354	302 (85.3%)	50 (14.1%)	1 (0.3%)	0	1 (0.3%)
White Blood Cell Decreased	354	281 (79.4%)	45 (12.7%)	26 (7.3%)	2 (0.6%)	0

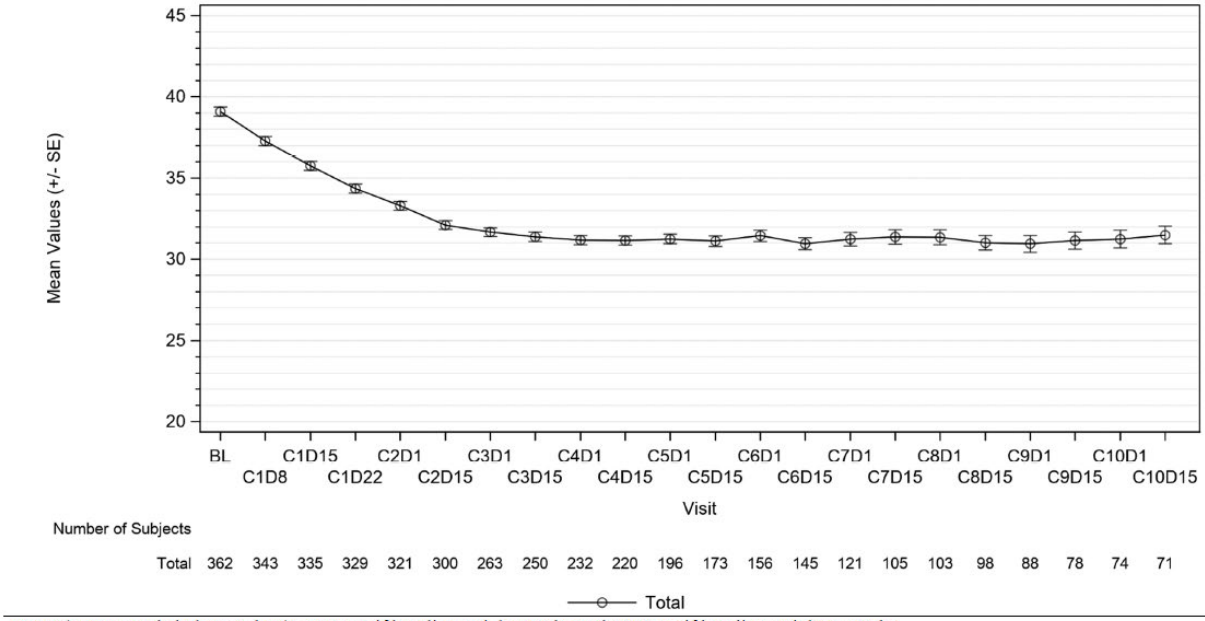
RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Prior Chemotherapy: subjects whose disease progressed on or after platinum-based chemotherapy.
Key: NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events
Note: N is the number of subjects with at least 1 postbaseline assessment for the specific lab test within the time period.

Hypoalbuminaemia

Hypoalbuminemia is a suspected consequence of the MET inhibition effect on hepatocyte protein synthesis. Albumin is the predominate protein that regulates the osmotic pressure in the blood vessels. Thus, when decreased albumin levels may result in peripheral oedema.

In Study EDI1001 the serum albumin levels over time on treatment 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 stabilise for the remainder of the time on treatment (Figure 20).

Hypoalbuminemia AEs were reported for 149 subjects (30.5%) in the All Treated population, 115 subjects (30.3%) in the All Treated at RP2D population and 60 subjects (39.2%) in the Exon 20ins + prior chemotherapy at RP2D treated population (Table 44; March 2021 cutoff). Hypoalbuminemia laboratory values were mostly Grade 1 or 2. Grade 3 hypoalbuminemia was experienced by 13 subjects (3.7%) in the All treated population. No subjects had Grade 4 hypoalbuminemia.



RP2D (recommended Phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight >= 80 kg.
Key: BL = baseline, C = cycle, D = day
Note: N is the number of subjects with non-missing values for the specific lab test at baseline and at each postbaseline visit within the time period.

Figure 18. Mean (+/- SE) Values for Albumin (g/L) Over Time Through Cycle 10; All Treated Analysis Set in Monotherapy (data cut-off 8 June, 2020)

Hepatoxicity (Increased Aminotransferases)

EGFR and MET signalling play complex and important roles in the maintenance of hepatic liver repair and regeneration. Aminotransferase elevations, including rare reports of hepatic failure with fatal outcomes, have been observed with the small-molecule EGFR tyrosine inhibitors.

Elevations of ALT and AST were observed during amivantamab treatment (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 (Table 46).

The majority of cases were Grade 1. The more serious cases described by the Applicant had other possible explanations (liver metastases, cholelithiasis).

Electrocardiograms

Within each treated population, approximately 65% of subjects with baseline ECG data had corresponding ECG data for the Cycle 2, Day 1 pre-dose timepoint and approximately 12 to 16% of subjects had corresponding ECG data for the Cycle 2, Day 1 post-dose timepoint (representing Cmax). Mean and median changes from baseline in all three treated populations were not considered clinically meaningful.

2.6.8.3. Safety in special populations

Age

In the All Treated population, subjects <65 years and 65 to 74 years of age accounted for 58.7% and 29.9%, respectively. Subjects 75 to 84 years and 85+ years of age accounted for 10.9% (N=53) and 0.6% (N=3), respectively, in the All Treated population. Interpretation of potential differences in safety profiles using subjects 75 to 84 years of age and those 85+ years was difficult due to small sample size and lack of a comparator group.

The overall TEAE profile among subjects <65 and those 65 to 74 years of age in the All Treated population was generally similar. There was no apparent difference in the overall frequency of TEAEs; related TEAEs; Grade 3 or higher TEAEs; or TEAEs leading to dose reduction, infusion modification, discontinuation, or death as a function of age for this population (difference in frequency <10%).

Although there was a higher incidence (difference >10%) of TEAEs leading to dose interruption and serious TEAEs among the 65 to 74 years subgroup compared with the <65 years subgroup, the incidence of related TEAEs leading to dose interruption and related serious TEAEs was similar (difference <10%).

MedDRA Terms	Age <65 number (percentage)	Age 65-74 number (percentage)	Age 75-84 number (percentage)	Age 85+ number (percentage)
Analysis set: All treated in monotherapy (JNJ-61186372)	287	146	53	3
Total AEs	286 (99.7%)	145 (99.3%)	53 (100.0%)	3 (100.0%)
Serious AEs – Total	67 (23.3%)	50 (34.2%)	22 (41.5%)	2 (66.7%)
- Fatal	12 (4.2%)	6 (4.1%)	5 (9.4%)	0
- Hospitalization/	61 (21.3%)	45 (30.8%)	18 (34.0%)	2 (66.7%)
Prolong existing hospitalization	15 (5.2%)	4 (2.7%)	1 (1.9%)	0
- Life-threatening	3 (1.0%)	2 (1.4%)	3 (5.7%)	0
- Disability/incapacity	1 (0.3%)	1 (0.7%)	0	0
- Other (medically significant)	4 (1.4%)	4 (2.7%)	5 (9.4%)	0
AE leading to drop-out	17 (5.9%)	15 (10.3%)	7 (13.2%)	0
Psychiatric disorders	59 (20.6%)	29 (19.9%)	9 (17.0%)	0
Nervous system disorders	99 (34.5%)	55 (37.7%)	13 (24.5%)	1 (33.3%)
Accidents and injuries	17 (5.9%)	20 (13.7%)	7 (13.2%)	0
Cardiac disorders	30 (10.5%)	20 (13.7%)	6 (11.3%)	0
Vascular disorders	50 (17.4%)	25 (17.1%)	15 (28.3%)	0
Cerebrovascular disorders	0	2 (1.4%)	2 (3.8%)	0
Infections and infestations	168 (58.5%)	93 (63.7%)	32 (60.4%)	2 (66.7%)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased				
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	39 (13.6%)	33 (22.6%)	7 (13.2%)	0
<other AE appearing more frequently in older patients>	N/A	N/A	N/A	N/A

Sex

Women represented 63% of the All Treated population. The overall TEAE profile in men and women was generally similar. There was higher frequency of rash among men (>10% difference). Among individual common TEAEs (>20% in either sex) dermatitis acneiform was reported at higher frequency in men (men 40.9% and women 30.8%).

The difference between women and men for Grade 3 or higher TEAEs was < 5% (42.5% for women and 37.6% for men). Furthermore, the frequency of related Grade 3 or higher TEAEs remained similar for both sexes.

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).

Race

Race was reported for 94.5% of subjects; 61% of the population was Asian.

The frequencies of Grade 3 or higher TEAEs and related Grade 3 or higher AEs, as well as TEAEs leading to dose reduction (including related dose reduction), dose interruption, or infusion modification (including related infusion modification) were consistently higher for the non-Asian subgroup compared with the Asian subgroup in the All Treated population (differences of 10% or higher). Data did, however, not reveal any single AE or cluster of AEs accounting for the observed differences between Asian and non- Asian subjects.

Among the most commonly reported TEAEs, 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. Other common (>20% in either racial subgroup) TEAEs for which there was a reporting difference (>10%) were fatigue, nausea, dizziness, and vomiting, all of which were reported at higher frequencies in non-Asian compared with Asian subjects.

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).

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.

Renal Impairment

No formal studies of amivantamab in patients with renal impairment have been conducted. In the 3 All Treated population, approximately half of the patients had normal baseline renal function. Of the remaining subjects, most had mild renal impairment, and a few had moderate renal impairment.

There was no apparent difference in the overall frequency of TEAEs, related TEAEs, or TEAEs leading to dose reduction, infusion modification, discontinuation, or death between subjects with normal renal function and those with mild or moderate renal impairment (difference in frequency <10%). However, the frequency of Grade 3 or higher TEAEs, related Grade 3 or higher TEAEs, and serious TEAEs was higher in subjects with moderate renal impairment compared with those with normal renal function or mild renal impairment. The frequency of subjects with dose interruption was higher in subjects with moderate renal impairment compared with those with normal renal function.

Given the large molecular mass of amivantamab (~148kD), its clearance is not anticipated to be affected by decreased renal function. No dosage adjustment is considered necessary for impaired patients with mild to moderately decreased renal function.

Hepatic Impairment

No formal studies of amivantamab in patients with hepatic impairment have been conducted. Amivantamab clearance is not anticipated to be affected by decreased hepatic function. In the All Treated population, most subjects had normal baseline hepatic function (total bilirubin ≤ ULN and AST ≤ ULN). The number of subjects with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5× ULN) was approximately 10% at baseline.

There was no apparent difference in the overall frequency of TEAEs, related TEAEs, TEAEs with an outcome of death, Grade 3 or higher TEAEs, serious TEAEs, or TEAEs leading to dose reduction, infusion modification, dose interruption, or discontinuation of study agent between subjects with normal hepatic function and mild hepatic impairment (difference in frequency <10%).

2.6.8.4. Immunological events

Immunogenicity

In the All Treated population, 347 subjects had at least 1 post baseline sample. Of these, only 3 (1.0%) subjects were considered positive for antibodies to amivantamab post-dose. One subject who received 350 mg of amivantamab had a titer of 1:10 at their follow up visit, 168 days after the first amivantamab administration. Another subject who received 1400 mg amivantamab had a 1:20 titer 59 days after the first amivantamab administration. Another subject who received 1400 mg amivantamab had a 1:40 titer 27 days after the first amivantamab administration.

The shape of the serum concentration-time profiles of the antibodies to amivantamab-positive subjects was consistent with the serum concentration-time profiles of the antibodies to amivantamab-negative subjects. There was no apparent association between the development of antibodies to antibody and the development of IRR.

The small number of subjects in each group of antibody titer level precludes drawing a definite conclusion regarding the impact of antibody titer levels on the clinical efficacy and safety of amivantamab.

2.6.8.5. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction studies have been performed with amivantamab.

Dose-finding results (Part 1 of Study EDI1001)

The safety analysis set from part I, the dose-finding part of the study, included a total of 77 subjects who received at least one dose of amivantamab. The maximum administered dose for amivantamab monotherapy in Part 1 was 1750 mg. No dose-limiting toxicity was identified up to the 1400 mg amivantamab dose in Korea. One of the initial US subjects in the 1050 mg dose cohort experienced a Grade 3 toxicity of myalgia, which met DLT criteria. This was the only AE meeting DLT criteria in Part 1. Thus, the MTD for amivantamab as monotherapy was not established.

A total of 12 subjects (15.6%) treated in Part 1 had a TEAE that resulted in a **dose reduction**, with all such events occurring in dose cohorts of 700 mg and higher and the highest incidence in the 1750 mg cohort (14.3%, 12.0%, 15.4%, and 50.0% of subjects in 700 mg, 1050 mg, 1400 mg, and 1750 mg cohorts, respectively).

Results from Part 1 may therefore indicate that amivantamab at monotherapy doses up to 1750 mg had an acceptable safety profile. The majority of TEAEs were Grade 1 or 2 in severity, with low rates of dose reduction (15.6%), discontinuation (9.1%), or related Grade 3 or higher events (11.7%). Two subjects (2.6%) had Grade 4 TEAEs, and few subjects (n=2) had TEAEs with an outcome of death. All Grade 4 and Grade 5 TEAEs in Part 1 were assessed as unrelated to study treatment.

The safety profile for amivantamab monotherapy in Part 1 was consistent with other agents that inhibit EGFR and MET pathways, with dermatitis acneiform, paronychia, rash, hypoalbuminemia, and stomatitis being observed in >15% of all subjects treated in this phase.

2.6.8.6. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

The safety evaluation of amivantamab is primarily based on the 489 patients receiving amivantamab monotherapy in Study EGI1001 (denoted the All treated population).

At time of submission of this initial MAA, an interim analysis (data cut-off 8 June, 2020) was provided. As the duration of treatment and median follow-up was then still short, an updated analysis (cut-off date 30 March, 2021) was provided during the evaluation, which meant an additional approximately 10 months follow-up. The updated safety information was overall consistent with the original analysis.

The safety evaluation is somewhat hampered by the lack of a control group, but this is considered acceptable in the currently applied indication.

Common adverse events

The safety profile of amivantamab was overall consistent with its on-target activity against both EGFR and MET pathways. Thus, many of the commonly reported AEs (≥10% of subjects) were known reactions to EGFR inhibition (dermatitis acneiform, rash, pruritus, dry skin, stomatitis, paronychia) or to MET inhibition (hypoalbuminaemia, peripheral oedema). Other AEs occurring in ≥10% of subjects were GI disorders (nausea, vomiting, diarrhoea and constipation), and general disorders such as pyrexia and fatigue.

The most commonly reported AE (preferred term), however, was infusion-related reaction (IRR), which can be expected for an antibody treatment. IRR occurred in around 2/3 of subjects in all three safety analysis populations. IRR of ≥Grade 3 occurred in about 2% of subjects, indicating that severe reactions could most often be prevented by prophylactic treatment. A relatively small percent of subjects (<10%) required post-infusion treatment to manage toxicity (i.e. within 48 hr after infusion).

The following commonly reported adverse reactions can be considered *not* related to amivantamab: dyspnoea, cough, myalgia, back pain, dizziness, headache, decreased appetite, increased ALT/ALP, pyrexia.

Grade ≥3 AEs were reported in 41% of subjects in the All treated safety population. In most of these cases the highest reported grade was Grade 3. The most common AEs of Grade ≥3 that were considered related to treatment with amivantamab (by the investigator) were diarrhoea and neutropenia, paronychia, dermatitis acneiform and IRR. Overall, the rate and nature of Grade ≥3 AEs is not of specific concern.

The SmPC Section 4.8 reflects data from exposure to amivantamab in 380 patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based chemotherapy. The most frequent adverse reactions all grades in this population were rash (76%), infusion related reactions (67%), nail toxicity (47%), hypoalbuminaemia (31%), oedema (26%), fatigue (26%), stomatitis (24%), nausea (23%), and constipation (23%). Serious adverse reactions included ILD (1.3%), IRR (1.1%), and rash (1.1%). Three percent of patients discontinued Rybrevant due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR (1.1%), ILD (0.5%), and nail toxicity (0.5%).

Deaths and serious adverse events

The majority of deaths during the study were due to progressive disease. None of the deaths that occurred during or within 30 days after amivantamab treatment were considered related to amivantamab treatment by the investigators. Overall, the pattern of deaths does not give raise to concern in a NSCLC population.

Among the totally 141 patients with serious adverse events during treatment with amivantamab monotherapy (All treated population, n=489), the events were by the investigator considered related to amivantamab in 27 patients (5.5%). The latter included rash, dermatitis acneiform, diarrhoea, interstitial lung disease, pulmonary embolism, cellulitis, impetigo, infected dermal cyst, toxic epidermal necrolysis, vomiting, atrial flutter, pericardial effusion, myalgia, conjunctival granuloma, fatigue.

The Applicant reviewed all serious events for potential inclusion in the SmPC as ADR. Serious events not considered treatment-related were reported primarily within the SOCs 'Respiratory, thoracic and mediastinal disorders' and 'Infections and infestations', and included dyspnoea (11), pulmonary embolism (5), pleural effusion (4), pneumothorax (4), respiratory failure (4), pneumonia (12), and respiratory tract infection (3). It is agreed that these events may be considered possibly or likely related to the underlying NSCLC.

Dose modifications

Dose reductions were made in 12% of subjects in the All treated population. Events within the SOC Skin and subcutaneous tissue disorders within the grouped term 'rash', such as dermatitis acneiform and rash, were the most common reasons for dose reductions. The second most common reason was events within SOC Infections and infestations (most commonly paronychia). Overall, there were few dose reductions due to other TEAEs than those that could be attributed to EGFR inhibition.

Dose interruption due to an AE was made in about 30% of subjects in the All treated population and was, thus, a more common dose modification than dose reduction. The most common reactions that led to dose interruption in the All treated safety populations included known reactions related to EGFR inhibition such as dermatitis acneiform, rash paronychia. Other reactions that were, in all cases, considered related to amivantamab by the investigator were neutropenia, fatigue and pneumonitis. Pneumonia was also commonly reported but was in none of the cases considered related to amivantamab.

Thus, in summary, dose interruption was made in about 30% and dose reduction in about 12% of subjects in the All treated population. In 9.5% both a dose interruption and a dose reduction were made. The most common reason for dose modification was reactions related to EGFR inhibition. The degree of and reasons for dose modification appears not to be of concern.

Modification of infusion was made in about 62% of subjects, the vast majority of cases were due to IRR.

Treatment discontinuations

In the All treatment population the rate of treatment discontinuation due to an AE was 8%. In about half of these subjects, treatment discontinuation was made due to an AE that was considered related to amivantamab. These events included mainly IRR and events associated with EGFR inhibition such as paronychia, dermatitis acneiform, stomatitis. There was also one serious event reported as toxic epidermal necrolysis, which was considered related to amivantamab by the investigator and led to treatment discontinuation.

Events leading to treatment discontinuation that were *not* considered related to amivantamab were mainly reported within SOC Infections and infestations, and there were some events of pleural effusion and musculoskeletal disorders. Overall, the same pattern in terms of AEs was observed for treatment discontinuations as for dose modifications and is not of major concern.

Discussion of specific adverse events

Infusion-related reactions

IRR is a known risk with antibody treatment, and IRRs were very common at amivantamab treatment. About 2/3 of subjects in the All treated population experienced IRR. The reactions were generally of grade 1-2 and could in most cases be managed by infusion modification. IRR of ≥Grade 3 occurred in about 3% of subjects in the All treated population, indicating that severe reactions could most often be prevented. Post-infusion medications were needed for about 10% of the study subjects. IRR is included as Important identified risk in the RMP. The risk and its handling are considered sufficiently well described in the SmPC.

Rash (grouped term)

Rash and other dermatologic side effects are frequently reported with EGFR tyrosine kinase inhibitors. Events within the grouped term rash was also commonly reported with amivantamab treatment, in about 3/4 of all subjects treated with at least one dose of amivantamab monotherapy. About half of the subjects with rash had more than 1 event, and about 25% had 3 or more events of rash. In most cases, the reactions were mild and non-serious. The reactions generally resolved on treatment or after dose interruption/dose reduction, and treatment discontinuation due to rash was made in two subjects. Eighteen subjects (3.7%) had a Grade 3 event. All Grade 3 reactions resolved, but in one case of toxic epidermal necrolysis (TEN), it led to treatment discontinuation. This TEAE was considered serious and probably related to amivantamab due to a plausible time to onset.

Interstitial lung disease (ILD)

ILD and ILD-like AEs have previously been associated with EGFR TKI use. There were 13 cases reported as ILD or pneumonitis at amivantamab monotherapy in the All treated population (n=489). Seven cases were considered serious. The risk of ILD and its handling is adequately described in section 4.4 of the proposed amivantamab SmPC, and the recommendations are in line with those given for other EGFR inhibitors.

Peripheral oedema

MET inhibition has been associated with peripheral oedema, with hypoalbuminaemia as a possible contributor. Peripheral oedema was observed in about 20% of the 489 subjects treated with amivantamab monotherapy. Some of the subjects had a preceding hypoalbuminaemia. The reactions were in most cases mild. None of the events were considered serious. In two subjects, the event led to dose reduction, but there were no treatment discontinuations due to peripheral oedema. Thus, overall, the peripheral oedema events appear to have been in most cases manageable and tolerable without leading to modification of amivantamab treatment. Peripheral oedema and hypoalbuminaemia are adequately listed as ADRs in section 4.8 of the SmPC.

Paronychia

Paronychia is an expected event due to EGFR inhibition and occurred in 42% of subjects treated with amivantamab monotherapy. The reactions appear to have been generally manageable by dose interruption.

Diarrhoea

Diarrhoea is very commonly reported with EGFR tyrosine kinase inhibitors and was also observed with amivantamab. Of the 54 patients (11% of the All treated with amivantamab monotherapy population) experiencing diarrhoea, most events were Grade 1-2, with 7 subjects having a Grade 3 event. There were two serious events which led to hospitalisation.

Eye disorders

Eye disorders is a known ADR from EGFR tyrosine kinase inhibitors and was also observed with amivantamab, in 12% of the All treated population.

Hypoalbuminaemia

Hypoalbuminaemia was reported as AE for 30% of subjects. Clinical chemistry data, however, indicated a change (decrease) from baseline in albumin in in a larger part of patients. The hypoalbuminemia was generally mild-moderate. Hypoalbuminaemia did in no case lead to dose modification or treatment discontinuation.

Hepatotoxicity (increased aminotransferases)

Increases in aminotransferases may be expected by an agent inhibiting EGFR and MET. The majority of cases were Grade 1. No case met criteria for Hy's law. The more serious cases had other possible explanations (liver metastases, cholelithiasis). Hepatotoxicity is included as an important potential risk in the list of Safety concerns in the RMP, which is considered adequate.

Effects on QT interval

Based on currently available data the potential of amivantamab to cause QT prolongation is considered low.

Dose finding

The safety analysis set from part I, the dose-finding part of the study, included a total of 77 subjects who received at least one dose of amivantamab.

Only one subject experienced toxicity that met the DLT criteria during the dose-finding part of the study, at the 1050 mg dose. A MTD was not defined.

There was no discernible pattern of dose dependency for on-target AEs, grad ≥3 events, dose interruptions or treatment discontinuations over the dose range 1050-1750 mg. A total of 12 subjects (15.6%) treated in Part 1 had a TEAE that resulted in a dose reduction, with all such events occurring in dose cohorts of 700 mg and higher and the highest incidence in the 1750 mg cohort (14.3%, 12.0%, 15.4%, and 50.0% of subjects in 700 mg, 1050 mg, 1400 mg, and 1750 mg cohorts, respectively). However, the number of subjects in the highest dose group was only 6 and no conclusions can be drawn with regard to a potential lower tolerability at the 1750 mg dose.

Safety in special populations

Age: Of the 489 subjects in the All treated population, 30 subjects ≥ 65 and < 75 years of age and 11% were ≥ 75 years. Due to the relatively low number of subjects ≥ 75 years, no separate subgroup analysis was made for this group. The overall AE profile was similar between older and younger subjects, however, there was a trend towards a higher incidence of SAEs in the elderly.

Sex: The overall TEAE profile in men and women was generally similar.

Race: Study EDI1001 included 217 Asian and 125 Non-Asian subjects in the All treated with amivantamab monotherapy safety population. The rate of serious TEAEs, ≥Grade 3 TEAEs, and TEAEs leading to treatment discontinuation or dose modification were consistently higher for the Non-Asian subjects in this population. This included TEAEs considered related to amivantamab. However, these differences do not imply that different dosing strategies should be used or that specific warnings should be given based on race.

The differences in the All treated 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. The rates of EGFR and MET toxicities were also similar between Asians and non-Asians.

Weight: The effect of weight on amivantamab PK is discussed in the Pharmacokinetic AR.

Renal impairment: Renal impairment might not be expected to affect the elimination and the PK of amivantamab. The higher frequency of ≥Grade 3 AEs (including AEs considered treatment related) and AEs leading to dose interruption in patients with moderate renal impairment as compared with patients with mild impairment or normal renal function might rather be due to a higher vulnerability of these subjects. The proposed SmPC gives no specific dosing instructions for patients with moderate renal impairment, which is considered adequate as these patients can likely be handled by the same dose modification strategies as other patients. Caution is advised in patients with severe renal impairment as there is no data in this population.

Hepatic impairment: Hepatic impairment might also not be expected to affect the elimination and the PK of amivantamab, and mild hepatic impairment did not have apparent effects on the safety profile. As for renal impairment, patients with hepatic disease might possibly be more susceptible to adverse reactions, related or not related to amivantamab. Caution is advised in patients with moderate or severe hepatic impairment as there is no data in this population.

Immunogenicity

The number of subjects with anti-amivantamab antibodies was low (1%) and that their antibody titres were low. Data are too limited to draw any conclusions on the potential effect of antibodies on the PK, efficacy or safety of amivantamab.

Drug-drug interactions

No formal drug-drug interaction studies have been performed with amivantamab. Pharmacokinetic drug-drug interactions might not be expected for an antibody.

Additional safety data needed in the context of a conditional MA

Additional safety data including comparative data will be provided as part of the specific obligation in order to fulfil a CMA. Study 61186372NSC3001 will allow a better characterisation of the long-term safety and a contextualisation of the safety data compared to the control arm.

2.6.10. Conclusions on the clinical safety

Amivantamab is a new, bispecific monoclonal antibody with well-known targets, EGFR and MET. Overall, the safety profile of amivantamab was consistent with EGFR and MET inhibition, and TEAEs due the pharmacological action was generally manageable by dose modifications (dose interruption and/or dose reduction) and/or specific treatment, e.g. of rash. There was also a high degree of infusion-related reactions, which can be expected for an antibody. Most of the IRRs were of NCI-CTCAE

Grade 1 and 2. This could generally be managed by pre- and post-infusion medication and by modification of infusion.

The presented safety data is considered sufficient for assessment of the risks of the product. From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

- In order to further confirm the efficacy and safety of amivantamab in the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, the MAH should submit the results of study 61186372NSC3001, a randomized, open-label phase 3 study comparing amivantamab in combination with carboplatin-pemetrexed therapy versus carboplatin-pemetrexed, in advanced or metastatic NSCLC patients with activating EGFR Exon 20 insertion mutations in the first-line setting. The CSR should be submitted by 31 March 2023.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 47: Summary of Safety Concerns

Important Identified Risks	Infusion-related reaction
Important Potential Risks	Hepatotoxicity
	Impaired fertility and embryofetal toxicity
Missing Information	None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities.

2.7.3. Risk minimisation measures

Table 48: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Infusion-related reaction	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 3	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• PL Section 4 • Recommendations to administer RYBREVANT in a setting with appropriate medical support, for administration of pre-infusionmedicinal products, for RYBREVANT initial infusion administration in split doses on Week 1 (Days 1 and 2), and for RYBREVANT administration via specific infusion rates are provided in SmPC Sections 4.2 and 4.4, and PL Section 3. • Recommendations regarding the management of IRRs (eg, interruption or discontinuation of infusion, administration of supportive medicinal products) are provided in SmPC Sections 4.2 and 4.4, and PL Section 4. • Patients with side effects during infusion of RYBREVANT should notify their doctor or nurse immediately, as described in PL Sections 2 and 4. • Legal status. **Additional risk minimization measures:** • None	
Hepatotoxicity	**Routine risk minimization measures:** • SmPC Section 4.8 (ALT, AST, and ALP increased) • PL Section 4 • Legal status. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Impaired fertility and embryofetal toxicity	**Routine risk minimization measures:** • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • Warnings for the potential harmful effects of EGFR inhibition on embryofetal development, and precautions to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of amivantamab, are provided in	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	SmPC Section 4.6 and PL Section 2. • Patients should notify their doctor or nurse immediately about a potential or confirmed pregnancy before and during treatment with RYBREVANT, as described in PL Section 2. • Legal status. **Additional risk minimization measures:** • None	

2.7.4. Conclusion

The CHMP considers that the risk management plan version v 1.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 21.05.2021. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, RYBREVANT (amivantamab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU;

- It is approved under a conditional marketing authorisation [REG Art 14-a]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Indication endorsed by CHMP:

- RYBREVANT as monotherapy is indicated for treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum-based therapy.

Definition of advanced NSCLC: Advanced NSCLC means that the cancer is unresectable, and that the disease is not amenable to curative treatment approaches.

Advanced NSCLC is a progressive, deadly disease. In this disease setting, the aim of treatment is to prolong progression-free survival and overall-survival, and/or to improve symptoms.

The most common oncogenic driver mutations in NSCLC are activating mutations in the epidermal growth factor receptor (EGFR), and multiple approved tyrosine kinase inhibitor (TKI) drugs are targeted against these molecular aberrations. The present application concerns a subset of patients with EGFR Exon 20 insertion mutations (Exon 20ins), who constitute approximately 10% of patients with activating EGFR mutation, and for whom no targeted drug is currently available.

3.1.2. Available therapies and unmet medical need

NSCLC with EGFR Exon 20ins are typically characterised by primary resistance to currently approved EGFR TKI treatments as a result of the insertion mutation sterically preventing effective binding of these TKIs. There are currently no approved therapies specifically for the treatment of patients with Exon 20ins disease and no specific treatment guidelines are given by the American Society of Clinical Oncology (ASCO) or the European Society for Medical Oncology (ESMO) for treatment of this population. The same regimens as for EGFR-negative patients are therefore used, the current standard of care for newly diagnosed patients with EGFR Exon 20ins NSCLC being platinum-based chemotherapy.

However, recent data suggest that certain variants of EGFR Ex20ins mutations may be sensitive to EGFR-targeted TKIs (Qin 2020). The American NCCN has therefore recently recommended subtyping of EGFR ex20ins tumours. However, as the data on these variants is scarce and the reported response rates are 11%-17% (1st to 3rd generation TKIs), an unmet medical need still exists. The present application concerns second-line treatment after failure on platinum-based chemotherapy. In this setting, single-agent chemotherapy, with response rates around 10-15%, or immunotherapy with immune checkpoint inhibitors are frequently used. Data from the pivotal trials of pembrolizumab, atezolizumab, and nivolumab, respectively, suggest lower ORRs in the EGFR-mutated subsets compared with the overall population (pembrolizumab and nivolumab, no data for atezolizumab),

favouring the comparator docetaxel, together with an OS HR above 1.0 (atezolizumab and nivolumab), or a substantially higher and statistically non-significant OS HR (pembrolizumab.) This implies that ORR data from the overall populations in immunotherapy studies may not reflect the expected outcome in the current subgroup of patients with EGFR Exon 20ins, and that, rather, the chemotherapy ORR may be the most relevant for comparison (see further discussion below, section 3.7.4)

The combination of ramucirumab and docetaxel has been more recently approved for use in second-line treatment of NSCLC, with 1.5 months OS advantage and ORR of 23% versus 14% in the docetaxel alone arm. Subsequently reported results from the pivotal study in patients with adenocarcinoma histology (where EGFR mutations predominantly occur) showed ORR 19% vs. 15% in the docetaxel alone arm (Paz-Ares 2017).

3.1.3. Main clinical studies

Study EDI1001 (CHRYSALIS) is a phase 1, first-in-human (FIH), single-arm trial (SAT) in non-resectable or metastatic NSCLC. The study had a dose escalation Part 1, and a dose expansion Part 2. In Part 2, cohorts were defined by the presence of different types of EGFR or MET aberrations. Different regimens, as monotherapy and in combination with other drugs were investigated in Study EDI1001; the current application only concerns monotherapy.

The primary efficacy population for the present application consists of 114 patients, pooled from Part 1 and two cohorts in Part 2, who fulfilled the selection criteria of having a tumour with EGFR Exon 20 insertion mutation and having received prior platinum therapy, who received amivantamab monotherapy at the recommended phase 2 dose (RP2D) identified in Part 1, and who had sufficient follow-up time as defined by a common inclusion date. This is an exploratory study with no meaningful pre-specification of efficacy hypotheses. The most recent data cut-off (DCO), 30 March 2021, with the most recent data set, i.e., the extended primary efficacy population with first dose on or before 04 June 2020, n= 114, are therefore considered pivotal. The primary endpoint was objective response rate (ORR); key secondary endpoints were duration of response (DOR), progression-free survival (PFS) and overall survival (OS).

3.2. Favourable effects

- Primary endpoint: ORR by investigator assessment (INV) was 36.8% (95% CI: 28.0%, 46.4%). Sensitivity analysis by BICR showed ORR 43.0% (95% CI: 33.7%, 52.6%).
- Median DOR by investigator assessment was 12.5 months (95% CI: 6.5, 16.1). Sensitivity analysis by BICR showed DOR 10.8 months (95% CI: 6.9, 15.0). The proportion of subjects with DoR ≥ 6 months was 64.3% (INV), and 55.1% (BICR)
- Time to response was 1.6 months in a majority of responding subjects. The latest response observed occurred before 10 months of treatment.
- Tumour shrinkage and objective responses were observed across Exon 20ins mutation subtypes.
- Median PFS by investigator assessment was 6.9 months (95% CI: 5.6, 8.6), at 71% event-rate. Sensitivity analysis by BICR showed PFS 6.7 months (95% CI: 5.5, 9.7), at 70% event rate.
- Median OS for the primary efficacy population was 22.8 months (95% CI: 17.5, not estimable), at 35% event rate; and the estimated 12-month survival rate was 73% (95% CI: 63%, 80%).

3.3. Uncertainties and limitations about favourable effects

- The exploratory nature of the study, with major protocol revisions based on study data and external data, lack of pre-specification and hypothesis testing, are major sources of uncertainty in the interpretation of the results. Inconsistencies between study protocol and SAP for Exon 20ins were noted, e.g. regarding primary endpoint. These inconsistencies and data-driven revisions are considered likely reflecting the phase 1 exploratory type of study rather than any major problems with study conduct, however, and do not prompt an inspection.
- There is a risk of upward bias in the efficacy results due to selection of the most promising cohort. A number of statistical analyses addressing the stability of the ORR estimate did not fully resolve the issue. However, the ORR estimates for investigator and independent review assessments, respectively, were consistent across 4 data cut-offs and 3 successively expanded efficacy populations, offering sufficient reassurance of the stability of the ORR estimate.
- The single-arm study design hampers contextualisation. Comparison with submitted real-world data should be done with caution. Inclusion criteria in clinical trials may select for a population with better prognosis than in routine health care, resulting in a non-conservative comparison.
- Time-dependent endpoints do not isolate a drug effect in single arm trials.

3.4. Unfavourable effects

The safety evaluation of amivantamab is based on the 489 patients who had received amivantamab monotherapy at the data cut-off 30 March 2021 in Study EGI1001 (denoted the All treated population). Of these, 380 received the RP2D dose, and 153 were considered to constitute the target population, i.e. having the Exon 20ins, prior chemotherapy and were treated at the RP2D. The median duration of treatment was 4.1 months, and the median follow-up was 6.6 months (All-treated population).

In general, the AE pattern was similar between the three safety populations.

Dose reductions were made in about 12% of subjects in the All treated population. Overall, there were few dose reductions due to other TEAEs than those that could be attributed to EGFR inhibition.

Dose interruption due to an AE was made in about 30% of subjects in the All treated population and in 32% of the RP2D population. In 9.5% of patients both dose interruption and dose reduction were made. The most common reactions that led to dose interruption included known reactions related to EGFR inhibition. Pneumonia was also commonly reported but was in none of the cases considered related to amivantamab.

The overall rate of treatment discontinuation due to an AE was 8% but only in 4.3% of subjects in the All treated population, treatment discontinuation was made due to an AE that was considered related to amivantamab. These events included mainly IRR and reactions associated with EGFR inhibition such as paronychia, dermatitis acneiform, stomatitis. There were single events of toxic epidermal necrolysis (TEN), asthenia, myalgia, akathisia, and pneumonitis that led to treatment discontinuation and were considered related to amivantamab by the investigator.

The most commonly reported AE was infusion-related reaction (IRR), which can be expected from antibody treatment. IRR occurred in around 2/3 of subjects in all three safety analysis populations. IRR of ≥Grade 3 occurred in about 2.5% of subjects. The vast majority of IRR reactions occurred during the first infusion. IRR could generally be handled by modification of infusion. Post-infusion medications

to treat IRR were needed for about 10% of the study subjects. IRR was reported as the reason for treatment discontinuation in 8 subjects (2.2%). The SmPC adequately describes risk minimisation of IRR.

The safety profile of amivantamab was otherwise consistent with its on-target activity against both EGFR and MET pathways. Thus, many of the commonly reported AEs were known reactions at EGFR inhibition (e.g. dermatitis acneiform, rash, pruritus, dry skin, stomatitis, paronychia) or at MET inhibition (hypoalbuminaemia, peripheral oedema). Other AEs occurring in ≥10% of subjects were GI disorders (nausea, vomiting, diarrhoea and constipation), and general disorders such as pyrexia and fatigue. Different eye disorders, also a known ADR from EGFR tyrosine kinase inhibitors, was observed in 12% of the All treated population with amivantamab. There were 13 cases reported as ILD or pneumonitis.

Laboratory parameters that worsened ≥20% in the target population included albumin decreased and ALT/AST increased. There were, however, no confirmed cases of drug-induced liver injury. Glucose increased was reported in about 50% of subjects, and creatinine increased in about 44% of subjects. Hyperglycaemia was, however, only reported as an adverse event in about 5% of subjects and blood creatinine increased in about 1%. In addition, lymphocyte count decreased in 35% of subjects in the target population.

Nearly all patients had adverse events of clinical importance: Rash in 75%, IRRs in 65%, peripheral oedema in 22% and interstitial lung disease in 2.7% of patients. Rash included several subgroups of which the most common were classified as dermatitis acneiformis, rash and rash maculo-papular.

Grade 3 or higher TEAEs were reported for 41% of subjects. AEs of Grade ≥3 that were considered related to treatment with amivantamab were reported for 16% of subjects in the All treated population. The most common of these were diarrhoea and neutropenia, paronychia and dermatitis acneiform, and IRR. There were overall 23 fatal events during or within 30 days post amivantamab-treatment. None of the fatal events were considered related to amivantamab.

Serious adverse events were reported in 29% of patients in the RP2D group. In 5.5% of patients, SAEs were assessed to be related to amivantamab. The most commonly reported SAEs concerned respiratory, thoracic and mediastinal disorders, dyspnoea being the most common of these. Infections and infestations were reported as SAEs in 7.2% of patients, pneumonia being the most common of these. The most commonly reported serious events (≥2 events) considered related to amivantamab were IRR, pneumonitis and diarrhoea.

Available data indicate that no specific recommendations are needed based on age, sex or race.

3.5. Uncertainties and limitations about unfavourable effects

The single arm study design does not allow for a conclusive causal attribution of the side effect profile of amivantamab, but this is considered acceptable in the applied indication.

There is no data in patients with severe renal impairment or moderate-severe hepatic impairment, and caution is therefore advised in such patients. Further, safety data in patients ≥75 years of age is limited, which is described in the SmPC.

The number of subjects with anti-amivantamab antibodies was low (<1%) and their antibody titres were low. There was no evidence of an altered PK, efficacy, or safety profile due to anti amivantamab antibodies, however data are too limited to draw conclusions on the potential effect of antibodies on the PK, efficacy or safety of amivantamab.

Data is not sufficient to make conclusions on potential hepatotoxicity, embryotoxicity and impaired fertility, and these items are listed as important potential risks in the safety specification for amivantamab and will be monitored post marketing.

3.6. Effects Table

Table 40. Effects table for Rybrevant in second-line NSCLC with EGFR Exon20ins mutation (data cut-off, 30 March 2021).

Effect	Short Description	Unit	Result	Uncertainties/ Strength of evidence/Comment
Favourable Effects				
ORR (INV)	Objective response rate: Proportion of patients with complete and partial response by RECIST 1.1	% (95% CI)	37 (28, 46)	EDI1001, Efficacy population, n= 114. Tumour response is with certainty a drug effect, as tumours do not shrink spontaneously.
DOR (INV)	Duration of response, from first response to progression or death	months (95% CI)	12.5 (6.5, 16.1)	Only applies to responding patients. Informs on the clinical value of the responses.
PFS (INV)	Progression-free survival: time from randomisation to progression or death	months (95% CI)	6.9 (5.6, 8.6)	Event rate: 71%, reasonably mature. Does not isolate a drug effect in a single-arm trial.
OS	Overall survival: time from randomisation to death	months (95% CI)	22.8 (17.5, NE)	Event rate 35%, immature. Does not isolate a drug effect in a single-arm trial.

Effect	Short Description	Incidence	References
Unfavourable Effects			
Grade 3/4 AEs		41%	
Infusion related reaction	dyspnoea, flushing, chills, nausea, chest discomfort, and vomiting	67%	EDI1001 All treated population (amivantamab monotherapy) n=489
Rash (grouped term)	Dermatitis acneiform, rash, rash pustular, pruritus, dry skin	75%	"
Paronychia		42%	"
Constipation		23%	"
Nausea		22%	"
Stomatitis		20%	"
Vomiting		12%	"
Diarrhoea		11%	"
Peripheral oedema		20%	"
Fatigue		20%	"
Hypoalbuminaemia		30%	"

Effect	Short Description	Unit	Result	Uncertainties/ Strength of evidence/Comment
Eye disorders (grouped term)	dry eye, vision blurred, eye pruritis, keratitis, lacrimation increased, visual impairment, ocular hyperaemia, eyelid ptosis, aberrant eyelash growth		12%	"
Interstitial lung disease (grouped term)	ILD, pneumonitis		2.7%	"

Abbreviations: INV: Investigator assessed

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients in the sought indication after progression on platinum-based chemotherapy have few established treatment alternatives. Due to primary resistance to currently approved EGFR-targeted TKIs in NSCLC, mainly single-agent chemotherapy and immunotherapy are used. Docetaxel is indicated in this patient group, with reported ORRs of 10-15%, and immune checkpoint inhibitor monotherapy was approved with ORR around 20%, at most. Due to the lack of sensitivity to currently approved targeted therapy, NSCLC patients with EGFR Exon20ins have a markedly shorter survival than patients with other activating EGFR mutations (16 versus 25 months, from start of first-line therapy, according to the Applicant's Flatiron-based RWD study). The unmet medical need is high.

In this setting, the submitted data suggest that amivantamab is reported to provide an objective response rate of approximately 35-40%, with a lower 95% CI of at least 25% in multiple analyses. If accepted at face value, this would appear as a relevant effect size and a motive for use as an alternative to e.g. single-agent chemotherapy. The reported duration of response of 12.5 months at the current data cut-off, is furthermore of a length that can be expected to provide clinical value to patients. Objective responses, and even smaller but clinically noticeable reductions in tumour size, may in themselves offer symptom reduction to patients, depending partly on the location of the lesions. In addition, severe or catastrophic consequences of continued tumour growth may be postponed or avoided (e.g. lesions to the spinal cord caused by bone metastases in vertebrae, causing paralysis). How the objective responses affect long-term clinical outcomes is not known, however.

As a drug effect cannot be isolated from single-arm time-to-event outcomes such as PFS and OS, no claims can be made with regard to the reported outcomes in the pivotal study, with median PFS 6.9 months and median OS 22.8 months. They might, however, provide some degree of reassurance of the utility of amivantamab, in relation to contextualising data, such as the observed OS estimates of up to median 14 months for EGFR Exon20ins NSCLC in second-line treatment in the Applicant's Flatiron study. Furthermore, in the Opdivo pivotal trial in this setting, from which detailed subgroup data is available in the EPAR, the median OS in the EGFR-mutated subset was 9 months for nivolumab and 11.5 months for docetaxel. These comparisons are not suggestive of any obvious risk of loss of chance if amivantamab were to be used in place of the currently used therapies. The limitations, potential biases and uncertainties associated with indirect comparisons in general and in particular between clinical trial data and RWD, noted above, should be duly considered, however.

The observed safety profile was consistent with antibody treatment (IRRs) and with inhibition of EGFR and MET. The treatment-related adverse events could generally be managed by dose modification or,

for IRRs, infusion modification and treatment of symptoms, and did in relatively few subjects lead to treatment discontinuation. There were no deaths that were considered related to amivantamab treatment.

3.7.2. Balance of benefits and risks

The efficacy results of ORR around or above 35% together with a substantial DOR around 12 months are considered to outweigh the risks in terms of side-effects of the treatment and any remaining uncertainties concerning the safety profile.

3.7.3. Additional considerations on the benefit-risk balance

Pivotal data set

In the absence of a pre-planned hypothesis testing analysis and analysis population, the most updated results in the most extended data set submitted (fulfilling predefined follow-up criteria) are considered the most informative and therefore pivotal to the approval. The claims in the SmPC 5.1 are therefore based on the 114-population.

Scope of the indication

The indication initially claimed by the Applicant was "after failure of platinum-based *chemo*therapy".

All subjects had received prior platinum-based systemic therapy. In addition, 44% of subjects had received prior immunotherapy, and 20% had received prior EGFR TKI therapy.

Subgroup analysis showed activity of amivantamab regardless of prior immunotherapy.

Among the 50 patients (44% of the 114 subjects in the pivotal efficacy population) who had received prior treatment with an immune checkpoint inhibitor, 17 (15% of the pivotal efficacy population) received a checkpoint inhibitor as part of a platinum-based chemo-immunotherapy regimen.

Since prior treatment with chemo-immunotherapy rather than only a platinum doublet alone, is not anticipated to impact the activity of Rybrevant, an indication encompassing also patient having received a checkpoint inhibitor in combination with chemotherapy is considered appropriate. Thus, removing the word "chemo" from the indication is considered justified, to "after failure of platinum-based therapy".

Posology – treatment duration

Among the 114 patients, data from 25 patients who received continued treatment with amivantamab post progression and who had a post-progression disease assessment, showed a duration of post-progression amivantamab treatment of mean 4.5 months, and median 4.2 months. 16% received post-progression therapy for ≥ 6 months. While it may be acknowledged that for selected individual cases, in patients who tolerate the treatment well, and depending on the form of PD, continued treatment after PD could be a reasonable treatment strategy in the absence of effective next line therapies. However, from a B/R perspective, in a situation where there is objective evidence of loss of tumour control (i.e. PD by RECIST), the clinical benefit of extended treatment is not considered established based on the available data. A positive B/R for such post-progression treatment can therefore not be established.

Efficacy

Due to both the single-arm design and the limited size of the pivotal trial, data are not considered comprehensive. The Applicant has therefore sought a conditional marketing authorisation. In this context, the efficacy and safety in relation to other available therapies are outlined.

- EGFR-targeted tyrosine kinase-inhibitors (TKIs):

EGFR ex20ins mutations induce a steric hindrance of the drug-binding pocket, which prevents binding of EGFR TKI. Preclinical models and patient-derived experimental models confirmed that EGFR ex20ins in the domain immediately following the C-helix confer poor response to erlotinib, gefitinib and afatinib. EGFR ex20ins are on average 100 times less sensitive than the common sensitizing EGFR mutations. For this reason, patients harbouring this mutation have generally been excluded from pivotal clinical trials, although they are formally included in the indications for Iressa, Tarceva and Giotrif. One exception is currently known and noted in the NCCN NSCLC guideline: the Exon 20 ins mutation Y764nsFQEA, which is associated with sensitivity to available EGFR TKIs.

Limited activity of TKIs on EGFR ex20ins has been seen in small clinical series, where in some cases also the TKI-sensitive Y764nsFQEA mutation is known to have been included in the activity estimates (Remon et al, 2020, Cardona et al, 2018). Consequently Iressa, Tarceva and Giotrif are not recommended for the treatment of patients with ex20ins (NCCN guidelines). The activity shown for Rybrevant is indicative of a major therapeutic advantage in terms of efficacy, over Iressa, Tarceva and Giotrif.

- Immunotherapies:

Available immunotherapies in second- or third-line NSCLC after first-line platinum-based chemotherapy has shown overall objective response rates of 20-21% versus 9% for pembrolizumab versus docetaxel (Keytruda SmPC), 14% (13.6%) versus 13% (13.4%) for atezolizumab versus docetaxel (Tecentriq SmPC, EPAR NCE), and 19% versus 12% for nivolumab vs docetaxel (Opdivo SmPC). The pivotal studies all included small proportions of patients with EGFR-mutated tumours, who were required, or allowed, to have received also prior EGFR targeted TKI therapy.

In Keynote-010, in the approved patient population with TPS ≥1%, a 10% difference in ORR between study arms was observed in the overall population favouring pembrolizumab, while in the EGFR-mutated subset (n=86), the difference in ORR was 25% in favour of docetaxel. The OS HR for pembrolizumab versus docetaxel was 0.67 (95% CI: 0,56; 0.80) in the total population, and 0.88 (95% CI 0.45; 1.70) in the EGFR mutation positive subset. (Keytruda EPAR, variation II-07, Figures 34 and 40; Herbst 2016. Note: The OS subgroup data presented in Herbst 2016 are the same as those in EPAR Figure 34.)

In the OAK study, the overall OS HR for atezolizumab vs docetaxel was 0.73 (95% CI:0.62: 0.87), while the subgroup with EGFR-mutation (n=85) had an OS HR of 1.24 (95% CI: 0.71; 2.18). (Tecentriq SmPC; Rittmeyer 2017. Note: The same OS subgroup data presented in Rittmeyer 2017 were also included in the MAH's NCE submission but were not published in the NCE EPAR.)

In Study CA209057, the overall ORR was 19% versus 12% for nivolumab versus docetaxel, as noted above. In the EGFR-mutated subset (n=82), however, the ORR was 11% versus 16% for nivolumab versus docetaxel. Furthermore, OS HR was 0.75 (95% CI: 0.62- 0.91) in the total population, favouring nivolumab, with median OS 12.2 versus 9.4 months. In the EGFR-mutated subset, OS HR was 1.18 (95% CI: 0.69- 2.06), with median OS 9.2 versus 11.5 months for nivolumab versus docetaxel. (Opdivo EPAR variation II-02, 2016, Table 24. Note: The OS subgroup data presented in Borghaei 2015 are the same as those in EPAR.)

Thus, available OS point estimates suggest a possible smaller or no effect (pembrolizumab), or even detrimental effect (atezolizumab and nivolumab) of immune checkpoint inhibitor treatment compared with single-agent docetaxel as second- or third-line treatment of NSCLC with EGFR mutation. In addition, while overall ORR favoured the immunotherapy, also ORR favoured docetaxel in patients with EGFR mutation for products where subgroup data was available (pembrolizumab, nivolumab).

Taken together, these data suggest that the overall ORR for these immunotherapies, based on the total population, may not reflect expected outcomes in the presently sought indication in patients whose tumours have EGFR Exon 20ins mutations. Taking into account also the data for ramucirumab plus docetaxel (see above, section 3.1.2). ORR above 20% does not seem likely to be expected from currently available treatment options in second-line NSCLC Exon 20ins.

Safety

The safety profile of amivantamab is somewhat different from potential alternative treatment options for this patient population, such as docetaxel and immune checkpoint inhibitors.

While both amivantamab and docetaxel are associated with gastrointestinal AEs, such as diarrhoea (with approximately similar rates of grade 3-4 diarrhoea) and stomatitis, treatment with docetaxel is associated with a higher rate of haematological AEs such as neutropenia, anaemia, thrombocytopenia. Other very common AEs include infections (grade 3-4 infections reported in about 5% of NSCLC patients) and neuropathies. Febrile neutropenia is reported as Common (≥1/100, <1/10) for docetaxel. For amivantamab, AEs within SOC Infections and infestations, although commonly reported, consisted primarily of paronychia and there were no serious infections that were considered related to amivantamab. The most commonly reported AEs for amivantamab were within the grouped term rash, where grade 3-4 reactions occurred in 3% of the safety population. There was one case of TEN, which led to treatment discontinuation. However, skin and nail reactions have been reported as Very Common also for docetaxel, with grade 3-4 skin reactions in about 6% of NSCLC patients.

Hypersensitivity reactions have been reported for docetaxel, mainly at the first infusion, but at a lower rate than for amivantamab. For both treatments, most of the IRR/hypersensitivity reactions occurred during the first infusion.

IRR, haematological and gastrointestinal reactions are reported also for immune checkpoint inhibitors. In contrast to amivantamab and docetaxel, the most serious AEs with immune checkpoint inhibitors are the immune-related AEs, which include e.g. pneumonitis, colitis, hepatitis, nephritis, endocrinopathies and skin reactions (including Steven-Johnsons syndrome and TEN).

The recently approved combination of ramucirumab and docetaxel was, compared with docetaxel only, associated with higher rates of stomatitis, bleeding or haemorrhage and hypertension.

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Article 14-a of Regulation (EC) No 726/2004 concerning conditional marketing authorisations as it aims at the treatment of a seriously debilitating and life-threatening disease.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

As specific obligation (**SOB)**, the Applicant will provide confirmatory efficacy and safety data from the ongoing study 61186372NSC3001, which is a randomized, open-label phase 3 study comparing amivantamab in combination with carboplatin-pemetrexed therapy versus carboplatin-pemetrexed, in advanced or metastatic NSCLC patients with activating EGFR Exon 20 insertion mutations in the first-line setting. This study will provide data on the add-on activity and efficacy of amivantamab in an earlier line of treatment. If positive, this could be considered to support the implication of observed ORR on time-to-event outcomes, while not formally "confirming" the ORR results from the present study. Safety data for combination with chemotherapy will furthermore be received. The randomised design will allow isolation of drug effects (ADRs) from symptoms of disease, which will add to the current safety information based on SAT data. Given the activity and tolerability demonstrated for Rybrevant to date, the proposed SOB in an earlier setting is considered acceptable.

The Applicant is recommended to submit results from any future data cut-offs from the pivotal Study EDI1001. Considering the maturity of the data submitted from study EDI1001, further analysis are not expected to contribute to the comprehensiveness of the data for Rybrevant.

- Unmet medical needs will be addressed, as patients with NSCLC with EGFR Exon 20ins who have progressed on platinum-based therapy have few available treatment options and currently available therapies have limited efficacy.

  There is a major therapeutic advantage over existing therapies. As outlined above, amivantamab is anticipated to be at least equally effective as existing treatment alternatives, while providing a major therapeutic advantage in the form of a differential safety profile compared to chemotherapy as well as immune therapy.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. Given the positive benefit/risk and the unmet medical need in the applied indications as described above, this is considered fulfilled.

3.8. Conclusions

The overall benefit/risk balance of RYBREVANT is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of RYBREVANT is favourable in the following indication(s):

Rybrevant as monotherapy is indicated for treatment of adult patients with advanced non small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (EGFR) Exon 20 insertion mutations, after failure of platinum based therapy.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to further confirm the efficacy and safety of amivantamab in the treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, the MAH should submit the results of study 61186372NSC3001, a randomized, open-label phase 3 study comparing amivantamab in combination with carboplatin-pemetrexed therapy versus carboplatin-pemetrexed, in advanced or metastatic NSCLC patients with activating EGFR Exon 20 insertion mutations in the first-line setting.	31 March 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that amivantamab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.