FULL PRESCRIBING INFORMATION

1 NAME OF THE MEDICINAL PRODUCT

RYBREVANT 160 mg/ml S.C.
Solution for injection.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RYBREVANT 1600 mg solution for injection
One mL of solution for injection contains 160 mg amivantamab.
One 10 mL vial of solution for injection contains 1600 mg of amivantamab.

RYBREVANT 2240 mg solution for injection
One mL of solution for injection contains 160 mg amivantamab.
One 14 mL vial of solution for injection contains 2240 mg of amivantamab.

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

Excipient with known effect:
One mL of solution contains 0.6 mg of polysorbate 80.

For the full list of excipients, see section 17.1.

3 PHARMACEUTICAL FORM

Solution for injection.
The solution is colourless to pale yellow.

4 INDICATIONS AND USAGE

RYBREVANT 160mg/ml S.C. is indicated for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) Exon 20 insertion mutation, as detected by an approved test whose disease has progressed on or after platinum based chemotherapy.

RYBREVANT 160mg/ml S.C. in combination with lazertinib, is indicated for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, as detected by an approved test.

5 DOSAGE AND ADMINISTRATION

5.1 Posology and method of administration

Treatment with RYBREVANT 160mg/ml S.C. should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Before initiation of RYBREVANT 160 mg/ml S.C., EGFR mutation status in tumour tissue or plasma specimens must be established using a validated test method. If no mutation is detected in a plasma specimen, tumour

tissue should be tested if available in sufficient amount and quality due to the potential for false negative results using a plasma-test. Once EGFR mutation status has been established, testing does not need to be repeated (see section 15.2).

RYBREVANT 160mg/ml S.C. should be administered by a healthcare professional with access to appropriate medical support to manage administration-related reactions if they occur.

Posology

Premedications should be administered to reduce the risk of administration-related reactions with RYBREVANT 160mg/ml S.C. (see below "Dose modifications" and "Recommended concomitant medicinal products").

The recommended dosages of RYBREVANT 160mg/ml S.C. in combination with lazertinib or as monotherapy based on baseline body weight, are provided in Table 1.

Table 1: Recommended dosage of RYBREVANT 160mg/ml S.C. formulation

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.

When given in combination with lazertinib, it is recommended to administer RYBREVANT 160mg/ml S.C. any time after lazertinib when given on the same day. Refer to section 5 of the lazertinib full prescribing information for recommended lazertinib dosing information.

Duration of treatment
It is recommended that patients are treated with RYBREVANT 160mg/ml S.C. until disease progression or unacceptable toxicity.

Missed dose
If a dose of RYBREVANT 160mg/ml S.C. is missed between Weeks 1 to 4, it should be administered within 24 hours. If a dose of RYBREVANT 160mg/ml S.C. is missed from Week 5 onward, it should be administered within 7 days. Otherwise, the missed dose should not be administered and the next dose should be administered per the usual dosing schedule.

Dose modifications
Dosing should be interrupted for Grade 3 or 4 adverse reactions until the adverse reaction resolves to ≤ Grade 1 or baseline. If an interruption is 7 days or less, restart at the current dose. If an interruption is longer than 7 days, it is recommended restarting at a reduced dose as presented in Table 2. See also specific dose modifications for specific adverse reactions below Table 2.

If used in combination with lazertinib, refer to section 5 of the lazertinib full prescribing information for information about dose modifications.

Table 2: Recommended dose modifications for adverse reactions

Dose*	**Dose after 1st interruption for adverse reaction**	**Dose after 2nd interruption for adverse reaction**	**Dose after 3rd interruption for adverse reaction**
1600 mg	1050 mg	700 mg	Discontinue RYBREVANT 160mg/ml S.C.
2240 mg	1600 mg	1050 mg	

* Dose at which the adverse reaction occurred

Administration-related reactions
Premedications should be administered to reduce the risk of administration-related reactions with RYBREVANT 160mg/ml S.C. (see "Recommended concomitant medicinal products"). Injections should be interrupted at the first sign of administration-related reactions. Additional supportive medicinal products (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated (see section 8.1).

- Grade 1-3 (mild-severe): Upon recovery of symptoms, resume RYBREVANT 160mg/ml S.C. injections. Concomitant medicinal products should be administered at the next dose, including dexamethasone (20 mg) or equivalent (see Table 3).
- Recurrent Grade 3 or Grade 4 (life-threatening): Permanently discontinue RYBREVANT.

Venous thromboembolic (VTE) events with concomitant use with lazertinib

When initiating treatment with RYBREVANT 160mg/ml S.C. in combination with lazertinib, administer anticoagulant prophylaxis to prevent venous thromboembolic (VTE) events for the first four months of treatment *(see section 8.3).* If there are no signs or symptoms of VTE during the first four months of treatment, consider discontinuation of anticoagulant prophylaxis at the discretion of the healthcare provider. Refer to the lazertinib full prescribing information for information about concomitant medications.

Dermatologic Adverse Reactions
Patients should be instructed to limit sun exposure during and for 2 months after RYBREVANT 160mg/ml S.C. therapy. Alcohol-free emollient cream is recommended for dry areas. For further information about prophylaxis for dermatologic adverse reactions, see section 8.4. If the patient develops a Grade 1-2 dermatologic adverse reaction supportive care should be initiated; if there is no improvement after 2 weeks, dose reduction should be considered for persistent Grade 2 rash (see Table 2). If the patient develops a Grade 3 dermatologic adverse reaction, supportive care should be initiated, and interruption of RYBREVANT 160mg/ml S.C. should be considered until the adverse reaction improves. Upon recovery of the dermatologic adverse reaction to ≤ Grade 2, RYBREVANT 160mg/ml S.C. should be resumed at a reduced dose. If the patient develops Grade 4 dermatologic adverse reactions, permanently discontinue RYBREVANT 160mg/ml S.C. (see section 8.4).

Interstitial lung disease/pneumonitis
RYBREVANT 160mg/ml S.C. should be withheld if interstitial lung disease (ILD) or ILD-like adverse reactions (pneumonitis) is suspected. If the patient is confirmed to have ILD or ILD-like adverse reactions (e.g., pneumonitis), permanently discontinue RYBREVANT 160mg/ml S.C. (see section 8.2).

<u>Recommended concomitant medicinal products</u>

Prior to the initial dose (Week 1, Day 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of administration-related reactions (see Table 3). For subsequent doses, antihistamines and antipyretics are required to be administered. Glucocorticoids should also be re-initiated after prolonged dose interruptions. Antiemetics should be administered as needed.

Table 3: Dosing schedule of premedications

Premedication	Dose	Route of administration	Recommended dosing window prior to RYBREVANT 160mg/ml S.C. administration
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Paracetamol/Acetaminophen (650 to 1000 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid†	Dexamethasone (20 mg) or equivalent	Intravenous	45 to 60 minutes
		Oral	At least 60 minutes
Glucocorticoid‡	Dexamethasone (10 mg) or equivalent	Intravenous	45 to 60 minutes
		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.

Special populations

Renal impairment
No formal studies of amivantamab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dose adjustment is necessary for patients with mild or moderate renal impairment. Caution is required in patients with severe renal impairment as amivantamab has not been studied in this patient population (see section 13.3). If treatment is started, patients should be monitored for adverse reactions with dose modifications per the recommendations above.

Hepatic impairment
No formal studies of amivantamab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dose adjustment is necessary for patients with mild hepatic impairment. Caution is required in patients with moderate or severe hepatic impairment as amivantamab has not been studied in this patient population (see-section 13.3). If treatment is started, patients should be monitored for adverse reactions with dose modifications per the recommendations above.

Method of administration

RYBREVANT 160mg/ml S.C. is for subcutaneous use only.

RYBREVANT 160mg/ml S.C. is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. See section 16 for instructions on handling of the medicinal product before administration.

Inject the required volume of RYBREVANT 160mg/ml S.C. into the subcutaneous tissue of the abdomen over approximately 5 minutes. Do not administer at other sites of the body as no data are available.

Pause or slow 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 that the full dose is delivered through the infusion set. Sodium chloride 9 mg/mL (0.9%) solution may be utilised to flush remaining medicinal 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 5 cm

around the periumbilical area.
Injection sites should be rotated for successive injections.

6 DOSAGE FORMS AND STRENGTHS

Solution for injection:
1600 mg (10 mL amivantamab 160 mg/ml)
2240 mg (14 mL amivantamab 160 mg/ml)

7 CONTRAINDICATIONS

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 17.1.

8 WARNINGS AND PRECAUTIONS

8.1 Hypersensitivity and Administration Related Reactions

RYBREVANT 160mg/ml S.C. can cause hypersensitivity and administration related reactions (ARR); signs and symptoms of ARR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension, and vomiting. The median time to ARR onset is approximately 2 hours. Local injection site reactions are described separately in Section 9.1.

RYBREVANT 160mg/ml S.C. with Lazertinib

In PALOMA-3 (see section 9.1), in the 206 patients who received RYBREVANT 160mg/ml S.C. in combination with lazertinib, all Grade ARR occurred in 13%, including 0.5% Grade 3. The majority of ARR events occurred with the initial dose (Week 1 Day 1.)

Premedicate with antihistamines, antipyretics, and glucocorticoids and administer RYBREVANT 160mg/ml S.C. as recommended [see Dosage and Administration (5.1)].

Monitor patients for any signs and symptoms of administration-related reactions during injection in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt RYBREVANT 160mg/ml S.C. injection, if ARR is suspected. Resume treatment upon resolution of symptoms or permanently discontinue RYBREVANT 160mg/ml S.C. based on severity [see Dosage and Administration (5.1)].

8.2 Interstitial Lung Disease/Pneumonitis

RYBREVANT 160mg/ml S.C. can cause severe and fatal interstitial lung disease (ILD)/pneumonitis.

RYBREVANT 160mg/ml S.C. with Lazertinib

In PALOMA-3 [see Adverse Reactions (9.1)], in 206 patients who received RYBREVANT 160mg/ml S.C. in combination with lazertinib, ILD/pneumonitis occurred in 5.8%, including Grade 3 in 1.5%, Grade 4 in 1.0%, Grade 5 in 0.5%. In total, 5% of patients permanently discontinued RYBREVANT 160mg/ml S.C. and lazertinib due to ILD/pneumonitis.

RYBREVANT intravenous formulation with Lazertinib

In MARIPOSA [see Adverse Reactions (9.1)], in 421 patients who received intravenous amivantamab in combination with lazertinib, ILD/pneumonitis occurred in 3.1%, including Grade 3 in 1% and Grade 4 in 0.2% of patients. There was one fatal case of ILD/pneumonitis and 2.9% of patients permanently discontinued intravenous amivantamab and lazertinib due to ILD/pneumonitis.

RYBREVANT intravenous formulation as a Single Agent

In CHRYSALIS, *[see Adverse Reactions (9.1)]*, in 302 patients who received RYBREVANT intravenous formulation as a single agent, ILD/pneumonitis occurred in 3.3% of patients including 0.7% Grade 3. Three patients (1%) permanently discontinued RYBREVANT intravenous formulation due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT 160mg/ml S.C. in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed [see Dosage and Administration (5.1)].

8.3 Venous Thromboembolic (VTE) Events with Concomitant Use of RYBREVANT and Lazertinib

RYBREVANT 160mg/ml S.C. in combination with lazertinib can cause serious and fatal venous thromboembolic (VTE) events, including deep vein thrombosis and pulmonary embolism. Without prophylactic anticoagulation, the majority of these events occurred during the first four months of therapy [see Adverse Reactions (9.1)].

RYBREVANT 160mg/ml S.C. with Lazertinib

In PALOMA-3 *[see Adverse Reactions (9.1)]*, in the 206 patients who received RYBREVANT 160mg/ml S.C. in combination with lazertinib, all Grade VTE occurred in 9.2%, including Grade 3 in 1.0%. Of the 206 patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib, 80% received prophylactic anticoagulation at study entry. In the 164 patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib who received prophylactic anticoagulation, all Grade VTE occurred in 7%. In the 42 patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib who did not receive prophylactic anticoagulation, all Grade VTE occurred in 17%. In total, 0.5% of patients had VTE leading to dose reductions of RYBREVANT 160mg/ml S.C. and no patients required permanent discontinuation. The median time to first VTE event was 43 days (range: 17.0; 170).

RYBREVANT intravenous formulation with Lazertinib.

In MARIPOSA *[see Adverse Reactions (9.1)],* in 421 patients who received intravenous amivantamab in combination with lazertinib, VTEs occurred in 36%, including Grade 3 in 10% and Grade 4 in 0.5% of patients. On-study VTEs occurred in 1.2% of patients (n=5) while receiving anticoagulation therapy. There were two fatal cases of VTE (0.5%), 9% of patients had VTE leading to dose interruptions of RYBREVANT intravenous formulation, 1% of patients had VTE leading to dose reductions of RYBREVANT intravenous formulation, and 3.1% of patients had VTE leading to permanent discontinuation of RYBREVANT intravenous formulation. The median time to onset of VTEs was 84 days (range: 6 to 777).

Administer prophylactic anticoagulation for the first four months of treatment. The use of Vitamin K antagonists is not recommended.

Monitor for signs and symptoms of VTE events and treat as medically appropriate. Withhold RYBREVANT 160mg/ml S.C. and lazertinib based on severity *[see Dosage and Administration (5.1)]*. Once anticoagulant treatment has been initiated, resume RYBREVANT 160mg/ml S.C. and lazertinib at the same dose level at the discretion of the healthcare provider *[see Dosage and Administration (5.1)]*. In the event of VTE recurrence despite therapeutic anticoagulation, permanently discontinue RYBREVANT 160mg/ml S.C.. Treatment can continue with lazertinib at the same dose level at the discretion of the healthcare provider *[see Dosage and Administration (5.1)]*. Refer to the lazertinib full prescribing information for recommended lazertinib dosage modification.

8.4 Dermatologic Adverse Reactions

RYBREVANT 160mg/ml S.C. can cause severe rash including toxic epidermal necrolysis (TEN), dermatitis acneiform, pruritus, dry skin and skin ulcer.

RYBREVANT 160mg/ml S.C. with Lazertinib

In PALOMA-3 [see Adverse Reactions (9.1)], in the 206 patients who received RYBREVANT 160mg/ml S.C. in combination with lazertinib, rash occurred in 79.5% of patients, including Grade 3 in 13.6% and Grade 4 in 0.5%. Rash leading to dose reduction occurred in 7.8% of patients, and RYBREVANT 160mg/ml S.C. was permanently discontinued due to rash in 0.5% of patients.

RYBREVANT intravenous formulation with Lazertinib
In MARIPOSA, *[see Adverse Reactions (9.1)]*, in 421 patients who received intravenous amivantamab in combination with lazertinib, rash occurred in 86% including 26% Grade 3. The median time to onset of rash was 14 days (range: 1 to 556 days). Rash leading to dose interruptions of intravenous RYBREVANT occurred in 37% of patients, rash leading to dose reductions of intravenous RYBREVANT occurred in 23% of patients, and rash leading to permanent discontinuation of RYBREVANT occurred in 5% of patients.

RYBREVANT intravenous formulation as a Single Agent
In CHRYSALIS *[see Adverse Reactions* (9.1), in 302 patients who received intravenous amivantamab as a single agent, rash occurred in 74%, including 3.3% Grade 3. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and intravenous RYBREVANT was permanently discontinued due to rash in 0.7% of patients. Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with intravenous RYBREVANT as a single agent.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT 160mg/ml S.C. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream is recommended for dry skin. A prophylactic approach to rash prevention should be considered.

When initiating treatment with RYBREVANT 160mg/ml S.C., administer alcohol free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of dermatologic adverse reactions. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions.

If skin reactions develop, start topical steroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. 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 160mg/ml S.C. based on severity [see *Dosage and Administration* (5.1)].

8.5 Ocular Toxicity

RYBREVANT 160mg/ml S.C. can cause ocular toxicity including keratitis, blepharitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, eye pruritus and uveitis.

RYBREVANT 160mg/ml S.C. with Lazertinib

In PALOMA-3 *[see Adverse Reactions (9.1)]*, in the 206 patients who received RYBREVANT 160mg/ml S.C. in combination with lazertinib, all grade ocular toxicity occurred in 10.7%, including 0% Grade 3.

RYBREVANT intravenous formulation with Lazertinib

In MARIPOSA *[see Adverse Reactions (9.1)]*, in 421 patients treated with intravenous amivantamab in combination with lazertinib, ocular toxicity occurred in 16%, including 0.7% Grade 3 or 4 ocular toxicity.

RYBREVANT intravenous formulation as a Single Agent

In CHRYSALIS, *[see Adverse Reactions (9.1)],* in 302 patients treated with intravenous amivantamab, keratitis occurred in 0.7% and uveitis occurred in 0.3%. All events were Grade 1-2.

Promptly refer patients with new or worsening eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT 160mg/ml S.C. based on severity *[see Dosage and Administration (5.1)]*.

8.6 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT 160mg/ml S.C. can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryo lethality, and abortion. Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT 160mg/ml S.C. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT 160mg/ml S.C. *[see Use in Specific Populations (10.1, 10.3)]*.

8.7 Sodium

This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially "sodium-free" (see section 17.1).

8.8 Polysorbate

This medicinal product contains 0.6 mg of polysorbate 80 in each mL, which is equivalent to 6 mg per 10 mL vial, or 8.4 mg per 14 mL vial. Polysorbates may cause hypersensitivity reactions.

9 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Hypersensitivity and Administration-Related Reactions *[see Warnings and Precautions (8.1)]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (8.2)]*
- Venous Thromboembolic Events *[see Warnings and Precautions (8.3)]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions (8.4)]*
- Ocular Toxicity *[see Warnings and Precautions (8.5)]*

9.1 Clinical Trials Experience

Summary of the safety profile

RYBREVANT as monotherapy

In the dataset of RYBREVANT intravenous formulation as monotherapy (N=380), the most frequent adverse reactions in all grades were rash (76%), infusion-related reactions (67%), nail toxicity (47%), hypoalbuminaemia

(31%), oedema (26%), fatigue (26%), stomatitis (24%), nausea (23%), and constipation (23%). Serious adverse reactions included ILD (1.3%), IRR (1.1%), and rash (1.1%). Three percent of patients discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR (1.1%), ILD (0.5%), and nail toxicity (0.5%).

Tabulated list of adverse reactions

Table 4 summarises the adverse drug reactions that occurred in patients receiving RYBREVANT as monotherapy.

The data reflects exposure to RYBREVANT intravenous formulation in 380 patients with locally advanced or metastatic non-small cell lung cancer after failure of platinum-based chemotherapy. Patients received amivantamab 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg). The median exposure to amivantamab was 4.1 months (range: 0.0 to 39.7 months).

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); and not known (frequency cannot be estimated from the available data).

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

Table 4: Adverse reactions in patients receiving RYBREVANT as monotherapy (N=380)

System organ class Adverse reaction	**Frequency category**	**Any grade (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders			
Hypoalbuminaemia* (see section 13.2)	Very common	31	2†
Decreased appetite		16	0.5†
Hypocalcaemia		10	0.3†
Hypokalaemia	Common	9	2
Hypomagnesaemia		8	0
Nervous system disorders			
Dizziness*	Very common	13	0.3†
Eye disorders			
Visual impairment*	Common	3	0
Growth of eyelashes*		1	0
Other eye disorders*		6	0
Keratitis	Uncommon	0.5	0
Uveitis		0.3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease*	Common	3	0.5†
Gastrointestinal disorders			
Diarrhoea	Very common	11	2†
Stomatitis*		24	0.5†
Nausea		23	0.5†
Constipation		23	0
Vomiting		12	0.5†
Abdominal pain*	Common	9	0.8†
Haemorrhoids		3.7	0
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	15	2
Aspartate aminotransferase increased		13	1
Blood alkaline phosphatase increased		12	0.5†
Skin and subcutaneous tissue disorders			
Rash*	Very common	76	3†
Nail toxicity*		47	2†
Dry skin*		19	0
Pruritus		18	0

Skin ulcer	Uncommon	0.8	0
Toxic epidermal necrolysis		0.3	0.3†
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	11	0.3†
General disorders and administration site conditions			
Oedema*	Very common	26	0.8†
Fatigue*		26	0.8†
Pyrexia		11	0
Injury, poisoning and procedural complications			
Infusion-related reaction	Very common	67	2

* Grouped terms

† Grade 3 events only

RYBREVANT in combination with lazertinib

Overall, the safety profile of RYBREVANT 160mg/ml S.C. was consistent with the established safety profile of RYBREVANT intravenous formulation, with a lower incidence of administration-related reactions and VTEs observed with the subcutaneous formulation compared to the intravenous formulation.

In the dataset of RYBREVANT (either intravenous or subcutaneous formulations) in combination with lazertinib (N=829), the most frequent adverse reactions of any grade (≥ 20% patients) were rash (87%), nail toxicity (68%), hypoalbuminaemia (49%), hepatotoxicity (43%), stomatitis (43%), oedema (42%), fatigue (34%), paraesthesia (29%), diarrhoea (26%), constipation (25%), dry skin (25%), nausea (24%), pruritus (24%) and decreased appetite (23%).

Clinically relevant differences between the intravenous and subcutaneous formulations, when given in combination with lazertinib, were observed for administration-related reactions (63% for intravenous vs. 14% for subcutaneous) and VTE (37% for intravenous vs. 11% for subcutaneous).

Serious adverse reactions were reported in 14% of patients who received RYBREVANT 160mg/ml S.C. in combination with lazertinib, including ILD (4.2%), VTE (2.2%), hepatotoxicity (2.2%), and fatigue (1.5%). Seven percent of patients discontinued RYBREVANT 160mg/ml S.C. due to adverse reactions. In patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib, the most frequent adverse reactions of any grade (≥ 1% patients) leading to discontinuation of RYBREVANT 160mg/ml S.C. were ILD (3.7%), rash (1.2%), and nail toxicity (1.0%).

Tabulated list of adverse reactions

The adverse reactions for RYBREVANT (either intravenous or subcutaneous formulation) when received in combination with lazertinib are summarised in Table 5.

The safety data below reflect exposure to RYBREVANT (either intravenous or subcutaneous formulation) in combination with lazertinib in 829 patients with locally advanced or metastatic NSCLC, including 421 patients in MARIPOSA, 202 patients in PALOMA-2 cohorts 1, 5 and 6, and 206 patients in PALOMA-3 subcutaneous arm. Patients received RYBREVANT (either intravenous or subcutaneous formulation) until disease progression or unacceptable toxicity. The median duration of treatment with amivantamab overall for both intravenous and subcutaneous formulations was 9.1 months (range: 0.1 to 31.4 months). Median duration on treatment for the subcutaneous formulation was 6.1 months (range: 0.1 to 13.2 months) while median duration on treatment for the intravenous formulation was 18.5 months (range: 0.2 to 31.4 months).

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); and not known (frequency cannot be estimated from the available data).

Table 5: Adverse reactions for Rybrevant (either intravenous or subcutaneous formulation) when received in combination with lazertinib (N=829)

System organ class Adverse reaction	Frequency category	Any grade (%)	Grade 3-4 (%)
Metabolism and nutrition disorders			
Hypoalbuminaemia*	Very common	49	4.6
Decreased appetite		23	0.7
Hypocalcaemia		18	1.1
Hypokalaemia		12	2.7
Hypomagnesaemia	Common	6	0
Nervous system disorders			
Paraesthesia*, a	Very common	29	1.2
Dizziness*		12	0
Eye disorders			
Other eye disorders*	Very common	19	0.5
Visual impairment*	Common	3.6	0
Keratitis		1.9	0.2
Growth of eyelashes*		1.8	0
Vascular disorders			
Venous thromboembolism			
Amivantamab intravenous*, b	Very common	37	11
Amivantamab subcutaneous*, c	Very common	11	0.7
Respiratory, thoracic, and mediastinal disorders			
Interstitial lung disease*	Common	3.6	1.7
Gastrointestinal disorders			
Stomatitis*	Very common	43	2.2
Diarrhoea		26	1.8
Constipation		25	0
Nausea		24	0.7
Vomiting		15	0.5
Abdominal pain*	Common	9	0.1
Haemorrhoids		8	0.1
Hepatobiliary disorders			
Hepatotoxicity*	Very common	43	7
Skin and subcutaneous tissue disorders			
Rash*	Very common	87	22
Nail toxicity*		68	8
Dry skin*		25	0.7
Pruritus		24	0.4
Skin ulcer	Common	3.7	0.5
Palmar-plantar erythrodysaesthesia syndrome		3.5	0.1
Urticaria		1.6	0
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	15	0.5
Muscle spasms		13	0.4
General disorders and administration site conditions			
Oedema*	Very common	42	2.4
Fatigue*		34	3.4
Pyrexia		11	0

Injection site reactions[*, c, d]	Common	6	0
Injury, poisoning and procedural complications			
Infusion-/Administration-related reactions			
Amivantamab intravenous[b, e]	Very common	63	6
Amivantamab subcutaneous[c, f]	Very common	14	0.5

[*] Grouped terms.

[a] Applicable only to lazertinib.

[b] Frequency based on amivantamab intravenous studies only (MARIPOSA [N=421]).

[c] Frequency based on amivantamab subcutaneous studies only (PALOMA-2 cohorts 1 and 6 [N=125], cohort 5 [N=77] and PALOMA-3 subcutaneous arm [N=206]).

[d] Injection site reactions are local signs and symptoms associated with subcutaneous mode of administration.

[e] Infusion-related reactions are systemic signs and symptoms associated with infusion of amivantamab intravenous.

[f] Administration-related reactions are systemic signs and symptoms associated with administration of amivantamab subcutaneous.

Description of selected adverse reactions

Administration-related reactions

Administration-related reactions were reported in 14% of patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib. The most frequent signs and symptoms of administration-related reactions include dyspnoea, flushing, fever, chills, nausea, and chest discomfort. In patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib, the median time to onset of first administration-related reactions was 1.9 hours (range: 0.0 to 176.5 hours), with most administration-related reactions (96%) being Grades 1 or 2 in severity. In PALOMA 3, administration related reactions were reported in 13% of patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib compared to 66% when treated with Rybrevant intravenous formulation in combination with lazertinib.

Injection site reactions

Injection site reactions occurred in 6% of patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib. All injection site reactions were Grade 1 or 2 in severity. The most frequent symptom of injection site reactions was erythema.

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD) or ILD-like adverse reactions have been reported with the use of amivantamab as well as with other EGFR inhibitors. ILD was reported in 3.6% of patients treated with RYBREVANT (either intravenous or subcutaneous formulation) in combination with lazertinib, including 2 (0.2%) patients with a fatal reaction. Patients with a medical history of ILD, including drug-induced ILD or radiation pneumonitis, were excluded from PALOMA-2 and PALOMA-3.

Venous thromboembolic (VTE) events with concomitant use with lazertinib

VTE events, including deep venous thrombosis (DVT) and pulmonary embolism (PE), were reported in 11% of patients receiving RYBREVANT 160mg/ml S.C. in combination with lazertinib in PALOMA-2 and PALOMA-3. Most cases were Grade 1 or 2, with Grade 3 events occurring in 3 (0.7%) patients. Additionally, 336 (82%) of these 408 patients receiving RYBREVANT 160mg/ml S.C. took prophylactic anticoagulants with a direct oral anticoagulant or low molecular weight heparin within the first four months of study treatment. In PALOMA-3, for the direct comparison between arms, the incidence of VTE events was 9% for patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib, versus 14% when treated with RYBREVANT intravenous formulation in combination with lazertinib, with similar rates of prophylactic anticoagulant use in both treatment arms (80% in the subcutaneous arm vs. 81% in the intravenous arm). For patients who did not receive prophylactic anticoagulants, the overall incidence of VTE events was 17% for patients treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib with all VTE events reported as Grade 1-2 and serious VTE events reported in 4.8% of these patients, compared to an overall incidence of 26% for patients treated

with RYBREVANT intravenous formulation in combination with lazertinib with Grade 3 VTE and Grade 4 events reported in 10% and 2.6% of patients, respectively, and serious VTE events reported in 10% of these patients.

Dermatologic reactions
Rash (including dermatitis acneiform), pruritus, and dry skin have occurred in patients treated with RYBREVANT (either intravenous or subcutaneous formulation). Rash occurred in 87% of patients treated with Rybrevant in combination with lazertinib, leading to discontinuation of RYBREVANT in 0.6% of patients. Among patients treated with Rybrevant in combination with lazertinib, most cases were Grade 1 or 2, with Grade 3 and Grade 4 reactions occurring in 22% and 0.1% of patients, respectively.

Eye disorders
Eye disorders occurred in patients treated with Rybrevant (either intravenous or subcutaneous formulation), including keratitis in 1.9% of patients treated with Rybrevant in combination with lazertinib. Other reported adverse reactions included growth of eyelashes, visual impairment, and other eye disorders.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:
https://sideeffects.health.gov.il

10 USE IN SPECIFIC POPULATIONS

10.1 Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT 160mg/ml S.C. can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT 160mg/ml S.C. in pregnant women or animal data to assess the risk of RYBREVANT 160mg/ml S.C. in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryo lethality, malformations, and post-natal death in animals (*see Data*). Advise pregnant women of the potential risk to a fetus.

Data

Animal Data

RYBREVANT 160mg/ml S.C. contains amivantamab and hyaluronidase [see Description (12)].

Amivantamab: No animal studies have been conducted to evaluate the effects of amivantamab on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT 160mg/ml S.C. can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with

disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab has the potential to be transmitted from the mother to the developing fetus.

Hyaluronidase: In an embryo-fetal study, mice were dosed daily by subcutaneous injection during the period of organogenesis with hyaluronidase (recombinant human) at dose levels up to 2,200,000 U/kg, which is > 3600 times higher than the human dose. The study found no evidence of teratogenicity. Reduced fetal weight and increased numbers of fetal resorptions were observed, with no effects found at a daily dose of 360,000 U/kg, which is > 600 times higher than the human dose. In a peri-and post-natal reproduction study, mice have been dosed daily by subcutaneous injection, with hyaluronidase (recombinant human) from implantation through lactation and weaning at dose levels up to 1,100,000 U/kg, which is > 1800 times higher than the human dose. The study found no adverse effects on sexual maturation, learning and memory or fertility of the offspring.

10.2 Lactation

Risk Summary

There are no data on the presence of amivantamab in human milk, or its effects on the breastfed child, or on milk production. Because of the potential for serious adverse reactions from RYBREVANT 160mg/ml S.C. in breast-fed children, advise women not to breast-feed during treatment with RYBREVANT 160mg/ml S.C. and for 3 months after the last dose.

10.3 Females and Males of Reproductive Potential

RYBREVANT 160mg/ml S.C. can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (10.1)].*

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT 160mg/ml S.C.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT 160mg/ml S.C.

10.4 Pediatric Use

The safety and efficacy of RYBREVANT 160 mg/ml S.C. have not been established in pediatric patients. RYBREVANT 160 mg/mL S.C. is not indicated for pediatric patients below 18 years.

10.5 Geriatric Use

No dose adjustments are necessary.
There are limited clinical data with amivantamab in patients 75 years of age or over.

Of the 206 patients with locally advanced or metastatic NSCLC treated with RYBREVANT 160mg/ml S.C. in combination with lazertinib (every 2-week dosing) in the PALOMA-3 study, 35% were ≥ 65 years of age, and 9% were ≥ 75 years of age.

The safety of RYBREVANT 160mg/ml S.C. in combination with other antineoplastic drugs or as a single agent for its approved indications [see Indications and Usage (4)] has been established in adequate and well-controlled studies of intravenous amivantamab in combination with other antineoplastic drugs and as a single agent.

- Of the 421 patients with locally advanced or metastatic NSCLC treated with intravenous amivantamab in combination with lazertinib in the MARIPOSA study, 45% were ≥ 65 years of age and 12% were ≥ 75 years of age.
- Of the 151 patients with locally advanced or metastatic NSCLC treated with intravenous amivantamab in combination with carboplatin and pemetrexed in the PAPILLON study, 37% were ≥ 65 years of age and 8% were ≥ 75 years of age.
- Of the 302 patients with locally advanced or metastatic NSCLC treated with intravenous amivantamab as a single agent in the CHRYSALIS study, 39% were ≥ 65 years of age and 11% were ≥ 75 years of age.

No clinically important differences in safety or efficacy were observed between patients who were ≥ 65 years of age and younger patients.

11 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

RYBREVANT 160mg/ml S.C. may have moderate influence on the ability to drive and use machines. See section 9.1 (e.g., dizziness, fatigue, visual impairment). If patients experience treatment-related symptoms, including vision-related adverse reactions, affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

12 DESCRIPTION

RYBREVANT 160mg/ml S.C contains recombinant human hyaluronidase (rHuPH20). rHuPH20 works locally and transiently to degrade hyaluronan ((HA), a naturally occurring glycoaminoglycan found throughout the body) in the extracellular matrix of the subcutaneous space by cleaving the linkage between the two sugars (N-acetylglucosamine and glucuronic acid), which comprise HA.

13 CLINICAL PHARMACOLOGY

13.1 Mechanism of Action

Amivantamab is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumours with activating EGFR mutations such as Exon 19 deletions, Exon 21 L858R substitution and Exon 20 insertion mutations. Amivantamab binds to the extracellular domains of EGFR and MET.

Amivantamab disrupts EGFR and MET signalling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumour growth and progression. The presence of EGFR and MET on the surface of tumour cells also allows for targeting of these cells for destruction by immune effector cells, such as natural killer cells and macrophages, through antibody-dependent cellular cytotoxicity (ADCC) and trogocytosis mechanisms, respectively.

13.2 Pharmacodynamics

After the first full dose of RYBREVANT 160mg/ml S.C., mean serum EGFR and MET concentrations decreased substantially and remained suppressed for the duration of treatment for all studied doses.

Albumin
RYBREVANT 160mg/ml S.C. decreased serum albumin concentration, a pharmacodynamic effect of MET

inhibition, typically during the first 8 weeks (see section 9.1); thereafter, albumin concentration stabilised for the remainder of amivantamab treatment.

13.3 Pharmacokinetics

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, based on the individual amivantamab PK parameter estimates for participants receiving subcutaneous administration in the population PK analysis.

For the every 2-week subcutaneous dosing regimen, the geometric mean (%CV) maximum trough concentration of amivantamab after the 4th weekly dose was 335 µg/mL (32.7%). The mean AUC_{1week} increased 3.5-fold from the first dose to Cycle 2 Day 1. Maximum trough concentration of amivantamab after subcutaneous administration as monotherapy and in combination with lazertinib is typically observed at the end of the weekly dosing (Cycle 2 Day 1). Amivantamab steady-state concentration is reached by approximately Week 13. The geometric mean (%CV) steady-state trough concentration of amivantamab at Cycle 4 Day 1 was 206 µg/mL (39.1%).

Table 6 lists the observed geometric mean (%CV) maximum trough concentrations (Cycle 2 Day 1 C_{trough}) and Cycle 2 area under the concentration time curve ($AUC_{Day\ 1\text{-}15}$) following the recommended doses of amivantamab administered subcutaneously and intravenously in patients with NSCLC. These PK endpoints were the basis for the demonstration of non-inferiority that supports the intravenous to subcutaneous bridging.

Table 6: Summary of serum pharmacokinetics parameters of amivantamab in patients with NSCLC (PALOMA-3 Study)

Parameter	RYBREVANT subcutaneous formulation 1600 mg (2240 mg for body weight ≥ 80 kg)	RYBREVANT intravenous formulation 1050 mg (1400 mg for body weight ≥ 80 kg)
	Geometric mean (%CV)	
Cycle 2 Day 1 C_{trough} (µg/mL)	335 (32.7%)	293 (31.7%)
Cycle 2 $AUC_{(Day1\text{-}15)}$ (µg/mL)	135861 (30.7%)	131704 (24.0%)

Distribution

Based on the individual amivantamab PK parameter estimates for participants receiving subcutaneous administration in the population PK analysis, the geometric mean (%CV) total volume of distribution for amivantamab administered subcutaneously is 5.69 L (23.8%).

Elimination

Based on the individual amivantamab PK parameter estimates for participants receiving subcutaneous administration in the population PK analysis, 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

Renal impairment

No clinically meaningful effect on the pharmacokinetics of amivantamab was observed in patients with mild (60 ≤ creatinine clearance [CrCl] < 90 mL/min), 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), but there is no evidence to suggest that dose adjustment is required in these patients. The effect of end-stage renal disease (CrCl < 15 mL/min) on amivantamab pharmacokinetics is unknown.

Hepatic impairment
Changes in hepatic function are unlikely to have any effect on the elimination of amivantamab since IgG1-based molecules such as amivantamab are not metabolised through hepatic pathways.

No clinically meaningful effect in the pharmacokinetics of amivantamab was observed based on mild [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN)] or moderate (1.5×ULN < total bilirubin ≤ 3×ULN and any AST) hepatic impairment. Data in patients with moderate hepatic impairment are limited (n=1), but there is no evidence to suggest that dose adjustment is required in these patients. The effect of severe (total bilirubin > 3 times ULN) hepatic impairment on amivantamab pharmacokinetics is unknown.

14 NONCLINICAL TOXICOLOGY

Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity.

Carcinogenicity and mutagenicity
No animal studies have been performed to establish the carcinogenic potential of amivantamab. Routine genotoxicity and 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 toxicology
No animal studies have been conducted to evaluate the effects on reproduction and foetal development; however, based on its mechanism of action, amivantamab can cause foetal harm or developmental anomalies. As reported in the literature, reduction, elimination, or disruption of embryo foetal or maternal EGFR signalling can prevent implantation, cause embryo foetal loss during various stages of gestation (through effects on placental development), cause developmental anomalies in multiple organs or early death in surviving foetuses. Similarly, knock out of MET or its ligand hepatocyte growth factor (HGF) was embryonic lethal due to severe defects in placental development, and foetuses displayed defects in muscle development in multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab has the potential to be transmitted from the mother to the developing foetus.

15 CLINICAL STUDIES

15.1 Clinical experience of RYBREVANT subcutaneous formulation

The efficacy of RYBREVANT 160mg/ml S.C. in patients with EGFR-mutated locally advanced or metastatic NSCLC is based on achieving non-inferior PK exposure to intravenous amivantamab in the non-inferiority study PALOMA-3 (see section 13.3). The study demonstrated non-inferior efficacy of subcutaneous to intravenous amivantamab given in combination with lazertinib in patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease has progressed on or after treatment with osimertinib and platinum-based chemotherapy.

15.2 Clinical experience of RYBREVANT intravenous formulation

First Line Treatment of NSCLC with Exon 19 deletion or Exon 21 L858R Substitution Mutation - MARIPOSA

NSC3003 (MARIPOSA) is a randomised, open-label, active-controlled, multicentre phase 3 study assessing the efficacy and safety of RYBREVANT intravenous formulation 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. Tumour tissue (94%) and/or plasma (6%) samples for all patients were tested locally to determine EGFR Exon 19 deletion and/or Exon 21 L858R substitution mutation status using polymerase chain reaction (PCR) in 65% and next generation sequencing (NGS) in 35% of patients.

A total of 1074 patients were randomised (2:2:1) to receive RYBREVANT intravenous formulation in combination with lazertinib, osimertinib monotherapy, or lazertinib monotherapy until disease progression or unacceptable toxicity. RYBREVANT intravenous formulation 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 thereafter starting at week 5. Lazertinib was administered at 240 mg orally once daily. Osimertinib was administered at a dose of 80 mg orally once daily. Randomisation was stratified by EGFR mutation type (Exon 19 deletion or Exon 21 L858R), race (Asian or non-Asian), and history of brain metastasis (yes or no).

Baseline demographics and disease characteristics were balanced across the treatment arms. The median age was 63 (range: 25–88) years with 45% of patients ≥ 65 years; 62% were female; and 59% were Asian, and 38% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (34%) or 1 (66%); 69% never smoked; 41% had prior brain metastases; and 90% had Stage IV cancer at initial diagnosis. With regard to EGFR mutation status, 60% were Exon 19 deletions and 40% were Exon 21 L858R substitution mutations.

RYBREVANT intravenous formulation in combination with lazertinib demonstrated a statistically significant improvement in progression-free survival (PFS) by BICR assessment.

The final analysis of OS demonstrated a statistically significant improvement in OS for Rybrevant intravenous formulation in combination with lazertinib compared to osimertinib (see Table 7 and Figure 2).

Table 7: Efficacy results in MARIPOSA

	RYBREVANT intravenous formulation + lazertinib (N=429)	**Osimertinib (N=429)**
Progression-free survival (PFS)[a]		
Number of events	192 (45%)	252 (59%)
Median, months (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
Hazard Ratio (95% CI); p-value	0.70 (0.58, 0.85); p=0.0002	
Overall survival (OS)		
Number of events	173 (40%)	217 (51%)
Median, months (95% CI)	NE(42.9, NE)	36.7 (33.4, 41.0)
Hazard Ratio (95% CI); p-value	0.75 (0.61, 0.92); p=0.0048	
Objective response rate (ORR)[a, b]		
ORR % (95% CI)	80% (76%, 84%)	77% (72%, 81%)
Duration of response (DOR)[a, b]		
Median (95% CI), months	25.8 (20.3, 33.9)	18.1 (14.8, 20.1)

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

PFS results are from data cut-off 11 August 2023 with a median follow-up of 22.0 months., DOR and ORR results are from data cut-off 13 May 2024 with a median follow-up of 31.3 months. OS results are from data cut-off 04 December 2024 with a median follow-up of 37.8 months.

[a] BICR by RECIST v1.1.

[b] Based on confirmed responders.

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

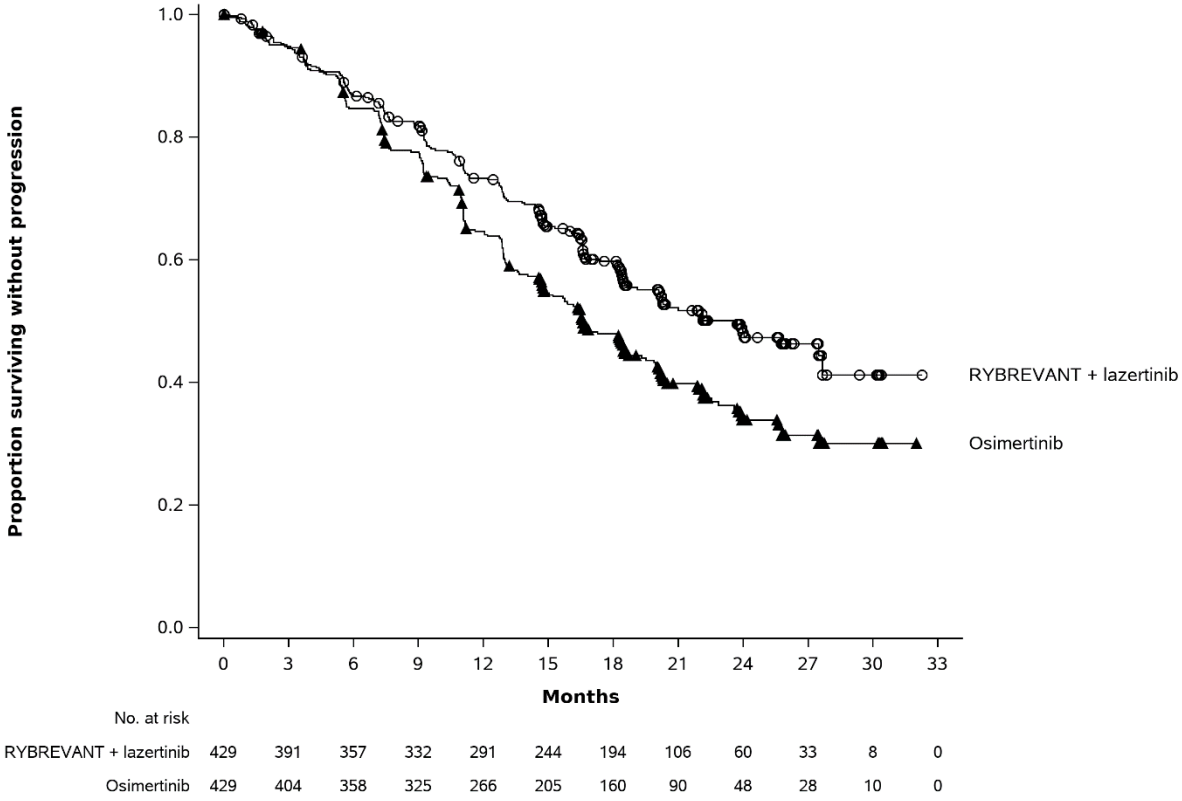
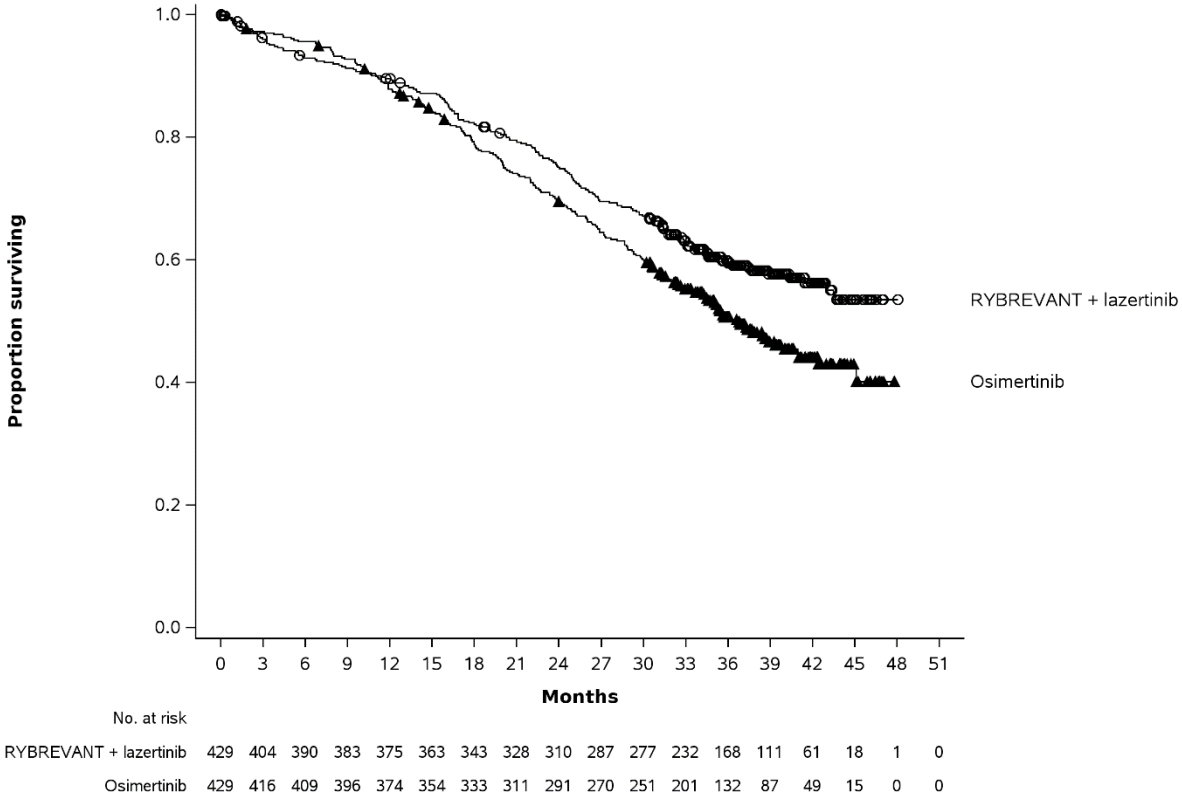


Figure 2: Kaplan-Meier curve of OS in previously untreated NSCLC patients



Intracranial ORR and DOR by BICR were pre-specified endpoints in MARIPOSA. In the subset of patients with

intracranial lesions at baseline, the combination of RYBREVANT intravenous formulation 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 summarised in Table 8.

Table 8: Intracranial ORR and DOR by BICR assessment in subjects with intracranial lesions at baseline - MARIPOSA

	RYBREVANT intravenous formulation + lazertinib (N=180)	**Osimertinib (N=186)**
Intracranial tumour response assessment		
Intracranial ORR (CR+PR), % (95% CI)	78% (71%, 84%)	77% (71%, 83%)
Complete response	64%	59%
Intracranial DOR		
Number of responders	140	144
Median, months (95% CI)	35.0 (20.4, NE)	25.1 (22.1, 31.2)

CI = confidence interval
NE = not estimable
Intracranial ORR and DOR results are from data cut-off 04 Dec 2024 with a median follow-up of 37.8 months.

Previously Treated NSCLC with Exon 20 Insertion Mutations-CHRYSALIS

CHRYSALIS is a multicentre, open-label, multi-cohort study conducted to assess the safety and efficacy of RYBREVANT intravenous formulation in patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 114 patients with locally advanced or metastatic NSCLC who had EGFR Exon 20 insertion mutations, whose disease had progressed on or after platinum-based chemotherapy, and who had a median follow-up of 12.5 months. Tumour tissue (93%) and/or plasma (10%) samples for all patients were tested locally to determine EGFR Exon 20 insertion mutation status using next generation sequencing (NGS) in 46% of patients and/or polymerase chain reaction (PCR) in 41% of patients; for 4% of patients, the testing methods were not specified. Patients with untreated brain metastases or a history of ILD requiring treatment with prolonged steroids or other immunosuppressive agents within the last 2 years were not eligible for the study. RYBREVANT intravenous formulation 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 loss of clinical benefit or unacceptable toxicity. The primary efficacy endpoint was investigator-assessed overall response rate (ORR), defined as confirmed complete response (CR) or partial response (PR) based on RECIST v1.1. In addition, the primary endpoint was assessed by a blinded independent central review (BICR). Secondary efficacy endpoints included duration of response (DOR).

The median age was 62 (range: 36-84) years, with 41% of the patients ≥ 65 years of age; 61% were female; and 52% were Asian and 37% were White. The median number of prior therapies was 2 (range: 1 to 7 therapies). At baseline, 29% had ECOG performance status of 0 and 70% had ECOG performance status of 1; 57% never smoked; 100% had Stage IV cancer; and 25% had previous treatment for brain metastases. Insertions in Exon 20 were observed at 8 different residues; the most common residues were A767 (22%), S768 (16%), D770 (12%), and N771 (11%).

Efficacy results are summarised in Table 9.

Table 9: Efficacy results in CHRYSALIS

	Investigator assessment (N=114)
Overall response rate[a, b] (95% CI)	37% (28%, 46%)
Complete response	0%
Partial response	37%

Duration of response	
Median[c] (95% CI), months	12.5 (6.5, 16.1)
Patients with DOR ≥ 6 months	64%

CI = Confidence interval

[a] Confirmed response

[b] ORR and DOR results by investigator assessment were consistent with those reported by BICR assessment; ORR by BICR assessment was 43% (34%, 53%), with a 3% CR rate and a 40% PR rate, median DOR by BICR assessment was 10.8 months (95% CI: 6.9, 15.0), and patients with DOR ≥ 6 months by BICR assessment was 55%.

[c] Based on Kaplan-Meier estimate.

Anti-tumour activity was observed across studied mutation subtypes.

Immunogenicity

Anti-drug antibodies (ADA) were uncommonly detected after treatment with RYBREVANT 160mg/ml S.C. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. Among the 741 participants who received RYBREVANT 160mg/ml S.C. 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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

10 mL solution in a Type 1 glass vial with an rubber stopper and aluminium seal with a flip-off cap containing 1600 mg amivantamab. Pack size of 1 vial.

14 mL solution in a Type 1 glass vial with an rubber stopper and an aluminium seal with a flip-off cap containing 2240 mg amivantamab. Pack size of 1 vial.

Storage

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

For storage conditions after preparing the syringe, see section 17.3.

Handling

RYBREVANT 160mg/ml S.C. is for single use only and is ready to use.

The solution for injection should be prepared using aseptic technique as follows:

Preparation:

- Determine the dose required and the appropriate RYBREVANT 160mg/ml S.C. formulation vial needed based on the patient's baseline weight (see section 5).
- Patients < 80 kg receive 1600 mg and for patients ≥ 80 kg, 2240 mg weekly from Weeks 1 to 4 and then every 2 weeks starting at Week 5 onwards.
- Remove the appropriate RYBREVANT 160mg/ml S.C. vial from refrigerated storage (2°C to 8°C).
- Check that the RYBREVANT 160mg/ml S.C. solution is colourless to pale yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Equilibrate RYBREVANT 160mg/ml S.C. to room temperature (15°C to 30°C) for at least 15 minutes. Do not warm RYBREVANT 160mg/ml S.C. in any other way. Do not shake.

- Withdraw the required injection volume of RYBREVANT 160mg/ml S.C. from the vial into an appropriately sized syringe using a transfer needle. Smaller syringes require less force during preparation and administration.
- RYBREVANT 160mg/ml S.C. is compatible with stainless steel injection needles, polypropolene and polycarbonate syringes, and polyethylene, polyurethane, and polyvinylchloride subcutaneous infusion sets. A sodium chloride 9 mg/mL (0.9%) solution may also be used to flush an infusion set if needed.
- Replace the transfer needle with the approriate 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 syringe should be administered immediately. If immediate administration is not possible, store the prepared syringe 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. The prepared syringe should be discarded if stored for more than 24 hours refrigerated or more than 24 hours at room temperature. If stored in the refrigerator, the solution should come up to room temperature before administration.

Disposal

This medicinal product is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

17 PHARMACEUTICAL PARTICULARS

17.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
Sucrose
Sodium acetate trihydrate
L-methionine
Polysorbate 80
Glacial acetic acid
EDTA disodium salt dihydrate
Water for injections

17.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 16.

17.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

Prepared syringe

Chemical and physical in-use stability has been demonstrated up to 24 hours at 2°C to 8°C followed by up to 24 hours at 15°C to 30°C. From a microbiological point of view, unless the method of dose preparation precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

MANUFACTURER

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MARKETING AUTHORISATION HOLDER

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