Product Monograph

Including Patient Medication Information

[Pr]RYBREVANT® SC

Amivantamab injection

Produced in mammalian cells using recombinant DNA technology

1600 mg / 10 mL (160 mg / mL)

2240 mg / 14 mL (160 mg / mL)

2400 mg / 15 mL (160 mg / mL)

3520 mg / 22 mL (160 mg / mL)

Solution for subcutaneous injection

Antineoplastic

RYBREVANT® SC indicated:

- for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy,

has been issued market authorization **with conditions**, pending the results of trials to verify its clinical benefit. Patients should be advised of the nature of the authorization. For further information for RYBREVANT® SC please refer to Health Canada's Notice of Compliance with conditions - drug products web site

RYBREVANT® SC indicated:

- in combination with lazertinib for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations,
- in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib,
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations,

have been issued a market authorization **without conditions.**

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Date of Authorization:
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What is a Notice of Compliance with Conditions (NOC/c)?

A NOC/c is a form of market approval granted to a product on the basis of promising evidence of clinical effectiveness following review of the submission by Health Canada.

Products authorized under Health Canada's NOC/c policy are intended for the treatment, prevention or diagnosis of a serious, life-threatening or severely debilitating illness. They have demonstrated promising benefit, are of high quality and possess an acceptable safety profile based on a benefit/risk assessment. In addition, they either respond to a serious unmet medical need in Canada or have demonstrated a significant improvement in the benefit/risk profile over existing therapies. Health Canada has provided access to this product on the condition that sponsors carry out additional clinical trials to verify the anticipated benefit within an agreed upon time frame.

Recent Major Label Changes

None at the time of the most recent authorization	

Certain sections or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

Table of Contents

Part 1: Healthcare Professional Information

This Product Monograph for RYBREVANT® SC (amivantamab injection) includes information based on RYBREVANT® (amivantamab for injection) which is the intravenous formulation.

1. Indications

RYBREVANT SC (amivantamab injection) is indicated:

- in combination with lazertinib for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations.
- in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with epidermal-growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib.
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with activating EGFR Exon 20 insertion mutations.
- as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

  Clinical effectiveness of RYBREVANT SC monotherapy is based on overall response rate (ORR) and duration of response (DOR) from a single-arm trial in patients with activating epidermal-growth factor receptor (EGFR) Exon 20 insertion mutations.

1.1. Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of RYBREVANT SC in pediatric patients (<18 years of age) has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (≥65 years of age): Among all patients treated with RYBREVANT SC, no overall differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

No clinically relevant differences in efficacy were observed between elderly patients (≥65 years of age) and younger patients when treated with RYBREVANT as a monotherapy or in combination with carboplatin and pemetrexed. Evidence from the clinical studies suggests that the use of RYBREVANT in the geriatric population is associated with differences in safety (see 7.1.4 Geriatrics).

Evidence from clinical studies suggests that use of RYBREVANT in combination with lazertinib in the geriatric population is associated with differences in safety. Differences were seen in subgroup analyses for efficacy in geriatrics patients, however no formal statistical testing of efficacy was planned for subgroup analyses by age and interpretation of these differences is non-conclusive (see 7.1.4 Geriatrics, 10.3 Pharmacokinetics, 14.1 Clinical Trials by Indication).

2. Contraindications

- RYBREVANT® SC is contraindicated in patients who are hypersensitive to this drug or to any

ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition, and Packaging.

4. Dosage and Administration

4.1. Dosing Considerations

- RYBREVANT SC is for subcutaneous use only. RYBREVANT SC has different dosage and administration instructions than intravenous amivantamab. Do not administer intravenously.
- RYBREVANT SC should be administered by a healthcare professional with appropriate medical support to manage administration-related reactions (ARRs) if they occur (see 7 Warnings and Precautions, Immune).
- Administer pre-medications before each dose of RYBREVANT SC as recommended (see 4.2 Recommended Dose and Dosage Adjustment).
- Before initiation of RYBREVANT SC, the presence of an EGFR Exon 19 deletion, Exon 21 L858R substitution, or Exon 20 insertion mutation must be determined using a validated test.
- Adult patients currently receiving intravenous amivantamab may switch to subcutaneous RYBREVANT SC at their next scheduled dose on Week 5 or later (see Table 1, Table 2 and Table 3 and 4.2 Recommended Dose and Dosage Adjustment).
- For patients currently receiving RYBREVANT SC at an every 2-week dosing regimen, an every 4-week dosing regimen may be used as an alternative starting at the next scheduled dose (see Table 1 and 4.2 Recommended Dose and Dosage Adjustment).

4.2. Recommended Dose and Dosage Adjustment

It is recommended that patients are treated with RYBREVANT SC until disease progression or unacceptable toxicity (see 4.4 Administration). Pre-medications should be administered prior to each RYBREVANT SC injection (see Pre-medications and Table 5).

RYBREVANT SC in combination with Lazertinib or monotherapy (Every 4-week or every 2-week dosing)

The recommended dosages of RYBREVANT SC monotherapy or in combination with lazertinib, based on baseline body weight, are provided in Table 1 (every 4-week dosing) and Table 2 (every 2-week dosing).

Table 1: Recommended Dose and Dosing Schedule for RYBREVANT SC in Combination with Lazertinib or Monotherapy (Every 4-week Dosing)

Body Weight at Baseline*	Recommended Dose	Dosing Schedule
Less than 80 kg	1600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4
	3520 mg	• Every 4 weeks starting at Week 5 onwards
Greater than or equal to 80 kg	2240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4
	4640 mg	• Every 4 weeks starting at Week 5 onwards

* Dose adjustments not required for subsequent body weight changes

Table 2: Recommended Dose and Dosing Schedule for RYBREVANT SC in Combination with Lazertinib or Monotherapy (Every 2-Week Dosing)

Body Weight at Baseline*	Recommended Dose	Dosing Schedule
Less than 80 kg	1600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards
Greater than or equal to 80 kg	2240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards

* Dose adjustments not required for subsequent body weight changes

The recommended dosage of lazertinib is 240 mg once daily, taken orally in combination with RYBREVANT SC. When used in combination with lazertinib, RYBREVANT SC should be administered anytime after lazertinib when given on the same day. Refer to the lazertinib product monograph for information on dosing and administration for lazertinib.

RYBREVANT SC in combination with carboplatin and pemetrexed (Every 3-week dosing)

The recommended dosages of RYBREVANT SC, when used in combination with carboplatin and pemetrexed (every 3-week dosing), based on baseline body weight, are provided in Table 3.

Table 3: Recommended Dose and Dosing Schedule for RYBREVANT SC in Combination with Carboplatin and Pemetrexed (Every 3-Week Dosing)

Body Weight at Baseline*	Recommended Dose	Dosing Schedule
Less than 80 kg	1600 mg	First dose at Week 1 Day 1
	2400 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards
Greater than or equal to 80 kg	2240 mg	First dose at Week 1 Day 1
	3360 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards

* Dose adjustments not required for subsequent body weight changes

When used in combination with carboplatin and pemetrexed, RYBREVANT SC should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin, and then RYBREVANT SC.

Table 4: Recommended order of administration and regimen for RYBREVANT SC in combination with carboplatin and pemetrexed

RYBREVANT SC in Combination with Carboplatin and Pemetrexed		
Administer the regimen in the following order: pemetrexed first, carboplatin second and RYBREVANT SC last.		
Drug	**Dose**	**Duration/Timing of Treatment**
Pemetrexed	Pemetrexed 500 mg/m^2 intravenously Refer to the pemetrexed Product Monograph for complete information.	Every 3 weeks, continue until disease progression or unacceptable toxicity.
Carboplatin	Carboplatin AUC 5 intravenously Refer to the carboplatin Product Monograph for complete information.	Every 3 weeks for up to 12 weeks.
RYBREVANT SC	RYBREVANT SC, subcutaneously See Table 3.	Weekly for the first 4 weeks (Week 1 to 4), then every 3 weeks starting at week 7 onwards, continue until disease progression or unacceptable toxicity.

Pre-medications

Prior to initial injection of RYBREVANT SC (Week 1 Day 1), administer pre-medications as described in Table 5 to reduce the risk of ARRs. For subsequent doses, administer antihistamines and antipyretics. Administer glucocorticoids as needed (see Table 5).

Table 5: Pre-Medications

Medication	**Dose**	**Route of Administration**	**Dosing Window Prior to RYBREVANT SC Administration**
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Acetaminophen (650 to 1000 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (20 mg) or equivalent	IV	45 to 60 minutes
		Oral	At least 60 minutes
Glucocorticoid§		IV	45 to 60 minutes

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT SC Administration
	Dexamethasone (10 mg) or equivalent	Oral	60 to 90 minutes

* Required at all doses

‡ Required at initial dose (Week 1 Day 1) or at the next subsequent dose in the event of an administration-related reaction.

§ Optional for subsequent doses

Dose Modifications

The recommended dose reductions for adverse reactions are listed in Table 6.

Table 6: Dose Reductions for Adverse Reactions for RYBREVANT SC

Dose at which the adverse reaction occurred	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
1600 mg	1050 mg*	700 mg†	Discontinue RYBREVANT SC
2240 mg	1600 mg‡	1050 mg*	
2400 mg	1600 mg‡	1050 mg*	
3360 mg	2240 mg§	1600 mg	
3520 mg	2400 mg¶	1600 mg‡	
4640 mg	3360 mg#	2240 mg§	

* The dose volume should be 6.6 mL for 1050 mg dose.

† The dose volume should be 4.4 mL for 700 mg dose.

‡ The dose volume should be 10 mL for 1600 mg dose.

§ The dose volume should be 14 mL for 2240 mg dose.

¶ The dose volume should be 15 mL for 2400 mg dose.

The dose volume should be 21 mL for 3360 mg dose.

The recommended dosage modifications and management for adverse reactions are provided in Table 7.

Table 7: Recommended Dosage Modifications and Management for Adverse Reactions for RYBREVANT SC

Adverse Reaction	Severity	Dose Modification
Administration-Related Reactions (ARRs) (see 7 Warnings and Precautions, Immune)	Grade 1-3	• Interrupt injection at the first sign of ARRs. Monitor patients until symptoms resolve. • Additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated. • Upon resolution of symptoms, resume RYBREVANT SC administration. • Include corticosteroid with pre-medications prior to the next dose (see Table 5).
	Grade 4 or recurrent Grade 3	Permanently discontinue RYBREVANT SC.

Adverse Reaction	Severity	Dose Modification
Interstitial Lung Disease (ILD) / Pneumonitis (see 7 Warnings and Precautions, Respiratory)	Suspected ILD/ pneumonitis (any Grade)	Withhold RYBREVANT SC
	Confirmed ILD /pneumonitis (any Grade)	Permanently discontinue RYBREVANT SC
Venous Thromboembolic (VTE) Events *(Applies to the combination with lazertinib,* see 7 Warnings and Precautions, Cardiovascular)	Grade 2 or 3	• Withhold RYBREVANT SC and lazertinib. • Administer anticoagulation treatment as clinically indicated. • Once anticoagulant treatment has been initiated, resume RYBREVANT SC and lazertinib at the same dose level, at the discretion of the healthcare professional.
	Grade 4 or recurrent Grade 2 or 3 despite therapeutic level of anticoagulation	• Permanently discontinue RYBREVANT SC and withhold lazertinib. • Administer anticoagulation treatment as clinically indicated. • Once anticoagulant treatment has been initiated, treatment can continue with lazertinib at the same dose level at the discretion of the healthcare professional.
Skin and Nail Reactions (see 7 Warnings and Precautions, Skin)	Grade 1	• Supportive care should be initiated. • Reassess after 2 weeks as clinically indicated.
	Grade 2	• Supportive care should be initiated as clinically indicated. • If there is no improvement after 2 weeks, consider reducing the dose (see Table 6).
	Grade 3	• Supportive care should be initiated as clinically indicated. • Withhold RYBREVANT SC until the adverse reaction improves to ≤ Grade 2. • Resume RYBREVANT SC at reduced dose (see Table 6). • If no improvement within 2 weeks, permanently discontinue treatment.
	Grade 4, and severe bullous, blistering or exfoliating skin conditions, including toxic epidermal necrolysis (TEN)	• Permanently discontinue RYBREVANT SC.

Adverse Reaction	Severity	Dose Modification
Other Adverse Reactions (see 8 Adverse Reactions)	Grade 3	• Withhold RYBREVANT SC until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at same dose if recovery occurs within 1 week. • Resume RYBREVANT SC at reduced dose (see Table 6) if recovery occurs after 1 week. • Permanently discontinue RYBREVANT SC if recovery does not occur within 4 weeks.
	Grade 4	• Withhold RYBREVANT SC until adverse reaction improves to ≤ Grade 1 or baseline. • Resume at reduced dose (see Table 6) if recovery occurs within 4 weeks. • Permanently discontinue RYBREVANT SC if recovery does not occur within 4 weeks. • Permanently discontinue RYBREVANT SC for recurrent Grade 4 reactions.

Recommended Dose Modifications for Adverse Reactions for RYBREVANT SC in Combination with Carboplatin and Pemetrexed or in Combination with Lazertinib

When administering RYBREVANT SC in combination with carboplatin and pemetrexed, or in combination with lazertinib, follow the recommended dose modifications for adverse reactions for RYBREVANT SC as shown in Table 7. Refer to the Product Monographs for carboplatin, pemetrexed, and lazertinib for their dosage modification recommendations.

Renal impairment

No formal studies of RYBERVANT SC in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min) or moderate (29 ≤ CrCl < 60 mL/min) renal impairment. Data in patients with severe renal impairment are limited. No data are available in patients with end stage renal disease (15 ≤ CrCl < 29 mL/min) (see 10.3 Pharmacokinetics).

Hepatic impairment

No formal studies of RYBREVANT SC in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustment is necessary for patients with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN)]. Data in patients with moderate hepatic impairment are limited (1.5 x ULN < total bilirubin ≤ 3 x ULN and any AST)). No data are available in patients with severe hepatic impairment (total bilirubin >3 x ULN) (see 10.3 Pharmacokinetics).

Pediatrics (<18 years)

The safety and efficacy of RYBREVANT SC have not been established in pediatric patients.

Geriatrics (≥65 years)

No dose adjustment of RYBREVANT SC is required in patients aged 65 years or older (see 7.1.4 Geriatrics and 10.3 Pharmacokinetics).

4.4. Administration

- RYBREVANT SC should be administered by a healthcare professional.
- To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is RYBREVANT SC for subcutaneous injection and not intravenous amivantamab. **RYBREVANT SC subcutaneous formulation is not intended for intravenous administration** and should be administered via a subcutaneous injection only.
- RYBREVANT SC is for single use only and is supplied ready to use.
- RYBREVANT SC should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if opaque particles, discoloration, or other foreign particles are present.
- Prepare the dosing syringe in aseptic conditions.
- Each injection volume should not exceed 15 mL.

Preparation for administration

Refer to Table 8 for the preparation of RYBREVANT SC.

Table 8: Dosing volumes for RYBREVANT SC

RYBREVANT SC Total Dose	Total Dose Volume
1600 mg	10 mL
2240 mg	14 mL
2400 mg	15 mL
3360 mg	21 mL†
3520 mg	22 mL†
4640 mg	29 mL†

† Divide the dose volume approximately equally into two syringes (each syringe should not exceed 15 mL).

- Remove the appropriate number of RYBREVANT SC vial(s) from refrigerated storage (2°C to 8°C)
- Once removed from refrigerated storage, equilibrate RYBREVANT SC to room temperature (15 °C to 30 °C) for at least 15 minutes. Do not warm RYBREVANT SC in any other way. Do not shake.
- Withdraw the required injection volume of RYBREVANT SC from the vial(s) into an appropriately sized syringe using a transfer needle (see Table 8). Smaller syringes require less force during preparation and administration.
- If preparation does not require the full vial contents, dispose of excess volume in accordance with local requirements.
- Each injection volume should not exceed 15 mL. Divide doses requiring greater than 15 mL into approximately equal volumes in multiple syringes.
- RYBREVANT SC is compatible with stainless steel injection needles, polypropylene and polycarbonate syringes, and polyethylene, polyurethane, and polyvinylchloride subcutaneous

infusion sets. A 0.9% sodium chloride solution may also be used to flush an infusion set if needed.

- Replace the transfer needle with appropriate ancillaries for transport or administration. Use of a 21G to 23G needle or infusion set is recommended to ensure ease of administration.

Storage of prepared syringe

The prepared syringes of RYBREVANT SC should be administered immediately. If immediate administration is not possible, store the prepared syringes of RYBREVANT SC refrigerated at 2°C to 8°C for up to 24 hours followed by at room temperature of 15°C to 30°C for up to 24 hours. Discard the prepared syringe if stored for more than 24 hours refrigerated or more than 24 hours of being at room temperature. If stored in the refrigerator, allow the solution to come to room temperature before administration.

Administration of RYBREVANT SC

- **If only one dosing syringe is required, the required volume of RYBREVANT SC should be injected into the subcutaneous tissue of the abdomen over approximately 5 minutes.**
- **If multiple dosing syringes are required, RYBREVANT SC injections should be consecutively administered in separate quadrants of the abdomen, with each injection taking approximately 5 minutes.**
- Rotate injection sites at the next scheduled dose.
- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- If administering with a subcutaneous infusion set, ensure the full dose is delivered through the infusion set. 0.9% sodium chloride solution may be utilized to flush the remaining drug product through the line.
- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard, not intact or within 2 inches (5 cm) around the periumbilical area.
- Any unused product or waste material should be disposed in accordance with local requirements.

4.5. Missed Dose

For a 4-week or 2-week dosing schedule:

- If a dose of RYBREVANT SC is missed between Weeks 1 to 4, administer within 24 hours.
- If a dose of RYBREVANT SC is missed from Week 5 onward, administer within 7 days.

For a 3-week dosing schedule:

- If a dose of RYBREVANT SC is missed between Weeks 1 to 3, administer within 24 hours.
- If a dose of RYBREVANT SC is missed from Week 4 onward, administer within 7 days.

If the missed dose is not administered according to this guidance, do **not** administer the missed dose. Administer the next dose per the usual dosing schedule.

5. Overdose

There is no information on overdosage with RYBREVANT SC. There is no known specific antidote for

RYBREVANT SC overdose. In the event of an overdose, stop RYBREVANT SC, monitor patient for any signs or symptoms of adverse reactions and undertake general supportive measures until clinical toxicity has diminished or resolved.

For the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

To help ensure the traceability of biologic products, healthcare professionals should record both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

Table 9: Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
Subcutaneous (SC) injection	Solution for Subcutaneous Injection 1600 mg / 10 mL (160 mg / mL) 2240 mg / 14 mL (160 mg / mL) 2400 mg / 15 mL (160 mg / mL) 3520 mg / 22 mL (160 mg / mL)	recombinant human hyaluronidase (rHuPH20)*, EDTA disodium salt dihydrate, glacial acetic acid, L-methionine, polysorbate 80, sodium acetate trihydrate, sucrose, water for injection

* Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously

Description

RYBREVANT SC is available as a colourless to pale yellow preservative-free solution for subcutaneous administration. Each single-dose vial contains 160 mg / mL of amivantamab.

7. Warnings and Precautions

Carcinogenesis and Genotoxicity

No animal studies have been performed to evaluate the carcinogenic or mutagenic potential of amivantamab (see 16 Non-Clinical Toxicology).

Cardiovascular

Left Ventricular Dysfunction and Cardiomyopathy

In patients treated with RYBREVANT SC in combination with lazertinib, left ventricular ejection fraction (LVEF) reductions (>10 percentage points and a drop below lower limit of normal) and cardiomyopathy events (defined as cardiac failure, chronic cardiac failure, congestive cardiac failure, pulmonary edema, ejection fraction decreased, left ventricular dysfunction) have been reported. Refer to the lazertinib product monograph (see 7 Warnings and Precautions, Monitoring and Laboratory Tests and 8.2 Clinical Trial Adverse Reactions, Select Adverse Reactions).

Venous Thromboembolic (VTE) Events

In patients treated with RYBREVANT SC in combination with lazertinib, venous thromboembolic (VTE) events, including deep venous thrombosis (DVT) and pulmonary embolism (PE), including fatal events, have been reported. VTE events occurred predominately in the first four months of therapy (see 8 Adverse Reactions and 8.2 Clinical Trial Adverse Reactions, Select Adverse Reactions).

Prophylactic anticoagulants are recommended to be used for the first four months of treatment to prevent VTE. Prophylactic anticoagulation beyond 4 months may be considered based on individual patient risk factors. Use of anticoagulants should align with clinical guidelines; use of Vitamin K antagonists is not recommended.

Monitor for signs and symptoms of VTE events. Treat patients with VTE events with anticoagulants as clinically indicated (see 4.2 Recommended Dose and Dosage Adjustment).

For patients with Grade 4 or recurrent Grade 2 or 3 VTE events despite therapeutic levels of anticoagulation, permanently discontinue RYBREVANT SC and withhold lazertinib. Administer anticoagulation treatment as clinically indicated. Once anticoagulation treatment has been initiated, treatment can continue with lazertinib at the same dose level at the discretion of the healthcare professional (see 4.2 Recommended Dose and Dosage Adjustment).

Driving and Operating Machinery

No studies on the effects on the ability to drive and use machines have been performed. Exercise caution when driving or operating a vehicle or potentially dangerous machinery.

If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Immune

Administration-related reactions (ARRs) may occur in patients treated with RYBREVANT SC. The most frequent signs and symptoms include chills, dyspnea, flushing, fever and chest discomfort (see 8. Adverse Reactions and 8.2 Clinical Trial Adverse Reactions, Select Adverse Reactions).

Prior to initial injection (Week 1, Day 1) of RYBEVANT SC, administer antihistamines, antipyretics and glucocorticoids to reduce the risk of ARRs (Table 5). For subsequent doses, administer antihistamines and antipyretics (see 4.2 Recommended Dose and Dosage Adjustment).

Treat patients with RYBEVANT SC in a setting with appropriate medical support necessary to treat ARRs. Interrupt RYBEVANT SC injection, if ongoing, at the first sign of ARRs and administer supportive care as clinically indicated. Upon resolution of symptoms, resume RYBEVANT SC administration. For Grade 4 or recurrent Grade 3 ARRs, permanently discontinue RYBEVANT SC (see 4.2 Recommended Dose and Dosage Adjustment).

Monitoring and Laboratory Tests

Prior to initiating therapy with RYBREVANT SC in combination with lazertinib, electrolyte levels (calcium, potassium, and magnesium) should be assessed. Refer to the lazertinib product monograph (see 8 Adverse Reactions).

For patients with cardiac risk factors and those with conditions that can affect left ventricular ejection fraction (LVEF), refer to the lazertinib product monograph.

Ophthalmologic

Eye disorders may occur in patients treated with RYBREVANT SC. These include keratitis, dry eye, blurred vision, eye pruritis, visual impairment, lacrimation increased, ocular hyperemia, eyelid ptosis, aberrant eyelash growth, conjunctival hyperemia, blepharitis, and uveitis (see 8. Adverse Reactions and 8.2 Clinical Trial Adverse Reactions, Select Adverse Reactions).

Refer patients presenting with worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated. Withhold, dose reduce or permanently discontinue RYBREVANT SC based on severity (see 4.2 Recommended Dose and Dosage Adjustment).

Reproductive Health

Due to the risk that RYBREVANT SC can cause fetal harm when administered to pregnant women, advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT SC (see 7.1.1 Pregnancy). Male patients must use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 months after the last dose of RYBREVANT SC.

- **Fertility**

  No data are available to determine potential effects of RYBREVANT SC on fertility in males or females (see 7.1.1 Pregnancy, 16 Non-Clinical Toxicology).

Respiratory

Interstitial lung disease (ILD)/ pneumonitis, including fatal events, may occur in patients treated with RYBREVANT SC (see 8 Adverse Reactions and 8.2 Clinical Trial Adverse Reactions, Select Adverse Reactions).

Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical studies.

Monitor patients for symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). If symptoms develop, interrupt treatment with RYBREVANT SC pending investigation of these symptoms. Evaluate suspected ILD and initiate appropriate treatment as necessary. Discontinue RYBREVANT SC in patients with confirmed ILD (see 4.2 Recommended Dose and Dosage Adjustment).

Skin

Skin and nail reactions may occur in patients treated with RYBREVANT SC. This includes severe rash, dermatitis acneiform, palmar-plantar erythrodysesthesia, pruritus, dry skin and paronychia. Toxic epidermal necrolysis (TEN) has occurred with RYBREVANT treatment (8. Adverse Reactions and 8.2 Clinical Trial Adverse Reactions, Select Adverse Reactions).

When initiating treatment with RYBREVANT SC, consider prophylactic therapy to reduce the risk and severity of skin and nail reactions. This includes administration of an oral antibiotic (doxycycline or minocycline, 100 mg twice daily) starting on Day 1 for the first 12 weeks of treatment. After completion of oral antibiotic therapy, application of a topical antibiotic lotion to the scalp (clindamycin 1% once daily), should be used for the next 9 months of RYBREVANT SC treatment. Recommend a non-comedogenic skin moisturizer (ceramide based or other formulations that provide long-lasting skin hydration and exclude drying agents are preferred) on the face and whole body (except scalp) and 4% chlorhexidine solution to wash hands and feet, while on treatment. Instruct patients to limit sun

exposure during and for 2 months after RYBREVANT SC therapy. Protective clothing and use of broad-spectrum UVA/UVB sunscreen are advisable.

If skin or nail reactions develop, administer supportive care, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 or poorly-tolerated Grade 2 events, add systemic antibiotics and oral steroids and consider dermatologic consultation. For Grade 4 skin reactions, permanently discontinue RYBREVANT SC. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT SC based on severity (see 4.2 Recommended Dose and Dosage Adjustment).

7.1. Special Populations

7.1.1. Pregnancy

There are no human or animal data to assess the risk of RYBREVANT SC in pregnancy. Administration of other EGFR and MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryo lethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT SC could cause fetal harm when administered to a pregnant woman.

RYBREVANT SC should not be used during pregnancy unless the benefit of treatment to the woman is considered to outweigh potential risks to the fetus. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

7.1.2. Breastfeeding

No studies have been conducted to determine if RYBREVANT SC is excreted in human or animal milk or affects milk production. RYBREVANT SC is a fully human, Immunoglobulin G1 (IgG1) based bispecific antibody. In general, human IgGs are known to be excreted in breast milk during the first few days after birth, which decreases to lower concentrations soon afterwards. Because of the potential for serious adverse reactions from RYBREVANT SC in breastfed infants, advise women not to breastfeed during treatment with RYBREVANT SC and for 3 months following the last dose of RYBREVANT SC.

7.1.3. Pediatrics

The efficacy and safety of RYBREVANT SC in pediatric patients has not been established; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4. Geriatrics

No overall differences in effectiveness were observed between patients treated with RYBREVANT SC who were ≥65 years of age and younger patients.

There are limited clinical data on the combination of RYBREVANT SC with lazertinib in patients 75 years or over.

In patients treated with RYBREVANT (intravenous formulation) as monotherapy, in combination with carboplatin and pemetrexed, or in combination with lazertinib, differences in safety were observed in patients who were ≥65 years of age as compared to younger patients, as described below.

In MARIPOSA, older patients (≥65 years of age) treated with RYBREVANT in combination with lazertinib reported more Grade 4 and Grade 5 adverse reactions compared to patients <65 years of age (21% vs.

7%). The incidence of serious adverse reactions was 62% in patients ≥65 years of age and 38% in patients <65 years of age. While the rates of drug interruptions and dose reductions were similar, the rate of adverse reactions leading to any treatment discontinuation was higher in patients ≥ 65 years of age compared to patients < 65 years of age (47% vs. 25%).

Of the 281 patients treated with RYBREVANT in PAPILLON and MARIPOSA-2, 38% were 65 years of age or older, and 9% were 75 years of age or older. No clinically relevant differences in effectiveness were observed based on age. Adverse events that led to discontinuation of any study agent were reported for 13.8% of patients under 65 years old and 33.6% of patients aged 65 years or older.

Of the 302 patients treated with RYBREVANT in CHRYSALIS (EDI1001), 39.4% were 65 years of age or older, and 11.3% were 75 years of age or older. No clinically relevant differences in effectiveness were observed based on age. There was a higher incidence of serious adverse events observed in patients aged 65 years or older (39.5%) as compared to younger patients (25.1%). There was also a higher incidence of adverse events leading to dose interruptions observed in patients aged 65 years or older (44.5%) as compared to younger patients (28.4%).

8. Adverse Reactions

8.1. Adverse Reaction Overview

The following adverse reactions observed with RYBREVANT SC or RYBREVANT when used in combination with lazertinib, or in combination with carboplatin and pemetrexed, or when used alone as a monotherapy are discussed in the Warnings and Precautions section (7. Warnings and Precautions and 8.2. Clinical Trial Adverse Reactions, Select Adverse Reactions).

- Left Ventricular Dysfunction and Cardiomyopathy and Venous Thromboembolic Events (see 7. Warnings and Precautions, Cardiovascular and 8.2. Clinical Trial Adverse Reactions, Select Adverse Reactions)
- Administration Related Reactions (see 7. Warnings and Precautions, Immune and 8.2. Clinical Trial Adverse Reactions, Select Adverse Reactions)
- Eye Disorders (see 7. Warnings and Precautions, Ophthalmologic and 8.2. Clinical Trial Adverse Reactions, Select Adverse Reactions)
- Interstitial Lung Disease (ILD)/Pneumonitis (see 7. Warnings and Precautions, Respiratory and 8.2. Clinical Trial Adverse Reactions, Select Adverse Reactions)
- Skin and Nail Reactions (see 7. Warnings and Precautions, Skin and 8.2. Clinical Trial Adverse Reactions, Select Adverse Reactions)

RYBREVANT SC (Subcutaneous Formulation)

RYBREVANT SC in combination with Lazertinib

Previously treated NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations

The safety of RYBREVANT SC in combination with lazertinib described in the Adverse Reactions section reflects the exposure of 206 patients enrolled in the PALOMA-3 study. The most common adverse reactions (≥20%) in patients who received RYBREVANT SC in combination with lazertinib were rash, nail toxicity, fatigue, stomatitis, edema, nausea, decreased appetite, vomiting, diarrhea and constipation. The most common Grade 3 or 4 laboratory abnormalities (≥2%) were decreased lymphocyte count, decreased sodium, decreased potassium, decreased albumin, increased alanine aminotransferase,

decreased platelet count, increased aspartate aminotransferase, increased gamma glutamyl transferase, and decreased hemoglobin.

RYBREVANT (Intravenous Formulation)

RYBREVANT in Combination with Lazertinib

First-line Treatment of NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutation

The safety of RYBREVANT in combination with lazertinib described in the Adverse Reactions section reflects the exposure of 421 patients enrolled in the MARIPOSA study. The most common adverse reactions (≥20%) of patients who received RYBREVANT in combination with lazertinib were paronychia, infusion related reaction (amivantamab-specific), rash, hypoalbuminemia (amivantamab-specific), alanine aminotransferase increased, edema peripheral, constipation, diarrhea, dermatitis acneiform, stomatitis, aspartate aminotransferase increased, COVID-19, decreased appetite, pruritus, anemia, nausea, and hypocalcemia. The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased albumin, increased alanine aminotransferase, decreased sodium, decreased potassium, decreased hemoglobin, increased aspartate aminotransferase, increased magnesium, and increased gamma-glutamyltransferase.

RYBREVANT in Combination with Carboplatin and Pemetrexed

The pooled safety population described in the Adverse Reactions section also reflects exposure to RYBREVANT in combination with carboplatin and pemetrexed in 281 patients in two studies:

- MARIPOSA-2 (NSC3002) in 130 patients
- PAPILLON (NSC3001) in 151 patients

Among 281 patients who received RYBREVANT in combination with carboplatin and pemetrexed, 65% were exposed for 6 months or longer and 24% were exposed for greater than one year.

Two hundred and eighty-one patients were exposed to RYBREVANT with carboplatin and pemetrexed in PAPILLON (N=151) and MARIPOSA-2 (N=130) for a median duration of 7.75 months (range 0 to 26.9) months and to carboplatin and pemetrexed (N=398) for a median duration of 4.86 (range 0 to 25.3) months.

The most common adverse reactions (≥20%) were rash, neutropenia, infusion related reactions, paronychia, fatigue, anemia, nausea, thrombocytopenia, stomatitis, constipation, edema, decreased appetite, leukopenia, hypoalbuminemia, alanine aminotransferase increased, aspartate aminotransferase increased, and vomiting.

The most common grade 3 to grade 4 laboratory abnormalities (≥2%) were decreased neutrophil count, decreased white blood cell count, decreased lymphocyte count, decreased platelet count, decreased hemoglobin, decreased potassium, decreased sodium, decreased albumin, increased alanine aminotransferase, and increased gamma glutamyl transferase.

RYBREVANT Monotherapy

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

The safety of RYBREVANT described in the Adverse Reactions section reflects the exposure of 129 patients enrolled in the CHRYSALIS study. The most common adverse reactions (≥20%) were dermatitis acneiform, rash, infusion related reactions (IRRs), nausea, paronychia, fatigue, hypoalbuminemia, constipation, stomatitis, peripheral edema, and alanine aminotransferase increased. The most common

Grade 3 to 4 laboratory abnormalities (≥2%) were decreased albumin, decreased phosphates, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyltransferase, decreased sodium, increased alanine aminotransferase, decreases in lymphocytes, neutrophils, hemoglobin, and white blood cells.

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug.

RYBREVANT SC (Subcutaneous Formulation)

RYBREVANT SC in combination with Lazertinib

Previously treated NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations

The safety of RYBREVANT SC in combination with lazertinib in patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletion or exon 21 L858R substitution mutation was evaluated in the PALOMA-3 study. Patients received RYBREVANT SC (N=206) or RYBREVANT (intravenous [IV] amivantamab; N=212), both in combination with lazertinib, at the recommended dosages in the PALOMA-3 study (see 14.1 Clinical Trials by Indication) Additionally, 164 patients (80%) receiving RYBREVANT SC and 171 patients (81%) receiving RYBREVANT took prophylactic anticoagulants with a direct oral anticoagulant or low molecular weight heparin within the first four months of study treatment. Among patients receiving RYBREVANT SC, 33% were exposed for ≥ 6 months and 3.4% were exposed for >1 year. For details on the study population, (see 14.1 Clinical Trials by Indication).

Overall, the safety profile of RYBREVANT SC was consistent with the established safety profile of RYBREVANT.

The most common adverse reactions (≥10%) observed in the PALOMA-3 study are reported in Table 10.

Permanent discontinuations of RYBREVANT SC due to an adverse reaction occurred in 7% of patients. Adverse reactions leading to RYBREVANT SC discontinuation in ≥ 1% of patients were ILD (4.9%) and rash (1.5%).

Adverse reactions requiring RYBREVANT SC dose interruption in ≥5% of patients were rash (18%) and nail toxicity (9%). Adverse reactions requiring RYBREVANT SC dose reductions in ≥ 5% of patients were rash (8%) and nail toxicity (6%).

Serious adverse reactions in ≥2% of patients who received RYBREVANT SC in combination with lazertinib included ILD (6%) and fatigue (2.4%). A fatal adverse reaction of ILD occurred in 1 (0.5%) patient who received RYBREVANT SC and 3 (1.4%) patients who received intravenous amivantamab, both in combination with lazertinib.

The overall incidence of VTE was 11%; the incidence of VTE in the RYBREVANT SC + lazertinib arm was 9% and in the intravenous amivantamab + lazertinib arm, was 13%. The rate of anticoagulation use was similar in the two treatment arms (80% for RYBREVANT SC and 81% for intravenous amivantamab). In patients treated with RYBREVANT SC in combination with lazertinib, the incidence of VTE was 16.7% among those who did not receive prophylactic anticoagulants and 6.5% among those who received prophylactic anticoagulants. For details on the study population, see 14. Clinical Trials.

Table 10 summarizes the adverse reactions (≥10%) in PALOMA-3.

Table 10: Adverse Reactions (≥10%) in Patients Who Received RYBREVANT SC or RYBREVANT (IV Amivantamab) in NSC3004 (PALOMA-3)

System Organ Class	RYRBEVANT SC + Lazertinib (N=206)		RYBREVANT + Lazertinib (N=210)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Eye disorders				
Other eye disorders[a]	12	0.5	8	0
Gastrointestinal disorders				
Stomatitis[b]	35	0.5	38	2.9
Nausea	29	0.5	25	1.4
Vomiting	21	1.0	20	0.5
Diarrhea	21	1.5	19	1.0
Constipation	20	0	20	0.5
General disorders and administration site conditions				
Fatigue[c]	43	3.4	36	2.9
Edema[d]	32	2.9	32	1.0
Pyrexia	12	0	10	0
Injection site reactions[e]	11	0	0	0
Injury, poisoning and procedural complications				
Administration-related reactions/Infusion-related reactions[†]	13	0.5	66	3.8
Metabolism and nutrition disorders				
Decreased appetite	22	0.5	25	1.4
Musculoskeletal and connective tissue disorders				
Myalgia	16	0	6	0
Nervous system disorders				
Dizziness	12	0	12	0
Skin and subcutaneous tissue disorders				
Rash[f]	80	14	79	11
Nail toxicity[g]	56	3.9	54	1.4
Dry skin[h]	19	0	18	0
Pruritus	16	0	12	0
Vascular disorders				
Venous thromboembolism[i]	9	1.0	13	2.9

[a] Includes Dry eye, Blepharitis, Conjunctival hyperaemia, Eye disorder, Ocular hyperaemia, Conjunctivitis, Lacrimation increased

[b] Includes Stomatitis, Mouth ulceration, Cheilitis, Aphthous ulcer, Mucosal inflammation, Glossitis

[c] Includes Asthenia, Fatigue, Malaise

[d] Includes Oedema peripheral, Oedema, Face oedema, Peripheral swelling, Localised oedema, Generalised oedema, Swelling face

[e] Includes Injection site erythema, Injection site haematoma, Injection site haemorrhage, Injection site reaction, Injection site pain, Injection site pruritus

[f] Includes Rash, Dermatitis acneiform, Dermatitis, Acne, Rash maculo-papular, Palmar-plantar erythrodysaesthesia syndrome, Rash papular, Rash pruritic, Skin lesion, Erythema, Rash macular, Rash pustular, Folliculitis, Impetigo, Perineal rash, Rash erythematous, Skin exfoliation, Rash follicular

[g] Includes Nail disorder, Onychoclasis, Onycholysis, Paronychia, Nail infection, Nail toxicity, Onychomadesis

System Organ Class	RYRBEVANT SC + Lazertinib (N=206)		RYBREVANT + Lazertinib (N=210)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)

[h] Includes Dry skin, Skin fissures, Xeroderma, Eczema, Xerosis

[i] Includes Pulmonary embolism, Deep vein thrombosis, Venous thrombosis limb, Thrombosis, Embolism, Embolism venous, Subclavian vein thrombosis

[†] Systemic reactions associated with subcutaneous administration of RYBREVANT SC are referred to as administration-related reactions. Systemic reactions associated with intravenously administered RYBREVANT (IV amivantamab) are referred to as infusion-related reactions.

RYBREVANT (Intravenous Formulation)

RYBREVANT in Combination with Lazertinib

First-line Treatment of NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutation

The safety data described below reflect exposure to RYBREVANT in combination with lazertinib in 421 treatment-naïve patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletion or exon 21 L858R substitution mutation in the MARIPOSA study. Patients in MARIPOSA received lazertinib 240 mg orally once daily and RYBREVANT intravenously at 1,050 mg (for patients <80 kg) or 1,400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Patients in the osimertinib arm received 80 mg osimertinib once daily.

The median treatment duration was 18.5 months (range 0.2 to 31.4 months) for the RYBREVANT + lazertinib arm and the median treatment duration was 18.0 months (range: 0.2 to 32.7 months) for the osimertinib arm. Among the 421 patients who received RYBREVANT in combination with lazertinib, 72.9% were exposed to RYBREVANT for ≥ 6 months and 59.1% were exposed to RYBREVANT for >1 year. For details on the study population, see 14. Clinical Trials by Indication.

The adverse reactions reported in ≥20% of patients who received RYBREVANT in combination with lazertinib were paronychia, infusion related reaction (amivantamab-specific), rash, hypoalbuminemia (amivantamab-specific), alanine aminotransferase increased, edema peripheral, constipation, diarrhea, dermatitis acneiform, stomatitis, aspartate aminotransferase increased, COVID-19, decreased appetite, pruritus, anemia, nausea, and hypocalcemia.

Dose interruptions of RYBREVANT in combination with lazertinib due to an adverse reaction occurred in 81% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included infusion related reactions, rash, nail toxicity, venous thromboembolism, alanine aminotransferase increased, edema, hypoalbuminemia, fatigue, stomatitis, and aspartate aminotransferase increased.

Dose reductions of RYBREVANT in combination with lazertinib due to an adverse reaction occurred in 42% of patients. Adverse reactions requiring dose reductions in ≥5% of patients included rash and nail toxicity.

Permanent discontinuations of RYBREVANT due to an adverse reaction occurred in 22% of patients. Adverse reactions leading to RYBREVANT discontinuation in ≥1% of patients were rash, nail toxicity, infusion related reactions, ILD, venous thromboembolism, edema, fatigue, and hypoalbuminemia.

Serious adverse reactions occurred in 49% of patients who received RYBREVANT in combination with lazertinib. Serious adverse reactions in >2% of patients who received RYBREVANT in combination with lazertinib included pulmonary embolism (6.2%), pneumonia (4.0%), deep vein thrombosis (2.9%),

ILD/pneumonitis (2.9%), COVID-19 (2.4%) infusion related reaction (2.1%; amivantamab-specific), rash (2.1%) and pleural effusion (2.1%).

Fatal adverse reactions occurred in 7% of patients who received RYBREVANT in combination with lazertinib, which included death not otherwise specified (1.2%); sepsis and respiratory failure (1% each); pneumonia, myocardial infarction, and sudden death (0.7% each); cerebral infarction, pulmonary embolism (PE), and COVID-19 infection (0.5% each); and ILD/pneumonitis, acute respiratory distress syndrome (ARDS), and cardiopulmonary arrest (0.2% each).

Table 11 summarizes the adverse reactions (≥ 10%) in MARIPOSA.

Table 11: Adverse Reactions (≥10%) in First-line Treatment of Patients with Locally Advanced or Metastatic NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA

System Organ Class Adverse Reaction	**RYBREVANT + Lazertinib n=421**		**Osimertinib n=428**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Eye disorders				
Ocular infections, irritations and inflammations[a]	15	0.5	4	0
Gastrointestinal disorders				
Stomatitis[b]	43	2	26	0.5
Constipation	29	0	13	0
Diarrhea	29	2	44	0.7
Nausea	21	1	14	0.2
Vomiting	12	0.5	5	0
Haemorrhoids	10	0.2	2	0.2
General disorders and administration site conditions				
Edema[c]	47	3	9	0
Fatigue[d]	32	4	20	2
Pyrexia	12	0	9	0
Infections and Infestations				
Paronychia	68	11	28	0.5
Injury, Poisoning and Procedural Complications				
Infusion related reaction[e]	63	6	0	0
Metabolism and nutrition disorders				
Decreased appetite	24	1	18	1
Musculoskeletal and connective tissue disorders				
Muscle spasms	17	0.5	7	0
Pain in extremity	15	0.2	5	0
Myalgia	13	0.7	4	0
Back pain	11	0.2	11	0
Nervous system disorders				
Paresthesia[f]	34	2	10	0.2
Headache	13	0.2	13	0
Dizziness	12	0	7	0

System Organ Class Adverse Reaction	RYBREVANT + Lazertinib n=421		Osimertinib n=428	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Skin and subcutaneous tissue disorders				
Rash[g]	88	26	47	0.7
Dry skin[h]	26	1	20	0.5
Pruritus	24	0.5	17	0.2
Vascular disorders				
Venous thromboembolism[i]	36	11	8	3

[a] Includes Blepharitis, Conjunctival hyperemia, Conjunctivitis, Episcleritis, Eye pruritus, Noninfective conjunctivitis, Ocular hyperemia
[b] Includes Angular cheilitis, Aphthous ulcer, Mouth ulceration, Mucosal inflammation, Stomatitis
[c] Includes Eye edema, Eyelid edema, Face edema, Generalized edema, Localized edema, Edema, Edema peripheral, Periorbital edema, Periorbital swelling, Peripheral swelling, Swelling face
[d] Includes Asthenia, Fatigue
[e] Amivantamab specific adverse reactions
[f] Includes Dysesthesia, Hypoesthesia, Neuropathy peripheral, Paresthesia, Peripheral motor neuropathy, Peripheral sensorimotor neuropathy, Peripheral sensory neuropathy, Polyneuropathy
[g] Includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Folliculitis, Rash, Rash erythematous, Rash macular, Rash maculo-papular, Rash pruritic, Rash pustular, Skin lesion
[h] Includes Dry skin, Eczema, Eczema asteatotic, Skin fissures, Xeroderma, Xerosis
[i] Includes Axillary vein thrombosis, Deep vein thrombosis, Embolism, Embolism venous, Jugular vein thrombosis, Portal vein thrombosis, Pulmonary embolism, Pulmonary infarction, Sigmoid sinus thrombosis, Superior sagittal sinus thrombosis, Thrombosis, Vena cava thrombosis, Venous thrombosis, Venous thrombosis limb

RYBREVANT in combination with carboplatin and pemetrexed

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The safety of RYBREVANT in combination with carboplatin and pemetrexed was evaluated in MARIPOSA-2 (NSC3002), which included patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations whose disease has progressed on or after treatment with osimertinib. (see 14.1 Clinical Trials by Indication). Patients received RYBREVANT, 1400 mg (for patients <80 kg) or 1750 mg (for patients ≥80 kg) by intravenous infusion once weekly for 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients <80 kg) or 2100 mg (for patients ≥80 kg) starting at Week 7 until disease progression or unacceptable toxicity.

Patients were exposed to RYBREVANT with carboplatin and pemetrexed (N=130) for a median treatment duration of 6.3 months (range: 0 to 14.7) months and to carboplatin and pemetrexed (N=243) for a median treatment duration of 3.7 months (range: 0 to 15.9) months.

The most common TEAE (≥20%) in patients who received RYBREVANT in combination with carboplatin and pemetrexed were infusion related reactions, neutropenia, nausea, rash, thrombocytopenia, anemia, constipation, paronychia, edema peripheral, stomatitis, decreased appetite, leukopenia, fatigue, asthenia, vomiting, hypoalbuminemia, COVID-19, alanine aminotransferase increased, and dermatitis acneiform. The most common TEAE (≥20%) in patients who received carboplatin and pemetrexed were neutropenia, anemia, nausea, thrombocytopenia, constipation, leukopenia, alanine aminotransferase increased, aspartate aminotransferase increased, and decreased appetite.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 60% of patients. Infusion related reactions (IRRs) requiring infusion interruptions occurred in 52% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included neutropenia, thrombocytopenia, COVID-19, leukopenia, and rash. Dose reductions of RYBREVANT due to an adverse reaction occurred in 17% of patients. The most commonly reported adverse reactions requiring dose reductions in ≥2% of patients included neutropenia and rash.

Fifteen percent of patients permanently discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation in ≥1% of patients were infusion related reactions.

The most common Grade 3 to 4 laboratory abnormalities (≥2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Serious adverse events occurred in 32.3% of patients who received RYBREVANT in combination with carboplatin and pemetrexed, and in 20.2% of patients treated with chemotherapy alone. In MARIPOSA-2 ACP arm, Grade ≥3 TEAEs were reported for 79.0% of Asians and in 64.1% of non-Asians. SAEs were reported for 40.3% of Asians and in 23.4% of non-Asians.

Serious adverse events in ≥2% of patients who received RYBREVANT in combination with carboplatin and pemetrexed included thrombocytopenia, dyspnea, sepsis, and pulmonary embolism. Serious adverse events in ≥2% who received chemotherapy alone included neutropenia, thrombocytopenia, febrile neutropenia, and pneumonia. Fatal adverse reactions, irrespective of relatedness to treatment occurred in 3 patients (2.3%) who received RYBREVANT in combination with carboplatin and pemetrexed. Fatal adverse reactions, irrespective of relatedness to treatment occurred in 3 patients (1.2%) who received chemotherapy alone. The fatal adverse events that occurred in patients treated with RYBREVANT in combination with carboplatin and pemetrexed included dyspnea, sepsis, and ventricular fibrillation. The fatal adverse reactions that occurred in patients treated with chemotherapy alone included dyspnea, pneumonia, and respiratory failure.

Table 12 summarizes TEAEs reported in ≥5% of patients in MARIPOSA-2.

Table 12: Treatment-Emergent Adverse Events (≥5%) in Previously Treated Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

System Organ Class Adverse Reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**		**Carboplatin + Pemetrexed (N=243)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Blood and lymphatic disorders				
Neutropenia	57	45	42	21
Thrombocytopenia	44	15	30	9.1
Anemia	39	12	40	10
Leukopenia	29	20	28	10
Eye disorders				
Eye disorders[a]	13	0	5	0
Gastrointestinal disorders				

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Nausea	45	0.8	37	0.8
Constipation	39	0.8	30	0
Stomatitis[b]	35	2.3	11	0
Vomiting	25	0.8	17	0.4
Diarrhea	14	0.8	6.6	0.4
Abdominal pain[c]	9.2	0	6.6	0
Hemorrhoids	5.4	0	0.4	0
General disorders and administration site conditions				
Fatigue[d]	51	3.8	35	3.7
Edema[e]	36	1.5	11	0.4
Pyrexia	12	0	10	0
Injury, poisoning and procedural complications				
Infusion related reaction	59	5.4	0.4	0
Infections and infestations				
Paronychia	37	2.3	0.4	0
COVID-19	21	1.5	10	0
Conjunctivitis	7.7	0	2.1	0
Investigations				
Alanine aminotransferase increased	20	5.4	28	4.1
Aspartate aminotransferase increased	15	0.8	24	0
Weight decreased	11	0	7.0	0.4
Blood alkaline phosphatase increased	6.9	0	5.3	0
Gamma-glutamyl transferase increased	5.4	2.3	10	0.4
Metabolism and nutrition disorders				
Decreased appetite	31	0	21	1.2
Hypoalbuminemia	22	2.3	8.6	0.4
Hypokalemia	19	4.6	6.2	2.5
Hyperglycemia	12	0.8	4.1	0
Hypocalcaemia	12	0.8	3.7	0
Hypomagnesemia	10	0.8	3.7	0
Hyponatremia	10	3.8	6.6	0.8
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain[f]	22	3.1	14	0.8
Nervous system disorders				
Dizziness[g]	9.2	0	6.6	0
Headache	8.5	0	12	0.4
Psychiatric disorders				
Insomnia	7.7	0	2.9	0
Respiratory, thoracic and mediastinal disorders				
Cough	11	0	12	0.4
Dyspnea	11	1.5	7.4	1.2

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Epistaxis	8.5	0	2.9	0
Skin and subcutaneous tissue disorders				
Rash[h]	72	11	12	0
Nail toxicity[i]	8.5	0	0	0
Pruritus	15	0	7.0	0
Dry skin[j]	15	0	2.5	0
Alopecia	6.2	0	3.3	0
Vascular disorders				
Venous thromboembolism[k]	6.9	2.3	3.3	2.5

Adverse events are coded using MedDRA Version 25.0

[a] includes Blepharitis, Conjunctival hyperemia, Dry eye, Eye pruritus, Keratitis, Noninfective conjunctivitis, Ocular hyperaemia, Trichomegaly, Uveitis, Vision blurred, Visual acuity reduced, Visual impairment

[b] includes Angular cheilitis, Aphthous ulcer, Cheilitis, Glossitis, Lip ulceration, Mouth ulceration, Mucosal inflammation, Stomatitis

[c] includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper

[d] includes Asthenia, Fatigue, Malaise

[e] includes Eye edema, Eyelid edema, Face edema, Generalised edema, Localised edema, Edema, Edema peripheral, Periorbital edema, Peripheral swelling, Swelling face

[f] includes Arthralgia, Back pain, Pain in extremity

[g] includes Dizziness, Vertigo

[h] includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Folliculitis, Impetigo, Palmar-plantar erythrodysaesthesia syndrome, Perioral dermatitis, Pustule, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Skin exfoliation, Skin lesion

[i] includes Ingrowing nail, Nail bed disorder, Nail bed inflammation, Nail disorder, Nail dystrophy, Nail infection, Onychoclasis, Onycholysis,

[j] includes Dry skin, Eczema, Skin fissures, Xeroderma, Xerosis

[k] includes Deep vein thrombosis and Pulmonary embolism

First-line Treatment of Non-Small Cell Lung Cancer (NSCLC) with EGFR Exon 20 Insertion Mutations

The safety of RYBREVANT in combination with carboplatin and pemetrexed was evaluated in the PAPILLON study, a randomized, open-label trial in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations (see 14.1. Clinical Trials by Indication). In the PAPILLON study, 151 patients were treated with RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage and 155 patients were treated with carboplatin and pemetrexed (chemotherapy alone). Among patients who received RYBREVANT in combination with carboplatin and pemetrexed, the median exposure was 9.7 months (range: 0.1 to 26.9 months). The median exposure for patients who received chemotherapy alone was 6.7 months (range: 0.0 to 25.3 months). The median age was 62 years (range: 27 to 92 years); 57.8% were female; 61.4% were Asian, 36.0% were White and 84.4% had baseline body weight <80 kg.

The most common TEAE (≥20%) in patients who received RYBREVANT in combination with carboplatin and pemetrexed were rash, neutropenia, paronychia, anaemia, stomatitis, infusion related reactions, hypoalbuminaemia, edema, constipation, leukopenia, nausea, thrombocytopenia, decreased appetite,

fatigue, ALT increased, AST increased, COVID-19, hypokalaemia, vomiting, and diarrhea. The most common TEAE (≥20%) in patients who received chemotherapy alone were anaemia, neutropenia, nausea, fatigue, ALT increased, AST increased, leukopenia, constipation, thrombocytopenia, and decreased appetite.

Serious adverse events occurred in 37.1% of patients who received RYBREVANT in combination with carboplatin and pemetrexed, and in 31.0% of patients treated with chemotherapy alone. Serious adverse events in ≥2% of patients who received RYBREVANT in combination with carboplatin and pemetrexed included pneumonia, COVID-19, pulmonary embolism, thrombocytopenia, rash, interstitial lung disease/pneumonitis, vomiting, and hypokalemia. Serious adverse events in ≥2% of patients who received chemotherapy alone included pneumonia, pulmonary embolism, dyspnoea, pleural effusion, thrombocytopenia, and anaemia. Fatal adverse events, irrespective of relatedness to treatment, occurred in 7 patients (4.6%) who received RYBREVANT in combination with carboplatin and pemetrexed and 4 (2.6%) patients who received chemotherapy alone. The fatal adverse events that occurred in patients who received RYBREVANT in combination with carboplatin and pemetrexed included pneumonia, cardiovascular accident, cardio-respiratory arrest, COVID-19, sepsis and death. The fatal adverse events that occurred in patients treated with chemotherapy alone included sepsis, acute myocardial infarction, dyspnoea and death.

Permanent discontinuation of RYBREVANT due to an adverse event occurred in 11.3% of patients. Adverse events resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were rash and ILD/pneumonitis.

Dose interruptions of RYBREVANT due to an adverse event occurred in 64.2% of patients. Infusion related reactions (IRRs) requiring infusion interruptions occurred in 37.7% of patients. Adverse events requiring dose interruption in ≥5% of patients included rash, neutropenia, paronychia, COVID-19, thrombocytopenia, and hypokalemia.

Dose reductions of RYBREVANT due to an adverse event occurred in 35.8% of patients. Adverse events requiring dose reductions in ≥5% of patients included rash and paronychia.

The most common Grade 3 to 4 laboratory abnormalities (≥2%) observed in patients who received RYBREVANT in combination with carboplatin and pemetrexed were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyltransferase, decreased sodium, decreased potassium, decreased magnesium and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes. The most common Grade 3 to 4 laboratory abnormalities (≥2%) observed in patients who received chemotherapy alone were decreased sodium, increased gamma-glutamyltransferase and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Table 13 summarizes the TEAEs reported in ≥5% of patients in the PAPILLON study.

Table 13: Treatment-emergent Adverse Events (≥5%) in Patients with NSCLC with Exon 20 Insertion Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=151)		Carboplatin + Pemetrexed (N=155)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Blood and Lymphatic system disorders				
Neutropenia	58.9	33.1	45.2	22.6
Anaemia	50.3	10.6	54.8	12.3
Leukopenia	37.7	11.3	32.3	3.2
Thrombocytopenia	36.4	9.9	29.7	10.3
Eye Disorders				
Eye disorders[a]	8.6	0	8.4	0
Gastrointestinal disorders				
Stomatitis[b]	43.0	4.0	11.0	0
Constipation	39.7	0	30.3	0.6
Nausea	36.4	0.7	41.9	0
Vomiting	21.2	3.3	18.7	0.6
Diarrhea	20.5	3.3	12.9	1.3
Hemorrhoids	11.9	1.3	1.3	0
Abdominal pain[c]	10.6	0.7	8.4	0
Gingival bleeding	5.3	0	1.3	0
Abdominal distension	4.6	0	6.5	0
General disorders and administration site conditions				
Edema[d]	40.4	1.3	18.7	0
Fatigue[e]	33.8	6.0	37.4	3.9
Pyrexia	15.9	0	5.8	0
Malaise	10.6	0	7.7	0
Hepatobiliary disorders				
Hyperbilirubinaemia	9.9	0.7	3.9	0
Infections and infestations				
Paronychia	56.3	6.6	0	0
COVID-19	23.8	1.3	13.5	0.6
Pneumonia	11.3	4.0	6.5	1.9
Conjunctivitis	6.0	0	4.5	0
Injury, poisoning and procedural complications				
Infusion related reaction	41.7	1.3	1.3	0
Investigations				
Alanine aminotransferase increased	33.1	4.0	36.1	1.3
Aspartate aminotransferase increased	31.1	0.7	32.9	0.6
Gamma-glutamyltransferase increased	13.9	2.6	16.8	3.9
Weight decreased	13.9	0.7	8.4	0

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=151)		Carboplatin + Pemetrexed (N=155)	
Blood alkaline phosphatase increased	12.6	0.7	7.7	0
Blood lactate dehydrogenase increased	8.6	0	5.2	0
Blood creatinine increased	7.3	1.3	9.7	0
Metabolism and nutrition disorders				
Hypoalbuminaemia	41.1	4.0	9.7	0
Decreased appetite	35.8	2.6	27.7	1.3
Hypokalaemia	21.2	8.6	8.4	1.3
Hypomagnesaemia	14.6	2.0	9.7	0.6
Hypocalcaemia	12.6	1.3	1.9	0
Hyponatraemia	12.6	2.0	7.7	0.6
Hypophosphataemia	6.6	0	1.3	0
Hypoproteinaemia	6.6	0	1.9	0
Hyperglycaemia	5.3	0	7.1	0.6
Musculoskeletal and connective tissue disorders				
Myalgia	5.3	1.3	3.2	0.6
Nervous system disorders				
Dizziness[f]	9.9	0	11.6	0
Dysgeusia	6.0	0	6.5	0
Respiratory, thoracic and mediastinal disorders				
Cough	13.9	0	15.5	0
Dyspnoea	10.6	1.3	14.8	2.6
Pulmonary embolism	7.9	3.3	4.5	3.9
Productive cough	6.0	0	1.9	0
Psychiatric disorders				
Insomnia	10.6	0	12.9	0
Skin and subcutaneous tissue disorders				
Rash[g]	90.1	19.2	18.7	0
Dry skin[h]	16.6	0	5.8	0
Alopecia	8.6	0	5.2	0
Nail toxicity[i]	7.9	0	3.2	0
Skin ulcer	6.6	1.3	0.6	0
Pruritus	6.6	0	7.7	0
Vascular disorders				
Deep vein thrombosis	6.6	0	1.9	0

Adverse events are coded using MedDRA Version 25.0

[a] includes Blepharitis, Conjunctival hyperaemia, Dry eye, Eye pruritus, Keratitis, Vision blurred, Visual acuity reduced, Visual impairment

[b] includes Angular cheilitis, Aphthous ulcer, Cheilitis, Lip ulceration, Mouth ulceration, Mucosal inflammation, Stomatitis

[c] includes Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Gastrointestinal pain

[d] includes Eye edema, Eyelid edema, Face edema, Generalised edema, Localised edema, Edema, Edema peripheral, Periorbital edema, Peripheral swelling, Swelling face

System Organ Class Adverse Reaction	RYBREVANT + Carboplatin + Pemetrexed (N=151)	Carboplatin + Pemetrexed (N=155)
[e] includes Asthenia, Fatigue [f] includes Dizziness, Vertigo [g] includes Acne, Dermatitis, Dermatitis acneiform, Erythema, Folliculitis, Palmar-plantar erythrodysaesthesia syndrome, Pustule, Rash, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Skin lesion [h] includes Dry skin, Eczema, Skin fissures, Xeroderma, Xerosis [i] includes Ingrowing nail, Nail bed inflammation, Nail disorder, Nail dystrophy, Nail infection, Onychoclasis, Onycholysis		

RYBREVANT monotherapy

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

The safety of RYBREVANT monotherapy in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy was evaluated in 129 patients enrolled in CHRYSALIS. Patients received RYBREVANT 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) by intravenous infusion once weekly for 4 weeks, then every 2 weeks starting at Week 5, until disease progression or unacceptable toxicity. The median treatment duration was 5.6 months (range: 0.03 to 23.9 months), with 44.2% of patients for at least 6 months. The median age was 62 years (range: 36 to 84 years) with 41.1% of patients 65 years of age or older, and 8.5% of patients 75 years of age or older; 61.2% were female; 55.0% were Asian, 2.3% were Black, and 34.9% were White. Eighty-two percent of patients (n=106) had baseline body weight <80 kg and 18% (n=23) had baseline body weight ≥80 kg.

The most common adverse reactions ≥20% were dermatitis acneiform, rash, infusion related reactions (IRRs), nausea, paronychia, fatigue, hypoalbuminemia, constipation, stomatitis, and peripheral edema, and alanine aminotransferase increased. Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥2% of patients included pulmonary embolism, pneumonitis, dyspnea, back pain, and muscular weakness. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis, and pleural effusion.

Dose reductions due to an adverse reaction occurred in 15% of patients who received RYBREVANT. Adverse reactions requiring dose reductions in ≥2% of patients included dermatitis acneiform, and paronychia.

Grade 5 treatment-emergent adverse events, irrespective of relatedness to RYBREVANT, were reported in 7.0% of patients. The most common events were pneumonia and dyspnea.

Table 14 presents adverse reactions reported in ≥5% of patients treated with RYBREVANT in CHRYSALIS. There were no new safety signals observed with longer term follow-up and additional patients, and therefore no meaningful changes occurred in the safety profile of RYBREVANT.

Table 14: Adverse reactions in CHRYSALIS Reported in ≥5% of Patients

System Organ Class Adverse Reaction	RYBREVANT Exon 20 Ins Prior Chemotherapy (RP2D) (N=129)	
	All Grades (%)	Grade 3-4* (%)
Eye disorders		
Eye disorder [a]	9.3	0
Gastrointestinal disorders		
Stomatitis [b]	26.4	0.8
Nausea	24.0	0
Constipation	23.3	0
Diarrhoea	14.7	3.1
Vomiting	13.2	0
Abdominal pain [c]	9.3	0.8
General disorders and administration site conditions		
Fatigue [d]	32.6	2.3
Oedema [e]	26.4	0.8
Pyrexia	13.2	0
Infections and infestations		
Paronychia	49.6	3.1
Pneumonia	7.8	0.8
Injury, poisoning and procedural complications		
Infusion related reaction	64.3	3.1
Investigations		
Alanine aminotransferase increased	17.1	0.8
Aspartate aminotransferase increased	13.2	0
Blood alkaline phosphatase increased	9.3	0.8
Gamma-glutamyltransferase increased	6.2	0.8
Metabolism and nutrition disorders		
Hypoalbuminemia [f]	32.6	3.1
Decreased appetite	14.7	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain [g]	45.0	0
Nervous system disorders		
Dizziness [h]	10.1	0.8
Paraesthesia	8.5	0
Headache	6.2	0.8
Respiratory, thoracic and mediastinal disorders		
Dyspnea	19.4	0.8
Cough	13.2	0
Skin and subcutaneous tissue disorders		
Rash [i]	82.2	3.9
Pruritus	16.3	0
Dry skin [j]	15.5	0
Skin fissures	8.5	0

System Organ Class Adverse Reaction	RYBREVANT Exon 20 Ins Prior Chemotherapy (RP2D) (N=129)	
	All Grades (%)	Grade 3-4* (%)

*No Grade 4 events observed
RP2D (recommended phase 2 dose): 1050 mg if baseline weight <80 kg and 1400 mg if baseline weight ≥80 kg.
Adverse events were coded using MedDRA version 23.0.
Note: Patients are counted only once for any given event, regardless of the number of times they actually experienced the event.
[a] includes Blepharitis, Conjunctival hyperaemia, Corneal irritation, Dry eye, Eye pruritus, Growth of eyelashes, Keratitis, Ocular hyperaemia, Uveitis, Vision blurred, Visual acuity reduced, Visual impairment
[b] includes Aphthous ulcer, Cheilitis, Glossitis, Mouth ulceration, Mucosal inflammation, Stomatitis
[c] includes Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort
[d] includes Asthenia, Fatigue
[e] includes Eyelid oedema, Face oedema, Generalised oedema, Oedema, Oedema peripheral, Periorbital oedema, Peripheral swelling
[f] includes Blood albumin decreased, Hypoalbuminaemia
[g] includes Arthralgia, Arthritis, Back pain, Bone pain, Musculoskeletal chest pain, Musculoskeletal discomfort, Musculoskeletal pain, Myalgia, Neck pain, Non-cardiac chest pain, Pain in extremity, Spinal pain.
[h] includes Dizziness
[i] includes Acne, Dermatitis, Dermatitis acneiform, Palmar-plantar erythrodysaesthesia syndrome, Perineal rash, Rash, Rash erythematous, Rash maculo-papular, Rash papular, Rash vesicular, Skin exfoliation
[j] includes Dry skin, Eczema, Eczema asteatotic

Select Adverse Reactions

The safety data presented under Select Adverse Reactions reflects the safety profile of 702 patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, this includes 421 patients who received RYBREVANT in combination with lazertinib in the MARIPOSA study and 281 who received RYBREVANT in combination with carboplatin and pemetrexed in the MARIPOSA-2 and PAPILLON studies. The safety data presented under Select Adverse Reactions also reflects the safety profile of 302 patients with locally advanced or metastatic NSCLC who received RYBREVANT as a monotherapy in the CHRYSALIS study. This includes 129 patients with locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy.

Left Ventricular Dysfunction and Cardiomyopathy

RYBREVANT in combination with lazertinib

Left Ventricular Ejection Fraction (LVEF) reductions of >10 percentage points and a drop to below lower limit of normal occurred in 3.4% of patients treated with RYBREVANT in combination with lazertinib and who had a baseline LVEF assessment. A total of 7.4% of patients treated with RYBREVANT in combination with lazertinib reported cardiomyopathy events (defined as cardiac failure, chronic cardiac failure, congestive cardiac failure, pulmonary edema, ejection fraction decreased, left ventricular dysfunction).

Venous Thromboembolic (VTE) Events

RYBREVANT in combination with lazertinib

Venous thromboembolic events (VTE) occurred in 35.6% of patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 10.7% of patients. VTE events with a fatal outcome was reported in 0.5% of patients. The median time to onset was 83.5 days (range 6 to 777

days). The incidence of RYBREVANT dose reduction and dose interruption due to VTE was 1.0% and 9.0%, respectively and twelve patients (2.9%) permanently discontinued RYBREVANT due to VTE.

Infusion-Related Reactions (IRR)

RYBREVANT in combination with lazertinib

Infusion related reactions (IRRs) occurred in 62.9% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 52.5% experienced an IRR, while the incidence of IRR was 3.2% with the Day 2 infusion, 1.3% with the Week 2 infusion, and cumulatively 1.4% with the Week 3 and Week 4 infusions. The majority of reported IRRs were Grade 1-2 (93.5%). Grade 3 IRRs were reported in 5.5% of patients and Grade 4 IRRs were reported in 1.0% of patients. The median time to onset was 1.0 hours (range 0 to 52.5 hours) after start of infusion. The incidence of RYBREVANT dose reduction due to IRR was 0.7%, and 4.5% of patients permanently discontinued RYBREVANT due to IRR.

RYBREVANT in combination with carboplatin and pemetrexed

IRRs occurred in 49.5% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 45.7% experienced an IRR, while the incidence of IRR was 1.5% with the Day 2 infusion, 2.1% with the Week 2 infusion, and cumulatively 8.2% with subsequent infusions. Of the cases that reported IRRs, 93.5.% were Grade 1-2, 6.5% were Grade 3, and 0% were Grade 4. The median time to onset was 1.0 hours (range 0.0 to 7 hours) after start of infusion. The incidence of dose reduction due to IRR was 0.4%, and 2.8% of patients permanently discontinued RYBREVANT due to IRR.

RYBREVANT as monotherapy

IRRs occurred in 66% of patients treated with RYBREVANT. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4% with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the cases that reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62.3% and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Eye Disorders

RYBREVANT in combination with lazertinib

Eye disorders including keratitis (2.6%), occurred in 26.4% of patients treated with RYBREVANT. Reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, ocular hyperemia, aberrant eyelash growth, conjunctival hyperemia, blepharitis, conjunctivitis, episcleritis, visual acuity reduced, non-infective conjunctivitis, and eye disorder. The majority of events were Grade 1-2, with Grade 3-4 occurring in 1.0% of patients.

RYBREVANT in combination with carboplatin and pemetrexed

Eye disorders, including keratitis (0.4%), occurred in 10.7% of patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, ocular hyperemia, aberrant eyelash growth, conjunctival hyperemia, blepharitis, and uveitis. All events were Grade 1-2.

RYBREVANT as monotherapy

Eye disorders, including keratitis (0.7%), occurred in 13.2% patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, lacrimation increased, visual impairment, ocular hyperemia, eyelid ptosis, aberrant eyelash growth, and uveitis. All events were Grade 1-2.

Interstitial lung disease (ILD)/pneumonitis

RYBREVANT in combination with lazertinib

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 3.1% of patients treated with RYBREVANT, with 1.2% of patients experiencing Grade 3-4 ILD. Twelve patients (2.9%) discontinued RYBREVANT due to ILD/pneumonitis.

RYBREVANT in combination with carboplatin and pemetrexed

ILD or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.1% of patients treated with RYBREVANT, with 1.8% of patients experiencing Grade 3 ILD. Six patients (2.1%) discontinued RYBREVANT due to ILD/pneumonitis.

RYBREVANT as monotherapy

ILD or ILD-like adverse reactions (e.g. pneumonitis) occurred in 3.3% of patients treated with RYBREVANT, with 0.7% of patients experiencing Grade 3 ILD. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Skin and Nail Reactions

RYBREVANT in combination with lazertinib

Rash (including dermatitis acneiform) (88.4%), pruritus (23.5%) and dry skin (26.1%) occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 26.4% of patients. Rash leading to dose reduction occurred in 23.5% of patients, and RYBREVANT discontinuation due to rash occurred in 5.0 % of patients. The median time to onset of rash was 14 days (range: 1 to 556 days). Nail toxicity occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3-4 nail toxicity occurring in 0.5% of patients.

RYBREVANT in combination with carboplatin and pemetrexed

Rash (including dermatitis acneiform) (81.9%), pruritus (10.7%) and dry skin (15.7%) occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 15.3% of patients. Rash leading to dose reduction occurred in 13.5% of patients, and RYBREVANT discontinuation due to rash occurred in 2.5% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days (range: 1 to 311 days). Nail toxicity occurred in patients treated with RYBREVANT. All events were Grade 1 or 2, with Grade 3-4 nail toxicity occurring in 0% of patients.

RYBREVANT as monotherapy

Rash (including dermatitis acneiform) (73.5%), pruritis (17.9%) and dry skin (10.9%) occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3.6% of patients. Rash leading to dose reduction occurred in 5% of patients and RYBREVANT discontinuation due to rash occurred in 0.7% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days (range: 1 to 276 days). Paronychia occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3 paronychia occurring in 1.4% of patients.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.2%) treated with RYBREVANT. Permanently discontinue RYBREVANT if TEN is confirmed.

8.3. Less Common Clinical Trial Adverse Reactions

RYBREVANT SC (Subcutaneous Formulation)

RYBREVANT SC in combination with Lazertinib

Previously treated NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT SC in combination with lazertinib in PALOMA-3 included:

Eye disorders: visual impairment (2.4%), growth of eyelashes (1.5%), keratitis (0.5%) (see 7. Warnings and Precautions, Ophthalmologic)

Gastrointestinal disorders: abdominal pain (8%), hemorrhoids (6%)

Respiratory, thoracic and mediastinal disorders: ILD (6%) (see 7. Warnings and Precautions, Respiratory)

RYBREVANT (Intravenous Formulation)

RYBREVANT in combination with Lazertinib

First-line Treatment of NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutation

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT in combination with lazertinib include:

Eye disorders: Dry eye (9%), vision blurred (3%), keratitis (3%), trichomegaly (1%), visual acuity reduced (1%), visual impairment (1%), eye disorders (1%), and growth of eyelashes (1%) (see 7. Warnings and Precautions, Ophthalmologic)

Hepatobiliary disorders: hyperbilirubinemia (7%)

Gastrointestinal disorders*:* gingival bleeding (5%)

Metabolism and nutrition disorders: Hypomagnesemia (5%)

Skin and subcutaneous tissue disorders: nail toxicity (8%, including ingrowing nail, nail disorder, nail infection, nail toxicity, onychoclasis, onycholysis, onychomadesis); palmar-plantar erythrodysesthesia syndrome (6%); skin ulcer (5%); alopecia (4%); and urticaria (1%) (see 7. Warnings and Precautions, Skin)

Renal and urinary disorders: hematuria (5%)

Respiratory, thoracic and mediastinal disorders: epistaxis (8%), interstitial lung disease (ILD) / pneumonitis (3%) (see 7. Warnings and Precautions, Respiratory)

RYBREVANT in combination with carboplatin and pemetrexed

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The following are clinically significant TEAEs reported in <5% of RYBREVANT-treated patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations in MARIPOSA-2:

Musculoskeletal and connective tissue disorders: myalgia

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease/Pneumonitis (see 7. Warnings and Precautions, Respiratory)

First-line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations

The following are clinically significant TEAEs reported in <5% of patients receiving RYBREVANT in the PAPILLON Study:

Infections and infestations: Skin infection

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease/Pneumonitis (see 7. Warnings and Precautions, Respiratory); Epistaxis

RYBREVANT monotherapy

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

The following are clinically significant adverse reactions reported in <5% of patients receiving RYBREVANT in the CHRYSALIS Study:

Respiratory, thoracic and mediastinal disorders: Interstitial lung disease (ILD) (see 7. Warnings and Precautions, Respiratory).

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis (TEN) (see 7. Warnings and Precautions, Skin).

Interstitial lung disease or ILD-like adverse reactions have been reported with the use of RYBREVANT as well as with other EGFR inhibitors.

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

RYBREVANT SC (Subcutaneous Formulation)

RYBREVANT SC in combination with Lazertinib

Previously treated NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations

Table 15 summarizes the laboratory abnormalities (≥20%) that worsened from baseline in patients with EGFR exon 19 deletions or exon 21 L858R substitution mutation treated with RYBREVANT SC in combination with lazertinib in PALOMA-3.

Table 15: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations in NSC3004 (PALOMA-3) †

Laboratory Abnormality	RYBREVANT SC + Lazertinib (N=206)		RYBREVANT + Lazertinib (N=210)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Chemistry				
Decreased Albumin	92	4.9	91	5
Increased Alkaline Phosphatase	47	1.5	37	0
Increased Alanine Aminotransferase	45	3.4	51	5
Decreased Sodium	36	5	43	8

Laboratory Abnormality	RYBREVANT SC + Lazertinib (N=206)		RYBREVANT + Lazertinib (N=210)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Increased Aspartate Aminotransferase	36	2.0	40	2.4
Decreased Calcium (Corrected)	33	0	36	0
Decreased Magnesium	27	0	30	1.4
Increased Gamma Glutamyl Transferase	26	2.0	27	1.9
Decreased Potassium	22	5	25	4.3
Hematology				
Decreased Lymphocyte Count	57	6	60	29
Decreased Platelet Count	37	2.4	42	1.9
Decreased White Blood Cell	36	0.5	31	0.5
Decreased Hemoglobin	34	2.0	36	2.4
[†]The denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test.				

RYBREVANT (Intravenous Formulation)

RYBREVANT in combination with Lazertinib

First-line Treatment of NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutation

Table 16 summarizes the laboratory abnormalities in MARIPOSA.

Table 16: Select Laboratory Abnormalities (≥20%) That Worsened from Baseline in First-line Patients with Locally Advanced or Metastatic NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA[+]

Laboratory Abnormality	RYBREVANT + Lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Chemistry				
Decreased Albumin	89	8	22	<1
Increased Alanine Aminotransferase	65	7	29	3
Increased Aspartate Aminotransferase	52	4	36	2
Increased alkaline phosphatase	45	0.5	15	0.5
Decreased Calcium (Corrected)	41	1	27	1
Increased Gamma Glutamyl Transferase	39	3	24	2
Decreased Sodium	38	7	35	5
Decreased potassium	30	5	16	1.2
Increased Creatinine	26	1	35	1

Laboratory Abnormality	RYBREVANT + Lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Decreased magnesium	25	0.7	10	0.2
Increased Magnesium	12	3	20	5
Hematology				
Decreased Platelet Count	52	1	57	1
Decreased Hemoglobin	47	4	56	2
Decreased White Blood Cell	38	1	66	1
Decreased Neutrophil Count	15	1	33	1

[+] The denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test.

RYBREVANT in combination with carboplatin and pemetrexed

Previously Treated NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

Table 17 summarizes the laboratory abnormalities in MARIPOSA-2.

Table 17: Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in MARIPOSA-2

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased Albumin	73	4	26	<1
Decreased Sodium	48	11	30	6
Increased Aspartate Aminotransferase	47	1	52	1
Increased Alkaline Phosphatase	42	0	29	<1
Increased alanine aminotransferase	39	4	56	6
Decreased Magnesium	38	1	17	<1
Decreased Potassium	37	11	12	3
Increased Gamma Glutamyl Transferase	30	3	41	1
Decreased Calcium (Corrected)	25	0	11	1
Hematology				
Decreased White Blood Cell	90	42	85	19
Decreased Neutrophil Count	74	49	64	25
Decreased Platelet Count	74	17	58	9
Decreased Hemoglobin	71	12	77	9

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Decreased Lymphocyte Count	69	28	58	18

First-line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations

Laboratory abnormalities in PAPILLON are summarized in Table 18

Table 18: Laboratory Abnormalities (≥20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 20 Insertion Mutations Treated with RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Laboratory Abnormality	RYBREVANT + Carboplatin + Pemetrexed[+]		Carboplatin + Pemetrexed	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Albumin Decreased	87	7	34	1
Aspartate Aminotransferase Increased	60	1	61	1
Alanine Aminotransferase Increased	57	4	54	1
Sodium Decreased	55	7	39	4
Alkaline Phosphatase Increased	51	1	28	0
Potassium Decreased	44	11	17	1
Magnesium Decreased	39	2	30	1
Gamma-glutamyltransferase Increased	38	4	43	4
Calcium (Corrected) Decreased	27	1	18	1
Hematology				
White Blood Cells Decreased	89	17	76	10
Hemoglobin Decreased	79	11	85	13
Neutrophils Decreased	76	36	61	23
Platelets Decreased	70	10	54	12
Lymphocytes Decreased	61	11	49	13

RYBREVANT monotherapy

Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations

Laboratory abnormalities in CHRYSALIS are summarized in Table 19.

Table 19: Laboratory Abnormalities (≥10%) Worsening from Baseline in Patients Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT (N=129)	
	Change from Baseline All Grades (%)	Change from Baseline Grade 3 or 4 (%)
Chemistry		
Albumin Decreased	79	8
Glucose Increased	56	4
Alkaline Phosphatase Increased	53	5
Creatinine Increased	46	0
Alanine Aminotransferase Increased	38	2
Phosphates Decreased	33	8
Aspartate Aminotransferase Increased	33	0
Gamma-glutamyltransferase Increased	27	4
Magnesium Decreased	27	0
Sodium Decreased	27	4
Potassium Decreased	26	6
Potassium Increased	14	1
Glucose Decreased	12	0
Hematology		
Lymphocyte Count Decreased	36	8
Hemoglobin Decreased	18	2
Neutrophil Count Decreased	18	3
Platelet Count Decreased	17	1
White Blood Cell Decreased	17	2
Note: Denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test		

8.5. Post Market Adverse Reactions

The following adverse reactions were identified during post marketing experience with amivantamab. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Skin ulcer

9. Drug Interactions

No drug interaction studies have been performed.

10. Clinical Pharmacology

10.1. Mechanism of Action

Amivantamab is a bispecific antibody that binds to the extracellular domains of the EGFR and MET receptors, disrupting EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of these receptors. 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 (ADCC) and trogocytosis mechanisms, respectively.

10.2. Pharmacodynamics

After the first full dose of RYBREVANT SC, mean serum EGFR and MET concentrations decreased substantially and remained suppressed for the duration of treatment for all studied doses.

Albumin

Amivantamab decreased serum albumin concentration, a pharmacodynamic effect of MET inhibition, typically during the first 8 weeks; thereafter, albumin concentration stabilized for the remainder of amivantamab treatment. SC administration is likely to slightly increase the incidence of hypoalbuminemia due to higher amivantamab exposure compared to IV administration

10.3. Pharmacokinetics

The exposure of RYBREVANT SC increases in a dose-proportional fashion across the recommended dosing regimen. Amivantamab maximum trough concentration is typically observed at the end of the weekly dosing (Cycle 2 Day 1). Amivantamab steady-state concentration is reached by approximately Week 13.

Amivantamab exposure and accumulation following the approved recommended dosages are provided in Table 20.

Table 20: Amivantamab Exposure and Accumulation

Amivantamab Dose	Frequency	Geometric Mean $C_{trough,max}$‡ (%CV)	Geometric Mean $C_{trough,steady\text{-}state}$† (%CV)	AUC_{1week}* Accumulation
1600 mg or 2240 mg	Every 2 Week	335 µg/mL (32.7%)	206 µg/mL (39.1%)	Increase 3.5-fold
2400 mg or 3360 mg	Every 3 Week	464 µg/mL (23.5%)	218 µg/mL (41.9%)	Increase 4.5-fold
3520 mg or 4640 mg	Every 4 Week	350 µg/mL (30.5%)	129 µg/mL (52.2%)	Increase 4.8-fold

‡$C_{trough,max}$ = observed maximum trough concentration (Cycle 2, Day 1 predose)

†$C_{trough,steady\text{-}state}$ = observed trough concentration at steady-state (Cycle 4, Day 1 predose)

*AUC_{1Week} = AUC 1 week after the Cycle 2, Day 1 dose, following the weekly dose regimen, compared with the first dose.

Adult patients with NSCLC were randomized (1:1) to RYBREVANT SC or intravenous amivantamab in combination with lazertinib in PALOMA-3, an open-label, randomized trial. The primary outcome measure was amivantamab steady-state C_{trough} (Cycle 4 Day 1) and Cycle 2 $AUC_{Day\ 1\text{-}15}$ of RYBREVANT SC as compared to intravenous amivantamab (see 14.1 Clinical Trials by Indication).

The PALOMA-3 study demonstrated noninferior exposures of RYBREVANT SC 1600 mg (2240 mg for body weight ≥80 kg) to RYBREVANT 1050 mg (1400 mg for body weight ≥80 kg) as shown in Table 21.

Table 21: Summary of subcutaneous amivantamab pharmacokinetic parameters in patients with NSLC (PALOMA-3); Geometric mean (%CV) and Geometric mean ratio (90% CI)

Parameter	RYBREVANT SC 1600 mg (2240 mg for body weight ≥ 80kg)	RYBREVANT 1050 mg (1400 mg for body weight ≥ 80kg)	Geometric Mean Ratio (90% CI)
	Geometric Mean (%CV)		
Cycle 2 $AUC_{(Day1-15)}$ (µg.h/mL)	135,861 (30.7%)	131,704 (24.0%)	1.03 (0.98-1.09)
Cycle 4 Day 1 C_{trough} (µg/mL)	206 (39.1%)	144 (41.5%)	1.43 (1.27-1.61)

Absorption

Following subcutaneous administration, the geometric mean (%CV) of amivantamab bioavailability is 66.6% (14.9%) with a median time to reach maximum concentration of 3 days.

Distribution

The geometric mean (%CV) total volume of distribution for amivantamab administered subcutaneously is 5.69 L (23.8%).

Elimination

Amivantamab is cleared by parallel linear and nonlinear saturable target mediated clearances after subcutaneous administration. The estimated geometric mean (%CV) linear CL and associated terminal half-life is 0.224 L/day (26.0%) and 18.8 days (34.3%), respectively.

Special populations and conditions

- **Pediatrics (<18 years):** The pharmacokinetics of RYBREVANT SC in pediatric patients have not been investigated.
- **Geriatrics (≥65 years):** No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (28-85 years).
- **Sex**: The clearance of amivantamab was 21% higher in males than in females; however, no clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on gender with weight-tiered dosage.
- **Pregnancy and breastfeeding**:

  No studies have been conducted to determine if RYBREVANT SC is excreted in human or animal milk or affects milk production.
- **Hepatic Insufficiency**: No clinically meaningful difference in the pharmacokinetics of amivantamab was observed in patients with mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN and any AST)] or moderate hepatic impairment (1.5 x ULN < total bilirubin ≤ 3 x ULN and any AST). Data in patients with moderate hepatic impairment are limited (n=1). The pharmacokinetics of amivantamab have not been studied in patients with severe hepatic impairment (total bilirubin > 3 x ULN and any AST).

- **Renal Insufficiency**: No clinically meaningful difference in the pharmacokinetics of amivantamab was observed in patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min) and moderate (29 ≤ CrCl < 60 mL/min) or severe (15 ≤ CrCl < 29 mL/min) renal impairment. Data in patients with severe renal impairment are limited (n=1). The pharmacokinetics of amivantamab have not been studied in patients with end stage renal disease (CrCl <15 mL/min).
- **Body Weight**: Increases in body weight increased the volume of distribution and clearance of RYBREVANT SC. With the recommended weight-tiered doses, exposures of RYBREVANT SC were comparable between patients who weighed <80 kg and received 1600 mg (every 2-week dosing)/2400 mg (every 3-week dosing)/3520 mg (every 4-week dosing) and patients who weighed ≥80 kg and received 2240 mg (every 2-week dosing)/3360 mg (every 3-week dosing)/4640 mg (every 4-week dosing).

10.4. Immunogenicity

All therapeutic proteins have the potential for immunogenicity.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies in the studies described below with the incidences of antibodies in other studies or to other products may be misleading.

Among the 729 participants who received RYBREVANT SC monotherapy or as part of combination therapy, 3 participants (0.4%) was positive for treatment-emergent antibodies to amivantamab. Due to the low incidence of immunogenicity to RYBREVANT SC, the effect of immunogenicity remains unknown.

Among the 741 participants who received RYBREVANT SC as monotherapy or as part of combination therapy, 66 participants (9%) were positive for treatment-emergent antibodies to rHuPH20. The immunogenicity to rHuPH20 observed in these participants did not impact the pharmacokinetics of amivantamab.

11. Storage, Stability, and Disposal

Unopened vials:

Store in a refrigerator at 2°C to 8°C. Do not shake or freeze. Store in the original package in order to protect from light.

Shelf life of prepared syringe:

The prepared syringes of RYBREVANT SC should be administered immediately. If immediate administration is not possible, store the prepared syringes of RYBREVANT SC refrigerated at 2°C to 8°C for up to 24 hours followed by at room temperature of 15°C to 30°C for up to 24 hours. Discard the prepared syringe if stored for more than 24 hours refrigerated or more than 24 hours of being at room temperature. If stored in the refrigerator, allow the solution to come to room temperature before administration.

Part 2: Scientific Information

13. Pharmaceutical Information

Drug Substance

Non-proprietary name of the drug substance(s): amivantamab

Molecular formula and molecular mass: 148 kDa

Structure (for biologics)/Structural formula: Amivantamab is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET

Physicochemical properties: RYBREVANT SC (amivantamab injection) is available as a colorless to pale yellow preservative-free solution for subcutaneous administration.

Product Characteristics:

Amivantamab is produced by a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology.

Recombinant human hyaluronidase is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

14. Clinical Trials

14.1. Clinical Trials by Indication

RYBREVANT SC (Subcutaneous Formulation)

Previously treated patients with Locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations

NSC3004 (PALOMA-3) Study [Every 2-week dosing]

Table 22: Summary of patient demographics for PALOMA-3 (NSC3004) in previously treated patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median Age (range)	Sex
NSC3004 (PALOMA-3)	Phase 3, open-label, randomized, non-inferiority study of RYBREVANT SC compared with RYBREVANT	RYBREVANT SC administered subcutaneously at 1600 mg (for patients < 80 kg) or 2240 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5 until	N=418 RYBREVANT SC: N=206 RYBREVANT: N=212	61 years (29-82)	Female: 67% Male: 33%

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median Age (range)	Sex
		disease progression or unacceptable toxicity. RYBREVANT administered by intravenous infusion at 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg), once weekly for 4 weeks followed by once every 2 weeks thereafter starting at Week 5 until disease progression or unacceptable toxicity. Lazertinib 240 mg administered orally once daily			

PALOMA-3 was a Phase 3, open-label, randomized study of RYBREVANT SC in combination with lazertinib compared with RYBREVANT + lazertinib in patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletion or Exon 21 L585R substitution mutations who have progressed on or after treatment with osimertinib (or another 3rd generation EGFR TKI) and platinum-based chemotherapy. A total of 418 patients were randomized (1:1) to receive RYBREVANT SC by subcutaneous injection in combination with lazertinib (N=206) or intravenous amivantamab (RYBREVANT) in combination with lazertinib (N=212), until documented clinical or radiographic disease progression (see Table 22 for dosing information).

This study was designed to demonstrate pharmacokinetic non-inferiority of treatment with RYBREVANT SC versus intravenous amivantamab based on C_{trough} of amivantamab at steady-state and $AUC_{D1\text{-}D15}$ in Cycle 2 (see 10.3 Pharmacokinetics). The efficacy of RYBREVANT SC was assessed as a secondary endpoint.

Of the 418 patients randomized (1:1) to receive RYBEVANT SC in combination with lazertinib or RYBREVANT in combination with lazertinib, the median age was 61 years with 40% of patients ≥ 65 years; 67% were female; and 61% were Asian, 37% were White, 1% were Black. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (29%) or 1 (72%); 68% never smoked; 34% had prior brain metastases; and 82% had Stage IV cancer at initial diagnosis. With regard to EGFR mutation status, 65% were exon 19 deletions and 35% were exon 21 L858R substitution mutations. The results show that the pharmacokinetics of RYBREVANT SC is non-inferior to amivantamab administered intravenously (RYBREVANT) (see 10.3 Pharmacokinetics).

The efficacy results for ORR from PALOMA-3 are provided in Table 23.

Table 23: Summary of Efficacy Results for NSC3004 (PALOMA-3)

	RYBREVANT SC + lazertinib (N=206)	RYBREVANT + lazertinib (N=212)
Objective Response Rate[a,b] (ORR; 95% CI)	26.7% (20.8%, 33.3%)	26.9% (21.0%, 33.4%)
Complete response (CR)	0.5%	0.5%
Partial response (PR)	26.2%	26.4%

[a] Investigator-assessed.
[b] Confirmed responses

RYBREVANT (Intravenous Formulation)

Clinical experience of amivantamab intravenous formulation

The following sections present clinical trial information from a separate Product Monograph for RYBREVANT intravenous formulation studies:

- In combination with lazertinib for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858% substitution mutations
- In combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with osimertinib
- In combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic NSCLC with EGFR exon 20 insertion mutations
- As monotherapy for the treatment of adult patients with locally advanced (not amenable to curative therapy) or metastatic non-small cell lung cancer (NSCLC) with EGFR Exon 20 insertion mutations whose disease has progressed on or after treatment with osimertinib

First-line Treatment of Adult Patients with Locally Advanced or Metastatic NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations.

NSC3003 (MARIPOSA) Study

Table 24: Description of the MARIPOSA Study in treatment-naïve patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations treated with intravenous amivantamab in combination with lazertinib

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median Age (range)	Sex
MARIPOSA: NSC3003	A Phase 3 randomized multicenter study to compare the efficacy and	**RYBREVANT + Lazertinib arm:** • RYBREVANT IV infusion (1050 mg for body weight <80 kg	**RYBREVANT + Lazertinib arm:** N=429 **Osimertinib arm:** N=429	63 (25-88)	Female: 61.9% Male: 38.4%

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median Age (range)	Sex
	safety of the combination of RYBREVANT and lazertinib (Arm A) versus osimertinib monotherapy (Arm B) and lazertinib monotherapy (Arm C) as first line treatment in patients with EGFRm NSCLC.	and 1400 mg for body weight ≥80 kg IV), once weekly for the first 4 weeks (split dose on Cycle 1 Days 1-2) and then once every 2 weeks). **Osimertinib arm:** • osimertinib (80 mg orally, once daily). **Lazertinib arm:** • lazertinib (240 mg orally, once daily).	**Lazertinib arm:** N=216		

The MARIPOSA study is a randomized, active-controlled, multicenter Phase 3 study assessing the efficacy and safety of RYBREVANT in combination with lazertinib as compared to osimertinib monotherapy as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Patient samples were required to have one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing.

The primary efficacy endpoint for the MARIPOSA study was progression-free survival (PFS), defined as the time from randomization until the date of objective disease progression or death, whichever came first, based on blinded independent central review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Key secondary endpoints were overall survival (OS), overall response rate (ORR) and duration of response (DOR).

A total of 1074 patients were randomized (2:2:1) to receive open label treatment with RYBREVANT in combination with lazertinib, and double-blinded treatment with osimertinib monotherapy, or lazertinib monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity. Randomization was stratified by EGFR mutation type (exon 19 deletion or exon 21 L858R substitution mutation), race (Asian or non-Asian), and history of brain metastasis (yes or no). Evaluation of efficacy relied upon comparison between the RYBREVANT + lazertinib arm and the osimertinib arm.

Baseline demographics and disease characteristics were balanced across the treatment arms. The median age in the RYBREVANT + lazertinib arm was 64 (range: 25–88) years, and 63 (range 28-88) years in the osimertinib arm. In the RYBREVANT + lazertinib arm, 45% of patients were ≥65 years, 64% were female, 58% were Asian, and 38% were White. In the osimertinib arm, 45% of patients were ≥65 years, 59% were female, 59% were Asian and 38% were White. In the RYBREVANT + lazertinib arm, baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (33%) or 1 (67%); 70% never smoked; 41% had prior brain metastases; and 97% had Stage IV cancer at screening. In the osimertinib arm, baseline ECOG performance status was 0 (35%) or 1 (65%); 69% never smoked; 40% had prior brain metastases, and 97% had Stage IV cancer at screening. With regard to EGFR mutation status, 60% were exon 19 deletions and 40% were exon 21 L858R substitution mutations for both treatment arms.

Table 25, Figure 1 and Figure 2 summarize key efficacy results for RYBREVANT in combination with lazertinib.

Table 25: Efficacy Results in the MARIPOSA Study by BICR Assessment

	RYBREVANT + lazertinib (N=429)	Osimertinib (N=429)
Progression-free survival (PFS)[a]		
Number of events	192	252
Median, months (95% CI)	23.7 (19.12, 27.66)	16.6 (14.78, 18.46)
HR (95% CI); p-value	0.70 (0.58, 0.85); p=0.0002	
Overall survival (OS)[b]		
Number of events	173	217
Median, months (95% CI)	NE (42.9, NE)	36.7 (33.4, 41.0)
HR (95% CI); p-value	0.75 (0.61, 0.92); p=0.0048	
Overall response rate (ORR)[a,c]		
ORR % (95% CI)	78% (71.4%, 82.1%)	73% (69.0%, 77.5%)
Complete response	5.4%	3.5%
Partial response	73.0%	69.9%
Duration of response (DOR)[a,d]		
Median (95% CI), months	25.8 (20.14, NE)	16.7 (14.75, 18.53)

BICR = blinded independent central review; CI = confidence interval; NE = not estimable

[a] BICR by RECIST v1.1.

[b] Based on the results of the final analysis of OS with a median follow-up of 37.8 months.

[c] Confirmed responses in ITT population.

[d] In confirmed responders

Figure 1: Kaplan-Meier curve of PFS in previously untreated NSCLC patients by BICR assessment

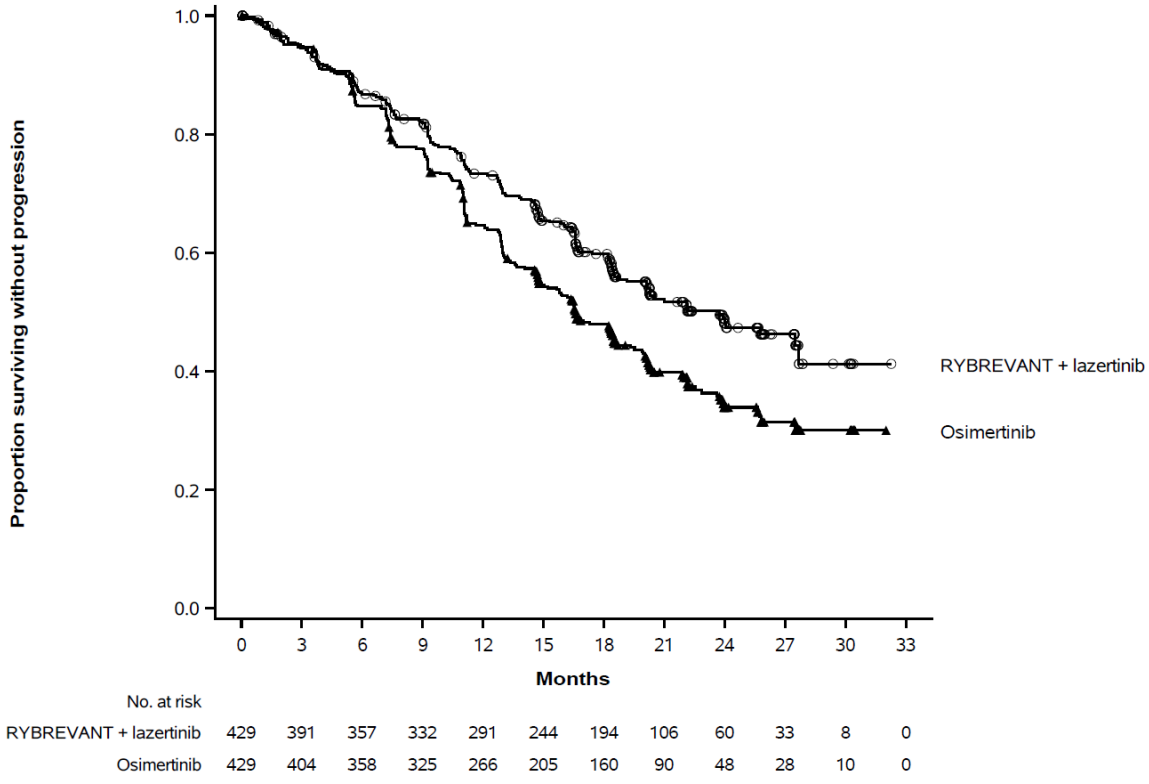
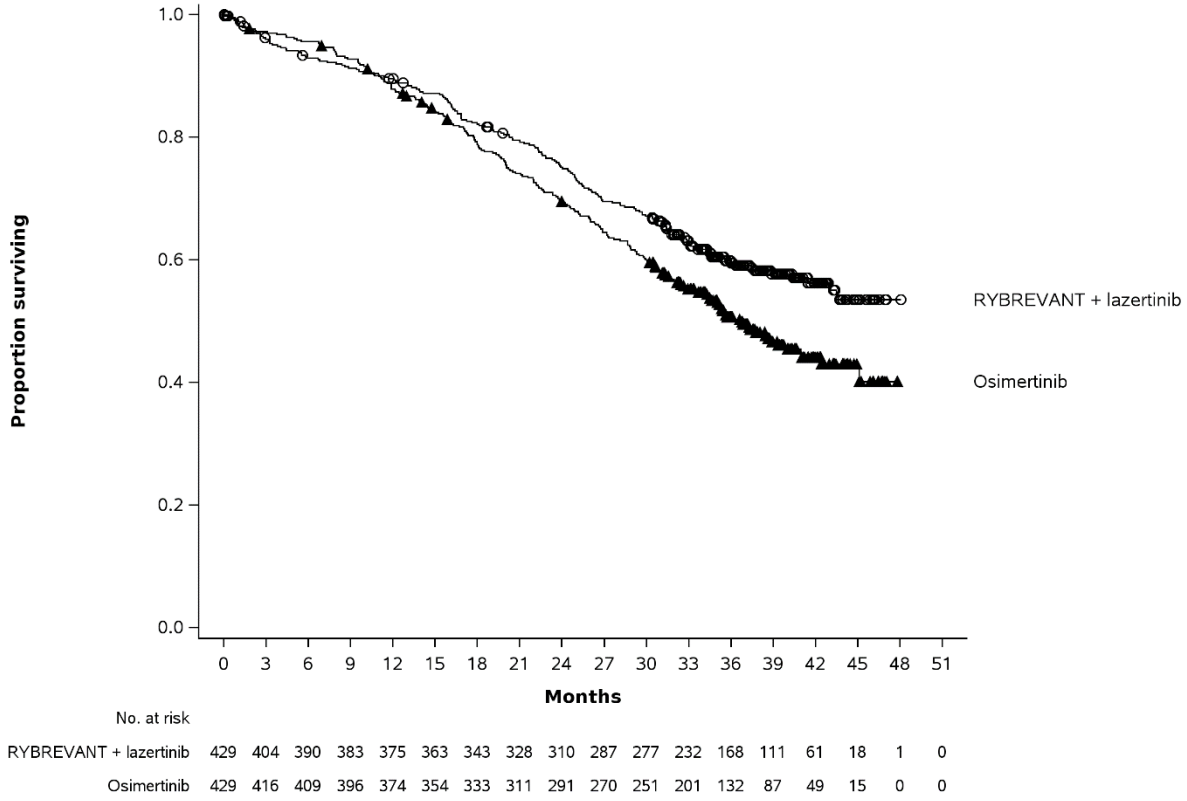


Figure 2: Kaplan-Meier curve of OS in previously untreated patients



Results of pre-specified exploratory analyses of central nervous system (CNS) ORR by BICR in the subset of patients with measurable intracranial lesions at baseline for the combination of RYBREVANT and lazertinib demonstrated similar intracranial ORR to the control. Per protocol, all patients in MARIPOSA had serial brain MRIs to assess intracranial response and duration. Results are summarized in Table 26.

Table 26: Intracranial ORR by BICR assessment in subjects with measurable intracranial lesions at baseline

	RYBREVANT + lazertinib (N=180)	**Osimertinib (N=187)**
Intracranial Tumor Response Assessment		
Number of confirmed responders	122	129
Intracranial ORR (CR+PR), % (95% CI)	67.8 (60.4, 74.5)	69.0 (61.8, 75.5)
Complete response %	55.0	52.4

Subgroup Analyses

The outcomes of the subgroup analyses for PFS and OS were generally consistent across the prespecified subgroups; however, differences were seen in subgroups of geriatric patients. No formal statistical testing was planned for subgroup analyses and the clinical interpretation of the subgroup analyses is therefore limited (see Table 27 and Table 28).

Table 27: Progression-Free survival for pre-defined subgroups based on age in MARIPOSA study by BICR assessment

Subgroups	HR (95% CI)	Events / N RYBREVANT + Lazertinib	Events / N Osimertinib
Age			
<65	0.50 (0.39, 0.65)	94/235	153/237
≥65	1.06 (0.80, 1.41)	98/194	99/192
<75	0.70 (0.57, 0.85)	165/378	220/376
≥75	0.77 (0.46, 1.30)	27/51	32/53

Table 28: Overall Survival for pre-defined subgroups based on age in MARIPOSA study

Subgroups	HR (95% CI)	Events / N RYBREVANT + Lazertinib	Events / N Osimertinib
Age			
<65	0.53 (0.40, 0.70)	76/235	123/237
≥65	1.11 (0.84, 1.48)	97/194	94/192
<75	0.75 (0.60, 0.93)	147/378	185/376
≥75	0.79 (0.47, 1.33)	26/51	32/53

Based on the results of the final analysis of OS with a median follow-up of 37.8 months

Previously Treated Patients with Locally Advanced or Metastatic NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

NSC3002 (MARIPOSA-2) Study

Table 29: Summary of patient demographics for MARIPOSA-2 clinical trial (NSC3002) in patients with previously treated NSLC with EGFR Exon 19 deletions or Exon 21 L585R Substitution Mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
NSC3002 (MARIPOSA-2)	Phase 3, randomized, open label, multicentre study	**RYBREVANT:** 1400 mg, <80 kg body weight, or 1750 mg, >80 kg body weight IV, once weekly through 4 weeks. Starting at Week 7 1,750 mg, < 80 kg body weight, or	N=394 RYBREVANT+ carboplatin+ pemetrexed n=131 carboplatin+ pemetrexed n=263	62 years (31-85)	Female: 60.4% Male: 39.6%

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
		2,100 mg, ≥ 80 kg body weight IV, once every 3 weeks until disease progression or unacceptable toxicity. **Carboplatin**: AUC 5*, IV, once every 3 weeks for up to 12 weeks. **Pemetrexed:** 500 mg/m^2, IV, once every 3 weeks until disease progression or unacceptable toxicity.			

*AUC5 = area under the concentration-time curve 5 mg/mL per minute

The efficacy of RYBREVANT was evaluated in patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (characterized by a validated test at or after the time of locally advanced or metastatic disease diagnosis, as identified by local or central testing) who had previously received osimertinib as first or second line therapy in MARIPOSA-2, an open-label, multicenter phase 3 clinical trial. In MARIPOSA-2, patients were randomized (2:2:1) to receive carboplatin and pemetrexed (CP, N=263), RYBREVANT in combination with carboplatin and pemetrexed (RYBREVANT-CP, N=131) and RYBREVANT in combination with lazertinib, carboplatin, and pemetrexed (N=263) in a separate arm of the study (an unapproved regimen for EGRFm NSCLC).

Patients were stratified by osimertinib line of therapy (first-line or second-line), prior brain metastases (yes or no), and Asian race (yes or no).

The primary efficacy endpoint was progression-free survival (PFS) as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy endpoints were overall response rate (ORR) and overall survival (OS). PFS and ORR were evaluated at the first interim analysis. There are two interim, and one final analysis planned for OS.

Of the 394 patients randomized to the RYBREVANT-CP arm or CP arm, the median age was 62 (range: 31–85) years, with 37.8% of the patients ≥ 65 years of age; 60.4% were female; and 48.2% were Asian and 46.4% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (39.6%) or 1 (60.4%); 65.5% never smoked; 45.2% had history of brain metastasis, and 91.6% had Stage IV cancer at initial diagnosis. Osimertinib had been given as first-line systemic therapy for 70.5% of participants and second-line therapy for 29.4% of participants.

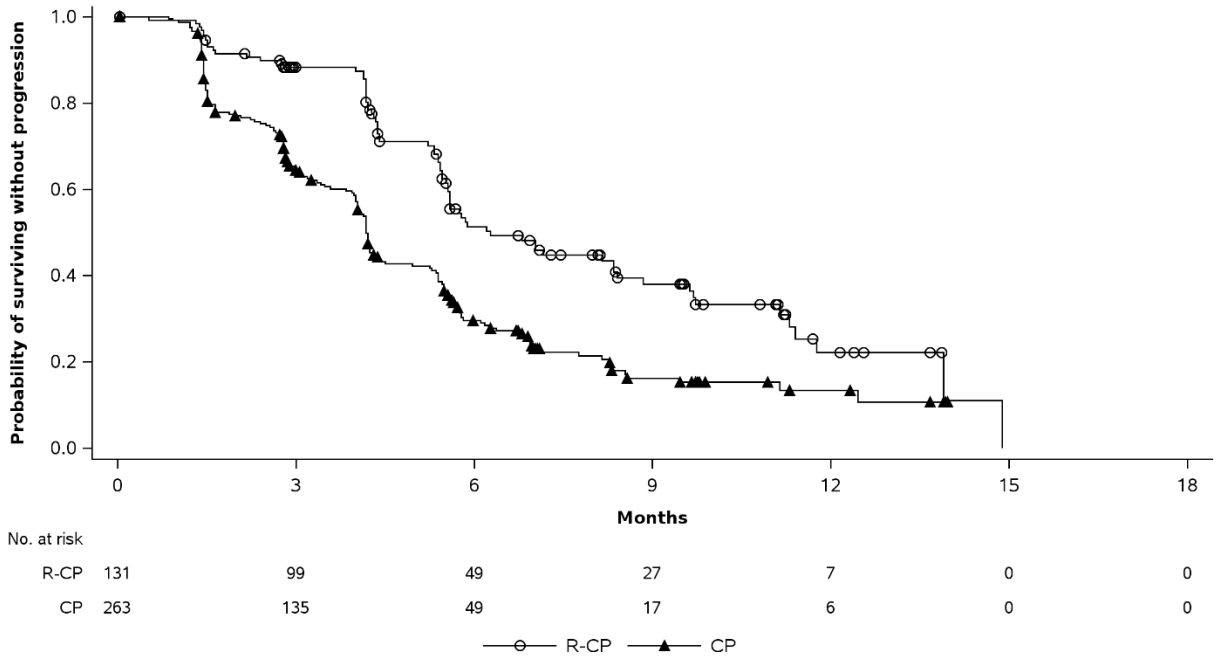
Efficacy results are summarized in Table 30 and Figure 3.

Table 30: Efficacy results in MARIPOSA-2

	RYBEVANT + Carboplatin + Pemetrexed (N=131)	Carboplatin + Pemetrexed (N=263)
Progression-free survival (PFS)[a]		
Number of events (%)	74 (56.5%)	171 (65.0%)
Median, months (95% CI)	6.28 (5.55, 8.41)	4.17 (4.04, 4.44)
HR (95% CI); p-value	0.48 (0.36, 0.64); p<0.0001	
Objective response rate[a]		
ORR, % (95% CI)	63.8% (55.0, 72.1)	36.2% (30.3, 42.3)
Complete response	1.5%	0.4%
Partial response	62.3%	35.8%

CI = confidence interval
NE = not estimatable
[a] Blinded Independent Central Review by RECIST v1.1

Figure 3: Kaplan-Meier curve of PFS in Previously Treated NSCLC Patients by BICR assessment - MARIPOSA-2



The median duration of response was 6.90 months (95% CI: 5.52, NE months) for patients who received RYBREVANT plus carboplatin and pemetrexed and 5.5 months (95% CI: 4.17, 9.56 months) for patients treated with carboplatin and pemetrexed alone.

The estimated OS HR at the first interim analysis was 0.77 [95% CI: 0.49, 1.21], however OS remains immature at the time of this analysis.

Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to be randomized in MARIPOSA-2. In an exploratory sub-group analysis, in patients with stable intracranial

metastases, the observed median intracranial PFS for RYBREVANT-CP was 12.45 months vs 8.31 months in the CP arm; HR=0.55 (95%CI 0.38, 0.79).

First-Line Treatment of Patients with Locally Advanced or Metastatic NSCLC with activating EGFR Exon 20 insertion mutations.

NSC2001 (PAPILLON) Study

Table 31: Summary of patient demographic for the PAPILLON clinical trial (NSC3001) in patients with previously untreated NSCLC with Exon 20ins mutations.

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
PAPILLON: NSC3001	Phase 3, randomized, open label, multicentre study	**Rybrevant**: 1400 mg, <80 kg body weight, or 1750 mg, >80 kg body weight IV, once weekly through 4 weeks. Starting at Week 7 1,750 mg, < 80 kg body weight, or 2,100 mg, ≥ 80 kg body weight IV, once every 3 weeks until disease progression or unacceptable toxicity. **Carboplatin**: AUC 5*, IV, once every 3 weeks for up to 12 weeks. **Pemetrexed:** 500 mg/m^2, IV, once every 3 weeks until disease progression or unacceptable toxicity.	N=308 RYBREVANT + carboplatin + pemetrexed n=153 Carboplatin + pemetrexed n=155	62 years (27-92)	Female: 58% Male: 42%

*AUC5 = area under the concentration-time curve 5 mg/mL per minute

PAPILLON (NSC3001) is a randomized, open-label, multicenter phase 3 study comparing treatment with RYBREVANT in combination with carboplatin and pemetrexed to treatment as compared to

chemotherapy alone (carboplatin and pemetrexed) in subjects with treatment-naïve, locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations, as identified prospectively by local testing.

Patients with squamous NSCLC, untreated brain metastases, with a medical history of ILD, or any evidence of clinically active ILD were excluded from the clinical study.

Randomization was stratified by ECOG performance status and prior brain metastases.

The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR) using RECIST 1.1. Secondary efficacy outcome measures were overall response rate (ORR) and overall survival (OS). Subjects randomized to the carboplatin and pemetrexed arm who had confirmed disease progression were permitted to cross over to receive RYBREVANT monotherapy.

A total of 308 subjects were randomized (1:1) to RYBREVANT in combination with carboplatin and pemetrexed (N=153) or carboplatin and pemetrexed (N=155). The median age was 62 (range: 27 to 92) years, with 39% of the subjects ≥65 years of age; 58% were female; and 61% were Asian and 36% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (35%) or 1 (65%); 58% never smoked; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis (99% had Stage IV cancer at screening).

The median follow-up time at the time of the PFS analysis was 14.9 (range: 0.3 to 27.0) months.

Efficacy results for PAPILLON are summarized in Table 32 and Figure 4.

Table 32: Efficacy Results in PAPILLON

	RYBREVANT + Carboplatin + Pemetrexed (N=153)	**Carboplatin+ pemetrexed (N=155)**
Progression-free survival (PFS) [a]		
Number of events (%)	84 (55%)	132 (85%)
Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI); p-valueb	0.40 (0.30, 0.53); p<0.0001	
Objective response rate (ORR)[a,c]		
ORR, % (95% CI)	73% (65%, 80%)	47% (39%, 56%)
p-value[d]	p<0.0001	
Complete response	3.9%	0.7%
Partial response	69%	47%

CI = confidence interval

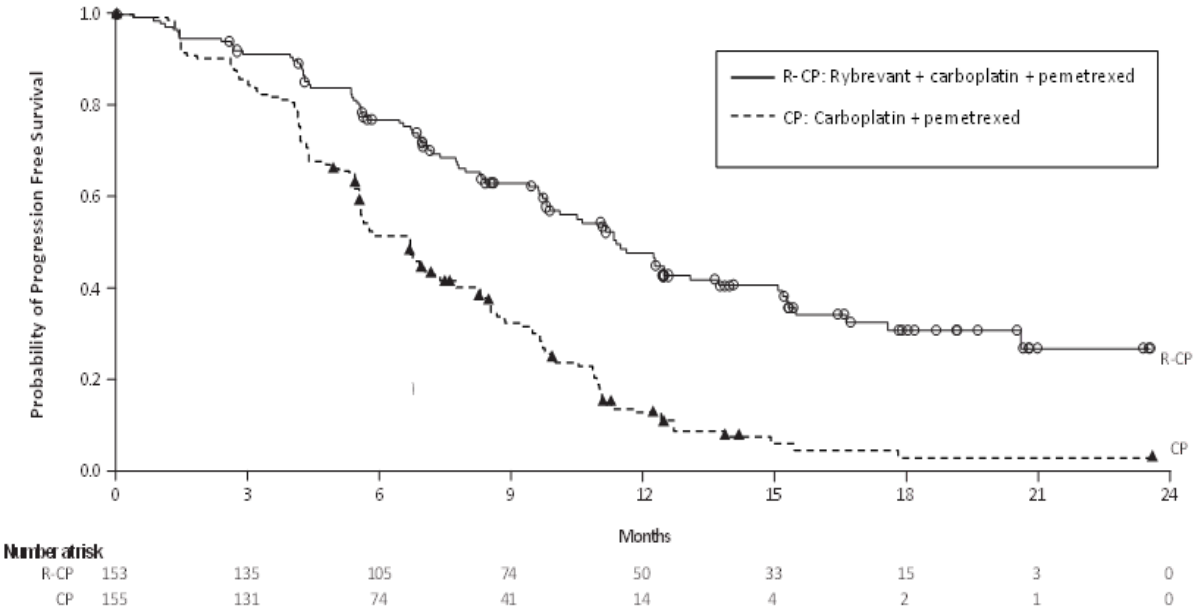
[a] Blinded Independent Central Review by RECIST v1.1

[b] p-value is from a log-rank test stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

[c] Including Unconfirmed Response.

[d] p-value is from a logistic regression model stratified by ECOG PS (0 or 1) and history of brain metastases (yes or no).

Figure 4: Kaplan-Meier Curve of PFS in Previously Untreated NSCLC Patients by BICR Assessment



The overall response rate (ORR) for patients who had a confirmed response was 67.1% for patients who received RYBREVANT plus carboplatin and pemetrexed and 36.2% for patients treated with carboplatin and pemetrexed alone. For patients who achieved a confirmed objective response, the median duration of response was 10.1 months (range: 1.4 to 22.3 months) for patients who received RYBREVANT plus carboplatin and pemetrexed and 5.6 months (range: 1.3 to 22.4 months) for patients treated with carboplatin and pemetrexed alone.

At this PFS analysis, 65 (42%) patients who were randomized to the carboplatin and pemetrexed arm had crossed over to receive subsequent RYBREVANT monotherapy. At the prespecified first interim analysis for overall survival (OS), conducted at the time of the primary analysis of PFS, statistical significance had not been reached (HR=0.72 [95% CI: 0.44, 1.17]).

Previously Treated NSCLC with EGFR Exon 20 insertion Mutations

EDI1001 (CHRYSALIS) Study

Table 33: Summary of patient demographics for the CHRYSALIS clinical trial (EDI1001) in patients with previously treated NSCLC with Exon 20ins mutations

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
CHRYSALIS: EDI1001	Phase 1, open label, single arm, multi-cohort study	1050 mg, <80 kg body weight 1400 mg, >80 kg body weight	N=81 (efficacy population)	62 years (42-84)	Female: 48 Male: 33

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Median age (Range)	Sex
		IV, once weekly in cycle 1; bi-weekly thereafter			

CHRYSALIS (EDI1001) was a multicenter, open-label, multi-cohort study conducted to assess the safety and efficacy of RYBREVANT in patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 patients with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutation, with measurable disease, whose disease had progressed on or after platinum-based chemotherapy. For enrollment, EGFR exon 20 insertion mutation status was determined prospectively by local testing using tissue and/or plasma samples. Patients with untreated brain metastases and patients with a history of ILD requiring treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study. The median follow-up for the efficacy population was 9.7 months.

RYBREVANT was administered intravenously at 1050 mg for patients <80 kg or 1400 mg for patients ≥80 kg once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR). Duration of response (DOR) by BICR was assessed as an additional measure of efficacy.

The median age was 62 (range: 42–84) years, with 9% of the patients ≥75 years of age; 59% were female; and 49% were Asian and 37% were White; 74% had baseline body weight <80 kg; 95% had adenocarcinoma; and 46% had received prior immunotherapy. The median number of prior therapies was 2 (range: 1 to 7 therapies). At baseline, 99% had Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; 53% never smoked; 75% had Stage IV cancer; and 22% had previous treatment for brain metastases. Insertions in Exon 20 were observed at 8 different residues; the most common residues were A767 (24%), S768 (16%), D770 (11%), and N771 (11%).

Efficacy results are summarized in Table 34.

Table 34: Results from CHRYSALIS: Patients with EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy

	Prior Platinum Chemotherapy Treated (N=81)
Overall Response Rate [a,b] (95% CI)	40% (29%, 51%)
Complete response (%)	3.7%
Partial response (%)	35.8%
Duration of Response [a] **(DOR)**	
Median (95% CI), months [c]	11.1 (6.9, NE)
Patients with DOR ≥6 months	63%

[a] Blinded Independent Central Review by RECIST v1.1

[b] Confirmed response.

[c] Based on Kaplan-Meier estimate.

NE=Not Estimable

15. Microbiology

No microbiology information is required for this product.

16. Non-Clinical Toxicology

In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 3 months and up to 125 mg/kg subcutaneously for 2 weeks. There were no effects on cardiovascular, respiratory, and nervous system function. Clinical pathology demonstrated non adverse elevations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and globulins, and non-adverse decreases in albumin when compared to the control group. All these values returned to normal ranges in recovery groups.

Genotoxicity: No animal studies have been performed to evaluate the genotoxic potential of amivantamab. Routine genotoxicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Carcinogenicity: No animal studies have been performed to establish the carcinogenic potential of amivantamab. Routine carcinogenicity studies are generally not applicable to biologic pharmaceuticals as large proteins cannot diffuse into cells and cannot interact with DNA or chromosomal material.

Reproductive and developmental toxicology: No long-term animal studies have been performed to evaluate whether amivantamab affects fertility in males or females or reproduction.

Based on its mechanism of action, amivantamab could cause fetal harm or developmental abnormalities when administered to a pregnant woman. Evidence from published literature showed that inhibition of EGFR and/or MET signaling pathways during pregnancy can cause impaired embryo-fetal development, embryo lethality and abortions in mice, rats and non-human primates. Therefore, it is reasonable to expect that amivantamab may cause adverse effects on embryo-fetal and postnatal development in humans.

No systemic exposure of hyaluronidase was detected in monkeys given 220,000 U/kg subcutaneously (at least 118 times higher than the human equivalent dose) and there were no effects on embryo-fetal development in pregnant mice given 330,000 U/kg hyaluronidase subcutaneously daily during organogenesis, which is at least 45 times higher than the human equivalent dose. There were no effects on pre- and post-natal development through sexual maturity in offspring of mice treated daily from implantation through lactation with 990,000 U/kg hyaluronidase subcutaneously, which is at least 134 times higher than the human equivalent doses.

17. Supporting Product Monographs

1. RYBREVANT (amivantamab, concentrate for intravenous infusion, 350 mg / 7mL), Product Monograph, Janssen Inc (a Johnson & Johnson Co.)

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]RYBREVANT® SC

amivantamab injection

This Patient Medication Information is written for the person who will be taking **RYBREVANT SC**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This Patient Medication Information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **RYBREVANT SC**, talk to a healthcare professional.

If your cancer is treated with **RYBREVANT SC** in combination with another medication called lazertinib, read the Patient Medication Information for lazertinib as well as this one.

What RYBREVANT SC is used for:

RYBREVANT SC is used in adults with a type of cancer called 'non-small cell lung cancer'. It is used when the cancer has spread in your body and has gone through certain genetic changes (EGFR Exon 19 deletions, Exon 21 L858R substitution mutations, or Exon 20 insertion mutations) in a gene called 'epidermal growth factor receptor' (EGFR).

For the following indication, RYBREVANT SC has been approved **with conditions (NOC/c)**. This means it has passed Health Canada's review and can be bought and sold in Canada, but the manufacturer has agreed to complete more studies to verify RYBREVANT's clinical benefit. For more information, talk to your healthcare professional.

RYBREVANT SC can be prescribed for you:

- after chemotherapy stops working against your cancer.

For the following indications, RYBREVANT SC has been approved **without conditions**. This means it has passed Health Canada's review and can be bought and sold in Canada.

RYBREVANT SC can be prescribed for you:

- as the first medicine you receive for your cancer in combination with another medicine called 'lazertinib'.
- in combination with chemotherapy after osimertinib stops working against your cancer.
- as the first medicine you receive for your cancer in combination with chemotherapy.

What is a Notice of Compliance with Conditions (NOC/c)?

A Notice of Compliance with Conditions (NOC/c) is a type of approval to sell a drug in Canada.

Health Canada only gives an NOC/c to a drug that treats, prevents, or helps identify a serious or life-threatening illness. The drug must show promising proof that it works well, is of high quality, and is reasonably safe. Also, the drug must either respond to a serious medical need in Canada, or be much

safer than existing treatments.

Drug makers must agree in writing to clearly state on the label that the drug was given an NOC/c, to complete more testing to make sure the drug works the way it should, to actively monitor the drug's performance after it has been sold, and to report their findings to Health Canada.

How RYBREVANT SC works:

Amivantamab is an antibody, that is a type of protein, that has been designed to recognize and attach to specific targets in the body. Amivantamab targets two proteins found on cancer cells:

- epidermal growth factor receptor (EGFR), and
- mesenchymal-epithelial transition factor (MET).

RYBREVANT SC works by attaching to these proteins. This may help to slow or stop your lung cancer from growing. It may also help to reduce the size of the tumour.

RYBREVANT SC may be given in combination with other anti-cancer medicines, such as chemotherapy (carboplatin and pemetrexed) or lazertinib. It is important that you also read the package inserts for these other medicines. If you have any questions about these medicines, ask your healthcare professional.

The ingredients in RYBREVANT SC are:

Medicinal ingredient: Amivantamab

Non-medicinal ingredients: Recombinant human hyaluronidase (rHuPH20), EDTA disodium salt dihydrate, glacial acetic acid, L-methionine, polysorbate 80, sodium acetate trihydrate, sucrose, and water for injections.

RYBREVANT SC comes in the following dosage form(s):

RYBREVANT SC is provided as a solution that is administered by subcutaneous (under the skin) injection. It comes in 160 mg / mL in the following dosage forms:

- 1600 mg / 10 mL
- 2240 mg / 14 mL
- 2400 mg / 15 mL
- 3520 mg / 22 mL

Do not use RYBREVANT SC if:

- you are allergic to amivantamab or any other ingredients of RYBREVANT SC (see "**The ingredients in RYBREVANT SC are:**")

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RYBREVANT SC. Talk about any health conditions or problems you may have, including if you:

- have a history of lung or breathing problems
- you have suffered from inflammation of your lungs (a condition called 'interstitial lung disease' or 'pneumonitis'
- have or have ever had heart problems
- are over the age of 65

Other warnings you should know about:

Administration-related reactions: Before each injection of RYBREVANT SC, you will be given medicines which help to lower the chance of administration-related reactions. These may include:

- Medicines for an allergic reaction (antihistamines)
- Medicines for inflammation (corticosteroids)
- Medicines for fever (such as acetaminophen)

You may also be given additional medicines based on any symptoms you may experience. If you have any further questions on the use of this medicine, ask your doctor or nurse.

Tell your doctor or nurse straight away while taking RYBREVANT SC if you get any of the following side effects:

- Any side effects during RYBREVANT SC administration.
- Sudden difficulty in breathing, cough, or fever that may suggest inflammation of the lungs.
- Sharp chest pain, shortness of breath, rapid breathing, leg pain, or swelling of your arms or legs when RYBREVANT SC is given in combination with lazertinib, that may suggest a blood clot in the veins and may lead to death. Your doctor may give you additional medication to help prevent blood clots during your treatment.
- Skin and nail problems. To reduce the risk and severity of skin and nail problems, wear protective clothing, apply broad-spectrum UVA/UVB sunscreen, and use moisturisers (ceramide-based or other formulations that provide long-lasting skin hydration and without drying components are preferred) regularly on your face and whole body (except scalp) while taking RYBREVANT SC. You will need to keep out of the sun and continue doing this for 2 months after you stop treatment. Your healthcare professional may recommend that you start an antibiotic(s) (topical and/or oral) and an antiseptic to wash your hands and feet to reduce the risk and severity of skin and nail problems. If you experience skin and/or nail reactions during treatment, your healthcare professional may treat you with a medicine(s) or send you to see a skin specialist (dermatologist).
- Eye problems. If you have vision problems or eye pain, contact your doctor or nurse straight away. If you use contact lenses and have any new eye symptoms, stop using contact lenses and tell your doctor straight away.

Other warnings you should know about:

Children and adolescents

- Do not give RYBREVANT SC to children or young people below 18 years of age. This is because it is not known whether the medicine will affect them.

Contraception

- If you or your partner could become pregnant, you must use effective contraception during and for 3 months after stopping treatment with RYBREVANT SC.

  Pregnancy and fertility - information for women

  Tell your doctor or nurse before you are given RYBREVANT SC if you are pregnant, think you might be pregnant, or are planning to have a baby.

  If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your baby.

Pregnancy and fertility – information for men

If your partner becomes pregnant while you are taking this medicine, tell your healthcare professional straight away.

Men should not donate or store semen during and for 3 months after stopping treatment with RYBREVANT SC.

Breastfeeding

- You should not breast-feed while taking this medicine and for 3 months after stopping treatment with RYBREVANT SC.

Driving and using machines

- If you feel tired, feel dizzy, or if your eyes are irritated or vision is affected after taking RYBREVANT SC, do not drive or use machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

Interactions with other drugs, vitamins, minerals, natural supplements or alternative medicines have not been established with RYBREVANT SC.

How to take RYBREVANT SC:

- RYBREVANT SC will be given to you by a healthcare professional as an injection under your skin (subcutaneous injection) over approximately 5 minutes per injection.
- It is given in the stomach area (abdomen), not in other sites of the body, and not into areas of the abdomen where the skin is red, bruised, tender, hard or where there are tattoos or scars. If you experience pain during the injection, the doctor or nurse may interrupt the injection and give you the remaining injection in another area of your abdomen.

Usual dose:

Your doctor will work out your dose of RYBREVANT SC. The dose of RYBREVANT SC will depend on your body weight at the start of your therapy. You will be treated with RYBREVANT SC once every 2, or 3, or 4 weeks according to the treatment your doctor decides for you.

The recommended dose of RYBREVANT SC when given alone or in combination with lazertinib every 4 weeks is:

- 1600 mg for the first 4 doses and 3520 mg for subsequent doses if you weigh less than 80 kg.
- 2240 mg for the first 4 doses and 4640 mg for subsequent doses if you weigh more than or equal to 80 kg.

RYBREVANT SC is given every 4 weeks as follows:

- once a week for the first 4 weeks
- then once every 4 weeks starting at Week 5 as long as you are getting benefit from the treatment.

The recommended dose of RYBREVANT SC when given alone or in combination with lazertinib every 2 weeks is:

- 1600 mg if you weigh less than 80 kg.
- 2240 mg if you weigh more than or equal to 80 kg.

RYBREVANT SC is given every 2 weeks as follows:

- once a week for the first 4 weeks
- then once every 2 weeks starting at Week 5 as long as you are getting benefit from the treatment.

The recommended dose of RYBREVANT SC when given with chemotherapy every 3 weeks is:

- 1600 mg for the first dose and 2400 mg for subsequent doses if you weigh less than 80 kg.
- 2240 mg for the first dose and 3360 mg for subsequent doses if you weigh more than or equal to 80 kg.

RYBREVANT SC is given every 3 weeks as follows:

- once a week for the first 4 weeks
- then once every 3 weeks starting at Week 7 as long as you are getting benefit from the treatment.

Medicines given during treatment with RYBREVANT SC

Before each injection of RYBREVANT SC, you will be given medicines which help to lower the chance of administration-related reactions and infusion-related reactions. These may include:

- medicines for an allergic reaction (antihistamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol)

You may also be given additional medicines based on any symptoms you may experience.

Overdose:

This medicine will be given by your healthcare professional. In the unlikely event that you are given too much (an overdose), your doctor will check you for side effects.

If you think you, or a person you are caring for, have taken too much RYBREVANT SC, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Missed dose:

It is very important to go to all your appointments. If you miss an appointment, make another appointment as soon as possible.

If you have any further questions on the use of this medicine, ask your healthcare professional.

Possible side effects from using RYBREVANT SC:

These are not all the possible side effects you may have when taking RYBREVANT SC. If you experience any side effects not listed here, tell your healthcare professional.

Very Common side effects (may affect more than 1 in 10 people)

- Rash
- Infected skin around the nail
- Dry skin
- Itching
- Constipation or diarrhoea
- Sores in the mouth
- Nausea or vomiting
- Feeling very tired
- Swollen hands, face, ankles or feet
- Decreased appetite
- Dizziness
- Fever
- Changes in eyesight
- Muscle pain
- Cough
- Shortness of breath
- Veins blocked by a blood clot when RYBREVANT SC is used with lazertinib
- Tingling, numbness, pain or loss of pain sensation when RYBREVANT SC is used with lazertinib

Common side effects (may affect between 1 and 10 people out of 100)

- Hemorrhoids
- Stomach pain
- Muscle aches and joint pain
- irritation or pain where the injection is given
- Bleeding (nosebleed, bleeding gums, blood in urine) when RYBREVANT SC is used with lazertinib

RYBREVANT SC can cause abnormal blood test. Your healthcare professional will decide when to perform blood tests and will interpret the results. RYBREVANT SC may cause:

- low level of 'albumin' in the blood
- increased level of liver enzymes 'alanine aminotransferase', 'aspartate aminotransferase', and 'gamma-glutamyltransferase' in the blood
- low level of sodium in the blood
- low number of white blood cells
- low number of red blood cells
- low number of platelets, cells that help blood to clot
- high level of 'bilirubin' in the blood
- low level of phosphate in the blood
- low level of protein in the blood
- high level of sugar in the blood

- increased level of blood lactate dehydrogenase
- increased level of 'creatinine' in the blood

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Stop taking this drug and get immediate medical help
	Only if severe	In all cases	
Very common (affecting more than 1 in 10 people)			
Administration Reactions: chills, feeling short of breath, feeling sick (nausea), flushing, chest discomfort, and fever. This can happen especially with the first dose. Your doctor may give you other medicines, or the injection may need to be stopped.		√	
Skin and Nail Problems: rash (including acne), infected skin around the nails, dry skin, itching, pain, blistering, and redness. Tell your healthcare professional if your skin or nail problems get worse.		√	
Venous Thromboembolism (a blood clot in the veins, especially in the lungs or legs when used in combination with lazertinib): sharp chest pain, shortness of breath, rapid breathing, leg pain and swelling of your arms or legs. Can be fatal.		√	
Eye Problems: dry eye, eye redness, itchy eyes, problems/changes with vision, growth of eyelashes, inflamed cornea (front part of the eye), excessive tearing, and swollen eyelid		√	
Common (affecting between 1 to 10 people out of every 100)			
Inflammation of the Lungs: sudden difficulty in breathing, cough, or fever. This could lead to permanent damage ('interstitial lung disease').		√	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

RYBREVANT SC will be stored at a hospital or clinic.

Store in a refrigerator at 2°C to 8°C. Do not shake or freeze. Protect from light.

Keep out of reach and sight of children.

If you want more information about RYBREVANT SC:

- Talk to your healthcare professional
- For questions or concerns, please contact the manufacturer, Janssen Inc., at innovativemedicine.jnj.com/canada
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (Drug Product Database: Access the database); the manufacturer's website (innovativemedicine.jnj.com/canada); or by calling 1-800-567-3331.

This leaflet was prepared by Janssen Inc., a Johnson & Johnson company.

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