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 350 mg concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of concentrate for solution for infusion contains 50 mg amivantamab.

One 7 mL vial contains 350 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

Concentrate for solution for infusion.

The solution is colourless to pale yellow, with a pH of 5.7 and an osmolality of approximately 310 mOsm/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Rybrevant 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.
- 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 should be initiated and supervised by a physician experienced in the use of anticancer medicinal products.

Rybrevant should be administered by a healthcare professional with access to appropriate medical support to manage infusion-related reactions (IRRs) if they occur.

Before initiation of Rybrevant therapy, 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. Testing may be performed at any time from initial diagnosis until the initiation of therapy; testing does not need to be repeated once EGFR mutation status has been established (see section 5.1).

Posology

Premedications should be administered to reduce the risk of IRRs with Rybrevant (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.

Every 3 weeks

The recommended dosages of Rybrevant, when used in combination with carboplatin and pemetrexed, is provided in Table 1 (see below "Infusion rates" and Table 5).

Table 1: Recommended dosage of Rybrevant every 3 weeks

Body weight at baseline[a]	**Rybrevant dose**	**Schedule**	**Number of vials**
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2	4

		• Weeks 2 to 4 - infusion on Day 1	
	1750 mg	Every 3 weeks starting at Week 7 onwards	5
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	5
	2100 mg	Every 3 weeks starting at Week 7 onwards	6

[a] Dose adjustments not required for subsequent body weight changes.

When used in combination with carboplatin and pemetrexed, Rybrevant 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.

Every 2 weeks

The recommended dosages of Rybrevant as monotherapy or in combination with lazertinib is provided in Table 2 (see below "Infusion rates" and Table 6).

Table 2: Recommended dosage of Rybrevant every 2 weeks

Body weight at baseline[a]	**Rybrevant dose**	**Schedule**	**Number of vials**
Less than 80 kg	1050 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	3
		Every 2 weeks starting at Week 5 onwards	
Greater than or equal to 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1	4
		Every 2 weeks starting at Week 5 onwards	

[a] Dose adjustments not required for subsequent body weight changes.

When given in combination with lazertinib, it is recommended to administer Rybrevant 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 until disease progression or unacceptable toxicity.

Missed dose

If a planned dose is missed, the dose should be administered as soon as possible and the dosing schedule should be adjusted accordingly, maintaining the treatment interval.

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 3. See also specific dose modifications for specific adverse reactions below Table 3. If used in combination with lazertinib, refer to section 4.2 of the lazertinib Summary of Product Characteristics for information about dose modifications.

Table 3: Recommended dose modifications for adverse reactions

Dose at which the adverse reaction occurred	Dose after 1st interruption for adverse reaction	Dose after 2nd interruption for adverse reaction	Dose after 3rd interruption for adverse reaction
1050 mg	700 mg	350 mg	Discontinue Rybrevant
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

Infusion-related reactions

Infusion should be interrupted at the first sign of IRRs. 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 infusion at 50% of the previous rate. If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Tables 5 and 6). Concomitant medicinal products should be administered at the next dose (including dexamethasone (20 mg) or equivalent (see Table 4).
- 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 medicinal products should be held 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.

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 3). If the patient develops a Grade 3 skin or nail reaction, supportive care should be initiated as clinically indicated, and interruption of Rybrevant should be considered until the adverse reaction improves. Upon recovery of the skin or nail reaction to ≤ Grade 2, Rybrevant 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 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

Two days before the first infusion:

During the two days prior to the initial Rybrevant infusion, patients should receive 8 mg dexamethasone orally, twice daily.

Day of infusion:

On the day of the initial infusion (Week 1, Day 1), patients should receive 8 mg dexamethasone orally, one hour prior to infusion in addition to intravenous dexamethasone to further reduce the risk of IRRs.

Prior to infusion (Week 1, Days 1 and 2), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs (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 4: Dosing schedule of premedications

Premedication	**Dose**	**Route of administration**	**Recommended dosing window prior to Rybrevant administration**
Antihistamine[*]	Chlorphenamine (10 mg) or equivalent	Intravenous	15 to 30 minutes

Premedication	Dose	Route of administration	Recommended dosing window prior to Rybrevant administration
Antipyretic[*]	Paracetamol (650 to 1000 mg)	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid[‡]	Dexamethasone (8 mg)	Oral	60 minutes
Glucocorticoid[‡]	Dexamethasone (20 mg) or equivalent	Intravenous	60 to 120 minutes
Glucocorticoid[+]	Dexamethasone (10 mg) or equivalent	Intravenous	45 to 60 minutes

[*] Required at all doses.
[‡] Required at initial dose (Week 1, Day 1); or at the next subsequent dose in the event of an IRR.
[+] Required at second dose (Week 1, Day 2); optional for subsequent doses.

Special populations

Paediatric population

There is no relevant use of amivantamab in the paediatric population in the treatment of non-small cell lung cancer.

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 is for intravenous use. It is administered as an intravenous infusion following dilution with sterile 5% glucose solution or sodium chloride 9 mg/mL (0.9%) solution for injection. Rybrevant must be administered with in-line filtration.

For instructions on dilution of the medicinal product before administration, see section 6.6.

Infusion rates

Following dilution, the infusion should be administered intravenously at the infusion rates presented in Table 5 or 6 below.

Due to the frequency of IRRs at the first dose, amivantamab should be infused via a peripheral vein at Week 1 and Week 2; infusion via a central line may be administered for subsequent weeks when the risk of IRR is lower (see section 6.6). It is recommended for the first dose to be prepared as close to administration as possible to maximise the likelihood of completing the infusion in the event of an IRR.

Table 5: Infusion rates for Rybrevant every 3 weeks

Body weight less than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1050 mg	33 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Week 4	1400 mg	125 mL/hr	
Subsequent weeks*	1750 mg	125 mL/hr	
Body weight greater than or equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1400 mg	25 mL/hr	50 mL/hr

Week 2	1750 mg	65 mL/hr
Week 3	1750 mg	85 mL/hr
Week 4	1750 mg	125 mL/hr
Subsequent weeks[*]	2100 mg	125 mL/hr

[*] Starting at Week 7, patients are dosed every 3 weeks.

[†] Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of infusion-related reactions.

Table 6: Infusion rates for Rybrevant every 2 weeks

Body weight less than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate**[‡]
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	700 mg	50 mL/hr	75 mL/hr
Week 2	1050 mg	85 mL/hr	
Subsequent weeks[*]	1050 mg	125 mL/hr	
Body weight greater than or equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial infusion rate**	**Subsequent infusion rate**[‡]
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50 mL/hr	75 mL/hr
Week 1 *Day 2*	1050 mg	35 mL/hr	50 mL/hr
Week 2	1400 mg	65 mL/hr	
Week 3	1400 mg	85 mL/hr	
Subsequent weeks[*]	1400 mg	125 mL/hr	

[*] After Week 5, patients are dosed every 2 weeks.

[‡] Increase the initial infusion rate to the subsequent infusion rate after 2 hours in the absence of IRRs.

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.

Infusion-related reactions

Infusion-related reactions commonly occurred in patients treated with amivantamab (see section 4.8).

Prior to initial infusion (Week 1), antihistamines, antipyretics, and glucocorticoids should be administered to reduce the risk of IRRs. For subsequent doses, antihistamines and antipyretics should be administered. The initial infusion should be administered in split doses on Week 1, Day 1 and 2.

Patients should be treated in a setting with appropriate medical support to treat IRRs. Infusions should be interrupted at the first sign of IRRs of any severity and post-infusion medicinal products should be administered as clinically indicated. Upon resolution of symptoms, the infusion should be resumed at 50% of the previous rate. For recurrent Grade 3 or Grade 4 IRRs, 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 Rybrevant in combination with lazertinib, VTE events, including deep vein thrombosis (DVT) and pulmonary embolism (PE), including fatal events, were reported (see section 4.8). 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.

Monitor for signs and symptoms of VTE events. Treat patients with VTE events with anticoagulation as clinically indicated. For VTE events associated with clinical instability treatment should be held 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”. This medicinal product may be diluted in sodium chloride 9 mg/mL (0.9%) solution for infusion. This should be taken into consideration for patients on a controlled sodium diet (see section 6.6).

Polysorbate content

This medicinal product contains 0.6 mg of polysorbate 80 in each mL, which is equivalent to 4.2 mg per 7 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

In the dataset of amivantamab 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 7 summarises the adverse drug reactions that occurred in patients receiving amivantamab as monotherapy.

The data reflects exposure to amivantamab 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 7: Adverse reactions in patients receiving amivantamab as monotherapy

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

Summary of the safety profile

In the dataset of amivantamab in combination with carboplatin and pemetrexed (N=301), the most frequent adverse reactions in all grades were rash (83%), neutropenia (57%), nail toxicity (53%), infusion related reactions (51%), fatigue (43%), stomatitis (39%), nausea (43%), thrombocytopenia (40%), constipation (40%), oedema (40%), decreased appetite (33%), hypoalbuminaemia (32%), alanine aminotransferase increased (26%), aspartate aminotransferase increased (23%), vomiting (22%), and hypokalaemia (20%). Serious adverse reactions included rash (2.7%), venous thromboembolism (2.3%), thrombocytopenia (2.3%) and ILD (2.0%). Eight percent of patients discontinued Rybrevant due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR (2.7%), rash (2.3%), ILD (2.3%), and nail toxicity (1.0%).

Table 8 summarises the adverse drug reactions that occurred in patients receiving amivantamab in combination with chemotherapy.

The data reflects exposure to amivantamab in combination with carboplatin and pemetrexed in 301 patients with locally advanced or metastatic non-small cell lung cancer. Patients received amivantamab 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) weekly for 4 weeks. Starting at Week 7, patients received amivantamab 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) every 3 weeks. The median exposure to amivantamab in combination with carboplatin and pemetrexed 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 (≥ 1/1000 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 8: Adverse reactions in patients receiving amivantamab in combination with carboplatin and pemetrexed

System organ class Adverse reaction	**Frequency category**	**Any Grade (%)**	**Grade 3-4 (%)**
Blood and lymphatic system disorders			
Neutropenia	Very common	57	39
Thrombocytopenia		40	12
Metabolism and nutrition disorders			
Decreased appetite	Very common	33	1.3
Hypoalbuminaemia*		32	3.7
Hypokalaemia		20	6.6
Hypomagnesaemia		13	1.3
Hypocalcaemia		12	1.0
Nervous system disorders			
Dizziness*	Common	10	0.3
Vascular disorders			
Venous thromboembolism*	Very common	14	3.0
Eye disorders			
Other eye disorders*	Common	7.3	0
Visual impairment*		3.0	0
Growth of eyelashes	Uncommon	0.3	0
Keratitis		0.3	0
Uveitis		0.3	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease*	Common	2.3	1.7
Gastrointestinal disorders			
Nausea	Very common	43	1.0
Constipation		40	0.3
Stomatitis*		39	3.0
Vomiting		22	2.0
Diarrhoea		19	2.3
Abdominal pain*	Common	11	0.3
Haemorrhoids		9.3	0.7
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	26	4.3
Aspartate aminotransferase increased		23	0.7

Blood alkaline phosphatase increased	Common	10	0.3
Skin and subcutaneous tissue disorders			
Rash*	Very common	83	14
Nail toxicity*		53	4.3
Dry skin*		16	0
Pruritus		10	0
Skin ulcer	Common	3.7	0.7
Musculoskeletal and connective tissue disorders			
Myalgia	Common	5.0	0.7
General disorders and administration site conditions			
Fatigue*	Very common	43	4.7
Oedema*		40	1.3
Pyrexia		14	0
Injury, poisoning and procedural complications			
Infusion related reaction	Very common	51	3.0

* Grouped terms

Summary of the safety profile

In the dataset of amivantamab in combination with lazertinib (N=421), the most frequent adverse reactions in all grades were rash (89%), nail toxicity (71%), infusion-related reactions (63%), hypoalbuminaemia (48%), oedema (47%), stomatitis (43%), venous thromboembolism (36%), alanine aminotransferase increased (36%), fatigue (32%), aspartate aminotransferase increased (29%), diarrhoea (29%), constipation (29%), dry skin (26%), pruritus (24%), decreased appetite (24%), hypocalcaemia (21%), nausea (21%) and other eye disorders (21%). The most frequent serious adverse reactions included venous thromboembolism (11%), ILD (2.9%), rash (2.4%), and IRR (2.1%). Twenty-two percent of patients discontinued Rybrevant due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were rash (5.5%), infusion related reactions (4.5%), nail toxicity (3.6%), ILD (2.9%) and VTE (2.9%).

Table 9 summarises the adverse drug reactions that occurred in patients receiving amivantamab in combination with lazertinib.

The data reflects exposure to amivantamab in combination with lazertinib in 421 patients with locally advanced or metastatic non-small cell lung cancer. Patients received amivantamab 1050 mg (for patients <80 kg) or 1400 mg (for patients ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter. The median exposure to study treatment in the amivantamab and lazertinib combination group was 18.5 months (range: 0.2 to 31.4 months).

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10);

common (≥ 1/100 to < 1/10); uncommon (≥ 1/1000 to < 1/100); rare (≥ 1/10000 to < 1/1000); very rare (< 1/10000); and not known (frequency cannot be estimated from the available data).

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

Table 9: Amivantamab adverse reactions in patients receiving amivantamab in combination with lazertinib

System organ class Adverse reaction	**Frequency category**	**Any Grade (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders			
Hypoalbuminaemia*	Very common	48	5.2
Decreased appetite		24	1.0
Hypocalcaemia		21	2.1
Hypokalaemia		14	3.1
Hypomagnesaemia	Common	5.0	0
Nervous system disorders			
Dizziness*	Very common	13	0
Vascular disorders			
Venous thromboembolism*‡	Very common	36	11
Eye disorders			
Other eye disorders*	Very common	21	0.5
Visual impairment*	Common	4.5	0
Keratitis		2.6	0.5
Growth of eyelashes*		1.9	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease*	Common	3.1	1.2
Gastrointestinal disorders			
Stomatitis*	Very common	43	2.4
Constipation		29	0
Diarrhoea		29	2.1
Nausea		21	1.2
Vomiting		12	0.5
Abdominal pain*		11	0

Haemorrhoids	Common	9.7	0.2
Hepatobiliary disorders			
Alanine aminotransferase increased	Very common	36	5.0
Aspartate aminotransferase increased		29	3.3
Blood alkaline phosphatase increased		12	1.2
Skin and subcutaneous tissue disorders			
Rash*	Very common	89	27
Nail toxicity*		71	11
Dry skin*		26	1.0
Pruritus		24	0.5
Skin ulcer	Common	5	0.7
Musculoskeletal and connective tissue disorders			
Myalgia	Very common	13	0.7
General disorders and administration site conditions			
Oedema*	Very common	47	2.9
Fatigue*		32	3.8
Pyrexia		12	0
Injury, poisoning and procedural complications			
Infusion related reaction	Very common	63	6.4

* Grouped terms
‡ Assessed as ADR for Rybrveant in combination with lazertinib only.

Refer to section 4.8 of the lazertinib Summary of Product Characteristics for a list of adverse reactions associated with lazertinib use.

Description of selected adverse reactions

Infusion-related reactions

In patients treated with amivantamab monotherapy, infusion-related reactions occurred in 67% of patients. Ninety-eight percent of IRRs were Grade 1-2. Ninety-nine percent of IRRs occurred at the first infusion with a median time to onset of 60 minutes, and the majority occurring within 2 hours of infusion start. The most frequent signs and symptoms include chills, dyspnoea, nausea, flushing, chest discomfort, and vomiting (see section 4.4).

In patients treated with amivantamab in combination with carboplatin and pemetrexed, infusion-related reactions occurred in 50% of patients. Greater than 94%

of IRRs were Grade 1-2. A majority of IRRs occurred at the first infusion with a median time to onset of 60 minutes (range 0-7 hours), and the majority occurring within 2 hours of infusion start.

In patients treated with amivantamab in combination with lazertinib, infusion related reactions occurred in 62.9% of patients. Ninety-four percent of IRRs were Grade 1-2. A majority of IRRs occurred at the first infusion with a median time to onset of 1 hour, and the majority occurring within 2 hours of infusion start. The most frequent signs and symptoms include chills, dyspnoea, nausea, flushing, chest discomfort, and vomiting (see section 4.4).

Occasionally an IRR can occur at re-initiation of amivantamab after prolonged dose interruptions of more than 6 weeks.

In a Phase 2, open-label, multicenter study in patients with NSCLC, patients were administered 8 mg dexamethasone orally, twice daily on both of the two days prior to the first Rybrevant infusion and 8 mg orally, 60 minutes prior to infusion on the day of the first infusion (5 doses total) in addition to intravenous dexamethasone. With the addition of oral dexamethasone, a 22.5% incidence of IRRs and no grade ≥3 IRRs were reported on the day of the initial infusion (see section 4.2).

Interstitial lung disease

Interstitial lung disease or ILD-like adverse reactions have been reported with the use of amivantamab as well as with other EGFR inhibitors. Interstitial lung disease or pneumonitis was reported in 2.6% of patients treated with amivantamab monotherapy, 2.3% of patients treated with amivantamab in combination with carboplatin and pemetrexed and 3.1% of patients treated with amivantamab in combination with lazertinib. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical study (see section 4.4).

Venous thromboembolic (VTE) events with concomitant use with lazertinib

When Rybrevant is used in combination with lazertinib, VTE events, including deep venous thrombosis (DVT) and pulmonary embolism (PE), were reported in 35.6% of the 421 patients treated. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 11% of patients, and Grade 5 events occurring in 0.5% of patients. In patients receiving Rybrevant is combination with lazertinib, the median time to first onset of a VTE event was 84 days.

The use of prophylactic anticoagulants was evaluated in the PALOMA-3 study. PALOMA-3 is a randomised, open-label, Phase 3 study assessing subcutaneous versus intravenous amivantamab, both in combination with lazertinib, in patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations whose disease has progressed on or after treatment with osimertinib and platinum-based chemotherapy. For patients treated with Rybrevant IV in combination with lazertinib in PALOMA-3 that received prophylactic anticoagulants, the overall incidence of VTE events was 11%, with Grade 3 VTE events reported in 1.2% and serious VTE events reported in 1.8%. For information on prophylactic anticoagulants and management of VTE events, see sections 4.2 and 4.4.

Skin and nail reactions

Rash (including dermatitis acneiform), pruritus, and dry skin occurred in 76% of patients treated with amivantamab alone. Most cases were Grade 1 or 2, with Grade 3 rash events occurring in 3% of patients. Rash leading to amivantamab discontinuation occurred in 0.3% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with amivantamab. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 1.8% of patients.

Rash (including dermatitis acneiform), occurred in 83% of patients treated with amivantamab in combination with carboplatin and pemetrexed. Most cases were Grade 1 or 2, with Grade 3 rash events occurring in 14% of patients. Rash leading to amivantamab discontinuation occurred in 2.3% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with amivantamab in combination with carboplatin and pemetrexed. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 4.3% of patients (see section 4.4).

Rash (including dermatitis acneiform), occurred in 89% of patients treated with amivantamab in combination with lazertinib. Most cases were Grade 1 or 2, with Grade 3 rash events occurring in 26.8% of patients. Rash leading to amivantamab discontinuation occurred in 5.5% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated with amivantamab in combination with lazertinib. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 11.4% of patients (see section 4.4).

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, including keratitis (0.5%), occurred in 9% of patients treated with amivantamab alone. Other reported adverse reactions included growth of eyelashes, visual impairment, and other eye disorders. All events were Grade 1-2.

Eye disorders, including keratitis (0.3%), occurred in 11% of patients treated with amivantamab in combination with carboplatin and pemetrexed. Other reported adverse reactions included growth of eyelashes, visual impairment, uveitis, and other eye disorders. All events were Grade 1-2 (see section 4.4).

Eye disorders, including keratitis (2.6%), occurred in 26.4% of patients treated with amivantamab in combination with lazertinib. Other reported adverse reactions

included growth of eyelashes, visual impairment, and other eye disorders. Most events were Grade 1-2 (see section 4.4).

Other special populations

Elderly

There are limited clinical data with amivantamab in patients 75 years of age or over (see section 5.1).

For patients treated with amivantamab alone or in combination with carboplatin and pemetrexed, no overall differences in safety were observed between patients ≥ 65 years of age and patients < 65 years of age.

For patients treated with the combination of amivantamab with Lazertinib, the rates of drug interruptions and dose reductions were similar, however there was a higher incidence of Grade 3 or higher adverse events, and adverse events leading to discontinuation of treatment in patients ≥ 65 years of age compared to patients <65 years of age.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity. In clinical studies of patients with locally advanced or metastatic NSCLC treated with amivantamab, 4 of the 1862 (0.2%) participants who were treated with Rybrevant and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab antibodies. There was no evidence of an altered pharmacokinetic, efficacy, or safety profile due to anti-amivantamab antibodies.

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: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

No maximum tolerated dose has been determined in a clinical study in which patients received up to 2100 mg administered intravenously. There is no known specific antidote for amivantamab 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.

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

Albumin

Amivantamab 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 efficacy and safety

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 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 in combination with lazertinib, osimertinib monotherapy, or lazertinib monotherapy until disease progression or unacceptable toxicity. Rybrevant was administered intravenously at 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks 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 in combination with lazertinib demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) by BICR assessment, with a 30% reduction in the risk of progression or death compared with osimertinib (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002). The corresponding median PFS was 23.72 months (95% CI: 19.12, 27.66) for the Rybrevant in combination with lazertinib arm and 16.59 months (95% CI: 14.78, 18.46) for the osimertinib arm.

The final analysis of OS demonstrated a statistically significant improvement in OS for Rybrevant in combination with lazertinib compared to osimertinib (see Table 10 and Figure 3). Rybrevant in combination with lazertinib also provided a benefit in the time to second progression or death (PFS2) (HR=0.75 [95% CI: 0.58, 0.98], p=0.0314). While the overall response rate (ORR) was comparable between the arms, the median duration of response (DOR) among confirmed responders was longer with Rybrevant in combination with lazertinib (25.76 vs 16.76 months). Rybrevant in combination with lazertinib also provided a benefit in the time to symptomatic progression (TTSP), a measure of the burden of lung cancer symptoms (HR=0.72 [95% CI: 0.57, 0.91], p=0.0049).

Table 10, Figure 1, and Figure 3 summarise efficacy results for Rybrevant in combination with lazertinib.

Table 10: Efficacy results in MARIPOSA

	Rybrevant + 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		

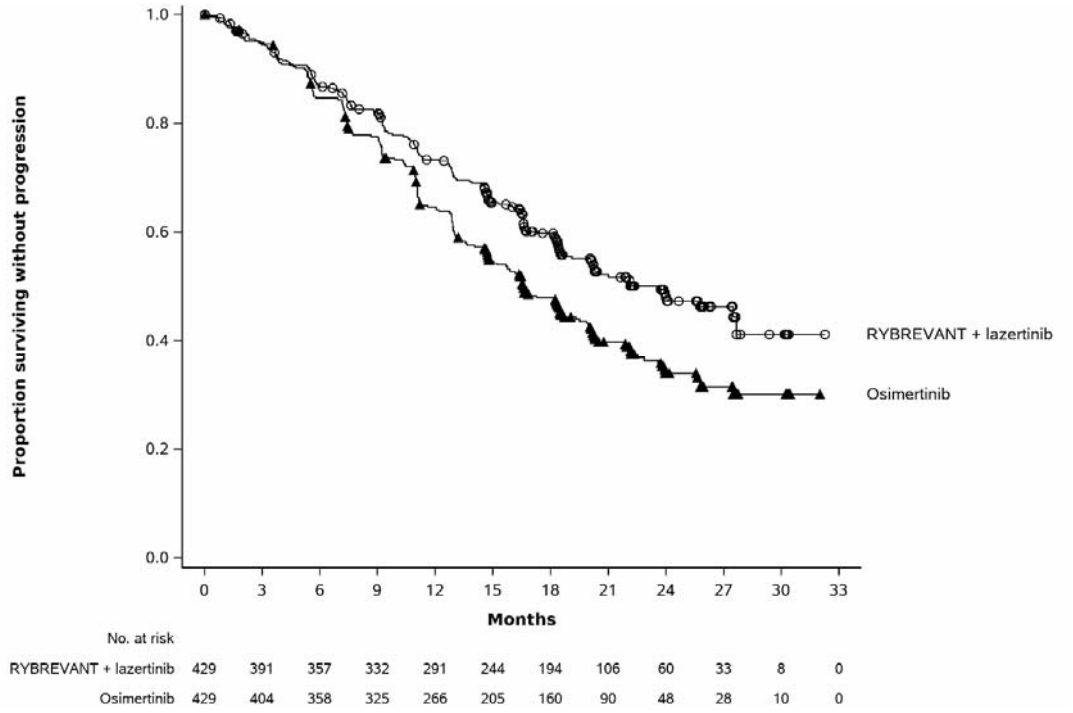
Overall survival (OS)			
Number of events	173 (40%)	217 (51%)	100 (46%)
Median, months (95% CI)	NE (42.9, NE)	36.7 (33.4, 41.0)	38.5 (36.5, 45.4)
Hazard Ratio (95% CI); p-value			
Rybrevant + lazertinib vs osimertinib	0.75 (0.61, 0.92); p=0.0048		
Rybrevant + lazertinib vs lazertinib	0.83 (0.65, 1.06); 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.

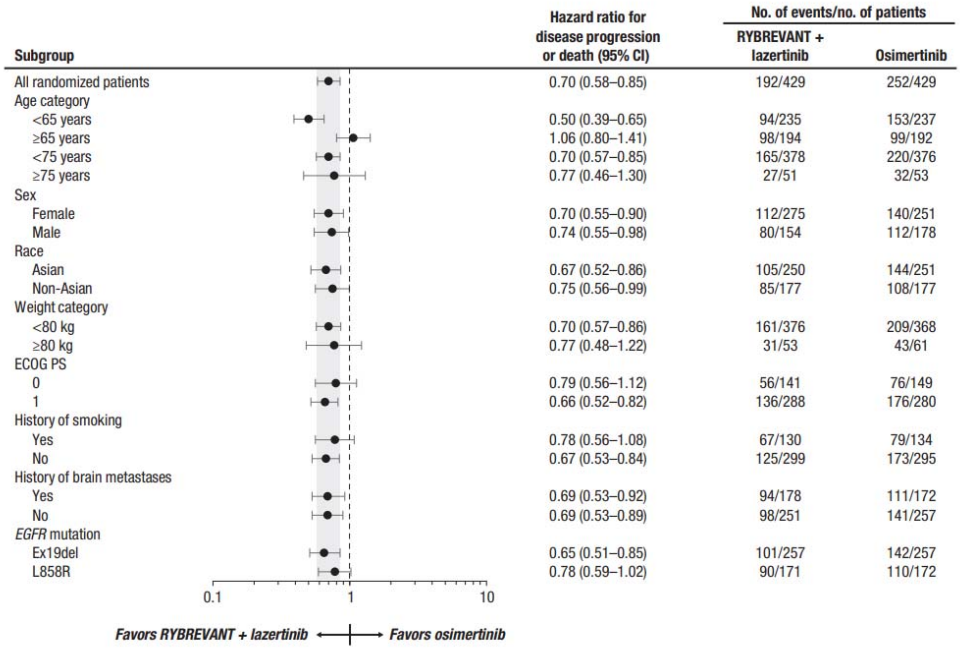
[b] BICR by RECIST v1.1 in confirmed responders

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



The PFS benefit of Rybrevant in combination with lazertinib as compared to osimertinib was generally consistent across prespecified, clinically relevant subgroups, including age group, sex, race, weight, mutation type, ECOG performance status, history of smoking, and history of brain metastasis at study entry (see Figure 2).

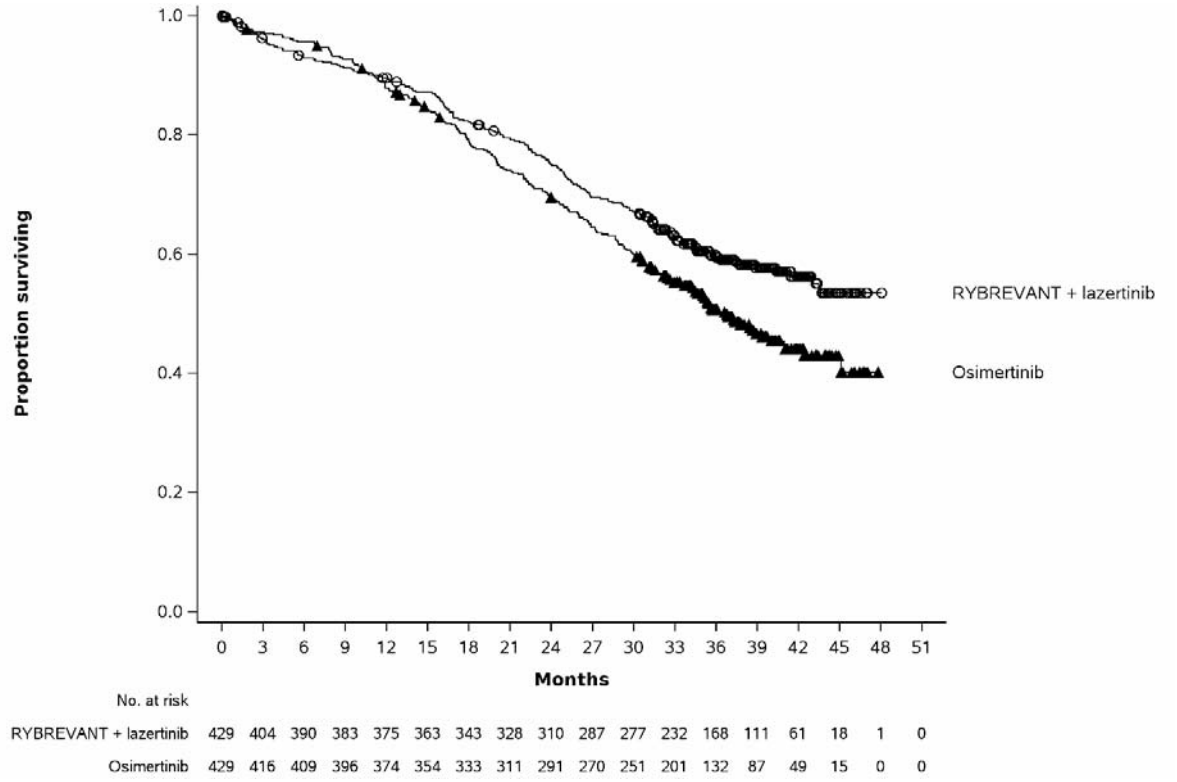
Figure 2: Forest plot: Subgroup analysis of PFS by BICR assessment - MARIPOSA Study



The MARIPOSA study included protocol-mandated brain magnetic resonance imaging (MRIs), which have historically not been used in trials evaluating EGFR-mutated NSCLC. This may have led to earlier detection of recurrences and associated shorter median values for PFS. To account for this, a sensitivity analysis was done whereby patients with brain only progression as the site of first progression were censored. Extracranial PFS based on BICR assessment was consistent with the treatment benefit observed in the primary analysis. The median extracranial PFS was 27.5 months with Rybrevant in combination with lazertinib, as compared to 18.37 months with osimertinib (HR=0.68 [95% CI: 0.55, 0.83], nominal p=0.0001). The stratified analysis of investigator-assessed PFS shows that the improved treatment effect of the combination of Rybrevant and lazertinib relative to osimertinib was also observed when assessed by investigator. Results for the analysis of ORR based on investigator assessment for comparison of the Rybrevant in combination with lazertinib arm versus the osimertinib arm were consistent with results for ORR based on BICR assessment.

With 82% of pre-specified deaths for the analysis reported, there was a favourable trend for overall survival (OS) towards the combination of Rybrevant and lazertinib compared with osimertinib (HR=0.75 [95% CI: 0.61, 0.92]; p=0.0048). A greater proportion of patients treated with Rybrevant in combination with lazertinib were alive at 12 months, 18 months, 24 months, 36 months and 42 months (90%, 82%, 75%, 60% and 56% respectively) compared to patients treated with osimertinib (88%, 79%, 70%, 51% and 44% respectively) (see Figure 3).

Figure 3: Kaplan-Meier curve of OS in previously untreated NSCLC patients



Results of pre-specified analyses of intracranial ORR and DOR by BICR, in the subset of patients with intracranial lesions at baseline for the combination of Rybrevant and lazertinib, demonstrated similar intracranial ORR to the control. Per protocol, all patients in MARIPOSA had serial brain MRIs to assess intracranial response and duration. Results are summarised in Table 11.

Table 11: Intracranial ORR and DOR by BICR assessment in subjects with intracranial lesions at baseline - MARIPOSA

	Rybrevant + 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 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 in combination with carboplatin and pemetrexed (Rybrevant-CP). Additionally, 236 patients were randomised to receive Rybrevant in combination with lazertinib, carboplatin, and pemetrexed in a separate arm of the study. Rybrevant was administered intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. 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.

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-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 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-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 12.

Table 12: Efficacy results in MARIPOSA-2

	Rybrevant+ 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%

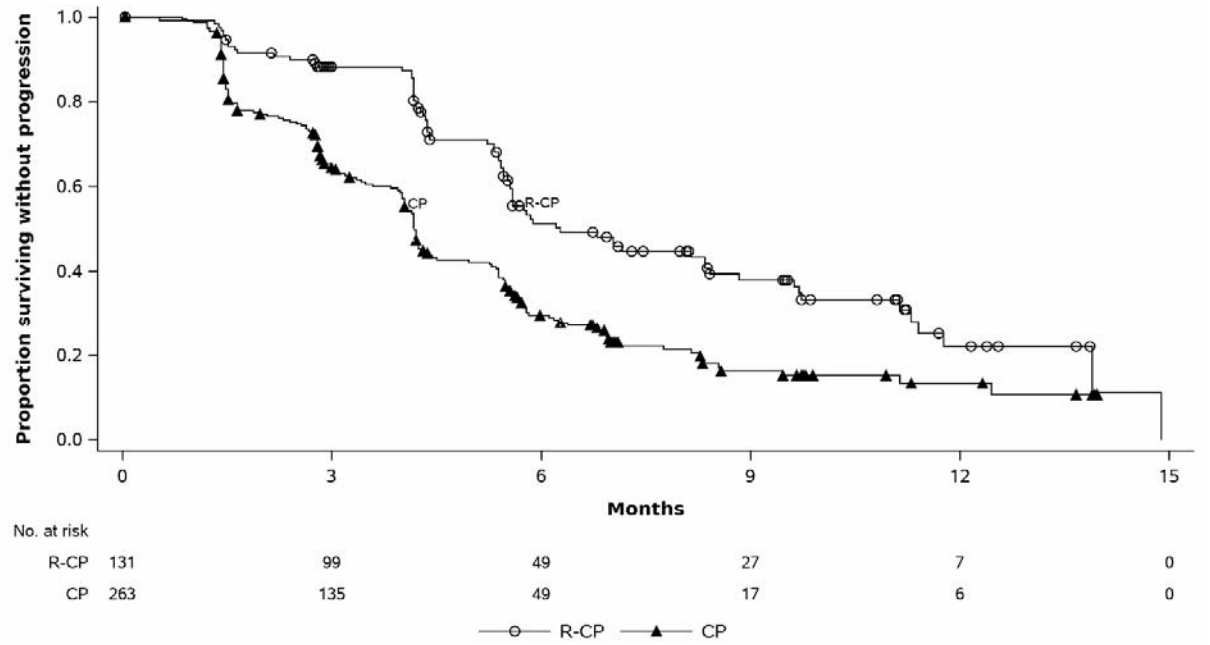
CI = Confidence Interval

PFS 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

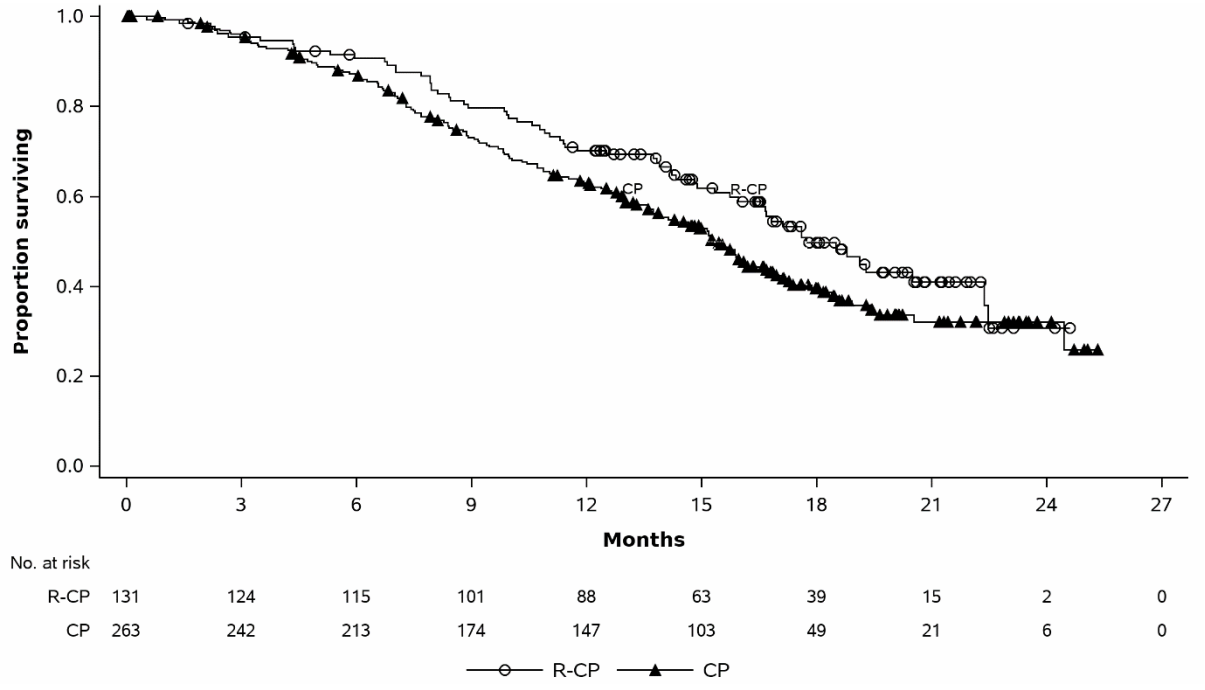
[b] The p-value is compared to a 2-sided significance level of 0.0142. Thus the OS results are not significant as of the second interim analysis.

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



The PFS benefit of Rybrevant-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 5: 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-CP was

associated with a numeric increase in intracranial ORR (23.3% for Rybrevant-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-CP arm compared with 2.2 months; 95% CI (1.4, NE) in the CP arm). The median follow-up for Rybrevant-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 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 was administered intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. 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 monotherapy.

A total of 308 subjects were randomised (1:1) to Rybrevant in combination with carboplatin and pemetrexed (N=153) or carboplatin and pemetrexed (N=155). The median age was 62 (range: 27 to 92) years, with 39% of the subjects ≥ 65 years of age; 58% were female; and 61% were Asian and 36% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (35%) or 1 (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).

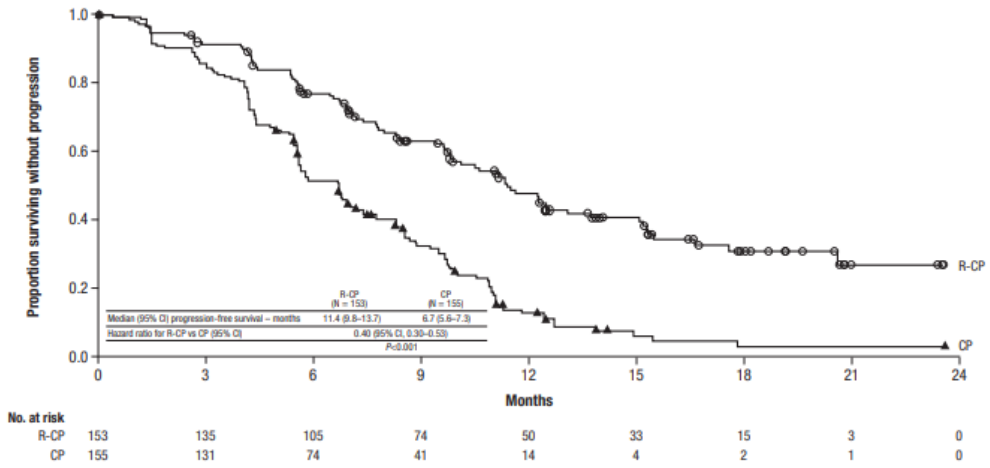
Efficacy results are summarised in Table 13.

Table 13: Efficacy results in PAPILLON

	Rybrevant + carboplatin+ pemetrexed (N=153)	**carboplatin+ pemetrexed (N=155)**
Progression-free survival (PFS) [a]		
Number of events	84 (55%)	132 (85%)
Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI); p-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 monotherapy treatment).

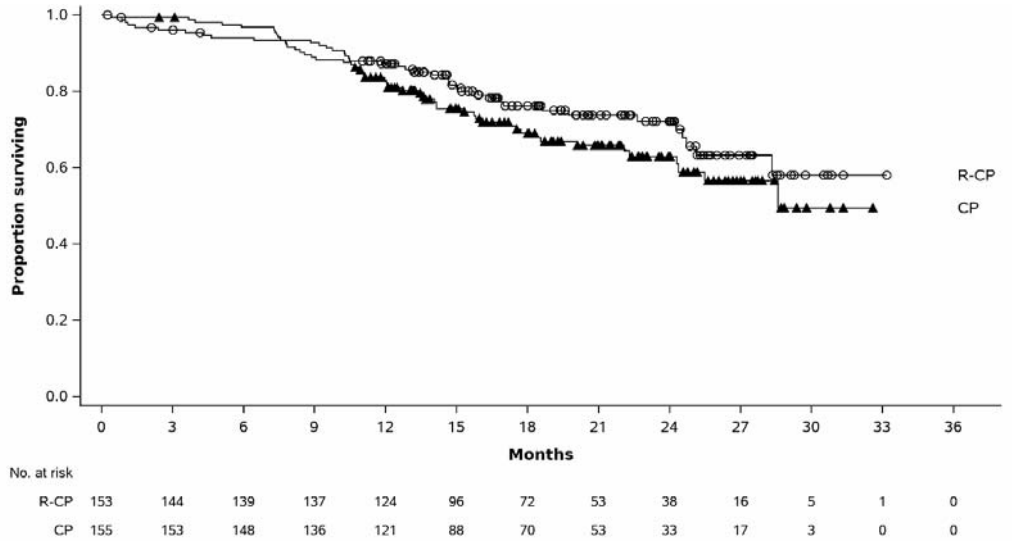
Figure 6: Kaplan-Meier curve of PFS in previously untreated NSCLC patients



The PFS benefit of Rybrevant 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 7: 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 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 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 Eastern Cooperative Oncology Group (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 14.

Table 14: 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.

Elderly

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

Paediatric population

The Licensing Authority has waived the obligation to submit the results of studies with Rybrevant in all subsets of the paediatric population in non-small cell lung cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Based on Rybrevant monotherapy data, amivantamab area under the concentration-time curve ($AUC_{1\ week}$) increases proportionally over a dose range from 350 to 1750 mg.

Based on simulations from the population pharmacokinetic model, $AUC_{1\ week}$ was approximately 2.8-fold higher after the fifth dose for the 2-week dosing regimen and 2.6-fold higher after the fourth dose for the 3-week dosing regimen. Steady-state concentrations of amivantamab were reached by Week 13 for both the 3-week and 2-week dosing regimen and the systemic accumulation was 1.9-fold.

Distribution

Based on the individual amivantamab PK parameter estimates in population PK analysis, the geometric mean (CV%) total volume of distribution, is 5.12 (27.8%) L, following administration of the recommended dose of Rybrevant.

Elimination

Based on the individual amivantamab PK parameter estimates in population PK analysis, the geometric mean (CV%) linear clearance (CL) and terminal half-life associated with linear clearance is 0.266 (30.4%) L/day and 13.7 (31.9%) days 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 pharmacokinetics of Rybrevant 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

Ethylenediaminetetraacetic acid (EDTA) disodium salt dihydrate

L-Histidine

L-Histidine hydrochloride monohydrate

L-Methionine

Polysorbate 80 (E433)

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

3 years

After dilution

Chemical and physical in-use stability has been demonstrated for 10 hours at 15°C to 25°C in room light. From a microbiological point of view, unless the

method of dilution 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 dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

7 mL concentrate in a Type 1 glass vial with an elastomeric closure and aluminium seal with a flip-off cap containing 350 mg amivantamab. Pack size of 1 vial.

6.6 Special precautions for disposal

Prepare the solution for intravenous infusion using aseptic technique as follows:

Preparation

- Determine the dose required and the number of Rybrevant vials needed based on patient's baseline weight (see section 4.2). Each vial contains 350 mg of amivantamab.
- For every 2-week dosing, patients < 80 kg receive 1050 mg and for patients ≥ 80 kg, 1400 mg once weekly for a total of 4 doses, then every 2 weeks starting at Week 5.
- For every 3-week dosing, patients < 80 kg receive 1400 mg once weekly for a total of 4 doses, then 1750 mg every 3 weeks starting at Week 7, and for patients ≥ 80 kg, 1750 mg once weekly for a total of 4 doses, then 2100 mg every 3 weeks starting at Week 7.
- Check that the Rybrevant solution is colourless to pale yellow. Do not use if discolouration or visible particles are present.
- Withdraw and then discard a volume of either 5% glucose solution or sodium chloride 9 mg/mL (0.9%) solution for injection from the 250 mL infusion bag that is equal to the required volume of Rybrevant solution to be added (discard 7 mL diluent from the infusion bag for each vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
- Withdraw 7 mL of Rybrevant from each vial needed then add it to the infusion bag. Each vial contains a 0.5 mL overfill to ensure sufficient extractable volume. The final volume in the infusion bag should be 250 mL. Discard any unused portion left in the vial.
- Gently invert the bag to mix the solution. Do not shake.

- Visually inspect for particulate matter and discolouration prior to administration. Do not use if discolouration or visible particles are observed.

Administration

- Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometre). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
- The administration set with filter must be primed with either 5% glucose solution or 0.9% sodium chloride solution prior to the initiation of each Rybrevant infusion.
- Do not infuse Rybrevant concomitantly in the same intravenous line with other agents.
- The diluted solution should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.
- Due to the frequency of IRRs at the first dose, amivantamab should be infused via a peripheral vein at Week 1 and Week 2; infusion via a central line may be administered for subsequent weeks when the risk of IRR is lower. See infusion rates in section 4.2.

Disposal

This medicinal product is for single use only and any unused medicinal product that is not administered within 10 hours should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

13/01/2026