▼This medicine is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

RYBREVANT® (amivantamab)

concentrate for solution for infusion

1. NAME OF THE MEDICINE

Amivantamab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-use vial contains 350 mg of amivantamab per 7 mL vial (or 50 mg of amivantamab per mL).

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 (see Section 5.1 Mechanism of action).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (injection).

RYBREVANT is available as a colourless to pale yellow preservative-free liquid concentrate for intravenous infusion after dilution.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RYBREVANT is indicated:

- in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations
- in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal-growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations, whose disease has progressed on or after treatment with an EGFR tyrosine kinase inhibitor (TKI)
- in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR exon 20 insertion mutations
- as monotherapy for the treatment of adult patients with locally advanced or metastatic NSCLC with activating EGFR exon 20 insertion mutations whose disease has progressed on or after platinum-based chemotherapy

4.2 DOSE AND METHOD OF ADMINISTRATION

RYBREVANT should be administered by a healthcare professional in a setting with appropriate medical support for the management of infusion-related reactions (IRRs), including equipment for cardiorespiratory resuscitation. See Section 4.4 Special warnings and precautions for use.

Administer pre-infusion medications (see Section 4.2 Pre-infusion medications).

Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 1 and 2, with the initial dose as a split across two infusions - on Day 1 and Day 2 of Week 1.

Prior to the use of RYBREVANT, the presence of EGFR exon 19 deletion, exon 21 L858R substitution, or exon 20 insertion mutation must be established (see Section 5.1 Clinical trials).

When initiating treatment with RYBREVANT in combination with lazertinib, it is recommended to administer anticoagulant prophylaxis to prevent venous thromboembolic (VTE) events for the first four months of treatment. Ongoing anticoagulation beyond four months is at clinician's discretion. Anticoagulants use should align with clinical guidelines, use of Vitamin K antagonists is not recommended (See Section 4.4 Special warnings and precautions for use).

Dosage

Dosage – adults (≥18 years)

Due to the frequency of IRRs at the first dose, infusion into a peripheral vein should be considered in Week 1 and Week 2 to minimise drug exposure in the event of an IRR; a central line may be used subsequently. Particularly for the first dose, prepare the dilution for infusion as close as possible to the time of administration (see subsection *Administration*), to allow for maximal flexibility in IRR management.

Dose regimens

The recommended dose regimen for RYBREVANT is once every two weeks (Q2W; Table 1) when used as monotherapy or in combination with lazertinib, and once every three weeks (Q3W; Table 2) when used in combination with carboplatin and pemetrexed (Table 3).

Table 1: RYBREVANT Q2W dose regimen (amivantamab monotherapy or in combination with lazertinib)

Body weight less than 80 kg at baseline*				
Week	**Dose (per 250 mL bag)**	**Number of 350mg/7mL RYBREVANT vials**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)				
Day 1	350 mg	1	50 mL/hr	75 mL/hr
Day 2	700 mg	2	50 mL/hr	75 mL/hr
Week 2 *Day 1*	1050 mg	3	85 mL/hr	
Week 3 *Day 1*	1050 mg	3	125 mL/hr	
Week 4 *Day 1*	1050 mg	3	125 mL/hr	
Subsequent weeks (every 2 weeks starting at Week 5 onwards)*	1050 mg	3	125 mL/hr	
Body weight greater than or equal to 80 kg at baseline*				
Week	**Dose (per 250 mL bag)**	**Number of 350mg/7mL RYBREVANT vials**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split dose infusion)				
Day 1	350 mg	1	50 mL/hr	75 mL/hr
Day 2	1050 mg	3	35 mL/hr	50 mL/hr
Week 2 *Day 1*	1400 mg	4	65 mL/hr	
Week 3 *Day 1*	1400 mg	4	85 mL/hr	
Week 4 *Day 1*	1400 mg	4	125 mL/hr	
Subsequent weeks (every 2 weeks starting at Week 5 onwards)*	1400 mg	4	125 mL/hr	

* Dose adjustments not required for subsequent body weight changes.

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

When used in combination with lazertinib, it is recommended to administer RYBREVANT any time after lazertinib when given on the same day.

Table 2: RYBREVANT Q3W dose regimen (in combination with carboplatin and pemetrexed)

Body weight less than 80 kg at baseline*				
Week	**Dose (per 250 mL bag)**	**Number of 350mg/7mL RYBREVANT vials**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split-dose infusion)				
Day 1	350 mg	1	50 mL/hr	75 mL/hr
Day 2	1050 mg	3	33 mL/hr	50 mL/hr
Week 2 *Day 1*	1400 mg	4	65 mL/hr	
Week 3 *Day 1*	1400 mg	4	85 mL/hr	
Week 4 *Day 1*	1400 mg	4	125 mL/hr	
Subsequent weeks (every 3 weeks starting at Week 7 onwards)*	1750 mg	5	125 mL/hr	
Body weight greater than or equal to 80 kg at baseline*				
Week	**Dose (per 250 mL bag)**	**Number of 350mg/7mL RYBREVANT vials**	**Initial infusion rate**	**Subsequent infusion rate†**
Week 1 (split-dose infusion)				
Day 1	350 mg	1	50 mL/hr	75 mL/hr
Day 2	1400 mg	4	25 mL/hr	50 mL/hr
Week 2 *Day 1*	1750 mg	5	65 mL/hr	
Week 3 *Day 1*	1750 mg	5	85 mL/hr	
Week 4 *Day 1*	1750 mg	5	125 mL/hr	
Subsequent weeks (every 3 weeks starting at Week 7 onwards)	2100 mg	6	125 mL/hr	

* Dose adjustments not required for subsequent body weight changes

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

Table 3: Order of administration and regimen for RYBREVANT in combination with carboplatin and pemetrexed

Order of administration	Medicine	Dose	Timing	Duration
First	Pemetrexed	500 mg/m^2 IV *	Once every 3 weeks	Until disease progression or unacceptable toxicity
Second	Carboplatin	AUC 5 IV *	Once every 3 weeks	Up to 12 weeks
Last	Amivantamab	(see Table 1) IV	Once every 3 weeks	Until disease progression or unacceptable toxicity

* Refer to the Product Information for the co-administered medicines for more information.

Duration of treatment

Administer RYBREVANT until disease progression or unacceptable toxicity.

Pre-infusion medications

Prior to initial infusion of RYBREVANT (Week 1, Days 1 and 2), administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer antiemetics as needed. Table 4 summarises the recommendations regarding pre-infusion medications.

Table 4: Pre-infusion medications

Medication	Dose	Route of administration	Dosing window prior to RYBREVANT administration
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Paracetamol (500 to 1,000 mg)	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (20 mg) or equivalent	IV	60 to 120 minutes
Glucocorticoid+	Dexamethasone (10 mg) or equivalent	IV	45 to 60 minutes

* Required at all doses.
‡ Required at initial dose (Week 1, Day 1);
+ Required at second dose (Week 1, Day 2); optional for subsequent doses.

Missed dose(s)

If a planned dose of RYBREVANT 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

The recommended dose reductions for adverse reactions (see Table 6) are listed in Table 5.

Table 5: RYBREVANT dose reductions for adverse reactions

Dose*	1st dose reduction	2nd dose reduction	3rd dose modification
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	

*Dose at which the adverse reaction occurred

The recommended dosage modifications for adverse reactions are provided in Table 6.

Table 6: RYBREVANT dosage modifications for adverse reactions

Adverse reaction	Severity	Dose modification
Infusion-related reactions (IRR) (see section 4.4)	Grade 1 to 3	• Interrupt infusion at the first sign of IRRs • Give supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) as clinically indicated • Upon resolution of symptoms, resume infusion at 50% of the previous rate • If there are no additional symptoms, the rate may be increased per the instructions in Table 1 and 2 • Administer pre-medications prior to next dose
	Recurrent Grade 3 or Grade 4	Permanently discontinue
Interstitial lung disease / pneumonitis (see section 4.4)	Suspected ILD/ pneumonitis	Withhold
	Confirmed ILD/ pneumonitis	Permanently discontinue
Venous Thromboembolic (VTE) Events *(Applies to the combination with lazertinib, see section 4.4)*	Grade 2 or 3	Withhold RYBREVANT and lazertinib until the patient is clinically stable. Thereafter, both drugs can be resumed at the same dose, at the discretion of the treating physician.
	Grade 4 or recurrent Grade 2 or 3 VTE despite therapeutic level anticoagulation	Permanently discontinue RYBREVANT. Treatment can continue with lazertinib at the same dose, if clinically warranted.
Skin and nail reactions (see section 4.4)	Grade 1	• Initiate supportive care • Reassess after 2 weeks
	Grade 2	• Initiate supportive care • If there is no improvement after 2 weeks, consider reducing the dose (see Table 5)
	Grade 3	• Initiate supportive care • Withhold until the adverse reaction improves to ≤ Grade 2 • Resume at reduced dose (see Table 5) • If no improvement within 2 weeks, permanently discontinue
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions such as toxic epidermal necrolysis (TEN))	Permanently discontinue

Adverse reaction	Severity	Dose modification
Other adverse reactions (see section 4.8)	Grade 3	• Withhold until adverse reaction improves to ≤ Grade 1 or baseline • Resume at same dose if recovery occurs within 1 week • Resume at reduced dose (see Table 5) if recovery occurs after 1 week • Permanently discontinue if recovery does not occur within 4 weeks
	Grade 4	• Withhold until adverse reaction improves to ≤Grade 1 or baseline • Resume at reduced dose (see Table 5) if recovery occurs within 4 weeks • Permanently discontinue if recovery does not occur within 4 weeks • Permanently discontinue for recurrent Grade 4 reactions

Special populations

Paediatrics (17 years of age and younger)

The safety and efficacy of RYBREVANT have not been established in paediatric patients.

Elderly (65 years of age and older)

Of the 661 patients treated with RYBREVANT in EDI1001 (CHRYSALIS), NSC3001 (PAPILLON) and NSC3002 (MARIPOSA-2), 40% were 65 years of age or older, and 10% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these patients and younger patients. No dosage adjustment is necessary (see Section 5.2 Pharmacokinetic properties).

Renal impairment

No formal studies of amivantamab in patients with renal impairment have been conducted. Based on population pharmacokinetic (PK) analyses, no dosage adjustment is necessary for patients with mild or moderate renal impairment. No data are available in patients with severe renal impairment (see Section 5.2 Pharmacokinetic properties).

Hepatic impairment

No formal studies of amivantamab in patients with hepatic impairment have been conducted. Based on population PK analyses, no dosage adjustment is necessary for patients with mild hepatic impairment. No data are available in patients with moderate or severe hepatic impairment (see Section 5.2 Pharmacokinetic properties).

Administration

Preparation for administration

RYBREVANT solution must be diluted and prepared for intravenous infusion by a healthcare professional using aseptic technique.

1. Determine the dose required and number of RYBREVANT vials needed based on patient's baseline weight (see Table 1 and 2). Each vial of RYBREVANT contains 350 mg of amivantamab.
2. Check that the RYBREVANT solution is colourless to pale yellow. Do not use if discolouration or visible particles are present.
3. Withdraw and then discard a volume of either 5% dextrose [glucose] solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).

4. Withdraw 7 mL of RYBREVANT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a 0.5 mL overfill to ensure sufficient extractable volume. Discard any unused portion left in the vial.
5. Gently invert the bag to mix the solution. Do not shake.
6. Visually inspect the diluted solution before administration. Do not use if discolouration or visible particles are observed.
7. Diluted solutions should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

Administration

1. Prior to administration, prime the infusion set with the diluent (either 5% dextrose [glucose] solution or 0.9% sodium chloride solution)
2. 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 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
3. Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.
4. Product is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

Hypersensitivity to amivantamab or to any of the excipients listed in section 6.1 List of Excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The data described in Special Warnings and Precautions for Use reflects the safety profile of patients with locally advanced or metastatic NSCLC, including 380 patients who received RYBREVANT monotherapy in Study EDI1001(CHRYSALIS), 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed in Study NSC3001 (PAPILLON), 130 patients who received RYBREVANT in combination with carboplatin and pemetrexed in Study NSC3002 (MARIPOSA-2) and 421 patients who received RYBREVANT in combination with lazertinib in Study NSC3003 (MARIPOSA),

Infusion-related reactions

IRRs may occur in patients treated with RYBREVANT. The most frequent signs and symptoms include chills, nausea, dyspnoea, flushing, chest discomfort, and vomiting.

IRRs were reported in 61% of patients treated with RYBREVANT, of which 93% were Grade 1-2. A majority of IRRs occurred at the first infusion with a median time to onset of 60 minutes. Signs and symptoms of IRR include dyspnoea, flushing, fever, chills, chest discomfort, hypotension, nausea and vomiting.

To reduce the risk of IRRs, premedicate with antihistamines, antipyretics, and glucocorticoids, and follow the infusion recommendations in Section 4.2 Dose and method of administration.

Give RYBREVANT infusions in a monitored setting with appropriate medical support for the treatment of IRRs, including cardiopulmonary resuscitation medication and equipment. Interrupt infusion if IRR is suspected, and reduce infusion rate or permanently discontinue RYBREVANT based on severity (see Section 4.2 Dose and method of administration, Table 6).

Interstitial lung disease/pneumonitis

Interstitial lung disease (ILD)/pneumonitis occurred in 2.7% of patients treated with RYBREVANT, including 0.1% fatal events. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD have not been studied.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed (see Section 4.2 Dose and method of administration, Table 6).

Venous Thromboembolic (VTE) Events with concomitant use with lazertinib

In patients receiving RYBREVANT in combination with lazertinib, venous thromboembolic (VTE) events, including deep venous thrombosis (DVT) and pulmonary embolism (PE) occurred in 36% of patients, predominantly in the first four months of therapy, including 0.5% fatal events. Prophylactic anticoagulants are recommended to be used for the first four months of treatment. Ongoing anticoagulation beyond four months is at clinician's discretion. Anticoagulants use should align with clinical guidelines, use of Vitamin K antagonists is not recommended.

For VTE events associated with clinical instability, RYBREVANT and lazertinib should be withheld until the patient is clinically stable. Thereafter, both drugs can be resumed at the discretion of the treating physician.

In the event of recurrence despite appropriate anticoagulation, permanently discontinue RYBREVANT. Treatment can continue with lazertinib at the same dose, if clinically warranted(see section 4.2 Dose and method of administration, Table 6).

Skin and nail reactions

Skin and nail reactions may occur in patients treated with RYBREVANT.

Rash (including dermatitis acneiform), pruritis and dry skin occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 15.5% of patients. Rash leading to RYBREVANT discontinuation occurred in 2.9% 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 RYBREVANT. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 6.3% of patients.

Toxic epidermal necrolysis (TEN) has been reported . Permanently discontinue RYBREVANT if TEN is confirmed.

A prophylactic approach to rash prevention should be considered. Instruct patients to limit sun exposure during and for 2 months after RYBREVANT therapy. Protective clothing and use of sunscreen is advisable. Alcohol-free emollient cream is recommended for dry skin. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 or poorly-tolerated Grade 2 events, add systemic antibiotics and oral steroids and consider dermatology consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce, or permanently discontinue RYBREVANT based on severity (see Section 4.2 Dose and method of administration, Table 6).

Eye disorders

Eye disorders, including keratitis (1.3%) and uveitis (0.09%) occurred in patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperaemia, conjunctival hyperaemia and blepharitis. Most events were Grade 1-2. Refer patients presenting with worsening eye symptoms promptly to

an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated. Withhold, dose reduce, or permanently discontinue RYBREVANT based on severity (see Section 4.2 Dose and method of administration, Table 6).

Use in the elderly

See section 4.2 Dose and method of administration.

Paediatric use

The safety and efficacy of RYBREVANT have not been established in paediatric patients.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No drug interaction studies have been performed.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effect of amivantamab on fertility has not been studied.

Use in pregnancy – Pregnancy Category D

Based on its mechanism of action and findings in animal studies, amivantamab could cause fetal harm if administered to a pregnant patient. Whilst the use of amivantamab during pregnancy has not been studied, administration of other EGFR or MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryolethality, and abortion. Human IgG1 is known to cross the placenta; therefore, amivantamab has the potential to be transmitted from a pregnant patient to the developing fetus. Advise patients of the potential risk to a fetus. Advise female patients of reproductive potential to use effective contraception (such as condoms) during treatment and for 3 months after the last dose of RYBREVANT. Advise male patients not to donate or store semen and to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT.

Use in lactation

It is not known whether amivantamab is excreted in milk or affects milk production. Because of the potential for serious adverse reactions from RYBREVANT in a breastfed child, advise patients not to breastfeed during treatment with RYBREVANT and for 3 months following the last dose of RYBREVANT.

4.7 EFFECTS OF ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed. If patients experience treatment-related symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines whilst affected.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical trial data

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

First-line treatment of NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation

The safety data described below reflect exposure to RYBREVANT in combination with lazertinib in 421 treatment-naïve patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletion or exon 21 L858R substitution mutation in MARIPOSA.

Patients received lazertinib 240 mg orally once daily and RYBREVANT 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. Median treatment duration was 18.5 months (range: 0.2 to 31.4 months) for the RYBREVANT in combination with lazertinib arm and the median treatment duration was 18.00 months (range: 0.2 to 32.7 months) for the osimertinib arm. Among the 421 patients who received RYBREVANT in combination with lazertinib, 73% were exposed to RYBREVANT for ≥ 6 months and 60% were exposed to RYBREVANT for > 1 year.

Serious adverse reactions occurred in 49% of patients who received RYBREVANT in combination with lazertinib. Serious adverse reactions occurring in ≥ 2% of patients included VTE (11%), pneumonia (4%), rash, and ILD/pneumonitis (2.9% each), COVID-19 (2.4%), pleural effusion and IRR (2.1% each). Fatal adverse reactions occurred in 7% of patients who received RYBREVANT in combination with lazertinib due to death not otherwise specified (1.2%); sepsis and respiratory failure (1% each); pneumonia, myocardial infarction and sudden death (0.7% each); cerebral infarction, pulmonary embolism (PE), and COVID-19 infection (0.5% each); and ILD/pneumonitis, acute respiratory distress syndrome (ARDS), and cardiopulmonary arrest (0.2% each).

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 34% of patients. Adverse reactions which resulted in permanent discontinuation in ≥ 1% of patients included rash, IRR, nail toxicity, VTE, ILD/pneumonitis, pneumonia, oedema, hypoalbuminaemia, fatigue, paraesthesia and dyspnoea.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 88% of patients. Adverse reactions which required dosage interruption in ≥ 5% of patients were IRRs, rash, nail toxicity, COVID-19, VTE, increased ALT, oedema, and hypoalbuminaemia.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 46% of patients. Adverse reactions requiring dose reductions in ≥ 5% of patients were rash and nail toxicity.

The most common adverse reactions (≥ 20%) were rash, nail toxicity, IRR, musculoskeletal pain, stomatitis, oedema, VTE, paraesthesia, fatigue, diarrhoea, constipation, COVID-19, haemorrhage, dry skin, decreased appetite, pruritus, and nausea. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, decreased sodium, increased alanine aminotransferase, decreased potassium, decreased haemoglobin, increased aspartate aminotransferase, increased gamma glutamyl transferase, and increased magnesium.

Table 7 summarises the adverse reactions (≥ 10%) in MARIPOSA.

Table 7: Adverse reactions (≥ 10%) in firstline patients with NSCLC with exon 19 insertion or exon 21 L858R substitution mutations in MARIPOSA

Adverse Reaction	RYBREVANT in combination with lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash*	86	26	48	1.2
Nail toxicity*	71	11	34	0.7
Dry skin*	25	1	18	0.2
Pruritus	24	0.5	17	0.2
Injury, poisoning and procedural complications				
Infusion-related reaction+	63	6	0	0
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	47	2.1	39	1.9
Gastrointestinal disorders				
Stomatitis*	43	2.4	27	0.5
Diarrhoea*	31	2.6	45	0.9
Constipation	29	0	13	0
Nausea	21	1.2	14	0.2
Vomiting	12	0.5	5	0
Abdominal pain*	11	0	10	0
Haemorrhoids	10	0.2	2.1	0.2
General disorders and administration site conditions				
Oedema*	43	2.6	8	0
Fatigue*	32	3.8	20	1.9
Pyrexia	12	0	9	0
Vascular disorders				
Venous thromboembolism*	36	11	8	2.8
Haemorrhage*	25	1	13	1.2
Nervous system disorders				
Paresthesia*	35	1.7	10	0.2
Dizziness*	14	0	10	0
Headache*	13	0.2	13	0
Infections and infestations				
COVID-19	26	1.7	24	1.4
Conjunctivitis	11	0.2	1.6	0
Metabolism and nutrition disorders				
Decreased appetite	24	1	18	1.4
Respiratory, thoracic, and mediastinal disorders				
Cough*	19	0	23	0
Dyspnoea*	14	1.7	17	3.5
Eye disorders				
Ocular toxicity*	16	0.7	7	0
Psychiatric disorders				
Insomnia	10	0	11	0

* Grouped terms
+ Applicable for RYBREVANT only

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT in combination with lazertinib included ILD/pneumonitis (3.1%).

Laboratory abnormalities

Table 8 summarises the laboratory abnormalities in MARIPOSA.

Table 8: Select laboratory abnormalities (≥ 20%) that worsened from baseline in firstline patients with NSCLC with EGFR exon 19 insertion or exon 21 L858R substitution mutations in MARIPOSA[+]

Laboratory abnormality	RYBREVANT + lazertinib (N=421)		osimertinib (N=428)	
	All grades (%)	Grades 3 or 4 (%)	All grades (%)	Grades 3 or 4 (%)
Chemistry				
Decreased albumin	89	8	22	<1
Increased alanine aminotransferase	65	7	29	3
Increased aspartate aminotransferase	52	4	36	2
Increased alkaline phosphatase	45	<1	15	<1
Decreased calcium (Corrected)	41	1	27	1
Increased gamma glutamyl transferase	39	3	24	2
Decreased sodium	38	7	35	5
Decreased potassium	30	5	15	1
Increased creatinine	26	1	35	1
Decreased magnesium	25	1	10	<1
Increased magnesium	12	3	20	5
Haematology				
Decreased platelet count	52	1	57	1
Decreased haemoglobin	47	4	56	2
Decreased white blood cell	38	1	66	1
Decreased neutrophil count	15	1	33	1

[+] The denominator used to calculate the rate is the number of patients with a baseline value and at least one post-treatment value for the specific lab test.

Treatment of NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after prior therapy

The safety of RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage (see Table 1 and 2) was evaluated in the MARIPOSA-2 study *(*see section 5.1 Pharmacodynamic Properties - Clinical trials), conducted in patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations whose disease had progressed on or after treatment with osimertinib. The median (range) treatment duration was 6.3 (0 to 14.7) months amongst 130 patients who received the combination including RYBREVANT, and 3.7 (0 to 15.9) months amongst 243 patients who received carboplatin plus pemetrexed in the comparator arm.

The median age was 62 years (range: 36 to 84 years); 62% were female; 48% were Asian, and 46% were White; and 87% had baseline body weight <80 kg.

Serious adverse reactions occurred in 32% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions that were reported in >2% of patients included dyspnoea (3.1%), thrombocytopenia (3.1%), sepsis (2.3%), and pulmonary embolism (2.3%). Fatal adverse reactions occurred in 2.3% of patients who received RYBREVANT in combination with carboplatin and pemetrexed; these included respiratory failure, sepsis, and ventricular fibrillation (0.8% each).

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 60% of patients. IRR requiring infusion interruptions occurred in 52% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included infusion-related reactions, rash and fatigue.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 17% of patients. Adverse reactions requiring dose reductions in ≥2% of patients included rash.

Eleven percent of patients permanently discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions that led to treatment discontinuation (≥5% of patients) were IRRs.

Table 9 summarises the most common adverse reactions in MARIPOSA-2.

Table 9: Adverse reactions (≥10%) in previously treated patients with NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations treated with RYBREVANT in combination with carboplatin and pemetrexed in MARIPOSA-2

System organ class Adverse reaction	**RYBREVANT + Carboplatin + Pemetrexed (N=130)**		**Carboplatin + Pemetrexed (N=243)**	
	All Grades (%)	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders				
Rash*	72	11	12	0
Nail toxicity*	45	2.3	0.4	0
Pruritus	15	0	7.0	0
Dry skin*	15	0	2.5	0
General disorders and administration site conditions				
Infusion-related reaction	59	5.4	0.4	0
Fatigue*	51	3.8	35	3.7
Oedema*	36	1.5	11	0.4
Pyrexia	12	0	10	0
Gastrointestinal disorders				
Nausea	45	0.8	37	0.8
Constipation	39	0.8	30	0
Stomatitis*	35	2.3	11	0
Vomiting	25	0.8	17	0.4
Diarrhoea*	15	1.5	7	0.8
Metabolism and nutrition disorders				
Decreased appetite	31	0	21	1.2
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain*	30	3.1	19	0.8
Infections and infestations				
COVID-19	21	1.5	10	0
Eye disorders				
Ocular toxicity*	17	0	3.7	0
Vascular disorders				
Haemorrhage*	14	0.8	4.9	0
Venous thromboembolism* (VTE)	10	2.3	4.5	2.9
Respiratory, thoracic, and mediastinal disorders				
Cough*	14	0	16	0.4
Dyspnoea*	13	1.5	8	1.2

* Grouped term

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT in combination with carboplatin and pemetrexed include: abdominal pain, haemorrhoids, dizziness, visual impairment, trichomegaly, keratitis, and interstitial lung disease.

Table 10 summarises the laboratory abnormalities in MARIPOSA-2.

Table 10: Select laboratory abnormalities (≥ 20%) that worsened from baseline in patients with NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations treated with RYBREVANT in combination with carboplatin and pemetrexed in MARIPOSA-2

Laboratory abnormality	RYBREVANT + Carboplatin + Pemetrexed (N=130)		Carboplatin + Pemetrexed (N=243)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased albumin	73	4	26	<1
Decreased sodium	48	11	30	6
Increased aspartate aminotransferase	47	1	52	1
Increased alkaline phosphatase	42	0	29	<1
Increased alanine aminotransferase	39	4	56	6
Decreased magnesium	38	1	17	<1
Decreased potassium	37	11	12	3
Increased gamma glutamyl transferase	30	3	41	1
Decreased calcium (corrected)	25	0	11	1
Haematology				
Decreased white blood cell	90	42	85	19
Decreased neutrophil count	74	49	64	25
Decreased platelet count	74	17	58	9
Decreased haemoglobin	71	12	77	9
Decreased lymphocyte count	69	28	58	18

First-line treatment of NSCLC with exon 20 insertion mutations

The safety of RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage (see Table 1 and 2) was evaluated in the PAPILLON study (see section 5.1 Pharmacodynamic Properties - Clinical trials) conducted in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Among 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed the median exposure was 9.7 months (range: 0.0 to 26.9 months).

The median age was 61 years (range: 27 to 86 years); 56% were female; 64% were Asian, 32% were White and 86% had baseline body weight <80 kg.

Serious adverse reactions occurred in 37% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions in ≥2% of patients included rash, pneumonia, interstitial lung disease, pulmonary embolism, vomiting, and COVID-19. Fatal adverse reactions occurred in 7 patients (4.6%) due to pneumonia, cerebrovascular accident, cardio-respiratory arrest, COVID-19, sepsis, and death not otherwise specified.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were rash and ILD.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 64% of patients. IRR requiring infusion interruptions occurred in 38% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included rash, nail toxicity, and hypokalaemia.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 36% of patients. Adverse reactions requiring dose reductions in ≥5% of patients included rash, and nail toxicity.

Table 11 summarises the most common adverse reactions in PAPILLON.

Table 11: Adverse reactions (≥10%) in first-line patients with NSCLC with exon 20 insertion mutations treated with RYBREVANT in combination with carboplatin and pemetrexed – PAPILLON

System organ class Adverse reaction	RYBREVANT + Carboplatin + Pemetrexed (N=151)		Carboplatin + Pemetrexed (N=155)	
	All Grades (%)	Grade 3-4 (%)	All Grades (%)	Grade 3-4 (%)
Skin and subcutaneous tissue disorders				
Rash*	90	19	19	0
Nail toxicity*	62	6.6	3	0
Dry skin*	17	0	6	0
General disorders and administration site conditions				
Oedema*	40	1.3	19	0
Fatigue*	42	6.0	45	3.9
Pyrexia	17	0	6	0
Gastrointestinal disorders				
Stomatitis*	43	4.0	11	0
Constipation	40	0	30	0.6
Nausea	36	0.7	42	0
Vomiting	21	3.3	19	0.6
Diarrhoea	21	3.3	12.9	1.3
Haemorrhoids	12	1.3	1.3	0
Abdominal pain*	10.6	0.7	8.4	0
Injury, poisoning and procedural complications				
Infusion related reaction	42	1.3	1.3	0
Metabolism and nutrition disorders				
Decreased appetite	36	2.6	28	1.3
Infections and infestations				
COVID-19	24	2	14	0.6
Pneumonia*	13	5	6	1.9
Vascular disorders				
Haemorrhage*	18	0.7	11	1.9
Respiratory, thoracic, and mediastinal disorders				
Cough*	17	0	16	0
Dyspnoea*	11	1.3	16	3.2
Investigations				
Weight decreased	14	0.7	8	0
Nervous system disorders				
Dizziness*	11	0	12	0
Psychiatric disorders				
Insomnia	11	0	13	0

* Grouped term

Events were graded using CTCAE v5.0

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT in combination with carboplatin and pemetrexed included pulmonary embolism, deep vein thrombosis, skin ulcer, conjunctivitis, and interstitial lung disease (ILD)/pneumonitis.

Table 12 summarises the laboratory abnormalities in PAPILLON.

Table 12: Select laboratory abnormalities (≥ 20%) that worsened from baseline in first-line patients with metastatic NSCLC with EGFR exon 20 insertion mutations in PAPILLON

Laboratory abnormality	RYBREVANT + Carboplatin + Pemetrexed[+]		Carboplatin + Pemetrexed	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased albumin	87	7	34	1
Increased aspartate aminotransferase	60	1	61	1
Increased alanine aminotransferase	57	4	54	1
Decreased sodium	55	7	39	4
Increased alkaline phosphatase	51	1	28	0
Decreased potassium	44	11	17	1
Decreased magnesium	39	2	30	1
Increased gamma-glutamyl transferase	38	4	43	4
Decreased calcium (corrected)	27	1	18	1
Haematology				
Decreased white blood cells	89	17	76	10
Decreased haemoglobin	79	11	85	13
Decreased neutrophils	76	36	61	23
Decreased platelets	70	10	54	12
Decreased lymphocytes	61	11	49	13

Treatment of NSCLC with EGFR exon 20 insertion mutations after prior therapy

The safety of RYBREVANT as monotherapy at the recommended dosage (see Table 1) was evaluated in CHRYSALIS , which included 153 patients with locally advanced or metastatic NSCLC with EGFR exon 20 mutations whose disease had progressed on or after platinum-based chemotherapy (see section 5.1 Pharmacodynamic Properties, Clinical trials). Patients received RYBREVANT 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥80 kg) by intravenous infusion once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The median treatment duration was 5.6 months (range: 0.0 to 23.9 months): 46% of patients were exposed for 6 months or longer and 22% were exposed for longer than a year.

The most common adverse reactions (≥20% incidence) were rash, IRR, nail toxicity, hypoalbuminaemia, fatigue, oedema, stomatitis, nausea, constipation, dry skin, and alanine aminotransferase increased. Serious adverse reactions in >1% of patients included ILD, diarrhoea, IRR, and rash. Five percent of patients discontinued RYBREVANT due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR and ILD.

Table 13: Adverse reactions (≥10%) in patients with NSCLC with exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy and received RYBREVANT in CHRYSALIS (N=153)

System Organ Class Adverse Reaction	**All Grades (%)**	**Grade 3-4 (%)**
Skin and subcutaneous tissue disorders		
Rash[a]	85	4
Nail toxicity[b]	56	3
Dry skin[c]	23	0
Pruritus	16	0
Gastrointestinal disorders		
Stomatitis[d]	28	0.7
Nausea	25	0.7
Constipation	24	0
Diarrhoea	14	3
Vomiting	14	0.7
Abdominal pain[e]	11	0.7
Injury, poisoning and procedural complications		
Infusion-related reaction	63	3
Metabolism and nutrition disorders		
Decreased appetite	18	0.7
General disorders and administration site conditions		
Fatigue[f]	33	2
Oedema[g]	29	0.7
Pyrexia	17	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[h]	48	0
Nervous system disorders		
Dizziness[i]	12	0.7
Peripheral neuropathy[j]	12	0
Headache[k]	10	0.7
Vascular disorders		
Haemorrhage[l]	24	0
Infections and infestations		
Pneumonia[m]	11	2.6

[a] Rash: acne, dermatitis, dermatitis acneiform, erythema, folliculitis, palmar-plantar erythrodysaesthesia syndrome, perineal rash, pustule, rash, rash erythematous, rash maculo-papular, rash general, rash pustular, rash vesicular, skin exfoliation, skin lesion

[b] Nail toxicity: nail bed infection, nail cuticle fissure, nail disorder, onychoclasis, onycholysis, paronychia

[c] Dry skin: dry skin, eczema, eczema asteatotic, skin fissures, xeroderma

[d] Stomatitis: aphthous ulcer, cheilitis, glossitis, lip ulceration, mouth ulceration, stomatitis

[e] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort

[f] Fatigue: asthenia, fatigue

[g] Oedema: eyelid oedema, face oedema, generalised oedema, oedema, oedema peripheral, periorbital oedema, periorbital swelling, peripheral swelling, swelling face

[h] Musculoskeletal pain: arthralgia, arthritis, back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, myalgia, neck pain, non-cardiac chest pain, pain in extremity, spinal pain

[i] Dizziness

[j] Peripheral neuropathy: hypoaesthesia, neuralgia, neuritis, paraesthesia, peripheral sensory neuropathy

[k] Headache: headache, migraine

[l] Haemorrhage: epistaxis, gastric haemorrhage, gingival bleeding, haematuria, haemoptysis, haemorrhage, mouth haemorrhage, mucosal haemorrhage

[m] Pneumonia: pneumonia, pneumonia aspiration, pulmonary sepsis

Clinically relevant adverse reactions that occurred in <10% of RYBREVANT-treated patients with NSCLC exon 20 insertion mutations in CHRYSALIS included those summarised in Table 14.

Table 14: Clinically relevant adverse reactions (<10%) in patients with NSCLC with exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy and who received RYBREVANT in CHRYSALIS (N=153)

System Organ Class Adverse Reaction	**Frequency Category**	**All Grades (%)**	**Grade 3-4 (%)**
Gastrointestinal disorders			
Abdominal pain[a]	Common	9	0.7
Eye disorders			
Other eye disorders[b]	Common	6	0
Visual impairment[c]	Common	2	0
Growth of eyelashes[d]	Common	1	0
Keratitis	Common	1	0
Uveitis	Uncommon	0.7	0
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease[e]	Common	4	0.7
Skin and subcutaneous tissue disorders			
Toxic epidermal necrolysis	Uncommon	0.7	0.7

[a] Abdominal pain: abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, epigastric discomfort

[b] Other eye disorders: blepharitis, conjunctival hyperaemia, corneal irritation, dry eye, episcleritis, eye pruritus, ocular hyperaemia

[c] Visual impairment: vision blurred, visual acuity reduced, visual impairment

[d] Growth of eyelashes: growth of eyelashes, trichomegaly

[e] Interstitial lung disease: interstitial lung disease, pneumonitis

Laboratory abnormalities

Table 15: Select laboratory abnormalities that worsened from baseline in at least 20% of patients with metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy and who received RYBREVANT in CHRYSALIS

Laboratory abnormality	**RYBREVANT[+] (N=153)**	
	All Grades (%)	**Grades 3 or 4 (%)**
Chemistry		
Decreased albumin	83	8
Increased glucose	56	4
Increased alkaline phosphatase	52	5
Increased creatinine	48	0
Increased alanine aminotransferase	40	2
Decreased phosphate	36	7
Increased aspartate aminotransferase	34	1
Increased gamma-glutamyl transferase	29	4
Decreased magnesium	28	0
Decreased potassium	28	5
Decreased sodium	25	3
Decreased calcium	21	1
Hematology		
Decreased lymphocytes	38	7

[+] The denominator used to calculate the rate was the number of patients with a baseline value and at least one post-treatment value.

Postmarketing Experience

The following adverse reactions associated with the use of RYBREVANT were identified. Because some of these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Skin ulcer

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no information on overdosage with RYBREVANT.

There is no known specific antidote for RYBREVANT overdose. In the event of an overdose, stop RYBREVANT, undertake general supportive measures until clinical toxicity has diminished or resolved.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

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 bispecific antibody that binds to the extracellular domains of EGFR and MET.

In preclinical studies, amivantamab disrupted EGFR and MET signalling functions through blocking ligand binding and, in exon 20 insertion mutation models, enhancing degradation of EGFR and MET. 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

Immunogenicity

Monoclonal antibodies can be immunogenic. Across the MARIPOSA, MARIPOSA-2, PAPILLON and CHRYSALIS clinical studies, there were a total of 1862 patients who received RYBREVANT (either as monotherapy or as part of a combination therapy) and had evaluable results for anti-drug antibody (ADA) testing. In this group, the incidence of treatment-emergent anti-amivantamab antibodies was 0.2% (n=4). Due to the small incidence, the effect of these antibodies on the pharmacokinetics, safety or efficacy of RYBREVANT can't be meaningfully assessed.

Clinical trials

NSCLC patients with EGFR exon 19 deletions or exon 21 L858R substitution mutations

Previously untreated

MARIPOSA is a randomised, active-controlled, multicentre phase 3 study assessing the efficacy and safety of RYBREVANT in combination with lazertinib as compared to osimertinib monotherapy as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Patient samples were required to have one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing.

A total of 1074 patients were randomised (2:2:1) to receive RYBREVANT in combination with lazertinib, osimertinib monotherapy, or lazertinib monotherapy (an unapproved regimen for NSCLC)

until disease progression or unacceptable toxicity. RYBREVANT was administered intravenously at 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Lazertinib was administered at 240 mg orally once daily. Osimertinib was administered at a dose of 80 mg orally once daily. Randomisation was stratified by EGFR mutation type (exon 19 deletion or exon 21 L858R), race (Asian or non-Asian), and history of brain metastasis (yes or no).

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

RYBREVANT in combination with lazertinib demonstrated a statistically significant and clinically meaningful improvement in progression-free survival (PFS) by BICR assessment, with a 30% reduction in the risk of progression or death compared with osimertinib (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002). The corresponding median PFS was 23.72 months (95% CI: 19.12, 27.66) for the RYBREVANT in combination with lazertinib arm and 16.59 months (95% CI: 14.78, 18.46) for the osimertinib arm.

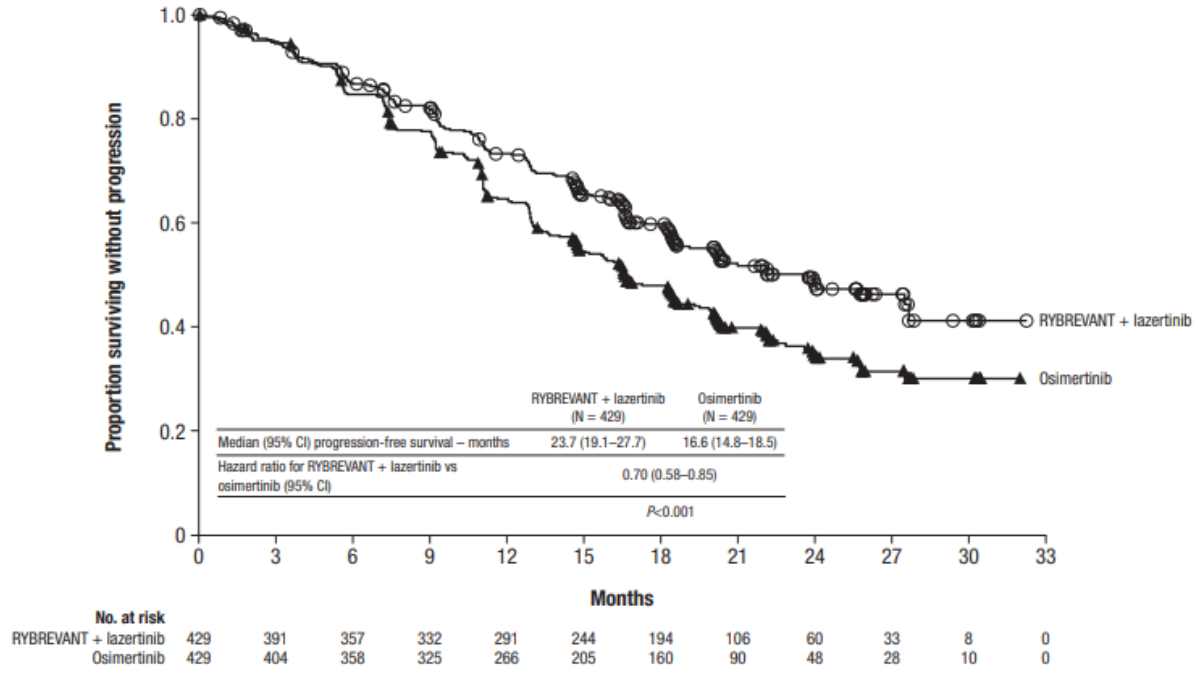
While OS results were immature at the current analysis, with 55% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed.

Table 16: Efficacy Results in MARIPOSA by BICR Assessment

	RYBREVANT in combination with lazertinib (N=429)	**Osimertinib (N=429)**
Progression-free survival (PFS)		
Number of events (%)	192 (45)	252 (59)
Median, months (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
HR[1,2] (95% CI); p-value[1,3]	0.70 (0.58, 0.85); p=0.0002	
Overall response rate (ORR)[4]		
ORR, % (95% CI)	78 (74, 82)	73 (69, 78)
Complete response, %	5.4	3.5
Partial response, %	73	70
Duration of response (DOR)[5]		
Median (95% CI), months	25.8 (20.1, NE)	16.7 (14.8, 18.5)
Patients with DOR ≥ 6 months[6], %	86	85
Patients with DOR ≥ 12 months[6], %	68	57

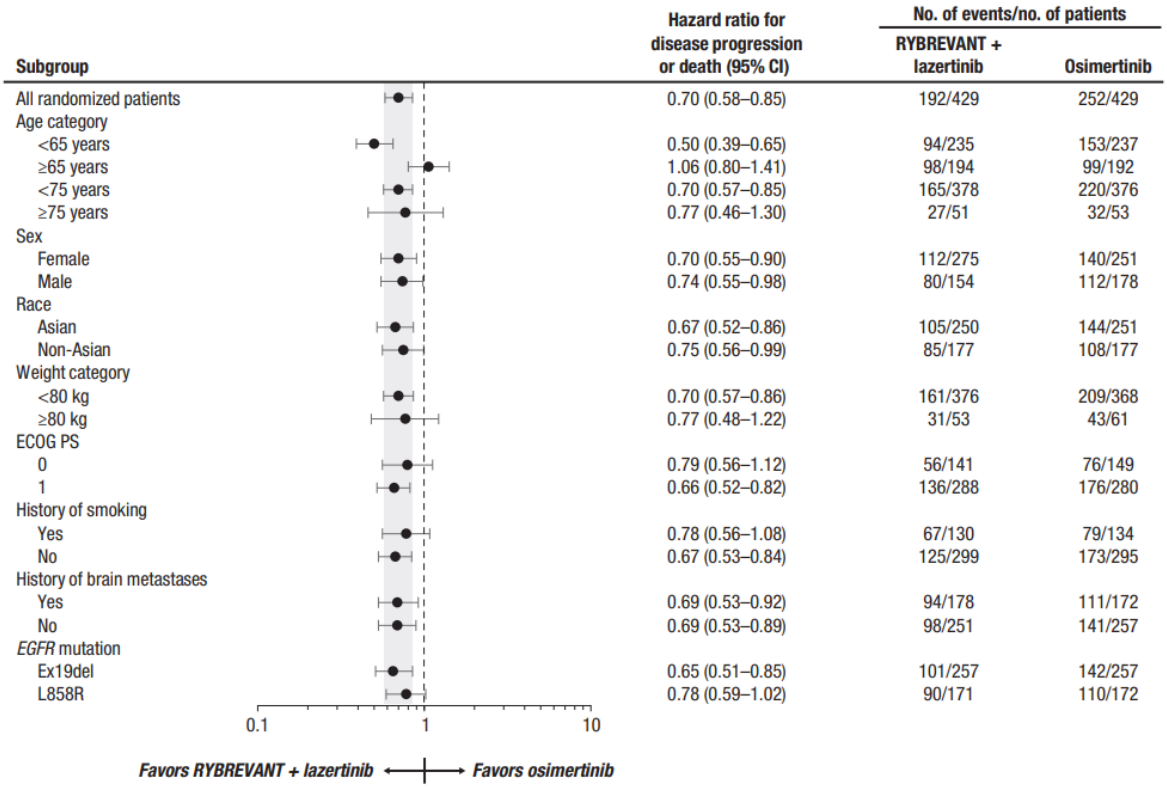
BICR = blinded independent central review; CI = confidence interval; NE = not estimable
1 Stratified by mutation type (Exon 19del or Exon 21 L858R), prior brain metastases (yes or no), and Asian race (yes or no).
2 Stratified Cox proportional hazards regression.
3 Stratified log-rank test.
4 Confirmed responses based on the ITT population.
5 In confirmed responders.
6 Based on observed rates.

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



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

Figure 2: **Forest plot of PFS in previously untreated NSCLC patients by BICR assessment**



The stratified analysis of investigator-assessed PFS shows that the improved treatment effect of the combination of RYBREVANT and lazertinib relative to osimertinib was also observed (median PFS

of 23.92 months in the RYBREVANT in combination with lazertinib arm, compared to median of 19.94 months in the osimertinib arm (HR of 0.79 [95% CI: 0.65, 0.95, nominal p=0.0139])) when assessed by investigator. Results for the analysis of ORR based on investigator assessment for comparison of the RYBREVANT in combination with lazertinib arm versus the osimertinib arm were consistent with results for ORR based on BICR assessment.

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

Results of pre-specified exploratory analyses of CNS ORR and DOR by BICR, in the subset of patients with measurable intracranial lesions at baseline for the combination of RYBREVANT and lazertinib, demonstrated similar intracranial ORR to the control. Per protocol, all patients in MARIPOSA had serial brain MRIs to assess intracranial response and duration. Results are summarised in Table 17.

Table 17: Intracranial ORR and DOR by BICR assessment in subjects with measurable intracranial lesions at baseline - MARIPOSA

	RYBREVANT + lazertinib (N=180)	**Osimertinib (N=187)**	**Lazertinib (N=93)**
Intracranial Tumor Response Assessment			
Intracranial ORR (CR+PR), % (95% CI)	76.7 (69.8, 82.6)	76.5 (69.7, 82.4)	74.2 (64.1, 82.7)
Complete response %	62.2	57.8	54.8
Intracranial DOR			
Number or responders	138	143	69
Response Duration ≥6 months, %	77.5	77.6	79.7
Response Duration ≥12 months, %	58.0	53.8	52.2
Response Duration ≥18 months, %	31.2	21.0	18.8

CI = confidence interval

Treatment of NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations after prior therapy

The efficacy of RYBREVANT in combination with carboplatin and pemetrexed for advanced NSCLC harbouring a common EGFR mutation after prior anti-EGFR tyrosine kinase inhibitor therapy was evaluated in MARIPOSA-2: a randomised, open-label, multicenter trial. Eligible patients had locally advanced or metastatic NSCLC with an EGFR exon 19 deletion or exon 21 L858R substitution mutation prospectively identified by validated local testing, and had developed progressive disease on or after receiving osimertinib. Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to enrol.

A total of 131 patients were randomised to receive RYBREVANT in combination with carboplatin and pemetrexed (ACP), and 263 were randomised to receive carboplatin and pemetrexed (CP). Randomisation was stratified by osimertinib line of therapy (first-line or second-line), prior brain metastases (yes or no), and Asian race (yes or no).

All patients received carboplatin intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks for up to 12 weeks. All patients also received pemetrexed intravenously at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity. In addition, patients randomised to the ACP arm received RYBREVANT intravenously in the following regimen:

- Weeks 1-4: 1400 mg (for patients <80 kg) or 1750 mg (for patients ≥80 kg) per week
- Week 7 onwards: 1750 mg (for patients <80 kg) or 2,100 mg (for patients ≥ 80 kg) once every three weeks, until disease progression or unacceptable toxicity.

Tumour assessments were performed every 6 weeks for the first 12 months and every 12 weeks thereafter. The major efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Overall survival (OS) and objective response rate (ORR) as assessed by BICR were key secondary outcome measures.

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

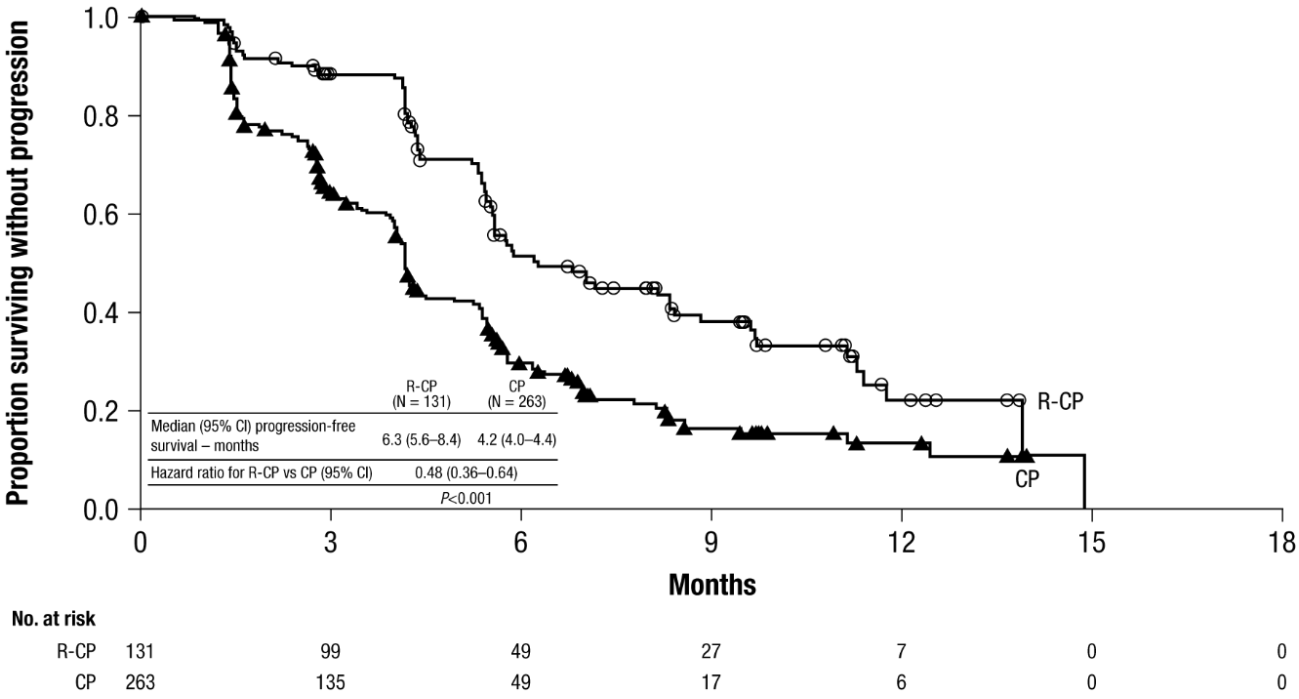
The efficacy results of MARIPOSA-2 are summarised in Table 18 and Figure 3.

Table 18: Efficacy results of MARIPOSA-2

	RYBREVANT + carboplatin + pemetrexed (N=131)	**carboplatin + pemetrexed (N=263)**
Progression-free survival (PFS) [a]		
Number of events (X%)	74 (56%)	171 (65%)
Median, months (95% CI)	6.3 (5.6, 8.4)	4.2 (4.0, 4.4)
HR (95% CI); [b,c] p-value [b,d]	0.48 (0.36, 0.64); p<0.0001	
Objective response rate (ORR) [a,e]		
ORR, % (95% CI)	63.8% (55.0, 72.1)	36.2% (30.3, 42.3)
p-value [b,f]	p <0.0001	
Complete response	1.5%	0.4%
Partial response	62.3%	35.8%
Duration of response (DOR) [a,e]		
Median (95% CI), months	6.90 (5.52, NE)	5.55 (4.17, 9.56)

CI = confidence interval
NE = not estimable
[a] Blinded Independent Central Review by RECIST v1.1
[b] Stratified by osimertinib line of therapy (first-line or second-line), prior brain metastases (yes or no), and Asian race (yes or no)
[c] Stratified Cox proportional hazards regression
[d] Stratified log-rank test
[e] Confirmed responses
[f] Stratified logistic regression analysis

Figure 3: Kaplan-Meier curve of PFS in MARIPOSA-2 (BICR)



At the prespecified second interim analysis of OS, with 85% of the deaths needed for the final analysis, there was no statistically significant difference in OS. The median OS was 17.7 months (95% CI: 16.0, 22.4) in the ACP arm and 15.3 months (95% CI: 13.7, 16.8) in the CP arm, with a hazard ratio of 0.73 (95% CI: 0.54, 0.99).

Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to be randomised in MARIPOSA-2. Baseline disease assessment, including brain magnetic resonance imaging (MRI) was performed at treatment initiation. All patients underwent serial brain MRI during the trial.

Pre-specified secondary analyses of intracranial ORR by BICR in the subset of 91 (23%) patients with baseline intracranial disease were performed. Data were only available for intracranial complete responses and not available for intracranial partial responses. Intracranial ORR was 20% (95% CI: 8, 39) in the 30 patients with baseline intracranial disease in the ACP arm and 7% (95% CI: 1.8, 16) in the 61 patients with baseline intracranial disease in the CP arm.

First-line treatment of locally advanced or metastatic NSCLC with exon 20 insertion mutations

The efficacy of RYBREVANT in combination with carboplatin and pemetrexed as a first line treatment for advanced NSCLC harbouring an EGFR exon 20 insertion mutation was evaluated in PAPILLON: a randomised, open-label, multicenter trial. Eligible patients had treatment-naïve, locally advanced or metastatic NSCLC with an EGFR exon 20 insertion mutation prospectively identified by validated local testing of either tumour tissue (92%) or plasma/ctDNA (8%). Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to enrol. Patients with historical or active interstitial lung disease were excluded from the clinical study.

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 dosing of all agents was the same as descried above for MARIPOSA-2. Randomisation was stratified by ECOG performance status (0 vs. 1) and prior brain metastases (yes vs. no), and prior EGFR TKI use (yes vs. no).

The primary efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Additional efficacy outcome measures included objective response rate (ORR), duration of response (DOR) and overall survival (OS). Cross-over to single agent RYBREVANT was permitted for patients who had confirmed disease progression on carboplatin and pemetrexed.

The median age was 62 (range: 27 to 92) years, with 40% of the subjects ≥ 65 years of age; 58% were female; 61% were Asian and 36% were Caucasian. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (35%) or 1 (65%); 58% had never smoked; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis. Four patients (including 1 in the ACP arm) had previously received an EGFR TKI, and this was omitted from stratification of analyses.

Efficacy results for PAPILLON are summarised in Table 19 and Figure 4.

Table 19: 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); [b,c] p-value [b,d]	0.40 (0.30, 0.53); p<0.0001	
Objective response rate (ORR) [a,e]		
ORR, % (95% CI)	73% (65%, 80%)	47% (39%, 56%)
Complete response	4%	1%
Partial response	69%	47%
Duration of response (DOR) [a,e]		
Median (95% CI), months	10.1 (8.5, 13.9)	5.6 (4.4, 6.9)

CI = confidence interval

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

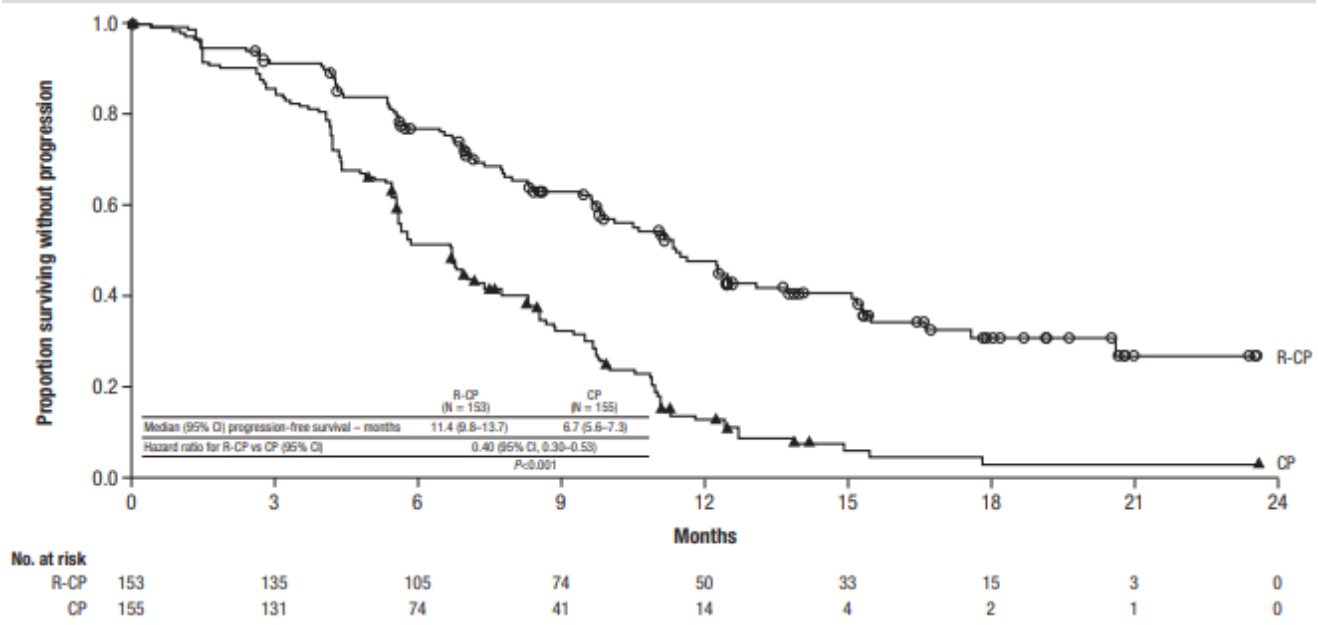
[b] Stratified by ECOG PS (1 or 0), and prior brain metastases (yes or no)

[c] Stratified Cox proportional hazards regression

[d] Stratified log-rank test

[e] Confirmed responses

Figure 4: Kaplan-Meier Curve of PFS in PAPILLON (BICR)



While OS results were immature at the current analysis, with 44% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed. Seventy-five (48%) of the

treated patients crossed over from the carboplatin and pemetrexed arm after confirmation of disease progression to receive RYBREVANT as a single agent.

Treatment of locally advanced or metastatic NSCLC with exon 20 insertion mutations after prior therapy

The efficacy and safety of RYBREVANT were evaluated in CHRYSALIS: a multicentre, open-label, multi-cohort study conducted in patients with locally advanced or metastatic NSCLC. Efficacy was evaluated in 81 subjects 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 14.5 months. Identification of an EGFR exon 20 insertion mutation was determined by prospective local testing using tumour tissue (94%) or plasma (6%) samples. Patients with untreated brain metastases and patients with 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 a dose of 1050 mg (for patients <80 kg) or 1400 mg (for subjects ≥80 kg) once weekly for 4 weeks, then every 2 weeks starting at Week 5 until disease progression or unacceptable toxicity. The primary efficacy endpoint was overall response rate (ORR), defined as confirmed complete response (CR) or partial response (PR) based on RECIST v1.1, assessed by a blinded independent central review (BICR). Secondary efficacy endpoints included duration of response (DOR) according to BICR.

The median age in the efficacy population was 62 (range: 42–84) years, with 9% of the patients ≥75 years of age; 59% were female; 49% were Asian and 37% were Caucasian; 74% had baseline body weight <80 kg; 95% had adenocarcinoma; and 46% had received prior immunotherapy. The median number of prior therapies was 2 (range: 1 to 7). At baseline, 32% had Eastern Cooperative Oncology Group (ECOG) performance status of 0 and 67% had ECOG performance status of 1; 53% had never smoked; all patients had metastatic disease; and 22% had previous treatment for brain metastases.

Efficacy results in the CHRYSALIS study are summarised in Table 20.

Table 20: Efficacy results in CHRYSALIS

	Patients with EGFR exon 20 insertion-positive NSCLC previously treated with platinum-based chemotherapy (N=81)
Overall response rate[a] (95% CI)	43% (32%, 55%)
Complete response (CR) rate	4%
Partial response (PR) rate	40%
Duration of response[a]	
Median (95% CI), months	11.0 (6.9, NE)
Patients with DOR ≥ 6 months	60%

CI = confidence interval; NE = not estimable
[a] Kaplan-Meier estimates, based on confirmed responses

Of the 81 patients with EGFR exon 20 insertion mutations according to local testing, plasma samples from 96% of patients were tested retrospectively using Guardant360® CDx (3.7% did not have plasma samples for testing). EGFR exon 20 insertion mutations were not identified on the Guardant360® CDx test for 20% of patients. For the 76% of patients in whom exon 20 insertion mutations were identified, the variants identified were A767 (23%), S768 (16%), D770 (11%), N771 (11%), H773 (9%), P772 (3%), V769 (1%) and A763 (1%). There were no mutation variants identified amongst the efficacy population that were associated with an absence of confirmed responses.

5.2 PHARMACOKINETIC PROPERTIES

Based on RYBREVANT monotherapy data, amivantamab exposure increases proportionally over a dose range from 350 to 1750 mg.

Based on the population pharmacokinetics of RYBREVANT, steady-state concentrations of RYBREVANT were reached by week 13 for both the approved (3-week and 2-week) dosing regimens and the systemic accumulation was 1.9- fold.

Distribution

The mean (±SD) volume of distribution of amivantamab is 5.34(±1.81) L.

Excretion

The geometric mean (% CV) linear clearance (CL) and terminal half-life associated with linear clearance estimated from population PK parameters were 0.266 L/day (30.4%), and 13.7 days (31.9%), respectively.

Special populations

Paediatrics (17 years of age and younger)

The pharmacokinetics of RYBREVANT in paediatric patients have not been investigated.

Elderly (65 years of age and older)

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 (creatinine clearance [CrCl] of 60 to <90 mL/min) and moderate (CrCl of 29 to <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. No data are available in patients with end stage renal disease (CrCl <15 mL/min).

Hepatic impairment

No clinically meaningful effect on the pharmacokinetics of amivantamab was observed based on mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 x ULN and any AST) or moderate hepatic impairment (1.5×ULN < total bilirubin ≤3×ULN and any AST). 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. No data are available in patients with severe hepatic impairment (total bilirubin > 3×ULN and any AST).
Changes in hepatic function are not expected to affect amivantamab elimination since IgG1-based molecules are not metabolised through hepatic pathways.

Sex

Amivantamab clearance was 24% higher in males than in females, but no clinically meaningful pharmacokinetic differences were observed between male and female patients.

Weight

The central volume of distribution and clearance of amivantamab increased with increasing body weight. Amivantamab exposure was 30-40% lower in patients who weighed ≥80 kg compared to patients with body weight <80 kg at the same dose. Similar amivantamab exposures were achieved at the recommended dose of RYBREVANT in patients with a body weight <80 kg who received 1050 mg and patients with a body weight ≥80 kg who received 1400 mg.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

As amivantamab is a monoclonal antibody, genotoxicity studies have not been conducted. Large protein molecules are not expected to interact directly with DNA or other chromosomal material.

Carcinogenicity

As amivantamab is a monoclonal antibody, carcinogenicity studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Disodium edetate
Histidine
Histidine hydrochloride monohydrate
Methionine
Polysorbate 80
Sucrose
Water for injections

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in Section 4.2 Dose and Method of administration.

6.3 SHELF LIFE

Unopened vials

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

After dilution:

Since amivantamab solutions do not contain a preservative, the product should be used immediately. Administer diluted solutions within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator at 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 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

Type 1 glass vial with butyl rubber elastomer stopper and aluminium seal with a flip-off cap.

RYBREVANT is available in cartons containing 1 single-use vial.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 Prescription Medicine

8. SPONSOR

Janssen-Cilag Pty Ltd
1-5 Khartoum Road,
Macquarie Park,
NSW, 2113, AUSTRALIA
Telephone: 1800 226 334

9. DATE OF FIRST APPROVAL

01 Dec 2022

10. DATE OF REVISION

15 Apr 2025

Summary table of changes

Section changed	Summary of new information
4.1, 4.2, 4.4, 4.8, 5.1, 5.2	Inclusion of information for new indications supported by MARIPOSA study