Highlights of Prescribing Information

These highlights do not include all the information needed to use RYBREVANT safely and effectively. See full prescribing information for RYBREVANT.

RYBREVANT® (amivantamab-vmjw) injection, for intravenous use
Initial U.S. Approval: 2021

----------RECENT MAJOR CHANGES----------

Indications and Usage (1)	08/2024
Dosage and Administration (2)	08/2024
Warnings and Precautions (5)	08/2024

----------INDICATIONS AND USAGE----------

RYBREVANT is a bispecific EGF receptor-directed and MET receptor-directed antibody indicated:

- in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations, as detected by an FDA-approved test. (1, 2.2)
- in combination with carboplatin and pemetrexed 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 20 insertion mutations, as detected by an FDA-approved test. (1, 2.2)
- as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy. (1, 2.2)

----------DOSAGE AND ADMINISTRATION----------

- The recommended dosage of RYBREVANT is based on baseline body weight and administered as an intravenous infusion after dilution. (2.3, 2.5, 2.6, 2.7)
- Administer premedications as recommended. (2.4)
- Administer via a peripheral line on Week 1 and Week 2. (2.7)
- Administer RYBREVANT in combination with chemotherapy weekly for 4 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 3 weeks starting at Week 7. (2.3)
- Administer RYBREVANT in combination with lazertinib or RYBREVANT as a single agent weekly for 5 weeks, with the initial dose as a split infusion in Week 1 on Day 1 and Day 2, then administer every 2 weeks starting at Week 7. (2.4)
- When administering RYBREVANT in combination with lazertinib, administer anticoagulant prophylaxis to prevent venous thromboembolic (VTE) events for the first four months of treatment. (2.4)
- Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 8 and 9. (2.8)

Body Weight (at Baseline)	Dosage	Recommended Dose
RYBREVANT in Combination with Carboplatin and Pemetrexed		
Less than 80 kg	Weeks 1-4	1400 mg
	Week 7 onwards	1750 mg
Greater than or equal to 80 kg	Weeks 1-4	1750 mg
	Week 7 onwards	2100 mg
RYBREVANT in Combination with Lazertinib or RYBREVANT as a Single Agent		
Less than 80 kg	Weeks 1-5 Week 7 onwards	1050 mg
Greater than or equal to 80 kg	Weeks 1-5 Week 7 onwards	1400 mg

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 350 mg/7 mL (50 mg/mL) solution in a single-dose vial (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Infusion-Related Reactions (IRR): Interrupt infusion at the first sign of IRRs. Reduce infusion rate or permanently discontinue RYBREVANT based on severity. (2.5, 5.1)
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening symptoms indicative of ILD. Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed. (2.5, 5.2)
- Venous Thromboembolic (VTE) Events with Concomitant Use with Lazertinib: Prophylactic anticoagulation is recommended for the first four months of treatment. Monitor for signs and symptoms of VTE and treat as medically appropriate. Withhold RYBREVANT and lazertinib based on severity. Once anticoagulant treatment has been initiated, resume RYBREVANT and lazertinib at the same dose at the discretion of the healthcare provider. Permanently discontinue RYBREVANT and continue lazertinib for recurrent VTE despite therapeutic anticoagulation. (2.5, 5.3)
- Dermatologic Adverse Reactions: Can cause severe rash including toxic epidermal necrolysis (TEN) and acneiform dermatitis. Withhold, reduce the dose or permanently discontinue RYBREVANT based on severity. (2.5, 5.4)
- Ocular Toxicity: Promptly refer patients with worsening eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity. (2.5, 5.5)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise females of reproductive potential of the potential risk to the fetus and to use effective contraception. (5.6, 8.1, 8.3)

----------ADVERSE REACTIONS----------

RYBREVANT in Combination with Lazertinib

- The most common adverse reactions (≥ 20%) were rash, nail toxicity, infusion-related reaction, musculoskeletal pain, stomatitis, edema, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, nausea and ocular toxicity. (6.1)
- The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, decreased sodium, increased ALT, decreased potassium, decreased hemoglobin, increased AST, increased GGT, and increased magnesium. (6.1)

RYBREVANT in Combination with Carboplatin and Pemetrexed

- The most common adverse reactions (≥ 20%) were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. (6.1)
- The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes. (6.1)

RYBREVANT as a Single Agent

- The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. (6.1)
- The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased alkaline phosphatase, increased glucose, increased gamma-glutamyl transferase, and decreased sodium. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-526-7736 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 First-Line Treatment of NSCLC with *EGFR* Exon 19 Deletions or Exon 21 L858R Substitution Mutations

RYBREVANT in combination with lazertinib, is indicated 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, as detected by an FDA-approved test. *[see Dosage and Administration (2.2)]*.

1.2 First-Line Treatment of NSCLC with *EGFR* Exon 20 Insertion Mutations

RYBREVANT is indicated in combination with carboplatin and pemetrexed for the first-line treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.2)]*.

1.3 Previously Treated NSCLC with *EGFR* Exon 20 Insertion Mutations

RYBREVANT is indicated as a single agent for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations, as detected by an FDA-approved test *[see Dosage and Administration (2.2)]*, whose disease has progressed on or after platinum-based chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage Information

- Administer premedications before each RYBREVANT infusion as recommended *[see Dosage and Administration (2.5)]*.
- Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 8 and 9, with the initial dose as a split infusion on Week 1 on Day 1 and Day 2 *[see Dosage and Administration (2.8)]*.
- Administer RYBREVANT via peripheral line for Week 1 Day 1 and 2 and Week 2 to reduce the risk of infusion-related reactions *[see Dosage and Administration 2.8]*.
- When administering RYBREVANT in combination with carboplatin and pemetrexed, infuse pemetrexed first, carboplatin second, and RYBREVANT last *[see Dosage and Administration 2.8]*.
- When administering RYBREVANT in combination with lazertinib, administer lazertinib orally any time before the RYBREVANT infusion *[see Dosage and Administration 2.8]*.
- When administering RYBREVANT in combination with lazertinib, administer anticoagulant prophylaxis to prevent venous thromboembolic (VTE) events for the first four months of treatment *[see Dosage and Administration 2.4]*.

2.2 Patient Selection

Select patients for treatment with RYBREVANT based on the presence of a mutation as detected by an FDA-approved test.

Table 1: Patient Selection

Indication	Treatment Regimen	Source for Testing
First-Line Treatment of NSCLC with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations *[see Indications and Usage (1.1)]*	RYBREVANT in combination with lazertinib	• Tumor or plasma specimens. • Testing may be performed at any time from initial diagnosis. • Testing does not need to be repeated once EGFR mutation status has been established.
First-Line Treatment of NSCLC with EGFR Exon 20 Insertion Mutations *[see Indications and Usage (1.2)]*	RYBREVANT in combination with carboplatin and pemetrexed	
Previously Treated NSCLC with EGFR Exon 20 Insertion Mutations *[see Indications and Usage (1.3)]*	RYBREVANT as a single agent	

Information on FDA approved tests is available at: http://www.fda.gov/CompanionDiagnostics.

2.3 Recommended Dosage of RYBREVANT for First-line Treatment of NSCLC with Exon 20 Insertion Mutations (RYBREVANT in Combination with Carboplatin and Pemetrexed) – Every 3-week dosing

The recommended dosage of RYBREVANT, administered in combination with carboplatin and pemetrexed, is based on baseline body weight is provided in Table 2.

Table 2: Recommended Dosage for RYBREVANT in Combination with Carboplatin and Pemetrexed

Body weight at Baseline[a]	**Recommended Dose**	**Dosing Schedule**
Less than 80 kg	1400 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Weeks 5 and 6 – no dose
	1750 mg	Every 3 weeks starting at Week 7 onwards
Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) from Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1 • Weeks 5 and 6 – no dose
	2100 mg	Every 3 weeks starting at Week 7 onwards

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

The recommended order of administration and regimen for RYBREVANT in combination with carboplatin and pemetrexed are provided in Table 3.

Table 3: Order of Administration and Regimen for RYBREVANT in Combination with Carboplatin and Pemetrexed

RYBREVANT in Combination with Carboplatin and Pemetrexed		
Administer the regimen in the following order: pemetrexed first, carboplatin second and RYBREVANT last.		
Drug	**Dose**	**Duration/Timing of Treatment**
Pemetrexed	Pemetrexed 500 mg/m^2 intravenously Refer to the pemetrexed Full Prescribing Information for complete information.	Every 3 weeks, continue until disease progression or unacceptable toxicity.
Carboplatin	Carboplatin AUC 5 intravenously Refer to the carboplatin Full Prescribing Information for complete information.	Every 3 weeks for up to 12 weeks.
RYBREVANT	RYBREVANT intravenously See Table 2.	Every 3 weeks, continue until disease progression or unacceptable toxicity.

2.4 Recommended Dosage of RYBREVANT in Combination with Lazertinib or RYBREVANT as a Single Agent - Every 2-week dosing

The recommended dosage of RYBREVANT in combination with lazertinib or RYBREVANT as a single agent, based on baseline body weight, are provided in Table 4.

Table 4: Recommended Dosage Schedule for RYBREVANT in Combination with Lazertinib or RYBREVANT as a Single Agent

Body weight at Baseline[a]	Recommended Dose	Dosing Schedule
Less than 80 kg	1050 mg	Weekly (total of 5 doses) from Weeks 1 to 5 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 5 - infusion on Day 1 • Week 6 – no dose
		Every 2 weeks starting at Week 7 onwards
Greater than or equal to 80 kg	1400 mg	Weekly (total of 5 doses) from Weeks 1 to 5 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 5 - infusion on Day 1 • Week 6 – no dose
		Every 2 weeks starting at Week 7 onwards

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

Administer RYBREVANT until disease progression or unacceptable toxicity.

RYBREVANT in Combination with Lazertinib

Order of Administration

When given in combination with lazertinib, administer RYBREVANT any time after lazertinib when given on the same day. Refer to the lazertinib prescribing information for recommended lazertinib dosing information. Administer RYBREVANT in combination with lazertinib until disease progression or unacceptable toxicity.

Concomitant Medications

When initiating treatment with RYBREVANT in combination with lazertinib, administer anticoagulant prophylaxis to prevent venous thromboembolic (VTE) events for the first four months of treatment *[see Warnings and Precautions (5.3)]*. If there are no signs or symptoms of VTE during the first four months of treatment, consider discontinuation of anticoagulant prophylaxis at the discretion of the healthcare provider. Refer to the lazertinib prescribing information for information about concomitant medications.

When initiating treatment with RYBREVANT in combination with lazertinib, administer alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream and encourage patients to limit sun exposure during and for 2 months after treatment, to wear protective clothing and use broad-spectrum UVA/UVB sunscreen to reduce the risk of dermatologic adverse reactions *[see Warnings and Precautions (5.4)]*. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions. Refer to the lazertinib prescribing information for information about concomitant medications.

2.5 Recommended Premedications

Prior to the initial infusion of RYBREVANT (Week 1, Day 1 and 2), administer premedications as described in Table 5 to reduce the risk of infusion-related reactions *[see Warnings and Precautions (5.1)]*.

Glucocorticoid administration is required for Week 1, Day 1 and 2 dose only and upon re-initiation after prolonged dose interruptions, then as necessary for subsequent infusions (see Table 5). Administer both antihistamine and antipyretic prior to all infusions.

Table 5: Premedications

Medication	Dose	Route of Administration	Dosing Window Prior to RYBREVANT Administration
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Acetaminophen (650 to 1,000 mg)	Intravenous	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (20 mg) or equivalent	Intravenous	45 to 60 minutes
Glucocorticoid+	Dexamethasone (10 mg) or equivalent	Intravenous	45 to 60 minutes

* Required at all doses.

‡ Required at initial dose (Week 1 Day 1)

\+ Required at second dose (Week 1 Day 2); optional for subsequent doses.

2.6 Dosage Modifications for Adverse Reactions

The recommended dose reductions for adverse reactions for RYBREVANT are listed in Table 6.

Table 6: Dose Reductions for Adverse Reactions for RYBREVANT

Dose at which the adverse reaction occurred	1st Dose Reduction	2nd Dose Reduction	3rd Dose Reduction
1050 mg	700 mg	350 mg	Discontinue RYBREVANT
1400 mg	1050 mg	700 mg	
1750 mg	1400 mg	1050 mg	
2100 mg	1750 mg	1400 mg	

The recommended dosage modifications and management for adverse reactions for RYBREVANT are provided in Table 7.

Table 7: Recommended Dosage Modifications and Management for Adverse Reactions for RYBREVANT

Adverse Reaction	Severity	Dosage Modifications
Infusion-related reactions (IRR) *[see Warnings and Precautions (5.1)]*	Grade 1 to 2	• Interrupt RYBREVANT infusion if IRR is suspected and monitor patient until reaction symptoms resolve. • Resume the infusion at 50% of the infusion rate at which the reaction occurred. • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Tables 8 and 9). • Include corticosteroid with premedications for subsequent dose (see Table 5).

	Grade 3	• Interrupt RYBREVANT infusion and administer supportive care medications. Continuously monitor patient until reaction symptoms resolve. • Resume the infusion at 50% of the infusion rate at which the reaction occurred. • If there are no additional symptoms after 30 minutes, the infusion rate may be escalated (see Tables 8 and 9). • Include corticosteroid with premedications for subsequent dose (see Table 5). For recurrent Grade 3, permanently discontinue RYBREVANT.
	Grade 4	• Permanently discontinue RYBREVANT.
Interstitial Lung Disease (ILD)/pneumonitis *[see Warnings and Precautions (5.2)]*	Any Grade	• Withhold RYBREVANT if ILD/pneumonitis is suspected. • Permanently discontinue RYBREVANT if ILD/pneumonitis is confirmed.
Venous Thromboembolic (VTE) Events *[Applies to the combination with lazertinib, see Warnings and Precautions (5.3)]*	Grade 2 or 3	• Withhold RYBREVANT and lazertinib. • Administer anticoagulant treatment as clinically indicated. • Once anticoagulant treatment has been initiated, resume RYBREVANT and lazertinib at the same dose level, at the discretion of the healthcare provider.
	Grade 4 or recurrent Grade 2 or 3 despite therapeutic level anticoagulation	• Withhold lazertinib and permanently discontinue RYBREVANT. • Administer anticoagulant treatment as clinically indicated. • Once anticoagulant treatment has been initiated, treatment can continue with lazertinib at the same dose level at the discretion of the healthcare provider.
Dermatologic Adverse Reactions (including dermatitis acneiform, pruritus, dry skin) *[see Warnings and Precautions (5.4)]*	Grade 1 or Grade 2	• Initiate supportive care management. • Reassess after 2 weeks; if rash does not improve, consider dose reduction.
	Grade 3	• Withhold RYBREVANT and initiate supportive care management. • Upon recovery to ≤ Grade 2, resume RYBREVANT at reduced dose. • If no improvement within 2 weeks, permanently discontinue treatment.
	Grade 4	• Permanently discontinue RYBREVANT.
	Severe bullous, blistering or exfoliating skin conditions (including toxic epidermal necrolysis (TEN)	• Permanently discontinue RYBREVANT.
Other Adverse Reactions *[see Adverse Reactions (6.1)]*	Grade 3	• Withhold RYBREVANT until recovery to ≤ Grade 1 or baseline. • Resume at the same dose if recovery occurs within 1 week. • Resume at reduced dose if recovery occurs after 1 week but within 4 weeks.

		• Permanently discontinue if recovery does not occur within 4 weeks.
	Grade 4	• Withhold RYBREVANT until recovery to ≤Grade 1 or baseline. • Resume at reduced dose if recovery occurs within 4 weeks. • Permanently discontinue if recovery does not occur within 4 weeks. • Permanently discontinue for recurrent Grade 4 reactions.

Recommended Dosage Modifications for Adverse Reactions for RYBREVANT in Combination with Lazertinib

When administering RYBREVANT in combination with lazertinib, if there is an adverse reaction requiring dose reduction after withholding treatment and resolution, reduce the dose of RYBREVANT first.

Refer to the lazertinib prescribing information for information about dosage modifications for lazertinib.

Recommended Dosage Modifications for Adverse Reactions for RYBREVANT in Combination with Carboplatin and Pemetrexed

When administering RYBREVANT in combination with carboplatin and pemetrexed, modify the dosage of one or more drugs. Withhold or discontinue RYBREVANT as shown in Table 7. Refer to prescribing information for carboplatin and pemetrexed for additional dosage modification information.

2.7 Preparation

Dilute and prepare RYBREVANT for intravenous infusion before administration.

- Check that the RYBREVANT solution is colorless to pale yellow. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if discoloration or visible particles are present.
- Determine the dose required and number of RYBREVANT vials needed based on patient's baseline weight *[see Dosage and Administration (2.3)]*. Each vial of RYBREVANT contains 350 mg of amivantamab-vmjw.
- Withdraw and then discard a volume of either 5% Dextrose Injection or 0.9% Sodium Chloride Injection from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Only use infusion bags made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).

- Withdraw 7 mL of RYBREVANT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Discard any unused portion left in the vial.
- Gently invert the bag to mix the solution. Do not shake.
- Diluted solutions should be administered within 10 hours (including infusion time) at room temperature 15°C to 25°C (59°F to 77°F).

2.8 Administration

- Administer the diluted RYBREVANT solution *[see Dosage and Administration (2.7)]* by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer).
- Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
- The administration set with filter, **must** be primed with either 5% Dextrose Injection or 0.9% Sodium Chloride Injection prior to the initiation of each RYBREVANT infusion.
- Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.

RYBREVANT in Combination with Carboplatin and Pemetrexed

- Administer RYBREVANT in combination with carboplatin and pemetrexed infusions every 3 weeks intravenously until disease progression or unacceptable toxicity according to the infusion rates in Table 8.
- Administer RYBREVANT via a peripheral line on Week 1 and Week 2 given the high incidence of infusion-related reactions during initial treatment *[see Warnings and Precautions (5.1)]*.
- RYBREVANT may be administered via central line for subsequent weeks.
- For the initial infusion, prepare RYBREVANT as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion related reaction.
- Administer the pemetrexed infusion first, carboplatin infusion second, and the RYBREVANT infusion last.

Table 8: Infusion Rates of RYBREVANT for First-line Treatment of NSCLC with Exon 20 Insertion Mutations (RYBREVANT in Combination with Carboplatin and Pemetrexed)

Body Weight Less Than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate (mL/hr)**	**Subsequent Infusion Rate† (mL/hr)**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50	75

Week 1 *Day 2*	1050 mg	33	50
Week 2	1400 mg	65	
Week 3	1400 mg	85	
Week 4	1400 mg	125	
Weeks 5 and 6	No dose		
Week 7 and every 3 weeks thereafter	1750 mg	125	
Body Weight Greater Than or Equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate (mL/hr)**	**Subsequent Infusion Rate (mL/hr)**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50	75
Week 1 *Day 2*	1400 mg	25	50
Week 2	1750 mg	65	
Week 3	1750 mg	85	
Week 4	1750 mg	125	
Week 5 and 6	No dose		
Week 7 and every 3 weeks thereafter	2100 mg	125	

† In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time approximately 4-6 hours for day 1 and 6-8 hours for day 2. Subsequent infusion time is approximately 2 hours.

RYBREVANT in Combination with Lazertinib or RYBREVANT as a Single Agent

- Administer RYBREVANT as a single agent infusion every 2 weeks intravenously until disease progression or unacceptable toxicity according to the infusion rates in Table 9.
- Administer RYBREVANT via a peripheral line on Week 1 and Week 2, given the high incidence of infusion-related reactions during initial treatment *[see Warnings and Precautions (5.1)]*.
- RYBREVANT may be administered via central line for subsequent weeks.
- For the initial infusion, prepare RYBREVANT as close to administration time as possible to allow for the possibility of extended infusion time in the event of an infusion related reaction.
- When given in combination with lazertinib, administer RYBREVANT any time after lazertinib when given on the same day.

Table 9: Infusion Rates of RYBREVANT in Combination with Lazertinib or RYBREVANT as Single Agent

Body Weight Less Than 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate (mL/hr)**	**Subsequent Infusion Rate† (mL/hr)**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50	75
Week 1 *Day 2*	700 mg	50	75
Week 2	1050 mg	85	
Week 3	1050 mg	125	
Week 4	1050 mg	125	
Week 5	1050 mg	125	
Week 6	No dose		
Week 7 and every 2 weeks thereafter	1050 mg	125	
Body Weight Greater Than or Equal to 80 kg			
Week	**Dose (per 250 mL bag)**	**Initial Infusion Rate (mL/hr)**	**Subsequent Infusion Rate† (mL/hr)**
Week 1 (split dose infusion)			
Week 1 *Day 1*	350 mg	50	75
Week 1 *Day 2*	1050 mg	35	50
Week 2	1400 mg	65	
Week 3	1400 mg	85	
Week 4	1400 mg	125	
Week 5	1400 mg	125	
Week 6	No dose		
Week 7 and every 2 weeks thereafter	1400 mg	125	

† In the absence of infusion-related reactions, increase the initial infusion rate to the subsequent infusion rate after 2 hours based on patient tolerance. Total infusion time approximately 4-6 hours for day 1 and 6-8 hours for day 2. Subsequent infusion time is approximately 2 hours.

3 DOSAGE FORMS AND STRENGTHS

Injection: 350 mg/7 mL (50 mg/mL) colorless to pale yellow solution in a single-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion-Related Reactions

RYBREVANT can cause infusion-related reactions (IRR); signs and symptoms of IRR include dyspnea, flushing, fever, chills, nausea, chest discomfort, hypotension and vomiting. The median time to IRR onset is approximately 1 hour.

RYBREVANT with Lazertinib

RYBREVANT in combination with lazertinib can cause infusion-related reactions. In MARIPOSA, *[see Adverse Reactions (6.1)]*, IRRs occurred in 63% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 in 5% and Grade 4 in 1% of patients. The incidence of infusion modifications due to IRR was 54%, and IRRs leading to dose reduction of RYBREVANT occurred in 0.7% of patients. Infusion-related reactions leading to permanent discontinuation of RYBREVANT occurred in 4.5% of patients receiving RYBREVANT in combination with lazertinib.

RYBREVANT with Carboplatin and Pemetrexed

In PAPILLON, *[see Adverse Reactions (6.1)]*, infusion-related reactions occurred in 42% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, including Grade 3 (1.3%) adverse reactions. The incidence of infusion modifications due to IRR was 40%, and 0.7% of patients permanently discontinued RYBREVANT.

RYBREVANT as a Single Agent

In CHRYSALIS, *[see Adverse Reactions (6.1)],* IRR occurred in 66% of patients treated with RYBREVANT as a single agent. Among patients receiving treatment on Week 1 Day 1, 65% experienced an IRR, while the incidence of IRR was 3.4%with the Day 2 infusion, 0.4% with the Week 2 infusion, and cumulatively 1.1% with subsequent infusions. Of the reported IRRs, 97% were Grade 1-2, 2.2% were Grade 3, and 0.4% were Grade 4. The median time to onset was 1 hour (range 0.1 to 18 hours) after start of infusion. The incidence of infusion modifications due to IRR was 62%, and 1.3% of patients permanently discontinued RYBREVANT due to IRR.

Premedicate with antihistamines, antipyretics, and glucocorticoids and infuse RYBREVANT as recommended *[see Dosage and Administration (2.4)]*. Administer RYBREVANT via a peripheral line on Week 1 and Week 2 to reduce the risk of infusion-related reactions *[see Dosage and Administration (2.7)]*.

Monitor patients for signs and symptoms of infusion reactions during RYBREVANT infusion in a setting where cardiopulmonary resuscitation medication and equipment are available. Interrupt infusion if IRR is suspected. Reduce the infusion rate or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.5)]*.

5.2 Interstitial Lung Disease/Pneumonitis

RYBREVANT can cause severe and fatal interstitial lung disease (ILD)/pneumonitis.

RYBREVANT with Lazertinib

In MARIPOSA, *[see Adverse Reactions (6.1)],* ILD/pneumonitis occurred in 3.1% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 in 1.0% and Grade 4 in 0.2% of patients. There was one fatal case of ILD/pneumonitis and 2.9% of patients permanently discontinued RYBREVANT and lazertinib due to ILD/pneumonitis *[see Adverse Reactions (6.1)].*

RYBREVANT with Carboplatin and Pemetrexed

In PAPILLON, *[see Adverse Reactions (6.1)],* Grade 3 ILD/pneumonitis occurred in 2.6% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, all patients required permanent discontinuation.

RYBREVANT as a Single Agent

In CHRYSALIS *[see Adverse Reactions (6.1)]*, ILD/pneumonitis occurred in 3.3% of patients treated with RYBREVANT as a single agent, with 0.7 % of patients experiencing Grade 3 ILD/pneumonitis. Three patients (1%) discontinued RYBREVANT due to ILD/pneumonitis.

Monitor patients for new or worsening symptoms indicative of ILD/pneumonitis (e.g., dyspnea, cough, fever). Immediately withhold RYBREVANT in patients with suspected ILD/pneumonitis and permanently discontinue if ILD/pneumonitis is confirmed *[see Dosage and Administration (2.5)]*.

5.3 Venous Thromboembolic (VTE) Events with Concomitant Use of RYBREVANT and Lazertinib

RYBREVANT in combination with lazertinib can cause serious and fatal venous thromboembolic (VTEs) events, including deep vein thrombosis and pulmonary embolism. The majority of these events occurred during the first four months of therapy *[see Adverse Reaction (6.1)]*.

In MARIPOSA *[see Adverse Reactions (6.1)],* VTEs occurred in 36% of patients receiving RYBREVANT in combination with lazertinib, including Grade 3 in 10% and Grade 4 in 0.5% of patients. On-study VTEs occurred in 1.2% of patients (n=5) while receiving anticoagulation therapy. There were two fatal cases of VTE (0.5%), 9% of patients had VTE leading to dose interruptions of RYBREVANT, 1% of patients had VTE leading to dose reductions of RYBREVANT, and 3.1% of patients had VTE leading to permanent discontinuation of RYBREVANT. The median time to onset of VTEs was 84 days (range: 6 to 777).Administer prophylactic anticoagulation for the first four months of treatment *[see Dosage and Administration (2.3)].* The use of Vitamin K antagonists is not recommended. Monitor for signs and symptoms of VTE events and treat as medically appropriate.

Withhold RYBREVANT and lazertinib based on severity *[see Dosage and Administration (2.6)]*. Once anticoagulant treatment has been initiated, resume RYBREVANT and lazertinib at the same dose level at the discretion of the healthcare provider *[see Dosage and Administration (2.4)].* In the event of VTE recurrence despite therapeutic anticoagulation, permanently discontinue RYBREVANT. Treatment can continue with lazertinib at the same dose level at the discretion of

the healthcare provider *[see Dosage and Administration (2.5)]*. Refer to the lazertinib prescribing information for recommended lazertinib dosage modification.

5.4 Dermatologic Adverse Reactions

RYBREVANT can cause severe rash including toxic epidermal necrolysis (TEN), dermatitis acneiform, pruritus and dry skin.

RYBREVANT with Lazertinib

In MARIPOSA, *[see Adverse Reactions (6.1)]*, rash occurred in 86% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 in 26% of patients. The median time to onset of rash was 14 days (range: 1 to 556 days). Rash leading to dose interruptions of RYBREVANT occurred in 37% of patients, rash leading to dose reductions of RYBREVANT occurred in 23% of patients, and rash leading to permanent discontinuation of RYBREVANT occurred in 5% of patients.

RYBREVANT with Carboplatin and Pemetrexed

In PAPILLON *[see Adverse Reactions (6.1)]*, rash occurred in 89% of patients treated with RYBREVANT in combination with carboplatin and pemetrexed, including Grade 3 (19%) adverse reactions. Rash leading to dose reductions occurred in 19% of patients, and 2% permanently discontinued RYBREVANT and 1.3% discontinued pemetrexed.

RYBREVANT as a Single Agent

In CHRYSALIS *[see Adverse Reactions (6.1)]*, rash occurred in 74% of patients treated with RYBREVANT as a single agent, including Grade 3 rash in 3.3% of patients. The median time to onset of rash was 14 days (range: 1 to 276 days). Rash leading to dose reduction occurred in 5% of patients, and RYBREVANT was permanently discontinued due to rash in 0.7% of patients *[see Adverse Reactions (6.1)]*.

Toxic epidermal necrolysis (TEN) occurred in one patient (0.3%) treated with RYBREVANT as a single agent.

Instruct patients to limit sun exposure during and for 2 months after treatment with RYBREVANT. Advise patients to wear protective clothing and use broad-spectrum UVA/UVB sunscreen. Alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream is recommended for dry skin.

When initiating treatment with RYBREVANT, administer alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of dermatologic adverse reactions. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions. If skin reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 reactions, add oral steroids and consider dermatologic consultation. Promptly refer patients presenting with severe rash, atypical appearance or distribution, or lack of improvement within 2 weeks to a dermatologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.6)]*.

5.5 Ocular Toxicity

RYBREVANT can cause ocular toxicity including keratitis, blepharitis, dry eye symptoms, conjunctival redness, blurred vision, visual impairment, ocular itching, eye pruritus and uveitis.

RYBREVANT with Lazertinib

In MARIPOSA *[see Adverse Reactions (6.1)]*, ocular toxicity occurred in 16% of patients treated with RYBREVANT in combination with lazertinib, including Grade 3 or 4 ocular toxicity in 0.7% of patients. Withhold, reduce the dose, or permanently discontinue RYBREVANT and continue lazertinib based on severity *[see Dosage and Administration (2.4)]*.

RYBREVANT with Carboplatin and Pemetrexed

In PAPILLON *[see Adverse Reactions (6.1)]*, ocular toxicity including blepharitis, dry eye, conjunctival redness, blurred vision, and eye pruritus occurred in 9%. All events were Grade 1-2.

RYBREVANT as a Single Agent

In CHRYSALIS *[see Adverse Reactions (6.1)],* keratitis occurred in 0.7% and uveitis occurred in 0.3% of patients treated with RYBREVANT. All events were Grade 1-2.

Promptly refer patients with new or worsening eye symptoms to an ophthalmologist. Withhold, dose reduce or permanently discontinue RYBREVANT based on severity *[see Dosage and Administration (2.6)].*

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action and findings from animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. Administration of other EGFR inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryo lethality, and abortion. Advise females of reproductive potential of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT. *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Infusion-Related Reactions *[see Warnings and Precautions (5.1)]*
- Interstitial Lung Disease/Pneumonitis *[see Warnings and Precautions (5.2)]*
- Venous Thromboembolic Events *[see Warnings and Precautions (5.3)]*
- Dermatologic Adverse Reactions *[see Warnings and Precautions (5.4)]*

- Ocular Toxicity *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

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.

The data described in the WARNINGS AND PRECAUTIONS reflect exposure to RYBREVANT in combination with lazertinib in the MARIPOSA study in 421 patients with previously untreated locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutations in MARIPOSA *[see Clinical Studies (14)]*. Patients received RYBREVANT intravenously at 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5 in combination with lazertinib, 240 mg orally once daily, until disease progression or unacceptable toxicity. Among 421 patients who received RYBREVANT in combination with lazertinib, 73% were exposed for 6 months or longer and 59% were exposed for greater than one year. The most common adverse reactions (≥20%) were rash, nail toxicity, infusion-related reaction, edema, musculoskeletal pain, stomatitis, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, dry skin, hemorrhage, decreased appetite, pruritus, nausea and ocular toxicity. The most common Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased ALT, decreased sodium, decreased hemoglobin, increased AST, increased GGT and increased magnesium.

The data described in the WARNINGS AND PRECAUTIONS also reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study in 151 patients with locally advanced or metastatic NSCLC. Patients received RYBREVANT intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity, in combination with carboplatin at area under the curve AUC 5 once every 3 weeks, for up to 12 weeks, and pemetrexed at 500 mg/m2 once every 3 weeks until disease progression or unacceptable toxicity. Among 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed, 76% were exposed for 6 months or longer and 38% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were increased alanine aminotransferase decreased albumin, decreased potassium and decreased magnesium.

The data in the WARNINGS AND PRECAUTIONS also reflect exposure to RYBREVANT as a single agent in the CHRYSALIS study in 302 patients with locally advanced or metastatic NSCLC. Patients received RYBREVANT at 1050 mg (for patient baseline body weight < 80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) once weekly for 4 weeks, then every 2 weeks thereafter until disease progression or unacceptable toxicity. Among 302 patients who received RYBREVANT as a single agent, 36% were exposed for 6 months or longer and 12% were exposed for greater than one year. In the safety population, the most common (≥ 20%) adverse reactions were rash, infusion-related reaction, paronychia, musculoskeletal pain, dyspnea, nausea, edema,

cough, fatigue, stomatitis, constipation, vomiting and pruritus. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were increased gamma glutamyl transference, decreased sodium, decreased potassium and increased alkaline phosphatase.

First-line Treatment of NSCLC with Exon 19 deletions or Exon 21 L858R substitution mutations

The safety data described below reflect exposure to RYBREVANT in combination with lazertinib in 421 previously untreated patients with locally advanced or metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 L858R substitution mutation in the MARIPOSA *[see Clinical Studies (14)]*. Patients received RYBREVANT intravenously at 1,050 mg (for patients < 80 kg) or 1,400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5 in combination with lazertinib, 240 mg orally once daily. Among the 421 patients who received RYBREVANT in combination with lazertinib, 73% were exposed to RYBREVANT for ≥ 6 months and 59% were exposed to RYBREVANT for > 1 year.

The median age of patients who received RYBREVANT in combination with lazertinib was 64 years (25 to 88); 64% were female; 59% were Asian, 38% were White, 1.7% were American Indian or Alaska Native, 0.7% were Black or African American, 1% were of unknown or other races; and 13% were Hispanic or Latino, 67% had Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 1, 33% had ECOG PS of 0, 60% had EGFR exon 19 deletions, and 40% had EGFR exon 21 L858R substitution mutations.

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

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 34% of patients. Adverse reactions which resulted in permanent discontinuation in ≥1% of patients included rash, infusion related reactions, nail toxicity, VTE, ILD/pneumonitis, pneumonia, edema, hypoalbuminemia, fatigue, paresthesia and dyspnea.

Dosage interruption of RYBREVANT due to an adverse reaction occurred in 88% of patients. Adverse reactions which required dosage interruption in ≥5% of patients were infusion related reactions, rash, nail toxicity, COVID-19, VTE, increased ALT, edema, and hypoalbuminemia.

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

The most common adverse reactions (≥20%) were rash, nail toxicity, infusion-related reaction, musculoskeletal pain, stomatitis, edema, VTE, paresthesia, fatigue, diarrhea, constipation, COVID-19, hemorrhage, dry skin, decreased appetite, pruritus, and nausea. The most common

Grade 3 or 4 laboratory abnormalities (≥ 2%) were decreased albumin, decreased sodium, increased ALT, decreased potassium, decreased hemoglobin, increased AST, increased GGT and increased magnesium.

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

Table 10: Adverse Reactions (≥10%) in Patients with NSCLC with Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA

Adverse Reaction	RYREVANT 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
Diarrhea*	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
Hemorrhoids	10	0.2	2.1	0.2
General disorders and administration site conditions				
Edema*	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
Hemorrhage*	25	1	13	1.2
Nervous system disorders				
Paresthesia*	35	1.7	10	0.2
Dizziness*	14	0	10	0
Headache*	13	0.2	13	0
Infections And Infestations				
COVID-19	26	1.7	24	1.4
Conjunctivitis	11	0.2	1.6	0
Metabolism and nutrition disorders				
Decreased appetite	24	1	18	1.4
Respiratory, Thoracic and Mediastinal Disorders				
Cough*	19	0	23	0
Dyspnea*	14	1.7	17	3.5
Eye disorders				
Ocular toxicity*	16	0.7	7	0
Psychiatric disorders				
Insomnia	10	0	11	0

* Grouped terms

\+ Applicable for RYBREVANT only

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

Table 11 summarizes the laboratory abnormalities in MARIPOSA.

Table 11: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients with NSCLC with EGFR Exon 19 Deletion or Exon 21 L858R Substitution Mutations in MARIPOSA+

Laboratory Abnormality	RYBREVANT in combination with lazertinib (N=421)		Osimertinib (N=428)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Chemistry				
Decreased albumin	89	8	22	0.2
Increased ALT	65	7	29	2.6
Increased AST	52	3.8	36	1.9
Increased alkaline phosphatase	45	0.5	15	0.5
Decreased calcium (corrected)	41	1.4	27	0.7
Increased GGT	39	2.6	24	1.9
Decreased Sodium	38	7	35	5
Decreased potassium	30	5	15	1.2
Increased creatinine	26	0.7	35	0.7
Decreased magnesium	25	0.7	10	0.2
Increased magnesium	12	2.6	20	4.8
Hematology				
Decreased platelet count	52	0.7	57	1.4
Decreased hemoglobin	47	3.8	56	1.9
Decreased white blood cell	38	1.0	66	0.7
Decreased neutrophils	15	1.4	33	1.4

+ 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.

First-line Treatment of Non-Small Cell Lung Cancer (NSCLC) with Exon 20 Insertion Mutations

The data described below reflect exposure to RYBREVANT in combination with carboplatin and pemetrexed at the recommended dosage in the PAPILLON trial *[see Clinical Studies (14.1)]* in 151 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations. Among patients who received RYBREVANT in combination with carboplatin and pemetrexed the median exposure was 9.7 months (range: 0.0 to 26.9 months). In patients that received carboplatin and pemetrexed alone, the median exposure was 6.7 months (range 0.0 to 25.3).

The median age was 61 years (range: 27 to 86 years); 56% were female; 64% were Asian, 32% were White, 1.3% were Black or African American, race was not reported in 1.3% of patients; 89% were not Hispanic or Latino; 86% had baseline body weight <80 kg.

Serious adverse reactions occurred in 37% of patients who received RYBREVANT in combination with carboplatin and pemetrexed. Serious adverse reactions in ≥ 2% of patients included rash, pneumonia, interstitial lung disease (ILD), pulmonary embolism, vomiting and COVID-19. Fatal

adverse reactions occurred in 7 patients (4.6%) due to pneumonia, cerebrovascular accident, cardio-respiratory arrest, COVID-19, sepsis and death not otherwise specified.

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

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

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

The most common adverse reactions (≥ 20%) were rash, nail toxicity, stomatitis, infusion-related reaction, fatigue, edema, constipation, decreased appetite, nausea, COVID-19, diarrhea, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased albumin, increased alanine aminotransferase, increased gamma-glutamyl transferase, decreased sodium, decreased potassium, decreased magnesium, and decreases in white blood cells, hemoglobin, neutrophils, platelets, and lymphocytes.

Table 12 summarizes the adverse reactions in PAPILLON.

Table 12: Adverse Reactions (≥10%) in Patients with Metastatic NSCLC with Exon 20 Insertion Mutations Who Received RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Adverse Reaction[1]	RYBREVANT in Combination with Carboplatin and Pemetrexed (n=151)		Carboplatin and Pemetrexed (n=155)	
	All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Skin and subcutaneous tissue disorders				
Rash[2]	90	19	19	0
Nail toxicity[2]	62	7	3	0
Dry skin[2]	17	0	6	0
Gastrointestinal disorders				
Stomatitis[2]	43	4	11	0
Constipation	40	0	30	0.7
Nausea	36	0.7	42	0
Vomiting	21	3.3	19	0.7
Diarrhea	21	3	13	1.3
Hemorrhoids	12	1	1.3	0
Abdominal pain[2]	11	0.7	8	0
General disorders and administration site conditions				
Infusion related reaction	42	1.3	1.3	0
Fatigue[2]	42	6	45	3.9
Edema[2]	40	1.3	19	0
Pyrexia[2]	17	0	6	0
Metabolism and nutrition disorders				
Decreased appetite	36	2.6	28	1.3
Infections and Infestations				
COVID-19	24	2	14	0.6
Pneumonia[2]	13	5	6	1.9

Vascular Disorders				
Hemorrhage[2]	18	0.7	11	1.9
Respiratory, thoracic and mediastinal disorders				
Cough[2]	17	0	16	0
Dyspnea[2]	11	1.3	16	3.2
Investigations				
Weight decreased	14	0.7	8	0
Nervous System Disorders				
Dizziness[2]	11	0	12	0
Psychiatric Disorders				
Insomnia	11	0	13	0

[1] Adverse reactions were graded using CTCAE version 5.0

[2] Grouped Term

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

Table 13 summarizes the laboratory abnormalities in PAPILLON.

Table 13: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Who Received RYBREVANT in Combination with Carboplatin and Pemetrexed in PAPILLON

Laboratory Abnormality[1]	**RYBREVANT in Combination with Carboplatin and Pemetrexed[2]**		**Carboplatin in Combination with Pemetrexed[3]**	
	All Grades (%)	**Grade 3 or 4 (%)**	**All Grades (%)**	**Grade 3 or 4 (%)**
Hematology				
Decreased white blood cells	89	17	76	10
Decreased hemoglobin	79	11	85	13
Decreased neutrophils	76	36	61	23
Decreased platelets	70	10	54	12
Decreased lymphocytes	61	11	49	13
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

[1] Adverse reactions were graded using CTCAE version 5.0

[2] The denominator used to calculate the rate varied from 113 to 150 based on the number of patients with a baseline value and at least one post-treatment value.

[3] The denominator used to calculate the rate varied from 119 to 154 based on the number of patients with a baseline value and at least one post-treatment value.

Previously Treated NSCLC Exon 20 Insertion Mutations

The data described below reflect exposure to RYBREVANT at the recommended dosage in 129 patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in the CHRYSALIS trial *[see Clinical Studies (14.2)],* whose disease had progressed on or after platinum-based chemotherapy. Among patients who received RYBREVANT, 44% were exposed for 6 months or longer and 12% were exposed for greater than one year.

The median age was 62 years (range: 36 to 84 years); 61% were female; 55% were Asian, 35% were White, and 2.3% were Black; and 82% had baseline body weight <80 kg.

Serious adverse reactions occurred in 30% of patients who received RYBREVANT. Serious adverse reactions in ≥ 2% of patients included pulmonary embolism, pneumonitis/ILD, dyspnea, musculoskeletal pain, pneumonia, and muscular weakness. Fatal adverse reactions occurred in 2 patients (1.5%) due to pneumonia and 1 patient (0.8%) due to sudden death.

Permanent discontinuation of RYBREVANT due to an adverse reaction occurred in 11% of patients. Adverse reactions resulting in permanent discontinuation of RYBREVANT in ≥1% of patients were pneumonia, IRR, pneumonitis/ILD, dyspnea, pleural effusion, and rash.

Dose interruptions of RYBREVANT due to an adverse reaction occurred in 78% of patients. Infusion-related reactions (IRR) requiring infusion interruptions occurred in 59% of patients. Adverse reactions requiring dose interruption in ≥5% of patients included dyspnea, nausea, rash, vomiting, fatigue, and diarrhea.

Dose reductions of RYBREVANT due to an adverse reaction occurred in 15% of patients. Adverse reactions requiring dose reductions in ≥ 2% of patients included rash and paronychia.

The most common adverse reactions (≥ 20%) were rash, IRR, paronychia, musculoskeletal pain, dyspnea, nausea, fatigue, edema, stomatitis, cough, constipation, and vomiting. The most common Grade 3 to 4 laboratory abnormalities (≥ 2%) were decreased lymphocytes, decreased albumin, decreased phosphate, decreased potassium, increased glucose, increased alkaline phosphatase, increased gamma-glutamyl transferase, and decreased sodium.

Table 14 summarizes the adverse reactions in CHRYSALIS.

Table 14: Adverse Reactions (≥ 10%) in Patients with NSCLC with Exon 20 Insertion Mutations Whose Disease Has Progressed on or after Platinum-based Chemotherapy and Received RYBREVANT in CHRYSALIS

Adverse Reactions	RYBREVANT[1] (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Skin and subcutaneous tissue disorders		
Rash*	84	3.9
Pruritus	18	0
Dry skin	14	0
General disorders and administration site conditions		
Infusion related reaction	64	3.1
Fatigue*	33	2.3
Edema*	27	0.8

Pyrexia	13	0
Infections and infestations		
Paronychia	50	3.1
Pneumonia*	10	0.8
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain*	47	0
Respiratory, thoracic and mediastinal disorders		
Dyspnea*	37	2.3
Cough*	25	0
Gastrointestinal disorders		
Nausea	36	0
Stomatitis*	26	0.8
Constipation	23	0
Vomiting	22	0
Diarrhea	16	3.1
Abdominal Pain*	11	0.8
Vascular disorders		
Hemorrhage*	19	0
Metabolism and nutrition disorders		
Decreased appetite	15	0
Nervous system disorders		
Peripheral neuropathy*	13	0
Dizziness	12	0.8
Headache*	10	0.8

*Grouped term

[1] Adverse reactions were graded using CTCAE version 4.03

Clinically relevant adverse reactions in <10% of patients who received RYBREVANT included ocular toxicity, ILD/pneumonitis, and toxic epidermal necrolysis (TEN).

Table 15 summarizes the laboratory abnormalities in CHRYSALIS.

Table 15: Select Laboratory Abnormalities (≥ 20%) That Worsened from Baseline in Patients With Metastatic NSCLC with EGFR Exon 20 Insertion Mutations Whose Disease Has Progressed on or After Platinum-based Chemotherapy and Who Received RYBREVANT in CHRYSALIS

Laboratory Abnormality	RYBREVANT+ (N=129)	
	All Grades (%)	Grades 3 or 4 (%)
Chemistry		
Decreased albumin	79	8
Increased glucose	56	4
Increased alkaline phosphatase	53	4.8
Increased creatinine	46	0
Increased alanine aminotransferase	38	1.6
Decreased phosphate	33	8
Increased aspartate aminotransferase	33	0
Decreased magnesium	27	0
Increased gamma-glutamyl transferase	27	4
Decreased sodium	27	4
Decreased potassium	26	6

Hematology		
Decreased lymphocytes	36	8

+ The denominator used to calculate the rate was 126 based on the number of patients with a baseline value and at least one post-treatment value.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action and findings in animal models, RYBREVANT can cause fetal harm when administered to a pregnant woman. There are no available data on the use of RYBREVANT in pregnant women or animal data to assess the risk of RYBREVANT in pregnancy. Disruption or depletion of EGFR in animal models resulted in impairment of embryo-fetal development including effects on placental, lung, cardiac, skin, and neural development. The absence of EGFR or MET signaling has resulted in embryo lethality, malformations, and post-natal death in animals (*see Data*). Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data

No animal studies have been conducted to evaluate the effects of amivantamab-vmjw on reproduction and fetal development; however, based on its mechanism of action, RYBREVANT can cause fetal harm or developmental anomalies. In mice, EGFR is critically important in reproductive and developmental processes including blastocyst implantation, placental development, and embryo-fetal/postnatal survival and development. Reduction or elimination of embryo-fetal or maternal EGFR signaling can prevent implantation, can cause embryo-fetal loss during various stages of gestation (through effects on placental development) and can cause developmental anomalies and early death in surviving fetuses. Adverse developmental outcomes were observed in multiple organs in embryos/neonates of mice with disrupted EGFR signaling. Similarly, knock out of MET or its ligand HGF was embryonic lethal due to severe defects in placental development, and fetuses displayed defects in muscle development in multiple organs. Human IgG1 is known to cross the placenta; therefore, amivantamab-vmjw has the potential to be transmitted from the mother to the developing fetus.

8.2 Lactation

Risk Summary

There are no data on the presence of amivantamab-vmjw in human milk, the effects on the breastfed child or on milk production. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed children, advise women not to breast-feed during treatment with RYBREVANT and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

RYBREVANT can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*.

Pregnancy Testing

Verify pregnancy status of females of reproductive potential prior to initiating RYBREVANT.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT.

8.4 Pediatric Use

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

8.5 Geriatric Use

- Of the 421 patients with locally advanced or metastatic NSCLC treated with RYBREVANT in combination with lazertinib in the MARIPOSA study, 45% were ≥65 years of age and 12% were ≥75 years of age.
- Of the 151 patients with locally advanced or metastatic NSCLC treated with RYBREVANT in combination with carboplatin and pemetrexed in the PAPILLON study, 37% were ≥65 years of age and 8% were ≥75 years of age.
- Of the 302 patients with locally advanced or metastatic NSCLC treated with RYBREVANT as a single agent in the CHRYSALIS study, 39% were ≥65 years of age and 11% were ≥75 years of age.

No clinically important differences in safety or efficacy were observed between patients who were ≥65 years of age and younger patients.

11 DESCRIPTION

Amivantamab-vmjw is a low-fucose human immunoglobulin G1-based bispecific antibody directed against the EGF and MET receptors, produced by mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology that has a molecular weight of approximately 148 kDa. RYBREVANT® (amivantamab-vmjw) injection for intravenous infusion is a sterile, preservative-free, colorless to pale yellow solution in single-dose vials. The pH is 5.7.

Each RYBREVANT vial contains 350 mg (50 mg/mL) amivantamab-vmjw, EDTA disodium salt dihydrate (0.14 mg), L-histidine (2.3 mg), L-histidine hydrochloride monohydrate (8.6 mg), L-methionine (7 mg), polysorbate 80 (4.2 mg), sucrose (595 mg), and water for injection, USP.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Amivantamab-vmjw is a bispecific antibody that binds to the extracellular domains of EGFR and MET.

In in vitro and in vivo studies amivantamab-vmjw was able to disrupt EGFR and MET signaling functions in mutation models of exon 19 deletions, exon 21 L858R substitutions, and exon 20 insertions through blocking ligand binding or degradation of EGFR and MET. The presence of EGFR and MET on the surface of tumor 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. Treatment with amivantamab in combination with lazertinib increased in vivo anti-tumor activity compared to either agent alone in a mouse xenograft model of human NSCLC with an EGFR L858R mutation.

12.2 Pharmacodynamics

The exposure-response relationship and time-course of pharmacodynamic response of amivantamab-vmjw have not been fully characterized in patients with NSCLC with EGFR mutations.

12.3 Pharmacokinetics

Amivantamab-vmjw exposures increased proportionally over a dosage range from 350 to 1750 mg (0.33 to 1.7 times the lowest approved recommended dosage) when RYBREVANT was administered as a single agent. Steady-state concentrations of RYBREVANT were reached by week 13 for both the 3-week and 2-week dosing regimen and the systemic accumulation was 1.9-fold.

Distribution

The amivantamab-vmjw mean (%CV) volume of distribution is 5 (24%) L.

Elimination

The mean (% CV) linear clearance (CL) is 0.26 L/day (30%) and mean terminal half-life is 14 days (33%).

Specific Populations

No clinically meaningful differences in the pharmacokinetics of amivantamab-vmjw were observed based on age (range: 21-88 years), body weight (31 to 140 kg), sex, race (White, Asian or Black or African American) and ethnicity (Hispanic/Latino or not Hispanic/Latino), mild or moderate renal impairment (eGFR 30 to 89 mL/min) or mild hepatic impairment [(total bilirubin ≤ ULN and AST > ULN) or (ULN < total bilirubin ≤ 1.5 times ULN)].

The effect of severe renal impairment (eGFR 15 to 29 mL/min), end-stage renal disease (eGFR<15 mL/min) or moderate to severe hepatic impairment (total bilirubin > 1.5 times ULN and any AST) on amivantamab-vmjw pharmacokinetics has not been studied.

Body Weight

Increases in body weight increased the volume of distribution and clearance of amivantamab-vmjw. Amivantamab-vmjw exposures are 30 to 40% lower in patients who weighed ≥ 80 kg compared to patients with body weight < 80 kg at the same dose. Exposures of amivantamab-vmjw were comparable between patients who weighed < 80 kg and received 1050 mg dose and patients who weighed ≥ 80 kg and received 1400 mg dose.

12.6 Immunogenicity

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 amivantamab-vmjw or amivantamab products.

During treatment in studies CHRYSALIS, CHRYSALIS-2, PAPILLON, MARIPOSA and MARIPOSA-2 (up to 39 months), 4 of the 1862 (0.2%) patients who received RYBREVANT as a single agent or in combination developed a treatment-emergent anti-amivantamab-vmjw antibodies. Given the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, safety or efficacy of RYBREVANT is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No studies have been performed to assess the potential of amivantamab-vmjw for carcinogenicity or genotoxicity. Fertility studies have not been performed to evaluate the potential effects of amivantamab-vmjw. In 6-week and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs.

14 CLINICAL STUDIES

14.1 First Line Treatment of NSCLC with Exon 19 deletion or Exon 21 L858R Substitution Mutation - MARIPOSA

The efficacy of RYBREVANT, in combination with lazertinib, was evaluated in MARIPOSA [NCT04487080], a randomized, active-controlled, multicenter trial. Eligible patients were required to have untreated locally advanced or metastatic NSCLC with either exon 19 deletions or exon 21 L858R substitution EGFR mutations identified by local testing, not amenable to curative therapy. Patients with asymptomatic or previously treated and stable intracranial metastases were eligible to enroll.

Patients were randomized (2:2:1) to receive RYBREVANT in combination with lazertinib (N=429), osimertinib monotherapy (N=429), or lazertinib monotherapy (an unapproved regimen

for NSCLC) until disease progression or unacceptable toxicity. The evaluation of efficacy for the treatment of untreated metastatic NSCLC relied upon comparison between:

- RYBREVANT 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 in combination with lazertinib administered at 240 mg orally once daily.
- Osimertinib administered at a dose of 80 mg orally once daily.

Randomization was stratified by EGFR mutation type (exon 19 deletion or exon 21 L858R substitution mutation), Asian race (yes or no), and history of brain metastasis (yes or no). Tumor assessments were performed every 8 weeks for 30 months, and then every 12 weeks until disease progression.

The major efficacy outcome measure was progression-free survival (PFS) as assessed by blinded independent central review (BICR). Additional efficacy outcome measures included overall survival (OS), overall response rate (ORR) and duration of response (DOR).

A total of 858 patients were randomized between the two study arms, 429 to the RYBREVANT in combination with lazertinib arm and 429 to the osimertinib arm. The median age was 63 (range: 25–88) years; 61% were female; 58% were Asian, and 38% were White, 1.6% were American Indian or Alaska Native, 0.8% were Black or African American, 0.2% were Native Hawaiian or other Pacific Islander, 0.6% were unknown race or multiple races; and 12% were Hispanic or Latino. Eastern Cooperative Oncology Group (ECOG) performance status was 0 (34%) or 1 (66%); 69% never smoked; 41% had prior brain metastases; and 89% had Stage IV cancer at initial diagnosis. Sixty percent of patients had tumors harboring exon 19 deletions and the remaining 40% had exon 21 L858R substitution mutations.

Among the 858 patients with EGFR exon 19 deletion or L858R substitution mutations that were randomized between the RYBREVANT plus lazertinib arm versus the osimertinib arm, available tissue samples from 544 (63%) patients had evaluable results when tested retrospectively using the cobas EGFR Mutation Test v2. Of the 544 patients with evaluable results, 527 (97%) patients were positive for EGFR exon 19 deletion or L858R substitution mutations, while 17 (3%) patients were negative. Available plasma samples from patients were retrospectively tested using an FDA-approved test to confirm the biomarker status.

The trial demonstrated a statistically significant improvement in PFS by BICR assessment for RYBREVANT in combination with lazertinib compared to osimertinib.

Efficacy results for RYBREVANT in combination with lazertinib are provide in Table 16.

Table 16: Efficacy Results in MARIPOSA by BICR Assessment

	RYBREVANT in combination with lazertinib (N=429)	**Osimertinib (N=429)**
Progression-free survival (PFS)		
Number of events (%)	192 (45)	252 (59)
Median, months (95% CI)	23.7 (19.1, 27.7)	16.6 (14.8, 18.5)
HR[1,2] (95% CI); p-value[1,3]	0.70 (0.58, 0.85); p=0.0002	
Overall response rate (ORR)[4]		
ORR, % (95% CI)	78 (74, 82)	73 (69, 78)
Complete response, %	5	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

CI = confidence interval; NE = not estimable

1 Stratified by mutation type (Exon 19del or Exon 21 L858R), prior brain metastases (yes or no), and Asian race (yes or no).

2 Stratified Cox proportional hazards regression.

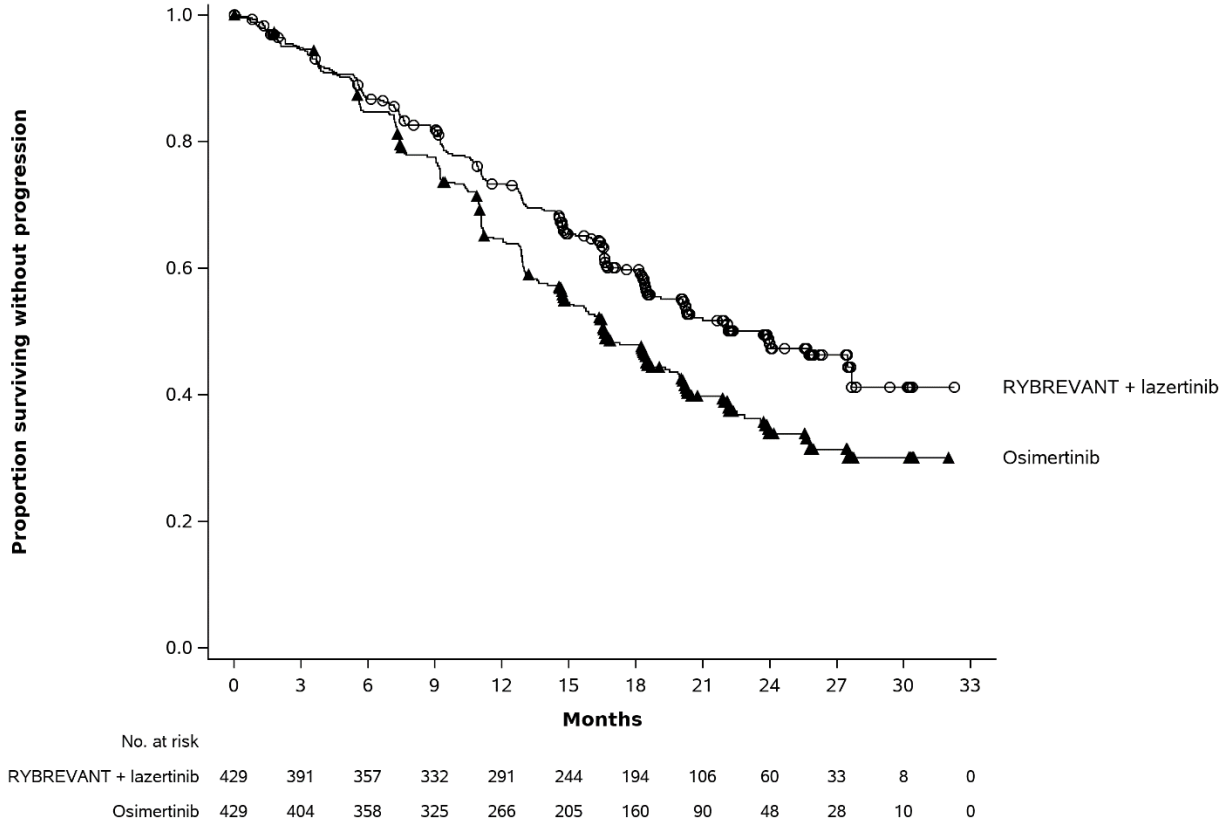
3 Stratified log-rank test.

4 Confirmed responses based on the ITT population.

5 In confirmed responders.

6 Based on observed rates.

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



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

Out of all randomized patients (n=858), 367 (43%) had baseline intracranial lesions assessed by BICR using modified RECIST. Results of pre-specified analyses of intracranial ORR and DOR by BICR in the subset of patients with intracranial lesions at baseline for the RYBREVANT in combination with lazertinib arm and the osimertinib arm are summarized in Table 17.

Table 17: Exploratory Analysis of Intracranial ORR and DOR by BICR assessment in subjects with intracranial lesions at baseline

	RYBREVANT in combination with lazertinib (N=180)	**Osimertinib (N=187)**
Intracranial Tumor Response Assessment		
Intracranial ORR[1], % (95% CI)	68 (60, 75)	69 (62, 76)
Complete response %	55	52
Intracranial DOR[2]		
Number of responders	122	129
Patients with DOR ≥12 months[3], %	66	59

Patients with DOR ≥18 months[3], %	35	23

CI = confidence interval
[1] Confirmed responses
[2] In confirmed responders
[3] Based on observed rates

14.2 First Line Treatment of NSCLC with Exon 20 Insertion Mutations-PAPILLON

The efficacy of RYBREVANT was evaluated in PAPILLON (NCT04538664), in a randomized, open-label, multicenter study. Eligible patients were required to have previously untreated locally advanced or metastatic NSCLC with EGFR Exon 20 insertion mutations measurable disease per RECIST v1.1, Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1, and adequate organ and bone marrow function. Patients with brain metastases at screening were eligible for participation once they were definitively treated, clinically stable, asymptomatic, and off corticosteroid treatment for at least 2 weeks prior to randomization. Patients with a medical history of interstitial lung disease or active ILD were excluded from the clinical study.

A total of 308 patients were randomized 1:1 to receive RYBREVANT in combination with carboplatin and pemetrexed (n=153) or carboplatin and pemetrexed (n=155). Patients received RYBREVANT intravenously at 1400 mg (for patients < 80 kg) or 1750 mg (for patients ≥ 80 kg) once weekly through 4 weeks, then every 3 weeks with a dose of 1750 mg (for patients < 80 kg) or 2100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 on once every 3 weeks until disease progression or unacceptable toxicity. Patients were stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1) and prior brain metastases (yes or no).

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

The median age was 62 (range: 27 to 92) years, with 40% of the patients ≥ 65 years of age; 58% were female; 61% were Asian and 36% were White, 0.7% were Black or African American and race was not reported in 2.3% of patients; 93% were not Hispanic or Latino. Baseline ECOG performance status was 0 (35%) or 1 (65%); 58% were never smokers; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis.

PAPILLON demonstrated a statistically significant improvement in progression free survival for patients randomized to RYBREVANT in combination with carboplatin and pemetrexed compared with carboplatin and pemetrexed.

Efficacy results are summarized in Table 18 and Figure 2.

Table 18: Efficacy Results in PAPILLON

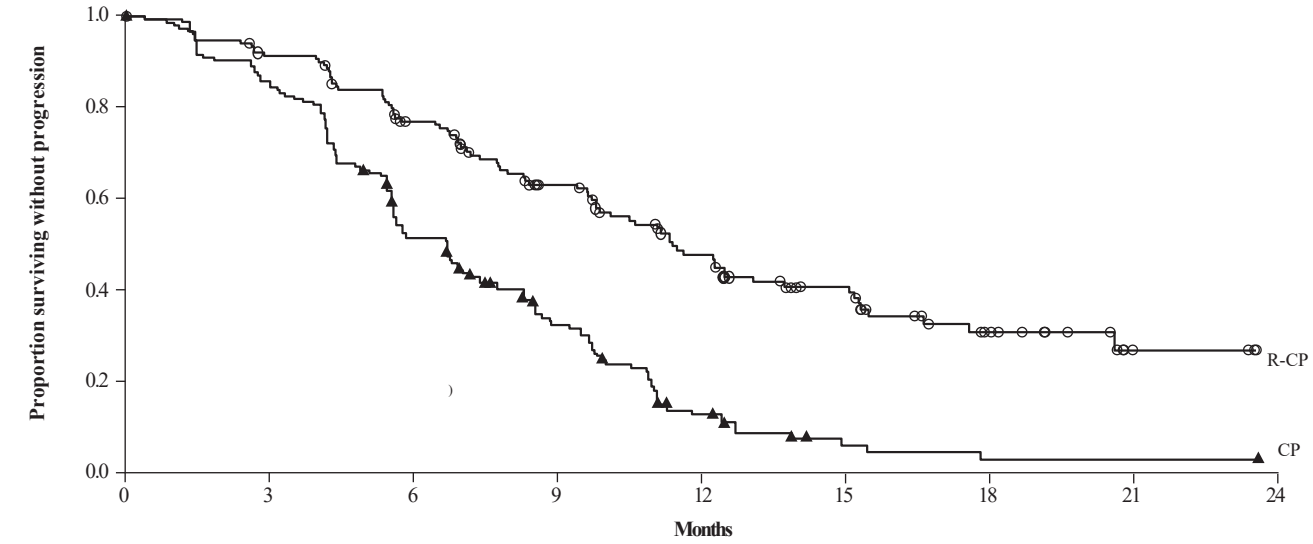
	RYBREVANT+ carboplatin+ pemetrexed (N=153)	carboplatin+ pemetrexed (N=155)
Progression-Free Survival (PFS)		
Number of events (%)	84 (55)	132 (85)
Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI)	0.40 (0.30, 0.53)	
p-value	p<0.0001	
Overall Response Rate (ORR)[1]		
ORR, % (95% CI)	67 (59, 75)	36 (29, 44)
Complete response, %	4	1
Partial response, %	63	36
Duration of response (DOR)[2]		
Median (95% CI), months	10.1 (8.5, 13.9)	5.6 (4.4, 6.9)

CI = confidence interval

[1] Confirmed responses.

[2] In confirmed responders.

Figure 2: Kaplan-Meier Curve of PFS in Previously Untreated NSCLC Patients by BICR Assessment – Papillon Study



While OS results were immature at the current analysis, with 44% of pre-specified deaths for the final analysis reported, no trend towards a detriment was observed. Seventy-five (48%) of the treated patients crossed over from the carboplatin and pemetrexed arm after confirmation of disease progression to receive RYBREVANT as a single agent.

14.3 Previously Treated NSCLC with Exon 20 Insertion Mutations-CHRYSALIS

The efficacy of RYBREVANT was evaluated in patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations in a multicenter, open-label, multi-cohort clinical trial (CHRYSALIS, NCT02609776). The study included patients with locally advanced or metastatic NSCLC with EGFR exon 20 insertion mutations whose disease had progressed on or after platinum-based chemotherapy. 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.

In the efficacy population, EGFR exon 20 insertion mutation status was determined by prospective local testing using tissue (94%) and/or plasma (6%) samples. Of the 81 patients with EGFR exon 20 insertion mutations identified by local testing, plasma samples from 78/81 (96%) patients were tested retrospectively using Guardant360® CDx, identifying 62/78 (79%) samples with an EGFR exon 20 insertion mutation; 16/78 (21%) samples did not have an EGFR exon 20 insertion mutation identified.

Patients received RYBREVANT at 1050 mg (for patient baseline body weight < 80 kg) or 1400 mg (for patient baseline body weight ≥80 kg) once weekly for 4 weeks, then every 2 weeks

thereafter until disease progression or unacceptable toxicity. The major efficacy outcome measure was overall response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) as evaluated by Blinded Independent Central Review (BICR). An additional efficacy outcome measure was duration of response (DOR) by BICR.

The efficacy population included 81 patients with NSCLC with EGFR exon 20 insertion mutation with measurable disease who were previously treated with platinum-based chemotherapy. The median age was 62 (range: 42 to 84) years, 59% were female; 49% were Asian, 37% were White, 2.5% were Black; 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, 67% had Eastern Cooperative Oncology Group (ECOG) performance status of 1; 53% never smoked; all patients had metastatic disease; and 22% had previously treated brain metastases.

Efficacy results are summarized in Table 19.

Table 19: Efficacy Results for CHRYSALIS

	Prior Platinum-based Chemotherapy Treated (N=81)
Overall Response Rate (95% CI)	40% (29%, 51%)
Complete response (CR)	3.7%
Partial response (PR)	36%
Duration of Response (DOR)	
Median, months (95% CI), months	11.1 (6.9, NE)
Patients with DOR ≥6 months	63%

Based on Kaplan-Meier estimates.
NE=Not Estimable, CI=confidence interval.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

RYBREVANT® (amivantamab-vmjw) injection is a sterile, preservative-free, colorless to pale yellow solution for intravenous infusion. Each single-dose vial contains 350 mg/7 mL (50 mg/mL) RYBREVANT. Each vial is individually packed in a single carton. (NDC 57894-501-01).

Storage and Handling

Store in a refrigerator at 2°C to 8°C (36°F to 46°F) in original carton to protect from light. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Infusion-Related Reactions

Advise patients that RYBREVANT can cause infusion-related reactions, the majority of which may occur with the first infusion. Advise patients to alert their healthcare provider immediately for any signs or symptoms of infusion-related reactions *[see Warnings and Precautions (5.1)]*.

Interstitial Lung Disease/Pneumonitis

Advise patients of the risks of interstitial lung disease (ILD)/pneumonitis. Advise patients to immediately contact their healthcare provider for new or worsening respiratory symptoms *[see Warnings and Precautions (5.2)]*.

Venous Thromboembolic Events with Concomitant Use with Lazertinib

When RYBREVANT is used in combination with lazertinib, advise patients of the risks of serious and life threatening venous thromboembolic (VTE) events, including deep venous thrombosis and pulmonary embolism. Advise patients that prophylactic anticoagulants are recommended to be used for the first four months of treatment. Advise patients to immediately contact their healthcare provider for signs and symptoms of venous thromboembolism *[see Warnings and Precautions (5.3)]*.

Dermatologic Adverse Reactions

Advise patients of the risk of dermatologic adverse reactions. Advise patients to apply alcohol-free (e.g., isopropanol-free, ethanol-free) emollient cream to reduce the risk of skin reactions. Consider prophylactic measures (e.g., use of oral antibiotics) to reduce the risk of dermatologic adverse reactions. Advise patients to limit direct sun exposure during and for 2 months after treatment, to use broad-spectrum UVA/UVB sunscreen, and to wear protective clothing during treatment with RYBREVANT *[see Warnings and Precautions (5.4)]*.

Ocular Toxicity

Advise patients of the risk of ocular toxicity. Advise patients to contact their ophthalmologist if they develop eye symptoms and advise discontinuation of contact lenses until symptoms are evaluated *[see Warnings and Precautions (5.5)]*.

Paronychia/Nail Toxicity

Advise patients of the risk of paronychia. Advise patients to contact their healthcare provider for signs or symptoms of paronychia *[see Adverse Reactions (6.1)]*.

Embryo-Fetal Toxicity

Advise females of reproductive potential of the potential risk to a fetus, to use effective contraception during treatment with RYBREVANT and for 3 months after the last dose, and to inform their healthcare provider of a known or suspected pregnancy. *[see Warnings and Precautions (5.6), Use in Specific Populations (8.1, 8.3)]*.

Lactation

Advise women not to breastfeed during treatment with RYBREVANT and for 3 months after the last dose *[see Use in Specific Populations (8.2)]*.

Product of Ireland

Manufactured by:
Janssen Biotech, Inc.
Horsham, PA 19044, USA
U.S. License Number 1864

For patent information: www.janssenpatents.com

PATIENT INFORMATION
RYBREVANT® (RYE–breh–vant)
(amivantamab-vmjw)
injection, for intravenous use

What is RYBREVANT?

RYBREVANT is a prescription medicine used to treat adults with non-small cell lung cancer (NSCLC) that has spread to other parts of the body (metastatic) or cannot be removed by surgery, and has certain abnormal epidermal growth factor receptor (EGFR) gene(s):

- in combination with lazertinib as a first-line treatment for non-small cell lung cancer (NSCLC)
- in combination with carboplatin and pemetrexed as a first-line treatment for NSCLC
- alone for the treatment of NSCLC whose disease has worsened on or after platinum-based chemotherapy.

Your healthcare provider will perform a test to make sure that RYBREVANT is right for you.

It is not known if RYBREVANT is safe and effective in children.

Before you receive RYBREVANT, tell your healthcare provider about all of your medical conditions, including if you:

- have a history of lung or breathing problems
- are pregnant or plan to become pregnant. RYBREVANT can harm your unborn baby.

  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with RYBREVANT.
  - You should use effective birth control (contraception) during treatment and for 3 months after your last dose of RYBREVANT.
  - Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with RYBREVANT.
- are breastfeeding or plan to breastfeed. It is not known if RYBREVANT passes into your breast milk. Do not breastfeed during treatment and for 3 months after your last dose of RYBREVANT.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

How will I receive RYBREVANT?

- RYBREVANT will be given to you by your healthcare provider by intravenous infusion into your vein.
- Your healthcare provider will decide the time between doses as well as how many treatments you will receive.
- Your healthcare provider will give you medicines before each dose of RYBREVANT to help reduce the risk of infusion-related reactions.
- RYBREVANT may be given in combination with the medicines carboplatin and pemetrexed. If you have any questions about these medicines, ask your healthcare provider.
- If your treatment with RYBREVANT is given in combination with the medicine lazertinib, you should take your dose of lazertinib by mouth anytime before your infusion with RYBREVANT.
- If you miss any appointments, call your healthcare provider as soon as possible to reschedule your appointment.

What should I avoid while receiving RYBREVANT?

RYBREVANT can cause skin reactions. You should limit your time in the sun during and for 2 months after your treatment with RYBREVANT. Wear protective clothing and use sunscreen during treatment with RYBREVANT.

What are the possible side effects of RYBREVANT?

RYBREVANT may cause serious side effects, including:

- **infusion-related reactions.** Infusion-related reactions are common but can be severe or serious. Tell your healthcare provider right away if you get any of the following symptoms during your infusion of RYBREVANT:
  - shortness of breath
  - fever
  - chills
  - nausea
  - flushing
  - chest discomfort
  - lightheadedness
  - vomiting
- **lung problems.** RYBREVANT may cause lung problems that may lead to death. Symptoms may be similar to those symptoms from lung cancer. Tell your healthcare provider right away if you get any new or worsening lung symptoms, including shortness of breath, cough, or fever.
- **blood clot problems.** Blood clots are a serious, but common side effect of RYBREVANT, when given together with another drug called lazertinib, may cause Blood clots in the veins of your legs (deep vein thrombosis) or lungs (pulmonary embolism) that may lead to death. Your healthcare provider will start you on medicine to prevent blood clots for the first 4 months of treatment. Tell your healthcare provider right away if you have any signs and symptoms of blood clots, including swelling, pain or tenderness in the leg, sudden unexplained chest pain, or shortness of breath.
- **skin problems.** RYBREVANT can cause severe rash; including blisters, peeling, skin pain and sores, redness, raised acne-like bumps, itching, and dry skin. You may use alcohol-free (isopropanol-free, ethanol-free) moisturizing cream for to reduce the risk of skin problems. Tell your healthcare provider right away if you get any skin reactions. Your healthcare provider may treat you with a medicine(s) or send you to see a skin specialist (dermatologist) if you get skin reactions during treatment with RYBREVANT. See “What should I avoid while receiving RYBREVANT?”
- **eye problems.** RYBREVANT may cause eye problems. Tell your healthcare provider right away if you get symptoms of eye problems which may include:
  - eye pain
  - inflammation of eye lids
  - dry eyes
  - eye redness
  - blurred vision
  - changes in vision
  - itchy eyes
  - excessive tearing
  - sensitivity to light

  Your healthcare provider may send you to see an eye specialist (ophthalmologist) if you get new or worsening eye problems during treatment with RYBREVANT. You should not use contact lenses until your eye symptoms are checked by a healthcare provider.

The most common side effects of RYBREVANT when given in combination with lazertinib include:

- rash
- infected skin around the nail
- muscle and joint pain
- diarrhea
- constipation
- COVID-19

- sores in the mouth
- swelling of hands, ankles, feet, face, or all of your body
- unusual feeling in the skin (such as tingling or a crawling feeling)
- feeling very tired
- dry skin
- bleeding
- decreased appetite
- itchy skin
- nausea
- changes in certain blood tests

The most common side effects of RYBREVANT in combination with carboplatin and pemetrexed include:

- rash
- infected skin around the nail
- sores in the mouth
- feeling very tired
- swelling of hands, ankles, feet, face, or all of your body
- constipation
- decreased appetite
- nausea
- COVID-19
- diarrhea
- vomiting
- changes in certain blood tests

The most common side effects of RYBREVANT when given alone:

- rash
- infected skin around the nail
- muscle and joint pain
- shortness of breath
- nausea
- feeling very tired
- swelling of hands, ankles, feet, face, or all of your body
- sores in the mouth
- cough
- constipation
- vomiting
- changes in certain blood tests

Your healthcare provider may temporarily stop, decrease your dose or completely stop your treatment with RYBREVANT if you have serious side effects.
These are not all of the possible side effects of RYBREVANT.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about safe and effective use of RYBREVANT

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your healthcare provider or pharmacist for information about RYBREVANT that is written for health professionals.

What are the ingredients of RYBREVANT?

Active ingredient: amivantamab-vmjw

Inactive ingredients: EDTA disodium salt dihydrate, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 80, sucrose, and water for injection.

Product of Ireland
Manufactured by: Janssen Biotech, Inc., Horsham, PA 19044, USA. U.S. License Number 1864
For patent information: www.janssenpatents.com

For more information, call 1-800-526-7736 or go to www.RYBREVANT.com.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 08/2024