European Union Risk Management Plan
LAZCLUZE (lazertinib)

Data lock point for current RMP	11 Aug 2023	Version number	1.4

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PPD

QPPV Name(s):	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of this RMP Submission	
Version Number	1.4
Rationale for submitting an updated RMP (if applicable)	Not applicable.
Summary of significant changes in this RMP:	Not applicable.

Other RMP Versions Under Evaluation:

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Not Applicable.		

Details of the Currently Approved RMP:

Version number of last agreed RMP:	Not applicable.
Approved within procedure	Not applicable.
Date of approval (Competent authority opinion date)	Not applicable.

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PART I: PRODUCT(S) OVERVIEW

Active substance(s) (INN or common name)	Lazertinib
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic agents, protein kinase inhibitors (L01EB09)
Marketing Authorization Applicant	Janssen-Cilag International NV
Medicinal products to which the RMP refers	1
Invented name(s) in the European Economic Area (EEA)	LAZCLUZE
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class The chemical name for lazertinib mesylate monohydrate is *N*-[5-[[4-[4-[(Dimethylamino)methyl]-3-phenyl-1*H*-pyrazol-1-yl]pyrimidin-2-yl]amino]-4-methoxy-2-(morpholin-4-yl)phenyl]acrylamide methanesulfonate hydrate (1:1:1).
	Summary of mode of action Lazertinib is an irreversible epidermal growth factor receptor (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.
	Important information about its composition Not applicable.
Reference to the Product Information	Module 1.3.1, Summary of Product Characteristics, Labelling and Package Leaflet
Indication(s) in the EEA	Current: LAZCLUZE in combination with amivantamab is indicated for the first-line treatment of adult patients with advanced non-small cell lung cancer (NSCLC) with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.
	Proposed: Not applicable.

Dosage in the EEA	Current: LAZCLUZE is for oral use. 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. The tablets should be swallowed whole with or without food.	
	Proposed: Not applicable.	
Pharmaceutical form(s) and strengths	Current: LAZCLUZE is formulated as film-coated tablets, available in 2 strengths: • 80-mg film-coated tablet: Yellow, 14 mm, oval tablet, debossed with "LZ" on one side and "80" on the other side containing 80 mg lazertinib (as mesylate monohydrate). • 240-mg film-coated tablet: Reddish purple, 20 mm, oval tablet, debossed with "LZ" on one side and "240" on the other side containing 240 mg lazertinib (as mesylate monohydrate).	
	Proposed: Not applicable.	
Is/will the product be subject to additional monitoring in the European Union (EU)?	☑ **Yes**	☐ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indication: Advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations

Below sections describe relevant available data on lung cancer, NSCLC, and EGFR mutations, along with any specific data on NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations.

Incidence:

Lung cancer remains the second most frequently diagnosed cancer in men and women, and its incidence continues to increase. In 2020, an estimated 2.2 million new cases of lung cancer were diagnosed globally, accounting for approximately 11.4% of the global cancer burden, with an age-standardized incidence rate of 22.5 per 100,000 persons (31.5 in male, 14.6 in female) (Ferlay 2020). In Europe, an estimated 477,534 new cases of lung cancer were reported in 2020 (Globocan 2020). According to the European Cancer Information System, the 27 EU countries projected 318,327 new cases of lung cancer by the end of 2020 (ECIS 2023). European countries exhibit wide geographic variations in lung cancer incidence. In general, rates are highest in Central and Eastern Europe (Barta 2019), with an age-standardized incidence rate of 53.5 per 100,000 persons (Planchard 2018).

Lung cancer makes up about 13% of all new cancer diagnoses (Tirzïte 2018). Lung cancer includes small cell lung cancer (SCLC) and NSCLC. In general, about 10% to 15% of all lung cancers are SCLC and 80% to 85% are NSCLC (Zappa 2016, American Cancer Society 2023). Approximately 60% of all patients with NSCLC present with metastatic disease at diagnosis (Amini 2019).

Mutations in the *EGFR* gene are commonly observed in NSCLC, particularly in tumors of adenocarcinoma histology (Midha 2015). EGFR mutations are the second most common oncogenic driver events in NSCLC, and the most common actionable driver event. Two mutations, ie, deletions in Exon 19 and the single amino acid substitution L858R in Exon 21, are often referred to as “classical” EGFR mutations and together account for 85% of observed EGFR mutations in NSCLC.

Prevalence:

The global 5-year prevalence for lung cancer was approximately 2.6 million persons in 2020 (Ferlay 2020). The 5-year prevalence of lung cancer in Europe was approximately 582,924 persons in 2020 (Ferlay 2020). Among the 27 EU countries, the estimated projected 5-year prevalence of lung cancer was 318,000 persons by the end of 2020 (ESMO 2020). In Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden) the estimated 5-year prevalence was 10.6 per 10,000 persons at the end of 2020 (NORDCAN 2023).

A literature review of 150 worldwide studies reporting EGFR mutation frequency in patients with NSCLC adenocarcinoma included 33,162 patients of which 9,749 had EGFR mutations (Midha 2015). In adenocarcinomas, EGFR mutations are detected with higher rates amongst

Asians (38.8%-64.0%) than amongst Caucasians (4.9%–17.4%) (Yoon 2020). In 2016, in a systematic review and meta-analysis, including data from 456 studies (of which 66% were conducted in Asian countries), 30,466 patients with EGFR mutations were reported among 115,815 patients with NSCLC. The overall pooled prevalence of EGFR mutations was 32.3%. The prevalence was higher in patients with adenocarcinoma (38.0%) compared to non-adenocarcinoma (11.7%) (Zhang 2016).

Demographics of the Population in the Authorized Indication - Age, Sex, Racial and/or Ethnic Origin, and Risk Factors for the Disease

Age

NSCLC is often considered a disease of the older population, with a median age at diagnosis of about 70 years; however, a significant proportion of patients with newly diagnosed NSCLC, ranging between 1% and 10%, are younger than 40 years (Thomas 2015). Recent studies, such as the one conducted by Suidan in 2019, have indicated that young patients diagnosed with NSCLC tend to exhibit a higher prevalence of driver mutations compared to older patients (Suidan 2019). Among individuals aged 20 to 46 years, NSCLC primarily affects more female patients who are nonsmokers.

Sex

Female sex is one of the most important known predictors for EGFR mutations. In the systematic review and meta-analysis by Zhang et al (2016), the pooled prevalence of EGFR mutations in patients with NSCLC was 43.7% in women and 24.0% in men. The EGFR mutation frequency in patients with NSCLC with adenocarcinoma histology was higher in women compared with men in all regions where data were available: 22% versus 9% in Europe, 60% versus 37% in Asia-Pacific, 48% versus 8% in Africa, and 28% versus 19% in North America (Midha 2015).

Racial and/or Ethnic Origin

Currently, black and white women have lower lung cancer incidence rates than men. Black men, who have the highest lung cancer rates, are about 12% more likely to get lung cancer than white men. Black women are 16% less likely to get lung cancer when compared with white women (ASCO 2023).

In the systematic review and meta-analysis by Zhang et al (2016), the prevalence of EGFR mutations in patients with NSCLC varied by location and ethnicity. Asia had the highest prevalence of EGFR mutations in patients with NSCLC (38.4%), followed by North and South America (24.4%), and Europe (14.1%). The prevalence among different ethnicities was similar to locations, with a prevalence of 38.8% in Asian populations, 17.4% in Caucasians, 17.2% in African Americans, and 27.0% in mixed populations (Zhang 2016). Several studies have compared the frequency of EGFR mutations between black and white patients with NSCLC, but the results are conflicting; while some studies found a lower frequency of EGFR mutations among black patients, others did not find a statistically significant difference between the 2 groups (Schabath 2016). This discordance could be driven by a lower testing rate among black/African American patients (Bruno 2022).

Risk Factors

Specific risk factors that may raise a person's risk of developing NSCLC include smoking, asbestos, radon, other substances (such as gases or chemicals at work or in the environment), air pollution, and genetics (ASCO 2022). Specific risk factors associated with EGFR-mutated advanced lung cancer are aging, history of being hospitalized for pneumonia, and gastroesophageal reflux disease (Choi 2019). However, the myriad risk factors for lung cancer most commonly include lifestyle and environmental and occupational exposures. The roles these factors play vary depending on geographic location, sex and race characteristics, genetic predisposition, as well as their synergistic interactions (Barta 2019).

The most important risk factor for the development of lung cancer is smoking. For smokers, the risk for lung cancer is on average 10-fold higher than for lifetime nonsmokers (defined as a person who has smoked <100 cigarettes in his or her lifetime). The risk increases with the quantity of cigarettes, duration of smoking, and younger starting age (PDQ Adult Treatment Editorial Board 2023). However, data emerging over the past several years demonstrate that lung cancers in nonsmokers are much more likely to carry activating EGFR mutations, and these EGFR-mutated lung cancers are less clearly linked to direct tobacco carcinogenesis (Rudin 2009, Kuśnierczyk 2023). In the systematic review and meta-analysis by Zhang et al (2016), the pooled prevalence of EGFR mutations in patients with NSCLC was 49.3% in nonsmokers versus 21.5% in past or current smokers.

Other risk factors for lung cancer include the following: exposure to cancer-causing substances in secondhand smoke, occupational exposure to asbestos, arsenic, chromium, beryllium, nickel, and other agents, radiation exposure from radiation therapy to the breast or chest, radon exposure in the home or workplace, medical imaging tests such as computed tomography scans, and atomic bomb radiation, living in an area with air pollution, family history of lung cancer, human immunodeficiency virus (HIV) infection, and beta-carotene supplements in heavy smokers (National Cancer Institute 2023).

Main Existing Treatment Options:

The treatment regimen for NSCLC depends on the histology of the tumor (ie, squamous cell, large cell, or adenocarcinoma), stage of the cancer at diagnosis, the presence or absence of a driver mutation (EGFR and others), and markers predictive of immunotherapy response (eg, programmed cell death-ligand 1 [PD-L1]). Treatment can include surgery, radiotherapy, immunotherapy, chemotherapy, and targeted therapy such as TKIs. In patients with metastatic disease, the European Society for Medical Oncology (ESMO) guidelines and American Society of Clinical Oncology (ASCO) guidelines recommend testing for driver mutations (tests available will vary between different health systems) (Hanna 2017, Planchard 2018, Hanna 2020), which are observed in approximately 60% of adenocarcinomas (Herbst 2018). If a driver mutation is identified and an active targeted agent for that mutation is available, this treatment may be indicated. In the absence of a driver mutation, treatment with an anti-programmed cell death protein-1 (PD-1), or PD-L1, antibody, either alone or in combination with chemotherapy (depending on PD-L1 expression), is the recommended first-line therapy.

The current standard of care for the first-line treatment of patients with locally advanced or metastatic NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations (EGFRm NSCLC) is a third-generation EGFR TKI, most commonly osimertinib (Soria 2018). Compared with first- and second-generation EGFR TKIs, third-generation EGFR TKIs provide activity against the T790M resistance mutation and may penetrate the blood-brain barrier better (Reungwetwattana 2018). This may delay the incidence of brain metastases, which are reported in up to one-third of patients with EGFRm NSCLC, a higher rate than that reported for EGFR wild-type NSCLC (Li 2017, Gillespie 2023). In the FLAURA study, a median progression-free survival (PFS) by blinded independent central review of 17.7 months and a median overall survival of 38.6 months were seen with osimertinib in the first-line setting (Soria 2018).

Despite the improved initial disease control, almost all patients treated with first-line osimertinib will develop resistance, and their disease will progress. There are currently no approved targeted therapies for the treatment of these patients once resistance has developed. The poor prognosis of patients with EGFRm NSCLC is more striking given the fact that patients with this disease are generally younger and healthier than other patients with lung cancer (Zhang 2016, O'Leary 2020, Pecci 2022, Nadal 2023). While osimertinib represents a significant advance over earlier EGFR TKIs, there is a need to improve first-line treatment options prior to the development of resistance in order to extend PFS beyond what is seen with osimertinib monotherapy. The most common mechanisms of resistance to osimertinib are due to alterations in the EGFR (eg, C797S mutation, EGFR amplification) and mesenchymal-epidermal transition (MET) (eg, MET amplification, MET Exon 14 skipping) pathways (Remon 2016). Given this, an agent with activity in tumors with activated EGFR and MET pathways may be of particular interest in EGFR-mutated NSCLC; targeting resistance mechanisms proactively may have been central to the improved outcomes seen with osimertinib in FLAURA.

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

NSCLC is associated with a relatively poor prognosis, not only owing to the high cancer-related mortality, but also from smoking- and age-related comorbidities (Amini 2019). Most patients diagnosed with NSCLC die within the first few years after diagnosis (Janssen-Heijnen 2012). In an observational study, the National Cancer Database was queried for cases of pathologically confirmed metastatic NSCLC with complete vital status and clinical information, diagnosed between 2006 and 2014. Of 346,681 patients, 45,861 (13%) experienced early mortality over the past decade, which remained relatively constant over time. Predictors of early mortality included advancing age (>65 years), male sex, Caucasian race, non-private insurance, lower income, greater number of comorbidities, residence in metropolitan and/or lesser-educated areas, treatment at community centers, and regional differences ($p<0.01$ for all). Early mortality was highest in patients older than 80 years with multiple comorbidities (29%). The majority of patients (71%) who died within 30 days did not receive any therapy (Amini 2019).

The overall 5-year survival rate for NSCLC is 24% (Howlader 2020); however, the rate varies greatly by the stage at diagnosis. Only 5% of patients with metastatic NSCLC are still alive 5 years after diagnosis (Garon 2019). The overall 5-year survival rate for people diagnosed with NSCLC between 2012 and 2018 was 65% for localized NSCLC, 37% for regional NSCLC, and 9% for distant NSCLC (American Cancer Society 2023).

Important Co-morbidities:

Comorbidities of NSCLC include cardiovascular disease, coronary and cerebrovascular diseases, chronic obstructive pulmonary diseases, and other types of cancer (Lembicz 2018, Rios 2018).

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

The nonclinical program for lazertinib was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) S6(R1), S7A, and S9 guidelines.

All nonclinical studies were conducted in accordance with best scientific principles. Pivotal nonclinical safety studies were conducted in conformance with Good Laboratory Practice ([GLP]; 21 CFR, Part 58) and/or the principles of Organisation for Economic Co-operation and Development (OECD)-GLP in countries that are part of the OECD Mutual Acceptance of Data process, and include the appropriate documentation.

Key Safety Findings	Relevance to Human Usage
Toxicity	
Single & repeat-dose toxicity	
Single-dose and repeat-dose oral toxicity studies of up to 4 and 13 weeks duration were conducted with lazertinib in the rat and dog. Single oral doses of lazertinib in male and female Sprague-Dawley rats were well tolerated at 200 and 600 mg/kg. In the 4-week oral gavage repeat-dose toxicity and toxicokinetic study in rats, the no observed adverse effect level (NOAEL) of 25 mg/kg/day was established based on the findings in liver (kupffer cell hypertrophy, single cell hepatocellular necrosis), kidney (papillary necrosis), duodenum (blunting/fusion of villi), and testes (tubular degeneration) with associated clinical pathology changes in animals administered ≥50 mg/kg/day. In the 13-week oral gavage repeat-dose toxicity and toxicokinetic study in rats, the NOAEL of 25 mg/kg/day was established based on the following findings in the 50 mg/kg/day group: lower mean body weights in males, eye (corneal atrophy), lung (alveolar macrophage infiltrate), rectum (degeneration/necrosis of perianal sebaceous glands), mandibular lymph node (lymphocyte hyperplasia), skin/subcutis (thinning haircoat over the entire body, scabs, rough haircoat, and red discolored haircoat or brown or red discolored skin in the nasal region, granulomatous inflammation and/or degeneration of hair follicles), kidney (papillary necrosis), ovary (decreased corpora lutea), and uterus and vagina (atrophy). At the NOAEL for male, the area under the curve (AUC) (11,700 ng·hr/mL)	Animal toxicology studies generally showed that the oral administration of lazertinib was tolerated in both rat and dog. Almost all observations and findings were consistent with consequences of the pharmacological inhibition of EGFR by lazertinib or sequelae secondary to primary effects. Prominent toxicity target organs included the liver, lung, kidney, esophagus, duodenum, testes, uterus, ovaries, eye, skin, and heart. Most of the toxicity findings are known class effects of EGFR TKIs and showed a tendency of partial or full reversibility after a recovery phase. Potential effects in humans of the animal toxicity findings observed in specific target organs/systems are described in the subsections below.

Key Safety Findings	Relevance to Human Usage
was 1.8-fold higher than the human steady-state AUC (6,541.4 ng·hr/mL) at the proposed clinical dose of 240 mg for the Phase 1/2 trial. In the 4-week oral gavage repeat-dose toxicity and toxicokinetic study in dogs, the highest non-severely toxic dose (HNSTD) of 10 mg/kg/day for males and 20 mg/kg/day for females was established based on the findings of epithelial atrophy in the cornea and esophagus, testicular tubular degeneration, bone marrow hypercellularity, and mononuclear cell infiltration in the liver. These findings, which were considered adverse, were present at ≥5 mg/kg/day. At 20 mg/kg/day, findings in the duodenum (blunting and fusion of villi), skin (epidermal atrophy), and kidney (inflammation of the pelvis) were observed, and 2 males had markedly increased cardiac troponin I concentration, which correlated microscopically with cardiac necrosis in 1 male and ventricular premature complex in the other male. At the HNSTD for male, the AUC (11,700 ng·hr/mL) was 1.8-fold higher than the human steady-state AUC (6,541.4 ng·hr/mL) at the proposed clinical dose of 240 mg for the Phase 1/2 trial. In the 13-week oral gavage repeat-dose toxicity and toxicokinetic study in dogs, a NOAEL was not established in males and was 2 mg/kg/day in females. The HNSTD was 4 mg/kg/day in males and 8 mg/kg/day in females. Adverse findings included inflammation of the renal papillae (1 male administered 2 mg/kg/day), as well as inflammation and hyperplasia in the lung (1 female administered 4 mg/kg/day and 1 male administered 8 mg/kg/day). At the HNSTD of male, the AUC (5,780 ng·hr/mL) was 0.9-fold compared to the human steady-state AUC (6,541.4 ng·hr/mL) at the proposed clinical dose of 240 mg for the Phase 1/2 trial. Toxicity studies in rats and dogs identified toxicities in the following target organs: <u>Skin</u> In rats, thinning of haircoat over the entire body, scabs, and rough haircoat, and red discolored haircoat or brown or red discolored skin in the nasal region, granulomatous inflammation and/or degeneration of hair follicles were observed at 50 mg/kg/day. Rough or thinning haircoat persisted through the end of the recovery phase,	Skin findings were present in both rats and dogs, and many lesions reversed during the recovery phase. Skin toxicities are a common adverse event observed with other EGFR TKIs drugs, which are manageable through standard clinical practice.

Key Safety Findings	Relevance to Human Usage
whereas discolored skin resolved. In dogs, epidermal atrophy of the skin/subcutis was present at 20 mg/kg/day, and it was not present in the recovery animals.	
Lung	
In rats, alveolar macrophage infiltrate was observed in the ≥25 mg/kg/day group and at a decreased incidence and severity in the 50 mg/kg/day recovery group with partial reversibility in males and full reversibility in females. In the recovery phase, 2 of 5 rats from both sexes in the control group had alveolar macrophage infiltrate, which was not present in main study control animals at terminal sacrifice. In dogs, inflammation and hyperplasia in the lung at 4 mg/kg/day in females and at 8 mg/kg/day in males were observed, which resolved in males and persisted in females.	Effects on the lung in dogs resolved in males and persisted in females. Effects in rats partially or fully recovered. Interstitial lung disease (ILD)/pneumonitis is a known and well characterized risk for oncology drugs targeting EGFR and the management of this risk is adequately described in the product information.
Kidney	
Renal findings, including papillary necrosis were observed in rats, and an inflammation of the renal papillae in 1 male dog. These observations either persisted at a decreased incidence/severity or fully resolved during the recovery phase of the study. Findings were not present in all animals in the group.	Nonclinical data do not indicate a safety concern for humans. Renal findings occurred infrequently, not in all animals, not in both sexes, and changes were partially or fully reversible. Available clinical data with lazertinib show no significant adverse incidence and effect on the kidney (Dhillon 2021).
Liver	
Nonclinical studies showed minimal to mild increase in serum liver enzymes (aspartate aminotransferase [AST], alanine aminotransferase [ALT], and bilirubin), which are suggestive of hepatocellular damage, and correlated with microscopic findings in the liver (Kupffer cell hypertrophy/hyperplasia, single cell hepatocellular necrosis) in rats. Mononuclear cell infiltrates were observed in dogs. Liver enzyme changes persisted but microscopic lesions were at reduced incidence and/or severity in the recovery phase of the study.	Liver enzyme increases occurred in both sexes of rats and persisted in the recovery phase, which is indicative of hepatocellular damage. Enzyme changes correlated with microscopic changes in the liver. Liver toxicities are a common adverse event observed with other EGFR TKIs drugs. Based on the nonclinical observations and the known class effect, hepatotoxicity is an important potential risk with the use of lazertinib in humans.
Eye	
Epithelial atrophy in the cornea, corneal erosion/ulcer of the eyelids, and chronic/active inflammation in the eyelids were observed in rats at 50 mg/kg/day. Microscopic findings in the eyelids correlated with the macroscopic observation of thickened eyelids. These changes partially reversed during recovery. In dogs, epithelial atrophy in the cornea of the eye was present in both sexes at ≥5 mg/kg/day but it was	Effects on the eye were observed in both rats and dogs. These effects are likely related to inhibition of EGFR. EGFR TKIs are known to cause adverse ocular effects, which are manageable through standard clinical practice.

Key Safety Findings	Relevance to Human Usage
not present in the recovery animals.	
Gastrointestinal system	
Minimal to slight villus blunting/fusion in duodenum was noted in both rats (≥50 mg/kg/day) and dogs (20 mg/kg/day). It persisted in rats but resolved in dogs. Additionally, increased incidence of liquid feces was observed in dogs and these were minimal in nature.	Since EGFR receptors are present at high levels in the epithelium of the gastrointestinal tract, any disruption of EGFR will lead to effects like diarrhea, which was observed in dogs. Based on the nonclinical data, gastrointestinal disorders may be observed in humans but the clinical impact on patients is expected to be minimal in relation to the severity of the indication treated, and gastrointestinal symptoms are manageable through standard clinical practice.
Developmental and reproductive toxicity	
In the repeat-dose toxicity studies in rats, changes in testes (minimal to slight tubular degeneration) and epididymis (minimal to slight luminal cellular debris) were observed in the dosing period and these findings persisted in the 2-week recovery phase. In the repeat-dose toxicity studies in dogs, minimal to moderate testicular tubular degeneration with reduced luminal sperm was observed in the dosing period and partially reversed in the recovery phase. In female rats, decreased numbers of corpora lutea were noted in the ovaries of rats exposed to lazertinib for ≥1 month; reversibility was observed in the 1-month study. In a fertility and early embryonic development study in male and female rats, lazertinib induced a decrease in the number of oestrus cycles, an increase in post-implantation loss, and decreased live litter size at or below the dose level that approximated the human clinical exposure at the recommended dose of 240 mg. In an embryofetal development toxicity study in rats, the NOAEL of 30 mg/kg/day for both maternal toxicity and fetal toxicity was established based on adverse decreases in body weight gain, body weight, food consumption, and gravid uterine and fetal weights at 60 mg/kg/day. At the NOAEL, the AUC_{24h} on gestation day 17 (11,100 ng·hr/mL) was 1.7-fold higher than the human steady-state AUC (6,541.4 ng·hr/mL) at the proposed clinical dose of 240 mg for the Phase 1/2 trial. In an embryofetal development toxicity study in rabbits, the NOAEL for maternal toxicity of 25 mg/kg/day and 45 mg/kg/day for fetal toxicity	Lazertinib showed reproductive and developmental toxicity at clinically relevant exposures. It may cause embryofetal toxicity when administered to pregnant women and may reduce female fertility by affecting the ability to become pregnant and maintenance of pregnancy. Lazertinib may impair spermatogenesis in men resulting in reduced fertility. Impaired fertility and embryofetal toxicity is a known class effect of EGFR inhibitors. Impaired fertility and embryofetal toxicity is an important potential risk for lazertinib.

Key Safety Findings	Relevance to Human Usage
was established based on adverse body weight loss and lower mean body weight gain, mean body weight, and food consumption for animals administered 45 mg/kg/day.	
Genotoxicity	
No evidence of genotoxicity was observed in an in vitro bacterial reverse mutation assay, in an in vitro chromosome aberration test using Chinese hamster lung cells, and in an in vivo micronucleus study in rats.	Nonclinical data do not indicate a safety concern for humans.
Carcinogenicity	
No carcinogenicity studies were conducted with lazertinib. Routine carcinogenicity studies are generally not applicable to therapeutics for specific cancer indications (ICH S9).	Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICH S9).
Safety pharmacology:	
Cardiovascular system (including potential for QT interval prolongation)	
In the in vitro human ether-à-go-go-related gene (hERG) assay, the IC_{50} of lazertinib was 5.3±2.0 µM on hERG channel current, which is 570-fold the free C_{max} plasma concentration (9.3 nM) at the 240 mg recommended dose. No changes in electrocardiogram outputs, arterial pressure or heart rate findings up to 20 mg/kg were found in a single oral cardiovascular telemetry study in Beagle dogs. No lazertinib-related change in cardiac troponin I level, no histological changes in heart, and no lazertinib-related differences in QT interval, corrected QT (QTc) interval, or heart rate were observed in the 13-week repeat-dose toxicity study in dogs at doses up to 8 mg/kg/day with a safety margin of approximately 2-fold. Cardiotoxicity (degeneration/necrosis of the myocardium, degeneration/necrosis of vessel, inflammation of vessel, mixed cell inflammation, fibrosis, thrombus, and hemorrhage) was observed in 2 out of 5 males at 20 mg/kg/day in the 4-week repeat-dose toxicity study in dogs. One male was sacrificed early due to moribund condition and the other male survived up to terminal necropsy. AUC_{24h} exposure in the male with cardiotoxicity was higher compared to the mean of other males (46,000 versus 26,633 ng·hr/mL) and the mean of all females (46,000 versus 14,900 ng·hr/mL) in the 20 mg/kg/day group, and 7x AUC exposure at the 240 mg once daily recommended human dose.	The IC_{50} of the hERG assay and the systemic exposure that caused the cardiotoxicity in the 4-week toxicity study in dogs was higher than the clinical exposure at the recommended human dose. Based on the nonclinical data, lazertinib is not expected to induce cardiovascular disorders in humans at the recommended human dose of 240 mg/day.

Key Safety Findings	Relevance to Human Usage
This higher exposure may have been associated with the adverse findings in the heart. This effect was not seen in females at 20 mg/kg/day.	
Nervous system	
No drug-related neurological changes were noted in the single-dose, 4-week and 13-week repeat-dose toxicity studies in rats and dogs.	Based on the nonclinical data, lazertinib is not expected to induce nervous system disorders in humans.
Respiratory system	
No drug-related changes in respiratory parameters (tidal volume, respiration rate, and minute volume) were noted in the single-dose toxicity study in rats.	No abnormal safety pharmacology findings of concern, relevant to humans, were detected.
No lazertinib-related respiratory parameter changes were noted in the 4- and 13-week rat and dog oral toxicity studies based on clinical observations at dose levels up to 100/75 mg/kg/day in rats and 20 mg/kg/day in dogs.	
Lazertinib did not induce changes in assessed respiratory parameters in rats and dogs. Although microscopic changes were observed in rats and dogs, these changes were either reversible or not dose related and did not affect the overall respiratory function as assessed by clinical observation.	
Other toxicity-related information or data	
Phototoxicity	
No evidence of phototoxicity was noted in BALB/c 3T3 mouse fibroblasts in an in vitro neutral red uptake assay.	Based on the nonclinical data, lazertinib is not expected to induce phototoxicity in humans.
Drug metabolism and pharmacokinetics	
Mechanisms for drug interactions	
Lazertinib is primarily metabolized by glutathione conjugation, either enzymatic via glutathione S-transferase (GST) or non-enzymatic, as well as by cytochrome P450 (CYP)3A4.	The impact of CYP3A4 inhibition or induction on lazertinib exposure was evaluated in a clinical drug-drug interaction (DDI) study. Inhibition of CYP3A4 resulted in a <2-fold increase in lazertinib exposure, which is not considered clinically relevant. Therefore, no initial dose adjustment is required when lazertinib is coadministered with a mild, moderate, or strong inhibitor of CYP3A4. Coadministration of lazertinib with a strong CYP3A4 inducer led to a significant decrease in lazertinib exposure. Such a decrease in exposure may lead to reduced efficacy and coadministration of lazertinib with strong CYP3A4 inducers should be avoided. The
In vitro results suggest that lazertinib may inhibit human CYP3A4 (reversible and time-dependent inhibition), UDP-glucuronosyltransferase (UGT)1A1, organic cation transporter (OCT)1, and breast cancer resistance protein (BCRP) at clinically relevant exposures.	

Key Safety Findings	Relevance to Human Usage
	coadministration of lazertinib with moderate CYP3A4 inducers may also decrease lazertinib plasma concentration and hence moderate CYP3A4 inducers should be used with caution. Glutathione S-transferase mu 1 (GSTM1) is a polymorphic enzyme. Patients with functional GSTM1 have slightly lower lazertinib exposure (<2-fold difference). The recommended dose of 240 mg daily accounts for this difference, and no dose adjustment is needed based on GSTM1 genotype. Inhibition of enzymes/transporters could lead to increased exposure of coadministered substrates. The impact of enzyme and transporter inhibition by lazertinib was evaluated in a clinical DDI study and further simulated using a physiologically-based pharmacokinetic model. The results suggest that lazertinib may inhibit CYP3A4 and BCRP at the recommended dose, leading to increased exposure of sensitive substrates. Therefore, narrow therapeutic index medicinal products that are CYP3A4 or BCRP substrates should be used with caution. Clinically relevant inhibition of UGT1A1 or OCT1 was not evident.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	Hepatotoxicity
	Impaired fertility and embryofetal toxicity
Missing information	None

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

The Marketing Authorization Applicant is developing 2 compounds (amivantamab and lazertinib) for the treatment of patients with NSCLC. Lazertinib is developed under a license and collaboration agreement between Yuhan Corporation and Janssen.

Lazertinib (a third-generation EGFR TKI) is currently approved in South Korea only, under the tradename LECLAZA™ (Yuhan Corporation), for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumors have EGFR Exon 19 deletions or Exon 21 L858R substitution mutations and for the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. The Marketing Authorization Applicant owns global development and marketing rights outside of Korea.

Lazertinib in combination with amivantamab (a bispecific antibody targeting EGFR and MET), target the intracellular active site of EGFR and the extracellular ligand binding domain, respectively, and have the potential to inhibit this pathway more potently than either agent alone. Combining these agents in the first-line treatment of patients with EGFR-mutated NSCLC may lead to improved treatment outcomes through synergistic anti-EGFR activity, prevention of EGFR- or MET-based resistance to a third-generation EGFR TKI, and potential recruitment of Fc-bearing immune cells in the anti-tumor response.

The safety of lazertinib in combination with amivantamab in the NSCLC population is supported by one clinical trial in this EU-RMP:

- Trial 73841937NSC3003 (hereafter referred to as NSC3003) is an ongoing, Phase 3 randomized, multicenter trial to compare the efficacy and safety of the combination of amivantamab and lazertinib versus osimertinib as first-line treatment in participants with EGFR-mutated locally advanced or metastatic NSCLC not amenable to curative therapy. The contribution of amivantamab to the activity of the combination is also being assessed by comparing the efficacy observed in the amivantamab and lazertinib combination arm with that in the lazertinib monotherapy arm.

Safety of lazertinib in combination with amivantamab was also evaluated in Trials 61186372EDI1001 and 73841937NSC1001. In addition, safety of lazertinib monotherapy was evaluated in Trials 73841937NSC1001, YH25448-201/73841937NSC2001, and YH25448-301/LASER301. However, as the advanced NSCLC populations in these trials are heterogeneous with respect to previous lines of therapy, EGFR mutation types, and dosing, data from these trials are not included in this EU-RMP because the focus is on the first-line treatment in combination with amivantamab of adult patients with advanced NSCLC with EGFR Exon 19 deletions or Exon 21 L858R substitution mutations, which is the population part of the indication.

SIII.2. Clinical Trial Exposure

Exposure in Randomized Clinical Trials

The randomized clinical trials population includes 1 trial:

- Trial NSC3003

Exposure to lazertinib in the randomized clinical trials population is summarized in Tables SIII.1 through SIII.4 for all participants by duration, by age group and sex, by dose, and by variable stratifications relevant to the product (ie, ethnic origin, race, renal impairment at baseline, and hepatic impairment at baseline).

Table SIII.1: Exposure by Duration: Randomized Clinical Trials Population

Duration of exposure (Months)	Patients	Person-months
Advanced NSCLC		
0 - <2	41	
2 - <4	33	
4 - <6	24	
6 - <8	26	
8 - <10	29	
10 - <12	24	
12 - <14	29	
14 - <16	37	
>= 16	391	
Total	634	10,605.5

Note: Trial included: Arm A (Amivantamab + Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003.
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Table SIII.2: Exposure by Age Group and Sex: Randomized Clinical Trials Population

	Men		Women	
Age Group (years)	Patients	Person-months	Patients	Person-months
Advanced NSCLC				
18-64	133	2,287.0	218	3,998.2
65-74	73	1,134.2	143	2,189.8
75-84	25	347.9	36	535.7
>=85	1	9.5	5	103.2
Total	232	3,778.6	402	6,826.9

Note: Trial included: Arm A (Amivantamab + Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003.
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Table SIII.3: Exposure by Dose: Randomized Clinical Trials Population

Dose of Exposure (mg)	Patients	Person-months
Advanced NSCLC		
240 mg	634	10,605.5
Total	634	10,605.5

Note: Trial included: Arm A (Amivantamab+Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003
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Table SIII.4: Exposure by Special Populations: Randomized Clinical Trials Population

Population	Patients	Person-Months
Advanced NSCLC		
Ethnicity		
Hispanic or Latino	79	1,317.5
Not-Hispanic or Latino	551	9,217.6
Not Reported	3	53.8
Unknown	1	16.6
Total	634	10,605.5
Race		
White	237	3,765.3
Black or African American	6	120.1
Native Hawaiian or other Pacific Islander	1	5.1
Asian	375	6,548.1
American Indian or Alaska Native	11	126.6
Not Reported	0	0
Multiple[a]	1	1.6
Other	3	38.7
Total	634	10,605.5
Renal impairment at baseline		
Normal (eGFR: >= 90 mL/min/1.73m^2)	358	6,091.7
Mild (eGFR: 60 to < 90 mL/min/1.73m^2)	246	4,028.3
Moderate (eGFR: 30 to < 60 mL/min/1.73m^2)	29	475.5
Severe (eGFR: < 30 mL/min/1.73m^2)	1	10.1
Missing	0	0
Total	634	10,605.5
Hepatic impairment at baseline[b]		
Normal	571	9,562.3
Mild	62	1,027.1
Moderate	1	16.1
Severe	0	0
Missing	0	0
Total	634	10,605.5

[a]Multiple = one or more category was selected.
[b]Normal: Total bilirubin <= ULN and AST <= ULN; Mild: (Total bilirubin <= ULN and AST > ULN) or (ULN < Total bilirubin <= 1.5 x ULN); Moderate: 1.5 x ULN < Total bilirubin <= 3 x ULN; Severe: Total bilirubin > 3 x ULN.
Key: ULN = upper limit of normal; eGFR = estimated glomerular filtration rate; ALT = alanine aminotransferase; AST = aspartate aminotransferase.
Note: Trial included: Arm A (Amivantamab+Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003
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Exposure in All Clinical Trials

The all clinical trials population includes 1 trial:

- Trial NSC3003

Exposure to lazertinib in the all clinical trials population is identical to that in the randomized clinical trials population as summarized in Tables SIII.1 through SIII.4.

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Participant has active cardiovascular disease including, but not limited to:** • **A medical history of deep vein thrombosis or pulmonary embolism (PE) within 1 month prior to randomization or any of the following within 6 months prior to randomization: myocardial infarction, unstable angina, stroke, transient ischemic attack, coronary/peripheral artery bypass graft, or any acute coronary syndrome. Clinically non-significant thrombosis, such as non-obstructive catheter-associated thrombus, incidental or asymptomatic PE, are not exclusionary.** • **Prolonged QTcF (QT corrected for heart rate using Fridericia's formula) interval >470 ms, clinically significant cardiac arrhythmia or abnormalities in conduction or morphology of electrocardiogram, or electrophysiologic disease (eg, placement of implantable cardioverter defibrillator), and any factors that increase the risk of QTc interval prolongation or risk of arrhythmic events.** • **Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg.** • **Congestive heart failure defined as New York Heart Association (NYHA) class III-IV or hospitalization for chronic heart failure (any NYHA class) within 6 months of randomization.** • **An active or past medical history of pericarditis, pericardial effusion that is clinically unstable, or myocarditis. Pericardial effusion considered due to the disease under study is permitted if clinically stable at screening.** • **Baseline left ventricular ejection fraction either <50% or below the lower limit of normal per institutional guidelines, as assessed by screening echocardiogram or multigated acquisition scan.**

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Reason for being an exclusion criterion	It is common clinical practice not to include participants with severe or unstable clinical status and potentially life-threatening cardiac conditions in trials on anticancer therapy because they potentially place participants with these comorbidities at increased risk for adverse events (AEs) and additionally may confound the interpretation of safety data.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Venous thromboembolic (VTE) events is an important identified risk for lazertinib in combination with amivantamab. There are no specific data available for use of lazertinib in patients with significant cardiac disease. The treating physician would be expected to weigh the benefit and risks for each individual patient. In nonclinical studies, no lazertinib-related differences in QT interval, QTc interval, or heart rate were observed and the results of an in vitro hERG assay did not suggest a clinical risk. The QTc interval prolongation potential of lazertinib was evaluated by exposure-response 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 exposure-response analysis revealed no clinically relevant relationship between lazertinib plasma concentration and change in QTc interval.
Criterion 2	**Participant is a woman who is pregnant, breast-feeding, or planning to become pregnant, or a man who plans to father a child while enrolled in this trial or within 6 months after the last dose of study treatment.**
Reason for being an exclusion criterion	Per ICH guidelines, pregnant women should normally be excluded from clinical trials. Based on its mechanism of action and findings in animal models, lazertinib could cause fetal harm when administered to pregnant women. Breast-feeding women are usually excluded from clinical trials. It is not known whether lazertinib or its metabolites are excreted in human or animal milk or affects milk production.
Considered to be included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	Impaired fertility and embryofetal toxicity is a known class effect of EGFR inhibitors. Summary of product characteristics (SmPC) Section 4.6 provides guidance to avoid pregnancy by using effective contraception during treatment and for 3 weeks after the last dose of LAZCLUZE. LAZCLUZE should not be used during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the fetus. In addition, female patients should be advised not to breastfeed during treatment and for 3 weeks after the last dose of LAZCLUZE.
Criterion 3	**Participants positive for HIV that is not well controlled, or participants with a positive test for hepatitis B surface antigen or hepatitis C antibody, or another clinically active infectious liver disease.**
Reason for being an exclusion criterion	It is common clinical practice to exclude participants with active infections, including infections that can lead to hepatotoxicity, from clinical trials on anticancer therapy because they potentially confound the interpretation of safety.
Considered to be included as missing information	No
Rationale (if not included as missing information)	It is consistent with standard-of-care not to treat patients with active infections. Hepatotoxicity is an important potential risk.
Criterion 4	**Active or past medical history of ILD/pneumonitis.**
Reason for being an exclusion criterion	It is common clinical practice not to include participants with severe and potentially life-threatening pulmonary conditions in trials on anticancer therapy because they potentially place participants with these comorbidities at increased risk for AEs and additionally may confound the interpretation of safety data. Medical history of ILD may increase the risk of recurrence. ILD is considered a class effect of EGFR inhibitors, such as monoclonal antibodies and TKIs.
Considered to be included as missing information	No

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program	
Rationale (if not included as missing information)	ILD or ILD-like adverse reactions (eg, pneumonitis) have been reported in participants treated with EGFR TKIs and ILD/pneumonitis is an adverse reaction in Section 4.8 of the lazertinib SmPC and specific guidance to minimize and manage the risk is included in SmPC Sections 4.2 and 4.4. The treating physician would be expected to weigh the benefit and risks for each individual patient.
Criterion 5	**Participant is currently receiving medications or herbal supplements known to be potent CYP3A4/5 inducers and is unable to stop use for an appropriate washout period prior to randomization.**
Reason for being an exclusion criterion	Data from a clinical DDI study indicated that coadministration of lazertinib with a strong CYP3A4 inducer leads to a significant decrease in lazertinib exposure, which may result in reduced efficacy. Inclusion of these participants could confound the efficacy evaluation.
Considered to be included as missing information	No
Rationale (if not included as missing information)	SmPC Section 4.5 includes a recommendation to avoid the coadministration of LAZCLUZE with strong CYP3A4 inducers.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.

Population with relevant different racial and/or ethnic origin	Of the 634 participants in the all clinical trials population, 375 (59.1%) participants were Asian, 237 (37.4%) were white, 11 (1.7%) were American Indian or Alaska Native, and <1% of participants were black or African American, or Native Hawaiian or other Pacific Islander. Seventy-nine (12.5%) participants were Hispanic or Latino.
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Pediatric population	Not included in the clinical development program.
Elderly population	Of the 634 participants in the all clinical trials population, 283 (44.6%) participants were ≥65 years of age and 67 (10.6%) participants were ≥75 years of age.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Of the 634 participants in the all clinical trials population, there were 62 (9.8%) participants with mild hepatic impairment at baseline (total bilirubin ≤ upper limit of normal [ULN] and AST > ULN, or ULN < total bilirubin ≤1.5 x ULN), 1 participant with moderate (1.5 x ULN < total bilirubin ≤3 x ULN), and no participants with severe (total bilirubin >3 x ULN) hepatic impairment at baseline.
Patients with renal impairment	Of the 634 participants in the all clinical trials population, there were 246 (38.8%) participants with mild renal impairment at baseline (estimated glomerular filtration rate [eGFR] 60 to <90 mL/min/1.73 m²), 29 (4.6%) participants with moderate (eGFR 30 to <60 mL/min/1.73 m²), and 1 participant with severe renal impairment at baseline (eGFR <30 mL/min/1.73 m²).
Patients with cardiovascular impairment	Participants with a history of or with recent/acute clinically significant cardiovascular disease were not included in the clinical development program.
Immunocompromised patients	Not applicable
Patients with a disease severity different from inclusion criteria in clinical trials	Not applicable

Summary of Missing Information Due to Limitations of the Clinical Trial Program

None

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

There is no postauthorization experience as lazertinib is not yet marketed as a combination treatment with amivantamab.

SV.1.1. Method used to Calculate Exposure

Not applicable.

SV.1.2. Exposure

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Lazertinib is an antineoplastic agent which will be prescribed by a healthcare professional and has no abuse potential. Therefore, there is no concern for potential illegal use.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Risks not Included in the List of Safety Concerns in the RMP
Risks with minimal clinical impact on patients (in relation to the severity of the indication treated):
Risk 1: Paraesthesia*, Dizziness*
Risk 2: Dry skin*, Pruritus, Palmar-plantar erythrodysaesthesia syndrome, Urticaria
Risk 3: Nail toxicity*
Risk 4: Fatigue*, Pyrexia
Risk 5: Stomatitis*, Constipation, Diarrhoea, Nausea, Vomiting, Abdominal pain*, Haemorrhoids
Risk 6: Decreased appetite, Hypocalcaemia, Hypokalaemia, Hypomagnesaemia
Risk 7: Muscle spasms, Myalgia
Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated:
Not applicable
Known risks that require no further characterization and are followed up via routine pharmacovigilance and for which the risk minimization messages in the product information are adhered by prescribers (eg, actions being part of standard clinical practice in each EU Member state where the product is authorized):
Risk 1: Other eye disorders*, Visual impairment*, Keratitis, Growth of eyelashes*
Risk 2: Interstitial lung disease (ILD)/pneumonitis*
Risk 3: Rash*
Known risks that do not impact the risk-benefit profile:
Not applicable

Risks not Included in the List of Safety Concerns in the RMP
Other reasons for considering the risks not important:
Not applicable

* Grouped terms.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Safety Concerns for Inclusion in the RMP	Risk-Benefit Impact
Important identified risks	
Venous thromboembolic (VTE) events*	Venous thromboembolism was identified as an adverse reaction associated with the use of lazertinib in combination with amivantamab based on data from Trial NSC3003. VTE events are potentially serious, and if not recognized or managed appropriately, may result in persistent or significant disability or incapacity, and hence require immediate medical intervention. Therefore, VTE events is considered an important identified risk with the use of lazertinib in combination with amivantamab. While the incidence of VTE events was higher in participants treated with the combination of lazertinib and amivantamab compared with lazertinib or osimertinib monotherapy in Trial NSC3003, the greatest discordance in events occurred during the first 4 months of study treatment, the events were predominantly Grade 2, non-serious, and were manageable with therapeutic anticoagulation. The SmPC and package leaflet (PL) provide information on how to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy in patients treated with lazertinib in combination with amivantamab.
Important potential risks	
Hepatotoxicity	Hepatotoxicity is known as a risk in the EGFR-TKI class of drugs. Hepatotoxicity-related reactions, mostly elevations of serum transaminases, were reported with the use of lazertinib in Trial NSC3003. Drug-induced liver injury (DILI) could be serious, potentially fatal, or lead to liver transplantation and therefore, hepatotoxicity is considered an important potential risk with the use of lazertinib. While increased liver enzymes have been observed in participants treated with lazertinib in Trial NSC3003, there have been no clinical sequelae of these elevations and no confirmed cases of DILI. The majority of liver AEs were non-serious, of low severity, and they rarely led to treatment discontinuation. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases

	treated and the potential efficacy in patients treated with lazertinib in combination with amivantamab.
Impaired fertility and embryofetal toxicity	Impaired fertility and embryofetal toxicity is a known class effect of EGFR inhibitors. There are no data on the use of lazertinib in pregnant women. However, based on the mechanism of action and findings in animal models, lazertinib may cause fetal harm when administered to a pregnant woman and may reduce female and male fertility. Therefore, impaired fertility and embryofetal toxicity is considered an important potential risk with the use of lazertinib. The SmPC includes a warning that lazertinib should not be used during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the fetus. Contraception recommendations included in the SmPC and PL are considered sufficient to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy for patients treated with lazertinib in combination with amivantamab.

Missing information

None

* Applies only to the combination of lazertinib and amivantamab.

SVII.2. New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

The important identified and potential risks for lazertinib presented in this RMP are based on nonclinical data as well as on clinical trial data from Trial NSC3003 for the indication with amivantamab.

Important identified risks

1. Venous thromboembolic (VTE) events*

Important potential risks

1. Hepatotoxicity
2. Impaired fertility and embryofetal toxicity

Missing Information:

There is no missing information for lazertinib.

* Applies only to the combination of lazertinib and amivantamab.

Medical Dictionary for Regulatory Activities (MedDRA) Search Strategies for the evaluation of the important identified and important potential risks are listed in Annex 7.3.

MedDRA version 25.0 was used to classify the clinical trials AE information that is summarized in this Section.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Venous thromboembolic (VTE) events*

Potential Mechanisms:

Despite prolonged use of EGFR inhibitors in the treatment of patients with cancer, a clear link between EGFR inhibitors and VTE events has not been established. There are reports in the clinical literature that suggest an increased risk of VTE events in patients treated with anti-EGFR therapies, as well as pre-clinical work proposing mechanisms for such an association (Miroddi 2016, Petrelli 2012). These potential mechanisms include antiangiogenic effects exerted by a significant decrease in tumor cell production of angiogenic growth factors such as basic fibroblast growth factor, vascular endothelial growth factor, and interleukin-8 (Miroddi 2016). The disruption of the regenerative capacity of endothelial cells can also lead to thrombosis via several mechanisms (Petrelli 2012). The applicability of these in vitro/preclinical observations to clinical risk of VTE events in patients with EGFR-mutated NSCLC, which exhibit a unique biology characteristically demonstrating a high level of tumor response to anti-EGFR therapy, is unknown. Furthermore, the clinical experience with combination anti-EGFR therapies (eg, TKI and monoclonal antibody) is limited, and the safety implications of the combination of lazertinib and amivantamab may be distinct from the safety profile of each agent when used as a monotherapy.

Evidence Source(s) and Strength of Evidence:

Venous thromboembolic (VTE) events is an important identified risk for lazertinib only when given in combination with amivantamab.

The incidence of VTE events was higher in participants treated with the combination of lazertinib and amivantamab versus lazertinib or osimertinib monotherapy in Trial NSC3003. The greatest discordance in events occurred during the first 4 months of study treatment. Importantly, the incidence rate of VTE events associated with lazertinib monotherapy is consistent with background rates associated with NSCLC. Venous thromboembolism was identified as an adverse reaction for the combination of lazertinib and amivantamab and is described in the SmPC for lazertinib.

* Applies only to the combination of lazertinib and amivantamab.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Venous Thromboembolic (VTE) Events

	Randomized Trials[a]			All Clinical Trials Population[b]
	Amivantamab+ Lazertinib Arm	Lazertinib Monotherapy Arm	Comparator Arm[c]	Lazertinib Monotherapy and as Combination
Advanced NSCLC				
Number of subjects treated	421	213	428	634
Frequency	157 (37.3%)	30 (14.1%)	39 (9.1%)	187 (29.5%)
Odds Ratio (95% CI)[d]	5.93 (4.04,8.71)	1.63 (0.98,2.72)		
Seriousness				
Was serious	46 (10.9%)	11 (5.2%)	15 (3.5%)	57 (9.0%)
Outcomes				
Fatal	2 (0.5%)	2 (0.9%)	2 (0.5%)	4 (0.6%)
Not Recovered/Not Resolved	41 (9.7%)	12 (5.6%)	12 (2.8%)	53 (8.4%)
Recovering/Resolving	47 (11.2%)	2 (0.9%)	13 (3.0%)	49 (7.7%)
Recovered/Resolved with sequelae	1 (0.2%)	1 (0.5%)	0	2 (0.3%)
Recovered/Resolved	66 (15.7%)	13 (6.1%)	12 (2.8%)	79 (12.5%)
Unknown	0	0	0	0
Severity				
Worst Grade=1	5 (1.2%)	1 (0.5%)	0	6 (0.9%)
Worst Grade=2	105 (24.9%)	17 (8.0%)	24 (5.6%)	122 (19.2%)
Worst Grade=3	43 (10.2%)	9 (4.2%)	12 (2.8%)	52 (8.2%)
Worst Grade=4	2 (0.5%)	1 (0.5%)	1 (0.2%)	3 (0.5%)
Worst Grade=5	2 (0.5%)	2 (0.9%)	2 (0.5%)	4 (0.6%)
Missing Grade	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardized MedDRA Queries (SMQs) for Venous Thromboembolic (VTE) Events.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst outcome or grade are used in case of multiple events, respectively.
Note: Unknown outcome category includes AE records with missing outcome in current data.
[a] Note: Trial included: Arm A (Amivantamab + Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003.
[b] Note: Trial included: Arm A (Amivantamab + Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003.
[c] Note: Comparator included: Osimertinib (NSC3003).
[d] Odds Ratio is for event comparison of Amivantamab + Lazertinib versus Comparator and Lazertinib monotherapy versus Comparator.

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VTE events are common in patients with lung cancer. In Trial NSC3003, the incidence of VTE events in the lazertinib monotherapy arm (14.1%) and the osimertinib arm (9.1%) is consistent with previous reports of patients with NSCLC (Vitale 2015). There was a higher incidence of VTE events in the amivantamab+lazertinib arm (37.3%) compared with the lazertinib monotherapy and osimertinib arms. The difference in overall incidence was primarily due to a higher incidence of Grade 2 VTE events. The incidence of Grade 4 and Grade 5 VTE events was <1% in all arms. The majority of VTE events were non-serious and the most frequently reported VTE events were PE and deep vein thrombosis.

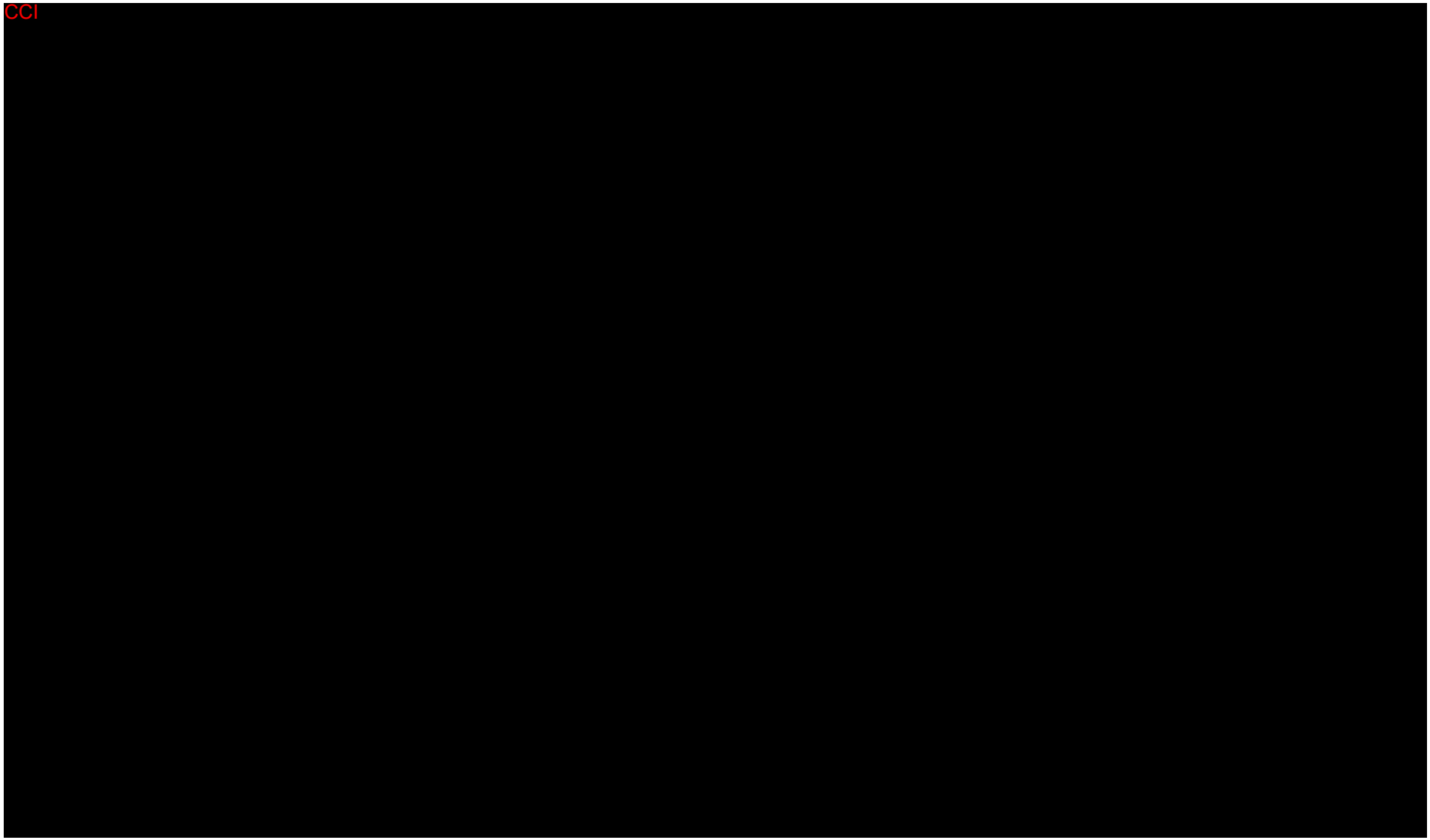
VTE events led to discontinuation of any study agent for 2.9% of participants in the amivantamab+lazertinib arm versus 1.4% of participants in the lazertinib monotherapy arm and 0.5% of participants in the osimertinib arm.

Median time to first VTE event was 84.0 days in the amivantamab+lazertinib arm, 240.5 days in the lazertinib monotherapy arm, and 194.0 days in the osimertinib arm. There was an early separation of the Kaplan-Meier curves indicating greater VTE risk in the amivantamab+lazertinib arm during the first approximately 4 months of treatment. This was followed by a stable separation of the curves for the remainder of the treatment phase (see figure below for the amivantamab+lazertinib arm versus the osimertinib arm).

For a large majority of participants (152/157 participants in the amivantamab+lazertinib arm, 30/30 participants in the lazertinib monotherapy arm, and 39/39 participants in the osimertinib arm), first VTE events occurred in the absence of concomitant anticoagulation. Following a first VTE event, large proportions of participants (139/152 participants in the amivantamab+lazertinib arm, 28/30 participants in the lazertinib monotherapy arm, and 33/39 participants in the osimertinib arm) started anticoagulation within 30 days. Recurrent VTE events while on anticoagulation were reported for 8 (1.9%) participants in the amivantamab+lazertinib arm, 1 (0.5%) participant in the lazertinib monotherapy arm, and no participants in the osimertinib arm. Many of these additionally reported events describe the same thromboembolic episode or were reported in participants who were not compliant with anticoagulation. The incidence of clinically significant bleeding AEs following the start of anticoagulation was low.

A large majority of the reported serious VTE events in the amivantamab+lazertinib arm were deemed serious because of the need for hospitalization for initiation of anticoagulation therapy or as required by local standard of care and not for VTE symptom management.

VTE events are potentially serious, and if not recognized or managed appropriately, may result in persistent or significant disability or incapacity, and hence require immediate medical intervention.


CCI

Risk Factors and Risk Groups:

Lung cancer is a risk factor for VTE events (Tesselaar 2007, Tagalakis 2007). Additional risk factors for VTE events associated with use of lazertinib in combination with amivantamab identified in open-label trials include age ≥60 years, Eastern Cooperative Oncology Group (ECOG)=1, and Responders (ie, patients with partial response or complete response) (Girard 2023).

Preventability:

Specific guidance is provided in the SmPC Sections 4.2 and 4.4 to minimize and manage the risk of VTE events. At the initiation of treatment, prophylactic anticoagulants should be administered to prevent VTE events in patients receiving LAZCLUZE in combination with amivantamab. Consistent with clinical guidelines, patients should receive prophylactic dosing of either a direct acting oral anticoagulant (DOAC) or a low-molecular weight heparin (LMWH). Use of Vitamin K antagonists is not recommended. Patients should be monitored for signs and symptoms of VTE events and patients with VTE events should be treated with anticoagulation as clinically indicated. For VTE events associated with clinical instability, LAZCLUZE and amivantamab should be withheld until the patient is clinically stable. Thereafter, both medicinal products can be resumed at the same dose. Amivantamab should be permanently discontinued in case of recurrent VTE events despite appropriate anticoagulation. Treatment can continue with LAZCLUZE at the same dose.

Impact on the Risk-Benefit Balance of the Product:

While the incidence of VTE events was higher in participants treated with the combination of lazertinib and amivantamab compared with lazertinib or osimertinib monotherapy in Trial NSC3003, the greatest discordance in events occurred during the first 4 months of study treatment, the events were predominantly Grade 2, non-serious, and were manageable with therapeutic anticoagulation. The SmPC and PL provide information on how to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy in patients treated with LAZCLUZE in combination with amivantamab.

Public Health Impact:

No public health impact is anticipated.

Annex 1 MedDRA Term:

MedDRA Standardised MedDRA Query (SMQ) Embolic and thrombotic events, venous (narrow)

Important Potential Risk: Hepatotoxicity

Potential Mechanisms:

Although the mechanism of hepatotoxicity by EGFR-TKI has not been fully elucidated, the occurrence of hepatotoxicity has been reported regardless of specific tyrosine kinase inhibition (Han 2019).

The mechanisms of hepatotoxicity by EGFR-TKI reported up to date include immune response, genetic polymorphism of metabolic enzyme CYP, and formation of active metabolites. Among them, the active metabolites directly bind to the macromolecule of the target cell, cause cell damage by altering the endogenous protein, lipid, and DNA functions, and change the homeostasis of the cell, causing apoptosis or organ failure through cell impairment (Hardy 2014, Shah 2013).

Evidence Source(s) and Strength of Evidence:

Hepatotoxicity is known as a risk in the EGFR-TKI class of drugs.

Nonclinical studies with lazertinib in rats showed liver enzyme increases that persisted in the recovery phase, which is indicative of hepatocellular damage.

Cases of ALT, AST, gamma-glutamyltransferase (GGT), and alkaline phosphatase (ALP) increased have been reported in participants treated with lazertinib in Trial NSC3003. Hepatotoxicity-related reactions, mostly elevations of serum transaminases, are described in the SmPC for lazertinib. There have been no confirmed cases of DILI.

Characterization of the Risk:

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity

	Randomized Trials[a]			All Clinical Trials Population[b]
	Amivantamab+ Lazertinib Arm	Lazertinib Monotherapy Arm	Comparator Arm[c]	Lazertinib Monotherapy and as Combination
Advanced NSCLC				
Number of subjects treated	421	213	428	634
Frequency	289 (68.6%)	81 (38.0%)	113 (26.4%)	370 (58.4%)
Odds Ratio (95% CI)[d]	6.10 (4.53,8.22)	1.71 (1.21,2.43)		
Seriousness				
Was serious	14 (3.3%)	5 (2.3%)	9 (2.1%)	19 (3.0%)
Outcomes				
Fatal	0	0	0	0
Not Recovered/Not Resolved	104 (24.7%)	24 (11.3%)	35 (8.2%)	128 (20.2%)
Recovering/Resolving	59 (14.0%)	5 (2.3%)	12 (2.8%)	64 (10.1%)
Recovered/Resolved with sequelae	4 (1.0%)	1 (0.5%)	0	5 (0.8%)
Recovered/Resolved	122 (29.0%)	51 (23.9%)	66 (15.4%)	173 (27.3%)
Unknown	0	0	0	0

Frequency, Seriousness, Outcomes, and Severity of Hepatotoxicity

	Randomized Trials[a]			All Clinical Trials Population[b]
	Amivantamab+ Lazertinib Arm	Lazertinib Monotherapy Arm	Comparator Arm[c]	Lazertinib Monotherapy and as Combination
Severity				
Worst Grade=1	77 (18.3%)	52 (24.4%)	80 (18.7%)	129 (20.3%)
Worst Grade=2	155 (36.8%)	20 (9.4%)	14 (3.3%)	175 (27.6%)
Worst Grade=3	55 (13.1%)	6 (2.8%)	18 (4.2%)	61 (9.6%)
Worst Grade=4	2 (0.5%)	3 (1.4%)	1 (0.2%)	5 (0.8%)
Worst Grade=5	0	0	0	0
Missing Grade	0	0	0	0

Includes all subjects who had one or more occurrences of an AE that coded to the MedDRA Standardized MedDRA Queries (SMQs) for hepatotoxicity.
The subject is counted only once regardless of the number of events or the number of occurrences. The worst outcome or grade are used in case of multiple events, respectively.
Note: Unknown outcome category includes AE records with missing outcome in current data.
[a] Note: Trial included: Arm A (Amivantamab + Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003.
[b] Note: Trial included: Arm A (Amivantamab + Lazertinib) and Arm C (Lazertinib monotherapy) from NSC3003.
[c] Note: Comparator included: Osimertinib (NSC3003).
[d] Odds Ratio is for event comparison of Amivantamab + Lazertinib versus Comparator and Lazertinib monotherapy versus Comparator.
[tsfae03tot.rtf] [xcp_oncology/z61186372_73841937/dbr_dwh_mariposa/re_laz_rmp_mariposa/tsfae03tot.sas] 14NOV2023, 10:53

Frequently reported AEs were ALT, AST, GGT, and ALP increased. The overall incidence of these AEs was higher in the amivantamab+lazertinib arm compared with the lazertinib monotherapy arm and the osimertinib arm. Increases in laboratory values for these liver enzymes were mostly Grade 1 or 2. With the exception of Grade 3 or 4 ALT increased, which occurred in 6.7% of participants in the amivantamab+lazertinib arm, all Grade 3 or 4 liver enzyme elevations occurred in <5% of participants in any treatment arm with a comparable incidence between the treatment arms.

Hepatotoxicity-related AEs rarely led to treatment discontinuation (<1% of participants in any treatment arm).

Four participants (1 in the amivantamab+lazertinib arm, 1 in the lazertinib monotherapy arm, and 2 in the osimertinib arm) met laboratory criteria for potential drug-induced serious hepatotoxicity (ie, ALT or AST ≥3x ULN and total bilirubin ≥2x ULN). Following further evaluation of these cases, including assessment of confounding factors, there was no evidence for DILI for lazertinib in combination with amivantamab.

Liver AEs and laboratory abnormalities are generally non-severe and without clinical sequelae. However, DILI could be serious, potentially fatal, or lead to liver transplantation.

Risk Factors and Risk Groups:

Risk factors associated with EGFR inhibitor-associated hepatotoxicity include pre-existing liver disease, worsening liver metastases, and the use of concomitant hepatotoxic medications (Kim 2018, Han 2020).

Preventability:

There are no specific recommendations that would prevent the occurrence of liver enzyme elevations. Guidance regarding treatment interruption and dose reduction for Grade 3 or 4 hepatotoxicity events, is provided in SmPC Section 4.2.

Impact on the Risk-Benefit Balance of the Product:

While increased liver enzymes have been observed in participants treated with lazertinib in Trial NSC3003, there have been no clinical sequelae of these elevations and no confirmed cases of DILI. The majority of liver AEs were non-serious, of low severity, and they rarely led to treatment discontinuation. The SmPC provides information on how to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy in patients treated with LAZCLUZE in combination with amivantamab.

Public Health Impact:

No public health impact is anticipated.

Annex 1 MedDRA Term:

Drug related hepatic disorders (SMQ)

Important Potential Risk: Impaired fertility and embryofetal toxicity

Potential Mechanisms:

Based on data from knockout mice and developmental studies with small molecule agents, disruption of the EGFR pathway is likely to cause adverse effects on embryofetal and postnatal development and survival, and further at the level of the placenta, lung, skin, heart, and nervous system. Developmental toxicity studies conducted in non-human primates show that the blockade of EGFR signaling also caused embryolethality and abortions (Adamson 1990, Birchmeier 1998, Bladt 1995, Leo 2011, Partanen 1990, Schmidt 1995, Sibilia 1998, Uehara 1995).

Evidence Source(s) and Strength of Evidence:

There are no human data to assess the risk of lazertinib during pregnancy. Clinical trials of lazertinib excluded pregnant participants and required adequate contraceptive measures during treatment. There have been no participants who became pregnant while on treatment with lazertinib in Trial NSC3003.

Reproductive toxicity studies with lazertinib showed a decrease in the number of oestrus cycles, an increase in post-implantation loss, a decrease in the number of live fetuses, and lower fetal weight in rats but not rabbits. In repeat-dose toxicity studies, decreased numbers of corpora lutea were noted in the ovaries of rats and degenerative changes were present in the testes of rats and dogs. Therefore, based on the mechanism of action and findings in animal models, lazertinib may cause fetal harm when administered to a pregnant woman and may reduce female and male fertility. Impaired fertility and embryofetal toxicity is considered a class warning for EGFR inhibitors (eg, TARCEVA United States Prescribing Information [USPI] 2016, IRESSA USPI 2018, TAGRISSO USPI 2023, ERBITUX USPI 2021, GILOTRIF USPI 2022).

The risk of impaired fertility and embryofetal toxicity is described in the SmPC for lazertinib.

Characterization of the Risk:

There have been no reports of pregnancy in participants taking lazertinib in Trial NSC3003.

Risk Factors and Risk Groups:

Patients of childbearing potential are at high risk for developing embryofetal toxicity during administration of lazertinib.

Preventability:

In the LAZCLUZE SmPC Section 4.6, the potential harmful effects of lazertinib on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 weeks after the last dose of LAZCLUZE are described.

LAZCLUZE should not be used during pregnancy unless the benefit of treatment of the woman is considered to outweigh potential risks to the fetus. If the patient becomes pregnant while taking this medicinal product, the patient should be informed of the potential risk to the fetus.

Impact on the Risk-Benefit Balance of the Product:

Contraception recommendations included in the SmPC and PL are considered sufficient to manage this risk. Overall, the risk-benefit balance is positive for the product considering the severity of the diseases treated and the potential efficacy for patients treated with LAZCLUZE in combination with amivantamab.

Public Health Impact:

No public health impact is anticipated.

Annex 1 MedDRA Term:

Pregnancy, puerperium and perinatal conditions (System Organ Class [SOC])

SVII.3.2. Presentation of the Missing Information

Not applicable.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

Important Identified Risks	Venous thromboembolic (VTE) events*
Important Potential Risks	Hepatotoxicity
	Impaired fertility and embryofetal toxicity
Missing Information	None

* Applies only to the combination of lazertinib and amivantamab.

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Follow-up Questionnaires for Safety Concerns	
Safety Concern	Purpose/Description
Not applicable	

Other Forms of Routine Pharmacovigilance Activities

Activity	Objective/Description	Milestones
Not appliable		

III.2. Additional Pharmacovigilance Activities

Additional Pharmacovigilance Activities
Not applicable

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Not applicable				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy Studies which are conditions of the marketing authorizations				
Not applicable				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Important Identified Risks	
Venous thromboembolic (VTE) events*	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. • Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4, and PL Section 2. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. **Other routine risk minimization measures beyond the Product Information:** • Legal status

Important Potential Risks	
Hepatotoxicity	**Routine risk communication:** • SmPC Section 4.2 • SmPC Section 4.8 • PL Section 4 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • Recommendations regarding the management of hepatotoxicity (ie, criteria for treatment interruption and dose reduction) are provided in SmPC Section 4.2. **Other routine risk minimization measures beyond the Product Information:** • Legal status
Impaired fertility and embryofetal toxicity	**Routine risk communication:** • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 **Routine risk minimization activities recommending specific clinical measures to address the risk:** • The potential harmful effects of lazertinib on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 weeks after the last dose of LAZCLUZE, are provided in SmPC Section 4.6 and PL Section 2. • Patients should notify their doctor immediately about a potential or confirmed pregnancy before and during treatment with LAZCLUZE, as described in PL Section 2. **Other routine risk minimization measures beyond the Product Information:** • Legal status

* Applies only to the combination of lazertinib and amivantamab.

V.2. Additional Risk Minimization Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.2.1. Removal of Additional Risk Minimization Activities

Activity	Safety Concern(s) Addressed/Rationale for the Removal of Additional Risk Minimization Activity
Not applicable	

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Venous thromboembolic (VTE) events*	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • An instruction for prophylactic-dose anticoagulation (DOAC or LMWH) use is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. • Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4, and PL Section 2. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Hepatotoxicity	**Routine risk minimization measures:** • SmPC Section 4.2 • SmPC Section 4.8 • PL Section 4 • Recommendations regarding the management of hepatotoxicity (ie, criteria for treatment interruption and dose reduction) are provided in SmPC Section 4.2. • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None
Impaired fertility and embryofetal toxicity	**Routine risk minimization measures:** • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • The potential harmful effects of lazertinib on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 weeks after the last dose of LAZCLUZE, are provided in SmPC Section 4.6 and PL Section 2. • Patients should notify their doctor immediately about a potential or confirmed pregnancy before and during treatment with LAZCLUZE, as described in PL Section 2. • Legal status **Additional risk minimization measures:** • None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** • None **Additional pharmacovigilance activities:** • None

* Applies only to the combination of lazertinib and amivantamab.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for LAZCLUZE (lazertinib)

This is a summary of the risk management plan (RMP) for LAZCLUZE. The RMP details important risks of LAZCLUZE, how these risks can be minimized, and how more information will be obtained about LAZCLUZE's risks and uncertainties (missing information).

LAZCLUZE's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how LAZCLUZE should be used.

This summary of the RMP for LAZCLUZE should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of LAZCLUZE's RMP.

I. The Medicine and What it is Used For

LAZCLUZE, in combination with amivantamab, is authorized 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 (see SmPC for the full indication). It contains lazertinib as the active substance and it is given as 80-mg or 240-mg film-coated tablets for oral administration.

Further information about the evaluation of LAZCLUZE's benefits can be found in LAZCLUZE's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage link to the EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of LAZCLUZE, together with measures to minimize such risks and the proposed studies for learning more about LAZCLUZE's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed, including Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II.A. List of Important Risks and Missing Information

Important risks of LAZCLUZE are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of LAZCLUZE. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	Venous thromboembolic (VTE) events*
Important potential risks	Hepatotoxicity Impaired fertility and embryofetal toxicity
Missing information	None

* Applies only to the combination of LAZCLUZE and amivantamab.

II.B. Summary of Important Risks

Important Identified Risk: Venous thromboembolic (VTE) events*	
Evidence for linking the risk to the medicine	Venous thromboembolic (VTE) events is an important identified risk for LAZCLUZE only when given in combination with amivantamab. The incidence of VTE events was higher in participants treated with the combination of LAZCLUZE and amivantamab versus LAZCLUZE or osimertinib monotherapy in Trial NSC3003. The greatest discordance in events occurred during the first 4 months of study treatment. Importantly, the incidence rate of VTE events associated with LAZCLUZE monotherapy is consistent with background rates associated with NSCLC. Venous thromboembolism was identified as an adverse reaction for the combination of LAZCLUZE and amivantamab and is described in the SmPC for LAZCLUZE.
Risk factors and risk groups	Lung cancer is a risk factor for VTE events. Additional risk factors for VTE events associated with use of LAZCLUZE in combination with amivantamab identified in open-label trials include age ≥60 years, Eastern Cooperative Oncology Group (ECOG)=1, and Responders (ie, patients with partial response or complete response).

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • An instruction for prophylactic-dose anticoagulation (direct acting oral anticoagulant [DOAC] or low-molecular weight heparin [LMWH]) use is provided in SmPC Sections 4.2 and 4.4. • An instruction to monitor for signs and symptoms of VTE events is provided in SmPC Section 4.4 and PL Section 2. • Instructions regarding the management of VTE events (ie, treatment with anticoagulation and criteria for treatment interruption and discontinuation) are provided in SmPC Sections 4.2 and 4.4, and PL Section 2. • Patients with signs or symptoms suggestive of a blood clot in the veins should notify their doctor immediately, as described in PL Section 2. • Legal status Additional risk minimization measures: • None

* Applies only to the combination of LAZCLUZE and amivantamab.

Important Potential Risk: Hepatotoxicity	
Evidence for linking the risk to the medicine	Hepatotoxicity is known as a risk in the EGFR-TKI class of drugs. Nonclinical studies with LAZCLUZE in rats showed liver enzyme increases that persisted in the recovery phase, which is indicative of hepatocellular damage. Cases of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase, and alkaline phosphatase increased have been reported in participants treated with LAZCLUZE in Trial NSC3003. Hepatotoxicity-related reactions, mostly elevations of serum transaminases, are described in the SmPC for LAZCLUZE. There have been no confirmed cases of drug-induced liver injury.
Risk factors and risk groups	Risk factors associated with EGFR inhibitor-associated hepatotoxicity include pre-existing liver disease, worsening liver metastases, and the use of concomitant hepatotoxic medications.

Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.8 • PL Section 4 • Recommendations regarding the management of hepatotoxicity (ie, criteria for treatment interruption and dose reduction) are provided in SmPC Section 4.2. • Legal status Additional risk minimization measures: • None

Important Potential Risk: Impaired fertility and embryofetal toxicity	
Evidence for linking the risk to the medicine	There are no human data to assess the risk of LAZCLUZE during pregnancy. Clinical trials of LAZCLUZE excluded pregnant participants and required adequate contraceptive measures during treatment. There have been no participants who became pregnant while on treatment with LAZCLUZE in Trial NSC3003. Reproductive toxicity studies with LAZCLUZE showed a decrease in the number of oestrus cycles, an increase in post-implantation loss, a decrease in the number of live fetuses, and lower fetal weight in rats but not rabbits. In repeat-dose toxicity studies, decreased numbers of corpora lutea were noted in the ovaries of rats and degenerative changes were present in the testes of rats and dogs. Therefore, based on the mechanism of action and findings in animal models, LAZCLUZE may cause fetal harm when administered to a pregnant woman and may reduce female and male fertility. Impaired fertility and embryofetal toxicity is considered a class warning for EGFR inhibitors. The risk of impaired fertility and embryofetal toxicity is described in the SmPC for LAZCLUZE.
Risk factors and risk groups	Patients of childbearing potential are at high risk for developing embryofetal toxicity during administration of LAZCLUZE.
Risk minimization measures	Routine risk minimization measures: • SmPC Section 4.6 • SmPC Section 5.3 • PL Section 2 • The potential harmful effects of LAZCLUZE on embryofetal development, and guidance to avoid pregnancy by using effective contraception during treatment and for 3 weeks after the last dose of LAZCLUZE, are provided in SmPC Section 4.6 and PL Section 2.

	• Patients should notify their doctor immediately about a potential or confirmed pregnancy before and during treatment with LAZCLUZE, as described in PL Section 2. • Legal status Additional risk minimization measures: • None

II.C. Postauthorization Development Plan

II.C.1. Studies Which are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of LAZCLUZE.

II.C.2. Other Studies in Postauthorization Development Plan

There are no studies required for LAZCLUZE.

PART VII: ANNEXES

Table of Contents

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities (if applicable)

Not applicable.