ANNEX I

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.

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 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").

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 • Weeks 2 to 4 - infusion on Day 1	4
	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 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 350 mg/7 mL Rybrevant 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 from 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
At the initiation of treatment, prophylactic anticoagulants should be administered to prevent VTE events in patients receiving Rybrevant in combination with lazertinib. Consistent with clinical guidelines, patients should receive prophylactic dosing of either a direct acting oral anticoagulant (DOAC) or a low-molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended.

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

Skin and nail reactions
Patients should be instructed to limit sun exposure during and for 2 months after Rybrevant therapy. Alcohol-free emollient cream is recommended for dry areas. 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; 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, 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
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*	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Paracetamol/Acetaminophen (650 to 1000 mg)	Intravenous	15 to 30 minutes
		Oral	30 to 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). Consistent with clinical guidelines, patients should receive prophylactic dosing of either a direct acting oral anticoagulant (DOAC) or a low-molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended.

Signs and symptoms of VTE events should be monitored. Patients with VTE events should be treated with anticoagulation as clinically indicated. For VTE events associated with clinical instability treatment should be withheld until the patient is clinically stable. Thereafter, both drugs can be resumed at the same dose.
In the event of recurrence despite appropriate anticoagulation, Rybrevant should be discontinued. Treatment can continue with lazertinib at the same dose (see section 4.2).

Skin and nail reactions
Rash (including dermatitis acneiform), pruritus and dry skin 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. Alcohol-free emollient cream is recommended for dry areas. A prophylactic approach to rash prevention should be considered. This includes prophylactic therapy with an oral antibiotic (e.g., doxycycline or minocycline, 100 mg twice daily) starting on Day 1 for the first 12 weeks of treatment and after completion of oral antibiotic therapy, topical antibiotic lotion to the scalp (e.g., clindamycin 1%) for the next 9 months of treatment. Non-comedogenic skin moisturiser on the face and whole body (except scalp) and chlorhexidine solution to wash hands and feet should be considered beginning on Day 1 and continued for the first 12 months 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, 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).

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
Toxic epidermal necrolysis	Uncommon	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
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%), hepatotoxicity (47%), oedema (47%), stomatitis (43%), venous thromboembolism (37%), paraesthesia (lazertinib) (34%), fatigue (32%), diarrhoea (29%), constipation (29%), dry skin (26%), pruritis (24%), decreased appetite (24%), hypocalcaemia (21%), nausea (21%) and other eye disorders (21%). The most frequent serious adverse reactions included venous thromboembolism (11%), pneumonia (4.0%), rash (3.1%), ILD/pneumonitis (2.9%), hepatotoxicity (2.4%), COVID-19 (2.4%), and IRR and pleural effusion (2.1%). Twenty-three percent of patients discontinued Rybrevant due to adverse reactions. The most frequent adverse reactions leading to Rybrevant 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
Decreased appetite		24	1.0
Hypocalcaemia		21	2.1
Hypokalaemia		14	3.1
Hypomagnesaemia	Common	5.0	0
Nervous system disorders			
Paraesthesia*‡	Very common	34	1.7
Dizziness*		13	0
Vascular disorders			
Venous thromboembolism*	Very common	37	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/Pneumonitis *	Common	3.1	1.2
Gastrointestinal disorders			
Stomatitis*	Very common	43	2.4
Diarrhoea		29	2.1
Constipation		29	0
Nausea		21	1.2
Vomiting		12	0.5
Abdominal pain*		11	0
Haemorrhoids	Common	10	0.2
Hepatobiliary disorders			
Hepatotoxicity†	Very common	47	9
Skin and subcutaneous tissue disorders			
Rash*	Very common	89	27
Nail toxicity*		71	11
Dry skin*		26	1.0
Pruritus		24	0.5
Palmar-plantar erythrodysaesthesia syndrome	Common	6	0.2
Urticaria		1.2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	Very common	17	0.5
Myalgia		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

* Grouped terms

‡ Assessed as ADR for lazertinib only.

† The most common events included increased ALT (36%), increased AST (29%) and increase blood alkaline phosphatase (12%).

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

In patients treated with amivantamab in combination with lazertinib, infusion-related reactions occurred in 63% 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.

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, including 1 (0.2%) fatal case. 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 37% of the 421 patients receiving Rybrevant in combination with lazertinib. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 11% of patients receiving Rybrevant in combination with lazertinib and deaths occurring in 0.5% of patients receiving Rybrevant in combination with lazertinib. For information on prophylactic anticoagulants and management of VTE events, see sections 4.2 and 4.4.
In patients receiving Rybrevant in combination with lazertinib, the median time to first onset of a VTE event was 84 days. VTE events led to Rybrevant treatment discontinuation in 2.9% of patients.

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 27% 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% of patients (see section 4.4).

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 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).

Special populations

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

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 national reporting system listed in Appendix V.

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, multicenter phase 3 study assessing the efficacy and safety of Rybrevant in combination with lazertinib as compared to osimertinib monotherapy as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Patient samples were required to have one of the two common EGFR mutations (Exon 19 deletion or Exon 21 L858R substitution mutation), as identified by local testing. 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 improvement in progression-free survival (PFS) by BICR assessment.

With a median follow up of approximately 31 months, the updated OS HR was 0.77; (95% CI: 0.61, 0.96; p=0.0185). This was not statistically significant as compared to a 2-sided significance level of 0.00001.

Table 10: Efficacy results in MARIPOSA

	Rybrevant + lazertinib (N=429)	**Osimertinib (N=429)**
Progression-free survival (PFS)[a]		
Number of events	192 (45%)	252 (59%)
Median, months (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
Hazard Ratio (95% CI); p-value	0.70 (0.58, 0.85); p=0.0002	
Overall survival (OS)		
Number of events	142 (33%)	177 (41%)
Median, months (95% CI)	NE (NE, NE)	37.3 (32.5, NE)
Hazard Ratio (95% CI); p-value[b]	0.77 (0.61, 0.96); p=0.0185	
Objective response rate (ORR)[a,c]		
ORR % (95% CI)	80% (76%, 84%)	77% (72%, 81%)

Duration of response (DOR)[a,c]		
Median (95% CI), months	25.8 (20.3, 33.9)	18.1 (14.8, 20.1)

BICR = blinded independent central review; CI = confidence interval; NE = not estimable
PFS results are from data cut-off 11 August 2023 with a median follow-up of 22.0 months. OS, DOR and ORR results are from data cut-off 13 May 2024 with a median follow-up of 31.3 months.

[a] BICR by RECIST v1.1.

[b] The p-value is compared to a 2-sided significance level of 0.00001. Thus the OS results are not statistically significant as of the latest interim analysis.

[c] Based on confirmed responders.

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

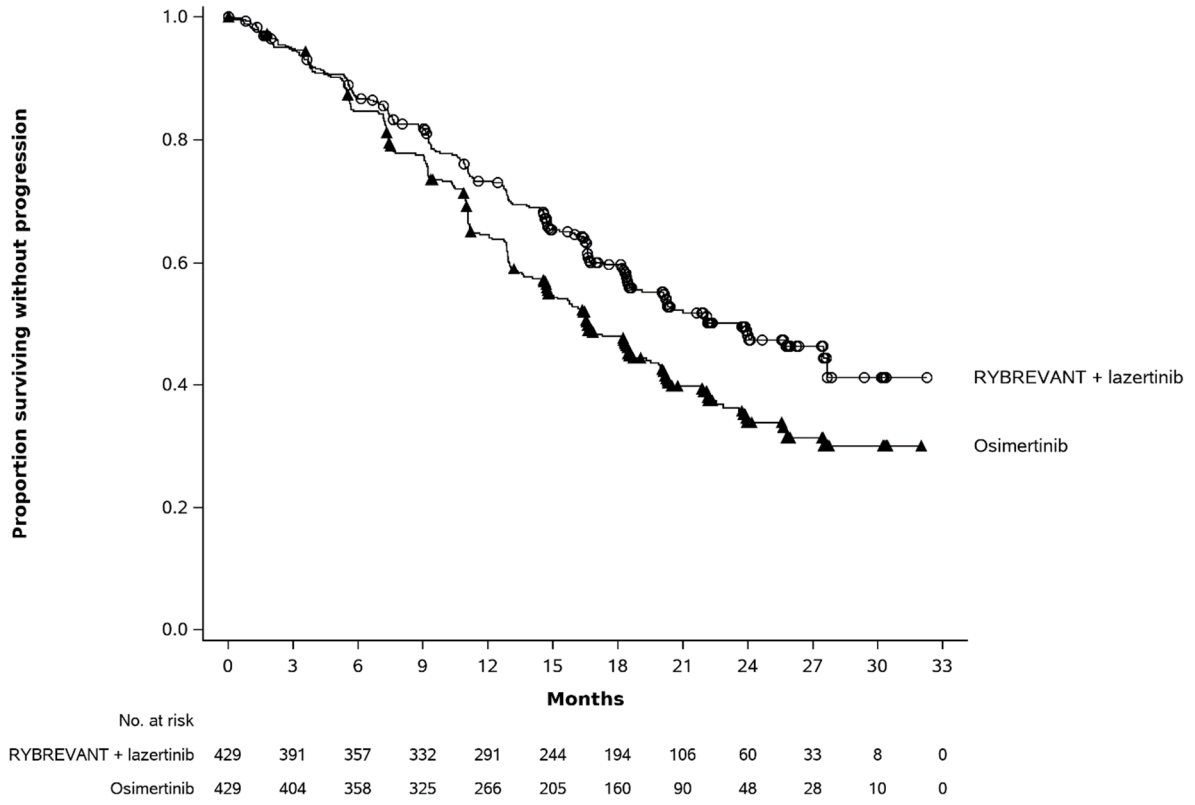
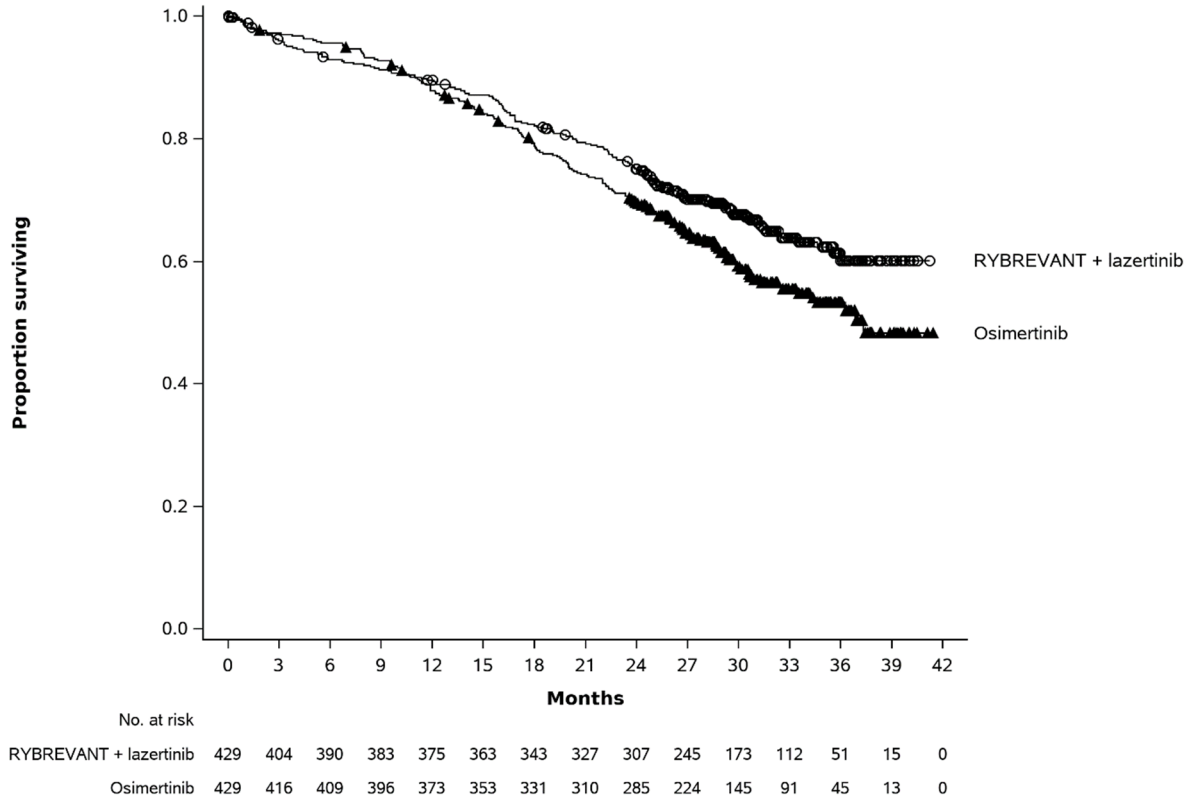


Figure 2: Kaplan-Meier curve of OS in previously untreated NSCLC patients



Intracranial ORR and DOR by BICR were pre-specified endpoints in MARIPOSA. In the subset of patients with intracranial lesions at baseline, the combination of Rybrevant 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)**
Intracranial Tumour Response Assessment		
Intracranial ORR (CR+PR), % (95% CI)	77% (70%, 83%)	77% (70%, 82%)
Complete response	63%	59%
Intracranial DOR		
Number of responders	139	144
Median, months (95% CI)	NE (21.4, NE)	24.4 (22.1, 31.2)

CI = confidence interval
NE = not estimable
Intracranial ORR and DOR results are from data cut-off 13 May 2024 with a median follow-up of 31.3 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, 263 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 on once every 3 weeks until disease progression or unacceptable toxicity.

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

Of the 394 patients randomised to the Rybrevant-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

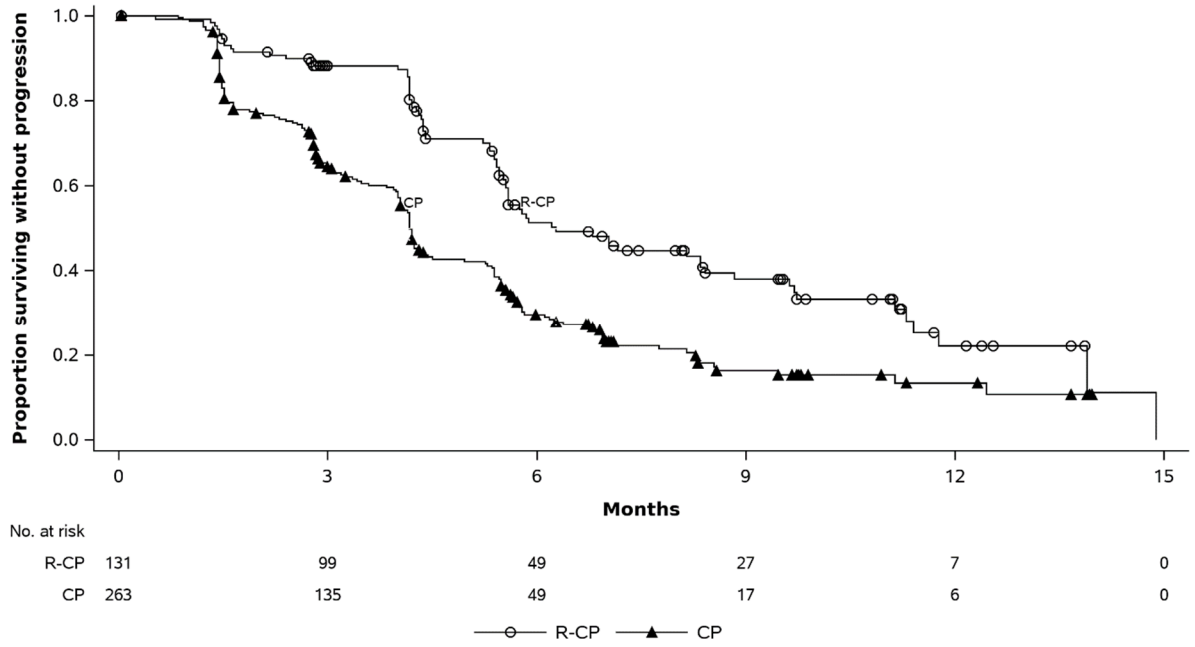
	Rybrevant+ carboplatin+ pemetrexed (N=131)	**carboplatin+ pemetrexed (N=263)**
Progression-free survival (PFS)[a]		
Number of events (%)	74 (57)	171 (65)
Median, months (95% CI)	6.3 (5.6, 8.4)	4.2 (4.0, 4.4)
HR (95% CI); p-value	0.48 (0.36, 0.64); p<0.0001	
Overall survival (OS)		
Number of events (%)	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
NE = not estimable
PFS, DOR and ORR results are from data cut-off 10 July-2023 when hypothesis testing and final analysis for these endpoints was performed. OS results are from data cut-off 26 April 2024 from the second interim OS analysis.

[a] BICR-assessed

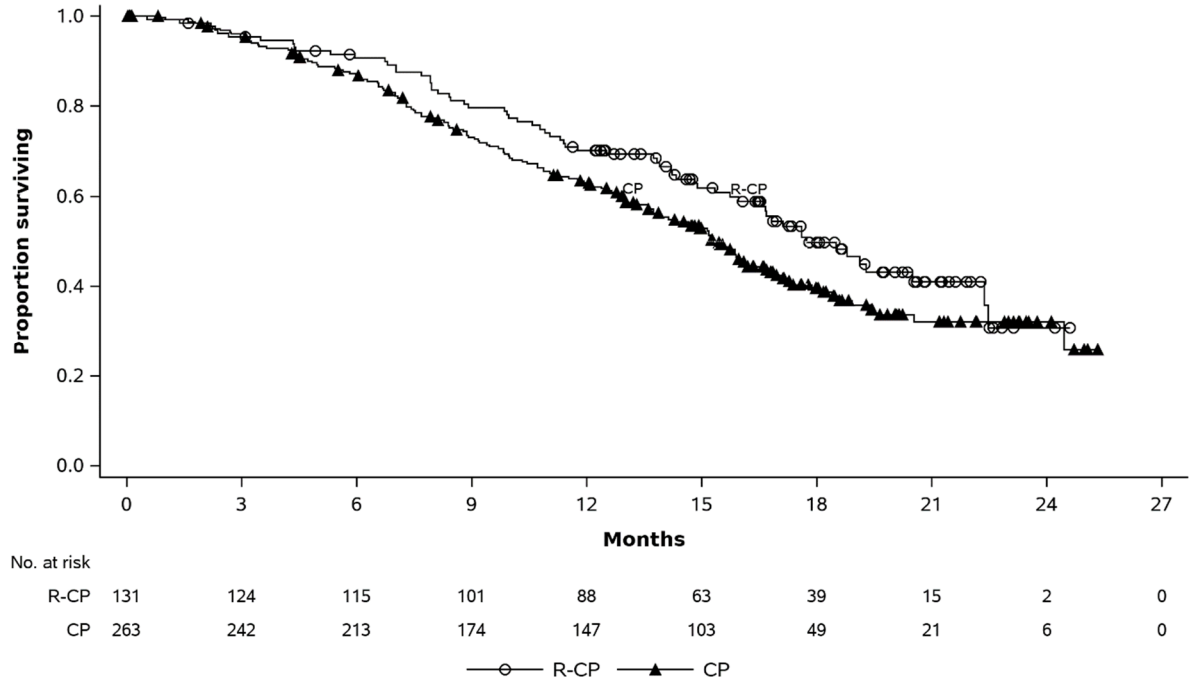
[b] The p-value is compared to a 2-sided significance level of 0.0142. Thus the OS results are not significant as of the second interim analysis.

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



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

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



Intracranial metastases efficacy data

Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to be randomised in MARIPOSA-2. Treatment with Rybrevant-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 on 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 was14.9 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	

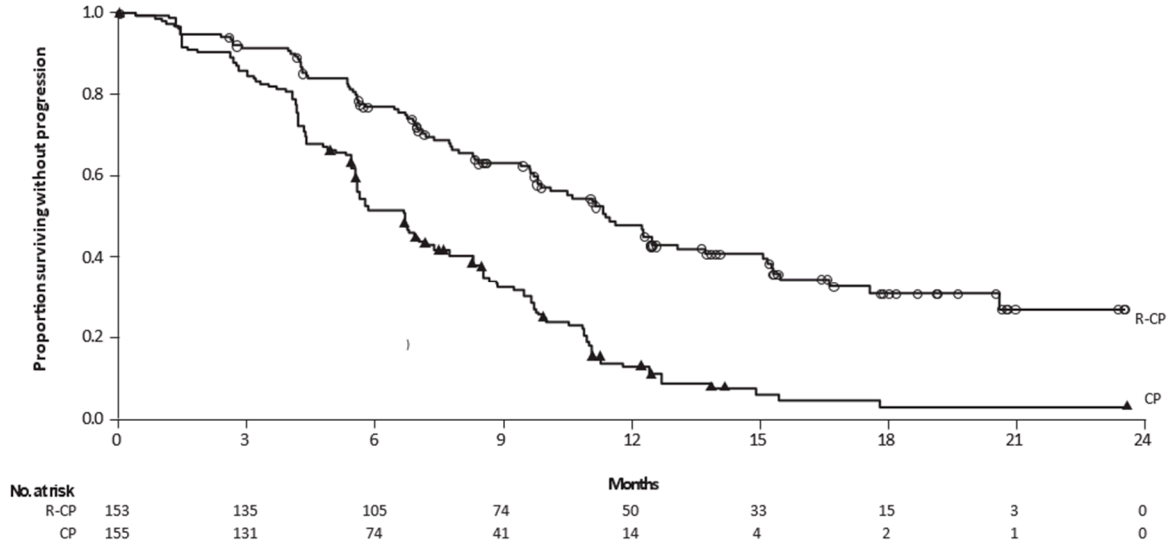
CI = confidence interval
NE = not estimable

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

[b] Based on Kaplan-Meier estimate.

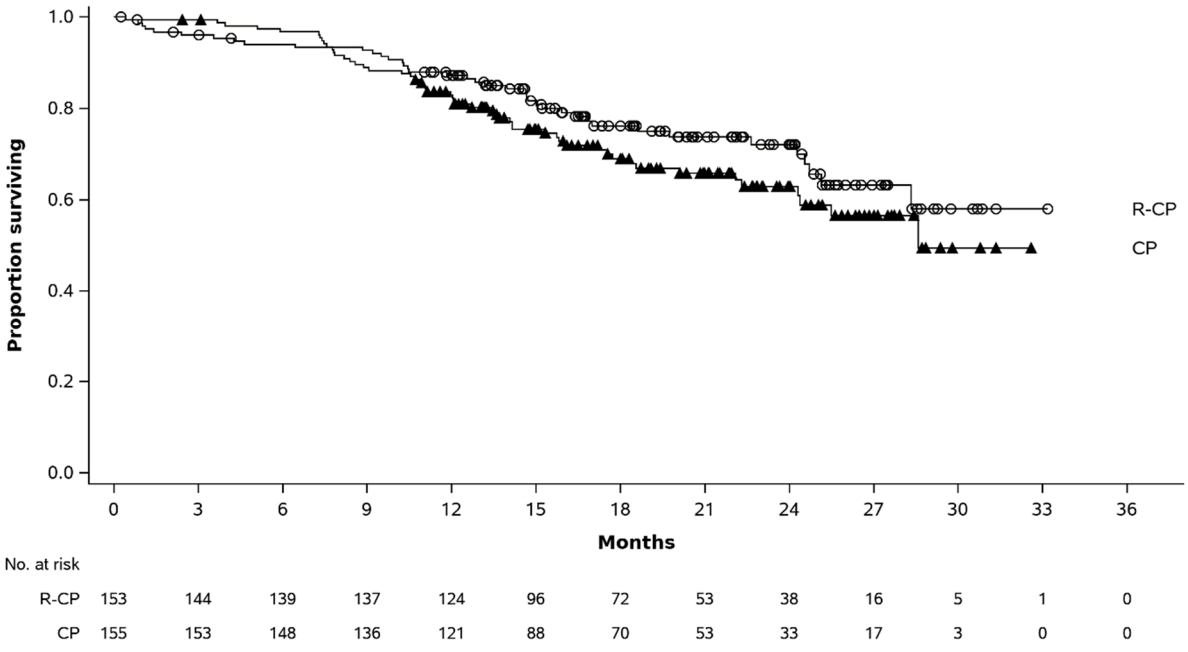
[c] Based on the results of an updated OS with median follow-up of 20.9 months. The OS analysis was not adjusted for the potentially confounding effects of crossover (78 [50.3%] patients on the carboplatin + pemetrexed arm who received subsequent Rybrevant monotherapy treatment).

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



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 6: Kaplan-Meier curve of OS in previously untreated NSCLC patients by BICR assessment



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 European Medicines Agency 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 signaling 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 and other handling

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 micrometer). 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

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1594/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Janssen Sciences Ireland UC
Barnahely
Ringaskiddy, Co. Cork
Ireland

Name and address of the manufacturer responsible for batch release

Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in Article 9 of Regulation (EC) No 507/2006 and, accordingly, the marketing authorisation holder (MAH) shall submit PSURs every 6 months.

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rybrevant 350 mg concentrate for solution for infusion
amivantamab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of 7 mL contains 350 mg of amivantamab (50 mg/mL).

3. LIST OF EXCIPIENTS

Excipients: ethylenediaminetetraacetic acid (EDTA), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use after dilution.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Do not shake.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Store in the original package in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1594/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE OF ADMINISTRATION

Rybrevant 350 mg sterile concentrate
amivantamab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

7 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rybrevant 350 mg concentrate for solution for infusion
amivantamab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rybrevant is and what it is used for

What Rybrevant is
Rybrevant is a cancer medicine. It contains the active substance 'amivantamab', which is an antibody (type of protein) designed to recognise and attach to specific targets in the body.

What Rybrevant is used for
Rybrevant is used in adults with a type of lung cancer called 'non-small cell lung cancer'. It is used when the cancer has spread to other parts of your body and has gone through certain changes in a gene called 'EGFR'.
Rybrevant can be prescribed for you:
- as the first medicine you receive for your cancer in combination with lazertinib.
- in combination with chemotherapy after failure of prior therapy including an EGFR tyrosine kinase inhibitor (TKI).
- as the first medicine you receive for your cancer in combination with chemotherapy, or
- when chemotherapy is no longer working against your cancer.

How Rybrevant works
The active substance in Rybrevant, amivantamab, targets two proteins found on cancer cells:
- epidermal growth factor receptor (EGFR), and
- mesenchymal-epithelial transition factor (MET).

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

Rybrevant may be given in combination with other anti-cancer medicines. It is important that you also read the package leaflets for these other medicines. If you have any questions about these medicines, ask your doctor.

2. What you need to know before you are given Rybrevant

Do not use Rybrevant if
- you are allergic to amivantamab or any of the other ingredients of this medicine (listed in section 6).

Do not use this medicine if the above applies to you. If you are not sure, talk to your doctor or nurse before you are given this medicine.

Warnings and precautions
Tell your doctor or nurse before you are given Rybrevant if:
- you have suffered from inflammation of your lungs (a condition called 'interstitial lung disease' or 'pneumonitis').

Tell your doctor or nurse straight away while taking this medicine if you get any of the following side effects (see section 4 for more information):
- Any side effect while the medicine is being given into your vein.
- Sudden difficulty in breathing, cough, or fever that may suggest inflammation of the lungs. The condition may be life-threatening, therefore healthcare professionals will monitor you for potential symptoms.
- When used with another drug called lazertinib; life-threatening side effects (due to blood clots in the veins) may occur. Your doctor will give you additional medication to help prevent blood clots during the course of your treatment and will monitor you for potential symptoms.
- Skin problems. To reduce the risk of skin problems, keep out of the sun, wear protective clothing, apply sunscreen, and use moisturisers regularly on your skin and nails while taking this medicine. You will need to continue doing this for 2 months after you stop treatment. Your doctor may recommend that you start a medicine(s) to prevent skin problems, may treat you with a medicine(s), or send you to see a skin specialist (dermatologist) if you get skin reactions during treatment.
- Eye problems. If you have vision problems or eye pain contact your doctor or nurse straight away. If you use contact lenses and have any new eye symptoms, stop using contact lenses and tell your doctor straight away.

Children and adolescents
Do not give this medicine to children or young people below 18 years of age. This is because it is not known whether the medicine is safe and effective in this age group.

Other medicines and Rybrevant
Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Contraception
- If you could become pregnant, you must use effective contraception during Rybrevant treatment and for 3 months after stopping treatment.

Pregnancy
- Tell your doctor or nurse before you are given this medicine if you are pregnant, think you might be pregnant, or are planning to have a baby.
- It is possible that this medicine may harm an unborn baby. If you become pregnant while being treated with this medicine, tell your doctor or nurse straight away. You and your doctor will decide if the benefit of having the medicine is greater than the risk to your unborn baby.

Breast-feeding
It is not known if Rybrevant passes into breast milk. Ask your doctor for advice before being given this medicine. You and your doctor will decide if the benefit of breast-feeding is greater than the risk to your baby.

Driving and using machines
If you feel tired, feel dizzy, or if your eyes are irritated or vision is affected after taking Rybrevant, do not drive or use machinery.

Rybrevant contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially 'sodium-free'. However, before Rybrevant is given to you, it may be mixed with a solution that contains sodium. Talk to your doctor if you are on a low salt diet.

Rybrevant contains polysorbate
This medicine contains 0.6 mg of polysorbate 80 in each mL, which is equivalent to 4.2 mg per 7 mL vial. Polysorbates may cause allergic reactions. Tell your doctor if you have any known allergies.

3. How Rybrevant is given

How much is given
Your doctor will work out the correct dose of Rybrevant for you. The dose of this medicine will depend on your body weight at the start of your therapy. You will be treated with Rybrevant once every 2 or 3 weeks according to the treatment your doctor decides for you.

The recommended dose of Rybrevant every 2 weeks is:
- 1050 mg if you weigh less than 80 kg.
- 1400 mg if you weigh more than or equal to 80 kg.

The recommended dose of Rybrevant every 3 weeks is:
- 1400 mg for the first 4 doses and 1750 mg for subsequent doses if you weigh less than 80 kg.
- 1750 mg for the first 4 doses and 2100 mg for subsequent doses if you weigh more than or equal to 80 kg.

How the medicine is given
This medicine will be given to you by a doctor or nurse. It is given as a drip into a vein ('intravenous infusion') over several hours.

Rybrevant is given as follows:
- once a week for the first 4 weeks
- then once every 2 weeks starting at week 5 or once every 3 weeks starting at week 7, for as long as you keep getting benefit from the treatment.

In the first week, your doctor will give you the Rybrevant dose split over two days.

Medicines given during treatment with Rybrevant
Before each infusion of Rybrevant, you will be given medicines which help lower the chance of infusion-related reactions. These may include:
- medicines for an allergic reaction (antihistamines)
- medicines for inflammation (corticosteroids)
- medicines for fever (such as paracetamol).

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

If you are given more Rybrevant than you should
This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose), your doctor will check you for side effects.

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

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor or nurse straight away if you notice the following serious side effects:

Very common (may affect more than 1 in 10 people):
- Signs of a reaction to the infusion - such as chills, feeling short of breath, feeling sick (nausea), flushing, chest discomfort, and vomiting while the medicine is being given. This can happen especially with the first dose. Your doctor may give you other medicines, or the infusion may need to be slowed down or stopped.
- When given together with another medicine called 'lazertinib', a blood clot in the veins, especially in the lungs or legs can occur. Signs may include sharp chest pain, shortness of breath, rapid breathing, leg pain, and swelling of your arms or legs.
- Skin problems - such as rash (including acne), infected skin around the nails, dry skin, itching, pain, and redness. Tell your doctor if your skin or nail problems get worse.

Common (may affect up to 1 in 10 people):
- Eye problems - such as dry eye, swollen eyelid, itchy eyes, problems with vision, growth of eyelashes.
- Signs of an inflammation in the lungs - such as sudden difficulty in breathing, cough, or fever. This could lead to permanent damage ('interstitial lung disease'). Your doctor may wish to stop Rybrevant if you get this side effect.

Uncommon (may affect up to 1 in 100 people):
- inflamed cornea (front part of the eye)
- inflammation inside the eye that may affect vision
- life-threatening rash with blisters and peeling skin over much of the body (toxic epidermal necrolysis).

The following side effects have been reported in clinical studies with Rybrevant in combination with lazertinib:

Other side effects
Tell your doctor if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):
- nail problems
- low level of the protein 'albumin' in the blood
- swelling caused by fluid build up in the body
- sores in the mouth
- increase levels of liver enzymes in the blood
- nerve damage that may cause tingling, numbness, pain or loss of pain sensation
- feeling very tired
- constipation
- diarrhoea
- decreased appetitie
- low level of calcium in the blood
- feeling sick (nausea)
- muscle spasms
- low level of potassium in the blood

- feeling dizzy
- muscle aches
- vomiting
- fever
- stomach pain

Common (may affect up to 1 in 10 people)
- haemorrhoids
- redness, swelling, peeling or tenderness, mainly on the hands or feet (palmar-plantar erythrodysesthesia syndrome)
- low level of magnesium in the blood
- itchy rash (hives)

The following side effects have been reported in clinical studies with Rybrevant when given alone:

Other side effects
Tell your doctor if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):
- low level of the protein 'albumin' in the blood
- swelling caused by fluid build up in the body
- feeling very tired
- sores in the mouth
- constipation or diarrhoea
- decreased appetite
- increased level of the liver enzyme 'alanine aminotransferase' in the blood, a possible sign of liver problems
- increased level of the enzyme 'aspartate aminotransferase' in the blood, a possible sign of liver problems
- feeling dizzy
- increased level of the enzyme 'alkaline phosphatase' in the blood
- muscle aches
- fever
- low level of calcium in the blood

Common (may affect up to 1 in 10 people)
- stomach pain
- low level of potassium in the blood
- low level of magnesium in the blood
- haemorrhoids

The following side effects have been reported in clinical studies with Rybrevant in combination with chemotherapy:

Other side effects
Tell your doctor if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people):
- low number of a type of white blood cell (neutropenia)
- low number of 'platelets'(cells that help blood to clot)
- blood clot in the veins
- feeling very tired
- nausea
- sores in the mouth
- constipation

- swelling caused by fluid build up in the body
- decreased appetite
- low level of the protein ‘albumin’ in the blood
- increased level of the liver enzyme ‘alanine aminotransferase’ in the blood, a possible sign of liver problems
- increased level of the enzyme ‘aspartate aminotransferase’ in the blood, a possible sign of liver problems
- vomiting
- low level of potassium in the blood
- diarrhoea
- fever
- low level of magnesium in the blood
- low level of calcium in the blood

Common (may affect up to 1 in 10 people)
- increased level of the enzyme ‘alkaline phosphatase’ in the blood
- stomach pain
- feeling dizzy
- haemorrhoids
- muscle aches

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Rybrevant

Rybrevant will be stored at the hospital or clinic.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after “EXP”. The expiry date refers to the last day of that month.

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.

Store in a refrigerator (2°C to 8°C). Do not freeze.

Store in the original package in order to protect from light.

Medicines should not be disposed of via wastewater or household waste. Your healthcare professional will throw away any medicines that are no longer being used. These measures will help protect the environment.

6. Contents of the pack and other information

What Rybrevant contains
- The active substance is amivantamab. One mL of concentrate for solution for infusion contains 50 mg of amivantamab. One vial of 7 mL concentrate contains 350 mg of amivantamab.

- The other ingredients are ethylenediaminetetraacetic acid (EDTA), L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injections (see section 2).

What Rybrevant looks like and contents of the pack
Rybrevant is a concentrate for solution for infusion and is a colourless to pale yellow liquid. This medicine is available in a carton pack containing 1 glass vial of 7 mL of concentrate.

Marketing Authorisation Holder
Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

Manufacturer
Janssen Biologics B.V.
Einsteinweg 101
2333 CB Leiden
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Janssen-Cilag NV
Tel/Tél: +32 14 64 94 11
janssen@jacbe.jnj.com

Lietuva
UAB “JOHNSON & JOHNSON”
Tel: +370 5 278 68 88
lt@its.jnj.com

България
„Джонсън & Джонсън България” ЕООД
Тел.: +359 2 489 94 00
jjsafety@its.jnj.com

Luxembourg/Luxemburg
Janssen-Cilag NV
Tél/Tel: +32 14 64 94 11
janssen@jacbe.jnj.com

Česká republika
Janssen-Cilag s.r.o.
Tel: +420 227 012 227

Magyarország
Janssen-Cilag Kft.
Tel.: +36 1 884 2858
janssenhu@its.jnj.com

Danmark
Janssen-Cilag A/S
Tlf.: +45 4594 8282
jacdk@its.jnj.com

Malta
AM MANGION LTD
Tel: +356 2397 6000

Deutschland
Janssen-Cilag GmbH
Tel: 0800 086 9247 / +49 2137 955 6955
jancil@its.jnj.com

Nederland
Janssen-Cilag B.V.
Tel: +31 76 711 1111
janssen@jacnl.jnj.com

Eesti
UAB "JOHNSON & JOHNSON" Eesti filiaal
Tel: +372 617 7410
ee@its.jnj.com

Norge
Janssen-Cilag AS
Tlf: +47 24 12 65 00
jacno@its.jnj.com

Ελλάδα
Janssen-Cilag Φαρμακευτική Μονοπρόσωπη A.E.B.E.
Τηλ: +30 210 80 90 000

España
Janssen-Cilag, S.A.
Tel: +34 91 722 81 00
contacto@its.jnj.com

France
Janssen-Cilag
Tél: 0 800 25 50 75 / +33 1 55 00 40 03
medisource@its.jnj.com

Hrvatska
Johnson & Johnson S.E. d.o.o.
Tel: +385 1 6610 700
jjsafety@JNJCR.JNJ.com

Ireland
Janssen Sciences Ireland UC
Tel: 1 800 709 122
medinfo@its.jnj.com

Ísland
Janssen-Cilag AB
c/o Vistor hf.
Sími: +354 535 7000
janssen@vistor.is

Italia
Janssen-Cilag SpA
Tel: 800.688.777 / +39 02 2510 1
janssenita@its.jnj.com

Κύπρος
Βαρνάβας Χατζηπαναγής Λτδ
Τηλ: +357 22 207 700

Latvija
UAB "JOHNSON & JOHNSON" filiāle Latvijā
Tel: +371 678 93561
lv@its.jnj.com

Österreich
Janssen-Cilag Pharma GmbH
Tel: +43 1 610 300

Polska
Janssen-Cilag Polska Sp. z o.o.
Tel.: +48 22 237 60 00

Portugal
Janssen-Cilag Farmacêutica, Lda.
Tel: +351 214 368 600

România
Johnson & Johnson România SRL
Tel: +40 21 207 1800

Slovenija
Johnson & Johnson d.o.o.
Tel: +386 1 401 18 00
Janssen_safety_slo@its.jnj.com

Slovenská republika
Johnson & Johnson, s.r.o.
Tel: +421 232 408 400

Suomi/Finland
Janssen-Cilag Oy
Puh/Tel: +358 207 531 300
jacfi@its.jnj.com

Sverige
Janssen-Cilag AB
Tfn: +46 8 626 50 00
jacse@its.jnj.com

United Kingdom (Northern Ireland)
Janssen Sciences Ireland UC
Tel: +44 1 494 567 444

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site https://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

This medicinal product must not be mixed with other medicinal products except those mentioned below.

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. Each vial of Rybrevant 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 micrometer). 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.

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.