swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Extension of therapeutic indication

Rybrevant

International non-proprietary name:	amivantamab
Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	350 mg/7 mL,
Route(s) of administration:	intravenous
Marketing authorisation holder:	Janssen-Cilag AG
Marketing authorisation no.:	68380
Decision and decision date:	approved on 07.02.2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

A+L	Amivantamab and lazertinib
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
BICR	Blinded independent central review
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
DCO	Data cut-off
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
Osi	Osimertinib
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VTE	Venous thromboembolism

2 Background information on the procedure

2.1 Applicant's request(s)

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is coordinated by the FDA and provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Rybrevant is indicated in combination with lazertinib for 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.

2.2.2 Approved indication

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 (see "Warnings and Precautions" and "Clinical Efficacy").

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	8 February 2024
Formal objection	13 February 2024
Preliminary decision	30 August 2024
Response to preliminary decision	20 October 2024
Labelling corrections and/or other aspects	26 November 2024
Response to labelling corrections and/or other aspects	29 December 2024
2nd round labelling corrections and/or other aspects	13 January 2025

Response to 2nd round labelling corrections and/or other aspects	23 January 2025
3rd round labelling corrections and/or other aspects	28 January 2025
Response to 3rd round labelling corrections and/or other aspects	30 January 2025
Final decision	7 February 2025
Decision	approval

3 Medical context

Treatment of lung cancer patients depends on the histology, molecular characteristics, tumour stage, and an assessment of the patient's overall medical condition. An improved understanding of the molecular pathways that drive malignancy in NSCLC has led to the development of agents that target specific molecular pathways in malignant cells. Therapy can then be individualised based on the specific abnormality, if any, present in a given patient. Among patients with NSCLC, the most prevalent of these abnormalities are driver mutations that result in the activation of EGFR, which are identified in approx. 10-15% of adenocarcinomas in Western populations. EGFR driver mutations in other histological subtypes are rare.

The most frequently identified EGFR mutations are exon 19del and L858R, prevalent in 80-85% of patients with activating EGFR mutations. These can be effectively targeted by multiple EGFR tyrosine kinase inhibitors (TKIs) that are already approved for the treatment of advanced or metastatic EGFR-mutated (mEGFR+) NSCLC.

4 Nonclinical aspects

The applicant submitted 2 primary pharmacodynamic studies with amivantamab for the extension of indication. The absence of additional studies is considered acceptable since there are no changes with regard to dosage or method of administration.
Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.
From the nonclinical point of view, there are no objections to approval of the proposed extension of indication.

5 Clinical aspects

5.1 Clinical pharmacology

The indication of amivantamab in combination with lazertinib for the treatment of patients with NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutations was supported by amivantamab population PK and exposure-response analyses with sparse PK data collected in the pivotal Phase 3 MARIPOSA study. These analyses indicated that the PK and exposure-response relationships of amivantamab in combination with lazertinib in the new patient population were consistent with other already approved patient populations.

5.2 Dose finding and dose recommendation

The recommended Phase 2 dose (RP2D) of amivantamab 1050 mg (<80 kg body weight)/1400 mg (≥80 kg body weight) and lazertinib 240 mg was selected based on the totality of exposure, safety, and efficacy data. No dose-limiting toxicities (DLTs) were observed with the proposed doses and regimens for both amivantamab and lazertinib, and the PK data analysis was consistent with no drug-drug interaction between amivantamab and lazertinib.
No clinical data are available for the combination of lazertinib with amivantamab at different dose levels. Therefore, no conclusion is possible regarding whether a lower dose of lazertinib is associated with comparable efficacy but lower toxicity.

5.3 Efficacy

The applicant submitted 1 pivotal Phase 3 study, the MARIPOSA study. MARIPOSA is a randomised study for evaluation of efficacy and safety of the combination of amivantamab and lazertinib (A+L) versus osimertinib (Osi) as a first-line treatment in participants with EGFRm NSCLC.

Patients were randomly assigned to study treatment in a 2:2:1 ratio (A+L arm, Osi arm, and Lazertinib only arm [not approved as a single agent]). Randomisation was stratified by mutation type (exon 19del versus exon 21 L858R), race (Asian versus non-Asian), and history of brain metastasis (present versus absent).

For details regarding dosing, please refer to the attached Information for healthcare professionals.

Eligible patients were aged ≥18 years, ECOG 0-1 with locally advanced or metastatic NSCLC with EGFR exon 19del or exon 21 L858R substitution. Patients were treatment-naïve and not amenable to curative therapy, including surgical resection or chemoradiation.

The primary endpoint was blinded independent central review (BICR) assessed progression-free survival (PFS) of the A+L combination compared with Osi. Overall survival (OS) was a relevant secondary endpoint.

At the time of the interim PFS analysis (data cut-off [DCO] 15 January 2023), there were 321 PFS events by BICR observed from the A+L and Osi arms combined. The efficacy stopping criteria had been met for PFS (HR=0.75 [95% CI: 0.60, 0.93], p=0.0097), in favour of the combination of A+L. At the time of the DCO for the interim PFS analysis, the median duration of follow-up was short at 15.1 months, meaning data observed at the interim analysis might not have reflected the true treatment effect. Therefore, the study continued, and blinding was maintained until the next protocol-specified PFS analysis (final PFS analysis based on 450 PFS events from the A+L and Osi arms combined).

At a median follow-up of 22 months, BICR-assessed PFS was statistically significantly improved for the A+L arm compared to the Osi arm, with a HR=0.70 (95% CI: 0.58, 0.85) and corresponding median PFS of 23.7 months for the A+L arm vs. 16.6 months for the Osi arm. At this DCO, PFS benefit was not translated into statistically significant OS.

The applicant provided updated OS data (latest cut-off 4 December 2024). The updated median follow-up was approximately 37.8 months and a total of 490 deaths were reported. The final OS analysis shows a statistically significant improvement OS for the combination of A+L over Osi (HR=0.75, 95% CI: 0.61, 0.92; p=0.00489).

Additional subgroup analyses were performed for PFS and OS. For patients ≥65 years the HR for PFS at DCO August 2023 was 1.06 (95% CI 0.80, 1.41) compared to HR of 0.50 (95% CI 0.39, 0.65) in patients <65 years. For patients ≥65 years the HR for OS at DCO December 2024 was 1.11 (95% CI 0.84, 1.48) compared to HR of 0.53 (95% CI 0.40, 0.70) in patients <65 years.

5.4 Safety

In the MARIPOSA study, treatment with A+L was associated with increased toxicity compared to Osi, including a higher frequency of grade ≥3 TEAEs (75.1% vs. 42.8%), SAEs (48.7% vs. 33.4%), and grade 5 AEs (9.3% vs. 6.8%).
The most common TEAEs (≥20%) in the A+L arm were paronychia, infusion-related reactions, rash, hypoalbuminaemia, ALT increased, oedema peripheral, dermatitis acneiform, constipation, diarrhoea, stomatitis, AST increased, COVID 19, decreased appetite, pruritus, nausea, and hypocalcaemia.

Treatment with amivantamab in combination with lazertinib is associated with relevant safety risks. In particular, the risk of venous thromboembolism (VTE) in patients treated in the A+L was increased compared to the Osi arm. A warning concerning prophylactic anticoagulation for the first 4 months in patients who are treated with A+L was included.

Treatment with A+L was associated with a higher frequency of ≥ grade 3 TEAEs, SAEs, and grade 5 TEAEs in patients ≥65 years compared to patients <65 years.

For details regarding safety, please refer to the attached Information for healthcare professionals.

5.5 Final clinical benefit-risk assessment

In the MARIPOSA study, statistically significant PFS and OS results were shown for amivantamab in combination with lazertinib compared to Osi. The associated toxicity is manageable, and safety, including specific risks such as VTEs and increased toxicity in older patients, is adequately described in the Information for healthcare professionals. Therefore, the benefit-risk assessment was regarded as positive for A+L for first-line treatment in patients with locally advanced and metastatic NSCLC with EGFR exon 19 deletion or exon 21 L858R substitution mutation.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Rybrevant was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

RYBREVANT®, concentrate for solution for infusion

Composition

Active substances

Amivantamab.
Amivantamab is an immunoglobulin G1 [IgG1]-based bispecific antibody produced in Chinese Hamster Ovary [CHO] cells using recombinant DNA technology.

Excipients

Disodium edetate, L-Histidine, L-Histidine hydrochloride monohydrate, L-Methionine, Polysorbate 80, Sucrose, Water for Injection.
Total sodium content: 17 µg/7 ml.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion. The solution is colourless to pale yellow.
Each vial contains 350 mg of amivantamab per 7 mL (50 mg of amivantamab per mL).

Indications/Uses

RYBREVANT is indicated

- in combination with lazertinib for the first-line treatment of adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations (see “Warning and Precautions” and "Clinical Efficacy").
- 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 (see “Clinical Efficacy”).
- in combination with carboplatin and pemetrexed for the treatment of adult patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitutions

mutations, whose disease has progressed on or after treatment with osimertinib (see “Clinical Efficacy”).

- as monotherapy for the treatment of patients with metastatic or unresectable NSCLC with activating EGFR Exon 20 insertion mutations whose disease has progressed on or after platinum-containing chemotherapy.

Dosage/Administration

RYBREVANT should be administered by a healthcare professional with appropriate medical support to manage infusion-related reactions (IRRs) if they occur (see “Warnings and Precautions”).
Administer pre-infusion medications (see “Dosage / Administration” – Pre-infusion Medications).
Administer diluted RYBREVANT intravenously according to the infusion rates in Tables 3 and 4, with the initial dose as a split infusion during Week 1 on Day 1 and Day 2.
If a positive EGFR mutation status is determined using a validated plasma or tissue-based test, the patient is suitable for treatment with RYBREVANT (see “Pharmacodynamics - Clinical efficacy”).
It is recommended that patients are treated with RYBREVANT until disease progression or unacceptable toxicity.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Usual dosage - Adults (≥18 years)

RYBREVANT in combination with carboplatin and pemetrexed

The recommended dosage of RYBREVANT, when used in combination with 4 cycles of carboplatin and pemetrexed, and afterwards continued in combination with pemetrexed until disease progression or toxicity, is provided in Table 1 (Infusion Rates – see Table 3).

Table 1: Recommended Dose and 3-week Dosing Schedule for RYBREVANT

Body weight at Baseline[a]	**RYBREVANT Dose**	**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
	1750 mg	Every 3 weeks starting at Week 7 onwards

Greater than or equal to 80 kg	1750 mg	Weekly (total of 4 doses) for Weeks 1 to 4 • Week 1 - split infusion on Day 1 and Day 2 • Weeks 2 to 4 - infusion on Day 1
	2100 mg	Every 3 weeks starting at Week 7 onwards
[a] Dose adjustments not required for subsequent body weight changes.		

When used in combination with carboplatin and pemetrexed, RYBREVANT should be administered after carboplatin and pemetrexed in the following order: pemetrexed, carboplatin and then RYBREVANT. See “Clinical Efficacy” and the manufacturer’s prescribing information for dosing instructions for carboplatin and pemetrexed.

Monotherapy or combination with Lazertinib

The recommended dosage of RYBREVANT monotherapy or in combination with lazertinib is provided in Table 2 (Infusion Rates – see Table 4).

Table 2: Recommended Dose and 2-week Dosing Schedule for RYBREVANT

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 adjustments not required for subsequent body weight changes.

When used in combination with lazertinib, RYBREVANT should be administered anytime after lazertinib when given on the same day. See Clinical Studies and the manufacturer’s prescribing information for dosing instructions for lazertinib.

Concomitant medication

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’). 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.

Infusion Rates

Administer RYBREVANT infusion every 3 weeks intravenously according to the infusion rates in Table 3 and administer RYBREVANT infusion every 2 weeks intravenously according to the infusion rates in Table 4.

Due to the frequency of IRRs at the first dose, infusion via a peripheral vein at Week 1 and Week 2 should be considered to minimize drug exposure in the event of an IRR; infusion via central line may be administered for subsequent weeks (from week 3). It is recommended for the first dose to be diluted as close to administration as possible to allow for maximal flexibility in IRR management.

Table 3: Infusion Rates for RYBREVANT Every 3 Weeks

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

Week 4	1750 mg	125 mL/hr
Week 5 and 6	No dose	
Week 7 and every 3 weeks thereafter	2100 mg	125 mL/hr

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

Table 4: Infusion Rates for RYBREVANT Every 2 Weeks

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

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

Pre-infusion medications

Prior to initial infusion of RYBREVANT (Week 1, Days 1 and 2), administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs (see table 5). As of week 2, administer antihistamines and antipyretics (see table 5). Administer antiemetics as needed.

Table 5: Pre-Medications

Medication	**Dose**	**Route of Administration**	**Dosing Window Prior to RYBREVANT Administration**
Antihistamine*	Diphenhydramine (25 to 50 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Antipyretic*	Paracetamol/Acetaminophen (650 to 1000 mg) or equivalent	IV	15 to 30 minutes
		Oral	30 to 60 minutes
Glucocorticoid‡	Dexamethasone (20 mg) or equivalent	IV	60 to 120 minutes
Glucocorticoid+	Dexamethasone (10 mg) or equivalent	IV	45 to 60 minutes

* Required at all doses.

‡ Required at initial dose (Week 1, Day 1).

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

Dose adjustment following undesirable effects

The recommended dose reductions for adverse reactions (see Table 7) are listed in Table 6.

Table 6: RYBREVANT Dose Reductions for Adverse Reactions

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

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

Table 7: RYBREVANT Dosage Modifications for Adverse Reactions

Adverse Reaction	**Severity**	**Dose Modification**
Infusion-Related Reactions (IRR) (see "Warnings and Precautions")	Grade 1 to 3	• Interrupt infusion at the first sign of IRRs. • Additional supportive medications (e.g., additional glucocorticoids, antihistamine, antipyretics and antiemetics) should be administered as clinically indicated. • Upon resolution of symptoms, resume infusion at 50% of the previous rate. • If there are no additional symptoms, the rate may be increased per the recommended infusion rate (see Tables 3 and 4). • Pre-medications should be administered prior to the next dose (see Table 5).
	Recurrent Grade 3 or Grade 4 (life-threatening)	Permanently discontinue.
Interstitial Lung Disease (ILD)/ Pneumonitis (see "Warnings and Precautions")	Suspected ILD/ pneumonitis	Withhold.
	Confirmed ILD/ pneumonitis	Permanently discontinue.
Venous Thromboembolic (VTE) Events (Applies to the combination with lazertinib, see Warnings and Precautions)	Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withhold both RYBREVANT and lazertinib until the patient is clinically stable. Thereafter, both drugs can be resumed at the same dose, at the discretion of the treating physician.
	Recurrent VTE despite therapeutic level anticoagulation	The combination of RYBREVANT and lazertinib should be permanently discontinued.
Skin and Nail Reactions	Grade 1	• Supportive care should be initiated. • Reassess after 2 weeks.
	Grade 2	• Supportive care should be initiated. • If there is no improvement after 2 weeks, consider reducing the dose (see Table 6).

(see “Warnings and Precautions”)	Grade 3	• Supportive care should be initiated. • Withhold until the adverse reaction improves to ≤ Grade 2. • Resume at reduced dose (see Table 6).
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions (including toxic epidermal necrolysis (TEN))	Permanently discontinue.
Other Adverse Reactions (see “Adverse Reactions”)	Grade 3-4	• Withhold treatment until adverse reaction improves to ≤ Grade 1 or baseline. • Resume treatment at reduced dose. • Permanently discontinue if recovery does not occur within 4 weeks.

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 information for professionals for information about dosage modifications for lazertinib.

Special dosage instructions

Patients with hepatic disorders

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 “Pharmacokinetics”).

Patients with renal disorders

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 “Pharmacokinetics”).

Elderly patients

Of the 661 patients treated with RYBREVANT in EDI1001 (CHRYSALIS), NSC3001 (PAPILLON) and NSC3002 (MARIPOSA-2), 40% were 65 years of age or older, and 10% were 75 years of age or older. No adjustment of the starting dose is recommended based on age. In elderly patients >65 years of age an increase in toxicity was observed with RYBREVANT in combination with lazertinib (see sections “Warnings and Precautions” and “Undesirable Effects: Elderly Patients”).

Children and adolescents (17 years of age and younger)

RYBREVANT is not approved for use in the pediatric population.

Delayed administration

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

Contraindications

Hypersensitivity to the active substance or to any of the excipients according to the composition.

Warnings and precautions

Venous Thromboembolic Events (VTE)

In patients treated with RYBREVANT as monotherapy or in combination with chemotherapy or lazertinib, VTE (e.g. deep vein thrombosis and pulmonary embolism), including serious and fatal events, may occur (see ”Undesirable Effects”).
VTE occurred in 36% of patients treated with RYBREVANT in combination with lazertinib, predominantly in the first four months of therapy, including Grade 3 in 10%, Grade 4 in 0.5% and two fatal cases of VTE (0.5%). In 62% of patients, the first VTE occurred within the first four months of treatment; 38% of VTE occurred after the fourth month. On-study VTEs occurred during anticoagulation therapy in 1.2% of patients. Prophylactic anticoagulants are recommended to be used for the first four months of treatment. Anticoagulants use should align with clinical guidelines, use of

Vitamin K antagonists is not recommended. In the event of recurrence despite appropriate anticoagulation, discontinue RYBREVANT and lazertinib.
Patients should be monitored for signs and symptoms of VTE and treated as medically appropriate (see section 'Dosage/Administration').

Infusion-Related Reactions (IRR)

Infusion-related reactions may occur in patients treated with RYBREVANT.
Infusion-related reactions occurred in 61% of patients treated with RYBREVANT. 93% of IRRs were Grade 1-2. A majority of IRRs occurred at the first infusion with a median time to onset of 60 minutes. The most frequent signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, and vomiting.
Prior to initial infusion (Week 1) of RYBREVANT, administer antihistamines, antipyretics, and glucocorticoids to reduce the risk of IRRs. For subsequent doses, administer antihistamines and antipyretics. Administer the initial infusion of RYBREVANT in split doses on Week 1, Days 1 and 2. (see "Dosage / Administration").
Treat patients with RYBREVANT in a setting with appropriate medical support necessary to treat IRRs. Interrupt RYBREVANT infusion at the first sign of IRRs and institute post-infusion medication (glucocorticoids, antihistamines, antipyretics) as clinically indicated. Upon resolution of symptoms, resume the infusion at 50% of the previous rate. For recurrent Grade 3 or 4 IRRs, permanently discontinue RYBREVANT (see "Dosage / Administration").

Interstitial Lung Disease (ILD/Pneumonitis)

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) occurred in 2.7% of patients treated with RYBREVANT, with Grade 3-4 events occurring in 1.1% of patients and one fatal case (0.1%) (see "Undesirable Effects"). Adverse reactions related to ILD leading to treatment discontinuation occurred in 1.8% of patients. 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 symptoms indicative of ILD/pneumonitis (e.g. dyspnea, cough, fever). If symptoms develop, interrupt treatment with RYBREVANT pending investigation of these symptoms. Evaluate suspected ILD and initiate appropriate treatment as necessary. Discontinue RYBREVANT in patients with confirmed ILD (see "Dosage / Administration" and "Undesirable Effects").

Skin and Nail Reactions

Skin and nail reactions may occur in patients treated with RYBREVANT.
Rash (including dermatitis acneiform and toxic epidermal necrolysis), pruritus and dry skin occurred in patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3 events occurring in 15.5% of patients. Rash leading to RYBREVANT discontinuation occurred in 2.9% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Toxic epidermal necrolysis (TEN) has been reported. Permanently discontinue RYBREVANT if TEN is confirmed. Nail toxicity occurred in patients treated with RYBREVANT. Most events were Grade 1 or 2, with Grade 3-4 nail toxicity occurring in 6.3% of patients.
A prophylactic approach to rash preventions should be considered. Instruct patients to limit sun exposure during and for 2 months after RYBREVANT therapy. Protective clothing and use of sunscreen is advisable. Alcohol-free emollient cream is recommended for dry areas with the use of RYBREVANT. If skin or nail reactions develop, start topical corticosteroids and topical and/or oral antibiotics. For Grade 3 events, administer 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 / Administration”).

Eye Disorders

Eye disorders, including keratitis (1.3%), occurred in patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperemia, conjunctival hyperemia, blepharitis and uveitis. Most events were Grade 1-2, Grade 3-4 keratitis events were observed in 0.2 % of patients. Refer patients presenting with new eye symptoms or worsening eye symptoms promptly to an ophthalmologist and advise discontinuation of contact lenses until symptoms are evaluated.

Age

Elderly patients (≥ 65 years) may be at increased risk of developing a serious adverse event. Close monitoring is recommended in these patients. In patients aged ≥65 who received RYBREVANT in combination with lazertinib an increase in serious adverse events and grade 5 undesirable effects was observed (see “Undesirable effects” section). In addition, there was a higher frequency of adverse events that led to discontinuation compared to patients < 65 years of age.

Excipients

RYBREVANT contains less than 1 mmol sodium (23 mg) per 1 vial, i.e. it is almost "sodium-free".

Interactions

No drug interaction studies have been performed.

Pregnancy, lactation

Women of childbearing age
Due to the risk that RYBREVANT can cause fetal harm when administered to pregnant women, advise female patients of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of RYBREVANT.

Pregnancy

There are no human or animal data to assess the risk of RYBREVANT in pregnancy. Administration of other EGFR and MET inhibitor molecules to pregnant animals has resulted in an increased incidence of impairment of embryo-fetal development, embryo lethality, and abortion. Therefore, based on its mechanism of action and findings in animal models, RYBREVANT could cause fetal harm when administered to a pregnant woman.
RYBREVANT must not be used during pregnancy unless the treatment with RYBREVANT is necessary because of the woman's clinical condition. If the patient becomes pregnant while taking this drug, the patient should be informed of the potential risk to the fetus.

Lactation

It is not known whether RYBREVANT is excreted in human or animal milk or affects milk production. Because of the potential for serious adverse reactions from RYBREVANT in breast-fed infants, advise women not to breast-feed during treatment with RYBREVANT and for 3 months following the last dose of RYBREVANT.

Fertility

No data are available to determine potential effects of RYBREVANT on fertility in males or females.

Effects on ability to drive and use machines

RYBREVANT may have moderate influence on the ability to drive and use machines (see section “Undesirable Effects” (e.g. dizziness, fatigue, visual impairment)). If patients experience treatment-related symptoms, including vision-related adverse reactions, affecting their ability to

concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

Undesirable effects

The safety data below reflect exposure to RYBREVANT in 1082 patients with locally advanced or metastatic NSCLC, including 380 patients who received RYBREVANT monotherapy in Study EDI1001 (CHRYSALIS), 151 patients who received RYBREVANT in combination with carboplatin and pemetrexed in Study NSC3001 (PAPILLON), 130 patients who received RYBREVANT in combination with carboplatin and pemetrexed in Study NSC3002 (MARIPOSA-2) and 421 patients who received RYBREVANT in combination with lazertinib in Study NSC3003 (MARIPOSA). Patients received RYBREVANT until disease progression or unacceptable toxicity.

The most common adverse reactions (≥ 20%) were rash (82%), IRR (61%), nail toxicity (58%), hypoalbuminemia (38%), oedema (37%), stomatitis (36%), fatigue (32%), constipation (30%), nausea (27%), decreased appetite (24%), increased alanine aminotransferase (26%), increased aspartate aminotransferase (22%) and venous thromboembolism (21%). The most common grade 3-4 events were venous thromboembolism (6.6%), rash (15.5%) and nail toxicity (6.3%). Serious adverse reactions included VTE (5.8%), ILD (2.1%), IRR (1.5%) and rash (2%). 12% of patients discontinued RYBREVANT due to adverse reactions. The most frequent adverse reaction leading to treatment discontinuation were IRR (2.9°%), ILD (1.9 %), nail toxicity (1.9%) and rash (2.9 %).

Table 8 presents adverse reactions reported in patients treated with RYBREVANT in studies EDI1001, NSC3001, NSC3002 and NSC3003.
Adverse reactions are listed by system organ class and frequency: very common (≥ 1/10), common (≥ 1/100, < 1/10), uncommon (≥ 1/1000, < 1/100), and rare (≥ 1/10,000, < 1/1000), very rare (< 1/10,000) and not known (frequency cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 8: Adverse Reactions in Patients with NSCLC, who received RYBREVANT in the studies EDI1001, NSC3001, NSC3002 and NSC3003 (N=1082)

System Organ Class **Frequency Category**	**Adverse Reaction**
Blood and lymphatic system disorders	
Very common	Neutropenia* (58%), Thrombocytopenia* (40%)

Metabolism and nutrition disorders	
Very common	Hypoalbuminaemia[a] (38%), Decreased appetite (24%), Hypocalcaemia (15%), Hypokalaemia (14%)
Common	Hypomagnesaemia
Nervous system disorders	
Very common	Dizziness[b] (12%)
Eye disorders	
Very common	Other eye disorders[c] (14%)
Common	Visual impairment[d], Keratitis, Growth of eyelashes[e]
Uncommon	Uveitis
Vascular disorders	
Very common	Venous thromboembolism[f] (21%)
Respiratory, thoracic and mediastinal disorders	
Common	Interstitial lung disease[g]
Gastrointestinal disorders	
Very common	Stomatitis[h] (36%), Constipation (30%), Nausea (27%), Diarrhoea (20%), Vomiting (15%), Abdominal pain[i] (10%)
Common	Haemorrhoids
Hepatobiliary disorders	
Very common	Alanine aminotransferase increased (26%), Aspartate aminotransferase increased (22%), Blood alkaline phosphatase increased (12%)
Skin and subcutaneous tissue disorders	
Very common	Rash[j] (82%), Nail toxicity[k] (58%), Dry skin[l] (21%), Pruritus (18%)
Uncommon	Toxic epidermal necrolysis
Musculoskeletal and connective tissue disorders	
Very common	Myalgia (10%)
General disorders and administration site conditions	

Very common	Oedema[m] (37%), Fatigue[n] (32%), Pyrexia (12%)
Injury, poisoning and procedural complications	
Very common	Infusion related reaction (61%)

* only in combination with chemotherapy (n=281)

a Blood albumin decreased, Hypoalbuminaemia

b Dizziness, Dizziness exertional, Vertigo

c Blepharitis, Conjunctival hyperaemia, Conjunctivitis, Corneal irritation, Dry eye, Episcleritis, Eye disorder, Eye pruritus, Noninfective conjunctivitis, Ocular hyperaemia

d Vision blurred, Visual acuity reduced, Visual impairment

e Growth of eyelashes, Trichomegaly

f Axillary vein thrombosis, Deep vein thrombosis, Embolism, Embolism venous, Jugular vein thrombosis, Portal vein thrombosis, Pulmonary embolism, Pulmonary infarction, Sigmoid sinus thrombosis, Superior sagittal sinus thrombosis, Thrombosis, Vena cava thrombosis, Venous thrombosis, Venous thrombosis limb

g Interstitial lung disease, Pneumonitis

h Angular cheilitis, Aphthous ulcer, Cheilitis, Glossitis, Lip ulceration, Mouth ulceration, Mucosal inflammation, Stomatitis

i Abdominal discomfort, Abdominal pain, Abdominal pain lower, Abdominal pain upper, Epigastric discomfort, Gastrointestinal pain

j Acne, Dermatitis, Dermatitis acneiform, Erythema, Erythema multiforme, Folliculitis, Impetigo, Palmar-plantar erythrodysaesthesia syndrome, Perineal rash, Perioral dermatitis, Pustule, Rash, Rash erythematous, Rash follicular, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash pustular, Rash vesicular, Skin exfoliation, Skin lesion

k Ingrowing nail, Nail bed disorder, Nail bed infection, Nail bed inflammation, Nail cuticle fissure, Nail disorder, Nail dystrophy, Nail infection, Nail ridging, Nail toxicity, Onychoclasis, Onycholysis, Onychomadesis, Paronychia

l Dry skin, Eczema, Eczema asteatotic, Skin fissures, Xeroderma, Xerosis

m Eye oedema, Eyelid oedema, Face oedema, Generalised oedema, Localised oedema, Oedema, Oedema peripheral, Periorbital oedema, Periorbital swelling, Peripheral swelling, Swelling face

n Asthenia, Fatigue

Venous Thromboembolic Events (VTE)

In patients treated with RYBREVANT as monotherapy or in combination with chemotherapy or lazertinib, VTE, including deep vein thrombosis and pulmonary embolism, occurred in 20.6% of patients including Grade 3-4 in 6.6% of patients. Two fatal cases of VTEs have also been reported in patients treated with RYBREVANT in combination with lazertinib.
In patients treated with RYBREVANT in combination with chemotherapy, VTE occurred in 13.2% patients including Grade 3 in 2.8%.
VTE events were reported in 36% of the 421 patients receiving RYBREVANT in combination with lazertinib in MARIPOSA. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 11% of patients receiving RYBREVANT in combination with lazertinib, and Grade 5 events occurring in 0.5% of patients (2 patients). For information on prophylactic anticoagulants and management of VTE events, see sections “Dosage/Administration” and “Warnings and Precautions”.

Infusion-related reactions (IRR)

Infusion-related reactions may occur in patients treated with RYBREVANT. Infusion-related reactions occurred in 61% of patients treated with RYBREVANT. 93% of IRRs were Grade 1-2. 80% of IRRs occurred at the first infusion with a median time to onset of 60 minutes. The most frequent signs and symptoms include chills, nausea, dyspnea, flushing, chest discomfort, and vomiting.
After a prolonged dose interruption of more than 6 weeks, an IRR may occasionally occur when resuming treatment with RYBREVANT.

Interstitial lung disease (ILD)

Interstitial lung disease or ILD-like adverse reactions have been reported with the use of RYBREVANT as well as with other EGFR inhibitors. Interstitial lung disease or pneumonitis were reported in 2.7% patients treated with RYBREVANT, with Grade 3-4 events occurring in 1.1% of patients and one fatal case (0.1%) (see “Warnings and Precautions”). Adverse events in connection with ILD leading to discontinuation occurred in 1.8% of patients.

Skin and nail reactions

Rash (including dermatitis acneiform) occurred in 82% patients treated with RYBREVANT. Most cases were Grade 1 or 2, with Grade 3-4 rash events occurring in 15.5% of patients. Rash leading to RYBREVANT discontinuation occurred in 2.9% of patients. Rash usually developed within the first 4 weeks of therapy, with a median time to onset of 14 days. Nail toxicity occurred in patients treated

with RYBREVANT. Most events were Grade 1 or 2, with Grade 3-4 nail toxicity occurring in 6.3% of patients.

Eye disorders

Eye disorders, including keratitis (1.3%), occurred in patients treated with RYBREVANT. Other reported adverse reactions included dry eye, blurred vision, eye pruritus, visual impairment, aberrant eyelash growth, ocular hyperemia, conjunctival hyperemia, blepharitis and uveitis. Most events were Grade 1-2, Grade 3-4 keratitis events were observed in 0.2 % of patients.

Special patient groups

Elderly
Out of 421 patients who participated in the MARIPOSA study and received RYBREVANT in combination with lazertinib, 45% were 65 years of age or older, and 12% of these were 75 years of age or older. There are limited clinical data with RYBREVANT in patients 75 years or over.
Older patients (≥ 65 years of age) reported more Grade 3 or higher adverse events (81% vs. 70%), more serious adverse events 62% vs. 38%) and more grade 5 events (14% vs. 3%) compared to patients < 65 years of age. While the rates of drug interruptions and dose reductions were similar, the rate of adverse events leading to any treatment discontinuation was higher in patients ≥ 65 years of age compared to patients < 65 years of age (47% vs. 25%).

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

There is no information on overdosage with RYBREVANT. There has been no experience of overdosage in clinical studies. No maximum tolerated dose has been determined in a clinical study in which patients received up to 1750 mg administered intravenously.

Treatment

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

Properties/Effects

ATC code

L01FX18

Mechanism of action

Amivantamab is a low-fucose, fully-human IgG1-based EGFR-MET bispecific antibody with immune cell-directing activity that targets tumors with activating and resistance EGFR mutations and MET mutations and amplifications. Amivantamab binds to the extracellular domains of EGFR and MET. Preclinical studies show amivantamab is active against tumors with primary EGFR activating Exon 20 insertion mutations, Exon 19 deletion and Exon 21 L858R substitution mutations. Amivantamab disrupts EGFR and MET signaling functions through blocking ligand binding and enhancing degradation of EGFR and MET, thereby preventing tumor growth and progression. 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.

Pharmacodynamics

Albumin

Amivantamab decreased serum albumin concentration, a pharmacodynamic effect of MET inhibition, typically during the first 8 weeks; thereafter, albumin concentration stabilized for the remainder of amivantamab treatment.

Immunogenicity

As with all therapeutic proteins, there is the potential for immunogenicity also for amivantamab. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample

collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in different studies may be misleading.
In clinical trials of patients with locally advanced or metastatic NSCLC as monotherapy or as part of a combination therapy, 4 of the 1862 (0.2%) participants who were treated with RYBREVANT and evaluable for the presence of anti-drug antibodies (ADA), tested positive for treatment-emergent anti-amivantamab antibodies. No evident effect of immunogenicity on efficacy, and safety events (including IRRs) has been observed.

Clinical efficacy

Previously untreated NSCLC

Previously-untreated NSCLC Patients with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

NSC3003 (MARIPOSA) is a randomized, active-controlled, multicenter phase 3 study assessing the efficacy and safety of RYBREVANT in combination with lazertinib as compared to osimertinib monotherapy as first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Patient samples were required to have one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing. 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), race (Asian or non-Asian), 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.

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 with 45% of patients ≥ 65 years; 61% were female; and 58% 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; 3% had Stage III NSCLC at screening and 97% had Stage IV NSCLC at screening. 97% of patients had adenocarcinoma. With regard to EGFR mutation status, 60% were exon 19 deletions and 40% were exon 21 L858R substitution mutations.

RYBREVANT in combination with lazertinib demonstrated a statistically significant improvement in progression-free survival (PFS, by BICR assessment, DCO August 2023) compared with osimertinib monotherapy (HR=0.70 [95% CI: 0.58, 0.85], p=0.0002; median PFS 23.7 months vs 16.6 months). The final OS analysis (DCO December 2024, with a median follow-up 37.8 months) showed a statistically significant improvement in OS for patients in the RYBREVANT in combination with lazertinib study arm compared to patients in the osimertinib arm (HR=0.75, 95% CI: 0.61, 0.92; p=0.0048).

The confirmed ORR according to BICR (DCO August 2023) was 80% (95% CI: 76%, 84%) in the Rybrevant+lazertinib arm and 76% (95% CI: 71%, 80%) in the osimertinib arm. The median duration of response (DOR, DCO August 2023) for confirmed response was 25.8 months (95% CI: 20.1, NE) in the Rybrevant+lazertinib arm versus 16.8 months (95% CI: 14.8, 18.5) in the osimertinib arm.

Subgroup Analysis

No formal statistical testing was planned for subgroup analyses and the clinical interpretation of the subgroup analyses is therefore limited.

Table 9: Progression-free Survival for Predefined Subgroups (DCO August 2023, median follow-up 22.0 months)

Subgroups	**HR (95% CI)**
Age	
<65	0.50 (0.39, 0.65)
≥65	1.06 (0.80, 1.41)
<75	0.70 (0.57, 0.85)
≥75	0.77 (0.46, 1.30)

Table 10: Overall Survival for Predefined Subgroups (DCO December 2024, median follow-up 37.8 months)

Subgroups	HR (95% CI)
Age	
<65	0.53 (0.40, 0.70)
≥65	1.11 (0.84, 1.48)
<75	0.75 (0.60, 0.93)
≥75	0.79 (0.47, 1.33)

The outcomes of the subgroup analyses with regard to age, sex, race, weight, mutation types, ECOG performance status, history of smoking, and history of brain metastasis were generally consistent with the primary analysis and can be considered supportive.

Of the total of 858 randomized patients, 367 (43%) had intracranial lesions at baseline (BICR, modified RECIST criteria). In an exploratory analysis in this population, the combination of Lazcluze and amivantamab demonstrated similar intracranial ORR (by BICR) to osimertinib (76.7% versus 76.5%), with an intracranial complete response rate of 62.2% versus 57.8%.

Previously untreated locally advanced or metastatic NSCLC with EGFR Exon 20 Insertion Mutations

NSC3001 (PAPILLON) is a randomized, open-label, multicenter phase 3 study comparing treatment with RYBREVANT in combination with carboplatin and pemetrexed to treatment with chemotherapy alone (carboplatin and pemetrexed) in adult subjects with treatment-naïve, locally advanced or metastatic non-squamous NSCLC with EGFR Exon 20 insertion mutations. Tumor tissue (92.2%) and/or plasma samples (7.8%) for all 308 patients were tested locally to determine EGFR Exon 20 insertion mutation status using Next Generation Sequencing (NGS) in 55.5% of patients and/or polymerase chain reaction (PCR) in 44.5% of patients.
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 ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical study. (Neo)adjuvant platinum-based doublet chemotherapy was permitted if completed 12 months prior.

RYBREVANT was administered intravenously at 1400 mg (for subjects < 80 kg) or 1750 mg (for subjects ≥ 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 subjects ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 once every 3 weeks until disease progression or unacceptable toxicity. Randomization was stratified by ECOG performance status and prior brain metastases. Subjects randomized to the carboplatin and pemetrexed arm who had confirmed disease progression were permitted to cross over to receive RYBREVANT monotherapy.

A total of 308 subjects were randomized (1:1) to RYBREVANT in combination with carboplatin and pemetrexed (N=153) or carboplatin and pemetrexed (N=155). The median age was 62 (range: 27 to 92) years, with 39% of the subjects ≥ 65 years of age; 58% were female; and 61% were Asian and 36% were White. Baseline ECOG performance status was 0 (35%) or 1 (65%); 58% never smoked; 23% had history of brain metastasis and 84% had Stage IV cancer at initial diagnosis.

RYBREVANT in combination with carboplatin and pemetrexed demonstrated a statistically significant improvement in PFS compared to carboplatin and pemetrexed, with a HR of 0.40 (95% CI: 0.30, 0.53; p<0.0001). At the time of primary analysis, there were 28 deaths occurring in the RYBREVANT + carboplatin + pemetrexed arm and 42 deaths in the carboplatin + pemetrexed arm. A greater proportion of patients treated with RYBREVANT in combination with carboplatin and pemetrexed were alive at 18 and 24 months (74% and 72%, respectively) compared to patients treated with carboplatin and pemetrexed (68% and 54%, respectively). Overall survival showed no statistically significant difference between treatment arms (at 44% of pre-specified deaths for the final analysis reported). 65 subjects (42%) who were randomized to receive carboplatin and pemetrexed crossed over to receive RYBREVANT monotherapy.

Efficacy results for Study 3001 are summarized in Table 11.

Table 11: Efficacy Results in Study 3001

	RYBREVANT + carboplatin + pemetrexed (N=153)	**carboplatin + pemetrexed (N=155)**
PFS [a]		
Number of events (%)	84 (55%)	132 (85%)

Median, months (95% CI)	11.4 (9.8, 13.7)	6.7 (5.6, 7.3)
HR (95% CI); p-value	0.40 (0.30, 0.53); p<0.0001	
ORR[a]		
ORR, % (95% CI)	73% (65%, 80%)	47% (39%, 56%)
Odds ratio (95% CI); p-value	3.0 (1.8, 4.8); p<0.0001	
Complete response	3.9%	0.7%
Partial response	69%	47%
DOR[a‡]		
Median[b] (95% CI), months	10.1 (8.5, 13.9)	5.6 (4,4, 6.9)
Patients with DOR ≥6 months	77%	44%
Patients with DOR ≥12 months	45%	11%

CI = confidence interval

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

[b] Based on the results of interim analysis of OS. The OS analysis was not adjusted for the potentially confounding effects of crossover (65 [42%] patients on the carboplatin + pemetrexed arm who received subsequent RYBREVANT monotherapy treatment).

[‡] In confirmed responders.

Previously treated NSCLC

Previously treated NSCLC Patients with EGFR Exon 19 Deletions or Exon 21 L858R Substitution Mutations

The efficacy of RYBREVANT was evaluated in patients with locally advanced or metastatic non-squamous NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (characterized by a validated test at or after the time of locally advanced or metastatic disease diagnosis, as identified by local or central testing) in a randomized (2:2:1), open-label, multicenter phase 3 clinical trial (MARIPOSA-2). Included patients had to demonstrate progression during or after osimertinib monotherapy. In MARIPOSA-2, patients received carboplatin and pemetrexed (CP, N=263) or RYBREVANT in combination with carboplatin and pemetrexed (RYBREVANT-CP, N=131) or RYBREVANT in combination with lazertinib, carboplatin and pemetrexed (an unapproved treatment for NSCLC). RYBREVANT was administered intravenously at 1,400 mg (for patients < 80 kg) or 1,750 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 3 weeks with a dose of 1,750 mg

(for patients < 80 kg) or 2,100 mg (for patients ≥ 80 kg) starting at Week 7 until disease progression or unacceptable toxicity. Carboplatin was administered intravenously at area under the concentration-time curve 5 mg/mL per minute (AUC 5) once every 3 weeks, for up to 12 weeks. Pemetrexed was administered intravenously at 500 mg/m^2 on once every 3 weeks until disease progression or unacceptable toxicity.

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

The primary efficacy endpoint was progression-free survival (PFS) by BICR. Other efficacy endpoints were overall survival (OS) and objective response rate (ORR).

Of the 394 patients randomized to the RYBREVANT-CP arm or CP arm, the median age was 62 (range: 31–85) years, with 37.8% of the patients ≥ 65 years of age; 60.4% were female; and 48.2% were Asian and 46.4% were White. Baseline Eastern Cooperative Oncology Group (ECOG) performance status was 0 (39.6%) or 1 (60.4%); 65.5% never smoked; 45.2% had history of brain metastasis, 0.9% had Stage III cancer at screening stage and 99.1% had Stage IV cancer at screening stage.

RYBREVANT in combination with carboplatin and pemetrexed demonstrated in the primary analysis of PFS (data cut-off July 2023) a statistically significant improvement in progression-free survival (PFS) compared to carboplatin and pemetrexed, with a HR of 0.48 (95% CI: 0.36, 0.64; p<0.0001, median PFS 6.3 months vs. 4.2 months). At the time of the second interim analysis for OS (data cut-off April 2024, with 52 % of pre-specified deaths for the final analysis reported), with a median follow-up of approximately 18.6 months for RYBREVANT-CP and approximately 17.8 months for CP, no statistically significant difference for OS between treatment arms was seen (HR=0.73; 95%CI: 0.54, 0.99; median OS 17.7 months vs. 15.3 months).

The ORR (data cut-off July 2023) was 63.8 % (95% CI: 55.0, 72.1) in the RYBREVANT-CP arm and 36.2% (95% CI: 30.3, 42.3) in the CP arm. In the RYBREVANT-CP arm 1.5% had a complete response and 62.3% a partial response vs. in the CP arm 0.4% had a complete response and 35.8% had a partial response.

Intracranial metastases efficacy data

Patients with asymptomatic or previously treated and stable intracranial metastases were eligible for randomization to MARIPOSA-2. At inclusion in the study, 30 patients in the RYBREVANT+CP arm and 60 patients in the CP arm had intracranial metastases.

The intracranial objective response rate (ORR) was 23.3% (7 patients) in the RYBREVANT-CP arm and 16.7% (10 patients) in the CP arm (odds ratio of 1.52; 95% CI: 0.51,4.50).

Previously-treated NSCLC with EGFR exon-20 insertion mutations

EDI1001 (CHRYSALIS) is a multicenter, open-label, multi-cohort study conducted to assess the safety and efficacy of RYBREVANT in subjects with locally advanced or metastatic NSCLC. Efficacy 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 median follow-up of 9.7 months. Identification of an EGFR exon 20 insertion mutation was determined locally using NGS or PCR on tumor tissue or plasma samples. RYBREVANT was administered intravenously at 1050 mg for subjects <80 kg or 1400 mg for subjects ≥80 kg once weekly for 4 weeks, then every 2 weeks starting at week 5 thereafter until disease progression or unacceptable toxicity.

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. Patients with planned invasive operative procedure, recent traumatic injury, expected major surgery 6 months after the last dose of study drug were also excluded. Intracranial responses were not assessed in the CHRYSALIS study.

The median age was 62 (range: 42–84) years, with 9% of the subjects ≥75 years of age; 59% were female; and 49% were Asian and 37% were White. The median number of prior therapies was 2 (range: 1 to 7 therapies). At baseline, 99% had ECOG performance status of 0 or 1 (99%); 53% never smoked; 75% had Stage IV cancer; and 22% had previous treatment for brain metastases. Insertions in Exon 20 were observed at 8 different residues; the most common residues were A767 (24%), S768 (16%), D770 (11%), and N771 (11%).

Efficacy results are summarized in Table 12.

Table 12: Efficacy Results for EDI1001 (CHRYSALIS)

	Prior Platinum Chemotherapy Treated (N=81)
ORR[a,b] (95% CI)	40% (29%, 51%)
Complete response	4%
Partial response	36%

DOR[a]	
Median (95% CI), months[c]	11.1 (6.9, NE)
Patients with DOR ≥ 6 months	63%
Median PFS[a] (95% CI), months	8.3 (6.5, 10.9)
Median OS (95% CI), months	22.8 (17.5, NE)

[a] Blinded Independent Central Review by RECIST v1.1
[b] Confirmed response.
[c] Based on Kaplan-Meier estimate.
NE=Not Estimable

Pharmacokinetics

Based on data from RYBREVANT monotherapy, the area under the concentration-time curve of amivantamab (AUC1 week) increased dose-proportionately over the dose range of 350 mg to 1750 mg.

Absorption

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

Distribution

Following administration of the recommended dose of RYBREVANT, the geometric mean (%CV) volume of distribution of amivantamab following administration of the recommended dose of RYBREVANT, as estimated based on a population pharmacokinetic analysis, was 5.04 L (23.7%).

Metabolism

No data.

Elimination

The geometric mean (% CV) linear clearance (CL) and terminal half-life associated with linear CL estimated from population pharmacokinetic parameters were 0.262 L/day (30.4%) and 13.9 days (32.6%), respectively.

Kinetics in specific patient groups

Hepatic impairment

No clinically meaningful effect in 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)]. Data in patients with moderate hepatic impairment (1.5 × ULN < total bilirubin ≤ 3 × ULN and any AST) are too limited (n=1) to assess effects on pharmacokinetics. No data are available in patients with severe hepatic impairment (total bilirubin > 3 × ULN and any AST).

Renal impairment

No clinically meaningful effect on the pharmacokinetics of amivantamab was observed in patients with mild (60 ≤ creatinine clearance [CrCl] <90 mL/min), or moderate (29 ≤ CrCl <60 mL/min) renal impairment. Data in patients with severe renal impairment (15 ≤ CrCl < 29 mL/min) are too limited (n=1) to assess effects on pharmacokinetics. No data are available in patients with end stage renal disease (CrCl <15 mL/min).

Elderly patients (65 years of age and older)

No clinically meaningful differences in the pharmacokinetics of amivantamab were observed based on age (21-88 years).

Children and adolescents (17 years of age and younger)

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

Gender

The clearance of amivantamab was 24% higher in males than in females; however, this difference was assessed as not clinically meaningful.

Weight

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

Preclinical data

In repeat-dose toxicity studies in cynomolgus monkeys, amivantamab was well-tolerated at weekly doses up to 120 mg/kg intravenously for 6 weeks or 3 months (~6-8x C_{max} and ~5-7x AUC human exposure for 1050 and 1400 mg intravenous doses). There were no effects on cardiovascular, respiratory, and nervous system function. Clinical pathology demonstrated non-adverse elevations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and globulins, and non-adverse decreases in albumin when compared to the control group. All these values returned to normal ranges in recovery groups.

Carcinogenicity and Mutagenicity

No animal studies have been performed to establish the carcinogenic and genotoxic potential of amivantamab.

Reproductive toxicity

No reproductive toxicology studies have been performed to evaluate the potential effects of amivantamab.

Other information

Incompatibilities

This medicinal product may be mixed only with those medicinal products listed under “Instructions for handling”.

Shelf life

Unopened vials:
Do not use this medicine after the expiry date marked as "EXP" on the pack.

Shelf life after opening

After dilution:
The diluted preparation for infusion is not preserved.
Chemical and physical stability of the diluted solution has been demonstrated for 10 hours at 15-25 °C. For microbiological reasons, the diluted solution should be used immediately, unless the dilution has taken place in controlled and validated aseptic conditions. If the solution is not used immediately, storage times and conditions are the responsibility of the user.

Administer diluted solutions within 10 hours (including infusion time) at room temperature (15-25°C) and in room light.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Store in the original packaging in order to protect the contents from light.
For storage conditions after dilution of the medicinal product, see “Shelf life after opening”.
Keep out of reach of children.

Instructions for handling

Preparation for Administration

RYBREVANT solution must be diluted and prepared for intravenous infusion by a healthcare professional using aseptic technique (see also “Other Information”).

1. Determine the dose required (either 1050 mg or 1400 mg) and number of RYBREVANT vials needed based on patient’s baseline weight (see “Dosage/Administration” and table below). Each vial (7 ml) of RYBREVANT contains 350 mg of amivantamab.

Recommended Dose	Number of vials
1050 mg	3
1400 mg	4
1750 mg	5
2100 mg	6

2. Check that the RYBREVANT solution is colorless to pale yellow. Do not use if discoloration or visible particles are present.
3. Withdraw and then discard a volume of either 5% glucose solution or 0.9% sodium chloride solution from the 250 mL infusion bag equal to the volume of RYBREVANT to be added (i.e., discard 7 mL diluent from the infusion bag for each RYBREVANT vial). Infusion bags must be made of polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE), or polyolefin blend (PP+PE).
4. Withdraw 7 mL of RYBREVANT from each vial and add it to the infusion bag. The final volume in the infusion bag should be 250 mL. Each vial contains a 0.5 mL overfill to ensure sufficient extractable volume. Discard any unused portion left in the vial.

5. Gently invert the bag to mix the solution. Do not shake.
6. Visually inspect the diluted solution before administration. Do not use if discoloration or visible particles are observed.
7. Diluted solutions should be administered within 10 hours (including infusion time) at room temperature (15°C to 25°C) and in room light.

Administration

1. Administer the diluted solution by intravenous infusion using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.2 micrometer). Administration sets must be made of either polyurethane (PU), polybutadiene (PBD), PVC, PP, or PE.
2. The infusion set with filter must be primed with the diluent (either 5% glucose solution or 0.9% sodium chloride solution) prior to each administration of RYBREVANT.
3. Do not infuse RYBREVANT concomitantly in the same intravenous line with other agents.
4. This medicinal product is for single use only. Any unused medicinal product should be disposed of in accordance with local requirements.

Authorisation number

68380 (Swissmedic).

Packs

Cartons with 1 single-use vial of 350mg/7mL [A].

Marketing authorisation holder

Janssen-Cilag AG, Zug, ZG

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