European Union Risk Management Plan
RYBREVANT (amivantamab)

Data lock point for current RMP	11 Aug 2023	Version number	5.2

CHMP Opinion Date: 14November2024

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RMP Version Number: 5.2
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EDMS Number: EDMS-RIM-1468980, 1.0

PPD

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	5.2
Rationale for submitting an updated RMP (if applicable)	Type II variation to broaden the existing amivantamab indication to include combination treatment with lazertinib for the first-line treatment of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.
Summary of significant changes in this RMP:	The following indication is added: 'RYBREVANT 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' based on data from Trial 73841937NSC3003. Venous thromboembolic (VTE) events is added as an important identified risk for amivantamab when given in combination with lazertinib.

Other RMP Versions Under Evaluation:

RMP Version Number	Submitted on	Procedure Number
4.1	29 May 2024	EMEA/H/C/005454/X/0014

Details of the Currently Approved RMP:

Version number of last agreed RMP:	3.2
Approved within procedure	EMEA/H/C/005454/II/0011
Date of approval (Competent authority opinion date)	25 July 2024

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) **(international nonproprietary name [INN] or common name)**	Amivantamab
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Monoclonal antibodies and antibody drug conjugates (L01FX18)
Marketing Authorization Holder (MAH)	Janssen-Cilag International NV
Medicinal products to which the Risk Management Plan (RMP) refers	1
Invented name(s) in the European Economic Area (EEA)	RYBREVANT
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** Fully human immunoglobulin G1 (IgG1)-based bispecific antibody
	Summary of mode of action Amivantamab is a fully human IgG1-based bispecific antibody directed against the epidermal growth factor receptor (EGFR) and mesenchymal-epidermal transition (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.
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet

<table>
<tr><td>Indication(s) in the EEA</td><td>Current:
RYBREVANT 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></td><td>Proposed: Not applicable</td></tr>
<tr><td>Dosage in the EEA</td><td>Current:
The recommended dosages of RYBREVANT 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>
<tr><td rowspan="2">≥80 kg</td><td>1,750 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>2,100 mg</td><td>Every 3 weeks starting at Week 7 onwards</td></tr>
</table>
[a] Dose adjustments not required for subsequent body weight changes.</td></tr>
</table>

The recommended dosages of RYBREVANT 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 is administered by intravenous (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.

Proposed: Not applicable

Pharmaceutical form(s) and strengths

Current:

RYBREVANT is available as a 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.

Proposed: Not applicable

Is/will the product be subject to additional monitoring in the European Union (EU)?	☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

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

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

In the literature, there are limited population data available specifically on advanced NSCLC with EGFR Exon 20 insertion (Exon 20ins) mutations. However, relevant available data on lung cancer, NSCLC, and EGFR mutations are presented below, along with any specific data on NSCLC with EGFR Exon 20ins mutations, Exon 19 deletions, or Exon 21 L858R substitution mutations.

Incidence:

Lung cancer remains the second most frequently diagnosed cancer in men and women, and its incidence continues to increase. In 2020, an estimated 2.2 million new cases of lung cancer were diagnosed globally, accounting for approximately 11.4% of the global cancer burden, with an age-standardized incidence rate of 22.5 per 100,000 persons (31.5 in male, 14.6 in female) (Ferlay 2020). In Europe, an estimated 477,534 new cases of lung cancer were reported in 2020 (Globocan 2020). According to the European Cancer Information System, the 27 EU countries projected 318,327 new cases of lung cancer by the end of 2020 (ECIS 2023). 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 small cell lung cancer (SCLC) and NSCLC. In general, about 10% to 15% of all lung cancers are SCLC and 80% to 85% are NSCLC (Zappa 2016, American Cancer Society 2023). 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 (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 (Yasuda 2012, Oxnard 2013, Vyse 2019).

Prevalence:

The global 5-year prevalence for lung cancer was approximately 2.6 million persons in 2020 (Ferlay 2020). The 5-year prevalence of lung cancer in Europe was approximately 582,924 persons in 2020 (Ferlay 2020). 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 10.6 per 10,000 persons at the end of 2020 (NORDCAN 2023).

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).

Demographics of the Population Within the Authorized Indication - Age, Sex, Racial and/or Ethnic Origin, 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

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 2023).

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 2022). 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 2023). 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 (Rudin 2009, Kuśnierczyk 2023). 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, human

immunodeficiency virus (HIV) infection, and beta-carotene supplements in heavy smokers (National Cancer Institute 2023).

Main Existing Treatment Options:

The treatment regimen for NSCLC depends on the histology of the tumor (ie, squamous cell, large cell, or adenocarcinoma), stage of the cancer at diagnosis, the presence or absence of a driver mutation (EGFR and others), and markers predictive of immunotherapy response (eg, programmed cell death-ligand 1 [PD-L1]). Treatment can include surgery, radiotherapy, immunotherapy, chemotherapy, and targeted therapy such as TKIs. In patients with metastatic disease, the European Society for Medical Oncology (ESMO) guidelines and American Society of Clinical Oncology (ASCO) guidelines recommend testing for driver mutations (tests available will vary between different health systems) (Hanna 2017, Planchard 2018, Hanna 2020), 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-programmed cell death protein-1 (PD-1), or PD-L1, antibody, either alone or in combination with chemotherapy (depending on PD-L1 expression), is the recommended first-line therapy.

Several approved TKIs, including erlotinib, gefitinib, and afatinib have been the standard-of-care first-line therapy for patients with NSCLC with tumors bearing specific EGFR mutations. Although most of these patients initially respond, virtually all eventually progress, with approximately 60% of patients acquiring a second-site EGFR point mutation, T790M, leading to resistance to first- and second-generation TKIs (Yu 2013). Patients with EGFR T790M+ mutant cancers can be treated in the second-line setting with third-generation TKIs (eg, osimertinib), which are active against this mutation. In contrast, relapsed tumors without EGFR T790M mutations are treated with chemotherapy. Following third-generation TKI treatment, resistance occurs in ~30% of cases through tertiary EGFR mutation at the C797S position (Chabon 2016). To date, no targeted therapy has been approved in the treatment of disease that carries the C797S mutation in this clinical setting.

There are no approved targeted therapies for first-line treatment of patients with EGFR Exon 20ins disease, and this subgroup of EGFR-mutated NSCLC remains less well-studied in comparison to TKI-sensitive EGFR L858R and Exon 19del disease. Approved first-, second- and third-generation EGFR TKIs have demonstrated limited benefit in patients with Exon 20ins in small retrospective analyses (Beau-Faller 2014, Naidoo 2015, Wu 2019). Exon 20ins have been excluded from many prospective trials of EGFR inhibitors due to the reports of resistance to EGFR TKIs (Oxnard 2013).

In the absence of approved targeted therapies, patients with EGFR Exon 20ins mutations are generally treated as if they are TKI resistant or molecular test negative. Based on the totality of the experience with immunotherapy in EGFR mutant disease, the ESMO and ASCO guidelines do not recommend immunotherapy for first-line treatment. Therefore, platinum-based doublet chemotherapy remains the standard-of-care first-line therapy for patients with NSCLC with EGFR Exon 20ins disease. Unfortunately, this standard-of-care has been associated with poor outcomes as evidenced by real-world evidence (ie, median real-world progression-free survival [PFS] of 6.6 months and median real-world overall survival [OS] of 17.4 months; Information Summary

2021). When compared to patients with classical EGFR mutations, the corresponding median real-world PFS and OS associated with EGFR TKI therapy were 10.3 months and 25.5 months, respectively.

After progression on platinum-based, doublet chemotherapy, amivantamab is the standard-of-care for Exon 20ins NSCLC. Single-agent chemotherapies are commonly utilized in patients with NSCLC but are associated with relatively low overall response rate (8%-12%) and median PFS (2-3 months) in randomized Phase 3 trials (Borghaei 2015, Hanna 2004). Single-agent immunotherapy with agents inhibiting PD-1 (anti-PD-1) or its ligand (anti-PD-L1), although approved for use in NSCLC in the second-line setting, has been suggested to be less effective than single-agent chemotherapy in patients with EGFR mutation disease (Borghaei 2015, Rittmeyer 2017). Given the demonstrated activity of amivantamab monotherapy in patients with EGFR Exon 20ins NSCLC in the second-line setting, the addition of amivantamab to standard-of-care first-line treatment is expected to address this unmet medical need by improving first-line therapy for this population, utilizing targeted therapy to provide deeper initial responses and prolonged disease control.

The current standard of care for the first-line treatment of locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (EGFRm NSCLC) is a third-generation EGFR TKI, most commonly osimertinib. Compared with first- and second-generation EGFR TKIs, third-generation EGFR TKIs provide activity against the T790M resistance mutation and may penetrate the blood-brain barrier better (Reungwetwattana 2018). This may delay the incidence of brain metastases, which are reported in up to one-third of patients with EGFRm NSCLC, a higher rate than that reported with EGFR wild-type NSCLC (Li 2017, Gillespie 2023). In the FLAURA study, a median PFS by blinded independent central review of 17.7 months and a median OS of 38.6 months were seen with osimertinib in the first-line setting (Soria 2018).

Despite the improved initial disease control with osimertinib, nearly all patients treated with osimertinib will develop resistance and their disease will progress. There are currently no approved targeted therapies for the treatment of these patients once resistance has developed. The poor prognosis of patients with EGFRm NSCLC is more striking given the fact that patients with this disease are generally younger and healthier than other patients with lung cancer (Zhang 2016, O'Leary 2020, Pecci 2022, Nadal 2023). While osimertinib represents a significant advance over earlier EGFR TKIs, there is a need to improve first-line treatment options prior to the development of resistance in order to extend PFS beyond what is seen with osimertinib monotherapy. The most common mechanisms of resistance to osimertinib are due to alterations in the EGFR (eg, C797S mutation, EGFR amplification) and MET (eg, MET amplification, MET Exon 14 skipping) pathways (Remon 2016). Given this, an agent with activity in tumors with activated EGFR and MET pathways may be of particular interest in EGFR-mutated NSCLC; targeting resistance mechanisms proactively may have been central to the improved outcomes seen with osimertinib in FLAURA.

There are currently no targeted therapies approved for patients with EGFRm NSCLC whose disease has progressed on or after osimertinib, despite evidence that the disease continues to be

heavily dependent on signaling through the EGFR pathway (Remon 2016). Standard of care remains platinum-based doublet chemotherapy, such as carboplatin and pemetrexed (Hendriks 2023; Planchard 2018). Treatment with carboplatin and pemetrexed after first- or second-generation EGFR TKIs is associated with limited efficacy, with an objective response rate of approximately 30% and a median PFS of 4-5 months (Mok 2017, Soria 2015). Real-world data looking at outcomes for patients with EGFRm NSCLC with disease progression on or after osimertinib, many of whom receive platinum doublet chemotherapy, show a median real-world PFS of 3.4 months (Sabari 2022).

Natural History of the Indicated Condition 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 2023).

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 24% (Howlader 2020); 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 (Pao 2004, DerSarkissian 2019).

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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (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 Good Laboratory Practice ([GLP]; 21 CFR, Part 58) and/or the principles of Organisation for Economic Co-operation and Development (OECD)-GLP in countries that are part of the OECD Mutual Acceptance of Data process, and include the appropriate documentation.

Key Safety Findings	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.

Key Safety Findings	Relevance to Human Usage
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. Immunoglobulin G (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.
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 interstitial lung disease (ILD) is a known class effect.

Key Safety Findings	Relevance to Human Usage
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.
Hepatotoxicity	
In toxicity studies in cynomolgus monkeys, non-adverse, slight increases in alanine aminotransferase (ALT) and aspartate aminotransferase (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 anti-drug antibodies (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 (interleukin [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.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	Hepatotoxicity
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The safety of amivantamab 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 pharmacokinetics 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 recommended Phase 2 dose (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 Independent Data Monitoring Committee (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, an urgent safety measure (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 61186372EDI1001 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 advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, which is the population part of the indication.

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

The randomized clinical trials population includes 3 trials:

- Trial NSC3001
- Trial NSC3002
- Trial NSC3003

Exposure to amivantamab in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.4 for all participants by duration, 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).

Table SIII.1: Exposure by Duration: Randomized Clinical Trials Population

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 by Age Group and Sex: Randomized Clinical Trials Population

	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 by Dose: Randomized Clinical Trials Population

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 by Special Populations: Randomized Clinical Trials 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 all clinical trials population includes 4 trials:

- 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.

Exposure to amivantamab in the all clinical trials population is summarized in Tables SIII.5 through SIII.8 for all participants by duration, 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).

Table SIII.5: Exposure by Duration: All Clinical Trials Population

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.6: Exposure by Age Group and Sex: All Clinical Trials Population

	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.7: Exposure by Dose: All Clinical Trials Population

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 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.8: Exposure by Special Populations: All Clinical Trials 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

Table SIII.8: Exposure by Special Populations: All Clinical Trials Population

Population	Patients	Person-months
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

[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, Arm A (Amivantamab + Lazertinib) from NSC3003, and Monotherapy from EDI1001 (at RP2D with Exon20ins mutation and prior exposure to chemotherapy).

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PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within 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 adverse events (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 infusion-related reaction (IRR) on first dose administration.
Considered to be included as missing information	No
Rationale (if not included as missing information)	The summary of product characteristics (SmPC) provides sufficient guidance to reduce the risk of IRRs, 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.
Considered to be 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.** • **Prolonged QTcF (QT corrected for heart rate using Fridericia's formula) 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 corrected QT (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 New York Heart Association (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.**
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.
Considered to be included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

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.
Considered to be 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.
Considered to be 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.
Considered to be 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 Detect Adverse Reactions in Clinical Trial Development Programs

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

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

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 in the all clinical trials population, 312 (36.5%) participants were white, while 501 (58.6%) participants were Asian, 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.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Pediatric population	Not included in the clinical development program.
Elderly	Of the 855 participants 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.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Of the 855 participants in the all clinical trials population, there were 88 (10.3%) participants with mild hepatic impairment at baseline (total bilirubin ≤ upper limit of normal (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.

Patients with renal impairment	Of the 855 participants in the all clinical trials population, there were 323 (37.8%) participants with mild renal impairment at baseline (estimated glomerular filtration rate [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).
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

Summary of Missing Information Due to Limitations of the Clinical Trial Program

None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

The postauthorization exposure presented in this section is for RYBREVANT monotherapy. RYBREVANT is currently not marketed as part of combination therapies.

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 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 (Launch to 31 May 2023)

Region	Total Milligrams	Treatment Courses
European Union	4,309,550	351
North America[a]	15,266,067	1,247
Rest of World	2,789,150	227
Total	22,364,767	1,825

Note: In the LYNX database, the sales data is only available for the entire month. Therefore, per the standard approach, the exposure estimates are calculated for the complete month.

[a] Sales were reported only for the United States and Canada

Based on 22,364,767 mg distributed worldwide by the MAH from launch to 31 May 2023, the estimated exposure to amivantamab is 1,825 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 Safety Concerns and Reclassification with a Submission of an Updated RMP

Venous thromboembolic (VTE) events is added as an important identified risk for amivantamab when given in combination with lazertinib. Following review of the unblinded safety and efficacy data during the protocol-specified futility analysis evaluation of Trial NSC3003, the IDMC observed an imbalance in the incidence of VTE events in participants treated with the combination of amivantamab and lazertinib as compared to the 2-blinded control TKI monotherapy arms (osimertinib and lazertinib), particularly within the first 4 months of treatment initiation with the combination of amivantamab and lazertinib, and an urgent safety measure notification was issued. Signal evaluation conclusions supported a causal association of VTE events with the use of combination anti-EGFR therapy with amivantamab and lazertinib in patients with EGFR-mutant NSCLC, as compared to TKI monotherapy. VTE was included as an important identified risk for

the combination of amivantamab and lazertinib in the Periodic Benefit Risk Evaluation Report for amivantamab. Further analysis of the unblinded NSC3003 safety data supports the safety signal conclusion. Importantly, the VTE events incidence rate associated with amivantamab monotherapy reported in Trial EDI1001 and with ACP in Trials NSC3001 and NSC3002 was consistent with background rates associated with NSCLC. Venous thromboembolism is included as an adverse reaction for the combination of amivantamab and lazertinib in Section 4.8 of the SmPC and specific guidance to minimize and manage the risk is included in SmPC Sections 4.2 and 4.4.

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

Important identified risks

1. Infusion-related reaction
2. Venous thromboembolic (VTE) events*

Important potential risks

1. Hepatotoxicity
2. Impaired fertility and embryofetal toxicity

Missing information

There is no missing information for amivantamab.

Medical Dictionary for Regulatory Activities (MedDRA) Search Strategies for the evaluation of the important identified and important potential risks are listed in Annex 7.3.

MedDRA version 25.0 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: Infusion-related reaction

Potential Mechanisms:

Unwanted systemic IRRs, including severe reactions, upon the introduction of a new protein therapeutic infusion are frequently observed but the mechanisms inducing the reactions are varied (Cáceres 2019, Matucci 2016). The exact pathophysiology of amivantamab IRRs is still unknown. However, translational studies utilizing serum samples drawn from a subset of participants prior to, during, and at the conclusion of the first dose of amivantamab have been able to exclude cytokine release syndrome, complement activation, tumor lysis syndrome, and mast cell degranulation as causative factors of amivantamab-related IRRs. Lastly, the low recurrence rate of IRRs after the initial amivantamab infusion suggests that a role of pre-formed IgEs or other immunoglobulins is inconsistent with the IRRs associated with amivantamab.

Evidence Source(s) and Strength of Evidence:

Cases of IRR have been reported in participants treated with amivantamab in clinical trials and IRR was identified as adverse reaction. The risk for IRR and IRR as an adverse reaction are described in the SmPC for RYBREVANT.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Infusion-related Reactions

	Randomized Trials With Non-Amivantamab Control[a]			Trials Without Non-Amivantamab Control[b]	All Clinical Trials Population[c]
	Amivantamab +Carboplatin +Pemetrexed[d]	Amivantamab +Lazertinib[e]	Comparator[f]	Amivantamab	Amivantamab
Advanced NSCLC					
Number of subjects treated	281	421	826	153	855
Frequency	139 (49.5%)	265 (62.9%)	3 (0.4%)	97 (63.4%)	501 (58.6%)
Odds Ratio (95% CI)[g]	268.53 (84.39,854.45)	466.00 (147.44,1,472.83)			
Seriousness					
Was serious	3 (1.1%)	9 (2.1%)	0	2 (1.3%)	14 (1.6%)
Outcomes					
Fatal	0	0	0	0	0
Not recovered/Not Resolved	0	0	0	0	0
Recovering/Resolving	0	3 (0.7%)	0	0	3 (0.4%)
Recovered/resolved with sequelae	0	3 (0.7%)	0	0	3 (0.4%)
Recovered/Resolved	139 (49.5%)	259 (61.5%)	3 (0.4%)	97 (63.4%)	495 (57.9%)
Unknown	0	0	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Infusion-related Reactions

	Randomized Trials With Non-Amivantamab Control[a]			Trials Without Non-Amivantamab Control[b]	All Clinical Trials Population[c]
	Amivantamab +Carboplatin +Pemetrexed[d]	Amivantamab +Lazertinib[e]	Comparator[f]	Amivantamab	Amivantamab
Severity					
Worst Grade=1	33 (11.7%)	111 (26.4%)	3 (0.4%)	16 (10.5%)	160 (18.7%)
Worst Grade=2	97 (34.5%)	127 (30.2%)	0	77 (50.3%)	301 (35.2%)
Worst Grade=3	9 (3.2%)	23 (5.5%)	0	4 (2.6%)	36 (4.2%)
Worst Grade=4	0	4 (1.0%)	0	0	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 Preferred Term (PT) infusion related reaction.
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: Trials included: NSC3001, NSC3002, and NSC3003.
[b] Note: Trial included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[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: Trials included: ACP arm from NSC3001 and ACP arm from NSC3002.
[e] Note: Trial included: Amivantamab + Lazertinib arm from NSC3003.
[f] Note: Comparators included: Carboplatin + Pemetrexed (NSC3001 and NSC3002), Osimertinib (NSC3003).
[g] Odds Ratio is for event comparison of Amivantamab + Carboplatin + Pemetrexed versus Comparator and Amivantamab + Lazertinib 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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Infusion-related reactions frequently occurred in participants treated with amivantamab in clinical trials. Almost all IRRs were Grade 1 or 2, were non-serious, and occurred at the first infusion with a median time to onset of 1 hour. The most frequent signs and symptoms include chills, dyspnea, nausea, flushing, chest discomfort, and vomiting. IRR was manageable with pre-infusion medicinal products, dose interruption or reduction, and supportive care. With appropriate management of IRR, discontinuations of study treatment were low.

Most IRRs are mild to moderate in severity, transient, and can be treated by amivantamab interruption, additional steroids, and antihistamines. They may lead to discomfort and inconvenience for patients. Although rare, serious IRRs may result in hospitalization and/or death.

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

Risk Factors and Risk Groups:

No risk factors for the development of IRRs have been identified.

Preventability:

Specific guidance in the SmPC Sections 4.2 and 4.4 is provided to minimize and manage the risk of IRRs. Pre-infusion medicinal products, including glucocorticoids on initial doses during Week 1 (Days 1 and 2), and antihistamines and antipyretics with all doses should be administered prior to

infusion of RYBREVANT to reduce the risk of IRRs. Optional glucocorticoids can be administered on subsequent doses as clinically indicated. Additionally, glucocorticoids should be administered at re-initiation of RYBREVANT after prolonged dose interruptions. In order to further minimize the risk of IRRs, the first dose of RYBREVANT is split over 2 days, with 350 mg IV given on Day 1 and the remainder of the dose given on Day 2. Drug interruption upon the initial recognition of IRR-associated symptoms is required. Additional supportive medicinal products including additional glucocorticoids, antihistamines, antipyretics, and antiemetics are recommended as clinically indicated. The SmPC states that the management of the IRRs is also based on the severity of the reaction, including discontinuation of RYBREVANT for recurrent severe or any life-threatening IRRs.

As stated in the SmPC Section 4.4, patients should be treated with RYBREVANT in a setting with appropriate medical support necessary to treat IRRs.

Impact on the Risk-Benefit Balance of the Product:

While IRRs were frequently observed in participants treated with amivantamab in clinical trials, 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. They rarely led to treatment discontinuation. 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.

Public Health Impact:

No public health impact is anticipated.

Annex 1 MedDRA Term:

Infusion related reaction (Preferred Term [PT])

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 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 monotherapy in Trial EDI1001 and with ACP in Trials NSC3001 and NSC3002 is consistent with background rates associated with NSCLC. 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

	Randomized Trials With Non-Amivantamab Control[a]			Trials Without Non-Amivantamab Control[b]	All Clinical Trials Population[c]
	Amivantamab +Carboplatin +Pemetrexed[d]	Amivantamab +Lazertinib[e]	Comparator[f]	Amivantamab	Amivantamab
Advanced NSCLC					
Number of subjects treated	281	421	826	153	855
Frequency	37 (13.2%)	157 (37.3%)	64 (7.7%)	15 (9.8%)	209 (24.4%)
Odds Ratio (95% CI)[g]	1.81 (1.17,2.77)	7.08 (5.13,9.77)			
Seriousness					
Was serious	7 (2.5%)	46 (10.9%)	24 (2.9%)	5 (3.3%)	58 (6.8%)
Outcomes					
Fatal	0	2 (0.5%)	2 (0.2%)	0	2 (0.2%)
Not recovered/Not Resolved	15 (5.3%)	41 (9.7%)	19 (2.3%)	4 (2.6%)	60 (7.0%)
Recovering/Resolving	3 (1.1%)	47 (11.2%)	18 (2.2%)	4 (2.6%)	54 (6.3%)
Recovered/resolved with sequelae	1 (0.4%)	1 (0.2%)	0	0	2 (0.2%)
Recovered/Resolved	18 (6.4%)	66 (15.7%)	25 (3.0%)	7 (4.6%)	91 (10.6%)
Unknown	0	0	0	0	0
Severity					
Worst Grade=1	2 (0.7%)	5 (1.2%)	3 (0.4%)	3 (2.0%)	10 (1.2%)
Worst Grade=2	27 (9.6%)	105 (24.9%)	33 (4.0%)	4 (2.6%)	136 (15.9%)
Worst Grade=3	8 (2.8%)	43 (10.2%)	24 (2.9%)	8 (5.2%)	59 (6.9%)
Worst Grade=4	0	2 (0.5%)	2 (0.2%)	0	2 (0.2%)
Worst Grade=5	0	2 (0.5%)	2 (0.2%)	0	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: Trials included: NSC3001, NSC3002, and NSC3003.
[b] Note: Trial included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[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: Trials included: ACP arm from NSC3001 and ACP arm from NSC3002.
[e] Note: Trial included: Amivantamab + Lazertinib arm from NSC3003.
[f] Note: Comparators included: Carboplatin + Pemetrexed (NSC3001 and NSC3002), Osimertinib (NSC3003).
[g] Odds Ratio is for event comparison of Amivantamab + Carboplatin + Pemetrexed versus Comparator and Amivantamab + Lazertinib 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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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 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+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 pulmonary embolism and deep vein thrombosis.

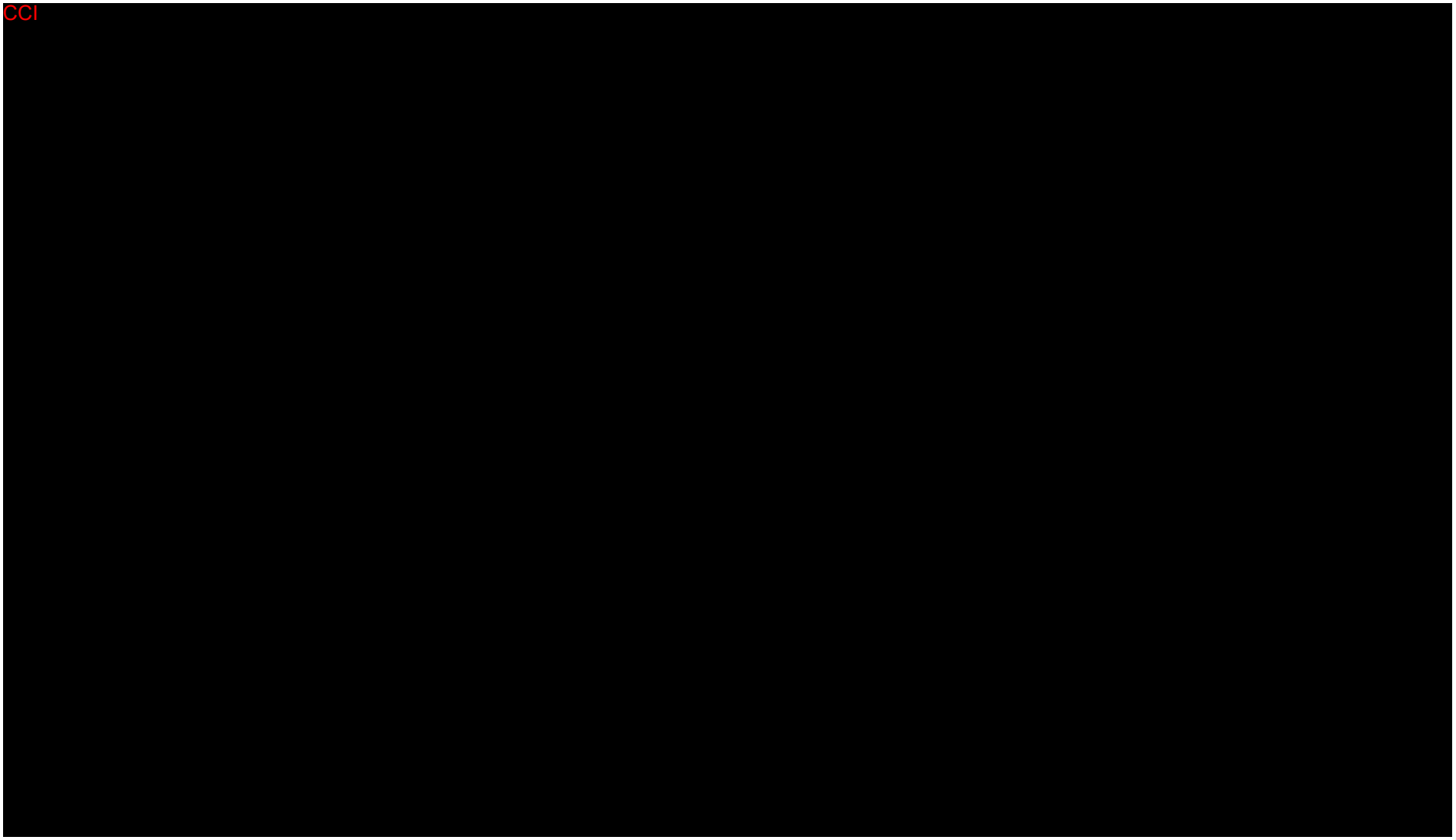
VTE events led to discontinuation of any study agent for 2.9% of participants in the amivantamab+lazertinib arm versus 0.5% of participants in the osimertinib arm.

Median time to first VTE event was 84.0 days in the amivantamab+lazertinib arm and 194.0 days in the osimertinib arm. There was an early separation of the Kaplan-Meier curves indicating greater VTE risk in the amivantamab+lazertinib arm during the first approximately 4 months of treatment. This was followed by a stable separation of the curves for the remainder of the treatment phase (see figure below).

For a large majority of participants (152/157 participants in the amivantamab+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+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+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+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.

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.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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, Eastern Cooperative Oncology Group (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 direct acting oral anticoagulant (DOAC) or a low-molecular weight heparin (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 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 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.

Annex 1 MedDRA Term:

MedDRA SMQ Embolic and thrombotic events, venous (narrow)

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 cytochrome P450 (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 gamma-glutamyltransferase (GGT) increased have been reported in participants treated with amivantamab 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 (DILI).

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity

	Randomized Trials With Non-Amivantamab Control[a]			Trials Without Non-Amivantamab Control[b]	All Clinical Trials Population[c]
	Amivantamab +Carboplatin +Pemetrexed[d]	Amivantamab +Lazertinib[e]	Comparator[f]	Amivantamab	Amivantamab
Advanced NSCLC					
Number of subjects treated	281	421	826	153	855
Frequency	147 (52.3%)	289 (68.6%)	292 (35.4%)	79 (51.6%)	515 (60.2%)
Odds Ratio (95% CI)[g]	2.01 (1.53,2.64)	4.00 (3.12,5.14)			
Seriousness					
Was serious	1 (0.4%)	14 (3.3%)	17 (2.1%)	0	15 (1.8%)
Outcomes					
Fatal	0	0	0	0	0
Not recovered/Not Resolved	51 (18.1%)	104 (24.7%)	81 (9.8%)	28 (18.3%)	183 (21.4%)
Recovering/Resolving	41 (14.6%)	59 (14.0%)	48 (5.8%)	16 (10.5%)	116 (13.6%)
Recovered/resolved with sequelae	0	4 (1.0%)	0	0	4 (0.5%)
Recovered/Resolved	55 (19.6%)	122 (29.0%)	162 (19.6%)	32 (20.9%)	209 (24.4%)
Unknown	0	0	1 (0.1%)	3 (2.0%)	3 (0.4%)

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity

	Randomized Trials With Non-Amivantamab Control[a]			Trials Without Non-Amivantamab Control[b]	All Clinical Trials Population[c]
	Amivantamab +Carboplatin +Pemetrexed[d]	Amivantamab +Lazertinib[e]	Comparator[f]	Amivantamab	Amivantamab
Severity					
Worst Grade=1	49 (17.4%)	77 (18.3%)	179 (21.7%)	27 (17.6%)	153 (17.9%)
Worst Grade=2	72 (25.6%)	155 (36.8%)	70 (8.5%)	41 (26.8%)	268 (31.3%)
Worst Grade=3	25 (8.9%)	55 (13.1%)	42 (5.1%)	10 (6.5%)	90 (10.5%)
Worst Grade=4	1 (0.4%)	2 (0.5%)	1 (0.1%)	1 (0.7%)	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: Trials included: NSC3001, NSC3002, and NSC3003.
[b] Note: Trial included: EDI1001 Monotherapy at RP2D with Exon 20ins mutation and prior exposure to chemotherapy.
[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: Trials included: ACP arm from NSC3001 and ACP arm from NSC3002.
[e] Note: Trial included: Amivantamab + Lazertinib arm from NSC3003.
[f] Note: Comparators included: Carboplatin + Pemetrexed (NSC3001 and NSC3002), Osimertinib (NSC3003).
[g] Odds Ratio is for event comparison of Amivantamab + Carboplatin + Pemetrexed versus Comparator and Amivantamab + Lazertinib 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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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.

Hepatotoxicity-related AEs rarely led to treatment discontinuation.

There were no participants treated with amivantamab 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.

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, 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.

Annex 1 MedDRA Term:

Drug related hepatic disorders (Standardised MedDRA Query [SMQ])

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 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, TARCEVA USPI 2016, IRESSA USPI 2018, TAGRISSO USPI 2023, 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:

There have been no reports of pregnancy in participants taking amivantamab 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.

Annex 1 MedDRA Term:

Pregnancy, puerperium and perinatal conditions (System Organ Class [SOC])

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Infusion-related reaction
	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 Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	Objective/Description	Milestones
Not applicable		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities
Not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns 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.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorizations				
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

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Infusion-related reaction	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations to administer RYBREVANT in a setting with appropriate medical support, for administration of pre-infusion medicinal products, for RYBREVANT initial infusion administration in split doses on Week 1 (Days 1 and 2), and for RYBREVANT administration via specific infusion rates are provided in SmPC Sections 4.2 and 4.4, and PL Section 3. • Recommendations regarding the management of IRRs (eg, interruption or discontinuation of infusion, administration of supportive medicinal products) are provided in SmPC Sections 4.2 and 4.4, and PL Section 4. • Patients with side effects during infusion of RYBREVANT should notify their doctor or nurse immediately, as described in PL Sections 2 and 4. **Other routine risk minimization measures beyond the Product Information:** • Legal status

Safety Concern	Routine Risk Minimization Activities
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
Important Potential Risks	
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

Safety Concern	Routine Risk Minimization Activities
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 ofamivantamab, 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

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

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

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Infusion-related reaction	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:**

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
	• PL Section 2 • PL Section 3 • PL Section 4 • Recommendations to administer RYBREVANT in a setting with appropriate medical support, for administration of pre-infusion medicinal products, for RYBREVANT initial infusion administration in split doses on Week 1 (Days 1 and 2), and for RYBREVANT administration via specific infusion rates are provided in SmPC Sections 4.2 and 4.4, and PL Section 3. • Recommendations regarding the management of IRRs (eg, interruption or discontinuation of infusion, administration of supportive medicinal products) are provided in SmPC Sections 4.2 and 4.4, and PL Section 4. • Patients with side effects during infusion of RYBREVANT should notify their doctor or nurse immediately, as described in PL Sections 2 and 4. • Legal status. **Additional risk minimization measures:** • None	• None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Venous thromboembolic (VTE) events*	**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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Hepatotoxicity	**Routine risk minimization measures:** • SmPC Section 4.8 • PL Section 4 • Legal status. **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Impaired fertility and embryofetal toxicity	**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 amivantamab, 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	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance 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 activating epidermal growth factor receptor (EGFR) Exon 20 insertion (Exon 20 ins) mutations, Exon 19 deletions, or Exon 21 L858R substitution mutations (see SmPC for the full indication). It contains amivantamab as the active substance and it is given by intravenous infusion.

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 proposed 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	Infusion-related reaction 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: Infusion-related reaction	
Evidence for linking the risk to the medicine	Cases of infusion-related reaction (IRR) have been reported in participants treated with RYBREVANT in clinical trials and IRR was identified as adverse reaction. The risk for IRR and IRR as an adverse reaction are described in the SmPC for RYBREVANT.
Risk factors and risk groups	No risk factors for the development of IRRs have been identified.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 3 • PL Section 4 • Recommendations to administer RYBREVANT in a setting with appropriate medical support, for administration of pre-infusion medicinal products, for RYBREVANT initial infusion administration in split doses on Week 1 (Days 1 and 2), and for RYBREVANT administration via specific infusion rates are provided in SmPC Sections 4.2 and 4.4, and PL Section 3. • Recommendations regarding the management of IRRs (eg, interruption or discontinuation of infusion, administration of supportive medicinal products) are provided in SmPC Sections 4.2 and 4.4, and PL Section 4. • Patients with side effects during infusion of RYBREVANT should notify their doctor or nurse immediately, as described in PL Sections 2 and 4. • Legal status. Additional risk minimization measures: • None

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 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 monotherapy in Trial EDI1001 and with RYBREVANT +carboplatin-pemetrexed in Trials NSC3001 and NSC3002 is consistent with background rates associated with NSCLC. 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 amivantamab 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 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 Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of RYBREVANT.

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

There are no other studies required for RYBREVANT.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.