SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Lazcluze 80 mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 80 mg lazertinib (as mesilate monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Yellow, 14 mm, oval tablet, debossed with “LZ” on one side and “80” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Lazcluze in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletions or exon 21 L858R substitution mutations.

4.2 Posology and method of administration

Treatment with Lazcluze should be initiated by a physician experienced in the use of anticancer medicinal products.

Before initiation of Lazcluze, EGFR mutation-positive status in tumour tissue or plasma specimens must be established using a validated test method. If no mutation is detected in a plasma specimen, tumour tissue should be tested if available in sufficient amount and quality due to the potential for false negative results using a plasma test. Testing may be performed at any time from initial diagnosis until the initiation of therapy; testing does not need to be repeated once EGFR mutation status has been established (see section 5.1).

Posology

The recommended dose of Lazcluze is 240 mg once daily in combination with amivantamab.

It is recommended to administer Lazcluze any time prior to amivantamab when given on the same day. Refer to section 4.2 of the amivantamab Summary of Product Characteristics for recommended amivantamab dosing information.

At the initiation of treatment, prophylactic anticoagulants are recommended to be used for the first four months of treatment. Consistent with clinical guidelines, patients should receive prophylactic dosing of appropriate anticoagulants, e.g. low-molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended. Patients should be instructed to limit sun exposure during and for 2 months after Lazcluze combination therapy and alcohol--free emollient cream is recommended for dry areas of skin. For further information about prophylaxis for VTE and skin and nail reactions, see section 4.4.

Duration of treatment

Treatment should continue until disease progression or unacceptable toxicity.

Missed dose

If a planned dose of Lazcluze is missed, it can be administered within 12 hours. If more than 12 hours have passed since the dose was to be given, the missed dose should **not** be administered and the next dose should be administered per the usual dosing schedule.

Dose modifications

The recommended dose reductions for adverse reactions are presented in Table 1.

Table 1: Recommended Lazcluze dose reductions for adverse reactions

Dose reduction	**Recommended dosage**
Initial dose	240 mg once daily
1st dose reduction	160 mg once daily
2nd dose reduction	80 mg once daily
3rd dose reduction	Discontinue Lazcluze

Dose modifications for specific adverse reactions are presented in Table 2.

Refer to section 4.2 of the amivantamab Summary of Product Characteristics for information about dose modifications for amivantamab.

Table 2: Recommended Lazcluze and amivantamab dose modifications for adverse reactions

Adverse reaction	**Severity**	**Dose modification**
Interstitial lung disease (ILD)	Any grade	• Withhold Lazcluze and amivantamab if ILD/pneumonitis is suspected. • Permanently discontinue Lazcluze and amivantamab if ILD/pneumonitis is confirmed.
Venous thromboembolic (VTE) events (see section 4.4)	Events with clinical instability (e.g., respiratory failure or cardiac dysfunction)	Withhold Lazcluze and amivantamab until the patient is clinically stable. Thereafter, both medicinal products can be resumed at the same dose, at the discretion of the treating physician.
	Recurrent VTE event despite therapeutic level anticoagulation	Permanently discontinue Lazcluze or amivantamab. Treatment can resume with either Lazcluze or amivantamab, but not both, at the discretion of the treating physician.
Skin and nail reactions (see section 4.4)	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, reduce amivantamab dose and continue Lazcluze. • Reassess every 2 weeks, if no improvement, reduce Lazcluze dose until ≤ Grade 1 (Table 1).
	Grade 3	• Supportive care should be initiated. Withhold Lazcluze and amivantamab. • Upon recovery to ≤ Grade 2, resume both medicinal products at the same dose or consider dose reduction, preferentially reducing the dose of amivantamab first. • If there is no improvement

		within 2 weeks, permanently discontinue both Lazcluze and amivantamab.
	Grade 4 (including severe bullous, blistering or exfoliating skin conditions)	- Permanently discontinue amivantamab and hold Lazcluze. - -Withhold Lazcluze until ≤ Grade 2 or baseline. - -Upon recovery to ≤ Grade 2, resume Lazcluze at the same dose or consider dose reduction.
Other adverse reactions	Grade 3-4	- Withhold Lazcluze and amivantamab until the adverse reaction resolves to ≤ Grade 1 or baseline. - Resume one or both medicinal products, preferentially resuming Lazcluze first at a reduced dose, unless the adverse reaction is strongly suspected to be related to Lazcluze. - Consider permanently discontinuing both Lazcluze and amivantamab if recovery does not occur within 4 weeks.

* Refer to section 4.2 of the amivantamab Summary of Product Characteristics for recommended amivantamab dosing information.

Special populations

Paediatric population

There is no relevant use of lazertinib in the paediatric population for the treatment of non-small cell lung cancer.

Elderly

No dose adjustment is required (see sections 4.8, 5.1 and 5.2).

Renal impairment

No formal studies of lazertinib in patients with renal impairment have been conducted.

No dose adjustment is required for patients with mild, moderate or severe renal impairment. The pharmacokinetics (PK) of lazertinib in patients with end stage renal disease is unknown (see section 5.2).

Hepatic impairment

No dose adjustment is required for patients with mild or moderate hepatic impairment. The PK of lazertinib in patients with severe hepatic impairment is unknown. Caution is required in patients with severe hepatic impairment (see section 5.2).

Method of administration

Lazcluze is for oral use. The tablets should be swallowed whole with or without food. Do not crush, split, or chew the tablets.

If vomiting occurs any time after taking Lazcluze, the next dose should be taken the next day.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Interstitial lung disease

Interstitial lung disease (ILD) or ILD-like adverse reactions (e.g., pneumonitis), including fatal events, have been reported in patients treated with lazertinib and amivantamab (see section 4.8). Patients should be monitored for symptoms indicative of ILD/pneumonitis (e.g., dyspnoea, cough, fever). If symptoms develop, treatment with Lazcluze should be interrupted pending investigation of these symptoms. Suspected ILD or ILD-like adverse reactions should be evaluated and appropriate treatment should be initiated as necessary. Lazcluze should be permanently discontinued in patients with confirmed ILD or ILD-like adverse reactions (see section 4.2).

Venous thromboembolic (VTE) events

Venous thromboembolic (VTE) events, including deep venous thrombosis (DVT) and pulmonary embolism (PE), including fatal events, were reported in patients receiving Lazcluze in combination with amivantamab (see section 4.8). VTE events occured predominantly in the first four months of therapy. Prophylactic anticoagulants are recommended to be used for the first four months of treatment (see section 4.2 and 4.8). Consistent with clinical guidelines, patients should receive prophylactic dosing of appropriate anticoagulants, e.g. LMWH. Use of Vitamin K antagonists is not recommended.

Monitor for signs and symptoms of VTE events. Treat patients with VTE events with anticoagulation as clinically indicated. For VTE events associated with clinical

instability treatment should be held until the patient is clinically stable. Thereafter, both drugs can be resumed at the discretion of the treating physician.

In the event of recurrence despite appropriate anticoagulation, discontinue Lazcluze or amivantamab. Treatment can continue with either Lazcluze or amivantamab, but not both, at discretion of the treating physician (see section 4.2).

Skin and nail reactions

Rash (including dermatitis acneiform), pruritus and dry skin occurred in patients treated with lazertinib in combination with amivantamab (see section 4.8). Patients should be instructed to limit sun exposure during and for 2 months after Lazcluze combination therapy. Protective clothing and use of broad-spectrum UVA/UVB sunscreen are advisable. Alcohol-free emollient cream is recommended for dry areas. A prophylactic approach to rash prevention should be considered. Prescriptions for topical and/or oral antibiotics and topical corticosteroids are recommended to be available at the time of initial dosing to minimise any delay in reactive management once rash is observed. Initiating prophylactic therapy with oral antibiotic should be considered to begin on Day 1 and continue for the first 12 weeks of treatment; after completion of oral antibiotic therapy, topical antibiotic lotion to the scalp should be considered for the next 9 months of treatment. Non-comedogenic skin moisturiser on the face and whole body (except scalp) and chlorhexidine solution to wash hands and feet should be considered to begin on Day 1 and continue for the first 12 months of treatment.

If skin or nail reactions develop, topical corticosteroids and topical and/or oral antibiotics should be administered. For Grade 3 or poorly-tolerated Grade 2 events, systemic antibiotics and oral steroids should be administered and dermatologic consultation should be considered. Dose reduction, interruption or permanent discontinuation of Lazcluze should be considered based on severity (see section 4.2).

Eye disorders

Keratitis occurred in patients treated with lazertinib in combination with amivantamab (see section 4.8). Patients presenting with worsening eye symptoms should promptly be referred to an ophthalmologist and should discontinue use of contact lenses until symptoms are evaluated.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect lazertinib exposures

Medicinal products that induce CYP3A4

The co-administration of 240 mg lazertinib with rifampin (strong CYP3A4 inducer) decreased lazertinib plasma exposure. Lazertinib geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}120h}$ were 0.28 (0.23, 0.34) and 0.17 (0.14, 0.19), respectively, when co-administered with rifampin, relative to lazertinib alone. The co-administration of Lazcluze with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort) should be avoided. Based on physiological based PK model analysis, no clinically relevant decrease in lazertinib exposure is expected when Lazcluze is co-administered with weak or moderate CYP3A4 inducers (e.g., bosentan, efavirenz, modafinil).

Medicinal products that inhibit CYP3A4

The co-administration of 160 mg lazertinib with itraconazole (strong CYP3A4 inhibitor) increased lazertinib plasma exposure by less than 50%. The lazertinib geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}120h}$ were 1.19 (1.08, 1.30) and 1.46 (1.39, 1.53), respectively, when co-administered with itraconazole, relative to lazertinib alone. No initial dose adjustment is required when Lazcluze is co-administered with CYP3A4 inhibitors (e.g., itraconazole, ketoconazole, ritonavir).

Gastric acid reducing agents

Results of a retrospective PK analysis from a patient population study suggest that there was no clinically relevant change in lazertinib plasma exposure when co-administered with gastric acid reducing agents (proton pump inhibitors and H2receptor antagonists). No dose adjustments are required when Lazcluze is used with gastric acid reducing agents (e.g., omeprazole, pantoprazole, ranitidine).

Potential for lazertinib to affect exposures to other medicinal products

Drug metabolising enzymes

Lazertinib is an inhibitor of CYP3A4 enzyme. The co-administration of midazolam (CYP3A4 substrate) with 160 mg lazertinib increased midazolam plasma exposure by less than 50%. The midazolam geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}last}$ were 1.39 (1.23, 1.58) and 1.47 (1.34, 1.60), respectively, when co-administered with lazertinib, relative to midazolam alone. Concomitant use of Lazcluze with medicinal products that are substrates of CYP3A4 can result in higher exposure to these medications. When substrates of CYP3A4 with narrow therapeutic index (e.g., cyclosporine, everolimus, pimozide, quinidine, sirolimus, tacrolimus) are co-administered with Lazcluze, monitoring for an adverse reaction of the substrate should be performed.

In vitro findings suggest that lazertinib may inhibit UGT1A1; however due to lack of effect on indirect bilirubin levels in clinical study and physiological based PK model analysis, no clinically relevant interaction is expected.

Drug transporters

Lazertinib is an inhibitor of breast cancer resistance protein (BCRP) transporter. The co-administration of rosuvastatin (BCRP substrate) with 160 mg lazertinib increased rosuvastatin plasma exposure by approximately 2-fold. The rosuvastatin geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}last}$ were 2.24 (1.82, 2.76) and 2.02 (1.70, 2.40), respectively, when co-administered with lazertinib, relative to rosuvastatin alone. Concomitant use of Lazcluze with medicinal products that are substrates of BCRP can result in higher exposure to these medications. When substrates of BCRP with narrow therapeutic index (e.g., sunitinib) are co-administered with Lazcluze, monitoring for an adverse reaction of the substrate should be performed.

Lazertinib is not an inhibitor of OCT1 transporter. The co-administration of metformin (OCT1 substrate) with 160 mg lazertinib did not increase metformin

plasma exposure. The metformin geometric mean ratios (90% CI) for C_{max} and $AUC_{0\text{-}last}$ were 0.81 (0.72, 0.91) and 0.94 (0.83, 1.06), respectively, when co-administered with lazertinib, relative to metformin alone.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

The pregnancy status of females of reproductive potential should be verified prior to initiating Lazcluze.

Women of childbearing potential should be advised to use effective contraception during treatment and up to 3 weeks after treatment. Male patients with female partners of reproductive potential should be advised to use effective contraception (e.g., condom) and not donate or store semen during treatment and for 3 weeks after the last dose of lazertinib.

Pregnancy

There are no data from the use of lazertinib in pregnant women. Studies in animals have shown reproductive toxicity (reduced embryo-foetal survival and foetal body weight) (see section 5.3). Based on its mechanism of action and animal data, lazertinib may cause foetal harm when administered to a pregnant woman. Lazertinib should not be used during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the foetus. If the patient becomes pregnant while taking this medicinal product the patient should be informed of the potential risk to the foetus.

Breast-feeding

It is unknown whether lazertinib or its metabolites are excreted in human milk or affects milk production. Because the risk to the breast-feeding child cannot be excluded, female patients should be advised not to breastfeed during treatment and for 3 weeks after the last dose of lazertinib.

Fertility

There are no data on the effect of Lazcluze on human fertility. Studies in animals have shown that lazertinib may impair female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lazcluze has no or negligible influence on the ability to drive and use machines. If patients experience treatment related symptoms (such as fatigue) affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions in all grades were rash (88%), nail toxicity (71%), stomatitis (43%), alanine aminotransferase increased (36%), venous thromboembolism (36%), paraesthesia (34%), fatigue (32%), constipation (29%), diarrhoea (29%), aspartate aminotransferase increased (29%), dry skin (26%), decreased appetite (24%), pruritus (24%), and nausea (21%). Serious adverse reactions included venous thromboembolism (11%), interstitial lung disease (2.9%), rash (2.1%), alanine aminotransferase increased (1.9%), and fatigue (1.2%). The most frequent adverse reactions leading to Lazcluze treatment discontinuation were interstitial lung disease (2.9%), venous thromboembolism (1.7%), and rash (1.2%).

Tabulated list of adverse reactions

Table 3 summarises the adverse reactions that occurred in patients receiving lazertinib in combination with amivantamab.

The data reflects exposure to lazertinib in 421 patients who received lazertinib in combination with amivantamab in MARIPOSA. The median exposure to lazertinib was 18.5 months (range: 0.2 to 31.4 months).

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); 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 the order of decreasing seriousness.

Table 3: Adverse reactions in patients receiving lazertinib in combination with amivantamab

System organ class Adverse reaction	**Frequency category**	**Any grade (%)**	**Grade 3-4 (%)**
Metabolism and nutrition disorders			
Decreased appetite	Very common	24	1.0
Nervous system disorders			
Paraesthesia [a]	Very common	34	1.7
Eye disorders			
Keratitis	Common	2.6	0.5
Vascular disorders			
Venous thromboembolism [a, b]	Very common	36	11
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease [a]	Common	3.1	1.2

Gastrointestinal disorders			
Diarrhoea	Very common	29	2.1
Nausea		21	1.2
Constipation		29	0
Stomatitis [a]		43	2.1
Vomiting		12	0.5
Skin and subcutaneous tissue disorders			
Rash [a]	Very common	88	26
Nail toxicity [a]		71	11
Dry skin [a]		26	1.0
Pruritus		24	0.5
Palmar-plantar erythrodysaesthesia syndrome	Common	6	0.2
Urticaria		1.2	0
Musculoskeletal and connective tissue disorders			
Muscle spasms	Very common	17	0.5
General disorders and administration site conditions			
Fatigue [a]		32	3.8
Pyrexia	Very common	12	0
Investigations			
Alanine aminotransferase increased	Very common	36	5
Aspartate aminotransferase increased		29	3.3

[a] grouped term

[b] assessed as ADR for lazertinib and amivantamab combination only.

Refer to section 4.8 of the amivantamab Summary of Product Characteristics for a list of adverse reactions associated with amivantamab use.

Description of selected adverse reactions

Venous thromboembolic (VTE) events with concomitant use with amivantamab
Venous thromboembolic (VTE) events, including deep venous thrombosis and pulmonary embolism (PE), were reported in 35.6% of patients receiving lazertinib in

combination with amivantamab. Most cases were Grade 1 or 2, with Grade 3-4 events occurring in 11% of patients and Grade 5 events occuring in 0.5% of patients. In patients receiving lazertinib in combination with amivantamab, the median time to first onset of a VTE event was 84 days.

The use of prophylactic anticoagulants was evaluated in the PALOMA-3 study. PALOMA-3 is a randomised, open-label, Phase 3 study assessing subcutaneous versus intravenous amivantamab, both in combination with lazertinib, in patients with locally advanced or metastatic NSCLC with EGFR exon 19 deletions or exon 21 L858R substitution mutations whose disease has progressed on or after treatment with osimertinib and platinum-based chemotherapy. For patients treated with lazertinib in combination with IV amivantamab in PALOMA-3 that received prophylactic anticoagulation, the overall incidence of VTE events was 11%, with Grade 3 VTE events reported in 1.2% and serious VTE events reported in 1.8%.
For information on prophylactic anticoagulants and management of VTE events, see sections 4.2 and 4.4.

Interstitial lung disease (ILD)

Interstitial lung disease or ILD-like adverse reactions have been reported with the use of lazertinib in combination with amivantamab as well as with other EGFR inhibitors. ILD or pneumonitis was reported in 3.1% of patients treated with lazertinib in combination with amivantamab, including 1 fatal case. Patients with a medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from the clinical study (see section 4.4).

Skin and nail reactions

Rash (including dermatitis acneiform), pruritus and dry skin has occurred. Rash occurred in 88.4% of patients treated with lazertinib in combination with amivantamab. Most cases were Grade 1 or 2, with Grade 3 events occurring in 26.4% of patients. Rash leading to Lazcluze discontinuation occurred in 1.2% 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 lazertinib in combination with amivantamab. Most events were Grade 1 or 2, with Grade 3 nail toxicity occurring in 11.4% of patients (see section 4.4).

Eye disorders

Keratitis occurred in 2.6% of patients treated with lazertinib in combination with amivantamab. Most events were Grade 1-2 (see section 4.4).

Other special populations

Elderly
There are limited clinical data with lazertinib in patients 75 years of age or over (see section 5.1). While the rates of drug interruptions and dose reductions were similar, there was a higher incidence of Grade 3 or higher adverse events, and adverse events leading to discontinuation of treatment in patients ≥ 65 years of age treated with the combination of lazertinib with amivantamab, compared to patients <65 years of age.
Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions

via the Yellow Card Scheme Website: https://yellowcard.mhra.gov.uk/ or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The maximum tolerated dose of Lazcluze has not been determined. In clinical trials, daily doses of up to 320 mg once daily have been administered.

There is no known specific antidote for Lazcluze overdose. In the event of an overdose, stop Lazcluze and undertake general supportive measures. Patients should be closely monitored for signs or symptoms of adverse reactions.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, ATC code: L01EB09.

Mechanism of action

Lazertinib is a highly potent, third generation, EGFR tyrosine kinase inhibitor (TKI). It selectively inhibits both primary activating EGFR mutations (exon 19 deletions and exon 21 L858R substitution mutations) and the EGFR T790M resistance mutation, while having less activity against wild-type EGFR.

Pharmacodynamic effects

Based on the exposure-response analyses for efficacy, no apparent relationship between lazertinib exposure and progression-free survival was observed at the dose regimen of 240 mg once daily. A similar exposure-response analyses for safety, concluded that paresthesia and stomatitis appeared to show a trend of increasing occurrence with increase in lazertinib exposure.

Cardiac electrophysiology

The QTc interval prolongation potential of lazertinib was evaluated by exposure-response (E-R) analysis conducted with clinical data from 243 NSCLC patients who received 20, 40, 80, 120, 160, 240 or 320 mg lazertinib once daily in a phase 1/II study. The E-R analysis revealed no clinically relevant relationship between lazertinib plasma concentration and change in QTc interval. The 2-sided upper bound of 90% CI at steady state C_{max} from the recommended dose of 240 mg once daily and highest tested clinical dose of 320 mg once daily was 5.83 and 7.23 msec, respectively.

Clinical efficacy and safety

MARIPOSA is a randomised, open-label, active-controlled, multicentre phase 3 study assessing the efficacy and safety of Lazcluze in combination with amivantamab as compared to osimertinib monotherapy in the first-line treatment in patients with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. Patient samples were required to have one of the two common EGFR mutations (exon 19 deletion or exon 21 L858R substitution mutation), as identified by local testing. Tumour tissue (94%) and/or plasma (6%) samples for all patients were tested locally to determine EGFR exon 19 deletion and/or exon 21 L858R substitution mutation status using polymerase chain reaction (PCR) in 65% and next generation sequencing (NGS) in 35% of patients.

A total of 1074 patients were randomised (2:2:1) to receive Lazcluze in combination with amivantamab, osimertinib monotherapy, or Lazcluze monotherapy until disease progression or unacceptable toxicity. Lazcluze was administered at 240 mg orally once daily. Amivantamab was administered intravenously at 1050 mg (for patients < 80 kg) or 1400 mg (for patients ≥ 80 kg) once weekly for 4 weeks, then every 2 weeks thereafter starting at week 5. Osimertinib was administered at a dose of 80 mg orally once daily. Randomisation was stratified by EGFR mutation type

(exon 19 deletion or exon 21 L858R substitution mutation), race (Asian or non-Asian), and history of brain metastasis (yes or no).

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

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

With 82% of pre-specified deaths for the analysis reported, there was a favourable trend for the overall survival (OS) towards the combination of Lazcluze and amivantamab compared with osimertinib. A greater proportion of patients treated with Lazcluze in combination with amivantamab were alive at 12 months, 18 months, and 24 months (90%, 82%, and 75% respectively) compared to patients treated with osimertinib (88%, 79%, and 70%, respectively). Lazcluze in combination with amivantamab also provided a benefit in the time to second progression or death (PFS2) (HR=0.75 [95% CI: 0.58, 0.98], p=0.0314). While the objective response rate (ORR) was comparable between the arms, the median duration of response (DOR) among confirmed responders was longer with Lazcluze in combination with amivantamab (25.76 vs 16.76 months). Lazcluze in combination with amivantamab also provided a benefit in the time to symptomatic progression (TTSP), a measure of the burden of lung cancer symptoms (HR=0.72

[95% CI: 0.57, 0.91], p=0.0049). Table 4, Figure 1 and Figure 3 summarise efficacy results for Lazcluze in combination with amivantamab.

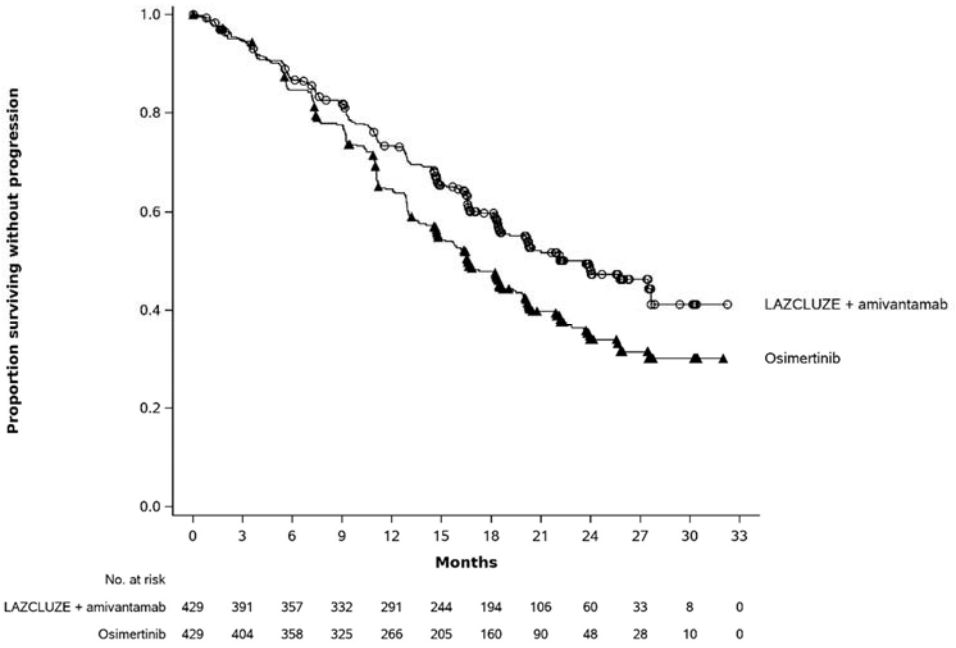
Table 4Efficacy results in MARIPOSA

	Lazcluze + amivantamab (N=429)	**Osimertinib (N=429)**	**Lazcluze (N=216)**
Progression-free survival (PFS)[a]			
Number of events	192 (45%)	252 (59%)	121 (56%)
Median, months (95% CI)	23.72 (19.12, 27.66)	16.59 (14.78, 18.46)	18.46 (14.75, 20.11)
HR (95% CI); p-value			
Lazcluze + amivantamab vs osimertinib	0.70 (0.58, 0.85); p=0.0002		
Lazcluze + amivantamab vs Lazcluze	0.72 (0.57, 0.90); p=0.0046		
Overall survival (OS)			
Number of events	142 (33%)	177 (41%)	80 (37%)
Median, months (95% CI)	NE (NE, NE)	37.3 (32.5, NE)	NE (33.0, NE)
Hazard ratio (95% CI); p-value			
Lazcluze + amivantamab vs osimertinib	0.77 (0.61, 0.96); p=0.0185[c]		
Lazcluze + amivantamab vs Lazcluze	0.84 (0.64, 1.10); p=0.2048		
12-month event-free rate, % (95% CI)	90 (86, 92)	88 (84, 91)	85 (80, 89)
18-month event-free rate, % (95% CI)	82 (78, 86)	79 (75, 83)	77 (71, 82)
24-month event-free rate, % (95% CI)	75 (71, 79)	70 (65, 74)	71 (65, 77)

Objective response rate (ORR)[a]			
ORR % (95% CI)	86.2 (82.6, 89.4)	84.5 (80.7, 87.9)	82.7 (77.0, 87.5)
Odds ratio (95% CI); p-value			
Lazcluze amivantamab vs osimertinib	1.15 (0.78, 1.70); p=0.4714		
Lazcluze + amivantamab vs Lazcluze	1.31 (0.83, 2.06); p=0.2409		
Complete response, %	6.9	3.6	4.2
Partial response, %	79.3	80.9	78.5
Duration of response (DOR)[b]			
Median, months (95% CI)	25.76 (20.14, NE)	16.76 (14.75,18.53)	16.56 (14.75, 20.21)
Patients with DOR ≥ 6 months, %	86.3	85.0	82.5
Patients with DOR ≥ 12 months, %	67.9	57.6	58.8

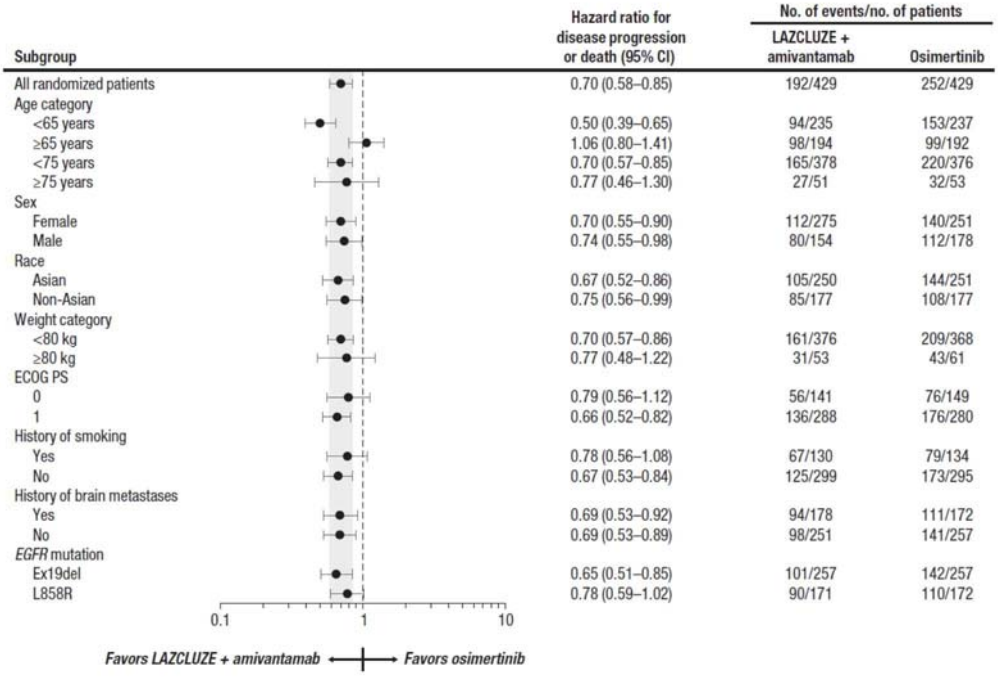
BICR = blinded independent central review; CI = confidence interval; NE = not estimable.
PFS, ORR and DOR results are from data cut-off 11 August 2023. OS results are from data cut-off 13 May 2024. [a] BICR by RECIST v1.1. [b] BICR by RECIST v1.1 in confirmed responders. [c] The p-value is compared to a 2-sided significance level of 0.00001.

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



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

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

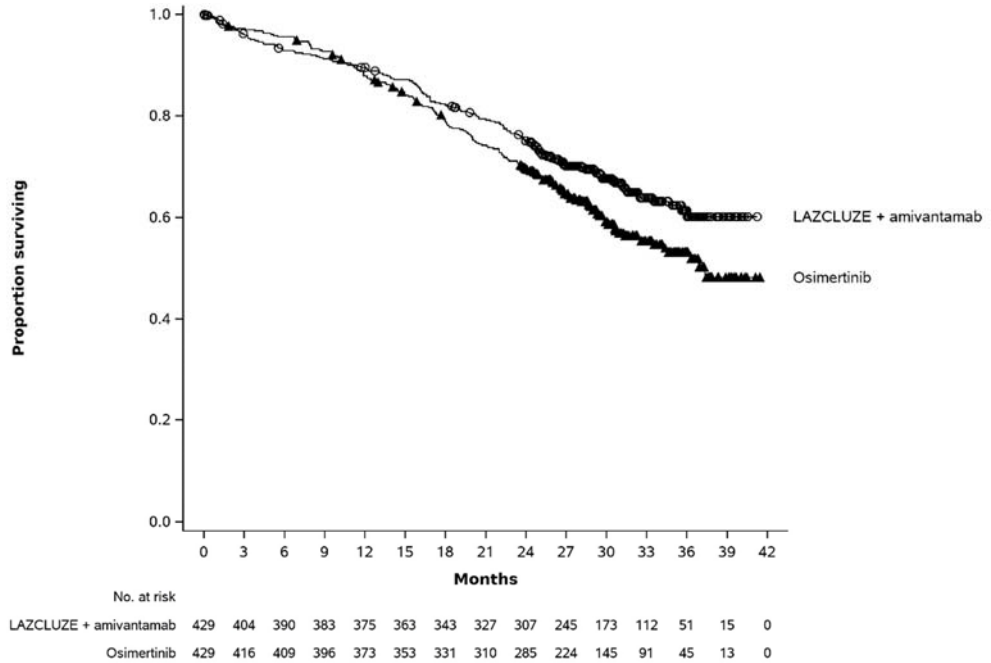


The MARIPOSA study included protocol-mandated brain magnetic resonance imaging (MRIs), which have historically not been used in trials evaluating EGFR-mutated NSCLC. This may have led to earlier detection of recurrences and associated shorter median values for PFS. To account for this, a sensitivity analysis was done whereby patients with brain-only progression as the site of first progression were censored. Extracranial PFS based on BICR assessment was

consistent with the treatment benefit observed in the primary analysis. The median extracranial PFS was 27.5 months with Lazcluze in combination with amivantamab, as compared to 18.37 months with osimertinib (HR=0.68 [95% CI: 0.55, 0.83], nominal p=0.0001).

The stratified analysis of investigator-assessed PFS shows that the improved treatment effect of the combination of Lazcluze and amivantamab relative to osimertinib was also observed when assessed by investigator. Results for the analysis of ORR based on investigator assessment for comparison of the Lazcluze in combination with amivantamab arm versus the osimertinib arm were consistent with results for ORR based on BICR assessment.

Figure 3: Kaplan-Meier curve of OS in previously untreated patients with NSCLC



Results of pre-specified analyses of intracranial ORR and DOR by BICR in the subset of patients with intracranial lesions at baseline for the combination of Lazcluze and amivantamab demonstrated similar intracranial ORR to the control. Per protocol, all patients in MARIPOSA had serial brain MRIs to assess intracranial response and duration. Results are summarised in Table 5

Table 5Intracranial ORR and DOR by BICR assessment in subjects with intracranial lesions at baseline

	Lazcluze + amivantamab (N=180)	**Osimertinib (N=187)**	**Lazertinib (N=93)**
Intracranial tumour response assessment			
Intracranial ORR (CR+PR), % (95% CI)	76.7 (69.8, 82.6)	76.5 (69.7, 82.4)	74.2 (64.1, 82.7)
Complete response %	62.2	57.8	54.8

Intracranial DOR			
Number or responders	138	143	69
Response duration ≥ 6 months, %	77.5	77.6	79.7
Response duration ≥ 12 months, %	58.0	53.8	52.2
Response duration ≥ 18 months, %	31.2	21.0	18.8

CI = confidence interval

Paediatric population

The Licensing Authority has waived the obligation to submit the results of studies with Lazcluze in all subsets of the paediatric population in non-small cell lung cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Following single and multiple once daily oral administration, lazertinib maximum plasma concentration (C_{max}) and area under plasma concentration time curve (AUC) increased approximately dose proportionally across 20 to 320 mg dose range.

The steady state plasma exposure was achieved by day 15 of once daily administration and approximately 2-fold accumulation was observed at steady state with 240 mg once daily dose.

The lazertinib plasma exposure was comparable when lazertinib was administered either in combination with amivantamab or as a monotherapy.

Absorption

The median time to reach single dose and steady state C_{max} was comparable and ranged from 2 to 4 hours.

Following administration of 240 mg lazertinib with a high-fat meal (800~1000 kcal, fat content approximately 50%), the C_{max} and AUC of lazertinib were comparable to that under fasting conditions suggesting lazertinib can be taken with or without food.

Distribution

Lazertinib was extensively distributed, with mean (CV%) apparent volume of distribution of 4264 (43.2%) L at 240 mg dose. Lazertinib mean (CV%) plasma protein binding was approximately 99.2% (0.13%) in humans.

Metabolism

Lazertinib is primarily metabolised by glutathione S-transferase mu 1 (GSTM1) mediated glutathione conjugation with a relatively minor contribution from CYP3A4 mediated oxidative metabolic pathway. The most abundant metabolites are glutathione catabolites and considered clinically inactive. The plasma exposure of lazertinib was affected by GSTM1 mediated metabolism, leading to lower exposure

(less than 2-fold difference) in Non-null GSTM1 patients. No dose adjustment is required based on GSTM1 status.

Elimination

The mean (CV%) apparent clearance and terminal elimination half-life of lazertinib at 240 mg dose were 44.5 (29.5%) L/h and 64.7 (32.8%) hours, respectively.

Excretion

Following a single oral dose of radiolabelled lazertinib, approximately 86% of the dose was recovered in faeces (< 5% as unchanged) and 4% in urine (< 0.5% as unchanged).

Special populations

Elderly

Based on population PK analysis, no clinically meaningful age-based differences in pharmacokinetics of lazertinib were observed.

Renal impairment

Based on population PK analysis, no dose adjustment is required for patients with mild, moderate or severe renal impairment with estimated glomerular filtration rate (eGFR) of 15 to 89 mL/min. Data in patients with severe renal impairment (eGFR of 15 to 29 mL/min) are limited (n=3), but there is no evidence to suggest that dose adjustment is required in these patients. No data are available in patients with end stage renal disease (eGFR < 15 mL/min).

Hepatic impairment

Based on findings from clinical pharmacology study, moderate hepatic impairment

(Child-Pugh Class B) had no clinically meaningful effect on lazertinib single dose PK. Based on population PK analysis, no dose adjustment is required for patients with mild (total bilirubin ≤ ULN and AST > ULN or ULN < total bilirubin

≤ 1.5×ULN and any AST) or moderate (1.5×ULN < total bilirubin ≤ 3×ULN and any AST) hepatic impairment. No data are available in patients with severe hepatic impairment (total bilirubin > 3×ULN and any AST).

Paediatric population

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

Other populations

No clinically meaningful differences in lazertinib PK were observed based on age, sex, body weight, race, ethnicity, hepatic function, renal function, baseline laboratory assessments (creatinine clearance, albumin, alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase), ECOG performance status, EGFR mutation type, initial diagnosis cancer stage, prior therapies, brain metastasis, and history of smoking.

5.3 Preclinical safety data

In repeat-dose toxicity studies with lazertinib in rats and dogs, organs and tissues (eye, skin, liver, lungs, kidney, duodenum, bone marrow, ovary, vagina and testis in

rat; and eye, skin, lungs, kidney, duodenum, oesophagus, jejunum, and testis in dog) containing epithelial cell lineages were affected with changes spanning from mild epithelial atrophy to degenerative erosions, inflammation, and necrosis. These findings were observed in animals in exposures ranges of 0.9-3.4x than estimated exposures of patients administered with the recommended dose (240 mg) and were fully or partially resolved during the recovery phases.

Carcinogenicity and Mutagenicity

No evidence of genotoxicity for lazertinib was observed in *in vitro* bacterial mutagenicity, *in vitro* chromosomal aberration, and *in vivo* micronucleus tests in rats. Long-term animal studies have not been conducted to evaluate the carcinogenic potential of lazertinib.

Reproductive Toxicology

In a fertility and early embryonic development study in male and female rats, lazertinib did not affect oestrous cyclicity, mating, fertility or sperm parameters, but induced an increase in post-implantation loss and decreased live litter size at 30 mg/kg/day, a dose level approximating the human clinical exposure at the recommended dose of 240 mg. In embryo-foetal development studies, decreases in foetal body weights in association with maternal toxicity were observed in rats at 60 mg/kg/day, a maternal exposure approximately 4 times higher than the human clinical exposure at 240 mg. There were no effects on embryo-foetal development in rabbits at 45 mg/kg/day, a maternal exposure approximating the human clinical exposure at 240 mg.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet Core
silica, hydrophobic colloidal
croscarmellose sodium (E 468)
cellulose, microcrystalline (E 460 (i))
mannitol (E 421) magnesium stearate
(E 572)
Film Coating
macrogols (E 1209)
polyvinyl alcohol (E 1203)
glycerol monocaprylocaprate type I (E 471)
titanium dioxide (E 171) talc (E 553b)
yellow iron oxide (E 172)

6.2 Incompatibilities

Not applicable

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Blister pack

Polyvinyl chloride – polychlorotrifluoroethylene (PVC-PCTFE) film and aluminium push-through foil.

 80 mg tablets packaged in 56-count blister pack (2 dose packs containing 28 tablets each).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Janssen-Cilag Ltd
50-100 Holmers Farm Way
High Wycombe
Buckinghamshire
HP12 4EG
UK

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00242/0763

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

06/03/2025

10 DATE OF REVISION OF THE TEXT

06/03/2025