▼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/safety/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

RYBREVANT® SC (amivantamab)

solution for injection

1. NAME OF THE MEDICINE

Amivantamab

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

10 mL vial: Each single-dose vial contains 1600 mg amivantamab (160 mg/mL)

14 mL vial: Each single-dose vial contains 2240 mg amivantamab (160 mg/mL)

15 mL vial: Each single-dose vial contains 2400 mg amivantamab (160 mg/mL)

22 mL vial: Each single-dose vial contains 3520 mg amivantamab (160 mg/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).

Recombinant human hyaluronidase (vorhyaluronidase alfa) is an endoglycosidase used to increase the dispersion and absorption of co-administered drugs when administered subcutaneously. It is produced by mammalian (CHO) cells containing a DNA plasmid encoding for a soluble fragment of human hyaluronidase (PH20). It is a glycosylated single-chain protein with an approximate molecular weight of 61 kD.

For the full list of excipients, see section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

RYBREVANT SC is a colourless to pale yellow preservative-free solution for subcutaneous administration.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

RYBREVANT SC 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 SC is for subcutaneous use only. RYBREVANT SC has different dosage and administration instructions than intravenous (IV) amivantamab. Do not administer RYBREVANT SC intravenously.

RYBREVANT SC should be administered by a healthcare professional in a setting with appropriate medical support to manage administration-related reactions (ARRs) if they occur (see section 4.4 Special warnings and precautions for use).

Administer pre-medications before each dose of RYBREVANT SC as recommended (see subsection *Recommended pre-medications*).

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

For patients currently receiving RYBREVANT SC subcutaneous formulation at an every-2-week dosing regimen, an every-4-week dosing regimen may be used as an alternative starting at the next scheduled dose.

When initiating treatment with RYBREVANT SC 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).

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

Dosage

Dosage – adults (≥18 years)

The recommended dose regimen for RYBREVANT SC is:

- once every two weeks (Table 1) or every four weeks (Table 2) when used either as monotherapy or in combination with lazertinib or
- once every three weeks (Table 3) when used in combination with carboplatin and pemetrexed.

All dosing regimens (every-2-week dosing; every-4-week dosing; and every-3-week dosing) commence with an initial loading phase of weekly dosing (see Table 1, Table 2 and Table 3).

RYBREVANT SC monotherapy or in combination with lazertinib (every-2-week or every-4-week dosing)

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

Table 1: Recommended dose and dosing schedule for RYBREVANT SC in combination with lazertinib or monotherapy (every-2-week dosing) by body weight tier

Body weight less than 80 kg at baseline*			
Week	**Dose (mg)**	**Dose Volume (mL)**	**Recommended number of dosing syringes**
Weekly from Weeks 1 to 4 (total of 4 doses)	1600 mg	10	1

Subsequent weeks (every 2 weeks starting at Week 5 onwards)	1600 mg	10	1
Body weight greater than or equal to 80 kg at baseline*			
Week	**Dose (mg)**	**Dose Volume (mL)**	**Recommended number of dosing syringes**
Weekly from Weeks 1 to 4 (total of 4 doses)	2240 mg	14	1
Subsequent weeks (every 2 weeks starting at Week 5 onwards)	2240 mg	14	1

* Dose adjustments not required for subsequent body weight changes

Table 2: Recommended dose and dosing schedule for RYBREVANT SC in combination with lazertinib or monotherapy (every-4-week dosing) by body weight tier

Body weight less than 80 kg at baseline*			
Week	**Dose (mg)**	**Dose Volume (mL)**	**Recommended number of dosing syringes**
Weekly from Weeks 1 to 4 (total of 4 doses)	1600 mg	10	1
Subsequent weeks (every 4 weeks starting at Week 5 onwards)	3520 mg	22	2†
Body weight greater than or equal to 80 kg at baseline*			
Week	**Dose (mg)**	**Dose Volume (mL)**	**Recommended number of dosing syringes**
Weekly from Weeks 1 to 4 (total of 4 doses)	2240 mg	14	1
Subsequent weeks (every 4 weeks starting at Week 5 onwards)	4640 mg	29‡	2†

* Dose adjustments not required for subsequent body weight changes
† Each injection volume should not exceed 15 mL. Divide the dose volume approximately equally into two syringes. For volumes requiring multiple dosing syringes, use different injection sites.
‡ For the 29 mL dose volume, use one 2,240 mg/14 mL vial and one 2,400 mg /15 mL vial to minimise waste. If a different combination of vials is used, dispose of unused volume in accordance with local requirements (see section 6.3 Shelf life).

When used in combination with lazertinib, if given on the same day, administer RYBREVANT SC second, any time after lazertinib. See section 5.1 Pharmacodynamic properties - Clinical trials and the dosing instructions for lazertinib in its Product Information.

RYBREVANT SC in combination with platinum-based chemotherapy (every-3-week dosing)

The recommended dosages of RYBREVANT SC, when used in combination with platinum-based chemotherapy, based on baseline body weight, are provided in Table 3.

For every-3-week dosing, the entire volume of both vials will not be used. Dispose of excess volume in accordance with local requirements (see section 6.3 Shelf life).

Table 3: Recommended dose and dosing schedule for RYBREVANT SC in combination with platinum-based chemotherapy (every-3-week dosing) by body weight tier

Body weight less than 80 kg at baseline*			
Week	**Dose (mg)**	**Dose Volume (mL)**	**Recommended number of dosing syringes**
Week 1 day 1	1600 mg	10	1
Weekly from Weeks 2 to 4 (total of 3 doses)	2400 mg	15	1
Subsequent weeks (every 3 weeks starting at Week 7 onwards)	2400 mg	15	1
Body weight greater than or equal to 80 kg at baseline*			
Week	**Dose (mg)**	**Dose Volume (mL)**	**Recommended number of dosing syringes**
Week 1 day 1	2240 mg	14	1
Weekly from Weeks 2 to 4 (total of 3 doses)	3360 mg	21‡	2†
Subsequent weeks (every 3 weeks starting at Week 7 onwards)	3360 mg	21‡	2†

* Dose adjustments not required for subsequent body weight changes
† Each injection volume should not exceed 15 mL. For a 3360 mg dose (21 mL), divide the volume approximately equally into two syringes. For volumes requiring multiple dosing syringes, use different injection sites.
‡ For the 21 mL dose volume, the entire contents of the 3520 mg/ 22 mL vial will not be needed. Dispose of unused volume in accordance with local requirements (see section 6.3 Shelf life).

When used in combination with carboplatin and pemetrexed, RYBREVANT SC should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then RYBREVANT SC. See section 5.1 Pharmacodynamic properties - Clinical trials and the Product Information for dosing instructions for carboplatin and pemetrexed.

Duration of treatment

Administer RYBREVANT SC until disease progression or unacceptable toxicity.

Recommended pre-medications

Prior to initial injection of RYBREVANT SC (Week 1, Day 1), administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of ARRs. For subsequent doses, administer antihistamines and antipyretics. Administer glucocorticoid as needed. Table 4 summarises the recommendations regarding pre-medications.

Table 4: Premedications

Medication	Dose	Route of administration	Dosing window prior to RYBREVANT SC administration
Antihistamine[*]	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous (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	45 to 60 minutes
		Oral	At least 60 minutes
Glucocorticoid[+]	Dexamethasone (10 mg) or equivalent	IV	45 to 60 minutes
		Oral	60 to 90 minutes

[*] Required at all doses.
[‡] Required at initial dose (Week 1, Day 1); or at the next subsequent dose in the event of an administration-related reaction.
[+] Optional for subsequent doses.

Missed dose

If a dose is initially missed, it can still be administered within the following timeframes.

For the every-4-week or every-2-week dosing schedule:

- If a dose of RYBREVANT SC is missed between Weeks 1 to 4, administer within 24 hours.
- If a dose of RYBREVANT SC is missed from Week 5 onward, administer within 7 days.

For the every-3-week dosing schedule:

- If a dose of RYBREVANT SC is missed between Weeks 1 to 3, administer within 24 hours.
- If a dose of RYBREVANT SC is missed from Week 4 onward, administer within 7 days.

If the missed dose is not administered within the timeframe nominated above, do not administer the missed dose. Administer the next dose per the usual dosing schedule.

Dose modifications

RYBREVANT SC dose modification for adverse reactions

The recommended RYBREVANT SC dose reductions for adverse reactions are listed in Table 5.

Table 5: Dose reductions for adverse reactions for RYBREVANT SC

Dose at which the adverse reaction occurred	1st dose reduction	2nd dose reduction	3rd dose modification
1600 mg	1050 mg*	700 mg†	Discontinue RYBREVANT SC
2240 mg	1600 mg‡	1050 mg*	
2400 mg	1600 mg‡	1050 mg*	
3360 mg	2240 mg§	1600 mg‡	
3520 mg	2400 mg¶	1600 mg‡	
4640 mg	3360 mg#	2240 mg§	

* The dose volume should be 6.6 mL for 1050 mg dose.
† The dose volume should be 4.4 mL for 700 mg dose.
‡ The dose volume should be 10 mL for 1600 mg dose.
§ The dose volume should be 14 mL for 2240 mg dose.
¶ The dose volume should be 15 mL for 2400 mg dose.
# The dose volume should be 21 mL for 3360 mg dose.

The recommended RYBREVANT SC dosage modifications and management for adverse reactions are provided in Table 6.

Table 6: Recommended dosage modifications and management for adverse reactions for RYBREVANT SC

Adverse reaction	Severity	Dose modification
Administration-related reactions (ARR) (see section 4.4)	Grade 1 to 3	• Interrupt injection at the first sign of ARRs • Give supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) as clinically indicated • Upon resolution of symptoms, resume RYBREVANT SC administration • Include corticosteroid with pre-medications prior to next dose (see Table 4)
	Recurrent Grade 3 or Grade 4	Permanently discontinue RYBREVANT SC
Interstitial lung disease / pneumonitis (see section 4.4)	Suspected ILD/ pneumonitis	Withhold
	Confirmed ILD/ pneumonitis	Permanently discontinue RYBREVANT SC
Venous thromboembolic (VTE) events *(Applies to the combination with lazertinib, see section 4.4)*	Grade 2 or 3	Withhold RYBREVANT SC 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 VTE, or recurrent Grade 2 or 3 VTE despite therapeutic level anticoagulation	Permanently discontinue RYBREVANT SC. 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 as clinically indicated. • Reassess after 2 weeks
	Grade 2	• Initiate supportive care as clinically indicated. • If there is no improvement after 2 weeks, consider reducing the dose (see Table 5)
	Grade 3	• Initiate supportive care as clinically indicated. • Withhold until the adverse reaction improves to ≤ Grade 2 • Resume at reduced dose (see Table 5) • If no improvement within 2 weeks, permanently discontinue

Adverse reaction	Severity	Dose modification
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions such as toxic epidermal necrolysis (TEN))	Permanently discontinue RYBREVANT SC
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

Dose modifications for adverse reactions when used in combination with lazertinib

If adverse reactions occur when RYBREVANT SC is used in combination with lazertinib, withhold or discontinue RYBREVANT SC as shown in Table 6. If dose reduction is required, reduce the dose of RYBREVANT SC before reducing the dose of lazertinib. Refer to the Product Information of lazertinib for additional dosage modification information.

Dose modifications for adverse reactions when used in combination with carboplatin and pemetrexed

If adverse reactions occur when RYBREVANT SC is used in combination with carboplatin and pemetrexed, modify the dosage of one or more drugs as clinically indicated. Withhold, reduce dose, or discontinue RYBREVANT SC as shown in Table 6. Refer to the Product Information of carboplatin and pemetrexed for additional dosage modification information.

Dosage in special populations

Paediatrics (17 years of age and younger)

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

Elderly (65 years of age and older)

No overall differences in safety or effectiveness were observed between patients who were ≥65 years of age 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).

Method of administration

RYBREVANT SC should be administered by a healthcare professional.

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is RYBREVANT SC for subcutaneous injection and not intravenous amivantamab. **RYBREVANT SC subcutaneous formulation is not intended for intravenous administration** and should be administered via a subcutaneous injection only.

RYBREVANT SC is for single use only and is ready to use. Use in one patient on one occasion only. Contains no antimicrobial preservative.

RYBREVANT SC should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit. Do not use if opaque particles, discolouration, or other foreign particles are present.

Prepare the dosing syringe in aseptic conditions.

Each injection volume should not exceed 15 mL.

Preparation for administration

Refer to Tables 1, 2 and 3 to assist dose preparation.

- Remove the appropriate RYBREVANT SC vial(s) from refrigerated storage (2°C to 8°C).
- Once removed from refrigerated storage, keep RYBREVANT SC at room temperature (15°C to 30°C) for at least 15 minutes to allow it to equilibrate to room temperature. Do not warm RYBREVANT SC in any other way. Do not shake.
- Withdraw the required injection volume of RYBREVANT SC from the vial(s) into an appropriately sized syringe using a transfer needle (see Tables 1, 2 and 3). Smaller syringes require less force during preparation and administration.

  If preparation does not require the full vial contents, dispose of excess volume in accordance with local requirements.
- Each injection volume should not exceed 15 mL. Divide doses requiring greater than 15 mL into approximately equal volumes in multiple syringes.
- RYBREVANT SC is compatible with stainless steel injection needles, polypropylene and polycarbonate syringes, and polyethylene, polyurethane, and polyvinylchloride subcutaneous infusion sets. A 0.9% sodium chloride solution may also be used to flush an infusion set if needed.
- Replace the transfer needle with appropriate ancillaries for transport or administration. Use of a 21G to 23G needle or infusion set is recommended to ensure ease of administration.

Storage of prepared syringe

Prepared syringes should be administered immediately. If immediate administration is not possible, the prepared syringe containing RYBREVANT SC solution can be stored:

- for up to 24 hours at room temperature (15°C to 30°C) before administration, or
- for up to 24 hours refrigerated (2°C to 8°C), then allowed to come to room temperature before administration within a further 24 hours.

Discard the prepared syringe if stored for more than 24 hours refrigerated or more than 24 hours of being at room temperature.

Administration of RYBREVANT SC

- **If only one dosing syringe is required, the required volume of RYBREVANT SC should be injected into the subcutaneous tissue of the abdomen over approximately 5 minutes.**

  No data are available on performing the injection at other sites of the body.
- **If multiple dosing syringes are required, RYBREVANT SC injections should be consecutively administered in separate quadrants of the abdomen, with each injection taking approximately 5 minutes.**

  No data are available on performing the injection at other sites of the body.

- Pause or slow down delivery rate if the patient experiences pain. In the event pain is not alleviated by pausing or slowing down delivery rate, a second injection site may be chosen on the opposite side of the abdomen to deliver the remainder of the dose.
- If administering with a subcutaneous infusion set, ensure that the full dose is delivered through the infusion set. 0.9% sodium chloride solution may be utilised to flush remaining drug product through the line.
- Do not inject into tattoos or scars or areas where the skin is red, bruised, tender, hard, not intact or within 2 inches (5 cm) around the periumbilical area.
- Any unused product or waste material should be disposed in accordance with local requirements.

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

Amivantamab was initially developed as an intravenous formulation. Unless otherwise stated, the data described in *Special warnings and precautions for use* come from patients with locally advanced or metastatic NSCLC who received intravenous amivantamab, including 380 patients who received it as monotherapy in Study EDI1001(CHRYSALIS), 151 patients who received intravenous amivantamab in combination with carboplatin and pemetrexed in Study NSC3001 (PAPILLON), 130 patients who received intravenous amivantamab in combination with carboplatin and pemetrexed in Study NSC3002 (MARIPOSA-2) and 421 patients who received intravenous amivantamab in combination with lazertinib in Study NSC3003 (MARIPOSA).

The non-inferiority of RYBREVANT SC to intravenous amivantamab was established in a randomised, open-label Phase 3 study (NSC3004, PALOMA-3) assessing the PK non-inferiority between the two formulations, both given in combination with lazertinib, in patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease had progressed on or after treatment with osimertinib and platinum-based chemotherapy.

Administration-related reactions

Systemic reactions to RYBREVANT SC (administration-related reactions; ARRs), occurred in 13% of patients who received RYBREVANT SC in PALOMA-3. The most frequent signs and symptoms include chills, dyspnoea, flushing, fever and chest discomfort (see section 4.8 Adverse effects (Undesirable effects)).

Prior to initial injection (Week 1, Day 1) of RYBREVANT SC, administer antihistamines, antipyretics and glucocorticoids to reduce the risk of ARRs. For subsequent doses, administer antihistamines and antipyretics (see section 4.2 Dose and method of administration, Table 4).

Only offer RYBREVANT SC in a setting that has the medical support necessary to treat ARRs. Interrupt RYBREVANT SC injection, if ongoing, at the first sign of ARRs and administer supportive care as clinically indicated. Upon resolution of symptoms, resume RYBREVANT SC administration. For Grade 4 or recurrent Grade 3 ARRs, permanently discontinue RYBREVANT SC (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 who received intravenous amivantamab, 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 SC 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 intravenous amivantamab 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. Amongst patients receiving RYBREVANT SC in combination with lazertinib in PALOMA-3, VTE events occurred in 9% of patients with use of prophylactic anticoagulation (see section 4.8 Adverse effects (Undesirable effects)).

Prophylactic anticoagulants are recommended for the first four months of treatment with amivantamab in combination with lazertinib. 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 of grade 2 or 3, associated with clinical instability, RYBREVANT SC and lazertinib should be withheld until the patient is clinically stable. Thereafter, both drugs can be resumed at the discretion of the treating physician.

For grade 4 VTE events or VTE recurrence despite appropriate anticoagulation, permanently discontinue RYBREVANT SC. 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 who receive amivantamab.

In patients who received intravenous amivantamab, most cases of rash (including dermatitis acneiform), pruritis and dry skin were Grade 1 or 2, with Grade 3 events occurring in 15.5% of patients. Rash leading to discontinuation of intravenous amivantamab 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. In patients who received intravenous amivantamab, most events of nail toxicity 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 SC if TEN is confirmed.

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

When initiating treatment with RYBREVANT SC, consider prophylactic therapy to reduce the risk and severity of skin and nail reactions. Administer an oral antibiotic (doxycycline or minocycline, 100 mg twice daily) starting on Day 1 for the first 12 weeks of treatment and topical antibiotic lotion to the scalp (clindamycin 1%), after completion of oral antibiotic therapy, daily for the next 9 months of treatment. Recommend a non-comedogenic skin moisturiser (ceramide-based or other formulations that provide long-lasting skin hydration and exclude drying agents are preferred) on the face and whole body (except scalp) and 4% chlorhexidine solution to wash hands and feet, daily while on treatment. Instruct patients to limit sun exposure during and for 2 months after RYBREVANT SC therapy. Protective clothing and use of broad-spectrum UVA/UVB sunscreen to reduce the risk and severity of skin and nail reactions are advisable.

If skin or nail reactions develop, administer supportive care, 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, reduce dose, or permanently discontinue RYBREVANT SC based on severity (see section 4.2 Dose and method of administration, Table 6).

Eye disorders

Eye disorders may occur in patients who receive amivantamab.

Amongst patients receiving intravenous amivantamab, keratitis was reported in 1.3% and uveitis was reported in 0.09%. Other reported adverse reactions include dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth (trichomegaly), 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, reduce dose, or permanently discontinue RYBREVANT SC 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 SC 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, embryo lethality, 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 all patients to use effective contraception (such as condoms) during treatment and for 3 months after the last dose of RYBREVANT SC. Advise male patients not to donate or store semen during treatment and for 3 months after the last dose of RYBREVANT SC.

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 SC in a breastfed child, advise patients not to breastfeed during treatment with RYBREVANT SC and for 3 months following the last dose of RYBREVANT SC.

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.

Overall, the safety profile of RYBREVANT SC was consistent with the established safety profile of intravenous amivantamab, with a lower incidence of administration-related reactions and a possible lower incidence of VTEs observed with RYBREVANT SC compared to intravenous amivantamab.

Clinical experience of amivantamab subcutaneous formulation

Non-inferiority of RYBREVANT SC versus intravenous amivantamab

The safety of RYBREVANT SC in combination with lazertinib in patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletion or exon 21 L858R substitution mutation was evaluated in the PALOMA-3 study.

Patients received RYBREVANT SC (N=206) or intravenous amivantamab (N=210), both in combination with lazertinib, at the recommended dosages in the PALOMA-3 study. Additionally, 164 patients (80%) receiving RYBREVANT SC and 171 patients (81%) receiving intravenous amivantamab took prophylactic anticoagulants with a direct oral anticoagulant or low molecular weight heparin within the first four months of study treatment. Among patients receiving RYBREVANT SC, 33% were exposed for ≥ 6 months and 3.4% were exposed for > 1 year.

Serious adverse reactions in ≥ 2% of patients who received RYBREVANT SC in combination with lazertinib included ILD (6%) and fatigue (2.4%). A fatal adverse reaction of ILD occurred in 1 (0.5%) patient who received RYBREVANT SC and 3 (1.4%) patients who received intravenous amivantamab, both in combination with lazertinib.

Permanent discontinuations of RYBREVANT SC due to an adverse reaction occurred in 7% of patients. Adverse reactions leading to RYBREVANT SC discontinuation in ≥ 1% of patients were ILD (4.9%) and rash (1.5%).

Adverse reactions requiring RYBREVANT SC dose interruption in ≥ 5% of patients were rash (18%) and nail toxicity (9%). Adverse reactions requiring RYBREVANT SC dose reductions in ≥ 5% of patients were rash (8%) and nail toxicity (6%).

The most common adverse reactions (≥ 20%) in patients who received RYBREVANT SC in combination with lazertinib were rash, nail toxicity, fatigue, stomatitis, oedema, nausea, decreased appetite, vomiting, diarrhoea and constipation. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased lymphocyte count, decreased sodium, decreased potassium, decreased albumin, increased alanine aminotransferase, decreased platelet count, increased aspartate aminotransferase, increased gamma glutamyl transferase, and decreased haemoglobin.

Overall, the safety profile of RYBREVANT SC appears consistent with the established safety profile of intravenous amivantamab with a lower incidence of administration-related reactions in PALOMA-3 with RYBREVANT SC compared to intravenous amivantamab (13% vs. 66%) and a possible lower incidence in VTE risk (9% vs. 13%) (see Description of selected adverse reactions, below).

Table 7 summarises the adverse reactions (≥ 10%) in PALOMA-3.

Table 7: Adverse reactions (≥ 10%) in patients who received RYBREVANT SC or intravenous amivantamab in PALOMA-3

System Organ Class Adverse Reaction	**Frequency**	**RYBREVANT SC + lazertinib (N=206)**		**Intravenous amivantamab + lazertinib (N=210)**	
		All Grades (%)	**Grades 3 or 4 (%)**	**All Grades (%)**	**Grades 3 or 4 (%)**
Skin and subcutaneous tissue disorders					
Rash*	Very common	80	14	79	11
Nail toxicity*		56	3.9	54	1.4
Dry skin*		19	0	18	0
Pruritus		16	0	12	0
General disorders and administration site conditions					
Fatigue*	Very common	43	3.4	36	2.9
Oedema*		32	2.9	32	1.0
Pyrexia		12	0	10	0
Injection site reactions*		11	0	0	0
Gastrointestinal disorders					
Stomatitis*	Very common	35	0.5	38	2.9
Nausea		29	0.5	25	1.4
Vomiting		21	1.0	20	0.5
Diarrhoea		21	1.5	19	1.0

Constipation		20	0	20	0.5
Metabolism and nutrition disorders					
Decreased appetite	Very common	22	0.5	25	1.4
Musculoskeletal and connective tissue disorders					
Myalgia	Very common	16	0	6	0
Injury, poisoning and procedural complications					
Administration-related reactions	Very common	13	0.5	66	3.8
Eye disorders					
Other eye disorders[*]	Very common	12	0.5	8	0
Nervous system disorders					
Dizziness	Very common	12	0	12	0
Vascular disorders					
Venous thromboembolism[*†]	Very common	11	1.5	18	4.8

[*] Grouped terms

[†] Assessed as adverse reaction for amivantamab and lazertinib combination only.

Clinically relevant adverse reactions in < 10% of patients who received RYBREVANT SC in combination with lazertinib not included in the table above were abdominal pain (8%), haemorrhoids (6%), ILD (6%), visual impairment (2.4%), growth of eyelashes (1.5%), and keratitis (0.5%).

Table 8 summarises the laboratory abnormalities in PALOMA-3.

Table 8: Select laboratory abnormalities (≥ 20%) that worsened from baseline in patients with NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations in PALOMA-3 [†]

Laboratory abnormality	RYBREVANT SC + lazertinib (N=206)		Intravenous amivantamab + lazertinib (N=210)	
	All Grades (%)	Grades 3 or 4 (%)	All Grades (%)	Grades 3 or 4 (%)
Chemistry				
Decreased albumin	92	4.9	91	5
Increased alkaline phosphatase	47	1.5	37	0
Increased alanine aminotransferase	45	3.4	51	5
Decreased sodium	36	5	43	8
Increased aspartate aminotransferase	36	2.0	40	2.4
Decreased calcium (corrected)	33	0	36	0
Decreased magnesium	27	0	30	1.4
Increased gamma glutamyl transferase	26	2.0	27	1.9
Decreased potassium	22	5	25	4.3
Haematology				
Decreased lymphocyte count	57	6	60	29
Decreased platelet count	37	2.4	42	1.9
Decreased white blood cell	36	0.5	31	0.5
Decreased haemoglobin	34	2.0	36	2.4

[†] 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.

Clinical experience of amivantamab intravenous formulation

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

The safety data described below reflect exposure to intravenous amivantamab 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 amivantamab 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 amivantamab 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 amivantamab in combination with lazertinib, 73% were exposed to amivantamab for ≥ 6 months and 60% were exposed to amivantamab for > 1 year.

Serious adverse reactions occurred in 49% of patients who received amivantamab 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 amivantamab 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 amivantamab 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 amivantamab 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 amivantamab 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 9 summarises the adverse reactions (≥ 10%) in MARIPOSA.

Table 9: Adverse reactions (≥ 10%) in patients with previously untreated NSCLC with exon 19 insertion or exon 21 L858R substitution mutations in MARIPOSA

Adverse reaction	Amivantamab 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				
Paraesthesia*	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 amivantamab in combination with lazertinib included ILD/pneumonitis (3.1%).

Table 10 summarises the laboratory abnormalities in MARIPOSA.

Table 10: Select laboratory abnormalities (≥ 20%) that worsened from baseline in patients with previously untreated NSCLC with EGFR exon 19 insertion or exon 21 L858R substitution mutations in MARIPOSA+

Laboratory abnormality	Amivantamab + 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 intravenous amivantamab in combination with carboplatin and pemetrexed at the recommended dosage 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 amivantamab, 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 amivantamab 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 amivantamab in combination with carboplatin and pemetrexed; these included respiratory failure, sepsis, and ventricular fibrillation (0.8% each).

Dose interruptions of amivantamab 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 amivantamab 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 amivantamab due to adverse reactions. The most frequent adverse reactions that led to treatment discontinuation (≥5% of patients) were IRRs.

Table 11 summarises the most common adverse reactions in MARIPOSA-2.

Table 11: Adverse reactions (≥10%) in previously treated patients with NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations who received amivantamab in combination with carboplatin and pemetrexed in MARIPOSA-2

System organ class Adverse reaction	**Amivantamab + 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 amivantamab in combination with carboplatin and pemetrexed include: abdominal pain, haemorrhoids, dizziness, visual impairment, trichomegaly, keratitis, and interstitial lung disease.

Table 12 summarises the laboratory abnormalities in MARIPOSA-2.

Table 12: Select laboratory abnormalities (≥ 20%) that worsened from baseline in patients with NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations who received amivantamab in combination

with carboplatin and pemetrexed in MARIPOSA-2

Laboratory abnormality	Amivantamab + 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 amivantamab in combination with carboplatin and pemetrexed at the recommended dosage 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 amivantamab 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 amivantamab 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 amivantamab due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of amivantamab in ≥1% of patients were rash and ILD.

Dose interruptions of amivantamab 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 amivantamab 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 13 summarises the most common adverse reactions in PAPILLON.

Table 13: Adverse reactions (≥10%) in first-line patients with NSCLC with exon 20 insertion mutations who received amivantamab in combination with carboplatin and pemetrexed – PAPILLON

System organ class Adverse reaction	Amivantamab + 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 amivantamab in combination with carboplatin and pemetrexed included pulmonary embolism, deep vein thrombosis, skin ulcer, conjunctivitis, and interstitial lung disease (ILD)/pneumonitis.

Table 14 summarises the laboratory abnormalities in PAPILLON.

Table 14: 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	Amivantamab + 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 amivantamab as monotherapy at the recommended dosage 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 amivantamab 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 amivantamab due to adverse reactions. The most frequent adverse reactions leading to treatment discontinuation were IRR and ILD.

Table 15: Adverse reactions (≥10%) in patients with NSCLC with exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy and received amivantamab 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 amivantamab-treated patients with NSCLC exon 20 insertion mutations in CHRYSALIS included those summarised in Table 16.

Table 16: 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 amivantamab 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

Table 17: 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 amivantamab in CHRYSALIS

Laboratory abnormality	Amivantamab+ (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.

Description of selected adverse reactions

Administration-related reactions (ARR)

In PALOMA-3, ARRs were reported in 13% of patients in the RYBREVANT SC+lazertinib arm and in 66% of patients in the amivantamab IV+lazertinib arm.

Venous thromboembolic (VTE) events with concomitant use with lazertinib

In PALOMA-3, the overall incidence of VTE across both arms was 14%. Prophylactic anticoagulants were received by 80% of the RYBREVANT SC+lazertinib arm and 81% of the intravenous amivantamab+lazertinib arm.

In the RYBREVANT SC+lazertinib arm, the median time to the first VTE was 74 days (range: 17-390). VTE events occurred in 16 out of 164 patients (10%) who were receiving prophylactic anticoagulation and 6 out of 42 (14%) of those who were not, including one Grade 3 event (2.4%).

In the intravenous amivantamab+lazertinib arm, the median time to the first VTE was 111 days (range: 12-325). VTE events occurred in 25 out of 171 patients (15%) who were receiving prophylactic anticoagulation and 12 out of 39 (31%) of those who were not, including five Grade 3 events (13%).

Postmarketing experience

The following adverse reactions associated with the use of RYBREVANT were identified during postmarketing experience with intravenous amivantamab in clinical studies or postmarketing reports. 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

Blood and lymphatic system disorder: Thrombocytopenia*, neutropenia*

* only applicable to amivantamab in combination with carboplatin and pemetrexed

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 SC.

There is no known specific antidote for RYBREVANT SC overdose. In the event of an overdose, stop RYBREVANT SC, 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.

RYBREVANT SC contains recombinant human hyaluronidase (vorhyaluronidase alfa, rHuPH20). Vorhyaluronidase alfa works locally and transiently to degrade hyaluronan ((HA), a naturally occurring glycoaminoglycan found throughout the body) in the extracellular matrix of the subcutaneous space by cleaving the linkage between the two sugars (N-acetylglucosamine and glucuronic acid) which comprise HA. Vorhyaluronidase alfa has a half-life in skin of less than 30 minutes. Hyaluronan levels in subcutaneous tissue return to normal within 24 to 48 hours because of the rapid biosynthesis of hyaluronan.

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. The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies (ADA) in the studies described below with the incidence of anti-drug antibodies in other studies, including those of other amivantamab products or other hyaluronidase products.

Among a pool of study participants who received RYBREVANT SC monotherapy or as part of combination therapy, evaluable results for amivantamab ADA testing were available for 729 participants. Three participants (0.4%) was positive for treatment-emergent antibodies to amivantamab. Due to the small incidence of immunogenicity to amivantamab, the effect of immunogenicity on pharmacokinetics, safety or efficacy of RYBREVANT SC remains unknown.

Among the same pool of study participants, evaluable results for hyaluronidase (rHuPH20) ADA testing were available for 741 participants. The immunogenicity to rHuPH20 observed in these participants did not impact the pharmacokinetics of amivantamab.

Clinical trials

Non-inferiority of RYBREVANT SC versus intravenous amivantamab – PALOMA-3

The efficacy of RYBREVANT SC in patients with EGFR-mutated locally advanced or metastatic NSCLC was established based on achieving non-inferior amivantamab exposure with the use of RYBREVANT SC by comparison to intravenous amivantamab in the pharmacokinetic non-inferiority study PALOMA-3.

This was a randomised, open-label Phase 3 study in which patients with EGFR-mutated (exon 19 deletion or exon 21 L858R substitution) locally advanced or metastatic NSCLC whose disease had progressed on or after treatment with osimertinib and platinum-based chemotherapy were randomised to receive either intravenous amivantamab or RYBREVANT SC. The study

demonstrated non-inferiority of RYBREVANT SC to intravenous amivantamab on both co-primary pharmacokinetic endpoints (see section 5.2 Pharmacokinetic properties).

Descriptive efficacy was a key secondary endpoint and supported the conclusion of non-inferiority of RYBREVANT SC compared to intravenous amivantamab. The efficacy and safety findings of the pivotal clinical studies conducted using intravenous amivantamab are therefore considered applicable to RYBREVANT SC (with the exception of infusion-related reactions).

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

Previously untreated NSCLC with common EGFR mutations

The efficacy and safety of intravenous amivantamab in combination with lazertinib as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy were studied in MARIPOSA: a randomised, active-controlled, multicentre phase 3 study. 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 amivantamab in combination with lazertinib, osimertinib monotherapy, or lazertinib monotherapy (an unapproved regimen for NSCLC) until disease progression or unacceptable toxicity. Amivantamab 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.

Amivantamab 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 amivantamab in combination with lazertinib arm and 16.59 months (95% CI: 14.78, 18.46) for the osimertinib arm.

The final analysis of overall survival (OS) demonstrated a statistically significant improvement in OS for amivantamab in combination with lazertinib compared with osimertinib (see Table 18 and Figure 1). Table 18, Figure 1, and Figure 2 summarise efficacy results for amivantamab in combination with lazertinib.

Table 18: Efficacy results in MARIPOSA by BICR assessment

	Amivantamab 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 survival (OS)		
Number of events (%)	173 (40)	217 (51)
Median, months (95% CI)	NE (42.9, NE)	36.7 (33.4, 41.0)
HR (95% CI); p-value	0.75 (0.61, 0.92); p=0.0048	
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

PFS, ORR and DOR results are from data cut-off 11 August 2023 with a median follow up of 22.0 months. OS results are from data cut-off 4 December 2024 with a median follow up of 37.8 months.
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 OS in previously untreated NSCLC patients

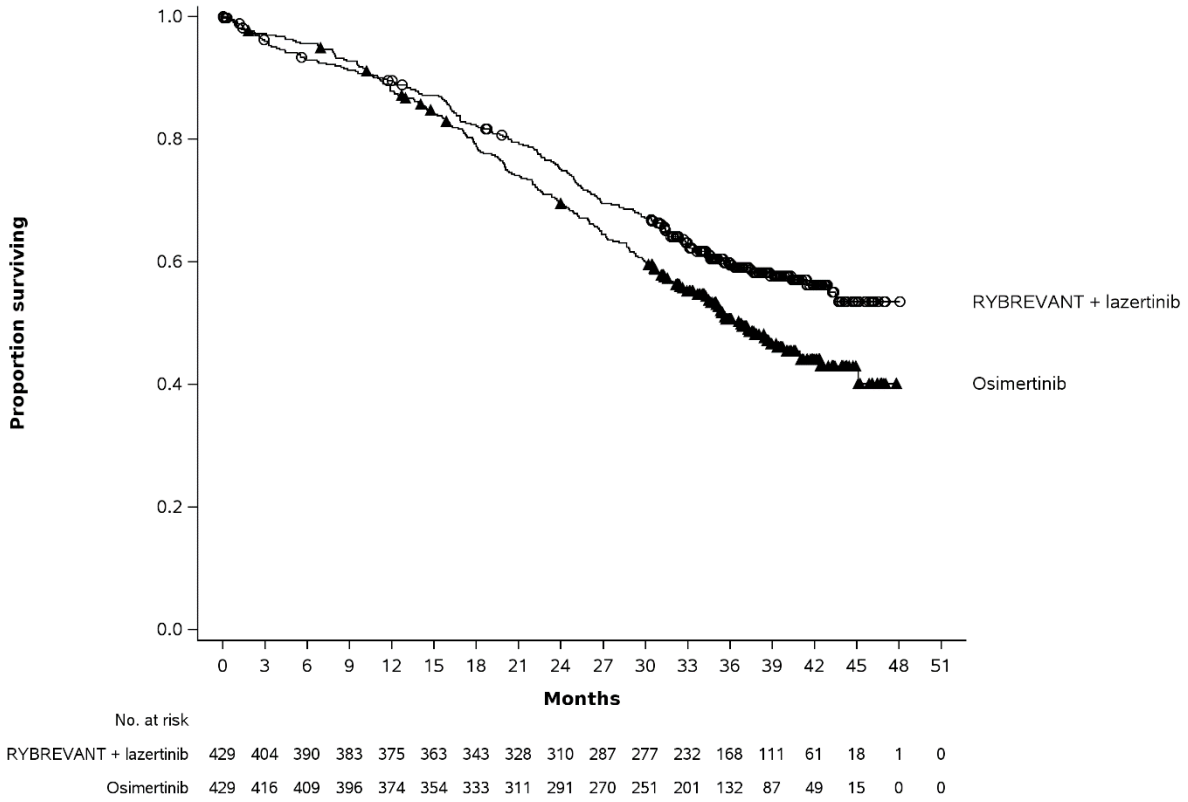
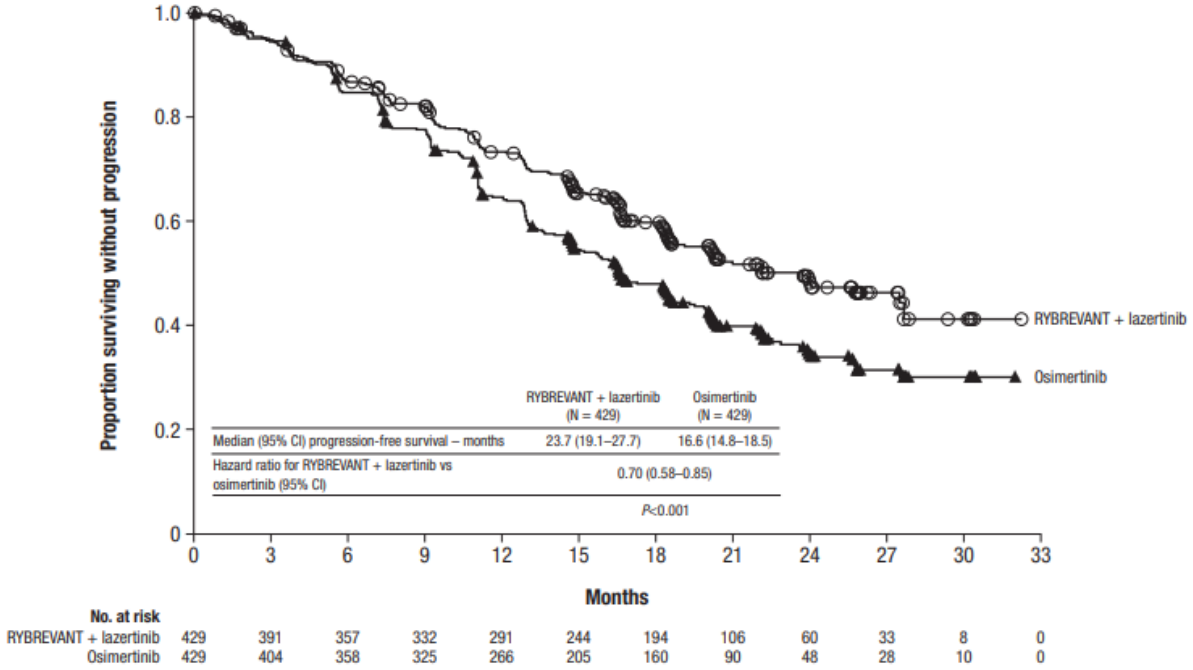
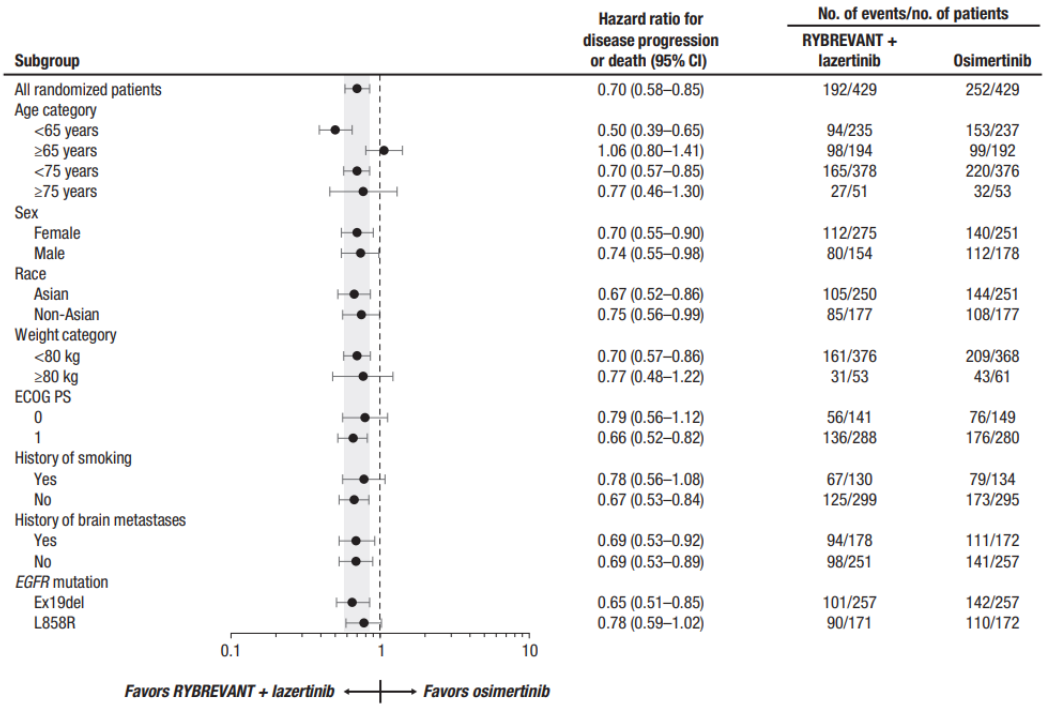


Figure 2: **Kaplan-Meier curve of PFS in previously untreated NSCLC patients by BICR assessment**



The PFS benefit of amivantamab 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 3).

Figure 3: **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 amivantamab and lazertinib relative to osimertinib was also observed (median PFS of 23.92 months in the amivantamab 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 amivantamab 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 amivantamab 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 amivantamab 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 19.

Table 19: Intracranial ORR and DOR by BICR assessment in subjects with measurable intracranial lesions at baseline - MARIPOSA

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

CI = confidence interval NE = not estimable
Intracranial ORR and DOR results are from data cut off 04 Dec 2024 with a median follow up of 37.8 months.

Previously treated NSCLC with common EGFR mutations

The efficacy of intravenous amivantamab 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 amivantamab 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 amivantamab 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 amivantamab-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.

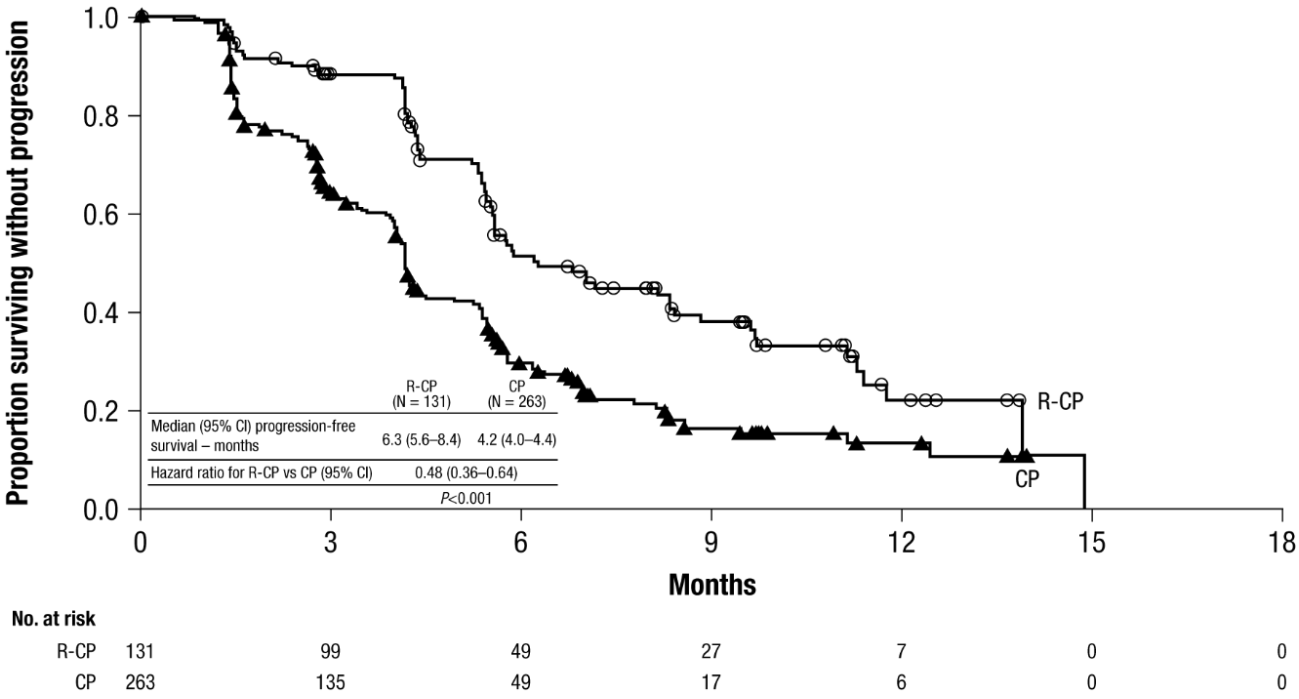
The efficacy results of MARIPOSA-2 are summarised in Table 20 and Figure 4.

Table 20: Efficacy results of MARIPOSA-2

	Amivantamab + 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 4: 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 intravenous amivantamab 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 amivantamab in combination with carboplatin and pemetrexed (N=153) or carboplatin and pemetrexed (N=155). The dosing of all agents was the same as described 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 amivantamab 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.

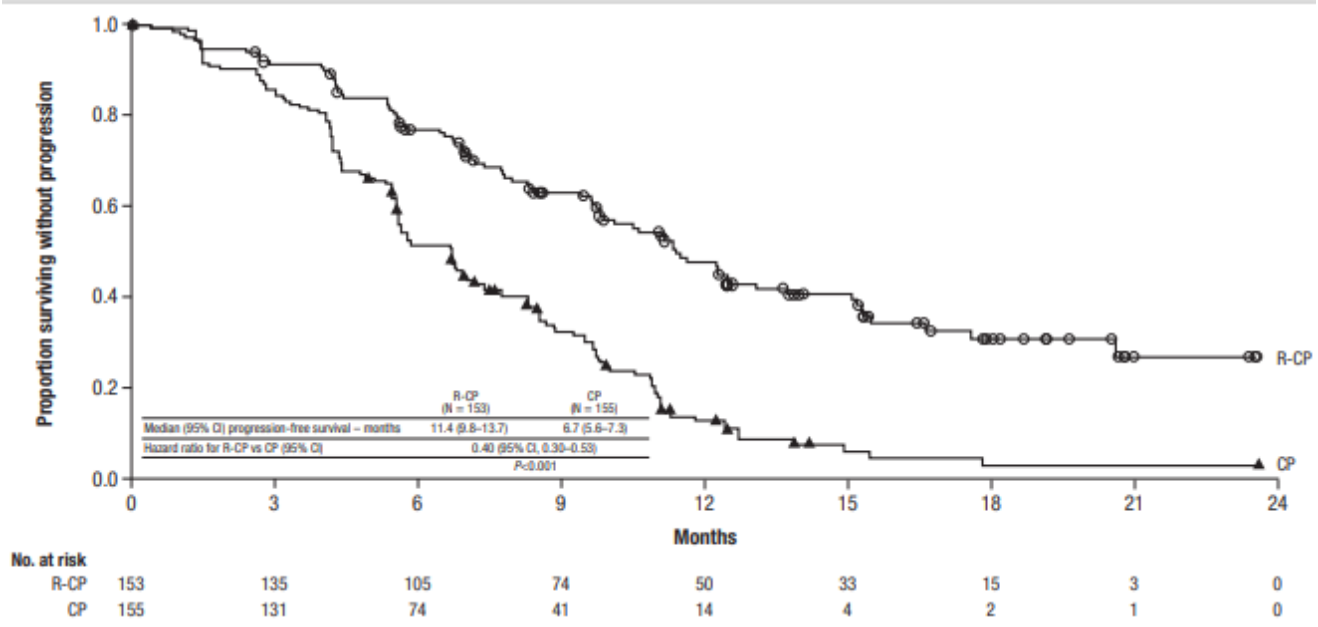
Efficacy results for PAPILLON are summarised in Table 21 and Figure 5.

Table 21: Efficacy results in PAPILLON

	Amivantamab + 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 5: 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 amivantamab as a single agent.

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

The efficacy and safety of intravenous amivantamab 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.

Amivantamab 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 22.

Table 22: 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

In alignment with dosing studied in clinical trials, three dosing regimens are approved for amivantamab: the 2-week regimen, the 3-week regimen and the 4-week regimen (see section 4.2 Dose and method of administration). The length of a treatment cycle was 28 days in studies of the every-2-week regimen and the every-4-week regimen; and was 21 days in studies of the every-3-week regimen.

The exposure of RYBREVANT SC increases in a dose proportional fashion at doses of 1050 mg (1400 mg for body weight ≥80 kg), 1600 mg (2240 mg for body weight ≥80 kg), and 2560 mg (3360 mg for body weight ≥80 kg). Maximum trough concentration (C_{trough}) is typically observed at Cycle 2 Day 1 (Day 29 with every-2-week and every-4-week dosing; Day 22 with every-3-week dosing). Steady state is reached by approximately Week 13.

PALOMA-3

The non-inferiority of RYBREVANT SC to intravenous amivantamab was established in a randomised, open-label Phase 3 study assessing the PK non-inferiority between the two formulations - both given in combination with lazertinib in 28-day cycles - to patients with EGFR-mutated locally advanced or metastatic NSCLC whose disease had progressed on or after treatment with osimertinib and platinum-based chemotherapy. Patients were required to have exon 19 deletion or exon 21 L858R substitution mutation.

Patients received RYBREVANT SC at 1600 mg (for patients < 80 kg) or 2240 mg (for patients ≥ 80 kg) by subcutaneous injection, or intravenous amivantamab at 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) by intravenous infusion; each administered once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5 until disease progression or unacceptable toxicity. In both arms, lazertinib was administered at 240 mg orally once daily. The median duration of RYBREVANT SC administration was ≤ 5 minutes compared to ≤ 5.0 hours for the intravenous formulation.

A total of 418 patients were randomised (1:1) to receive RYBREVANT SC by subcutaneous injection in combination with lazertinib (N=206) or intravenous amivantamab in combination with lazertinib (N=212), until documented clinical or radiographic disease progression.

Baseline demographics and disease characteristics were balanced across the treatment arms. The median age was 61 (range: 29-82) years with 40% of patients ≥ 65 years; 67% were female; and 61% were Asian, 37% were White, 1% were Black. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (29%) or 1 (72%); 68% never smoked; 34% had prior brain metastases; and 82% had Stage IV cancer at initial diagnosis. With regard to EGFR mutation status, 65% were exon 19 deletions and 35% were exon 21 L858R substitution mutations.

The co-primary endpoints were C_{trough} of amivantamab at steady state and AUC_{D1-D15} in Cycle 2.

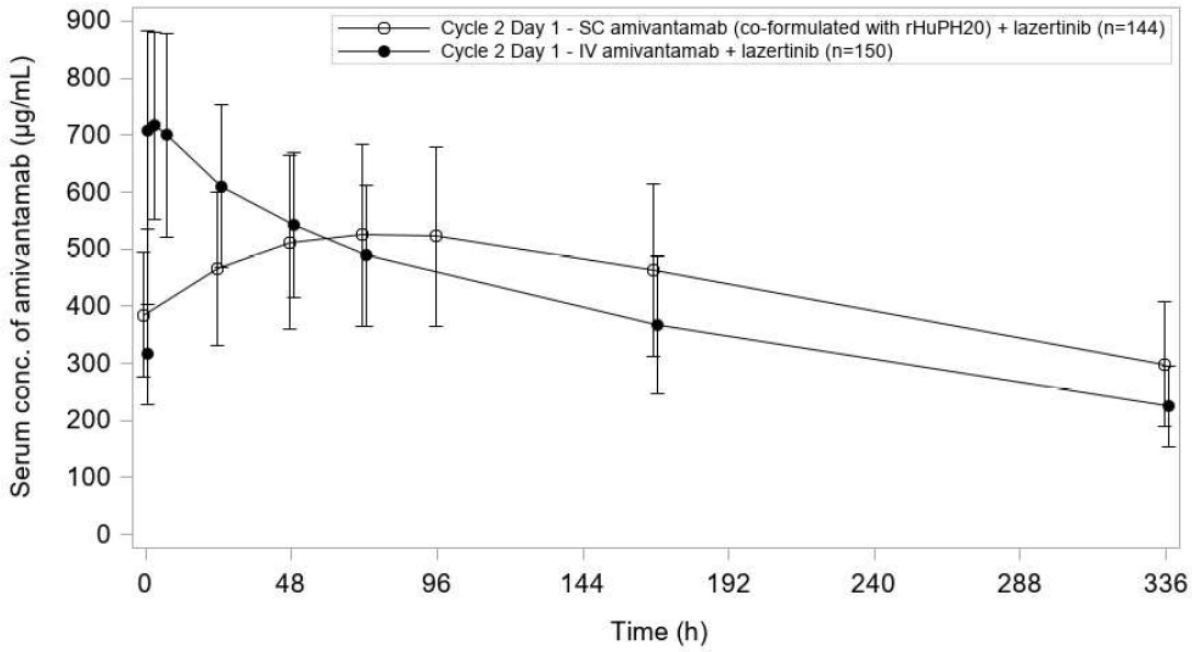
RYBREVANT SC administered subcutaneously was non-inferior to amivantamab administered intravenously in both co-primary endpoints (Table 23).

Table 23 lists the observed geometric mean (%CV) maximum trough concentrations (Cycle 2 Day 1 C_{trough}), Cycle 2 area under the concentration-time curve ($AUC_{Day\ 1-15}$), and Cycle 4 Day 1 C_{trough} following the recommended every-2-week dosing regimen of amivantamab administered subcutaneously and intravenously in patients with NSCLC. Figure 6 displays the concentration-time curve for both arms after Cycle 2 Day 1 dose.

Table 23: Summary of serum PK parameters of amivantamab in patients with NSCLC (PALOMA-3 Study)

Parameter	RYBREVANT SC 1600 mg (2240 mg for body weight ≥80 kg)	Intravenous Amivantamab 1050 mg (1400 mg for body weight ≥80 kg)
	Geometric Mean (%CV)	
Cycle 2 Day 1 C_{trough} (µg/mL)	335 (32.7%)	293 (31.7%)
Cycle 2 $AUC_{(Day1-15)}$ (µg.h/mL)	135,861 (30.7%)	131,704 (24.0%)
Cycle 4 Day 1 C_{trough} (µg/mL)	206 (39.1%)	144 (41.5%)

Figure 6: Mean serum concentration-time curves of amivantamab after Cycle 2 Day 1 dose



Absorption

Following subcutaneous administration, the geometric mean (%CV) of amivantamab bioavailability is 66.6% (14.9%) with a median time to reach maximum concentration of 3 days.

Distribution

The geometric mean (%CV) total volume of distribution for amivantamab administered subcutaneously is 5.69 L (23.8%).

Excretion

Amivantamab is cleared by parallel linear and nonlinear saturable target mediated clearances after subcutaneous administration. The estimated geometric mean (% CV) linear CL and associated-terminal half-life is 0.224 L/day (26.0%) and 18.8 days (34.3%), respectively.

Special populations

Paediatrics (17 years of age and younger)

The pharmacokinetics of RYBREVANT SC 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 (21-85 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 21% higher in males than in females, but no clinically meaningful pharmacokinetic differences were observed between male and female patients.

Weight

Increases in body weight increased the volume of distribution and clearance of RYBREVANT SC. With the recommended weight-tiered doses, exposures of RYBREVANT SC were comparable between patients who weighed < 80 kg and received 1600 mg (every-2-week dosing)/2400 mg (every-3-week dosing)/3520 mg (every-4-week dosing) and patients who weighed ≥ 80 kg and received 2240 mg (every-2-week dosing)/3360 mg (every-3-week dosing)/4640 mg (every-4-week dosing).

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
Glacial acetic acid
Sodium acetate trihydrate
Methionine
Polysorbate 80
Sucrose
Vorhyaluronidase alfa (recombinant human hyaluronidase; rHuPH20)
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.

Shelf life of prepared syringes:

The prepared syringes should be administered immediately. If immediate administration is not possible, store the prepared syringe containing RYBREVANT SC solution refrigerated at 2°C to 8°C for up to 24 hours followed by at room temperature of 15°C to 30°C for up to 24 hours. Discard the prepared syringe if stored for more than 24 hours refrigerated or more than 24 hours of being at room temperature.

If stored in the refrigerator, allow the solution to come to room temperature before administration.

Any excess volume from opened vials should be discarded (see section 6.6 Special precautions for disposal).

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 of the prepared syringe, see section 6.3 Shelf life.

6.5 NATURE AND CONTENTS OF CONTAINER

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

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

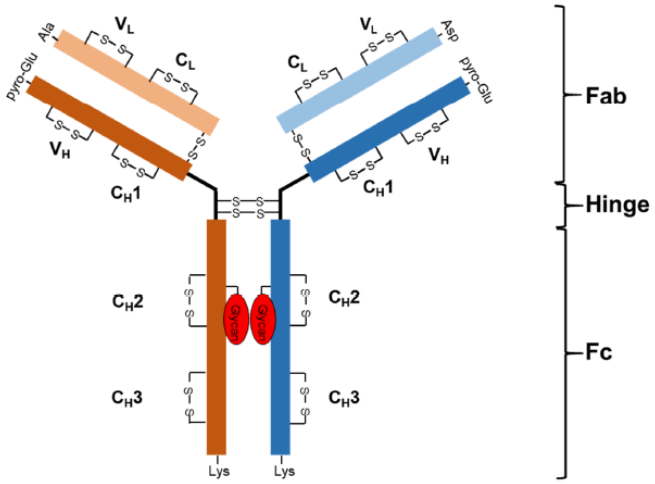
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSIOCHEMICAL PROPERTIES

Chemical structure

Figure 7: General structure of amivantamab



CAS registry number: 2171511-58-1

7. MEDICINE SCHEDULE (POISON STANDARD)

S4 Prescription Medicine

8. SPONSOR

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

9. DATE OF FIRST APPROVAL

03 October 2025

10. DATE OF REVISION

25 August 2026

Summary table of changes

Section changed	Summary of new information
2, 4,2	Addition of every-4-week dosing
4.4	Addition of prophylactic therapy to reduce the risk and severity of skin and nail reactions. Addition of adverse reactions to post-marketing experience section.
5.1	Addition of final OS data from MARIPOSA study
5.2	Addition of data pertaining to every-4-week dosing
6.7	Addition of physiochemical properties