

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 1600 mg 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.

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 epidermal growth factor receptor (EGFR) Exon 19 deletions or Exon 21 L858R substitution mutations.
- as monotherapy for treatment of adult patients with advanced NSCLC with activating EGFR Exon 20 insertion mutations, after failure of platinum-based therapy.

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.

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”).

In patients receiving Rybrevant in combination with lazertinib, prophylactic anticoagulants are recommended to be used for the first four months of treatment. Consistent with clinical guidelines, patients should receive prophylactic dosing of appropriate anticoagulants, e.g. low-molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended. Patients should be instructed to limit sun exposure during and for 2 months after Rybrevant therapy. For further information about prophylaxis for VTE and skin and nail reactions, see section 4.4.

The recommended dosages of Rybrevant subcutaneous formulation in combination with lazertinib or as monotherapy based on baseline body weight, are provided in Table 1.

Table 1: Recommended dosage of Rybrevant subcutaneous 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

		<ul style="list-style-type: none"> • Every 2 weeks starting at Week 5 onwards
Greater than or equal to 80 kg	2240 mg ^a	<ul style="list-style-type: none"> • 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.

^a See SmPC for Rybrevant 2240 mg solution for injection.

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.

Duration of treatment

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

Missed dose

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. 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 4.2 of the lazertinib Summary of Product Characteristics 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 subcutaneous formulation
2240 mg ^a	1600 mg	1050 mg	

* Dose at which the adverse reaction occurred

^a See SmPC for Rybrevant 2240 mg solution for injection.

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 3).
- Recurrent Grade 3 or Grade 4 (life-threatening): Permanently discontinue Rybrevant.

Venous thromboembolic (VTE) events with concomitant use with lazertinib

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, at the discretion of the treating physician. In the event of recurrence despite therapeutic level anticoagulation, the combination of Rybrevant and lazertinib should be permanently discontinued. Treatment can continue with either Rybrevant or lazertinib, but not both at the discretion of the treating physician (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 2). 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 \leq 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 4). 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 subcutaneous formulation administration
Antihistamine [*]	Chlorphenamine (10 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic [*]	Paracetamol (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

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. VTE events occurred predominantly in the first four months of therapy. Prophylactic anticoagulants are recommended to be used for the first four months of treatment (see section 4.2 and 4.8).

Consistent with clinical guidelines, patients should receive prophylactic dosing of appropriate anticoagulant, e.g. 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 at the discretion of the treating physician.

In the event of recurrence despite appropriate anticoagulation, discontinue Rybrevant or lazertinib. Treatment can continue with Rybrevant or lazertinib, but not both, at the discretion of the treating physician (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 starting on Day 1 for the first 12 weeks of treatment and after completion of oral antibiotic therapy, topical antibiotic lotion to the scalp 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, or 8.4 mg per 14 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

Rybrevent 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

Rybrevent as monotherapy

In the dataset of Rybrevent 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 Rybrevent 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 Rybrevent as monotherapy.

The data reflects exposure to Rybrevent 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 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

Rybrevent in combination with lazertinib

Overall, the safety profile of Rybrevent subcutaneous formulation was consistent with the established safety profile of Rybrevent 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 Rybrevent (either intravenous or subcutaneous formulations) in combination with lazertinib (N=752), the most frequent adverse reactions of any grade ($\geq 20\%$ patients) were rash (87%), nail toxicity (67%), hypoalbuminaemia (48%), hepatotoxicity (43%), stomatitis (43%), oedema (42%), fatigue (35%), paraesthesia (29%), constipation (26%), diarrhoea (26%), dry skin (25%), decreased appetite (24%), nausea (24%), and pruritus (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 Rybrevent subcutaneous formulation in combination with lazertinib, including ILD (4.2%), VTE (2.7%), hepatotoxicity (2.1%), and fatigue (1.5%). Seven percent of patients discontinued Rybrevent subcutaneous formulation due to adverse reactions. In patients treated with Rybrevent subcutaneous formulation in combination with lazertinib, the most frequent adverse reactions of any grade ($\geq 1\%$ patients) leading to discontinuation of Rybrevent subcutaneous formulation were ILD (3.6%) and rash (1.5%).

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 752 patients with locally advanced or metastatic NSCLC, including 421 patients in MARIPOSA, 125 patients in PALOMA-2 cohorts 1 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 9.9 months (range: 0.1 to 31.4 months). Median duration on treatment for the subcutaneous formulation was 5.7 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 ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10000$ 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=752)

System Organ Class Adverse Reaction	Frequency category	Any grade (%)	Grade 3-4 (%)
Metabolism and nutrition disorders			
Hypoalbuminaemia*	Very common	48	4.5
Decreased appetite		24	0.8
Hypocalcaemia		19	1.2
Hypokalaemia		13	2.7
Hypomagnesaemia	Common	6	0
Nervous system disorders			
Paraesthesia* ^a	Very common	29	1.3
Dizziness*		12	0
Eye disorders			
Other eye disorders*	Very common	19	0.5
Visual impairment*	Common	3.6	0
Keratitis		1.7	0.3
Growth of eyelashes*		1.7	0

Vascular disorders			
Venous thromboembolism			
Amivantamab intravenous* ^b	Very common	37	11
Amivantamab subcutaneous* ^c	Very common	11	0.9
Respiratory, thoracic, and mediastinal disorders			
Interstitial lung disease*	Common	3.6	1.7
Gastrointestinal disorders			
Stomatitis*	Very common	43	2.0
Constipation		26	0
Diarrhoea		26	1.7
Nausea		24	0.8
Vomiting		15	0.5
Abdominal pain*		10	0.1
Haemorrhoids	Common	8	0.1
Hepatobiliary disorders			
Hepatotoxicity*	Very common	43	7
Skin and subcutaneous tissue disorders			
Rash*	Very common	87	23
Nail toxicity*		67	8
Dry skin*		25	0.7
Pruritus		23	0.3
Skin ulcer	Common	3.9	0.5
Palmar-plantar erythrodysesthesia syndrome		3.9	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	2.7
Fatigue*		35	3.5
Pyrexia		11	0
Injection site reactions* ^{c, d}	Common	8	0
Injury, poisoning, and procedural complications			
Infusion-/Administration-related reactions			
Amivantamab intravenous ^{b, c}	Very common	63	6

Amivantamab subcutaneous ^{c, f}	Very common	14	0.3
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* Grouped terms.

^a Applicable only to lazertinib.

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

^c Frequency based on amivantamab subcutaneous studies only (PALOMA-2 cohorts 1 and 6 [N=125] 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

Overall, administration-related reactions occurred in 14% of patients treated with Rybrevant subcutaneous formulation in combination with lazertinib. 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. The most frequent signs and symptoms of administration-related reactions include dyspnoea, flushing, fever, chills, nausea, and chest discomfort. Median time to onset of first administration-related reactions was 2.1 hours (range: 0.0 to 176.5 hours). Most administration-related reactions (98%) were Grades 1 or 2 in severity.

Injection site reactions

Overall, injection site reactions occurred in 8% of patients treated with Rybrevant subcutaneous formulation 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

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 (0.3%) 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 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 (0.9%) patients. Additionally, 269 (81%) of these 331 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, the incidence of VTE reactions was 9% for patients treated with Rybrevant subcutaneous formulation in combination with lazertinib, compared to 13% 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 was 17% for patients treated with Rybrevant subcutaneous formulation in combination with lazertinib with all VTE reactions reported as Grade 1-2 and serious VTE reactions reported in 4.8% of these patients, compared to an overall incidence of 23% for patients treated with Rybrevant intravenous formulation in combination with lazertinib with Grade 3 VTE reactions reported in 10% and serious VTE reactions reported in 8% 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) in combination with lazertinib. Rash occurred in 87% of patients, leading to discontinuation of Rybrevant in 0.7% of patients. Most cases were Grade 1 or 2, with Grade 3 and Grade 4 reactions occurring in 23% and 0.1% of patients, respectively.

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 \geq 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 \geq 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, including keratitis (1.7%), occurred in patients treated with Rybrevant (either intravenous or subcutaneous formulation). 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 \geq 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 Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 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 6 and Figure 2).

Table 6: Efficacy results in MARIPOSA

	Rybrevant intravenous formulation + lazertinib (N=429)	Osimertinib (N=429)	Lazertinib (N=216)
Progression-free survival (PFS)^a			
Number of events	192 (45%)	252 (59%)	121 (56%)
Median, months (95% CI)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)	18.46 (14.75, 20.11)
Hazard Ratio (95% CI); p-value			
Rybrevant + lazertinib vs osimertinib	0.70 (0.58, 0.85); p=0.0002		
Rybrevant + lazertinib vs lazertinib	0.72 (0.57, 0.90); p=0.0046		
Overall survival (OS)			
Number of events	173 (40%)	217 (51%)	100 (46%)
Median, months (95% CI)	NE (42.9, NE)	36.7 (33.4, 41.0)	38.5 (36.5, 45.4)
Hazard Ratio (95% CI); p-value			
Rybrevant + lazertinib vs osimertinib	0.75 (0.61, 0.92); p=0.0048		
Rybrevant + lazertinib vs lazertinib	0.83 (0.65, 1.06); p=0.1416		
12-month event-free rate, %	90 (86, 92)	88 (84, 91)	85 (80, 89)
18-month event-free rate, %	82 (78, 86)	79 (75, 83)	77 (71, 82)
24-month event-free rate, %	75 (71, 79)	70 (65, 74)	72 (65, 77)
Overall response rate (ORR)^a			
ORR % (95% CI)	86.2 (82.6, 89.4)	84.5 (80.7, 87.9)	82.7 (77.0, 87.5)

Odds ratio (95% CI); p-value			
Rybrevant + lazertinib vs osimertinib	1.15 (0.78, 1.70); p=0.4714		
Rybrevant + lazertinib vs lazertinib	1.31 (0.83, 2.06); p=0.2409		
Complete response, %	6.9	3.6	4.2
Partial response, %	79.3	80.9	78.5
Duration of response (DOR)^b			
Median (95% CI), months	25.76 (20.14, NE)	16.76 (14.75, 18.53)	16.56 (14.75, 20.21)
Patients with DOR ≥ 6 months, %	86.3	85.0	82.5
Patients with DOR ≥ 12 months, %	67.9	57.6	58.8

BICR = blinded independent central review; CI = confidence interval; NE = not estimable
PFS, ORR and DOR results are from data cut-off 11 August 2023. 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 BICR by RECIST v1.1 in confirmed responders

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

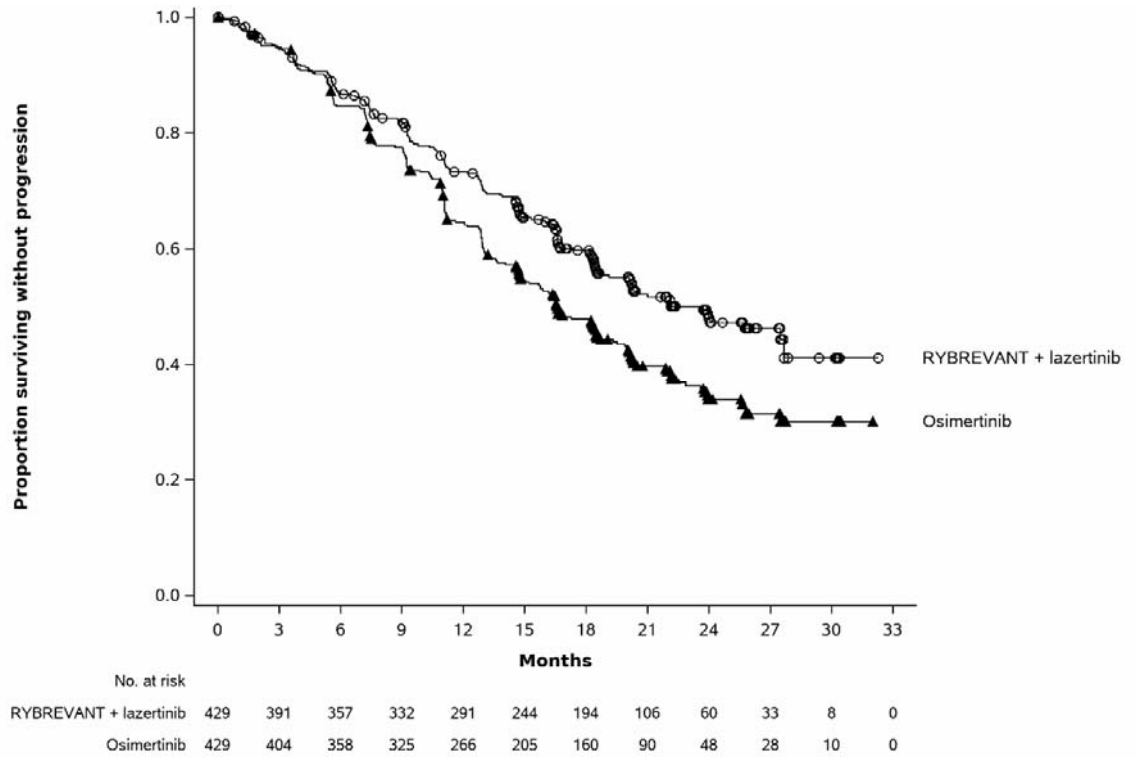
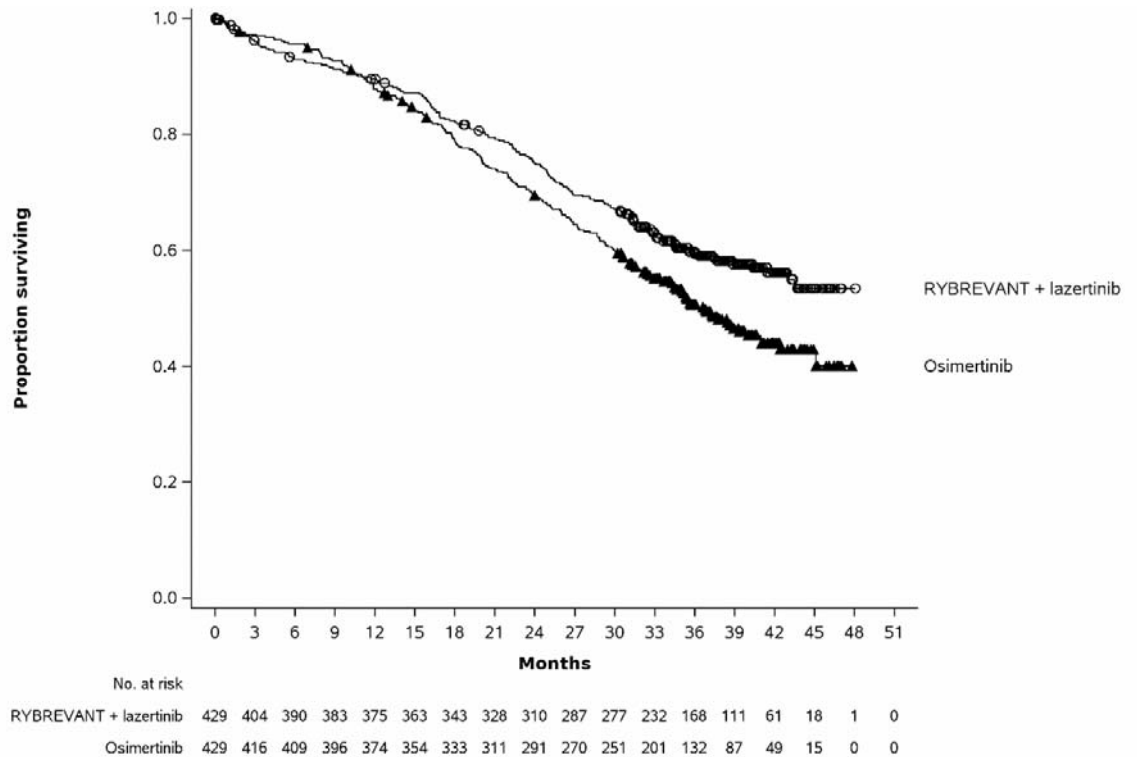


Figure 2: Kaplan-Meier curve of OS in previously untreated NSCLC patients



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 7.

Table 7: Intracranial ORR and DOR by BICR assessment in subjects with intracranial lesions at baseline - MARIPOSA

	Rybrevant intravenous formulation + lazertinib (N=180)	Osimertinib (N=186)	Lazertinib (N=93)
Intracranial tumour response assessment			
Intracranial ORR (CR+PR), % (95% CI)	77.8 (71.0, 83.6)	77.4 (70.7, 83.2)	75.0 (64.9, 83.4)
Complete response %	63.9	58.6	54.3
Intracranial DOR			
Number of responders	140	144	69
Median, months (95% CI)	35.0 (20.4, NE)	25.1 (22.1, 31.2)	22.5 (18.8, 31.1)
Response duration ≥ 6 months, %	78.6	79.9	81.2
Response duration ≥ 12 months, %	63.6	61.1	60.9
Response duration ≥ 18 months, %	52.1	41.0	40.6

CI = confidence interval

Intracranial ORR and DOR results are from data cut-off 04 Dec 2024 with a median follow-up of 37.8 months.

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 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 8.

Table 8: 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 389 participants who received Rybrevant subcutaneous formulation as monotherapy or as part of combination therapy, 37 participants (10%) 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 Licencing Authority 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 $\mu\text{g/mL}$ (32.7%). The mean $\text{AUC}_{1\text{week}}$ 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 $\mu\text{g/mL}$ (39.1%).

Table 9 lists the observed geometric mean (%CV) maximum trough concentrations (Cycle 2 Day 1 C_{trough}) and Cycle 2 area under the concentration time curve ($\text{AUC}_{\text{Day 1-15}}$) 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 9: Summary of serum pharmacokinetics parameters of amivantamab in patients with NSCLC (PALOMA-3 Study)

Parameter	Rybrevant subcutaneous formulation	Rybrevant intravenous formulation
		1600 mg (2240 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 _(Day1-15) (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

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 ($60 \leq \text{creatinine clearance [CrCl]} < 90 \text{ mL/min}$), moderate ($29 \leq \text{CrCl} < 60 \text{ mL/min}$) or severe ($15 \leq \text{CrCl} < 29 \text{ mL/min}$) 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 ($\text{CrCl} < 15 \text{ mL/min}$) 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 \leq ULN and AST $>$ ULN) or (ULN $<$ total bilirubin \leq 1.5 x ULN)] or moderate ($1.5 \times \text{ULN} < \text{total bilirubin} \leq 3 \times \text{ULN}$ 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

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 aluminium seal with a flip-off cap containing 1600 mg amivantamab. Pack size of 1 vial.

6.6 Special precautions for disposal

Rybrevent 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 Rybrevent subcutaneous formulation vial needed based on the patient's baseline weight (see section 4.2).

- 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 subcutaneous formulation vial 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.
- Rybrevant subcutaneous formulation is compatible with stainless steel injection needles, polypropylene 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 appropriate ancillaries for transport or administration. Use of a 21G to 23G needle or infusion set is recommended to ensure ease of administration.

Storage of prepared syringe

The prepared 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

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8 MARKETING AUTHORISATION NUMBER(S)

PL 00242/0771

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

09/07/2025

10 DATE OF REVISION OF THE TEXT

13/01/2026