European Union Risk Management Plan
RYBREVANT (amivantamab)

Details of this RMP Submission

RMP version number: 7.1
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RMP Version Number: 7.1
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EDMS Number: EDMS-RIM-1563407, 1.0

[redacted]

Rationale for Submitting an Updated RMP

Line extension application for amivantamab SC to include additional drug product presentations and to further expand the amivantamab SC product information to include the combination with CP indications that are currently approved for amivantamab IV, and according Q3W dose regimen; and to introduce a new Q4W dose regimen for amivantamab SC for the monotherapy and combination with lazertinib indications.

Summary of Significant Changes in this RMP

The following indications are included for amivantamab SC:

- RYBREVANT is indicated in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).
- RYBREVANT is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.

The dose regimen for amivantamab SC Q3W in combination with CP is added. Additionally, an extended Q4W dose regimen is added for amivantamab SC as monotherapy or in combination with lazertinib.

Exposure and safety data from Trial 61186372NSC2002 Cohorts 2 and 3b (Q3W) and Cohort 5 (Q4W) are added; exposure and safety data from Cohorts 1 and 6 (Q2W) are updated.

Other RMP Versions Under Evaluation:

Version Number	Date Submitted	Procedure Number
Not applicable		

Details of the Currently Approved RMP

Version number: 6.1
Approved with procedure: EMEA/H/C/005454/X/0014
Date of approval: 4 April 2025 (EC decision date)

QPPV Details

QPPV Name: Dr. Laurence Oster-Gozet, PharmD, PhD

QPPV Oversight Declaration: The QPPV has reviewed and approved this RMP (electronic signature on file, as applicable).

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[redacted]

ABBREVIATIONS

ACP	amivantamab+carboplatin-pemetrexed
ACP-L	amivantamab, carboplatin, pemetrexed, and lazertinib (lazertinib started after carboplatin is completed)
ADA	anti-drug antibody
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARR	administration-related reaction
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CP	carboplatin-pemetrexed
CYP	cytochrome P450
DILI	drug-induced liver injury
DOAC	direct acting oral anticoagulant
DVT	deep vein thrombosis
ECOG	Eastern Cooperative Oncology Group
EEA	European Economic Area
eGFR	estimated glomerular filtration rate
EGFR	epidermal growth factor receptor
EGFRm NSCLC	locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations
ESMO	European Society for Medical Oncology
EU	European Union
Exon 20ins	Exon 20 insertion
GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IgG(1)	immunoglobulin G(1)
IL	interleukin
ILD	interstitial lung disease
INN	international nonproprietary name
IRR	infusion-related reaction
IV	intravenous(ly)
LACP	lazertinib, amivantamab, carboplatin, and pemetrexed (all drugs started Cycle 1 Day 1)
LMWH	low-molecular weight heparin
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MET	mesenchymal-epidermal transition
NSCLC	non-small cell lung cancer
NYHA	New York Heart Association
OECD	Organisation for Economic Co-operation and Development
OS	overall survival

PD-1	programmed cell death protein-1
PD-L1	programmed cell death-ligand 1
PE	pulmonary embolism
PFS	progression-free survival
PK	pharmacokinetic(s)
PL	package leaflet
Q2W	(once) every 2 weeks
Q3W	(once) every 3 weeks
Q4W	(once) every 4 weeks
QTc	corrected QT
QTcF	QT corrected for heart rate using Fridericia's formula
rHuPH20	recombinant human hyaluronidase
RMP	Risk Management Plan
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SC	subcutaneous(ly)
SCLC	small cell lung cancer
SMQ	Standardised MedDRA Query
SmPC	summary of product characteristics
SOC	System Organ Class
TKI	tyrosine kinase inhibitor
ULN	upper limit of normal
USM	urgent safety measure
USPI	United States Prescribing Information
VTE	venous thromboembolic

PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Amivantamab
Pharmacotherapeutic group(s) (ATC Code)	Monoclonal antibodies and antibody drug conjugates (L01FX18)
Marketing Authorization Holder	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the EEA	RYBREVANT
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** Fully human IgG1-based bispecific antibody **Summary of mode of action** Amivantamab is a fully human IgG1-based bispecific antibody directed against the EGFR and MET receptor. Amivantamab disrupts EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumor growth and progression. The presence of EGFR and MET on the surface of tumor cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity and trogocytosis mechanisms, respectively. **Important information about its composition** Amivantamab is produced by a mammalian cell line (Chinese Hamster Ovary) using recombinant DNA technology. The SC formulation of amivantamab contains rHuPH20.
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet

<table>
<tr><td rowspan="2">Indications in the EEA</td><td>Current:
RYBREVANT (intravenous [IV] formulation) is indicated:
• in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).
• in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.
RYBREVANT (IV and SC formulation) is indicated:
• in combination with lazertinib for the first-line treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.
• as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.</td></tr>
<tr><td>Proposed:
RYBREVANT (IV and SC formulation) is indicated:
• in combination with lazertinib for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.
• in combination with carboplatin and pemetrexed for the treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).
• in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations.
• as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.</td></tr>
<tr><td>Dosages in the EEA</td><td>Current:
<u>RYBREVANT IV formulation</u>
The recommended dosages of RYBREVANT IV when used in combination with carboplatin and pemetrexed (CP) are:
<table>
<tr><th>Body weight at baseline[a]</th><th>Dose</th><th>Schedule</th></tr>
<tr><td rowspan="2"><80 kg</td><td>1,400 mg</td><td>Weekly (total of 4 doses) from Weeks 1 to 4
• Week 1 - split infusion on Day 1 and Day 2
• Weeks 2 to 4 - infusion on Day 1</td></tr>
<tr><td>1,750 mg</td><td>Every 3 weeks starting at Week 7 onwards</td></tr>
</table>
</td></tr>
</table>

≥80 kg	1,750 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1
	2,100 mg	Every 3 weeks starting at Week 7 onwards

[a] Dose adjustments not required for subsequent body weight changes.

The recommended dosages of RYBREVANT IV as monotherapy or in combination with lazertinib are:

Body weight at baseline[a]	**Dose**	**Schedule**
<80 kg	1,050 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1
		Every 2 weeks starting at Week 5 onwards
≥80 kg	1,400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1
		Every 2 weeks starting at Week 5 onwards

[a] Dose adjustments not required for subsequent body weight changes.

RYBREVANT IV formulation is administered by IV infusion. When used in combination with CP, RYBREVANT should be administered after CP in the following order: pemetrexed, carboplatin and then RYBREVANT. When given in combination with lazertinib, it is recommended to administer RYBREVANT any time after lazertinib when given on the same day.

RYBREVANT SC formulation

The recommended dosages of RYBREVANT SC as monotherapy or in combination with lazertinib are:

Body weight at baseline[a]	**Dose**	**Schedule**
<80 kg	1,600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards
≥80 kg	2,240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards

[a] Dose adjustments not required for subsequent body weight changes.

RYBREVANT SC formulation is not intended for IV administration and should be given by SC injection only. When given in combination with lazertinib, it is recommended to administer RYBREVANT SC formulation any time after lazertinib when given on the same day.

Proposed:

RYBREVANT IV formulation

The recommended dosages of RYBREVANT IV as monotherapy or in combination with lazertinib (Q2W dosing) are:

Body weight at baseline*	**Dose**	**Schedule**
<80 kg	1,050 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1
		Every 2 weeks starting at Week 5 onwards
≥80 kg	1,400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1
		Every 2 weeks starting at Week 5 onwards

* Dose adjustments not required for subsequent body weight changes.

The recommended dosages of RYBREVANT IV when used in combination with CP (Q3W dosing) are:

Body weight at baseline*	**Dose**	**Schedule**
<80 kg	1,400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1

	1,750 mg	Every 3 weeks starting at Week 7 onwards
≥80 kg	1,750 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1
	2,100 mg	Every 3 weeks starting at Week 7 onwards

* Dose adjustments not required for subsequent body weight changes.

RYBREVANT IV formulation is administered by IV infusion. When given in combination with lazertinib, it is recommended to administer RYBREVANT any time after lazertinib when given on the same day. When used in combination with CP, RYBREVANT should be administered after CP in the following order: pemetrexed, carboplatin and then RYBREVANT.

RYBREVANT SC formulation

The recommended dosages of RYBREVANT SC as monotherapy or in combination with lazertinib (Q4W dosing) are:

Body weight at baseline*	**Dose**	**Schedule**
<80 kg	1,600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4
	3,520 mg	• Every 4 weeks starting at Week 5 onwards
≥80 kg	2,240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4
	4,640 mg	• Every 4 weeks starting at Week 5 onwards

* Dose adjustments not required for subsequent body weight changes.

The recommended dosages of RYBREVANT SC as monotherapy or in combination with lazertinib (Q2W dosing) are:

Body weight at baseline*	**Dose**	**Schedule**
<80 kg	1,600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards
≥80 kg	2,240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards

*Dose adjustments not required for subsequent body weight changes.

The recommended dosages of RYBREVANT SC when used in combination with CP (Q3W dosing) are:

Body Weight at Baseline*	Dose	Schedule
<80 kg	1,600 mg	First dose at Week 1 Day 1
	2,400 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards
≥80 kg	2,240 mg	First dose at Week 1 Day 1
	3,360 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards

* Dose adjustments not required for subsequent body weight changes.

RYBREVANT SC formulation is not intended for IV administration and should be given by SC injection only. When given in combination with lazertinib, it is recommended to administer RYBREVANT SC formulation any time after lazertinib when given on the same day. When used in combination with CP, RYBREVANT should be administered after CP in the following order: pemetrexed, carboplatin and then RYBREVANT.

Pharmaceutical forms and strengths

Current:

RYBREVANT IV formulation

Colorless to pale yellow concentrate for solution for infusion. One mL of concentrate for solution for infusion contains 50 mg amivantamab. One 7-mL vial contains 350 mg of amivantamab.

RYBREVANT SC formulation

Colorless to pale yellow solution for injection. One 10-mL vial of solution for injection contains 1,600 mg of amivantamab (160 mg/mL). One 14-mL vial of solution for injection contains 2,240 mg of amivantamab (160 mg/mL).

	Proposed: RYBREVANT IV formulation Colorless to pale yellow concentrate for solution for infusion. One mL of concentrate for solution for infusion contains 50 mg amivantamab. One 7-mL vial contains 350 mg of amivantamab. RYBREVANT SC formulation Colorless to pale yellow solution for injection. One mL of solution for injection contains 160 mg amivantamab. One 10-mL vial of solution for injection contains 1,600 mg of amivantamab, one 14-mL vial of solution for injection contains 2,240 mg of amivantamab, one 15-mL vial of solution for injection contains 2,400 mg of amivantamab, and one 22-mL vial of solution for injection contains 3,520 mg of amivantamab.	
Is/will the product be subject to additional monitoring in the EU?	☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Advanced NSCLC with EGFR Exon 19 deletions, Exon 21 L858R substitution mutations, or activating EGFR Exon 20 insertion mutations

Relevant available data on lung cancer, NSCLC, and EGFR mutations are presented below, along with any specific data on NSCLC with EGFR Exon 19 deletions, Exon 21 L858R substitution mutations, or Exon 20ins mutations.

Incidence

Lung cancer remains the second most frequently diagnosed cancer in men and women, and its incidence continues to increase. In 2022, an estimated 2.4 million new cases of lung cancer were diagnosed globally, accounting for approximately 11.7% of the global cancer burden, with an age-standardized incidence rate of 23.6 per 100,000 persons (32.1 in men, 16.2 in women) (Ferlay 2024). In Europe, an estimated 484,306 new cases of lung cancer were reported in 2022 (Globocan 2024). According to the European Cancer Information System, the 27 EU countries projected 319,236 new cases of lung cancer by the end of 2022 (ECIS 2025). European countries exhibit wide geographic variations in lung cancer incidence. In general, rates are highest in Central and Eastern Europe (Barta 2019), with an age-standardized incidence rate of 53.5 per 100,000 persons (Planchard 2018).

Lung cancer makes up about 13% of all new cancer diagnoses (Tirzïte 2018). Lung cancer includes SCLC and NSCLC. In general, about 10% to 15% of all lung cancers are SCLC and 80% to 85% are NSCLC (American Cancer Society 2023; Zappa 2016). Approximately 60% of all patients with NSCLC present with metastatic disease at diagnosis (Amini 2019).

Mutations in the *EGFR* gene are commonly observed in NSCLC, particularly in tumors of adenocarcinoma histology (Lemine 2021; Midha 2015). EGFR mutations are the second most common oncogenic driver events in NSCLC, and the most common actionable driver event. Two mutations, ie, deletions in Exon 19 and the single amino acid substitution L858R in Exon 21, are often referred to as “classical” EGFR mutations and together account for 85% of observed EGFR mutations in NSCLC. Rare EGFR mutations account for the remaining 15% of EGFR mutations in NSCLC and include point mutations, deletions, and insertions within Exons 18 to 25 of the EGFR gene. It is estimated that over 30,000 new NSCLC diagnoses per year will harbor rare EGFR mutations (Harrison 2020). After classical mutations, EGFR Exon 20ins mutations are the next most common EGFR mutations in NSCLC, with frequencies reported between 4% and 10% of all observed EGFR mutations (Hou 2022; Oxnard 2013; Vyse 2019; Yasuda 2012).

Prevalence

The global 5-year prevalence for lung cancer was approximately 3.2 million persons in 2022 (Ferlay 2024). The 5-year prevalence of lung cancer in Europe was approximately 610,169 persons in 2022 (Ferlay 2024). Among the 27 EU countries, the estimated projected 5-year prevalence of lung cancer was 318,000 persons by the end of 2020 (ESMO 2020). In Nordic countries (Denmark,

Finland, Iceland, Norway, and Sweden) the estimated 5-year prevalence was 11.3 per 10,000 persons at the end of 2022 (NORDCAN 2024).

NSCLC accounts for 85% to 90% of lung cancers and is classified into 3 main types: adenocarcinoma, squamous cell carcinoma, and large-cell carcinoma. Adenocarcinoma is the most common type of NSCLC and accounts for approximately 40% of lung cancers. Squamous cell carcinomas represent 25% to 30% of lung cancers and large-cell carcinomas account for approximately 5% to 10% of all lung cancers (Zappa 2016).

A literature review of 150 worldwide studies reporting EGFR mutation frequency in patients with NSCLC adenocarcinoma included 33,162 patients of which 9,749 had EGFR mutations (Midha 2015). In adenocarcinomas, EGFR mutations are detected with higher rates amongst Asians (38.8%-64.0%) than amongst Caucasians (4.9%–17.4%) (Yoon 2020). In 2016, in a systematic review and meta-analysis, including data from 456 studies (of which 66% were conducted in Asian countries), 30,466 patients with EGFR mutations were reported among 115,815 patients with NSCLC. The overall pooled prevalence of EGFR mutations was 32.3%. The prevalence was higher in patients with adenocarcinoma (38.0%) compared to non-adenocarcinoma (11.7%) (Zhang 2016). The prevalence of EGFR mutations in lung adenocarcinoma varies by geographic distribution, with approximately 15% in Western populations (Friedlaender 2024).

Demographics of the Population in Advanced NSCLC and Risk Factors for the Disease

Age

NSCLC is often considered a disease of the older population, with a median age at diagnosis of about 70 years; however, a significant proportion of patients with newly diagnosed NSCLC, ranging between 1% and 10%, are younger than 40 years (Thomas 2015). Recent studies, such as the one conducted by Suidan in 2019, have indicated that young patients diagnosed with NSCLC tend to exhibit a higher prevalence of driver mutations compared to older patients (Suidan 2019). Among individuals aged 20 to 46 years, NSCLC primarily affects more female patients who are nonsmokers. Furthermore, these patients often present with advanced adenocarcinoma, suggesting a disease course primarily influenced by heritable mutations rather than environmental mutagens (Thandra 2021).

Sex

Sex influences NSCLC pathogenesis, diagnosis, and treatment. Men generally have higher lung cancer incidence and mortality rates than women. On the contrary, women are more likely to have actionable molecular alterations, such as EGFR mutations, particularly among never-smokers (Leporati, 2024). Adenocarcinoma is the most common histologic subtype of lung cancer in both smoking and nonsmoking men and women; 41.4% of lung cancer in women is adenocarcinoma compared to 34.1% in men. Female sex is one of the most important known predictors for EGFR mutations. In the systematic review and meta-analysis by Zhang et al (2016), the pooled prevalence of EGFR mutations in patients with NSCLC was 43.7% in women and 24.0% in men. The EGFR mutation frequency in patients with NSCLC with adenocarcinoma histology was higher in women compared with men in all regions where data were available: 22% versus 9% in Europe, 60%

versus 37% in Asia-Pacific, 48% versus 8% in Africa, and 28% versus 19% in North America (Midha 2015).

Racial and/or Ethnic Origin

Currently, black and white women have lower lung cancer incidence rates than men. Black men, who have the highest lung cancer rates, are about 12% more likely to get lung cancer than white men. Black women are 16% less likely to get lung cancer when compared with white women (ASCO 2025).

In the systematic review and meta-analysis by Zhang et al (2016), the prevalence of EGFR mutations in patients with NSCLC varied by location and ethnicity. Asia had the highest prevalence of EGFR mutations in patients with NSCLC (38.4%), followed by North and South America (24.4%), and Europe (14.1%). The prevalence among different ethnicities was similar to locations, with a prevalence of 38.8% in Asian populations, 17.4% in Caucasians, 17.2% in African Americans, and 27.0% in mixed populations. Several studies have compared the frequency of EGFR mutations between black and white patients with NSCLC, but the results are conflicting; while some studies found a lower frequency of EGFR mutations among black patients, others did not find a statistically significant difference between the 2 groups (Schabath 2016). This discordance could be driven by a lower testing rate among black/African American patients (Bruno 2022).

Risk Factors

Specific risk factors that may raise a person's risk of developing NSCLC include smoking, asbestos, radon, other substances (such as gases or chemicals at work or in the environment), air pollution, and genetics (ASCO 2024). Specific risk factors associated with EGFR-mutated advanced lung cancer are aging, history of being hospitalized for pneumonia, and gastroesophageal reflux disease (Choi 2019). However, the myriad risk factors for lung cancer most commonly include lifestyle and environmental and occupational exposures. The roles these factors play vary depending on geographic location, sex and race characteristics, genetic predisposition, as well as their synergistic interactions (Barta 2019).

The most important risk factor for the development of lung cancer is smoking. For smokers, the risk for lung cancer is on average 10-fold higher than for lifetime nonsmokers (defined as a person who has smoked <100 cigarettes in his or her lifetime). The risk increases with the quantity of cigarettes, duration of smoking, and younger starting age (PDQ Adult Treatment Editorial Board 2024). However, data emerging over the past several years demonstrate that lung cancers in nonsmokers are much more likely to carry activating EGFR mutations, and these EGFR-mutated lung cancers are less clearly linked to direct tobacco carcinogenesis (Kuśnierczyk 2023; Rudin 2009). In the systematic review and meta-analysis by Zhang et al (2016), the pooled prevalence of EGFR mutations in patients with NSCLC was 49.3% in nonsmokers versus 21.5% in past or current smokers.

Other risk factors for lung cancer include the following: exposure to cancer-causing substances in secondhand smoke, occupational exposure to asbestos, arsenic, chromium, beryllium, nickel, and other agents, radiation exposure from radiation therapy to the breast or chest, radon exposure in

the home or workplace, medical imaging tests such as computed tomography scans, and atomic bomb radiation, living in an area with air pollution, family history of lung cancer, HIV infection, and beta-carotene supplements in heavy smokers (National Cancer Institute 2025).

Main Existing Treatment Options

In patients with locally advanced or metastatic NSCLC, the ESMO guidelines and ASCO guidelines recommend testing for driver mutations (tests available will vary between different health systems) (Hanna 2017, 2020; Planchard 2018), which are observed in approximately 60% of adenocarcinomas (Herbst 2018). If a driver mutation is identified and an active targeted agent for that mutation is available, this treatment may be indicated. In the absence of a driver mutation, treatment with an anti-PD-1 or PD-L1 antibody, either alone or in combination with chemotherapy (depending on PD-L1 expression), is the recommended first-line therapy.

Historically, 3rd generation EGFR TKIs (most commonly osimertinib) have been the recommended first-line treatment of locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (EGFRm NSCLC) (Soria 2018). Despite improved initial disease control with osimertinib front-line therapy, all patients treated with osimertinib will relapse. Once emergence of resistance renders treatment with osimertinib ineffective, there had not been targeted therapies approved in osimertinib-relapsed disease, despite evidence that the disease continues to be dependent on signaling through either the EGFR and/or MET pathways (Leonetti 2019). Platinum-based chemotherapy therefore has been the mainstay treatment in the second-line setting after progression on osimertinib, though outcomes remain poor for these patients, with an overall response rate of approximately 30% and a median PFS of ~4-5 months (Mok 2017; Soria 2015).

For patients with EGFR Exon 20ins NSCLC, in the absence of effective targeted therapies, the recommended first-line treatment has historically been platinum-based chemotherapy, which is associated with poor outcomes (Information Summary 2021).

Based on clinical trial data from the MAH, evaluating amivantamab in patients with EGFRm NSCLC and in patients with EGFR Exon 20ins-mutated NSCLC, the IV formulation of amivantamab has been approved in the EU as monotherapy and in combination with either lazertinib or CP in EGFRm and EGFR Exon 20ins NSCLC across multiple treatment lines.

Natural History of Advanced NSCLC in the Untreated Population, Including Mortality and Morbidity:

NSCLC arises from the epithelial cells of the lung from the central bronchi to terminal alveoli. The histological type of NSCLC correlates with the site of origin, reflecting the variation in respiratory tract epithelium of the bronchi to alveoli. Squamous cell carcinoma usually starts near a central bronchus. Adenocarcinoma and bronchioloalveolar carcinoma usually originate in peripheral lung tissue. Smoking-related lung carcinogenesis is a multistep process. Squamous cell carcinoma and adenocarcinoma have defined premalignant precursor lesions. Before becoming invasive, lung epithelium may undergo morphological changes that include hyperplasia, metaplasia, dysplasia, and carcinoma in situ. Dysplasia and carcinoma in situ are considered the principal premalignant

lesions because they are more likely to progress to invasive cancer and less likely to spontaneously regress (PDQ Adult Treatment Editorial Board 2024).

NSCLC is associated with a relatively poor prognosis, not only owing to the high cancer-related mortality, but also from smoking- and age-related comorbidities (Amini 2019). Most patients diagnosed with NSCLC die within the first few years after diagnosis (Janssen-Heijnen 2012). In an observational study, the National Cancer Database was queried for cases of pathologically confirmed metastatic NSCLC with complete vital status and clinical information, diagnosed between 2006 and 2014. Of 346,681 patients, 45,861 (13%) experienced early mortality over the past decade, which remained relatively constant over time. Predictors of early mortality included advancing age (>65 years), male sex, Caucasian race, non-private insurance, lower income, greater number of comorbidities, residence in metropolitan and/or lesser-educated areas, treatment at community centers, patients with no prior history of cancer, and regional differences ($p<0.01$ for all). Early mortality was highest in patients older than 80 years with multiple comorbidities (29%). The majority of patients (71%) who died within 30 days did not receive any therapy (Amini 2019).

The overall 5-year survival rate for NSCLC is 28% (American Cancer Society 2023); however, the rate varies greatly by the stage at diagnosis. Only 5% of patients with metastatic NSCLC are still alive 5 years after diagnosis (Garon 2019). The overall 5-year survival rate for people diagnosed with NSCLC between 2012 and 2018 was 65% for localized NSCLC, 37% for regional NSCLC, and 9% for distant NSCLC (American Cancer Society 2023). The median OS for patients with classical 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 whose median OS is still limited to about 16 months at the same stage of the disease (DerSarkissian 2019; Pao 2004).

Important Comorbidities

Comorbidities of NSCLC include cardiovascular disease, coronary and cerebrovascular diseases, chronic obstructive pulmonary diseases, and other types of cancer (Lembicz 2018; Rios 2018).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical program for amivantamab was conducted in accordance with the ICH S6(R1), S7A, and S9 guidelines. Consistent with the S6(R1) and S9 guidelines, no genotoxicity, carcinogenicity, or specific reproductive or developmental toxicology testing have been conducted, as amivantamab is an antibody indicated for use in advanced cancer.

All nonclinical studies were conducted in accordance with best scientific principles. Pivotal nonclinical safety studies were conducted in conformance with GLP, 21 CFR, Part 58, and/or the principles of OECD-GLP in countries that are part of the OECD Mutual Acceptance of Data process, and include the appropriate documentation.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
No single-dose toxicity studies were conducted with amivantamab. In repeat-dose toxicity studies in cynomolgus monkeys, nonadverse transient, mildly increased neutrophil counts, white blood cell counts, and globulin levels were observed at 120 mg/kg/week following 6 weeks of dosing. In addition, decreased albumin levels and adrenal gland weights were observed at 20, 60, and 120 mg/kg/week following 6 weeks of dosing. Also decreased albumin and globulin levels were observed at 60 and 120 mg/kg/week following 3 months of dosing.	Hypoalbuminemia was noted following repeated dosing in cynomolgus monkeys and is considered a relevant safety effect in humans. Albumin is the predominant protein that regulates the osmotic pressure in the blood vessels. Thus, when albumin levels are decreased, there is a decrease in osmotic pressure and peripheral edema may result from a shift of the fluid in the interstitial spaces (Gatta 2012). While hypoalbuminemia may occur, the clinical consequences, such as edema, are not anticipated to impact the risk-benefit balance of oncologic products that are used for life-threatening indications.
Reproductive toxicity	
No reproductive toxicity studies were conducted with amivantamab. Reproductive toxicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	Reproductive toxicity studies were not considered essential to inform risk to pregnant patients. Impaired fertility and embryofetal toxicity is a known class effect of EGFR and MET inhibitors.
Developmental toxicity	
No developmental toxicity studies were conducted with amivantamab. Developmental toxicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	Developmental toxicity studies were not considered essential to inform risk to pregnant patients. Impaired fertility and embryofetal toxicity is a known class effect of EGFR and MET inhibitors. IgG antibodies are known to cross the human placenta during pregnancy and have been detected in the serum of infants born to patients treated with therapeutic antibodies.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Genotoxicity	
No genotoxicity studies were conducted with amivantamab. Routine genotoxicity studies are generally not applicable to biological pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material (ICH S6).	Amivantamab is not expected to be genotoxic in humans due to the nature of IgG1.
Carcinogenicity	
No carcinogenicity studies were conducted with amivantamab. Routine carcinogenicity studies are generally not applicable to therapies for advanced cancer indications (ICH S9).	Amivantamab is not expected to be carcinogenic in humans.
Safety pharmacology:	
Cardiovascular system (including potential for QT interval prolongation)	
In toxicity studies in cynomolgus monkeys, no cardiovascular findings were reported at 120 mg/kg/week following 3 months of IV dosing.	Based on the nonclinical data, amivantamab is not expected to induce cardiovascular disorders in humans.
Nervous system	
In toxicity studies in cynomolgus monkeys, no observational central nervous system findings were reported at 120 mg/kg/week following 3 months of IV dosing.	Based on the nonclinical data, amivantamab is not expected to induce nervous system disorders in humans.
Respiratory system	
In toxicity studies in cynomolgus monkeys, no respiratory findings were reported at 120 mg/kg/week following 3 months of IV dosing.	Based on the nonclinical data, amivantamab is not expected to induce respiratory disorders in humans. However, the findings of the nonclinical data might not be predictive of the human response, as ILD is a known class effect.
Nephrotoxicity	
In toxicity studies in cynomolgus monkeys, non-adverse, mild to minimal histopathological changes in the kidney (tubular regeneration with associated interstitial mixed cell infiltrates) were observed at 60 and 120 mg/kg/week following 3 months of IV dosing.	Based on the nonclinical data, amivantamab is not expected to induce renal disorders in humans.

Key Safety Findings From Nonclinical Studies	Relevance to Human Usage
Hepatotoxicity	
In toxicity studies in cynomolgus monkeys, non-adverse, slight increases in ALT and AST were observed at 20, 60, and 120 mg/kg/week following 6 weeks of IV dosing. Kupffer cell hypertrophy and cytoplasmic pigment were observed at 60 and 120 mg/kg/week following 3 months of IV dosing.	Based on the nonclinical observations of AST/ALT increases and the known class effect, hepatotoxicity is an important potential risk with the use of amivantamab in humans.
Other toxicity-related information or data	
Immunogenicity	
In a repeat-dose toxicity study, 6 out of 46 cynomolgus monkeys were reported with positive ADAs at 20, 60, and 120 mg/kg/week following 6 weeks of dosing, of which 3 exhibited a faster decrease in amivantamab concentration. No cynomolgus monkeys had any ADA-related toxicity.	The relationship between immunogenicity in animals and humans is not well established, and results in animals are not expected to be predictive of the human immunogenic response.
Cytokine release assay	
Amivantamab was evaluated for potential to stimulate release of cytokines when immobilized on Protein A-coated polystyrene beads and incubated with diluted human whole blood from 16 donors for 48 hours. Results with JNJ-61186372 were similar to those of the negative control autologous plasma. Predictive model algorithms showed that amivantamab was similar in response to entities with a low risk of cytokine release syndrome (phosphate-buffered saline and autologous plasma). The positive control stimulator, anti-CD28 super agonist on coated beads, caused a significant increase in the various cytokines assayed (IL-2, IL-4, IL-6, IL-10, IL-12p70, IL-17, interferon-γ, and monomer and trimer of tumor necrosis factor-α).	These results indicate that compared with anti-CD28 monoclonal antibodies, the risk for amivantamab to cause cytokine release syndrome in humans is considered low.

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Overview of Clinical Trials in the RMP

Advanced NSCLC

The clinical development program for amivantamab includes clinical trials with an IV formulation and clinical trials with an SC formulation.

The safety of amivantamab IV in the NSCLC population is supported by 4 clinical trials in this EU-RMP:

- Trial 61186372EDI1001 (hereafter referred to as EDI1001) is an ongoing, Phase 1, first-in-human, open-label trial of amivantamab being conducted in participants at least 18 years of age with advanced or metastatic NSCLC. The trial consists of 2 parts: a dose escalation phase (Part 1) to determine the recommended dose for Phase 2 in participants with advanced NSCLC and a dose expansion phase (Part 2) to better characterize the safety and PK of amivantamab at the recommended dose and to explore its clinical activity within molecularly-defined tumor subgroups (ie, participants with advanced EGFR-mutated and/or MET-mutated NSCLC, after standard-of-care therapy).

  While this trial explores the activity of amivantamab in different populations of NSCLC with EGFR or MET alterations with unmet medical need, the focus of data derived from Trial EDI1001 in this EU-RMP is on participants with EGFR Exon 20ins mutations, as this population is part of the indication.

  In this trial, amivantamab was administered either as monotherapy, in combination with the investigational third-generation EGFR TKI lazertinib (combination therapy), or in combination with standard-of-care CP (chemotherapy combination). Information about the amivantamab combination therapy cohorts from Trial EDI1001 is not presented or discussed in this EU-RMP.

  As the amivantamab monotherapy indication is for the treatment of patients with advanced NSCLC with activating EGFR Exon 20ins mutations, after failure of platinum-based therapy, only data from the 153 participants in Trial EDI1001 who received amivantamab monotherapy at the RP2D with Exon 20ins NSCLC who had progressed on or after prior platinum-based therapy, are included within the EU-RMP.

- Trial 61186372NSC3001 (hereafter referred to as NSC3001) is an ongoing, Phase 3, randomized, open-label trial in participants at least 18 years of age with newly diagnosed, locally advanced or metastatic EGFR Exon 20ins NSCLC, which was designed to demonstrate improved efficacy of amivantamab in combination with standard-of-care carboplatin-pemetrexed (ACP) versus CP alone for the first-line treatment of patients with EGFR Exon 20ins NSCLC.
- Trial 61186372NSC3002 (hereafter referred to as NSC3002) is an ongoing, Phase 3, randomized, open-label trial in participants at least 18 years of age with EGFRm NSCLC,

whose disease has progressed on or after treatment with the third-generation TKI osimertinib, to compare the efficacy and safety of ACP versus CP and the combination of lazertinib, amivantamab, carboplatin, and pemetrexed (LACP/ACP-L) versus CP.

In the original design of the trial, the primary objective was to compare the efficacy of lazertinib, amivantamab, carboplatin, and pemetrexed (all given starting from Cycle 1 Day 1; LACP dosing) with CP. The initial protocol also had an allocation for hypothesis testing for a biomarker-driven subgroup. However, as the biomarker was not confirmed to support this analysis, the protocol was amended to repurpose the alpha spend intended for biomarker analysis to implement a dual primary hypothesis to independently evaluate LACP versus CP and ACP versus CP.

During IDMC review of safety data, an imbalance in SAE, related SAE, and Grade 4 AE incidence was observed for participants receiving LACP compared with CP. The reported AEs were those traditionally associated with the use of chemotherapy (eg, neutropenia, thrombocytopenia, febrile neutropenia, nausea, and stomatitis) and were predominantly occurring during the first 4 treatment cycles. Based on these findings, a USM was implemented to delay lazertinib administration until Cycle 5 Day 1, or earlier if carboplatin was discontinued prior to Cycle 4 (ACP-L dosing). In addition, an extension cohort was added to further characterize the safety and efficacy of the ACP-L dosing schedule.

Due to the USM and dosing schedule change implemented in the LACP/ACP-L arm, with limited follow-up of participants receiving ACP-L in the main study and extension cohort at the time of the clinical cutoff for the trial, data from the LACP/ACP-L arm are not presented in the current EU-RMP.

- Trial 73841937NSC3003 (hereafter referred to as NSC3003) is an ongoing, Phase 3 randomized, multicenter trial to compare the efficacy and safety of the combination of amivantamab and lazertinib versus osimertinib as first-line treatment in participants at least 18 years of age with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. The contribution of amivantamab to the activity of the combination is also being assessed by comparing the efficacy observed in the amivantamab and lazertinib combination arm with that in the lazertinib monotherapy arm.

  Safety for the combination of amivantamab and lazertinib was also evaluated in Trials EDI1001 and 73841937NSC1001. However, as the advanced NSCLC populations in these trials are heterogeneous with respect to previous lines of therapy, EGFR mutation types, and dosing, data from these trials are not included in this EU-RMP because the focus is on the first-line treatment in combination with lazertinib of adult patients with EGFRm NSCLC, which is the population part of the indication.

To enhance safety and convenience, an SC formulation of amivantamab has been developed. This formulation reduces IRRs, simplifies administration, shortens administration times, and eliminates the need for splitting the initial dose over 2 days. Three clinical trials are evaluating this formulation:

- Trial 61186372NSC1003 (hereafter referred to as NSC1003) is an ongoing Phase 1b, open-label, non-randomized, multicenter trial to evaluate the PK and safety of SC delivery of amivantamab to participants with advanced solid malignancies using different formulations.
- Trial 61186372NSC2002 (hereafter referred to as NSC2002) is an ongoing Phase 2, open-label, parallel cohort, interventional trial to evaluate the efficacy, safety, and PK of

amivantamab SC administered via manual injection in multiple combinations and treatment settings of participants with EGFR-mutated locally advanced or metastatic NSCLC, which have been previously investigated with amivantamab IV administration.

- Trial 61186372NSC3004 (hereafter referred to as NSC3004) is an ongoing Phase 3, open-label, randomized noninferiority trial of amivantamab SC Q2W or amivantamab IV Q2W, in combination with oral lazertinib for the treatment of participants with EGFR-mutated advanced or metastatic NSCLC after progression on osimertinib and chemotherapy.

Trial NSC2002 Cohorts 1 and 6 evaluate the first-line treatment with amivantamab SC Q2W in combination with lazertinib in patients with EGFRm NSCLC. Prophylactic anticoagulation is mandated for all participants in Cohort 6, while it is recommended in Cohort 1. Trial NSC2002 Cohort 2 assesses the first-line treatment of the combination of amivantamab SC Q3W with CP in patients with locally advanced or metastatic NSCLC and an EGFR Exon20ins mutation, and Cohort 3b investigates this combination treatment in patients with EGFRm NSCLC whose disease has progressed on or after treatment with the third generation EGFR TKI osimertinib. Data from Trial NSC2002 Cohorts 1, 2, 3b, and 6 are included in the EU-RMP.

In efforts to further reduce patient burden and optimize the patient experience in receiving treatment with amivantamab SC, a new Q4W dose regimen for amivantamab SC has been evaluated in Trial NSC2002 Cohort 5. The clinical data from this cohort is used to support extending the dosing interval from Q2W to Q4W in the indications dosed under the Q2W dose regimen and is included in the EU-RMP.

Data from Trials NSC3004 and NSC1003 are not discussed in the RMP, as the RMP focuses on data in the indicated population.

SIII.2. Clinical Trial Exposure

Clinical trial exposure to amivantamab is presented in the following tables by duration of exposure, by age group and sex, by dose, and by variable stratifications relevant to the product (ie, by ethnic origin, race, renal impairment at baseline, and hepatic impairment at baseline).

Exposure in Randomized Clinical Trials

The tables below present amivantamab exposure from the following randomized clinical trials:

<u>Amivantamab IV:</u>

- Trial NSC3001
- Trial NSC3002
- Trial NSC3003

Table SIII.1: Exposure to Amivantamab IV in Randomized Clinical Trials by Duration of Exposure

Duration of exposure (Months)	Patients	Person-months
Advanced NSCLC		
0 - <2	63	
2 - <4	51	
4 - <6	53	
6 - <8	56	
8 - <10	54	
10 - <12	51	
12 - <14	45	
14 - <16	31	
>= 16	298	
Total	702	9,568.8

Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, and Arm A (Amivantamab+Lazertinib) from NSC3003.
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Table SIII.2: Exposure to Amivantamab IV in Randomized Clinical Trials by Age Group and Sex

	Men		Women	
Age Group (years)	Patients	Person-months	Patients	Person-months
Advanced NSCLC				
18-64	165	2,290.0	242	3,582.5
65-74	74	876.5	147	1,868.2
75-84	29	346.1	39	517.9
>=85	1	9.5	5	78.3
Total	269	3,522.0	433	6,046.8

Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, and Arm A (Amivantamab+Lazertinib) from NSC3003.
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Table SIII.3: Exposure to Amivantamab IV in Randomized Clinical Trials by Dose

Dose of Exposure (mg)	Patients	Person-months
Advanced NSCLC		
NSC3003		
1,050 mg (<80kg)	369	6,285.3
1,400 mg (>=80kg)	52	862.8
NSC3001 and NSC3002[a]		
1,400-1,750mg (<80kg)	243	2,110.9
1,750-2,100 mg (>=80kg)	38	309.9
Total	702	9,568.8

Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, and Arm A (Amivantamab + Lazertinib) from NSC3003.
[a] Per protocol amivantamab is dosed as 1,400 mg if body weight is <80 kg (1,750 mg if body weight is >=80 kg) once weekly up to Cycle 2 Day 1, then 1,750 mg if body weight is <80 kg (2,100 mg if body weight is >=80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.
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Table SIII.4: Exposure to Amivantamab IV in Randomized Clinical Trials by Special Population

Population	Patients	Person-months
Advanced NSCLC		
Ethnicity		
Hispanic or Latino	77	1,104.1
Not-Hispanic or Latino	616	8,393.8
Not Reported	5	48.9
Unknown	4	22.0
Total	702	9,568.8
Race		
White	267	3,376.1
Black or African American	8	96.9
Native Hawaiian or other Pacific Islander	1	5.1
Asian	406	5,952.5
American Indian or Alaska Native	9	70.2
Not Reported	4	28.1
Multiple[a]	2	9.3
Other	5	30.5
Total	702	9,568.8
Renal impairment at baseline		
Normal (eGFR: >= 90 mL/min/1.73m^2)	413	5,662.4
Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	256	3,477.5
Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	32	418.8
Severe (eGFR: < 30 mL/min/1.73m^2)	1	10.1
Missing	0	0
Total	702	9,568.8
Hepatic impairment at baseline[b]		
Normal	626	8,610.5
Mild	75	948.6
Moderate	1	9.7
Severe	0	0
Missing	0	0
Total	702	9,568.8

[a] Multiple=one or more category was selected
[b] Normal: Total bilirubin <= ULN and AST <= ULN; Mild: (Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin <= 3 x ULN; Severe: Total bilirubin > 3 x ULN
Key: ULN = upper limit of normal; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, and Arm A (Amivantamab+Lazertinib) from NSC3003.
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Exposure in All Clinical Trials

The tables below present amivantamab exposure from all clinical trials:

Amivantamab IV:

- Trial NSC3001
- Trial NSC3002
- Trial NSC3003
- Trial EDI1001

Trial EDI1001 is a non-randomized, open-label trial without comparator treatment. From this trial, only the 153 participants with the EGFR Exon 20ins mutation who had progressed on or after prior platinum-based therapy and who were treated at the RP2D for amivantamab monotherapy are included in this EU-RMP.

Amivantamab SC:

- Trial NSC2002

From Trial NSC2002, only data from Cohorts 1 and 6 (Q2W dosing regimen), Cohort 5 (Q4W dosing regimen), and Cohorts 2 and 3b (Q3W dosing regimen), investigating the amivantamab SC formulation in combination with either lazertinib or CP in the indicated populations, are included in the EU-RMP.

Table SIII.5a: Exposure to Amivantamab IV in All Clinical Trials by Duration of Exposure

Duration of exposure (Months)	Patients	Person-months
Advanced NSCLC		
0 - <2	94	
2 - <4	77	
4 - <6	78	
6 - <8	74	
8 - <10	60	
10 - <12	64	
12 - <14	57	
14 - <16	37	
>= 16	314	
Total	855	10,683.1

Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, Arm A (Amivantamab + Lazertinib) from NSC3003, and Monotherapy from EDI1001 (at RP2D with Exon20ins mutation and prior exposure to chemotherapy).

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Table SIII.5b: Exposure to Amivantamab SC in All Clinical Trials by Duration of Exposure

Duration of exposure (Months)	Patients	Person-months
Advanced NSCLC		
Amivantamab SC Q2W Dosing Regimen[a]		
0 - <2	7	
2 - <4	14	
4 - <6	5	
6 - <8	5	
8 - <10	4	
10 - <12	7	
12 - <14	5	
14 - <16	28	
>= 16	60	
Total	135	1,844.2
Amivantamab SC Q4W Dosing Regimen[b]		
0 - <2	3	
2 - <4	3	
4 - <6	12	
6 - <8	52	
8 - <10	7	
10 - <12	0	
12 - <14	0	
14 - <16	0	
>= 16	0	
Total	77	496.1
Amivantamab SC Q3W Dosing Regimen[c]		
0 - <2	11	
2 - <4	17	
4 - <6	23	
6 - <8	44	
8 - <10	24	
10 - <12	18	
12 - <14	4	
14 - <16	2	
>= 16	0	
Total	143	983.1
Amivantamab SC[d]		
0 - <2	21	
2 - <4	34	
4 - <6	40	
6 - <8	101	
8 - <10	35	
10 - <12	25	
12 - <14	9	
14 - <16	30	
>= 16	60	
Total	355	3,323.4

[a] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib) from NSC2002.
[b] Note: Trial included: Cohort 5 (Amivantamab SC Q4W + Lazertinib) from NSC2002.
[c] Note: Trial included: Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[d] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib), Cohort 5 (Amivantamab SC Q4W + Lazertinib) and Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
Key: Q2W = once every 2 weeks; Q3W = once every 3 weeks, Q4W = once every 4 weeks.

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Table SIII.6a: Exposure to Amivantamab IV in All Clinical Trials by Age Group and Sex

	Men		Women	
Age Group (years)	**Patients**	**Person-months**	**Patients**	**Person-months**
Advanced NSCLC				
18-64	199	2,529.1	303	4,010.7
65-74	93	1,046.4	174	2,038.0
75-84	35	405.6	45	565.6
>=85	1	9.5	5	78.3
Total	328	3,990.6	527	6,692.5

Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, Arm A (Amivantamab + Lazertinib) from NSC3003, and Monotherapy from EDI1001 (at RP2D with Exon20ins mutation and prior exposure to chemotherapy).

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Table SIII.6b: Exposure to Amivantamab SC in All Clinical Trials by Age Group and Sex

	Men		Women	
Age Group (years)	**Patients**	**Person-months**	**Patients**	**Person-months**
Advanced NSCLC				
Amivantamab SC Q2W Dosing Regimen[a]				
18-64	34	514.4	55	769.6
65-74	10	153.5	20	224.1
75-84	6	76.4	9	105.2
>=85	1	1.1	0	0
Total	51	745.3	84	1,098.8
Amivantamab SC Q4W Dosing Regimen[b]				
18-64	15	109.0	25	162.0
65-74	10	62.0	24	149.4
75-84	0	0	3	13.6
>=85	0	0	0	0
Total	25	171.1	52	325.0
Amivantamab SC Q3W Dosing Regimen[c]				
18-64	31	249.6	46	339.6
65-74	30	185.9	26	159.5
75-84	6	37.5	4	10.9
>=85	0	0	0	0
Total	67	473.0	76	510.1
Amivantamab SC[d]				
18-64	80	873.0	126	1,271.2
65-74	50	401.4	70	533.0
75-84	12	113.8	16	129.7
>=85	1	1.1	0	0
Total	143	1,389.4	212	1,934.0

[a] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib) from NSC2002.
[b] Note: Trial included: Cohort 5 (Amivantamab SC Q4W + Lazertinib) from NSC2002.
[c] Note: Trial included: Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[d] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib), Cohort 5 (Amivantamab SC Q4W + Lazertinib) and Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
Key: Q2W = once every 2 weeks; Q3W = once every 3 weeks, Q4W = once every 4 weeks.

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Table SIII.7a: Exposure to Amivantamab IV in All Clinical Trials by Dose

Dose of Exposure (mg)	Patients	Person-months
Advanced NSCLC		
EDI1001 and NSC3003		
1,050 mg (<80kg)	496	7,149.7
1,400 mg (>=80kg)	78	1,112.6
NSC3001 and NSC3002[a]		
1,400-1,750 mg (<80kg)	243	2,110.9
1,750-2,100 mg (>=80kg)	38	309.9
Total	855	10,683.1

Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, Arm A (Amivantamab + Lazertinib) from NSC3003, and Monotherapy from EDI1001 (at RP2D with Exon20ins mutation and prior exposure to chemotherapy).

[a] Per protocol amivantamab IV is dosed as 1,400 mg if body weight is <80 kg (1,750 mg if body weight is >=80 kg) once weekly up to Cycle 2 Day 1, then 1,750 mg if body weight is <80 kg (2,100 mg if body weight is >=80 kg) on Day 1 of each 21-day cycle, starting with Cycle 3.

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Table SIII.7b: Exposure to Amivantamab SC in All Clinical Trials by Dose

Dose of Exposure (mg)	Patients	Person-months
Advanced NSCLC		
Amivantamab SC Q2W Dosing Regimen[a,e]		
1,600 mg (<80kg)	114	1,574.9
2,240 mg (>=80kg)	21	269.3
Total	135	1,844.2
Amivantamab SC Q4W Dosing Regimen[b f]		
1,600 – 3,520 mg (<80kg)	72	462.2
2,240 – 4,640 mg (>=80kg)	5	33.9
Total	77	496.1
Amivantamab SC Q3W Dosing Regimen[c,g]		
1,600 – 2,400 mg (<80kg)	123	846.0
2,240 – 3,360 mg (>=80kg)	20	137.1
Total	143	983.1
Amivantamab SC[d]		
Total	355	3,323.4

[a] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib) from NSC2002.
[b] Note: Trial included: Cohort 5 (Amivantamab SC Q4W + Lazertinib) from NSC2002.
[c] Note: Trial included: Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[d] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib), Cohort 5 (Amivantamab SC Q4W + Lazertinib) and Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[e] Per protocol the recommended dosing schedule for Amivantamab SC involves manual injection of 1,600 mg for patients with a body weight of <80 kg and 2,240 mg for patients with a body weight >= 80 kg, administered on Cycle 1 Days 1, 8, 15, and 22, followed by Day 1 and 15 of each subsequent 28-day cycle, starting from Cycle 2.
[f] Per protocol the recommended dosing schedule for amivantamab SC involves manual injection of 1,600 mg for patients with a body weight <80 kg and 2,240 mg for patients with a body weight >= 80 kg, administered on Cycle 1 Days 1, 8, 15, and 22, followed by 3,520 mg for patients with a body weight <80 kg and 4,640 mg for patients with a body weight >= 80 kg on Day 1 of each subsequent 28-day cycle, starting from Cycle 2.
[g] Per protocol the recommended dosing schedule for Amivantamab SC involves manual injection of 1,600 mg for patients with a body weight of <80 kg and 2,240 mg for patients with a body weight >= 80 kg administered on Cycle 1 Day 1, 2,400 mg for patients with a body weight of <80 kg and 3,360 mg for patients with a body weight >= 80 kg administered on Cycle 1 Days 8 and 15 and on Day 1 of each subsequent 21-day cycle, starting from Cycle 2.
Key: Q2W = once every 2 weeks; Q3W = once every 3 weeks, Q4W = once every 4 weeks.

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Table SIII.8a: Exposure to Amivantamab IV in All Clinical Trials by Special Population

Population	Patients	Person-months
Advanced NSCLC		
Ethnicity		
Hispanic or Latino	81	1,137.3
Not-Hispanic or Latino	754	9,379.0
Not Reported	16	144.8
Unknown	4	22.0
Total	855	10,683.1
Race		
White	312	3,727.7
Black or African American	11	137.9
Native Hawaiian or other Pacific Islander	1	5.1
Asian	501	6,574.1
American Indian or Alaska Native	9	70.2
Not Reported	14	128.2
Multiple[a]	2	9.3
Other	5	30.5
Total	855	10,683.1
Renal impairment at baseline		
Normal (eGFR: >= 90 mL/min/1.73m^2)	486	6,173.2
Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	323	4,007.9
Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	45	491.9
Severe (eGFR: < 30 mL/min/1.73m^2)	1	10.1
Missing	0	0
Total	855	10,683.1
Hepatic impairment at baseline[b]		
Normal	766	9,654.5
Mild	88	1,018.9
Moderate	1	9.7
Severe	0	0
Missing	0	0
Total	855	10,683.1

Note: Trials included: Arm A (ACP) from NSC3001, Arm C (ACP) from NSC3002, Arm A (Amivantamab + Lazertinib) from NSC3003, and Monotherapy from EDI1001 (at RP2D with Exon20ins mutation and prior exposure to chemotherapy).
[a] Multiple=one or more category was selected
[b] Normal: Total bilirubin <= ULN and AST <= ULN; Mild: (Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin <= 3 x ULN; Severe: Total bilirubin > 3 x ULN
Key: ULN = upper limit of normal; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

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Table SIII.8b: Exposure to Amivantamab SC in All Clinical Trials by Special Population

Population	Patients	Person-months
Advanced NSCLC		
Amivantamab SC Q2W Dosing Regimen[a]		
Ethnicity		
Hispanic or Latino	20	317.5
Not-Hispanic or Latino	115	1,526.7
Not Reported	0	0
Unknown	0	0
Total	135	1,844.2
Race		
White	37	512.3
Black or African American	6	76.2
Native Hawaiian or other Pacific Islander	1	4.5
Asian	91	1,251.3
American Indian or Alaska Native	0	0
Not Reported	0	0
Multiple[e]	0	0
Other	0	0
Total	135	1,844.2
Renal impairment at baseline		
Normal (eGFR: >= 90 mL/min/1.73m^2)	87	1,182.5
Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	45	627.0
Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	2	33.3
Severe (eGFR: < 30 mL/min/1.73m^2)	1	1.4
Missing	0	0
Total	135	1,844.2
Hepatic impairment at baseline[f]		
Normal	121	1,625.1
Mild	14	219.1
Moderate	0	0
Severe	0	0
Missing	0	0
Total	135	1,844.2
Amivantamab SC Q4W Dosing Regimen[b]		
Ethnicity		
Hispanic or Latino	11	65.7
Not-Hispanic or Latino	66	430.4
Not Reported	0	0
Unknown	0	0
Total	77	496.1
Race		
White	27	163.9
Black or African American	1	6.8
Native Hawaiian or other Pacific Islander	0	0
Asian	48	318.0
American Indian or Alaska Native	0	0
Not Reported	0	0
Multiple[e]	1	7.5
Other	0	0
Total	77	496.1
Renal impairment at baseline		
Normal (eGFR: >= 90 mL/min/1.73m^2)	45	295.9
Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	31	193.0
Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	1	7.3
Severe (eGFR: < 30 mL/min/1.73m^2)	0	0
Missing	0	0

Table SIII.8b: Exposure to Amivantamab SC in All Clinical Trials by Special Population

Population	Patients	Person-months
Total	77	496.1
Hepatic impairment at baseline[f]		
Normal	67	437.5
Mild	10	58.6
Moderate	0	0
Severe	0	0
Missing	0	0
Total	77	496.1
Amivantamab SC Q3W Dosing Regimen[e]		
Ethnicity		
Hispanic or Latino	13	95.6
Not-Hispanic or Latino	130	887.5
Not Reported	0	0
Unknown	0	0
Total	143	983.1
Race		
White	64	408.2
Black or African American	3	22.6
Native Hawaiian or other Pacific Islander	1	8.5
Asian	75	543.7
American Indian or Alaska Native	0	0
Not Reported	0	0
Multiple[e]	0	0
Other	0	0
Total	143	983.1
Renal impairment at baseline		
Normal (eGFR: >= 90 mL/min/1.73m^2)	73	552.6
Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	65	406.2
Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	5	24.3
Severe (eGFR: < 30 mL/min/1.73m^2)	0	0
Missing	0	0
Total	143	983.1
Hepatic impairment at baseline[f]		
Normal	130	890.8
Mild	13	92.3
Moderate	0	0
Severe	0	0
Missing	0	0
Total	143	983.1
Amivantamab SC[d]		
Ethnicity		
Hispanic or Latino	44	478.8
Not-Hispanic or Latino	311	2,844.6
Not Reported	0	0
Unknown	0	0
Total	355	3,323.4
Race		
White	128	1,084.4
Black or African American	10	105.5
Native Hawaiian or other Pacific Islander	2	13.0
Asian	214	2,113.0
American Indian or Alaska Native	0	0
Not Reported	0	0
Multiple[e]	1	7.5
Other	0	0
Total	355	3,323.4

Table SIII.8b: Exposure to Amivantamab SC in All Clinical Trials by Special Population

Population	Patients	Person-months
Renal impairment at baseline		
Normal (eGFR: >= 90 mL/min/1.73m^2)	205	2,030.9
Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	141	1,226.2
Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	8	64.9
Severe (eGFR: < 30 mL/min/1.73m^2)	1	1.4
Missing	0	0
Total	355	3,323.4
Hepatic impairment at baseline[f]		
Normal	318	2,953.3
Mild	37	370.0
Moderate	0	0
Severe	0	0
Missing	0	0
Total	355	3,323.4

[a] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib) from NSC2002.
[b] Note: Trial included: Cohort 5 (Amivantamab SC Q4W + Lazertinib) from NSC2002.
[c] Note: Trial included: Cohorts 2&3b (Amivantamab SC Q3W +Carboplatin+Pemetrexed) from NSC2002.
[d] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib), Cohort 5 (Amivantamab SC Q4W + Lazertinib) and Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[e] Multiple = one or more category was selected.
[f] Normal: Total bilirubin <= ULN and AST <= ULN; Mild: (Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin <= 3 x ULN; Severe: Total bilirubin > 3 x ULN.
Key: ULN = upper limit normal; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Q2W = once every 2 weeks; Q3W = once every 3 weeks, Q4W = once every 4 weeks.

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Participant has uncontrolled intercurrent illness, including participants with medical conditions requiring chronic continuous oxygen therapy.**
Reason for being an exclusion criterion	It is common clinical practice not to include participants with uncontrolled intercurrent illness in trials on anticancer therapy because it potentially places participants with these comorbidities at increased risk for AEs, may confound the interpretation of safety data, and impede the participant's ability to comply with all trial-related requirements. In addition, low oxygenation reserve can complicate the ability to tolerate transient hypoxia/dyspnea associated with IRRs/ ARRs on first dose administration.
Included as missing information?	No
Rationale if not included as missing information	The SmPC provides sufficient guidance to reduce the risk of IRRs and ARRs, which are predominantly characterized by symptoms of dyspnea.
Criterion 2	**Participant has had prior chemotherapy, targeted cancer therapy, immunotherapy, or treatment with an investigational anticancer agent within 2 weeks or 4 half-lives, whichever is longer, before the first administration of study drug.**
Reason for being an exclusion criterion	A minimal interval of time after prior therapy was required to avoid overlapping toxicities from anticancer therapies.
Included as missing information?	No
Rationale if not included as missing information	This is consistent with standard-of-care.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 3	**Participant has a history of clinically significant cardiovascular disease including, but not limited to:** • **Diagnosis of deep vein thrombosis or pulmonary embolism within 4 weeks prior to the first dose of study drug, or any of the following within 6 months prior to the first dose of study drug: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated thrombus, incidental or asymptomatic pulmonary embolism, are not exclusionary.** • **For regimens potentially including lazertinib: Participant has a significant genetic predisposition to VTE events such as Factor V Leiden.** • **For regimens potentially including lazertinib: Participant has a prior history of VTE events and is not on appropriate therapeutic anticoagulation as per National Comprehensive Cancer Network or local guidelines.** • **Prolonged QTcF interval >470 ms, clinically significant cardiac arrhythmia or abnormalities in conduction or morphology of electrocardiogram, or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator or atrial fibrillation with uncontrolled rate), and any factors that increase the risk of QTc interval prolongation or risk of arrhythmic events.** • **Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg.** • **Congestive heart failure defined as NYHA class III-IV or hospitalization for chronic heart failure (any NYHA class) within 6 months before first administration of study drug.** • **Pericarditis/clinically significant pericardial effusion.** • **Myocarditis.** • **Baseline left ventricular ejection fraction either <50% or below the lower limit of normal per institutional guidelines, as assessed by screening echocardiogram or multigated acquisition scan.**

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Reason for being an exclusion criterion	It is common clinical practice not to include participants with severe or unstable clinical status and potentially life-threatening cardiac conditions in trials on anticancer therapy because they potentially place participants with these comorbidities at increased risk for AEs and additionally may confound the interpretation of safety data.
Included as missing information?	No
Rationale if not included as missing information	Venous thromboembolic (VTE) events is an important identified risk for amivantamab in combination with lazertinib. There are no specific data available for use of amivantamab in patients with significant cardiac disease. The treating physician would be expected to weigh the benefit and risks for each individual patient. Amivantamab, as a large protein, has a low likelihood of direct ion channel interactions. There is no evidence from nonclinical or clinical data to suggest that amivantamab has the potential to delay ventricular repolarization.
Criterion 4	**Participant is a woman who is pregnant, or breast-feeding, or planning to become pregnant, or a man who plans to father a child while enrolled in this trial or within 6 months after the last dose of study drug.**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant participants should normally be excluded from clinical trials. Based on its mechanism of action and findings in animal models, amivantamab could cause fetal harm when administered to pregnant participants. Breast-feeding participants are usually excluded from clinical trials. It is not known whether amivantamab is excreted in human or animal milk or affects milk production.
Included as missing information?	No
Rationale if not included as missing information	Impaired fertility and embryofetal toxicity is a known class effect of EGFR and MET inhibitors. SmPC Section 4.6 states that women of childbearing potential should use effective contraception during and for 3 months after cessation of RYBREVANT treatment. RYBREVANT should not be given during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the fetus. In addition, as it is not known whether RYBREVANT is excreted into human milk, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from RYBREVANT therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 5	**Participants known to be positive for HIV that is not well controlled, or participants with a positive test for hepatitis B surface antigen or hepatitis C antibody, or another clinically active infectious liver disease.**
Reason for being an exclusion criterion	It is common clinical practice to exclude participants with active infections, including infections that can lead to hepatotoxicity, from clinical trials on anticancer therapy because they potentially confound the interpretation of safety.
Included as missing information?	No
Rationale if not included as missing information	It is consistent with standard-of-care not to treat patients with active infections. Hepatotoxicity is considered an important potential risk.
Criterion 6	**Active or past medical history of ILD/pneumonitis.**
Reason for being an exclusion criterion	It is common clinical practice not to include participants with severe and potentially life-threatening pulmonary conditions in trials on anticancer therapy because they potentially place participants with these comorbidities at increased risk for AEs and additionally may confound the interpretation of safety data. Medical history of ILD may increase the risk of recurrence. ILD is considered a class effect of EGFR inhibitors, such as monoclonal antibodies and TKIs.
Included as missing information?	No
Rationale if not included as missing information	Interstitial lung disease is an identified risk based on clinical trial observations. However, the majority of the events were managed with interruption or discontinuation of amivantamab treatment and initiation of steroids. The SmPC provides adequate instructions and guidelines for risk mitigation measures. The treating physician would be expected to weigh the benefit and risks for each individual patient.

SIV.2. Limitations to Detecting Adverse Reactions in the Clinical Development Program

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, and adverse reactions caused by prolonged or cumulative exposure.

SIV.3. Limitations With Respect to Populations Typically Under-represented in the Clinical Development Program

Table Module SIV.3: Exposure of Special Populations Included or Not in the Clinical Development Program

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breast-feeding women	Not included in the clinical development program.
Population with relevant different racial and/or ethnic origin	Of the 855 participants who received amivantamab IV in the all clinical trials population, 501 (58.6%) participants were Asian, 312 (36.5%) participants were white, 11 (1.3%) participants were black or African American, 9 (1.1%) participants were American Indian or Alaska Native, and 1 (<1%) participant was Native Hawaiian or other Pacific Islander. Eighty-one (9.5%) participants were Hispanic or Latino. Of the 355 participants who received amivantamab SC in the all clinical trials population, 214 (60.3%) participants were Asian, 128 (36.1%) participants were white, 10 (2.8%) participants were black or African American, and 2 (<1%) participants were Native Hawaiian or other Pacific Islander. Forty-four (12.4%) participants were Hispanic or Latino.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Pediatric population	Not included in the clinical development program.
Elderly	Of the 855 participants who received amivantamab IV in the all clinical trials population, 353 (41.3%) participants were ≥65 years of age and 86 (10.1%) participants were ≥75 years of age. Of the 355 participants who received amivantamab SC in the all clinical trials population, 149 (42.0%) participants were ≥65 years of age and 29 (8.2%) participants were ≥75 years of age.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Of the 855 participants who received

	amivantamab IV in the all clinical trials population, there were 88 (10.3%) participants with mild hepatic impairment at baseline (total bilirubin ≤ ULN and AST > ULN, or ULN < total bilirubin ≤1.5 x ULN), 1 (<1%) participant with moderate (1.5 x ULN < total bilirubin ≤3 x ULN), and no participants with severe (total bilirubin >3 x ULN) hepatic impairment at baseline. Of the 355 participants who received amivantamab SC in the all clinical trials population, there were 37 (10.4%) participants with mild hepatic impairment at baseline and no participants with moderate or severe hepatic impairment at baseline.
Patients with renal impairment	Of the 855 participants who received amivantamab IV in the all clinical trials population, there were 323 (37.8%) participants with mild renal impairment at baseline (eGFR 60 to <90 mL/min/1.73 m²), 45 (5.3%) participants with moderate renal impairment at baseline (eGFR 30 to <60 mL/min/1.73 m²), and 1 (<1%) participant with severe renal impairment at baseline (eGFR <30 mL/min/1.73 m²). Of the 355 participants who received amivantamab SC in the all clinical trials population, there were 141 (39.7%) participants with mild renal impairment at baseline, 8 (2.3%) participants with moderate renal impairment at baseline, and 1 (<1%) participant with severe renal impairment at baseline.
Patients with cardiovascular impairment	Participants with a history of or with recent/acute clinically significant cardiovascular disease were not included in the clinical development program.
Immunocompromised patients	Not applicable
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

The postauthorization exposure presented in this section is for RYBREVANT IV monotherapy. While the MAH received approval for RYBREVANT IV in combination with CP, for RYBREVANT IV in combination with lazertinib, and for RYBREVANT SC (as monotherapy and in combination with lazertinib), considering that the approvals were recent (in 2024 and 2025), the MAH has not revised the patient exposure estimate methodology. Also, as the sales data cannot distinguish different amivantamab indications, the MAH plans to gather insights on the sales distribution across different indications and will revise the methodology to include all approved indications in future reports.

SV.1.1. Method Used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the time a medication is distributed until it is used by a patient. Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. The recommended RYBREVANT IV monotherapy dosing is based on weight, ie, 1,050 mg for patients <80 kg and 1,400 mg for patients ≥80 kg. The dosing schedule is weekly for the first 4 weeks, and after Week 5, the dosing would be once every other week. Assuming that the average duration of treatment is 16 weeks, the total drug exposure for patients <80 kg is 10,500 mg, and 14,000 mg for patients ≥80 kg. The average total drug exposure for the 2 dosing regimens is estimated to be 12,250 mg. Therefore, 12,250 mg is equivalent to 1 treatment course.

SV.1.2. Exposure

Cumulative Exposure to Amivantamab IV Monotherapy (Launch to 30 November 2024)

Region	Total Milligrams	Treatment Courses
European Union	19,425,000	1,586
North America	48,642,079	3,971
Rest of World	19,546,100	1,596
Total	87,613,179	7,153

Note: In the Signify database, the sales data is only available for the entire month. Therefore, per the standard approach, the exposure estimates are calculated until 30 November 2024.

Based on 87,613,179 mg distributed worldwide by the MAH from launch to 30 November 2024, the estimated exposure to amivantamab IV monotherapy is 7,153 treatment courses.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

RYBREVANT is an antineoplastic agent which will be administered by a healthcare professional and has no abuse potential. Therefore, there is no concern for potential illegal use.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Risk 1: dry skin[a], pruritus
Risk 2: nail toxicity[b]
Risk 3: fatigue[c], oedema[d]
Risk 4: hypoalbuminaemia[e], decreased appetite, hypocalcaemia
Risk 5: myalgia
Risk 6: dizziness[f]
Risk 7: stomatitis[g], nausea, constipation, vomiting, diarrhoea, abdominal pain[h]
Risk 8: immunogenicity
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Risk 1: toxic epidermal necrolysis
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Risk 1: rash[i]
Risk 2: ILD[j]
Risk 3: visual impairment[k], growth of eyelashes[l], keratitis, uveitis, other eye disorders[m]
Known risks that do not impact the risk-benefit profile:
Not applicable

Risks not Included in the List of Safety Concerns in the RMP
Other reasons for considering the risks not important:
Not applicable

[a] Includes dry skin, eczema, eczema asteatotic, skin fissures, xeroderma
[b] Includes ingrowing nail, nail bed infection, nail cuticle fissure, nail disorder, nail ridging, onychoclasis, onycholysis, paronychia
[c] Includes asthenia, fatigue
[d] Includes eye oedema, eyelid oedema, face oedema, generalised oedema, localised oedema, oedema, oedema peripheral, periorbital oedema, periorbital swelling, peripheral swelling, swelling face
[e] Includes blood albumin decreased, hypoalbuminaemia
[f] Includes dizziness, dizziness exertional, vertigo
[g] Includes aphthous ulcer, cheilitis, glossitis, lip ulceration, mouth ulceration, mucosal inflammation, stomatitis
[h] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort, gastrointestinal pain
[i] Includes 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] Includes interstitial lung disease, pneumonitis
[k] Includes vision blurred, visual acuity reduced, visual impairment
[l] Includes growth of eyelashes, trichomegaly
[m] Includes blepharitis, conjunctival hyperaemia, corneal irritation, dry eye, episcleritis, eye disorder, eye pruritus, noninfective conjunctivitis, ocular hyperaemia

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important identified risks	
Infusion-related reaction	IRR was identified as an adverse reaction associated with the use of amivantamab. Serious IRRs may result in hospitalization and/or death and therefore, is considered an important identified risk with the use of amivantamab. While IRRs were observed in the majority of the subjects, they occurred primarily on the first dose early in the course of the infusion, were predominantly grade 1 or 2, and were generally (prophylactically) managed with pre-infusion medicinal products, split dosing, and drug or infusion modification. Only few required post-infusion treatment. The SmPC and package leaflet (PL) provide information on how to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy in patients treated with RYBREVANT.

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important potential risks	
Hepatotoxicity	ALT/AST increased are considered a class effect of EGFR and MET inhibitors. ALT, AST, and blood alkaline phosphatase (ALP) increased were identified as adverse reactions associated with the use of amivantamab. Drug-induced liver injury could be serious, potentially fatal, or lead to liver transplantation and therefore, hepatotoxicity is considered an important potential risk. While increased liver enzymes have been observed in subjects treated with amivantamab, there have been no clinical sequelae of these elevations. All liver AEs were non-serious and the majority were reversible and considered related to amivantamab treatment. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy for patients treated with RYBREVANT.
Impaired fertility and embryofetal toxicity	Impaired fertility and embryofetal toxicity is a known class effect of EGFR and MET inhibitors. There are no data on the use of amivantamab in pregnant women. However, based on the mechanism of action and findings in animal models, amivantamab could cause fetal harm when administered to pregnant women and therefore, is considered an important potential risk with the use of amivantamab. The warnings and precautions, including contraception recommendations, in the SmPC and PL are considered sufficient to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy for patients treated with RYBREVANT.
Missing information	
None	

SVII.2. New, Reclassified, and Removed Safety Concerns with Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks

1. Venous thromboembolic (VTE) events*

Important potential risks

1. Hepatotoxicity
2. Impaired fertility and embryofetal toxicity

Missing information

There is no missing information for amivantamab.

MedDRA Search Strategies for the evaluation of the important identified and important potential risks are listed in Annex 7.3.

MedDRA version 25.1 was used to classify the clinical trials AE information that is summarized in this section.

* Applies only to the combination of amivantamab and lazertinib.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Venous thromboembolic (VTE) events*

Potential Mechanisms

Despite prolonged use of EGFR inhibitors in the treatment of patients with cancer, a clear link between EGFR inhibitors and VTE events has not been established. There are reports in the clinical literature that suggest an increased risk of VTE events in patients treated with anti-EGFR therapies, as well as pre-clinical work proposing mechanisms for such an association (Miroddi 2016; Petrelli 2012). These potential mechanisms include antiangiogenic effects exerted by a significant decrease in tumor cell production of angiogenic growth factors such as basic fibroblast growth factor, vascular endothelial growth factor, and interleukin-8 (Miroddi 2016). The disruption of the regenerative capacity of endothelial cells can also lead to thrombosis via several mechanisms (Petrelli 2012). The applicability of these in vitro/preclinical observations to clinical risk of VTE events in patients with EGFR-mutated NSCLC, which exhibit a unique biology characteristically demonstrating a high level of tumor response to anti-EGFR therapy, is unknown. Furthermore, their relevance to amivantamab, the first antibody targeting EGFR (and MET) approved for EGFR mutated NSCLC, is also unknown. Finally, the clinical experience with combination anti-EGFR therapies (eg, TKI and monoclonal antibody) is limited, and the safety implications of the combination of amivantamab and lazertinib may be distinct from the safety profile of each agent when used as a monotherapy.

Evidence Source(s) and Strength of Evidence

Venous thromboembolic (VTE) events is an important identified risk for amivantamab only when given in combination with lazertinib.

The incidence of VTE events was higher in participants treated with the combination of amivantamab IV and lazertinib versus osimertinib in Trial NSC3003. The greatest discordance in events occurred during the first 4 months of study treatment. Importantly, the incidence rate of VTE events associated with amivantamab IV monotherapy in Trial EDI1001 and with ACP in Trials NSC3001 and NSC3002 is consistent with background rates associated with NSCLC. The incidence of VTE events was lower in participants treated with amivantamab SC and lazertinib in Trial NSC2002 than in participants receiving amivantamab IV and lazertinib in Trial NSC3003. Venous thromboembolism was identified as an adverse reaction for the combination of amivantamab and lazertinib and is described in the SmPC for amivantamab.

* Applies only to the combination of amivantamab and lazertinib.

Characterization of the Risk

Frequency, Seriousness, Outcomes, and Severity of Venous Thromboembolic (VTE) Events – Amivantamab IV Trials

	IV Trials				
	Non-randomized Trials[a]	Randomized Trials[b]			All Clinical IV Trials Population[c]
	Amivantamab[d]	Amivantamab +Lazertinib[e]	Amivantamab +Carboplatin +Pemetrexed[f]	Comparator[g]	Amivantamab
Advanced NSCLC					
Number of subjects treated	153	421	281	826	855
Frequency	15 (9.8%)	157 (37.3%)	37 (13.2%)	64 (7.7%)	209 (24.4%)
Odds Ratio (95% CI)[h]		7.08 (5.13,9.77)	1.81 (1.17,2.77)		
Seriousness					
Was serious	5 (3.3%)	46 (10.9%)	7 (2.5%)	24 (2.9%)	58 (6.8%)
Outcomes					
Fatal	0	2 (0.5%)	0	2 (0.2%)	2 (0.2%)
Not Recovered/Not Resolved	4 (2.6%)	41 (9.7%)	15 (5.3%)	19 (2.3%)	60 (7.0%)
Recovering/Resolving	4 (2.6%)	47 (11.2%)	3 (1.1%)	18 (2.2%)	54 (6.3%)
Recovered/Resolved with sequelae	0	1 (0.2%)	1 (0.4%)	0	2 (0.2%)
Recovered/Resolved	7 (4.6%)	66 (15.7%)	18 (6.4%)	25 (3.0%)	91 (10.6%)
Unknown	0	0	0	0	0
Severity					
Worst Grade=1	3 (2.0%)	5 (1.2%)	2 (0.7%)	3 (0.4%)	10 (1.2%)
Worst Grade=2	4 (2.6%)	105 (24.9%)	27 (9.6%)	33 (4.0%)	136 (15.9%)
Worst Grade=3	8 (5.2%)	43 (10.2%)	8 (2.8%)	24 (2.9%)	59 (6.9%)
Worst Grade=4	0	2 (0.5%)	0	2 (0.2%)	2 (0.2%)
Worst Grade=5	0	2 (0.5%)	0	2 (0.2%)	2 (0.2%)
Missing Grade	0	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardized MedDRA Queries (SMQs) for Venous Thromboembolic (VTE) Events.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst outcome or grade are used in case of multiple events, respectively.
Note: Unknown outcome category includes AE records with missing outcome in current data.
[a] Note: Non-randomized trials included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[b] Note: Randomized trials included: NSC3001, NSC3002 and NSC3003.
[c] Note: Trials included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy, ACP arm from NSC3001, ACP arm from NSC3002, and Amivantamab + Lazertinib arm from NSC3003.
[d] Note: Trial included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[e] Note: Trial included: Amivantamab + Lazertinib arm from NSC3003.
[f] Note: Trials included: ACP arm from NSC3001 and ACP arm from NSC3002.
[g] Note: Comparators included: Carboplatin + Pemetrexed (NSC3001 and NSC3002), Osimertinib (NSC3003).
[h] Odds Ratio is for event comparison of Amivantamab + Lazertinib versus Comparator and Amivantamab + Carboplatin + Pemetrexed versus Comparator.
RP2D (recommended Phase 2 dose): 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight >=80 kg.

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Frequency, Seriousness, Outcomes, and Severity of Venous Thromboembolic (VTE) Events – Amivantamab SC Trials

	SC Trials			
	Non-randomized Trials[a]			
	Amivantamab SC (Q2W) + Lazertinib[b]	Amivantamab SC (Q4W) + Lazertinib[c]	Amivantamab SC (Q3W) + Carboplatin + Pemetrexed[d]	All Clinical SC Trials Population[e]
Advanced NSCLC				
Number of subjects treated	135	77	143	355
Frequency	27 (20.0%)	10 (13.0%)	25 (17.5%)	62 (17.5%)
Seriousness				
Was serious	7 (5.2%)	0	3 (2.1%)	10 (2.8%)
Outcomes				
Fatal	0	0	1 (0.7%)	1 (0.3%)
Not Recovered/Not Resolved	13 (9.6%)	8 (10.4%)	14 (9.8%)	35 (9.9%)
Recovering/Resolving	2 (1.5%)	0	1 (0.7%)	3 (0.8%)
Recovered/Resolved with sequelae	0	0	1 (0.7%)	1 (0.3%)
Recovered/Resolved	12 (8.9%)	1 (1.3%)	8 (5.6%)	21 (5.9%)
Unknown	0	1 (1.3%)	0	1 (0.3%)
Severity				
Worst Grade=1	4 (3.0%)	1 (1.3%)	3 (2.1%)	8 (2.3%)
Worst Grade=2	20 (14.8%)	9 (11.7%)	17 (11.9%)	46 (13.0%)
Worst Grade=3	3 (2.2%)	0	4 (2.8%)	7 (2.0%)
Worst Grade=4	0	0	0	0
Worst Grade=5	0	0	1 (0.7%)	1 (0.3%)
Missing Grade	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardized MedDRA Queries (SMQs) for Venous Thromboembolic (VTE) Events.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst outcome or grade are used in case of multiple events, respectively.
Note: Unknown outcome category includes AE records with missing outcome in current data.
[a] Note: Non-randomized trials included: NSC2002 Cohorts 1&6, Cohort 5, and Cohorts 2&3b.
[b] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib) from NSC2002.
[c] Note: Trial included: Cohort 5 (Amivantamab SC Q4W + Lazertinib) from NSC2002.
[d] Note: Trial included: Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[e] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib), Cohort 5 (Amivantamab SC Q4W + Lazertinib), and Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
Key: Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q4W = once every 4 weeks.

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VTE events are common in patients with lung cancer. The incidence of VTE events in participants treated with osimertinib (9.1%) in Trial NSC3003, in participants treated with amivantamab IV monotherapy (9.8%) in Trial EDI1001, and in participants treated with ACP (13.2%) in Trials NSC3001 and NSC3002 is consistent with previous reports of patients with NSCLC (Vitale 2015).

In Trial NSC3003, there was a higher incidence of VTE events in the amivantamab IV+lazertinib arm (37.3%) compared with the osimertinib arm (9.1%). The difference in overall incidence was primarily due to a higher incidence of Grade 2 VTE events. The incidence of Grade 4 and Grade 5 VTE events was ≤0.5% in both arms. The majority of VTE events were non-serious and the most frequently reported VTE events were PE and DVT.

VTE events led to discontinuation of any study agent for 2.9% of participants in the amivantamab IV+lazertinib arm versus 0.5% of participants in the osimertinib arm.

Median time to first VTE event was 84.0 days in the amivantamab IV+lazertinib arm and 194.0 days in the osimertinib arm. The observed pattern of VTE events indicated that the increased risk of VTE in the amivantamab IV+lazertinib arm was largely during the first 4 months of treatment.

For a large majority of participants (152/157 participants in the amivantamab IV+lazertinib arm and 39/39 participants in the osimertinib arm), first VTE events occurred in the absence of concomitant anticoagulation. Following a first VTE event, large proportions of participants (139/152 participants in the amivantamab IV+lazertinib arm and 33/39 participants in the osimertinib arm) started anticoagulation within 30 days. Recurrent VTE events while on anticoagulation were reported for 8 (1.9%) participants in the amivantamab IV+lazertinib arm and no participants in the osimertinib arm. Many of these additionally reported events describe the same thromboembolic episode or were reported in participants who were not compliant with anticoagulation. The incidence of clinically significant bleeding AEs following the start of anticoagulation was low.

A large majority of the reported serious VTE events in the amivantamab IV+lazertinib arm were deemed serious because of the need for hospitalization for initiation of anticoagulation therapy or as required by local standard of care and not for VTE symptom management.

The incidence of VTE events was lower in participants treated with amivantamab SC+lazertinib in Trial NSC2002 (20% in Cohorts 1 and 6 combined; 13.0% in Cohort 5) than in participants receiving amivantamab IV+lazertinib in Trial NSC3003 (37.3%). Of note, the study protocols had different recommendations for anticoagulant use, resulting in most participants not taking anticoagulation in Trial NSC3003. In Trial NSC2002, 70.6% of participants in Cohort 1, 98.5% of participants in Cohort 6, and 87.0% of participants in Cohort 5 received prophylactic anticoagulation. In Cohorts 1 and 6 combined, the incidence of VTE events for participants who received prophylactic anticoagulants was 19.3% (22 participants of 114) as compared to 23.8% (5 participants of 21) in participants who did not receive prophylactic anticoagulants. In Cohort 5, the incidence of VTE events for participants who received prophylactic anticoagulants was 10.4% (7 participants of 67) as compared to 30.0% (3 participants of 10) in participants who did not receive prophylactic anticoagulants. Notably the incidence of VTE in participants treated with amivantamab SC+lazertinib while not on anticoagulation (23.8% in Cohorts 1 and 6 combined; 10.4% in Cohort 5) was lower than the incidence of VTE in participants treated with amivantamab IV+lazertinib in Trial NSC3003 (37.3%). Most VTE events following treatment with amivantamab SC+lazertinib were Grade 1 or 2. Three participants had a Grade 3 VTE event of PE; 2 of them (both in Cohort 6) received prophylactic anticoagulants and 1 participant (in Cohort 1) did not receive prophylactic anticoagulants. The majority of VTE events were non-serious and no study treatment discontinuation due to VTE was reported. The use of anticoagulant prophylaxis was not associated with a significant increase in serious bleeding events.

VTE events are potentially serious, and if not recognized or managed appropriately, may result in persistent or significant disability or incapacity, and hence require immediate medical intervention.

Risk Factors and Risk Groups

Lung cancer is a risk factor for VTE events (Tesselaar 2007; Tagalakis 2007). Additional risk factors for VTE events associated with use of amivantamab in combination with lazertinib identified in open-label trials include age ≥60 years, ECOG=1, and Responders (ie, patients with partial response or complete response) (Girard 2023).

Preventability

Specific guidance is provided in the SmPC Sections 4.2 and 4.4 to minimize and manage the risk of VTE events. At the initiation of treatment, prophylactic anticoagulants should be administered to prevent VTE events in patients receiving RYBREVANT in combination with lazertinib. Consistent with clinical guidelines, patients should receive prophylactic dosing of either a DOAC or a LMWH. Use of Vitamin K antagonists is not recommended. Patients should be monitored for signs and symptoms of VTE events and patients with VTE events should be treated with anticoagulation as clinically indicated. For VTE events associated with clinical instability, RYBREVANT and lazertinib should be withheld until the patient is clinically stable. Thereafter, both medicinal products can be resumed at the same dose. RYBREVANT should be permanently discontinued in case of recurrent VTE events despite appropriate anticoagulation. Treatment can continue with lazertinib at the same dose.

Impact on the Risk-Benefit Balance of the Product

While the incidence of VTE events was higher in participants treated with the combination of amivantamab IV and lazertinib compared with osimertinib in Trial NSC3003, the greatest discordance in events occurred during the first 4 months of study treatment, the events were predominantly Grade 2, non-serious, and were manageable with therapeutic anticoagulation. The incidence of VTE events was lower in participants treated with amivantamab SC and lazertinib in Trial NSC2002 than in participants receiving amivantamab IV with lazertinib in Trial NSC3003. Of note, the study protocols had different recommendations for anticoagulant use, resulting in most participants not taking anticoagulation in Trial NSC3003. The use of recommended or mandatory prophylactic anticoagulation was shown to be safe and effective, without a notable increase in serious bleeding events. The SmPC and PL provide information on how to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy in patients treated with RYBREVANT in combination with lazertinib.

Public Health Impact

No public health impact is anticipated.

Important Potential Risk: Hepatotoxicity

Potential Mechanisms

EGFR and MET signaling play complex and important roles in the maintenance of hepatic liver repair and regeneration (Komposch 2015). Thus, inhibition of these pathways may lead to aminotransferase elevations and hepatic dysfunction. Aminotransferase elevations, including rare reports of hepatic failure with fatal outcomes, have been observed with the small-molecule EGFR tyrosine inhibitors (Huang 2020; TARCEVA SmPC 2023; IRESSA SmPC 2023; GIOTRIF SmPC 2023). While CYP metabolism may play a role in the development of liver abnormalities due to reactive metabolites or immune-mediated injury with some of the TKI small molecules (Hardy 2014; Shah 2013), patients treated with the EGFR inhibitor monoclonal antibodies have also experienced increased aminotransferases (ERBITUX SmPC 2022).

Evidence Source(s) and Strength of Evidence

In repeat-dose toxicity studies in cynomolgus monkeys, slight elevations in serum ALT and AST were not considered adverse.

Cases of ALT, AST, ALP, bilirubin, and GGT increased have been reported in participants treated with amivantamab IV and SC in clinical trials. Hepatotoxicity-related reactions, mostly elevations of serum transaminases, are described in the SmPC for RYBREVANT. There have been no confirmed cases of DILI.

Characterization of the Risk

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity – Amivantamab IV Trials

	IV Trials				
	Non-randomized Trials[a]	Randomized Trials[b]			All Clinical IV Trials Population[c]
	Amivantamab[d]	Amivantamab +Lazertinib[e]	Amivantamab Carboplatin +Pemetrexed[f]	Comparator[g]	Amivantamab
Advanced NSCLC					
Number of subjects treated	153	421	281	826	855
Frequency	79 (51.6%)	289 (68.6%)	147 (52.3%)	292 (35.4%)	515 (60.2%)
Odds Ratio (95% CI)[h]		4.00 (3.12,5.14)	2.01 (1.53,2.64)		
Seriousness					
Was serious	0	14 (3.3%)	1 (0.4%)	17 (2.1%)	15 (1.8%)
Outcomes					
Fatal	0	0	0	0	0
Not recovered/Not Resolved	28 (18.3%)	104 (24.7%)	51 (18.1%)	81 (9.8%)	183 (21.4%)
Recovering/Resolving	16 (10.5%)	59 (14.0%)	41 (14.6%)	48 (5.8%)	116 (13.6%)
Recovered/resolved with sequelae	0	4 (1.0%)	0	0	4 (0.5%)
Recovered/Resolved	32 (20.9%)	122 (29.0%)	55 (19.6%)	162 (19.6%)	209 (24.4%)
Unknown	3 (2.0%)	0	0	1 (0.1%)	3 (0.4%)

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity – Amivantamab IV Trials

	IV Trials				
	Non-randomized Trials[a]	Randomized Trials[b]			All Clinical IV Trials Population[c]
	Amivantamab[d]	Amivantamab +Lazertinib[e]	Amivantamab Carboplatin +Pemetrexed[f]	Comparator[g]	Amivantamab
Severity					
Worst Grade=1	27 (17.6%)	77 (18.3%)	49 (17.4%)	179 (21.7%)	153 (17.9%)
Worst Grade=2	41 (26.8%)	155 (36.8%)	72 (25.6%)	70 (8.5%)	268 (31.3%)
Worst Grade=3	10 (6.5%)	55 (13.1%)	25 (8.9%)	42 (5.1%)	90 (10.5%)
Worst Grade=4	1 (0.7%)	2 (0.5%)	1 (0.4%)	1 (0.1%)	4 (0.5%)
Worst Grade=5	0	0	0	0	0
Missing Grade	0	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardised MedDRA Queries (SMQs) for Hepatotoxicity.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst "outcome" or "grade" are used in case of multiple events, respectively.
Note: "Unknown" outcome category includes AE records with missing outcome in current data.
[a] Note: Non-randomized trials included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[b] Note: Randomized trials included: NSC3001, NSC3002 and NSC3003.
[c] Note: Trials included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy, ACP arm from NSC3001, ACP arm from NSC3002, and Amivantamab + Lazertinib arm from NSC3003.
[d] Note: Trial included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[e] Note: Trial included: Amivantamab + Lazertinib arm from NSC3003.
[f] Note: Trials included: ACP arm from NSC3001 and ACP arm from NSC3002.
[g] Note: Comparators included: Carboplatin + Pemetrexed (NSC3001 and NSC3002), Osimertinib (NSC3003).
[h] Odds Ratio is for event comparison of Amivantamab + Lazertinib versus Comparator and Amivantamab + Carboplatin + Pemetrexed versus Comparator.
RP2D (recommended Phase 2 dose): 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight >=80 kg.

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Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity – Amivantamab SC Trials

	SC Trials			
	Non-randomized Trials[a]			
	Amivantamab SC (Q2W) + Lazertinib[b]	Amivantamab SC (Q4W) + Lazertinib[c]	Amivantamab SC (Q3W) + Carboplatin + Pemetrexed[d]	All Clinical SC Trials Population[e]
Advanced NSCLC				
Number of subjects treated	135	77	143	355
Frequency	104 (77.0%)	59 (76.6%)	95 (66.4%)	258 (72.7%)
Seriousness				
Was serious	4 (3.0%)	2 (2.6%)	2 (1.4%)	8 (2.3%)
Outcomes				
Fatal	0	0	0	0
Not Recovered/Not Resolved	29 (21.5%)	26 (33.8%)	41 (28.7%)	96 (27.0%)
Recovering/Resolving	27 (20.0%)	14 (18.2%)	15 (10.5%)	56 (15.8%)
Recovered/Resolved with sequelae	0	0	0	0
Recovered/Resolved	40 (29.6%)	15 (19.5%)	37 (25.9%)	92 (25.9%)
Unknown	8 (5.9%)	4 (5.2%)	2 (1.4%)	14 (3.9%)

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity – Amivantamab SC Trials

	SC Trials			
	Non-randomized Trials[a]			
	Amivantamab SC (Q2W) + Lazertinib[b]	Amivantamab SC (Q4W) + Lazertinib[c]	Amivantamab SC (Q3W) + Carboplatin + Pemetrexed[d]	All Clinical SC Trials Population[e]
Severity				
Worst Grade=1	38 (28.1%)	20 (26.0%)	32 (22.4%)	90 (25.4%)
Worst Grade=2	51 (37.8%)	32 (41.6%)	45 (31.5%)	128 (36.1%)
Worst Grade=3	14 (10.4%)	6 (7.8%)	18 (12.6%)	38 (10.7%)
Worst Grade=4	1 (0.7%)	1 (1.3%)	0	2 (0.6%)
Worst Grade=5	0	0	0	0
Missing Grade	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardized MedDRA Queries (SMQs) for Hepatotoxicity.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst outcome or grade are used in case of multiple events, respectively.
Note: Unknown outcome category includes AE records with missing outcome in current data.
[a] Note: Non-randomized trials included: NSC2002 Cohorts 1&6, Cohort 5, and Cohorts 2&3b.
[b] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib) from NSC2002.
[c] Note: Trial included: Cohort 5 (Amivantamab SC Q4W + Lazertinib) from NSC2002.
[d] Note: Trial included: Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[e] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib), Cohort 5 (Amivantamab SC Q4W + Lazertinib), and Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
Key: Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q4W = once every 4 weeks.

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In participants treated with amivantamab IV, frequently observed AEs with amivantamab monotherapy were ALT, AST, ALP, and GGT increased; however, in participants treated with ACP, the incidence of these AEs was comparable with the incidence in participants treated with CP. Increases in laboratory values for these liver enzymes were observed in participants on amivantamab monotherapy, while increases were comparable between ACP and CP treated participants. In Trial NSC3003, the overall incidence of these AEs was higher in the amivantamab+lazertinib arm compared with the osimertinib arm. Liver enzyme elevations were mostly Grade 1 or 2. In Trial NSC3003, the incidence of Grade ≥3 ALT, AST, ALP, and GGT elevations was comparable in participants treated with amivantamab+lazertinib and those treated with osimertinib.

Although there was a higher incidence of AEs of hyperbilirubinemia in participants treated with ACP compared with participants who received CP in Trial NSC3001, most events were Grade 1 and increases in blood bilirubin levels were transient. In Trial NSC3002, there was no difference in incidence of hyperbilirubinemia AEs between ACP and CP treated participants. In Trial NSC3003, the incidence of hyperbilirubinemia AEs was comparable in participants treated with amivantamab+lazertinib and those treated with osimertinib.

In participants treated with amivantamab SC+lazertinib or amivantamab SC+CP (Trial NSC2002), the incidences of AEs for liver enzyme increases were comparable with the incidences in participants who received amivantamab IV+lazertinib (Trial NSC3003) or amivantamab IV+CP (Trials NSC3001 and NSC3002), respectively. Of note, in participants treated with amivantamab SC+lazertinib in Trial NSC2002, a considerable number of participants who had either Grade ≥3

ALT increased and/or Grade ≥3 AST increased, had liver metastases at baseline (4 of 9 participants in Cohort 1 and 6 combined and 3 of 4 participants in Cohort 5).

Hepatotoxicity-related AEs rarely led to treatment discontinuation.

There were no participants treated with amivantamab IV monotherapy or ACP who met criteria for Hy's law (ie, ALT or AST elevations ≥3 × ULN with concurrent total bilirubin ≥2 × ULN and ALP <2 × ULN). In Trial NSC3003, 1 participant in the amivanatamab+lazertinib arm and 2 participants in the osimertinib arm met laboratory criteria for potential drug-induced serious hepatotoxicity (ie, ALT or AST ≥3x ULN and total bilirubin ≥2x ULN). Following further evaluation of these cases, including assessment of confounding factors, there was no evidence for DILI for amivantamab in combination with lazertinib. No participants treated with amivantamab SC either in combination with lazertinib or in combination with CP met laboratory criteria for drug-induced serious hepatotoxicity.

Liver AEs and laboratory abnormalities are generally non-severe and without clinical sequelae. However, drug-induced liver injury could be serious, potentially fatal, or lead to liver transplantation.

No new safety information that impacts the risk-benefit balance of the product has emerged from postmarketing experience.

Risk Factors and Risk Groups

Risk factors associated with EGFR inhibitor-associated hepatotoxicity include pre-existing liver disease, worsening liver metastases, and the use of concomitant hepatotoxic medications (Kim 2018; Han 2020).

Preventability

There are no specific recommendations that would prevent the occurrence of liver enzyme elevations.

Impact on the Risk-Benefit Balance of the Product

While increased liver enzymes have been observed in participants treated with amivantamab IV and SC, there have been no clinical sequelae of these elevations and no confirmed cases of DILI. The majority of liver AEs were non-serious, of low severity, and they rarely led to treatment discontinuation. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy for patients treated with RYBREVANT.

Public Health Impact

No public health impact is anticipated.

Important Potential Risk: Impaired fertility and embryofetal toxicity

Potential Mechanisms

Based on data from knockout mice and developmental studies with small-molecule agents, disruption of the EGFR and MET pathways are likely to cause adverse effects on embryofetal and postnatal development and survival, and further at the level of the placenta, lung, skin, heart, and nervous system. Developmental toxicity studies conducted in non-human primates show that the blockade of EGFR and MET signaling also caused embryolethality and abortions (Adamson 1990; Birchmeier 1998; Bladt 1995; Leo 2011; Partanen 1990; Schmidt 1995; Sibilia 1998; Uehara 1995).

Evidence Source(s) and Strength of Evidence

There are no human or animal data to assess the risk of amivantamab during pregnancy. Clinical trials of amivantamab excluded pregnant participants and required adequate contraceptive measures during treatment. There have been no participants who became pregnant while on treatment with amivantamab IV or SC during clinical trials.

Administration of other EGFR and MET inhibitors to pregnant animals has resulted in an increased incidence of impairment of embryofetal development, embryolethality, and abortion. Therefore, based on the mechanism of action and findings in animal models, amivantamab could cause fetal harm when administered to a pregnant patient. Embryofetal toxicity is considered a class warning for EGFR and MET inhibitors (eg, IRESSA USPI 2021; TAGRISSO USPI 2024; ERBITUX USPI 2021; GILOTRIF USPI 2022).

The risk of impaired fertility and embryofetal toxicity is described in the SmPC for amivantamab.

Characterization of the Risk

Frequency, Seriousness, Outcomes, and Severity of Impaired Fertility and Embryofetal Toxicity – Amivantamab IV Trials

	IV Trials				
	Non-randomized Trials[a]	Randomized Trials[b]			All Clinical IV Trials Population[c]
	Amivantamab[d]	Amivantamab +Lazertinib[e]	Amivantamab +Carboplatin +Pemetrexed[f]	Comparator[g]	Amivantamab
Advanced NSCLC					
Number of subjects treated	153	421	281	826	855
Frequency	3 (2.0%)	4 (1.0%)	1 (0.4%)	0	8 (0.9%)
Odds Ratio (95% CI)[h]		-	-		
Seriousness					
Was serious	0	0	0	0	0
Outcomes					
Fatal	0	0	0	0	0
Not Recovered/Not Resolved	1 (0.7%)	2 (0.5%)	0	0	3 (0.4%)
Recovering/Resolving	0	0	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Impaired Fertility and Embryofetal Toxicity – Amivantamab IV Trials

	IV Trials				
	Non-randomized Trials[a]	Randomized Trials[b]			All Clinical IV Trials Population[c]
	Amivantamab[d]	Amivantamab +Lazertinib[e]	Amivantamab +Carboplatin +Pemetrexed[f]	Comparator[g]	Amivantamab
Recovered/Resolved with sequelae	0	0	0	0	0
Recovered/Resolved	2 (1.3%)	2 (0.5%)	1 (0.4%)	0	5 (0.6%)
Unknown	0	0	0	0	0
Severity					
Worst Grade=1	3 (2.0%)	4 (1.0%)	1 (0.4%)	0	8 (0.9%)
Worst Grade=2	0	0	0	0	0
Worst Grade=3	0	0	0	0	0
Worst Grade=4	0	0	0	0	0
Worst Grade=5	0	0	0	0	0
Missing Grade	0	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardized MedDRA Queries (SMQs) for Fertility disorders (narrow search) OR the System Organ Class (SOC) of Pregnancy, Puerperium and Perinatal Conditions OR SOC of Congenital, familial and genetic disorders for subjects aged <=2 years.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst outcome or grade are used in case of multiple events, respectively.
Note: Unknown outcome category includes AE records with missing outcome in current data.
[a] Note: Non-randomized trials included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[b] Note: Randomized trials included: NSC3001, NSC3002 and NSC3003.
[c] Note: Trials included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy, ACP arm from NSC3001, ACP arm from NSC3002, and Amivantamab + Lazertinib arm from NSC3003.
[d] Note: Trial included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[e] Note: Trial included: Amivantamab + Lazertinib arm from NSC3003.
[f] Note: Trials included: ACP arm from NSC3001 and ACP arm from NSC3002.
[g] Note: Comparators included: Carboplatin + Pemetrexed (NSC3001 and NSC3002), Osimertinib (NSC3003).
[h] Odds Ratio is for event comparison of Amivantamab + Lazertinib versus Comparator and Amivantamab + Carboplatin + Pemetrexed versus Comparator.
RP2D (recommended Phase 2 dose): 1,050 mg if baseline weight <80 kg and 1,400 mg if baseline weight >=80 kg.

Modified from: [TSFAE05TOT.RTF] [XCP_ONCOLOGY/Z61186372_73841937/DBR_DWH_PALOMA_2025/RE_RMP_PALOMA/PROD/TSFAE05TOT.SAS] 26MAR2025, 09:09

Frequency, Seriousness, Outcomes, and Severity of Impaired Fertility and Embryofetal Toxicity – Amivantamab SC Trials

	SC Trials			
	Non-randomized Trials[a]			
	Amivantamab SC (Q2W) + Lazertinib[b]	Amivantamab SC (Q4W) + Lazertinib[c]	Amivantamab SC (Q3W) + Carboplatin + Pemetrexed[d]	All Clinical SC Trials Population[e]
Advanced NSCLC				
Number of subjects treated	135	77	143	355
Frequency	4 (3.0%)	1 (1.3%)	3 (2.1%)	8 (2.3%)
Seriousness				
Was serious	0	0	0	0
Outcomes				
Fatal	0	0	0	0
Not Recovered/Not Resolved	2 (1.5%)	1 (1.3%)	2 (1.4%)	5 (1.4%)
Recovering/Resolving	0	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Impaired Fertility and Embryofetal Toxicity – Amivantamab SC Trials

	SC Trials			
	Non-randomized Trials[a]			
	Amivantamab SC (Q2W) + Lazertinib[b]	Amivantamab SC (Q4W) + Lazertinib[c]	Amivantamab SC (Q3W) + Carboplatin + Pemetrexed[d]	All Clinical SC Trials Population[e]
Recovered/Resolved with sequelae	0	0	0	0
Recovered/Resolved	2 (1.5%)	0	1 (0.7%)	3 (0.8%)
Unknown	0	0	0	0
Severity				
Worst Grade=1	3 (2.2%)	1 (1.3%)	3 (2.1%)	7 (2.0%)
Worst Grade=2	1 (0.7%)	0	0	1 (0.3%)
Worst Grade=3	0	0	0	0
Worst Grade=4	0	0	0	0
Worst Grade=5	0	0	0	0
Missing Grade	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardized MedDRA Queries (SMQs)for Fertility disorders (narrow search) OR the System Organ Class (SOC) of Pregnancy, Puerperium and Perinatal Conditions OR SOC of Congenital, familial and genetic disorders for subjects aged <=2 years.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst outcome or grade are used in case of multiple events, respectively.
Note: Unknown outcome category includes AE records with missing outcome in current data.
[a] Note: Non-randomized trials included: NSC2002 Cohorts 1&6, Cohort 5 and Cohorts 2&3b.
[b] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib) from NSC2002.
[c] Note: Trial included: Cohort 5 (Amivantamab SC Q4W + Lazertinib) from NSC2002.
[d] Note: Trial included: Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
[e] Note: Trial included: Cohorts 1&6 (Amivantamab SC Q2W + Lazertinib), Cohort 5 (Amivantamab SC Q4W + Lazertinib), and Cohorts 2&3b (Amivantamab SC Q3W + Carboplatin + Pemetrexed) from NSC2002.
Key: Q2W = once every 2 weeks; Q3W = once every 3 weeks, Q4W = once every 4 weeks.

Modified from: [TSFAE05TOTC.RTF] [XCP_ONCOLOGY/Z61186372_73841937/DBR_DWH_PALOMA_2025/RE_RMP_PALOMA/PROD/TSFAE05TOTC.SAS] 25MAR2025, 19:26

There were 16 cases retrieved in participants receiving amivantamab IV or SC, all with the preferred term of Hematospermia. All cases occurred in adult men with a median age of 58 years (range: 25-73 years). Hematospermia is a usually benign condition that resolves spontaneously and is not indicative of infertility.

There have been no reports of pregnancy in participants taking amivantamab IV or SC in clinical trials.

Risk Factors and Risk Groups

Patients of childbearing potential are at high risk for developing embryofetal toxicity during administration of amivantamab.

Preventability

In the RYBREVANT SmPC Section 4.6, the potential harmful effects of EGFR inhibition on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of amivantamab are described.

Amivantamab should not be given during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the fetus. If the patient becomes pregnant while taking this medicinal product, the patient should be informed of the potential risk to the fetus.

Impact on the Risk-Benefit Balance of the Product

Contraception recommendations included in the SmPC and PL are considered sufficient to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy for patients treated with RYBREVANT.

Public Health Impact

No public health impact is anticipated.

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table Module SVIII: Summary of Safety Concerns

Important Identified Risks	Venous thromboembolic (VTE) events*
Important Potential Risks	Hepatotoxicity
	Impaired fertility and embryofetal toxicity
Missing Information	None

* Applies only to the combination of amivantamab and lazertinib.

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires

Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.3: Ongoing and Planned Additional Pharmacovigilance Activities

Study and Status	Summary of Objectives	Safety Concern(s) Addressed	Milestones	Due Dates
Category 1: Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2: Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3: Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study and Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorization				
Not applicable				
Efficacy studies which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Venous thromboembolic (VTE) events*
Routine risk communication • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** • An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. • Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4 and PL Section 2. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. **Other routine risk minimization measures beyond the Product Information** • Legal status
Hepatotoxicity
Routine risk communication • SmPC Section 4.8 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk** • None **Other routine risk minimization measures beyond the Product Information** • Legal status

Impaired fertility and embryofetal toxicity
Routine risk communication • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk** • The potential harmful effects of EGFR inhibition on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of RYBREVANT, are provided in 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. **Other routine risk minimization measures beyond the Product Information** • Legal status

* Applies only to the combination of amivantamab and lazertinib.

V.2. Additional Risk Minimization Measures

Not applicable. Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of RYBREVANT.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable.

V.3. Summary of Risk Minimization Measures

Table Part V.3: Summary of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Venous thromboembolic (VTE) events*	**Routine risk minimization activities** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** • None **Additional pharmacovigilance activities** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	events is provided in SmPC Section 4.4 and PL Section 2. • Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4 and PL Section 2. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. • Legal status. **Additional risk minimization activities** • None	
Hepatotoxicity	**Routine risk minimization activities** • SmPC Section 4.8 • PL Section 4 • Legal status. **Additional risk minimization activities** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** • None **Additional pharmacovigilance activities** • None
Impaired fertility and embryofetal toxicity	**Routine risk minimization activities** • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • The potential harmful effects of EGFR inhibition on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of RYBREVANT, are provided in 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** • None **Additional pharmacovigilance activities** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	treatment with RYBREVANT, as described in PL Section 2. • Legal status. **Additional risk minimization activities** • None	

* Applies only to the combination of amivantamab and lazertinib.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for RYBREVANT (amivantamab)

This is a summary of the risk management plan (RMP) for RYBREVANT. The RMP details important risks of RYBREVANT, how these risks can be minimized, and how more information will be obtained about RYBREVANT's risks and uncertainties (missing information).

RYBREVANT's Summary of Product Characteristics (SmPC) and its Package Leaflet (PL) give essential information to healthcare professionals and patients on how RYBREVANT should be used.

This summary of the RMP for RYBREVANT should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of RYBREVANT's RMP.

I. The Medicine and What it is Used For

RYBREVANT is authorized for the treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions, Exon 21 L858R substitution mutations, or activating EGFR Exon 20 insertion (Exon 20 ins) mutations (see SmPC for the full indication). It contains amivantamab as the active substance and it is given by intravenous (IV) infusion or subcutaneous (SC) injection.

Further information about the evaluation of RYBREVANT's benefits can be found in RYBREVANT's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website under the medicine's webpage link to the EPAR summary landing page: https://www.ema.europa.eu/en/medicines/human/EPAR/rybrevant.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of RYBREVANT, together with measures to minimize such risks and the studies for learning more about RYBREVANT's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of Important Risks and Missing Information

Important risks of RYBREVANT are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of RYBREVANT. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Venous thromboembolic (VTE) events*
Important potential risks	Hepatotoxicity Impaired fertility and embryofetal toxicity
Missing information	None

* Applies only to the combination of RYBREVANT and lazertinib.

II.B. Summary of Important Risks

Important Identified Risk: Venous thromboembolic (VTE) events*	
Evidence for linking the risk to the medicine	Venous thromboembolic (VTE) events is an important identified risk for RYBREVANT only when given in combination with lazertinib. The incidence of VTE events was higher in participants treated with the combination of RYBREVANT IV and lazertinib versus osimertinib in Trial NSC3003. The greatest discordance in events occurred during the first 4 months of study treatment. Importantly, the incidence rate of VTE events associated with RYBREVANT IV monotherapy in Trial EDI1001 and with RYBREVANT +carboplatin-pemetrexed in Trials NSC3001 and NSC3002 is consistent with background rates associated with NSCLC. The incidence of VTE events was lower in participants treated with RYBREVANT SC and lazertinib in Trial NSC2002 than in participants receiving RYBREVANT IV and lazertinib in Trial NSC3003. Venous thromboembolism was identified as an adverse reaction for the combination of RYBREVANT and lazertinib and is described in the SmPC for RYBREVANT.

Risk factors and risk groups	Lung cancer is a risk factor for VTE events. Additional risk factors for VTE events associated with use of RYBREVANT in combination with lazertinib identified in open-label trials include age ≥60 years, Eastern Cooperative Oncology Group (ECOG)=1, and Responders (ie, patients with partial response or complete response).
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. • Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4 and PL Section 2. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. • Legal status. **Additional risk minimization measures** • None

* Applies only to the combination of RYBREVANT and lazertinib.

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	In repeat-dose toxicity studies in cynomolgus monkeys, slight elevations in serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were not considered adverse. Cases of ALT, AST, blood alkaline phosphatase (ALP), bilirubin, and gamma-glutamyltransferase increased have been reported in participants treated with RYBREVANT IV and SC in clinical trials. Hepatotoxicity-related reactions, mostly elevations of serum transaminases, are described in the SmPC for RYBREVANT. There have been no confirmed cases of drug-induced liver injury.
Risk factors and risk groups	Risk factors associated with EGFR inhibitor-associated hepatotoxicity include pre-existing liver disease, worsening liver metastases, and the use of concomitant hepatotoxic medications.

Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.8 • PL Section 4 • Legal status. **Additional risk minimization measures** • None

Important Potential Risk: Impaired fertility and embryofetal toxicity	
Evidence for linking the risk to the medicine	There are no human or animal data to assess the risk of RYBREVANT during pregnancy. Clinical trials of RYBREVANT excluded pregnant participants and required adequate contraceptive measures during treatment. There have been no participants who became pregnant while on treatment with RYBREVANT IV or SC during clinical trials. Administration of other EGFR and mesenchymal-epidermal transition (MET) inhibitors to pregnant animals has resulted in an increased incidence of impairment of embryofetal development, embryolethality, and abortion. Therefore, based on the mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant patient. Embryofetal toxicity is considered a class warning for EGFR and MET inhibitors. The risk of impaired fertility and embryofetal toxicity is described in the SmPC for RYBREVANT.
Risk factors and risk groups	Patients of childbearing potential are at high risk for developing embryofetal toxicity during administration of RYBREVANT.
Risk minimization measures	**Routine risk minimization measures** • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • The potential harmful effects of EGFR inhibition on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 months after the last dose of RYBREVANT, are provided in 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

II.C. Postauthorization Development Plan

II.C.1. Studies That are Conditions of the Marketing Authorization

No studies are conditions of the marketing authorization or specific obligation of RYBREVANT.

II.C.2. Other Studies in Postauthorization Development Plan

No studies are required for RYBREVANT.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Reaction Follow-up Questionnaires

Not applicable.

Annex 6: Details of Additional Risk Minimization Activities

Key Messages of Additional Risk Minimization Activities

Not applicable.