SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Rybrevant 1 600 mg solution for injection
Rybrevant 2 240 mg solution for injection
Rybrevant 2 400 mg solution for injection
Rybrevant 3 520 mg solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Rybrevant 1 600 mg solution for injection
One mL of solution for injection contains 160 mg amivantamab.
One 10 mL vial of solution for injection contains 1 600 mg of amivantamab.

Rybrevant 2 240 mg solution for injection
One mL of solution for injection contains 160 mg amivantamab.
One 14 mL vial of solution for injection contains 2 240 mg of amivantamab.

Rybrevant 2 400 mg solution for injection
One mL of solution for injection contains 160 mg amivantamab.
One 15 mL vial of solution for injection contains 2 400 mg of amivantamab.

Rybrevant 3 520 mg solution for injection
One mL of solution for injection contains 160 mg amivantamab.
One 22 mL vial of solution for injection contains 3 520 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 6.1.

3. PHARMACEUTICAL FORM

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rybrevant subcutaneous formulation is indicated:

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

4.2 Posology and method of administration

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

Before initiation of Rybrevant subcutaneous formulation, 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 5.1).

Rybrevant subcutaneous formulation should be administered by a healthcare professional with access to appropriate medical support to manage administration-related reactions if they occur.

For patients currently receiving amivantamab intravenous formulation, Rybrevant subcutaneous formulation may be used as an alternative to the intravenous amivantamab formulation starting at the next scheduled dose.

For patients currently receiving Rybrevant subcutaneous formulation 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.

Posology

Premedications should be administered to reduce the risk of administration-related reactions with Rybrevant subcutaneous formulation (see below “Dose modifications” and “Recommended concomitant medicinal products”).

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

Table 1: Recommended dosage of Rybrevant subcutaneous formulation in combination with lazertinib or as monotherapy (Every 4-week dosing)

Body weight at baseline*	**Recommended dose**	**Dosing schedule**
Less than 80 kg	1 600 mg	• Weekly (total of 4 doses) from Weeks 1 to 4
	3 520 mg	• Every 4 weeks starting at Week 5 onwards
Greater than or equal to 80 kg	2 240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4
	4 640 mg	• Every 4 weeks starting at Week 5 onwards

* Dose adjustments not required for subsequent body weight changes.

Table 2: Recommended dosage of Rybrevant subcutaneous formulation in combination with lazertinib or as monotherapy (Every 2-week dosing)

Body weight at baseline*	Recommended dose	Dosing schedule
Less than 80 kg	1 600 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	2 240 mg	• Weekly (total of 4 doses) from Weeks 1 to 4 • Every 2 weeks starting at Week 5 onwards

* Dose adjustments not required for subsequent body weight changes.

When given in combination with lazertinib, it is recommended to administer Rybrevant subcutaneous formulation any time after lazertinib when given on the same day. Refer to section 4.2 of the lazertinib Summary of Product Characteristics for recommended lazertinib dosing information.

Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed
The recommended dosages of Rybrevant subcutaneous formulation when used in combination with carboplatin and pemetrexed, based on baseline body weight, are provided in Table 3.

Table 3: Recommended dosage of Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed (Every 3-week dosing)

Body weight at baseline*	Recommended dose	Dosing schedule
Less than 80 kg	1 600 mg	First dose at Week 1 Day 1
	2 400 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards
Greater than or equal to 80 kg	2 240 mg	First dose at Week 1 Day 1
	3 360 mg	• Weekly (total of 3 doses) from Weeks 2 to 4 • Every 3 weeks starting at Week 7 onwards

* Dose adjustments not required for subsequent body weight changes.

When used in combination with carboplatin and pemetrexed, Rybrevant subcutaneous formulation should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then Rybrevant. See section 5.1 and the manufacturer's prescribing information for dosing instructions for carboplatin and pemetrexed.

Duration of treatment
It is recommended that patients are treated with Rybrevant subcutaneous formulation until disease progression or unacceptable toxicity.

Missed dose
Every 4-week or every 2-week dosing: If a dose of Rybrevant subcutaneous formulation is missed between Weeks 1 to 4, it should be administered within 24 hours. If a dose of Rybrevant subcutaneous formulation is missed from Week 5 onward, it should be administered within 7 days.

Every 3-week dosing: If a dose of Rybrevant subcutaneous formulation is missed between Weeks 1 to 3, it should be administered within 24 hours. If a dose of Rybrevant subcutaneous formulation is missed from Week 4 onward, it should be administered within 7 days.

If the missed dose is not administered according to this guidance, 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 4. See also specific dose modifications for specific adverse reactions below Table 4.

If used in combination with lazertinib, refer to section 4.2 of the lazertinib Summary of Product Characteristics for information about dose modifications.

Table 4: 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
1 600 mg	1 050 mg	700 mg	Discontinue Rybrevant subcutaneous formulation
2 240 mg	1 600 mg	1 050 mg	
2 400 mg	1 600 mg	1 050 mg	
3 360 mg	2 240 mg	1 600 mg	
3 520 mg	2 400 mg	1 600 mg	
4 640 mg	3 360 mg	2 240 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 subcutaneous formulation (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 4.4).

- Grade 1-3 (mild-severe): Upon recovery of symptoms, resume Rybrevant subcutaneous formulation injections. Concomitant medicinal products should be administered at the next dose, including dexamethasone (20 mg) or equivalent (see Table 5).
- Recurrent Grade 3 or Grade 4 (life-threatening): Permanently discontinue Rybrevant.

Venous thromboembolic (VTE) events with concomitant use with lazertinib
At the initiation of treatment, prophylactic anticoagulants should be administered to prevent VTE events in patients receiving Rybrevant subcutaneous formulation in combination with lazertinib. Consistent with clinical guidelines, patients should receive prophylactic dosing of either a direct acting oral anticoagulant (DOAC) or a low-molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended.

For VTE events associated with clinical instability (e.g., respiratory failure or cardiac dysfunction), both drugs should be withheld until the patient is clinically stable. Thereafter, both medicinal products can be resumed at the same dose. In the event of recurrence despite appropriate anticoagulation, discontinue Rybrevant. Treatment can continue with lazertinib at the same dose (see section 4.4).

Skin and nail reactions
Prophylactic therapy with oral and topical antibiotics is recommended to reduce the risk and severity of skin and nail reactions in patients receiving Rybrevant. Non-comedogenic skin moisturiser (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 chlorhexidine solution to wash hands and feet is also recommended. Patients should be instructed to limit sun exposure during and for 2 months after Rybrevant therapy. For further information about prophylaxis for skin and nail reactions, see section 4.4.

If the patient develops a Grade 1-2 skin or nail reaction, supportive care should be initiated as clinically indicated; if there is no improvement after 2 weeks, dose reduction should be considered for persistent Grade 2 rash (see Table 4). If the patient develops a Grade 3 skin or nail reaction, supportive care should be initiated as clinically indicated, and interruption of Rybrevant subcutaneous

formulation should be considered until the adverse reaction improves. Upon recovery of the skin or nail reaction to ≤ Grade 2, Rybrevant subcutaneous formulation should be resumed at a reduced dose. If the patient develops Grade 4 skin reactions, permanently discontinue Rybrevant (see section 4.4).

Interstitial lung disease
Rybrevant subcutaneous formulation 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 (see section 4.4).

Recommended concomitant medicinal products

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 5). 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 5: Dosing schedule of premedications

Premedication	**Dose**	**Route of administration**	**Recommended dosing window prior to Rybrevant subcutaneous formulation administration**
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Paracetamol/Acetaminophen (650 to 1 000 mg) 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

Paediatric population
There is no relevant use of amivantamab in the paediatric population in the treatment of NSCLC.

Elderly
No dose adjustments are necessary (see section 4.8, section 5.1, and section 5.2).

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 5.2). 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 5.2). If treatment is started, patients should be monitored for adverse reactions with dose modifications per the recommendations above.

Method of administration

Rybrevant solution for injection is for subcutaneous use only.

Rybrevant subcutaneous formulation is not intended for intravenous administration and should be given by subcutaneous injection only, using the doses specified. See section 6.6 for instructions on handling of the medicinal product before administration.

Inject the required volume of Rybrevant subcutaneous formulation 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.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Administration-related reactions
Administration-related reactions occurred in patients treated with Rybrevant subcutaneous formulation (see section 4.8).

Prior to the initial injection (Week 1 Day 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of administration-related reactions. For subsequent doses, antihistamines and antipyretics should be administered.

Patients should be treated in a setting with appropriate medical support to treat administration-related reactions. At the first sign of administration-related reactions of any severity, injections should be interrupted, if ongoing, and post-injection medicinal products should be administered as clinically indicated. Upon resolution of symptoms, the injection should be resumed. For Grade 4 or recurrent Grade 3 administration-related reactions, Rybrevant should be permanently discontinued (see section 4.2).

Interstitial lung disease
Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g., pneumonitis) have been reported in patients treated with amivantamab, including fatal events (see section 4.8). Patients should be monitored for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). If symptoms develop, treatment with Rybrevant should be interrupted pending investigation of these symptoms. Suspected ILD or ILD-like adverse reactions should be evaluated and appropriate treatment should be initiated as necessary. Rybrevant should be permanently discontinued in patients with confirmed ILD or ILD-like adverse reactions (see section 4.2).

Venous thromboembolic (VTE) events with concomitant use with lazertinib

In patients receiving amivantamab in combination with lazertinib, VTE events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), were reported (see section 4.8). Fatal events were observed with amivantamab intravenous formulation.

Consistent with clinical guidelines, patients should receive prophylactic dosing of either a direct acting oral anticoagulant (DOAC) or a low molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended.

Signs and symptoms of VTE events should be monitored. Patients with VTE events should be treated with anticoagulation as clinically indicated. For VTE events associated with clinical instability, treatment should be withheld until the patient is clinically stable. Thereafter, both drugs can be resumed at the same dose.

In the event of recurrence despite appropriate anticoagulation, Rybrevant should be discontinued. Treatment can continue with lazertinib at the same dose (see section 4.2).

Skin and nail reactions
Rash (including dermatitis acneiform), pruritus, dry skin, and skin ulcer occurred in patients treated with amivantamab (see section 4.8). Patients should be instructed to limit sun exposure during and for 2 months after Rybrevant therapy. Protective clothing and use of broad-spectrum UVA/UVB sunscreen are advisable. A prophylactic approach to rash prevention is recommended. This includes prophylactic therapy, at treatment initiation, with an oral antibiotic (e.g., doxycycline or minocycline, 100 mg twice daily) starting on Day 1 for the first 12 weeks of treatment and after completion of oral antibiotic therapy, topical antibiotic lotion to the scalp (e.g., clindamycin 1%) for the next 9 months of treatment. Non-comedogenic skin moisturiser (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 chlorhexidine solution to wash hands and feet is recommended beginning on Day 1 and continued for the duration of treatment.

Prescriptions for topical and/or oral antibiotics and topical corticosteroids are recommended to be available at the time of initial dosing to minimise any delay in reactive management should rash develop despite prophylactic treatment. If skin reactions develop, supportive care, topical corticosteroids and topical and/or oral antibiotics should be administered. For Grade 3 or poorly-tolerated Grade 2 events, systemic antibiotics and oral steroids should also be administered. Patients presenting with severe rash that has an atypical appearance or distribution or lack improvement within 2 weeks should be referred promptly to a dermatologist. Rybrevant should be dose reduced, interrupted, or permanently discontinued based on severity (see section 4.2).

Toxic epidermal necrolysis (TEN) has been reported. Treatment with this medicinal product should be discontinued if TEN is confirmed.

Eye disorders
Eye disorders, including keratitis, occurred in patients treated with amivantamab (see section 4.8). Patients presenting with worsening eye symptoms should promptly be referred to an ophthalmologist

and should discontinue use of contact lenses until symptoms are evaluated. For dose modifications for Grade 3 or 4 eye disorders, see section 4.2.

Sodium content
This medicinal product contains less than 1 mmol (23 mg) sodium per dose, that is to say essentially "sodium-free" (see section 6.6).

Polysorbate content
This medicinal product contains 0.6 mg of polysorbate 80 in each mL, which is equivalent to 6 mg per 10 mL vial, 8.4 mg per 14 mL vial, 9 mg per 15 mL vial, or 13.2 mg per 22 mL vial. Polysorbates may cause hypersensitivity reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No drug interaction studies have been performed. As an IgG1 monoclonal antibody, renal excretion and hepatic enzyme-mediated metabolism of intact amivantamab are unlikely to be major elimination routes. As such, variations in drug-metabolising enzymes are not expected to affect the elimination of amivantamab. Due to the high affinity to a unique epitope on EGFR and MET, amivantamab is not anticipated to alter drug-metabolising enzymes.

Vaccines
No clinical data are available on the efficacy and safety of vaccinations in patients taking amivantamab. Avoid the use of live or live-attenuated vaccines while patients are taking amivantamab.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception
Women of child-bearing potential should use effective contraception during and for 3 months after cessation of amivantamab treatment.

Pregnancy
There are no human data to assess the risk of amivantamab use during pregnancy. No animal reproductive studies were conducted to inform a drug-associated risk. Administration of EGFR and MET inhibitor molecules in pregnant animals resulted in an increased incidence of impairment of embryo-foetal development, embryo lethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, amivantamab could cause foetal harm when administered to a pregnant woman. Amivantamab should not be given during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the foetus. If the patient becomes pregnant while taking this medicinal product, the patient should be informed of the potential risk to the foetus (see section 5.3).

Breast-feeding
It is unknown whether amivantamab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards. A risk to the breast-fed child cannot be excluded during this short period just after birth, although IgGs are likely to be degraded in the gastrointestinal tract of the breast-fed child and not absorbed. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from amivantamab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on the effect of amivantamab on human fertility. Effects on male and female fertility have not been evaluated in animal studies.

4.7 Effects on ability to drive and use machines

Rybrevant may have moderate influence on the ability to drive and use machines. Please see section 4.8 (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.

4.8 Undesirable effects

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 6 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 1 050 mg (for patients < 80 kg) or 1 400 mg (for patients ≥ 80 kg). The median exposure to amivantamab was 4.1 months (range: 0.0 to 39.7 months).

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

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

Table 6: 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 5.1)	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 subcutaneous formulation 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 subcutaneous formulation in combination with lazertinib, including ILD (4.2%), VTE (2.2%), hepatotoxicity (2.2%), and fatigue (1.5%). Seven percent of patients discontinued Rybrevant subcutaneous formulation due to adverse reactions. In patients treated with Rybrevant subcutaneous formulation in combination with lazertinib, the most frequent adverse reactions of any grade (≥ 1% patients) leading

to discontinuation of Rybrevant subcutaneous formulation 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 7.

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 (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (frequency cannot be estimated from the available data).

Table 7: 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.

Rybrevant in combination with carboplatin and pemetrexed

In the dataset of Rybrevant (either intravenous or subcutaneous formulations) in combination with carboplatin and pemetrexed (N=444), the most frequent adverse reactions of any grade (≥20% patients) were rash (83%), nail toxicity (57%), neutropenia (56%), fatigue (46%), nausea (44%), stomatitis (42%), oedema (41%), thrombocytopenia (40%), constipation (39%), hypoalbuminaemia (36%), decreased appetite (32%), alanine aminotransferase increased (28%), aspartate aminotransferase increased (24%), and vomiting (23%).

Serious adverse reactions were reported in 19% of patients who received Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed, including vomiting (2.8%), ILD (2.8%), nausea (2.1%), fatigue (2.1%), VTE (2.1%), neutropenia (2.1%), diarrhoea (1.4%), and hypocalcaemia (1.4%). 6% of patients discontinued Rybrevant subcutaneous formulation due to adverse reactions. In patients treated with Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed, the most frequent adverse reactions of any grade (≥ 1% patients) leading to discontinuation of Rybrevant subcutaneous formulation were ILD (2.8%) and rash (1.4%).

Tabulated list of adverse reactions

The adverse reactions for Rybrevant (either intravenous or subcutaneous formulation) when received in combination with carboplatin and pemetrexed are summarised in Table 8.

The safety data below reflect exposure to Rybrevant (either intravenous or subcutaneous formulation) in combination with carboplatin and pemetrexed in 444 patients with locally advanced or metastatic NSCLC, including 151 patients in PAPILLON, 130 patients in MARIPOSA-2, 20 patients in CHRYSALIS, and 143 patients in PALOMA-2 cohorts 2 and 3b. 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 7.4 months (range: 0.0 to 28.1 months). Median duration on treatment for the subcutaneous formulation was 6.9 months (range: 0.0 to 15.4 months) while median duration on treatment for the intravenous formulation was 7.7 months (range: 0.0 to 28.1 months).

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

Table 8: Adverse reactions for Rybrevant (either intravenous or subcutaneous formulation) when received in combination with carboplatin and pemetrexed (N=444)

System organ class Adverse reaction	**Frequency category**	**Any grade (%)**	**Grade 3-4 (%)**
Blood and lymphatic system disorders			
Neutropenia	Very common	56	36
Thrombocytopenia		40	13
Metabolism and nutrition disorders			
Hypoalbuminaemia*	Very common	36	5
Decreased appetite		32	1.1
Hypokalaemia		19	7
Hypocalcaemia		14	2.0
Hypomagnesaemia		11	1.8
Nervous system disorders			
Dizziness*	Very common	10	0.5
Eye disorders			
Other eye disorders*	Very common	15	0
Visual impairment*	Common	2.9	0
Growth of eyelashes	Uncommon	0.7	0
Keratitis		0.2	0
Uveitis		0.2	0
Vascular disorders			
Venous thromboembolism			
Amivantamab intravenous*, [a]	Very common	14	3.0
Amivantamab subcutaneous*, [b]	Very common	18	2.8
Respiratory, thoracic, and mediastinal disorders			
Interstitial lung disease*	Common	2.5	1.4
Gastrointestinal disorders			
Nausea	Very common	44	1.4
Stomatitis*		42	4.3
Constipation		39	0.2
Vomiting		23	2.9
Diarrhoea		19	2.5
Abdominal pain*		12	0.5
Haemorrhoids	Common	8	0.5
Skin and subcutaneous tissue disorders			
Rash*	Very common	83	14
Nail toxicity*		57	4.3

Dry skin*		14	0.2
Pruritus		12	0
Skin ulcer	Common	3.2	0.7
Musculoskeletal and connective tissue disorders			
Myalgia	Common	6	0.5
General disorders and administration site conditions			
Fatigue*	Very common	46	6
Oedema*		41	1.4
Pyrexia		13	0.2
Injection site reactions*, b, c	Common	3.5	0
Investigations			
Alanine aminotransferase increased	Very common	28	4.1
Aspartate aminotransferase increased		24	1.4
Blood alkaline phosphatase increased	Common	8	0.2
Injury, poisoning and procedural complications			
Infusion-/Administration-related reactions			
Amivantamab intravenous[a, d]	Very common	51	3.0
Amivantamab subcutaneous[b, e]	Common	7	0

* Grouped terms.

[a] Frequency based on amivantamab intravenous studies only (CHRYSALIS [N=20], PAPILLON [N=151], MARIPOSA-2 [N=130]).

[b] Frequency based on amivantamab subcutaneous studies only (PALOMA-2 cohorts 2 and 3B [N=143]).

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

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

[e] 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 subcutaneous formulation in combination with lazertinib, and 7% of patients treated with Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed. The most frequent signs and symptoms of administration-related reactions include dyspnoea, flushing, fever, chills, nausea, and chest discomfort. In patients treated with Rybrevant subcutaneous formulation 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 patients treated with Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed, the median time to onset of first administration-related reactions was 2.1 hours (range: 0.7 to 3.1 hours), with all administration-related reactions being Grades 1 or 2 in severity. In PALOMA-3, administration-related reactions were reported in 13% of patients treated with Rybrevant subcutaneous formulation 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 subcutaneous formulation in combination with lazertinib and 3.5% of patients treated with Rybrevant subcutaneous formulation in combination with carboplatin and pemetrexed. All injection site reactions were Grade 1 or 2 in severity. The most frequent symptom of injection site reactions was erythema.

Interstitial lung disease

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, and 2.5% of patients treated with Rybrevant (either intravenous or subcutaneous formulation) in combination with carboplatin and pemetrexed. 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 subcutaneous formulation 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 subcutaneous formulation 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 subcutaneous formulation 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 subcutaneous formulation 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 and Grade 4 VTE events reported in 10% and 2.6% of patients, respectively, and serious VTE events reported in 10% of these patients.

Skin and nail 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; and 83% of patients treated with Rybrevant in combination with carboplatin and pemetrexed, leading to discontinuation of Rybrevant in 0.5% 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. Among patients treated with Rybrevant in combination with carboplatin and pemetrexed, most cases were Grade 1 or 2, with Grade 3 reactions occurring in 14% of patients.

A Phase 2 study in patients treated with Rybrevant in combination with lazertinib was conducted to assess the use of prophylactic therapy with an oral antibiotic, a topical antibiotic on the scalp, a moisturiser on the face and whole body (except scalp), and an antiseptic on hands and feet (see sections 4.2 and 4.4). A reduction in the incidence of ≥ Grade 2 dermatologic adverse events during the first 12 weeks of treatment was demonstrated, compared with the standard dermatologic management used in clinical practice (38.6% vs. 76.5%, $p<0.0001$). In addition, there was a reduction in ≥ Grade 2 adverse events involving the scalp in the first 12 weeks of treatment (8.6% vs. 29.4%) along with lower incidence of dose reductions (7.1% vs. 19.1%), interruptions (15.7% vs. 33.8%), and treatment discontinuations (1.4% vs. 4.4%) due to dermatological adverse events.

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 and 0.2% of patients treated with Rybrevant in combination with carboplatin and pemetrexed. Other reported adverse reactions included growth of eyelashes, visual impairment, and other eye disorders.

Special populations

Elderly
There are limited clinical data with amivantamab in patients 75 years of age or over (see section 5.1). No overall differences in safety were observed between patients ≥ 65 years of age and patients < 65 years of age.

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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

There is no information on overdose with Rybrevant subcutaneous formulation and no known specific antidote for overdose. In the event of an overdose, treatment with Rybrevant should be stopped, the patient should be monitored for any signs or symptoms of adverse events and appropriate general supportive measures should be instituted immediately until clinical toxicity has diminished or resolved.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Monoclonal antibodies and antibody drug conjugates, ATC code: L01FX18.

Rybrevant subcutaneous formulation 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.

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.

Pharmacodynamic effects

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

Albumin
Rybrevant subcutaneous formulation decreased serum albumin concentration, a pharmacodynamic effect of MET inhibition, typically during the first 8 weeks (see section 4.8); thereafter, albumin concentration stabilised for the remainder of amivantamab treatment.

Clinical experience of Rybrevant subcutaneous formulation

The efficacy of Rybrevant subcutaneous formulation 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 5.2). 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.

Clinical experience of Rybrevant intravenous formulation

Previously-untreated NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (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 1 074 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 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. 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 9 and Figure 2).

Table 9: 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

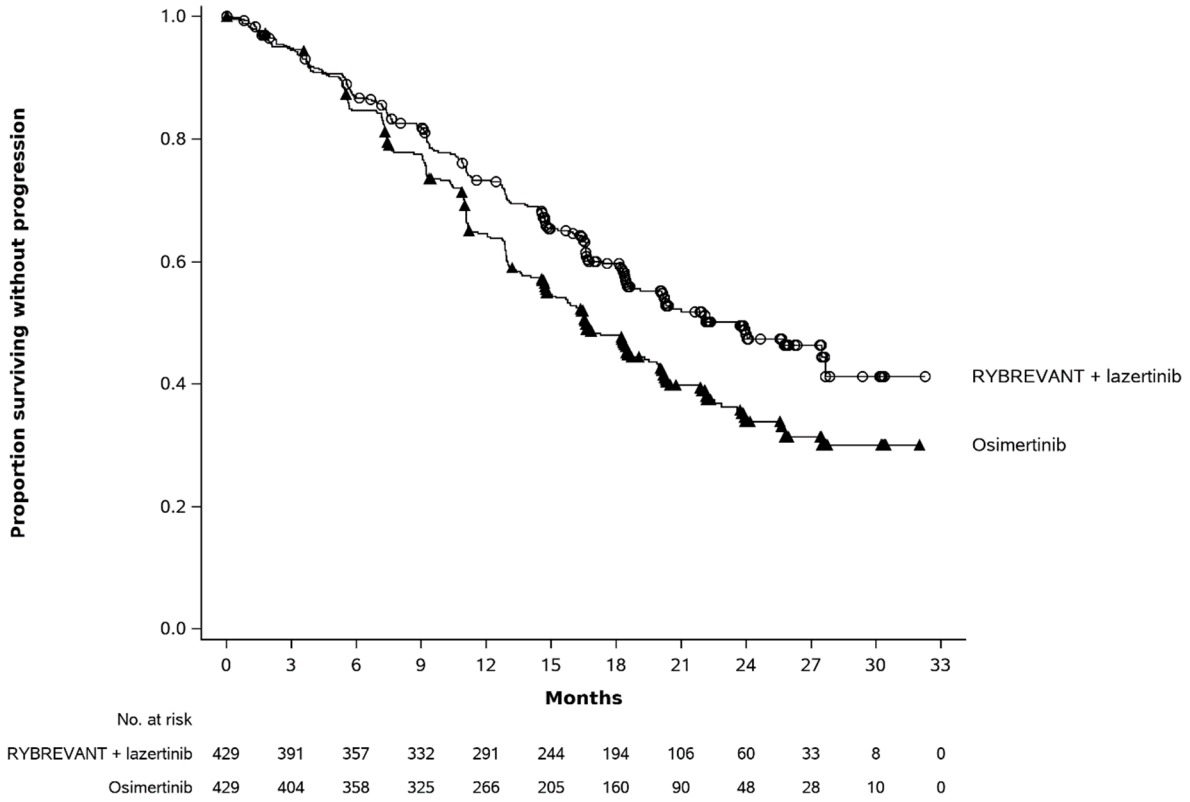
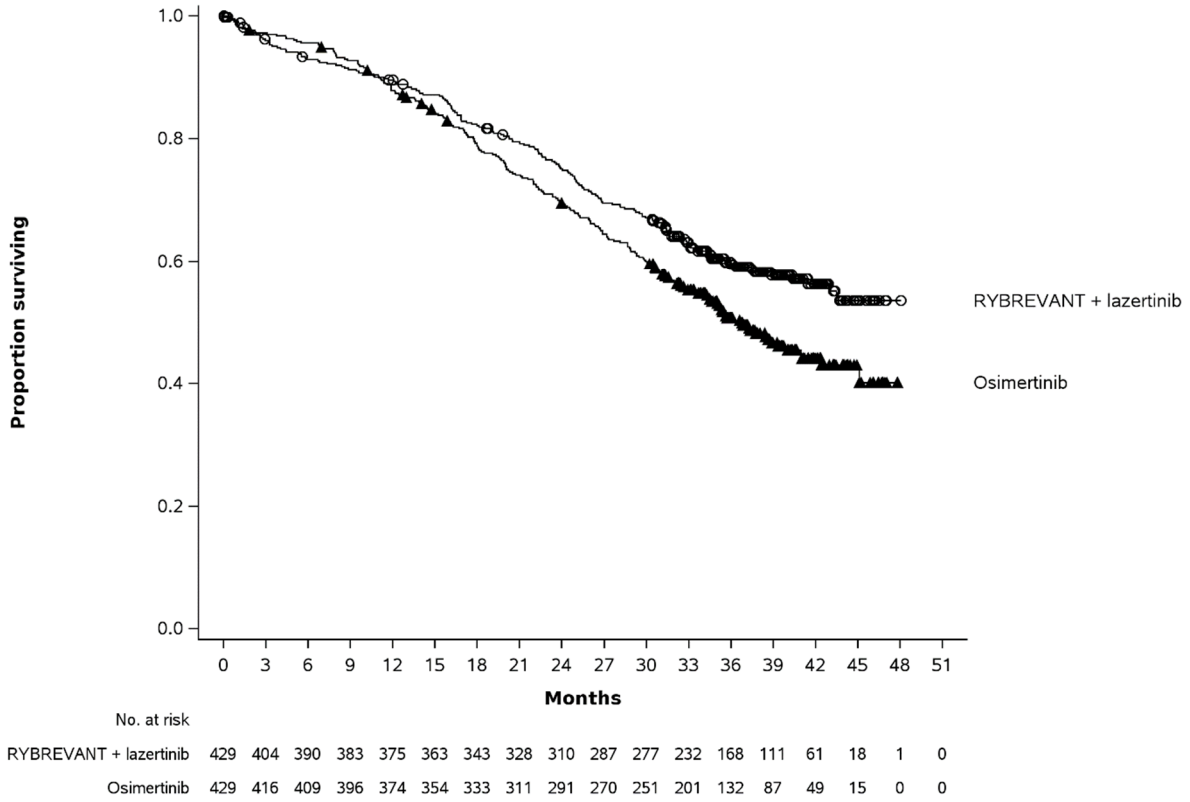


Figure 2: Kaplan-Meier curve of OS in previously untreated NSCLC patients



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 10.

Table 10: 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 EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (MARIPOSA-2)

MARIPOSA-2 is a randomised (2:2:1) open-label, multicentre Phase 3 study in patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (mutation testing could have been performed at or after the time of locally advanced or metastatic disease diagnosis. Testing did not need to be repeated at the time of study entry once EGFR mutation status was previously established) after failure of prior therapy including a third-generation EGFR tyrosine kinase inhibitor (TKI). A total of 657 patients were randomised in the study, of which 263 received carboplatin and pemetrexed (CP); and 131 which received Rybrevant intravenous formulation in combination with carboplatin and pemetrexed (Rybrevant intravenous formulation-CP). Additionally, 263 patients were randomised to receive Rybrevant intravenous formulation in combination with lazertinib, carboplatin, and pemetrexed in a separate arm of the study. Rybrevant intravenous formulation was administered intravenously at 1 400 mg (for patients < 80 kg) or 1 750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1 750 mg (for patients < 80 kg) or 2 100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 on once every 3 weeks until disease progression or unacceptable toxicity.

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).

Of the 394 patients randomised to the Rybrevant intravenous formulation-CP arm or CP arm, the median age was 62 (range: 31-85) years, with 38% of the patients ≥ 65 years of age; 60% were female; and 48% were Asian and 46% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (40%) or 1 (60%); 66% never smoked; 45% had history of brain metastasis, and 92% had Stage IV cancer at initial diagnosis.

Rybrevant intravenous formulation in combination with carboplatin and pemetrexed demonstrated a statistically significant improvement in progression-free survival (PFS) compared to carboplatin and pemetrexed, with a HR of 0.48 (95% CI: 0.36, 0.64; p<0.0001). At the time of the second interim analysis for OS, with a median follow-up of approximately 18.6 months for Rybrevant intravenous formulation-CP and approximately 17.8 months for CP, the OS HR was 0.73 (95% CI: 0.54, 0.99; p=0.0386). This was not statistically significant (tested at a prespecified significance level of 0.0142).

Efficacy results are summarised in Table 11.

Table 11: Efficacy results in MARIPOSA-2

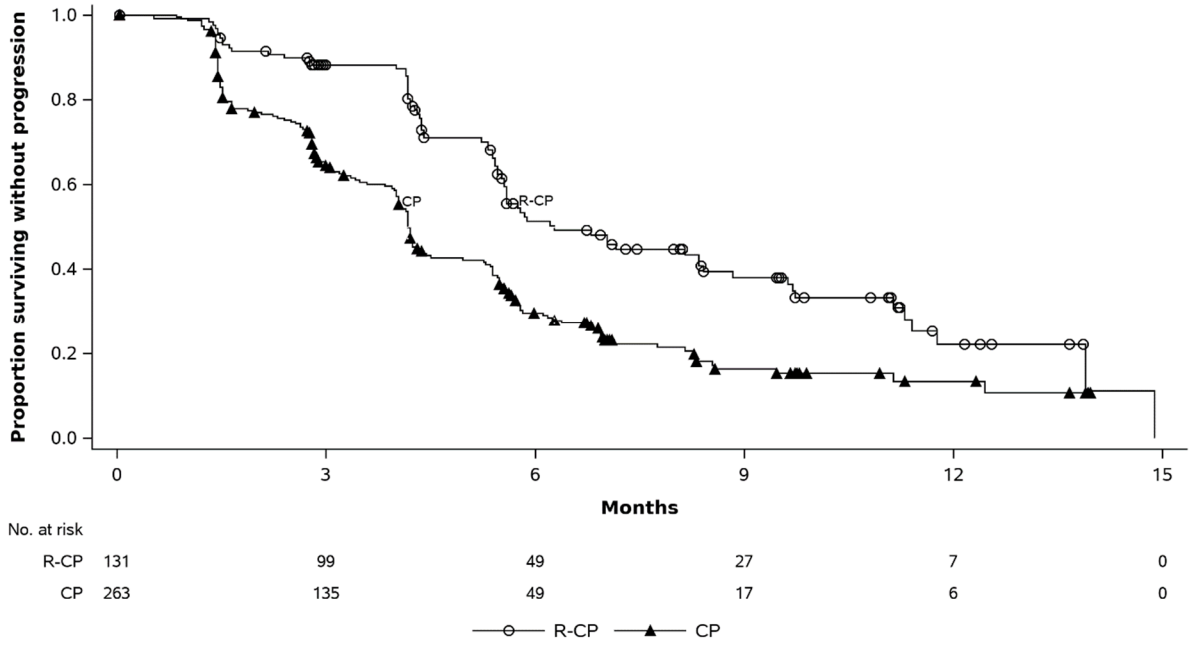
	Rybrevant intravenous formulation+ carboplatin+ pemetrexed (N=131)	**carboplatin+ pemetrexed (N=263)**
Progression-free survival (PFS)[a]		
Number of events (%)	74 (57)	171 (65)
Median, months (95% CI)	6.3 (5.6, 8.4)	4.2 (4.0, 4.4)
HR (95% CI); p-value	0.48 (0.36, 0.64); p<0.0001	
Overall survival (OS)		
Number of events (%)	65 (50)	143 (54)
Median, months (95% CI)	17.7 (16.0, 22.4)	15.3 (13.7, 16.8)
HR (95% CI); p-value[b]	0.73 (0.54, 0.99); p=0.0386	
Objective response rate[a]		
ORR, % (95% CI)	64% (55%, 72%)	36% (30%, 42%)
Odds Ratio (95% CI); p-value	3.10 (2.00, 4.80); p<0.0001	
Duration of response (DOR) [a]		
Median (95% CI), months	6.90 (5.52, NE)	5.55 (4.17, 9.56)
Patients with DOR ≥ 6 months	31.9%	20.0%

CI = Confidence Interval
NE = not estimable
PFS, DOR and ORR results are from data cut-off 10 July-2023 when hypothesis testing and final analysis for these endpoints was performed. OS results are from data cut-off 26 April 2024 from the second interim OS analysis.

[a] BICR-assessed

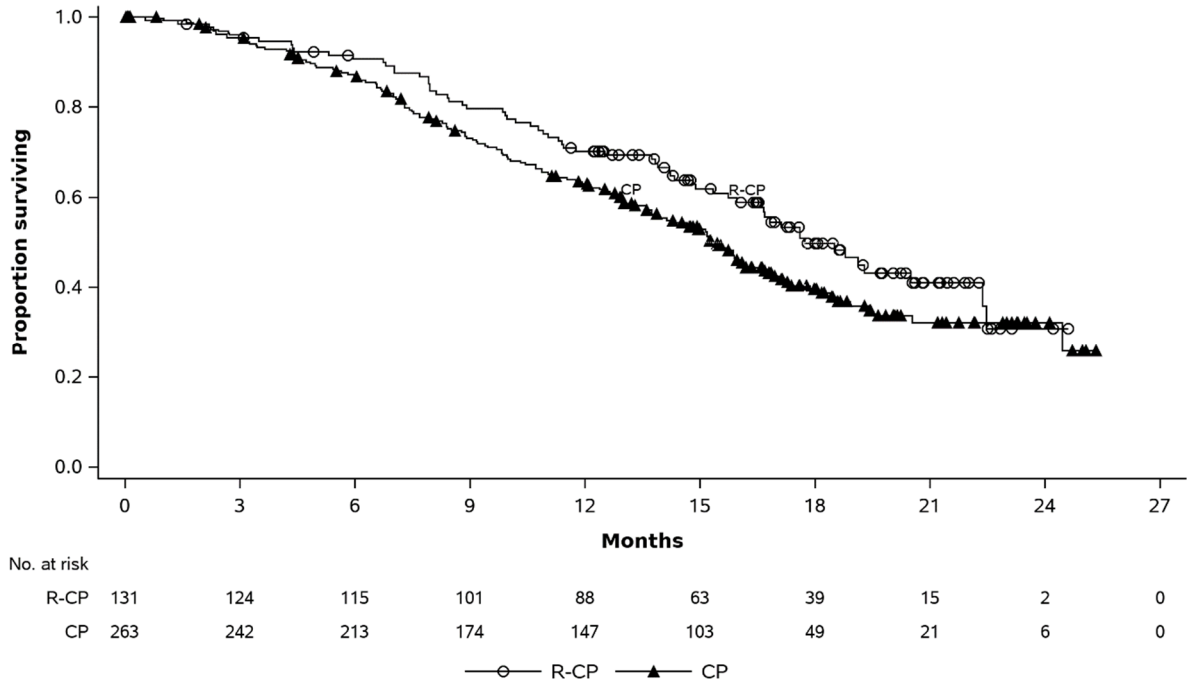
[b] The p-value is compared to a 2-sided significance level of 0.0142. Thus the OS results are not significant as of the second interim analysis.

Figure 3: Kaplan-Meier curve of PFS in previously treated NSCLC patients by BICR assessment



The PFS benefit of Rybrevant intravenous formulation-CP compared to CP was consistent across all the predefined subgroups analysed, including ethnicity, age, gender, smoking history, and CNS metastases status at study entry.

Figure 4: Kaplan-Meier curve of OS in previously treated NSCLC patients



Intracranial metastases efficacy data
Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to be randomised in MARIPOSA-2. Treatment with Rybrevant intravenous formulation-CP was associated with a numeric increase in intracranial ORR (23.3% for Rybrevant intravenous formulation-CP versus 16.7% for CP, odds ratio of 1.52; 95% CI (0.51, 4.50), and intracranial DOR (13.3 months; 95% CI (1.4, NE) in the Rybrevant intravenous formulation-CP arm compared with 2.2 months; 95% CI (1.4, NE) in the CP arm). The median follow-up for Rybrevant intravenous formulation-CP was approximately 18.6 months.

Previously-untreated non-small cell lung cancer (NSCLC) with Exon 20 insertion mutations (PAPILLON)

PAPILLON is a randomised, open-label, multicentre Phase 3 study comparing treatment with Rybrevant intravenous formulation in combination with carboplatin and pemetrexed to chemotherapy alone (carboplatin and pemetrexed) in patients with treatment-naïve, locally advanced or metastatic NSCLC with activating EGFR Exon 20 insertion mutations. Tumour tissue (92.2%) and/or plasma (7.8%) samples for all 308 patients were tested locally to determine EGFR Exon 20 insertion mutation status using next generation sequencing (NGS) in 55.5% of patients and/or polymerase chain reaction (PCR) in 44.5% of patients. Central testing was also performed using the AmoyDx® LC10 tissue test, Thermo Fisher Oncomine Dx Target Test, and the Guardant 360® CDx plasma test.

Patients with brain metastases at screening were eligible for participation once they were definitively treated, clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomisation.

Rybrevant intravenous formulation was administered intravenously at 1 400 mg (for patients < 80 kg) or 1 750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1 750 mg (for patients < 80 kg) or 2 100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 once every 3 weeks until disease

progression or unacceptable toxicity. Randomisation was stratified by ECOG performance status (0 or 1), and prior brain metastases (yes or no). Patients randomised to the carboplatin and pemetrexed arm who had confirmed disease progression were permitted to cross over to receive Rybrevant intravenous formulation monotherapy.

A total of 308 subjects were randomised (1:1) to Rybrevant intravenous formulation 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 (64%); 58% never smoked; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis.

The primary endpoint for PAPILLON was PFS, as assessed by BICR. The median follow-up was 14.9 months (range: 0.3 to 27.0).

Efficacy results are summarised in Table 12.

Table 12: Efficacy results in PAPILLON

	Rybrevant intravenous formulation + 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-value	0.395 (0.29, 0.52); p<0.0001	
Objective response rate[a, b]		
ORR, % (95% CI)	73% (65%, 80%)	47% (39%, 56%)
Odds ratio (95% CI); p-value	3.0 (1.8, 4.8); p<0.0001	
Complete response	3.9%	0.7%
Partial response	69%	47%
Overall survival (OS)[c]		
Number of events	40	52
Median OS, months (95% CI)	NE (28.3, NE)	28.6 (24.4, NE)
HR (95% CI); p-value	0.756 (0.50, 1.14); p=0.1825	

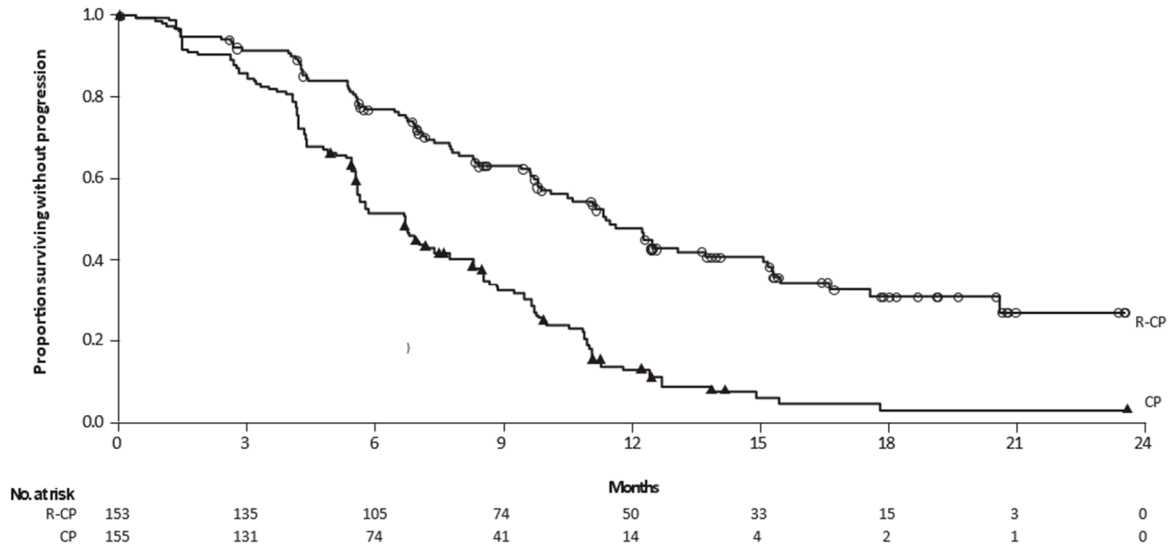
CI = confidence interval
NE = not estimable

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

[b] Based on Kaplan-Meier estimate.

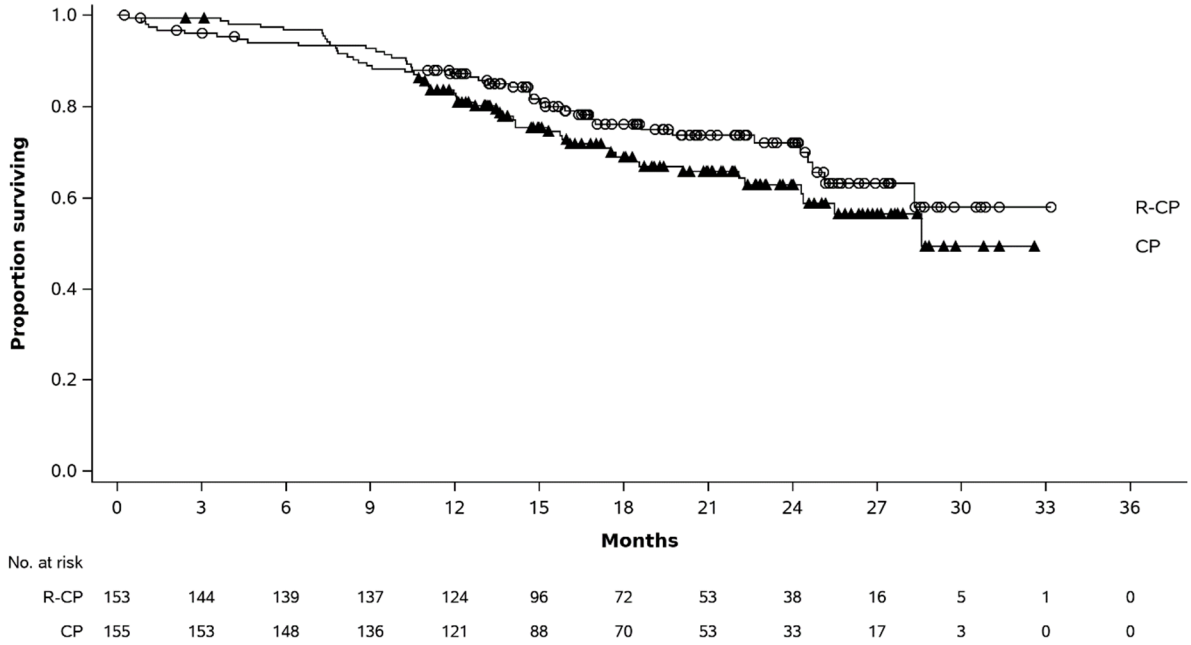
[c] Based on the results of an updated OS with median follow-up of 20.9 months. The OS analysis was not adjusted for the potentially confounding effects of crossover (78 [50.3%] patients on the carboplatin + pemetrexed arm who received subsequent Rybrevant intravenous formulation monotherapy treatment).

Figure 5: Kaplan-Meier curve of PFS in previously untreated NSCLC patients by BICR assessment



The PFS benefit of Rybrevant intravenous formulation in combination with carboplatin and pemetrexed compared to carboplatin and pemetrexed was consistent across all the predefined subgroups of brain metastases at study entry (yes or no), age (< 65 or ≥ 65), sex (male or female), race (Asian or non-Asian), weight (< 80 kg or ≥ 80 kg), ECOG performance status (0 or 1), and smoking history (yes or no).

Figure 6: Kaplan-Meier curve of OS in previously untreated NSCLC patients



Previously-treated non-small cell lung cancer (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 1 050 mg for patients < 80 kg or 1 400 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 13.

Table 13: 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 subcutaneous formulation. No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed. Among the 741 participants who received Rybrevant subcutaneous formulation 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.

Elderly

No overall differences in effectiveness were observed between patients ≥ 65 years of age and patients < 65 years of age.

Paediatric population
The European Medicines Agency has waived the obligation to submit the results of studies with Rybrevant in all subsets of the paediatric population in NSCLC (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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 $AUC_{1\ week}$ 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 14 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 14: Summary of serum pharmacokinetics parameters of amivantamab in patients with NSCLC (PALOMA-3 Study)

Parameter	Rybrevant subcutaneous formulation 1 600 mg (2 240 mg for body weight ≥ 80 kg)	Rybrevant intravenous formulation 1 050 mg (1 400 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)	135 861 (30.7%)	131 704 (24.0%)

For the every 3-week subcutaneous dosing regimen, the geometric mean (%CV) maximum trough concentration of amivantamab after the 3rd weekly dose was 438 µg/mL (26.6%). The geometric mean (%CV) steady-state trough concentration of amivantamab was 208 µg/mL (35.6%).

For the every 4-week subcutaneous dosing regimen, the geometric mean (%CV) maximum trough concentration of amivantamab after the 4th weekly dose was 350 µg/mL (30.5%). The geometric mean (%CV) steady state trough concentration of amivantamab was 131 µg/mL (55.9%).

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

Elderly
No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (21-88 years).

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.

Paediatric population
The PK of amivantamab in paediatric patients have not been investigated.

5.3 Preclinical safety data

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Recombinant human hyaluronidase (rHuPH20)
EDTA disodium salt dihydrate
Glacial acetic acid
L-methionine
Polysorbate 80 (E433)
Sodium acetate trihydrate
Sucrose
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial
2 years

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.

6.4 Special precautions for 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 6.3.

6.5 Nature and contents of container

10 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off cap containing 1 600 mg amivantamab. Pack size of 1 vial.

14 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off cap containing 2 240 mg amivantamab. Pack size of 1 vial.

15 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off cap containing 2 400 mg amivantamab. Pack size of 1 vial.

22 mL solution in a Type 1 glass vial with an elastomeric closure and an aluminium seal with a flip-off cap containing 3 520 mg amivantamab. Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Rybrevant subcutaneous formulation 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 subcutaneous formulation vial(s) needed based on the patient's baseline weight (see section 4.2).
- For every 4-week dosing, patients < 80 kg receive 1 600 mg weekly from Weeks 1 to 4, then 3 520 mg every 4 weeks starting at Week 5 onwards. Patients ≥ 80 kg receive 2 240 mg weekly from Weeks 1 to 4, then 4 640 mg every 4 weeks starting at Week 5 onwards.
- For every 2-week dosing, patients < 80 kg receive 1 600 mg and patients ≥ 80 kg receive 2 240 mg weekly from Weeks 1 to 4, and then every 2 weeks starting at Week 5 onwards.
- For every 3-week dosing, patients < 80 kg receive 1 600 mg on Week 1 Day 1, then 2 400 mg weekly from Weeks 2 to 4, and then every 3 weeks starting at Week 7 onwards. Patients ≥ 80 kg receive 2 240 mg on Week 1 Day 1, then 3 360 mg weekly from Weeks 2 to 4, and then every 3 weeks starting at Week 7 onwards.
- Remove the appropriate Rybrevant subcutaneous formulation vial(s) from refrigerated storage (2°C to 8°C).
- Check that the Rybrevant solution is colourless to pale yellow. Do not use if opaque particles, discolouration or other foreign particles are present.
- Equilibrate Rybrevant subcutaneous formulation to room temperature (15°C to 30°C) for at least 15 minutes. Do not warm Rybrevant subcutaneous formulation in any other way. Do not shake.
- Withdraw the required injection volume of Rybrevant subcutaneous formulation from the vial into an appropriately sized syringe using a transfer needle. Smaller syringes require less force during preparation and administration.
- Each injection volume should not exceed 15 mL. Divide doses requiring greater than 15 mL into approximately equal volumes in multiple syringes.
- Rybrevant subcutaneous formulation 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.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 09 December 2021
Date of latest renewal: 11 September 2023

9. DATE OF REVISION OF THE TEXT

11 December 2025