EU RMP

Drug Substance	Osimertinib (AZD9291)
Version Number	18
Succession Number	1
Data lock point	31 December 2025
Date of final sign off	See e-signature page

EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) for TAGRISSO™ (osimertinib, AZD9291)

The content of this EU RMP has been reviewed and approved by the Marketing Authorisation Holder's QPPV or deputy QPPV, as delegated by the QPPV in the EU.

Administrative Information

Rationale for submitting an updated RMP*:* Update to RMP to version 18.0 to add important potential risk of rhabdomyolysis and to follow the new RMP template including all the relevant annexures within the document

Summary of significant changes in this RMP

Part II SI

- II: SV - Updated post-authorisation exposure data
- II: SVII:2- New safety concern added (rhabdomyolysis as new important potential risk).
- II: SVII:3.1.3- Added presentation of important potential risk of rhabdomyolysis.
- II: SVIII:1- Summary of the safety concerns (added rhabdomyolysis as important potential risk).

Part III

- III.1 : Routine pharmacovigilance activités (added the text of targeted follow-up questionnaire for rhabdomyolysis).

Part V

- V.1 : Added information regarding routine risk communication and routine risk minimisation activities recommending specific clinical measures to address the risk of rhabdomyolysis.
- V.3 : Summary of risk minimisation measures for important potential risk of rhabdomyolysis.

Part VI

- VI.2.1 : Added rhabdomyolysis as important potential risk.
- VI.2.2 : Added summary for rhabdomyolysis.

Part VII

- VII.4.3: Questionnaire for adverse events associated with Rhabdomyolysis

Other RMP versions under evaluation	Not applicable
Details of currently approved RMP	**Version Number**: 17 **Approved with procedure**: EMEA/H/C/004124/II/0056 **Date of approval:** 19 December 2024

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation/ Special term	Definition/Explanation
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCRP	Breast Cancer Resistance Protein
CI	Confidence Interval
CIOMS	Council For International Organizations of Medical Sciences
C_{max}	Maximum plasma concentration
COPD	Chronic Obstructive Pulmonary Disease
CRT	Chemoradiation therapy
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450 isoenzyme
DBL	Database Lock
DCO	Data Cut-Off
DCR	Disease Control Rate
DDI	Drug-Drug Interaction
DoR	Duration of Response
dP/dt_{max}	Maximum rate of left ventricular pressure change. An index of cardiac contractility.
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Co-operative Oncology Group
EEA	European Economic Area
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EGFR T790M	EGFR mutation(s) resulting in threonine (T) replacement by methionine (M) at position 790 of EGFR
EGFR T790M mutation positive	Tumour positive for the TKI-resistance conferring mutation T790M
EGFR TK	Epidermal Growth Factor Receptor Tyrosine Kinase
EGFR TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor
EGFRm	Tumour positive status for TKI-sensitivity conferring mutations in the tyrosine kinase domain of EGFR, which spans exons 18 to 24

Abbreviation/ Special term	**Definition/Explanation**
EMA	European Medicines Agency
EU	European Union
FPI	First Patient In
GI	Gastrointestinal
GLP	Good Laboratory Practice
hERG	Human Ether-A-Go-Go-Related Gene
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICD	International Classification of Disease
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILD	Interstitial Lung Disease
LPLS	Last Patient Last Sample
LSLV	Last Subject Last Visit
LVEF	Left Ventricular Ejection Fraction
LUCID	Lung Cancer Incidence Data
MAA	Market Authorisation Application
MATE	Multidrug and Toxin Extrusion Protein
MedDRA	Medical Dictionary for Regulatory Activities
NRG	Name Review Group
NSCLC	Non-Small Cell Lung Cancer
OAT	Organic Anion Transporter
ORR	Objective Response Rate
OS	Overall Survival
PBPK	Physiologically Based Pharmacokinetics
PBRER	Periodic-Benefit Risk Evaluation Report
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PIL	Patient Information Leaflet
PR	ECG interval measured from the beginning of the P wave to the beginning of the QRS complex
PSUR	Periodic Safety Update Report
PT	Preferred Term
QoL	Quality of Life

Abbreviation/ Special term	**Definition/Explanation**
QRS	ECG interval measured from the beginning of the Q wave to the end of the S wave
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
QTc	Heart rate corrected QT interval
QTcB	Heart rate corrected QT interval using Bazett's formula
QTcF	Heart rate corrected QT interval using Friderica's formula
QTcR	Heart rate corrected QT interval on an individual animal using the Ollerstam correction
RMP	Risk Management Plan
RoW	Rest of the World
SAE	Serious Adverse Event
SD	Standard Deviation
SEER	Surveillance, Epidemiology, and End Results
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Queries
SoC	Standard of Care
SOC	System Organ Class
TdP	Torsade de Pointes
TFUQ	Targeted Follow-Up Questionnaire
TKI	Tyrosine Kinase Inhibitor
UK	United Kingdom
ULN	Upper Limit of Normal
US	United States
WHO	World Health Organization

1 PART I: PRODUCT OVERVIEW

Table 1-1 Product Overview

Active substance(s) (INN or common name)	Osimertinib (formerly AZD9291)
Pharmacotherapeutic group(s) (ATC Code)	L01XE
Marketing Authorisation Holder	AstraZeneca
Medicinal products to which this RMP refers	Osimertinib
Invented name(s) in the European Economic Area (EEA)	TAGRISSO™
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Mono-anilino pyrimidine.
	Summary of mode of action: Selective, irreversible inhibitor of both the single EGFRm (TKI-sensitivity conferring mutation) and dual EGFRm/EGFR T790M (TKI-resistance conferring mutation) receptor forms of EGFR.
	Important information about its composition: N-(2-{2-dimethylaminoethylmethylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl) pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesylate salt.
Hyperlink to the Product Information	TAGRISSO, Summary of Product Characteristics

Table 1-1 Product Overview

Indication(s) in the EEA	**Current:** TAGRISSO™ as monotherapy is indicated for: • Treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC). • The first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations. • The adjuvant treatment after complete tumour resection in patients with NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations • Treatment of adult patients with locally advanced, unresectable (stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy TAGRISSO™ is indicated in combination with • pemetrexed and platinum-based chemotherapy for the first-line treatment of patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations **Proposed:** Not applicable
Dosage in the EEA	**Current:** 40 mg or 80 mg tablet for once daily oral administration. **Proposed:** Not applicable
Pharmaceutical form(s) and strengths	**Current:** Form: Beige film-coated tablets for oral administration. Strength: Tablets containing 40 mg or 80 mg of osimertinib mesylate plus excipients. **Proposed:** Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

Incidence

Lung cancer (all histologies) is the most common cancer worldwide, with approximately 2.1 million new cases reported each year and 1.7 million deaths in 2018 (GLOBOCAN 2018). The incidence rates of lung cancer are highly variable and depend largely on local smoking prevalence (GLOBOCAN 2018). Across six global World Health Organisation (WHO) regions, the incidence rates per 100,000/year vary from 1.2 in Africa to 49.3 in Europe (GLOBOCAN 2018). In Europe, 470,000 new lung cancer cases occurred in 2018, with the highest rate reported in Hungary (77.4/100,000) and the lowest rate in Cyprus (24.4/100,000) (GLOBOCAN 2018). In total, 387,913 lung cancer deaths occurred in Europe in 2018, yielding a crude death rate of 52.7 per 100,000 population, with Hungary (81.8/100,000) having the highest mortality rate and Cyprus (22.8/100,00) the lowest (GLOBOCAN 2018).

Approximately 80% to 90% of all lung cancers are NSCLC (Janssen-Heijnen et al 2005; Cataldo et al 2011). Despite progress in early detection and treatment, NSCLC is diagnosed at a locally advanced or metastatic stage in 70% to 80% of patients. The incidence of NSCLC varies by stage as follows: 26% stage I, 9% stage II, 25% stage III, and 40% stage IV (Global Data EpiCast. 2016). Of the 20% to 30% of patients presenting with Stage III disease at diagnosis, 60% to 90% have unresectable disease (Kato et al 2024, Goldstraw et al 2016, Agbarya et al 2022).

Mutations in the EGFR tyrosine kinase are seen in approximately 20% of patients with NSCLC, with greater incidence in Asia than Europe and North America (Midha et al 2015). The EGFR mutation rate and type are reported similarly between early-stage and advanced-stage adenocarcinoma patients (Pi et al 2018).

Among various types of EGFR mutations, in-frame deletions of exon19 (about 44%) and the single amino acid mutation L858R in exon 21 (about 41%) are the most common mutations. Thus around 90% of EGFR mutations are either exon 19 deletions or exon 21 (L858R) substitution mutations (Lee et al 2013) and these confer sensitivity to EGFR TKIs such as gefitinib, erlotinib or afatinib.

The epidemiology of patients with EGFRm and EGFR T790M mutation positive NSCLC is not fully known. Prior to treatment with EGFR TKIs, the reported rate of pre-treatment EGFR T790M mutation is highly dependent on the sensitivity of the method of detection and the true frequency in untreated patients remains unknown (Wu et al 2011;Sequist et al 2008; Li et al

2014b; Su et al 2012; Rosell et al 2009; Fujita et al 2012; Maheswaran et al 2008; Yu et al 2014; Watanabe et al 2015; Costa et al 2014).

Prevalence:

According to GLOBOCAN, it is estimated that in 2018 there were 497,283 patients living with the diagnosis of lung cancer in Europe ([5-year prevalence, both sexes] GLOBOCAN 2018, Ferlay et al 2013). Furthermore, Cancer Research UK estimates that NSCLC makes up about 87% of lung cancers in the UK (Cancer Research UK 2014). Patients with EGFRm and EGFR T790M NSCLC are a subset of the cohort of patients with EGFRm NSCLC.

The published literature indicates that the prevalence rates of EGFR mutation in NSCLC patients in different geographic regions are: Europe (15%), Asia-Pacific (47%), North America (22%), Indian sub-continent (26%), South America (36%), Africa (21%), and Oceania (12%) (Midha et al 2015). In 5 studies published from 2012 to 2014, recruiting a total of 2,483 NSCLC patients at diagnosis or across treatment lines, EGFRm status ranged from 6.5% to 10.6% (Castro et al 2013, Gahr et al 2013, Janssens et al 2014, Smits et al 2012, Szumara-Cieckiewicz et al 2013). The pooled frequency was 9.5% with a median of 9.8%.

Demographics of the population in the authorised indication – age, gender, racial and/or ethnic origin and risk factors for the disease:

Most diagnoses of lung cancer are in patients aged over 50 years, with the median age in US SEER data being 70 years (Ries et al 2007). Currently lung cancer is more common in the developed world. The highest rates are observed in Central-Eastern and Southern Europe, North America and Eastern Asia, whereas very low rates are still estimated in Middle and Eastern Africa (Ferlay et al 2010).

A study summarising 450 published studies, with 62 studies from Europe, revealed that amongst NSCLC patients, the prevalence of EGFR were: 43.7% (females) vs 24.0% (males); 49.3% (non-smokers) vs 21.5 (past or current smokers); 38.0 (adenocarcinoma) vs 11.7% (non-adenocarcinoma); 38.8% (Asian) vs 17.4 (Caucasian). Similar trends were observed in Caucasian only populations (Zhang 2016). In the Caucasian patient population, EGFR mutations are reported in approximately 10-20% of adenocarcinomas and <5% of squamous cell carcinomas (Marchetti et al 2005; Dec and Fuster 1994; Rosell et al 2009; D'Angelo et al 2011). EGFR mutation rates are higher in Asian populations, occurring in 40 to 50% of adenocarcinomas and 5 to 8% of squamous cell carcinomas (Dearden et al 2013, Choi et al 2013, Shi et al 2014, Yatabe et al 2015, Han et al 2015, Reck et al 2015).

Prior studies indicate the risk factors associated with EGFRm NSCLC include female sex, non-smokers, adenocarcinoma histology type, and individuals of East Asian origin (Kosaka et al 2004; Matsuo et al 2007, Pao et al 2005, Shigematsu et al 2005, Rosell et al 2009).

EGFR mutation rate and type are similar between early-stage and advanced-stage adenocarcinoma NSCLC patients, after adjusting for baseline (e.g. smoking status) and clinical characteristics of patients (Pi et al 2018).

In a single site US study of 93 patients with acquired resistance to prior EGFR TKI, demographics for patients with EGFR T790M were similar to those without (Oxnard et al 2011), and consistent with those reported for patients with EGFRm.

Once an EGFRm tumour is treated, risks of resistance to EGFR TKIs may be host dependent as well as treatment dependent. Host factors include cigarette smoke which is known to affect metabolism via CYP1A1 and impaired receptor turnover via reactive oxidative signalling and receptor autophosphorylation. Low or intermediate levels of BIM expression, important for apoptosis, may also contribute to worse PFS (Cortot and Pasi 2014).

The main existing treatment options:

The recommended treatment for patients with early stage (I and II) NSCLC is surgical resection with or without adjuvant chemotherapy, and for stage IIIA patients is combined modality approaches that may include chemotherapy, radiation and surgery (Pirker 2012). Following surgery, patients with stage IIB-IIIA disease will typically receive platinum-based chemotherapy. Adjuvant osimertinib is recommended in those patients with stage IB-IIIA disease with EGFR exon 19 deletions or L858R who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy (NCCN Guidelines 2022).

Definitive concurrent chemoradiotherapy (CCRT) is considered the SoC for patients with unresectable Stage III NSCLC, irrespective of EGFRm status (NCCN 2023, ESMO Treatment Guidelines 2023[Hendriks et al 2023]). Durvalumab treatment is also recommended by ASCO, NCCN, ATORG and ESMO Asia guidelines for patients with unresectable (Stage III) NSCLC who have not progressed after CRT regardless of PD-L1 status, whereas the ESMO guidelines recommend durvalumab use only in patients whose tumours express PD-L1 on ≥1% of tumour cells (NCCN Guidelines 2024, ESMO Treatment Guidelines 2023 [Hendriks et al 2023], ASCO Living Guideline 2022 [Owen et al 2022], ATORG Guideline 2020 [Tan et al 2020], ESMO Asia Guidelines 2020[Park et al 2020]).

The National Comprehensive Cancer Network (NCCN) has recommended testing all advanced NSCLC adenocarcinomas for EGFR mutations (NCCN Guidelines 2022). If a sensitising EGFR mutation is discovered prior to first-line systemic therapy, the preferred first line treatment of NSCLC is osimertinib. Other treatments may include erlotinib, afatinib, gefitinib or dacomitinib until disease progression. If sensitising EGFR mutation is discovered during first-line systemic therapy (e.g. combination chemotherapy, combination chemotherapy and targeted therapy with a monoclonal antibody, external radiation therapy, laser therapy

and/or internal radiation therapy) NCCN recommends completion of the planned systemic therapy, including maintenance therapy or interruption of treatment followed by osimertinib (preferred) or one of either erlotinib, afatinib, gefitinib or dacomitinib until disease progression.

Effective treatment options for patients following disease progression after treatment with an EGFR-TKI remain extremely limited.

Natural history of the indicated condition in the untreated population, including mortality and morbidity:

Lung cancer is a fatal disease with little recent improvement in prognosis; therefore, changes in lung cancer mortality rates are mainly influenced by trends in the underlying incidence rates (Jemal et al 2007). Approximately 20% of patients with newly diagnosed NSCLC are unresectable due to distant metastatic disease (Stage IV) (Quint 2004). In addition, patients with Stage IIIb disease are potentially unresectable, and a fair proportion of Stage IIIa patients have unresectable, bulky nodal disease (Quint 2004). Metastatic spread to distant organs is the reason for most cancer deaths. Studies, including a large Swedish study with nearly 10,000 lung cancer patients, have demonstrated that the most frequent metastatic sites were the nervous system (39%), bone (34%), liver (20%), respiratory system (18%), and adrenal gland (8%) and metastases were associated with shorter survival (Riihimäki et al 2014, Lu et al 2016).

In the general population of lung cancer, the overall five-year survival rate for lung cancer is 18% and varies by stage as follows: 68%-92% stage I, 53-60% stage II, 13-16% stage III, and <1-10% stage IV (Global Data EpiCast. 2016). In a systematic review of the prognosis of untreated NSCLC, the median survival was on average about 7.15 months (Wao et al 2013). In the European Union general population (EU-27), lung cancer deaths in 2012 were estimated to be 264,800 for both sexes (183,400 in males and 81,400 in females), resulting in age standardised mortality rate (European standard population) of 36.5 for both sexes (56.4 for males and 20.6 for females) for lung cancer per 100,000/year. These rates varied between 45.4 (Northern Europe) and 69.3 (Central and Eastern Europe) in males and between 12.0 (Central and Eastern Europe) and 28.7 (Northern Europe) in females (GLOBOCAN 2018). Patients whose advanced or metastatic disease are appropriate for first-line metastatic treatment or salvage therapy are, as yet, incurable and in the last months of life.

The presence of an activating EGFR mutation robustly predicts for higher response rates, longer progression-free survival (PFS) and an improved quality of life when treated with the first and second generation TKI inhibitors when compared to platinum-based chemotherapy (Yap et al 2016).). Furthermore, EGFR mutation is suggested to be one of the predictors for subsequent brain metastases in stage I-III NSCLC patients (Chang et al 2018).

Despite these improved patient outcomes, disease progression is inevitable in the majority of patients. The substitution of methionine for threonine at position 790 of EGFR (T790M) alters the drug-binding ability to the ATP portion of EGFR and is observed in approximately 50% of cases of acquired EGFR TKI resistance (Yap et al 2016). However, osimertinib is effective against this particular resistance mechanism and more research is needed to further elucidate potential treatment options for other mechanisms of treatment resistance.

Important co-morbidities:

- Hypertension
- Diabetes
- Coronary artery disease
- Cerebrovascular accident
- Heart failure
- Interstitial lung disease
- Chronic obstructive pulmonary disease

2.2 MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from non-clinical studies and relevance to human usage

2.2.1 Toxicity

Key issues identified from acute or repeat-dose toxicity studies

Skin

Atrophy, inflammation and/or degenerative changes were present in the skin of rats and dogs. The finding in rats mainly comprised follicular/peri-follicular inflammation, occasionally accompanied by epidermal inflammation/ulceration, crust formation and hyperkeratosis at 1-, 3- and 6-months. In mice, skin findings (pustules, epidermal hyperplasia and hyperkeratosis, inflammation, follicular dysplasia) were seen in animals dosed for 6 weeks.

In dogs, minimal to mild epidermal atrophy/degeneration was seen in the 14-day and 1-month studies but was not present at 3- or 9-months. The findings seen in the 1-month studies showed complete recovery following 1 month off-dose.

Subsequent clinical and post-marketing data determined the relevance of these observations to be limited to the ADRs grouped under the terms rash, dry skin, paronychia and pruritis, which are listed as ADRs in Section 4.8 (Undesirable effects) of the osimertinib EU SmPC with no justification for inclusion as a safety concern in the RMP.

Ocular

Corneal epithelial atrophy, generally of minimal to moderate severity, was present in mice, rats and dogs following administration of osimertinib for ≥6 days. Ocular effects were dose limiting in dogs and consisted of corneal translucency, corneal epithelial ulceration or erosion, conjunctival reddening and lachrymation. These effects rapidly resolved when animals were taken off dose or following dose reduction. Corneal opacities were noted in rats (6 month study) and dogs (3- and 9-month studies) and would not be expected to be reversible. Corneal changes were noted at clinically relevant plasma levels.

In the 104-week carcinogenicity study in rats a higher incidence and severity of lens fibre degeneration were observed in animals administered osimertinib at the mid and high dose when compared with other groups (including controls). This finding was consistent with the ophthalmoscopic observation of lens opacities, which were first noted in high dose males from Week 52 and showed gradual increase in incidence and severity with increased duration of dosing. The opacities originated in the posterior region and in some animals progressed to affect the whole lens. There was generally good alignment between ophthalmology and histopathology findings in the lens at an individual animal level.

Subsequent review of clinical and post-marketing data did not identify cataracts as a safety signal for osimertinib. Osimertinib EU SmPC Section 4.4 (Warnings and precautions) notes that patients presenting with acute or worsening blurred vision should be referred promptly to an ophthalmology specialist. No additional risk minimisation measures are deemed necessary.

Therefore, the inclusion of ocular events as an important potential risk in the RMP is not justified.

Haematopoietic

Increases in white blood cell counts and fibrinogen and decreases in red blood cell parameters were seen in a number of rat and dog studies and are considered to be secondary to the degenerative and inflammatory changes seen in tissues such as the skin and GI tract. These effects were reversible in the 1-month rat study (not seen in dogs at 1 month). Under the investigations MedDRA SOC, the PTs platelet count decreased, leukocytes decreased, lymphocytes decreased, and neutrophils decreased are listed as ADRs in Section 4.8 (*Undesirable effects*) of the osimertinib EU SmPC.

Reproductive/developmental toxicity

Seminiferous tubular degeneration/atrophy and/or spermatid retention were observed in the 1 and 3-moth rat and dog studies. There were no pathology findings in the testes in the 6-month rat study, but atrophic changes were present in the prostate gland and seminal vesicles. The

mechanism underlying these findings is unclear. An adverse effect on male fertility in the 3-month rat study was also observed.

Non-clinical studies identified anoestrus and early embryonic deaths in female rats. Consequently, the EU SmPC recommends that women of childbearing potential avoid becoming pregnant and use highly effective contraception.

Genotoxicity

No key findings identified.

Carcinogenicity

In both carcinogenicity studies (rat and transgenic mice) exposure to osimertinib at all tested dose levels was below that in humans at the 80 mg dose.

There were no treatment related neoplastic histopathology findings when osimertinib was administered orally to CByB6F1/Tg rasH2 Hemizygous (transgenic) mice for 26 weeks.

In the rat 104-week carcinogenicity study there was a higher incidence of haemangioma in the mesenteric lymph nodes in high dose animals and a higher incidence of angiomatous hyperplasia in the mesenteric lymph nodes of high dose females when compared with other groups, including controls. There was no increase in malignant vascular tumours in the rat carcinogenicity study and no vascular proliferation was noted in the toxicity studies conducted in the dog or transgenic mouse. The histologic similarity between the angiomatous hyperplasia noted in the rat study and vascular transformation of lymph node sinuses in humans, a benign proliferative lesion which is not considered to be pre-neoplastic, suggests that lymph node angiomatous hyperplasia would have no clinical impact should its equivalent occur in patients. Mesenteric lymph node haemangioma is considered to be a non-clinical entity, reflecting the inherent sensitivity of the rat (Giknis and Clifford 2011). Benign vascular lesions (haemangiomas) are not known to progress from benign to malignant lesions in animals or humans (Radi and Morton 2012 and Weiss et al 2008). The benign behaviour of human lymph node haemangioma suggests that even if they were to occur in humans, it would have no clinical impact. AstraZeneca therefore considers that the isolated haemangioma signal observed in the rat carcinogenicity study conducted with osimertinib is not relevant to humans, and therefore not relevant for inclusion as a safety concern in the RMP.

2.2.2 Safety pharmacology

Cardiovascular system, including potential effect on the QT interval

Osimertinib inhibited the function of the hERG-encoded potassium channel with an IC50 of 0.69 μM. There were no findings of biological significance in a dog telemetry study. In a non-

GLP investigative study in the anaesthetised guinea pig, intravenous (IV) infusion of osimertinib was associated with small increases in the QTcB interval at very high exposures.

In *in vitro* pharmacology studies, osimertinib and its metabolites, AZ5104 and AZ7550, were shown to inhibit HER2 but at a lower potency compared to other HER2 inhibitors. Although a small decrease in positive dP/dtmax (an index of cardiac contractility) was seen in a guinea pig study it was only observed at very high exposures following IV infusion in this anaesthetised model and rapid recovery was seen during the final washout period and therefore it is considered to be of limited clinical significance.

Gastrointestinal

In 7- and 14-day studies in rats and dogs, GI pathology (epithelial atrophy, degeneration, ulceration/erosion and/or inflammation) was confined to non-tolerated doses and was associated with body weight loss, reduced food consumption, soft/fluid faeces and emesis (dogs). In longer duration studies at lower doses the GI pathology was less marked. Complete recovery of findings seen in a 1-month was recorded after 1 month off drug. Osimertinib was found to inhibit GI transit in a rat safety pharmacology study (single doses of ≥10 mg/kg).

Subsequent clinical and post-marketing data determined the relevance of these observations to be limited to the ADRs diarrhoea and stomatitis which are listed as ADRs in Section 4.8 (*Undesirable effects*) of the osimertinib EU SmPC.

2.3 MODULE SIII: CLINICAL TRIAL EXPOSURE

The monotherapy pooled data set includes clinical trials from the Phase I to III studies in advanced NSCLC and adjuvant treatment after complete tumour resection in NSCLC (ADAURA). Please note that the data in the pool refers only to patients who received osimertinib monotherapy. Data from the LAURA study is not included in the osimertinib monotherapy pool as the LAURA study has different underlying patient population.

Studies contributing to the osimertinib exposure data are tabulated in Table 2-1 below.

Table 2-1 Duration of exposure

Duration of exposure	**Monotherapy**					**Chemotherapy combination (N=276)**
	Adjuvant NSCLC (N=337)	**Advanced/metastatic NSCLC**		**Monotherapy pooled dataset (N=1813)**	**Unresectable NSCLC post chemoradiation therapy (N=143)**	
		First-line (N=643)	**Second-line and later (N=833)**			
ADAURA (D5164C00001) DCO: 11 April 2022	X			X		
AURA1 (D5160C00001) DCO: 01 November 2016 (AURA1A, AURA1B), 01 May 2018 (AURA1C)		X	X	X		
AURA2 (D5160C00002) *DCO: 01 May 2018*			X	X		
AURA3 (D5160C00003) *DCO: 15 March 2019*			X	X		
FLAURA (D5160C00007) DCO: 25 June 2019		X		X		
FLAURA2a (D5169C00001) DCO: 03 April 2023		X		X[a]		X[b]
LAURA ((D5160C00048) DCO: 05 January 2024					X	

[a] Osimertinib monotherapy arm only (N=275) [b] Osimertinib combination arm only (N=276)

2.3.1 EGFR mutation positive unresectable (Stage III) NSCLC- LAURA

Patients with locally advanced, unresectable (stage III) NSCLC whose disease has not progressed following definitive platinum based-chemoradiation therapy and who received at least one dose of osimertinib 80mg are included.

The total number of patients included in the osimertinib arm of LAURA study is 143.

Table 2-2 Duration of exposure (LAURA)

	Osimertinib (N=143)	
Total treatment duration (months)[a]	Mean	23.70
	SD	14.46
	Median	24.0
	Min	0.39
	Max	62.88
	Total treatment years	282.54

[a] Total treatment duration= Number of days subject received study drug as recorded in the Exposure page / (365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group. Max = Maximum, Min = Minimum, SD = Standard deviation

Table 2-3 Duration of exposure-Categorical (LAURA)

	Osimertinib (N=143)	
Total treatment duration (months)[a]	≥ 1 day	143 (100)
	≥ 6 months	117 (81.8)
	≥ 12 months	107 (74.8)
	≥ 18 months	98 (68.5)
	≥ 24 months	71 (49.7)
	≥ 30 months	50 (35.0)
	≥ 36 months	32 (22.4)

[a] Total treatment duration= (last dose date- first dose date +1)/ (365.25/12)

Table 2-4 Duration of exposure by gender (LAURA)

		Osimertinib (N=143)	
		Male (N=53)	**Female (N=90)**
Total treatment duration (months)[a]	Mean	25.6	22.6
	SD	15.41	13.85

Table 2-4 Duration of exposure by gender (LAURA)

		Osimertinib (N=143)	
	Median	26.8	22.8
	Min	0.39	0.46
	Max	58.09	62.88
	Total treatment years	112.97	169.57

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).

Total treatment years was calculated by adding the durations for each patient in the treatment group. Max = Maximum, Min = Minimum, SD = Standard deviation

Table 2-5 Duration of exposure by race (LAURA)

		Osimertinib (N=143)			
		White (N=20)	**Black[a] (N=0)**	**Asian (N=116)**	**Other (N=7)**
Total treatment duration (months)[b]	Mean	23.3	0	24.2	16.2
	SD	14.47	0	14.74	7.22
	Median	23.4	0	25.2	19.2
	Min	2.53	0	0.39	4.63
	Max	58.09	0	62.88	23.03
	Total treatment years	38.76	0	234.32	9.47

[a] Includes African American patients

[b] Total treatment duration= (last dose date - first dose date +1)/(365.25/12).

Total treatment years was calculated by adding the durations for each patient in the treatment group. Max = Maximum, Min = Minimum, SD = Standard deviation

Table 2-6 Duration of exposure by age group (LAURA)

		Osimertinib (N=143)			
		<65 years (N=81)	**65-74 years (N=49)**	**≥ 65 years (N=62)**	**≥75 years (N=13)**
Total treatment duration (months)[a]	Mean	24.9	23.8	22.2	16.3
	SD	14.03	15.48	14.99	11.66
	Median	25.1	25.7	21.1	16.7
	Min	1.84	0.39	0.39	1.61
	Max	62.88	51.38	51.38	38.70
	Total treatment years	167.76	97.10	114.78	17.68

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).

Total treatment years was calculated by adding the durations for each patient in the treatment group. Max = Maximum, Min = Minimum, SD = Standard deviation

2.3.2 Chemotherapy combination

Exposure data for osimertinib in combination with chemotherapy are derived from FLAURA2.

Patients with locally advanced (stage IIIB, IIIC) or metastatic EGFR mutation positive NSCLC (stage IVA or IVB) who received at least one dose of osimertinib 80mg with platinum plus pemetrexed chemotherapy as first-line treatment are included.

The total number of patients included in the first-line osimertinib plus chemotherapy arm for FLAURA2 is 276.

Table 2-7 Duration of exposure (FLAURA2)

	Osimertinib plus chemotherapy First line (N=276)	
Total treatment duration (months)[a]	Mean	19.7
	SD	9.05
	Median	22.3
	Min	0.07
	Max	33.84
	Total treatment years	452.30

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group. SD = standard deviation

Table 2-8 Duration of exposure-Categorical (FLAURA2)

	Osimertinib plus chemotherapy First line (N=276)	
Total treatment duration (months)[a]	≥ 1 day	276 (100)
	≥ 6 months	238 (86.2)
	≥ 12 months	214 (77.5)
	≥ 18 months	181 (65.6)
	≥ 24 months	109 (39.5)
	≥ 30 months	27 (9.8)
	≥ 36 months	0

[a] Total treatment duration= (last dose date- first dose date +1)/ (365.25/12)

Table 2-9 Duration of exposure by gender (FLAURA2)

		Osimertinib plus chemotherapy First line (N=276)	
		Male (N=104)	**Female (N=172)**
Total treatment duration (months)[a]	Mean	19.8	19.6
	SD	8.73	9.27
	Median	22.0	22.5
	Min	0.39	0.07
	Max	33.84	33.12
	Total treatment years	171.64	280.66

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group. Max = Maximum, Min = Minimum, SD = Standard deviation

Table 2-10 Duration of exposure by race (FLAURA2)

		Osimertinib plus chemotherapy First line (N=276)			
		White (N=74)	**Black[a] (N=2)**	**Asian (N=176)**	**Other (N=24)**
Total treatment duration (months)[b]	Mean	17.2	12.8	20.9	19.2
	SD	8.47	15.29	9.10	8.74
	Median	19.1	12.8	23.8	23.8
	Min	0.43	2.00	0.10	0.07
	Max	32.66	23.62	33.84	30.59
	Total treatment years	105.78	2.14	305.96	38.43

[a] Includes African American patients

[b] Total treatment duration= (last dose date - first dose date +1)/(365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group. Max = Maximum, Min = Minimum, SD = Standard deviation

Table 2-11 Duration of exposure by age group (FLAURA2)

		Osimertinib plus chemotherapy First line (N=276)		
		<65 years (N=172)	**65 - 74 years (N=81)**	**≥75 years (N=23)**
Total treatment duration (months)[a]	Mean	21.4	17.9	12.7
	SD	8.42	9.06	9.44
	Median	23.8	19.4	11.4
	Min	0.10	0.07	0.36
	Max	33.84	32.62	27.96

		Osimertinib plus chemotherapy First line (N=276)		
	Total treatment years	307.01	120.89	24.40

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group. Max = Maximum, Min = Minimum, SD = Standard deviation

2.3.3 EGFR mutation positive NSCLC- Monotherapy pooled dataset

Table 2-12 Duration of exposure (Monotherapy pooled dataset)

		Adjuvant NSCLC (ADAURA Study) (N=337)	Advanced / metastatic NSCLC Studies		Monotherapy pooled dataset Total (N=1813)
			Osimertinib First-line (N=643)	Osimertinib ≥Second-line (N=833)	
Total treatment duration (months)[a]	Mean	28.4	20.8	17.7	20.8
	SD	12.4	12.54	13.32	13.45
	Median	35.8	20.0	14.3	19.3
	Min	0.07	0.07	0.03	0.03
	Max	37.98	49.84	52.24	52.24
	Total treatment years	798.15	1113.81	1230.78	3142.75

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group. SD = standard deviation

Table 2-13 Duration of exposure- Categorical (Monotherapy pooled dataset)

		Adjuvant NSCLC (ADAURA Study) (N=337)	Advanced / metastatic NSCLC Studies		Monotherapy pooled dataset Total (N=1813)
			Osimertinib First-line (N=643)	Osimertinib ≥Second-line (N=833)	
Total treatment duration (months)[a]	≥ 1 day	337 (100)	643 (100)	833 (100)	1813 (100)
	≥ 6 months	296 (87.8)	554 (86.2)	647 (77.7)	1497 (82.6)
	≥ 12 months	280 (83.1)	463 (72.0)	480 (57.6)	1223 (67.5)
	≥ 18 months	259 (76.9)	356 (55.4)	343 (41.2)	958 (52.8)
	≥ 24 months	245 (72.7)	235 (36.5)	230 (27.6)	710 (39.2)
	≥ 30 months	239 (70.9)	152 (23.6)	164 (19.7)	555 (30.6)
	≥ 36 months	69 (20.5)	91 (14.2)	108 (13.0)	268 (14.8)

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).

Table 2-14 Duration of exposure (Monotherapy pooled dataset)

		Adjuvant NSCLC (ADAURA Study) (N=337)		Advanced / metastatic NSCLC Studies				Monotherapy pooled dataset Total (N=1813)	
				Osimertinib First-line (N=643)		Osimertinib ≥Second-line (N=833)			
		Male (N=109)	Female (N=228)	Male (N=243)	Female (N=400)	Male (N=289)	Female (N=544)	Male (N=641)	Female (N=1172)
Total treatment duration (months)[a]	Mean	26.8	29.2	19.2	21.7	16.8	18.2	19.4	21.6
	SD	13.39	11.85	11.92	12.82	13.03	13.46	13.14	13.56
	Median	35.8	35.8	18.3	21.0	13.9	15.1	17.0	20.7
	Min	0.13	0.07	0.92	0.07	0.03	0.07	0.03	0.07
	Max	36.86	37.98	48.03	49.84	51.19	52.24	51.19	52.24
	Total treatment years	243.24	554.92	389.22	724.59	404.74	826.05	1037.20	2105.55

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group. SD = standard deviation

Table 2-15 Duration of exposure, by race (Monotherapy pooled dataset)

		Adjuvant NSCLC (ADAURA Study) (N=337)				Advanced/metastatic NSCLC Studies								Monotherapy pooled dataset Total (N=1813)			
						Osimertinib First-line (N=643)				Osimertinib ≥Second-line (N=833)							
		White (N=121)	Black[a] (N=0)	Asian (N=215)	Other (N=1)	White (N=190)	Black[a] (N=4)	Asian (N=432)	Other (N=16)	White (N=282)	Black[a] (N=10)	Asian (N=523)	Other (N=11)	White (N=593)	Black[a] (N=14)	Asian (N=1170)	Other (N=28)
Total treatment duration (months)[b]	Mean	26.9	0	29.2	36.0	21.1	22.3	20.7	16.9	17.8	18.0	17.8	15.9	20.7	19.2	21.0	17.2
	SD	12.96	NC	12.04	NC	13.28	14.04	12.37	6.55	13.60	10.38	13.34	10.69	13.79	11.14	13.40	8.94
	Median	35.8	0	35.9	36.0	18.4	27.3	20.7	18.8	14.1	17.7	14.3	15.2	18.2	21.7	20.1	18.4
	Min	0.07	0	0.10	35.98	0.07	1.81	0.20	3.78	0.26	3.65	0.03	3.45	0.07	1.81	0.03	3.45
	Max	37.98	0	37.16	35.98	49.71	32.89	49.84	25.95	52.24	37.78	51.19	32.56	52.24	37.78	51.19	35.98
	Total treatment years	271.19	0	523.96	3.00	334.13	7.44	746.99	22.55	417.17	15.02	774.52	14.58	1022.49	22.46	2045.48	40.12

[a] Includes African American patients

[b] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).

SD = standard deviation

NC = Not calculable

Table 2-16 Duration of exposure, by age group (Monotherapy pooled dataset)

		Adjuvant NSCLC (ADAURA Study) (N=337)			Advanced/metastatic NSCLC Studies						Monotherapy pooled dataset Total (N=1813)		
					Osimertinib First-line (N=643)			Osimertinib ≥Second-line (N=833)					
		<65 years (N=184)	65 – 74 years (N=117)	≥75 years (N=36)	<65 years (N=372)	65 - 74 years (N=209)	≥75 years (N=62)	<65 years (N=487)	65 - 74 years (N=237)	≥75 years (N=109)	<65 years (N=1043)	65 - 74 years (N=563)	≥75 years (N=207)
Total treatment duration (months)[a]	Mean	30.3	27.6	21.7	21.5	20.5	17.2	16.9	19.1	18.4	20.9	21.4	18.6
	SD	10.99	13.01	14.67	12.0	13.18	12.99	13.02	13.58	13.92	13.22	13.68	13.80
	Median	35.9	35.8	23.5	20.9	19.4	13.8	13.8	15.2	16.5	19.3	20.1	16.2
	Min	0.10	0.07	1.05	0.56	0.10	0.07	0.03	0.13	0.49	0.03	0.07	0.07
	Max	37.06	37.98	37.22	49.71	49.84	48.03	51.19	52.04	52.24	51.19	52.04	52.24
	Total treatment years	464.36	268.79	65.01	667.96	357.0	88.84	685.19	378.09	167.51	1817.51	1003.89	321.36

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
Total treatment years was calculated by adding the durations for each patient in the treatment group.
SD = standard deviation

2.4 MODULE SIV: Populations not studied in clinical trials

2.4.1 Exclusion Criteria in pivotal clinical studies within the development programme

Table 2-17 Exclusion Criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information ?	Rationale
History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.	To ensure patient safety.	No	There is no substantial evidence from the clinical development programme or from post-marketed use of a different safety profile to that of the general target population.
Patients under the age of 18 years (20 years in Japan)	This population was excluded from the clinical trial program based on the general principle that pediatric patients are not exposed to the investigational product where the benefit-risk profile for the intended adult population has not yet been established.	No	Use in the paediatric population is not indicated and therefore is not relevant for consideration as missing information.
Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≥2	To ensure that patients were well enough to attend the trial site and comply with study procedures, to allow adequate assessment of the efficacy and safety profile of osimertinib.	No	From cumulative experience, to date, there is no evidence of any specific safety concern or potential safety signal in patients with a PS≥2 who have received osimertinib treatment. Considering this, in addition to there being no ongoing additional PV activities, the use of osimertinib in patients with a PS≥2 is not considered to be an area of missing information.

Table 2-17 Exclusion Criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information ?	Rationale
Prior treatment with any of the following: Specific anti-cancer agents within various timeframes of starting osimertinib treatment Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment Radiotherapy within specific timeframes, dependent on the location and field.	To avoid confounding toxicities with the experimental treatment, in order to ensure optimal assessment of the efficacy and safety profile of osimertinib.	No	These exclusion criteria are relevant only to patients enrolled in clinical studies in order to allow for homogeneous data collection and subsequent meaningful data interpretation, and there is no evidence to suggest that prior use of these treatment options within the timeframes stated result in a specific safety concern, or a different safety profile to that of the general target population.
Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of osimertinib) medications or herbal supplements known to be potent inhibitors of CYP2C8 and potent inhibitors or inducers of CYP3A4.	To avoid interactions with the experimental treatment, in order to ensure optimal assessment of the efficacy and safety profile of osimertinib.	No	The EU SmPC includes recommendations to avoid the concomitant administration of strong inducers of CYP3A (e.g., phenytoin, rifampicin, and carbamazepine) and recommendations to monitor for signs of change in tolerability with concurrent administration of medications where disposition is dependent upon BCRP (e.g. rosuvastatin) whilst receiving osimertinib. Based on the low clinical significance and impact of these interactions and the fact that use in this population is anticipated to be low due to the EU SmPC warning, this patient population is not relevant for inclusion as missing information.

Table 2-17 Exclusion Criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information ?	Rationale
Any unresolved toxicities from prior therapy greater than CTCAE Grade 1 at the time of starting osimertinib (with the exception of alopecia) and Grade 2 neuropathy related to prior platinum-therapy	To ensure the optimal assessment of the safety profile in the patient population, and to minimise the impact of previous anticancer treatment toxicities on the evaluation of safety.	No	There is no evidence to suggest that the use of osimertinib in patients with unresolved toxicities from prior therapy may result in a specific safety concern, or a different outcome to previously identified risks. The prescriber may provide the patient with medication to manage these toxicities, providing that this concomitant medication is not precluded according to the osimertinib EU SmPC (Section 4.5 [*Interaction with other medicinal products and other forms of interaction*], and Section 5.2 [*Pharmacokinetic properties*]).
Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment	To ensure ability for the patient to tolerate treatment and to ensure optimal assessment of efficacy of osimertinib.	No	The potential for a significantly different safety profile in patients with symptomatic rather than asymptomatic brain metastases relates in part to the potential use of concomitant medications for the management of symptoms in these patients; however provided the guidance on the use of concomitant medications in Section 4.5 (*Interaction with other medicinal products and other forms of interaction*) of the osimertinib EU SmPC is followed, there is no clinical reason why these patients should not receive osimertinib. To date, no safety concerns on the use of osimertinib in these patients has been identified. Considering this, the use of osimertinib in patients with symptomatic brain metastases is not considered to be an area of missing information.

Table 2-17 Exclusion Criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information ?	Rationale
Any evidence of severe or uncontrolled systemic diseases (including uncontrolled hypertension and active bleeding diatheses) which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol.	To ensure the ability of the patient to tolerate treatment and to ensure the optimal assessment of the efficacy and safety profile of osimertinib.	No	There is no evidence to suggest that the use of osimertinib in patients with severe or uncontrolled systemic diseases leads to a specific safety concern, or a different outcome to previously identified risks. There is no evidence to suggest that the safety profile in this patient population is different to that of the general target population and, therefore, 'patients with severe or uncontrolled systemic diseases' is not considered to be an area of missing information.
Active infection including hepatitis B, hepatitis C and HIV.	To reduce the risk to laboratory staff during collection/ handling of blood/tissue samples and to ensure the optimal assessment of the efficacy and safety profile of osimertinib.	No	No safety concerns relevant to the use of osimertinib in these patients has been identified. Therefore, the use of osimertinib in patients with active infection (including hepatitis B, hepatitis C, and HIV) is not considered to be an area of missing information.
Refractory nausea and vomiting, chronic GI diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib.	To exclude patients who may have impaired absorption in order to ensure patients received the optimal dose of treatment and to ensure the accurate assessment of the efficacy profile of osimertinib.	No	There is no scientific rationale to suspect that the safety profile for this patient population may differ to that which has been characterised in the general, target population. Therefore, the use of osimertinib in patients with refractory nausea and vomiting, chronic GI disease, inability to swallow the formulated product or previous significant bowel resection is not considered to be an area of missing information.

Table 2-17 Exclusion Criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information ?	Rationale
Any of the following cardiac criteria: • Mean resting QTc interval >470 msec (obtained from 3 ECGs); • Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG; • Any factors that increase the risk of QTc prolongation or risk of arrhythmic events.	To ensure optimal assessment of safety profile in the patient population, as mandated in the ICH E14 guidelines.	No	Detailed analysis of QTcF data obtained from patients included in the osimertinib clinical development program has established a causal association between osimertinib and QT prolongation. However, to date, no evidence of any clinical consequences of QT prolongation has been observed in clinical studies or from post-marketing sources. Guidance for the management of osimertinib-related QT prolongation in patients with a predisposition to, or baseline prolonged QT interval is highlighted in Section 4.4 (*Special warnings and special precautions for use*) of the EU SmPC and Section 4.8 (*Undesirable effects*) lists QT prolongation as an ADR. Consequently, use in this patient population is not considered to be an area of missing information.
Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active ILD.	To minimise the risk of re-occurrence of ILD.	No	ILD (grouped term) is listed as an ADR in Section 4.8 (*Undesirable effects*) of the osimertinib EU SmPC, with additional details provided in Section 4.4 (*Special warnings and special precautions for use*) and Section 4.2 (*Posology and method of administration*). This guidance advises the permanent discontinuation of osimertinib upon the confirmation of a diagnosis of ILD. Consequently, use in this patient population is not considered to be an area of missing information.

Table 2-17 Exclusion Criteria in pivotal clinical studies within the development programme

Criteria	Reason for exclusion	Is it considered to be included as missing information ?	Rationale
Inadequate bone marrow reserve or organ function, as demonstrated by specific laboratory values.	Subjects with inadequate bone marrow reserves were excluded from clinical studies due to pre-clinical findings of decreases in red blood cell parameters in repeat dose rat and dog studies. Patients with severely impaired organ function were excluded from the clinical trials in order to improve patient safety until more data can be obtained on the effects of osimertinib in this patient population.	No	Decreases in platelet count, leukocytes, lymphocytes and neutrophils (including the relevant cytopenia terms) are listed as ADRs in Section 4.8 (Undesirable effects) of the osimertinib EU SmPC, with further guidance on the nature of the changes in these haematological parameters upon initiating osimertinib treatment also provided. Consequently, use in this patient population is not considered to be an area of missing information. Study D5160C00035, a PASS designed to assess the use of osimertinib in patients with renal impairment did not identify any new safety findings and provides evidence that the safety profile in this previously under studied patient population is consistent with the known safety profile for osimertinib. Consequently, use in patients with severe renal impairment is not considered to be an area of missing information.
Women who are pregnant or breastfeeding	To avoid potential harm to the unborn foetus. It is not known whether osimertinib or its metabolites are excreted in human milk and lactating females are excluded to avoid potential harm to the breastfeeding newborn.	No	Section 4.6 (*Pregnancy, lactation and fertility*) of the EU SmPC advises female patients to avoid becoming pregnant and to use effective contraception. Therefore, exposure in this population is expected to be very limited and consideration for inclusion as missing information is not relevant.

Abbreviations: ADR, adverse drug reaction; AE, Adverse event; CTCAE, Common Terminology Criteria for Adverse Events; CYP, cytochrome P450 isoenzyme; DDI, drug drug interaction; ECG, electrocardiogram; EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor; EGFRm, epidermal growth factor mutation; ECOG, Eastern Co-operative Oncology Group; EMA, European Medicines Agency; FDA, Food and Drug Administration; GI, gastrointestinal; HIV, human immunodeficiency virus; ICH, International Conference on Harmonisation; ILD, interstitial lung disease; NSCLC, Non-small cell lung cancer; PDCO, Paediatric Committee; P-gp, Pglycoprotein; PS, Performance status; PXR, Pregnane X receptor; QT, ECG interval measured from the beginning of the QRS complex to the end of the T wave; QTc, heart rate corrected QT interval; QTcF, heart rate corrected QT interval using Fridericia's formula.

2.4.2 Limitations to detect adverse reactions in clinical trial development programmes

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

2.4.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Table 2-18 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development programme. Despite the exclusion criteria, AstraZeneca has received isolated case reports relevant to this population
Breast feeding women	Not included in the clinical development programme.
Patients with relevant comorbidities: Hepatic impairment (ALT/AST >2.5 x ULN if no demonstrable liver metastases, or > 5 x ULN in the presence of liver metastases total bilirubin 1.5 x ULN if no liver metastases or > 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinemia) or liver metastases were also excluded.	Not included in the clinical development programme. Despite the exclusion criteria, a small number of hepatically impaired patients have been included in the osimertinib clinical development programme. Furthermore, a clinical study to investigate the impact of hepatic impairment (based on Child Pugh classification) on osimertinib PK (Study D5160C00008) has been conducted which included the following patients: Mild hepatic impairment *(Child Pugh A, n = 7)* Moderate hepatic **impairment** *(Child Pugh B, n=5)* Normal hepatic function *(n=10)*

Table 2-18 Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Patients with relevant comorbidities: Renal impairment creatinine >1.5 times ULN concurrent with creatinine clearance (CLcr) <50 mL/min to be excluded	Not included in the clinical development programme. Despite the exclusion criterion, a small number of renally impaired patients have been included in the osimertinib clinical development programme. Furthermore, a clinical study to investigate the impact of severe renal impairment on osimertinib PK (Study D5160C00035) has been conducted, which included the following patients: Normal renal function *(CrCl ≥90 mL/min, n=9)* Severe renal impairment *(CrCl <30 mL/min, n=7)*
Patients with relevant comorbidities: History of ILD	Not included in the clinical development programme.
Patients with relevant comorbidities: Pre-existing QT prolongation (QT interval >470msec or with risk factors that may increase the risks of QT prolongation)	Not included in the clinical development programme.
Patients with a disease severity different from inclusion criteria in clinical trials: ECOG Performance Status ≥2	Not included in the clinical development programme. Furthermore, a clinical study to investigate osimertinib in patients with leptomeningeal metastases (Study D6030C00001) included a total of 21 patients with an ECOG PS of 2.
Patients with a disease severity different from inclusion criteria in clinical trials: Symptomatic brain metastases	The FLAURA study included patients with stable symptomatic brain metastases and the BLOOM clinical study included leptomeningeal patients with (or without) brain metastases. Although these patients were included, data are not available on the number of patients that were recruited with this baseline condition.
Patients with relevant different ethnic origin	The number of patients exposed to osimertinib, by race, in the pooled dataset are: White = 593 patients Black or African American = 14 patients Asian = 1170 patients Other = 28 patients Missing = 8 patients
Subpopulations carrying relevant genetic polymorphisms	There are no relevant genetic polymorphisms identified at this time.

2.5 MODULE SV: POST-AUTHORISATION EXPERIENCE

2.5.1 Method used to calculate exposure

Post-marketing exposure data for osimertinib is estimated based on actual, ex-factory sales data to wholesalers. Patient exposure has been calculated from the number of tablets delivered to various distribution channels (wholesalers, pharmacies etc.) worldwide, as recorded in AstraZeneca's Enterprise Performance Visibility (EPV) database. This database stores monthly actual osimertinib ex-factory sales and volume from each local country's marketing company. The sales volume is provided as the number of packs sold and the individual tablets sold.

In order to calculate an estimate of exposure to osimertinib in patient years, it has been assumed that for the 40 mg dose, the total daily dose is 40 mg; and for the 80 mg dose, the total daily dose is 80 mg. Hence, for the 40 mg and 80 mg doses, the exposure in patient years is equal to the number of tablets sold, divided by 365.25 days.

2.5.2 Exposure

The cumulative global post-marketing patient exposure to TAGRISSO (40 mg and 80 mg), since launch (date of first marketing authorisation, 13 November 2015) to 31 December 2025, has been estimated to be approximately 1222881 patient-years.

Table 2-19 TAGRISSO cumulative patient exposure in patient-years (DCO 31 December 2025), number of 40 mg and 80 mg tablets, by region*

Formulation	Europe	North America	Japan	Rest of the world	Total
40 mg Tablets	21820	13636	40790	4391	80638
80 mg Tablets	139952	91411	86606	824274	1142243

*excluding 58 patient-years where strength is not available

2.6 MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Osimertinib does not have any particular pharmacological effects or characteristics that make misuse for illegal purposes likely.

2.7 MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

2.7.1 Identification of safety concerns in the initial RMP submission

Not applicable

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

Rhabdomyolysis is a new important potential risk:

Cases of rhabdomyolysis in patients that have been treated with osimertinib have been reported from post-marketing sources. No case reports of rhabdomyolysis have been reported in the clinical development programme of osimertinib. Case reports of blood CPK increased (1.9%, all grades) have been reported with osimertinib in osimertinib monotherapy clinical trial pooled dataset (n=1813), including CTCAE Grades ≥ 3 (0.3%). Considering the seriousness of rhabdomyolysis and its potential for significant morbidity or mortality, rhabdomyolysis is regarded as an important potential risk to be included in the list of safety concerns for osimertinib.

2.7.3 Details of important identified risks, important potential risks and missing information

2.7.3.1 Presentation of important identified risks and important potential risks

2.7.3.1.1 Interstitial lung disease

Potential mechanisms

Although ILD refers to a broad range of chronic lung disorders, most cases present as epithelial injury, followed by fibroblastic proliferation and development pulmonary fibrosis involving fibroblastic foci and an excess deposition of matrix. The EGFR pathway plays an important role in pulmonary function via the regulation of epithelial cells under both normal and fibrotic conditions. Ligand/EGFR activation transduce signals across cellular membranes controlling key cellular processes such as self-renewal, wound-healing, proliferation, survival, adhesion, migration, and differentiation. Pathologically bronchial epithelium cells, smooth muscle cells, and fibroblasts are all involved in fibrogenesis and have high EGFR, EGF, and transforming growth factor-α (TGF-α) gene expression.

The pathogenesis of ILD in association with anti-cancer agents is likely to be a multi-step process, with one of the key initiating factors the apoptosis of non-neoplastic pneumocytes and injured alveolar epithelium. The mechanism of EGFR-TKIs-induced ILD has not been fully elucidated. Previous findings demonstrate that EGFR and its family members are usually upregulated early in the response to acute lung injury (Madtes et al 1994, Madtes et al 1998) and that EGFR inhibition may reduce the ability of pneumocytes to respond to lung injury

(Tsuboi and Le Chevalier 2006). Thus, inhibition of EGFR signalling could exacerbate pulmonary injury and then impair the repair of lung injury.

Additionally, preclinical in vivo models suggest that EGFR inhibition can result in reduced surfactant A expression and can promote upregulation of pro-inflammatory genes that could result in prolonged inflammation (Dy and Adjei 2013). An allergic reaction to EGFR-TKIs has also been suggested as a possible cause (Aoe et al 2005).

Evidence source(s) and strength of evidence

Detailed case reports of pneumonitis have been received from clinical studies and postmarketing use. It is consistent with the known safety profile of EGFR TKIs.

An imbalance was observed in the ADAURA study (DCO 11 April 2022): 11 patients (3.3%) receiving osimertinib experienced ILD/ pneumonitis compared to none in the placebo arm.

Incidence and severity of ILD/pneumonitis was comparable across both arms in the FLAURA2 study (3.3% osimertinib plus chemotherapy vs 3.6% osimertinib monotherapy), indicating that there is no impact on this risk when osimertinib is combined with chemotherapy, such as pemetrexed and platinum-based chemotherapy.

Overall, AEs of ILD/pneumonitis in the LAURA study were reported in a low but numerically higher proportion of patients in the osimertinib arm (11 [7.7%]) compared to the osimertinib monotherapy pooled safety dataset (73 [4.0%]). Of note, 2 patients who reported adverse events of pulmonary fibrosis/pneumonitis in the LAURA study had an ongoing medical history of the same conditions upon entry to the study (permitted per CSP eligibility criteria), which is generally regarded as a non-reversible condition. CRT is a recognized risk factor for the development/worsening of ILD/pneumonitis following TKI therapy and the nominal increase in the number of patients with ILD in the LAURA study can be explained by the medical history and the CRT use. No safety signal in relation to an increase in the frequency and/or severity of these events was observed from a review of study data.

Characterisation of the risk

Table 2-20 Important identified risk: Interstitial lung disease (group term[a])

	Frequency N (%) patients with ILD	Serious	Median time to onset (days) [range]	Severity (CTCAE Grade[b])				
				1	2	3	4	5
Monotherapy pooled dataset								
Adjuvant AZD9291 80mg (N=337)	11 (3.3)	2 (0.6)	84.0 [56-1002]	6 (1.8)	5 (1.5)	0	0	0
First line AZD9291 80mg (N=643)	26 (4.0)	15 (2.3)	99.0 [1-526]	4 (0.6)	12 (1.9)	8 (1.2)	1 (0.2)	1 (0.2)
Second line setting and later AZD9291 80mg (N=833)	36 (4.3)	20 (2.4)	85.0 [8-1035]	10 (1.2)	11 (1.3)	9 (1.1)	0	6 (0.7)
Pooled dataset (N=1813)	73 (4.0)	37 (2.0)	85.0 [1-1035]	20 (1.1)	28 (1.5)	17 (0.9)	1 (0.1)	7 (0.4)
Monotherapy (LAURA)								
AZD9291 80mg (N=143)	11 (7.7)	3 (2.1)	57.0 [26-755]	4 (2.8)	4 (2.8)	2 (1.4)	0	1 (0.7)
Combination therapy dataset (FLAURA2)								
First line osimertinib plus chemotherapy (N=276)	9 (3.3)	3 (1.1)	161 [14-730]	2 (0.7)	5 (1.8)	1 (0.4)	0	1 (0.4)

The ethnic distribution of patients who developed ILD is as follows (in the pooled population of 1813 patients):

Japanese: 36/322 patients (11.2%)

Non-Asian: 20/749 patients (2.7%)

Asian and non-Japanese patients: 17/742 patients (2.3%)

[a] Patients with multiple events in the same category are only counted once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Each patient has only been represented with the maximum reported CTCAE grade for each preferred term. Presented as a % of the total number of patients.

Table 2-21 Event level outcome for interstitial lung disease (grouped terms)

	Outcome at event level (%)				
	Recovered	**Recovering**	**Recovered/resolved with sequelae**	**Not recovered/ Not resolved**	**Fatal**
Monotherapy pooled dataset					
Adjuvant AZD9291 80mg (N=337)	11 (100.0)	0	0	0	0
First line AZD9291 80mg (N=643)	12 (46.2)	7 (26.9)	1 (3.8)	6 (23.1)	0
Second line setting and later AZD9291 80mg (N=833)	15 (41.7)	6 (16.7)	0	9 (25.0)	6 (16.7)
Pooled dataset (N=1813)	38 (52.1)	13 (17.8)	1 (1.4)	15 (20.5)	6 (8.2)[a]
Monotherapy (LAURA)					
AZD9291 80mg (N=143)	3 (25.0)	1 (8.3)	0	7 (58.3)	1 (8.3)
Combination therapy dataset (FLAURA2)					
First line osimertinib plus chemotherapy (N=276)	5 (55.6)	0	0	3 (33.3)	1 (11.1)

[a] In the pooled dataset (N=1813) there was 7 CTCAE grade 5 events. Only 6 fatal events are noted in the outcome at event level table. One patient in the FLAURA2 osimertinib monotherapy arm experienced organising pneumonia which started before DCO. The patient died one day after DCO and, as maximum grade was collected, the site captured this event as CTCAE grade 5.

Risk factors and risk groups

Risk factors include previous chemotherapy treatment, previous radiation therapy to the lungs, pre-existing parenchymal lung disease, metastatic lung disease, concomitant pulmonary infection (Cataldo et al 2011) and previous or concurrent IO (immuno-oncology) therapy (Adderley et al 2021). Kudoh and colleagues report that other risk factors of ILD include older age, poor ECOG performance status (≥2), smoking, recent NSCLC diagnosis, reduced normal lung on CT scan, pre-existing chronic ILD, concurrent cardiac disease, and Japanese ethnicity (Kudoh et al 2008).

In a case control study of 227 ILD patients from the Lung Tissue Research Consortium based in the US, an EGF mutation associated with EGF level changes and increased cancer risk, also demonstrated an elevated risk of ILD (OR=1.33, 95% CI=1.07–1.66, P=0.0099) with the A allele frequency being significantly higher in the cases (64%) than the controls (57%). The genotype association remained significant after adjusting for age and gender (P=0.0087) (Li et al 2014a).

Preventability

The careful selection and close monitoring of patients may avert this relatively uncommon and serious condition. The EU SmPC contains advice for health care professionals on how to address pulmonary symptoms indicative of ILD/pneumonitis.

Impact on the risk-benefit balance of the product

The severity of symptoms due to ILD can vary from mild symptoms (eg, cough) to life threatening shortness of breath. Severe ILD, if not recognised or managed appropriately, can become life-threatening or fatal.

Public health impact:

As the impact is to the treated population only, there is no public health impact.

2.7.3.1.2 Cardiac failure

Individual PTs of cardiac failure and LVEF decreased are listed as ADRs in the EU SmPC, however the remainder of the PTs in the medical concept of cardiac failure (SMQs: Cardiac Failure (narrow), Cardiomyopathy (narrow)) are not considered as ADRs.

Potential mechanisms

The mechanism for a potential HER2 (erbB2) mediated cardiac function effect is not understood, but there are published literature reports linking erbB2 with cardiac function. Neuregulin-1 signalling (via erbB2/4 receptor dimer) has been shown to be important in

cardiac development in mice, with erbB2 or erbB4 homozygous knock-out mice die before day E11, probably due to poor heart development (Kramer et al 1996); however, there are no reports that directly link HER2 inhibition and reduced cardiac contractility (and hence the undesirable clinical outcome of cardiac failure) in developed hearts.

Evidence source(s) and strength of evidence

In the in vitro pharmacology studies, osimertinib and metabolites AZ5104 and AZ7550 were shown to inhibit HER2 (also known as erbB2) in the context of cancer cell lines. HER2 inhibition has previously been associated with a potential risk of a decrease in LVEF in some patients given trastuzumab following anthracycline-based therapy (Ewer and O'Shaughnessy 2007); however analyses of LVEF in more recent HER2 small molecule inhibitors, including irreversible inhibitors, shows the link between HER2 inhibition and LVEF decrease is not conclusive (Ades et al 2014, Ewer et al 2014, Perez et al 2008). Additionally, more recent HER2 inhibitors (e.g. afatinib) have been shown not to be associated with this risk (Ewer et al 2015).

Upon review of the data obtained in the AURA3 study, a numerical imbalance in the number of patients with an AE from the Cardiac failure or Cardiomyopathy SMQs, and in LVEF decreases between the 2 treatment arms (osimertinib versus chemotherapy) was noted. A similar numerical imbalance was also noted between treatment arms (osimertinib versus standard of care therapy [erlotinib or gefitinib]) in the FLAURA study. However, in a placebo-controlled trial (ADAURA), there was no difference between treatment arms in the number of patients who experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50% <in either patients treated with TAGRISSO™ or patients treated with placebo, 1.5% (5/337); 1.5% (5/343), respectively.

A numerical imbalance was observed in the incidence of cardiac effects events (cardiomyopathy or cardiac failure SMQs) in osimertinib plus chemotherapy (9.4%) when compared to osimertinib monotherapy (3.6%) in the FLAURA2 study. This difference was primarily driven by adverse events of ejection fraction decreased. Overall, a review of AEs indicative of cardiac failure was comparable with the type and frequency of AEs reported in the osimertinib monotherapy clinical development programme to date; no new safety signal for cardiac effects was identified. On a study population level, no notable changes in cardiac contractility (as measured by LVEF) over time were observed in either treatment arm. In the osimertinib + chemotherapy arm, median LVEF at baseline was 65.0%, which remained stable over time, with a lowest recorded median LVEF value of 64.0%. In the osimertinib arm, median LVEF was 66.0% at baseline, which remained stable over time, with a lowest recorded median LVEF value of 64.0%. Events of cardiac failure were observed in patients with underlying risk factors which could put patients at higher risk. The benefit risk profile of

osimertinib and chemotherapy has not been impacted such that additional risk minimisation measures or further characterisation are warranted.

In the LAURA study, no notable differences between treatment arms were observed in relation to cardiac contractility (as characterised by LVEF measurements). One patient (0.7%) in osimertinib arm and 0 patients in the placebo arm had an AE in the cardiac effects (cardiomyopathy or cardiac failure SMQs) grouped term.

Characterisation of the risk

Table 2-22 Important potential risk: Cardiac failure (Cardiomyopathy or Cardiac failure SMQs)a

	Frequency N (%) patients with Cardiac failure	Serious	Median time to onset (days) [range]	Severity (CTCAE Grade[b])				
				1	2	3	4	5
Monotherapy pooled dataset								
Adjuvant AZD9291 80mg (N=337)	19 (5.6)	2 (0.6)	421.0 [53-1027]	7 (2.1)	8 (2.4)	4 (1.2)	0	0
First line AZD9291 80mg (N=643)	28 (4.4)	2 (0.3)	174.5 [18-925]	4 (0.6)	14 (2.2)	10 (1.6)	0	0
Second line setting and later AZD9291 80mg (N=833)	21 (2.5)	3 (0.4)	169.0 [27-1050]	2 (0.2)	11 (1.3)	7 (0.8)	0	1 (0.1)
Pooled dataset (N=1813)	68 (3.8)	7 (0.4)	240.5 [18-1050]	13 (0.7)	33 (1.8)	21 (1.2)	0	1 (0.1)
Monotherapy (LAURA)								
AZD9291 80mg (N=143)	1 (0.7)	0	57.0 [57-57]	0	1 (0.7)	0	0	0
Combination therapy dataset (FLAURA2)								
First line osimertinib plus chemotherapy (N=276)	26 (9.4)	4 (1.4)	295.0 [9-927]	6 (2.2)	8 (2.9)	9 (3.3)	0	3 (1.1)

[a] Patients with multiple events in the same category are only counted once in that category. Patients with events in more than one category are counted once in each of those categories.

[b] Each patient has only been represented with the maximum reported CTCAE grade for each preferred term. Presented as a % of the total number of patients.

Table 2-23 Event level outcome for cardiac failure (cardiomyopathy or cardiac failure SMQs)

	Recovered	Recovering	Not recovered/ Not resolved	Fatal
Monotherapy pooled dataset				
Adjuvant AZD9291 80mg (N=337)	14 (63.6)	1 (4.5)	7 (31.8)	0
First line AZD9291 80mg (N=643)	21 (65.6)	3 (9.4)	8 (25.0)	0
Second line setting and later AZD9291 80mg (N=833)	12 (40.0)	2 (6.7)	15 (50.0)	1 (3.3)
Pooled dataset (N=1813)	47 (56.0)	6 (7.1)	30 (35.7)	1 (1.2)
Monotherapy (LAURA)				
AZD9291 80mg (N=143)	0	0	1 (100)	0
Combination therapy dataset (FLAURA2)				
First line osimertinib plus chemotherapy (N=276)	13 (44.8)	2 (6.9)	11 (37.9)	3 (10.3)

Risk factors and risk groups:

Risk factors for the development of cardiac failure (NHLBI, 2017) include:

- Age (increased risk in patients over 65 years) and race (increased risk in Black patients compared to those from other races).
- Other cardiac conditions such as arrhythmia, cardiomyopathy, congenital heart defects, or cardiac valve disease
- Coronary heart disease
- Previous cardiac damage from myocardial infarction
- Diabetes or other metabolic diseases
- Severe obesity
- Long-term alcoholism or drug abuse
- Long-term high blood pressure
- Prior cancer treatments, e.g. anthracyclines or radiotherapy to the chest.

Preventability

There are no specific recommendations to prevent this risk with osimertinib, however, steps can be taken in relation to the known risk factors such as avoiding the use of alcohol, healthy eating, physical activity, quitting smoking, managing stress, and appropriate control of high blood pressure, high blood cholesterol, and diabetes.

Monitoring of high-risk patients may allow early identification and treatment of this condition. Consequently, the EU SmPC for osimertinib contains advice for health care professionals on the potential risk of changes in cardiac contractility.

Impact on the risk-benefit balance of the product

Cardiac failure, if not recognised or managed appropriately, can become life-threatening or fatal.

Public health impact

As the impact is to the treated population only, there is no public health impact.

2.7.3.1.3 Rhabdomyolysis

Potential mechanisms

Rhabdomyolysis is the result of skeletal muscle breakdown with release of potentially toxic substances such as electrolytes, myoglobin, and sarcoplasmic proteins into the bloodstream. The pathophysiology underlying all cases of rhabdomyolysis is disruption of the myocyte cell

membrane and leakage of cell contents into circulation. This may result from direct myocyte injury related to trauma or from metabolic disturbances affecting supply of ATP within the myocyte (Kodadek et al 2022). Rhabdomyolysis is considered a Designated Medical Event (DME) by the European Medicines Agency, that is, a rare, serious, and clinically significant adverse event that is often causally linked to medication use.

The mechanism by which EGFR TKIs may cause rhabdomyolysis is still unknown.

Evidence source(s) and strength of evidence

Cases of rhabdomyolysis in patients that have been treated with osimertinib have been reported from post-marketing sources. Blood CPK increase is a safety concern for a range of TKIs including third generation EGFR TKIs (Parafianowicz et al 2020, Sugimoto et al 2022, Zhang et al 2024).Reports of rhabdomyolysis and other clinical manifestations of muscle damage are much less common than reports of CPK increases with EGFR TKIs.

These include a report of rhabdomyolysis following an overdose of a first-generation EGFR TKI (Obayashi et al 2022), reports of rhabdomyolysis following treatment with third generation EGFR TKIs (Lee et al 2025, Ishikawa et al 2016), and reports of rhabdomyolysis from interaction of first-generation EGFR TKI with statin / Oxycodone (Veeraputhiran et al 2008, Kahler and Hanna 2005, Korsic et al 2015).

Characterisation of the risk

Clinical data:

Rhabdomyolysis as an adverse event was not reported in osimertinib monotherapy pooled dataset. Case reports of blood CPK increased (1.9%, all grades) have been reported with osimertinib in osimertinib monotherapy pooled dataset (n=1813), including CTCAE Grades ≥ 3 (0.3%).

Post-marketing data:

Case reports of rhabdomyolysis have been reported in post-marketing data for osimertinib.

Risk factors and risk groups

An analysis to identify specific risk factors and risk groups for rhabdomyolysis has not been conducted for osimertinib.

Risk factors for rhabdomyolysis include:

Genetic: metabolic disorders- long chain fatty acid oxidation, glycogen metabolism disorders; mitochondrial disorders; calcium influx disorders and caveolinopathy; muscular dystrophies; sickle cell trait.

Acquired: Crush injury, drugs, toxins and alcohol, strenuous exercise, infections including COVID-19, metabolic/dyselectrolytemias/ endocrine disorders; hyperthermia/ electric current; ischemia, idiopathic (Gupta et al 2021).

Preventability

There are currently no means of preventing rhabdomyolysis. However, a low threshold of clinical suspicion in the proper laboratory and historical context is warranted to initiate appropriate therapy (Kodadek et al 2022) .

Patients should be advised to report any unexplained muscle pain, tenderness, or weakness, trouble moving arms or legs, dark tea-coloured urine, or decreased urination. Sign and symptoms of rhabdomyolysis should warrant an appropriate clinical evaluation and treatment as indicated.

Impact on the risk-benefit balance of the product

The benefit-risk balance of osimertinib is not impacted by this risk considering the severity of treatment indication (advanced/metastatic NSCLC). Blood CPK increases are generally asymptomatic and manageable with appropriate monitoring and dose adjustment. Rhabdomyolysis, if not recognised or managed appropriately, can become life-threatening or fatal.

Public health impact

As the impact is to the treated population only, there is no public health impact.

2.8 MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

2.8.1 Summary of the safety concerns

The osimertinib safety specification includes the following important identified risks, important potential risks and areas of missing information (Table 2-24).

Table 2-24 Summary of safety concerns

Important identified risks	Interstitial lung disease Cardiac failure

Table 2-24 Summary of safety concerns

Important potential risks	Rhabdomyolysis
Missing information	None

3 PART III: PHARMACOVIGILANCE PLAN

3.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Specific adverse reaction follow-up questionnaires for ILD, cardiac failure and rhabdomyolysis:

Specific adverse event follow-up questionnaires for the following safety concerns are provided in Annex 4:

- A targeted follow-up questionnaire (TFUQ) for case reports of Interstitial Lung Disease (ILD).

- A TFUQ for case reports indicative of cardiac failure (as identified by MedDRA PTs in the Cardiomyopathy and Cardiac failure SMQs). Detailed information about the patient's underlying disease, past medical history, potential risk factors and sequence of events such as details on previous cancer treatment regimens, radiotherapy, osimertinib dose, additional diagnosis details, clinical progression, complications, action taken with osimertinib, and final outcome. The collection of this information will allow for a more accurate assessment of the post-marketing safety profile of osimertinib.
- A TFUQ for case reports of Rhabdomyolysis.

3.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

None

3.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable

5 PART V: RISK MINIMISATION MEASURES

5.1 ROUTINE RISK MINIMISATION MEASURES

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risks	
Interstitial lung disease	**Routine risk communication:** • EU SmPC Section 4.8 (*Undesirable effects*) and PIL Section 4 (*Possible side effects*) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Guidance on the permanent discontinuation of osimertinib in cases of confirmed ILD/pneumonitis is included in Section 4.2 (*Posology and method of administration*) and Section 4.4 (*Special warnings and precautions for use*) of the osimertinib EU SmPC. • PIL Section 2 (What you need to know before you take TAGRISSO) instructs patients to inform their HCP of any history of ILD, describes the early signs and symptoms of ILD and the importance of reporting these to the HCP.
Cardiac failure	**Routine risk communication:** • PTs cardiac failure and LVEF decreased: EU SmPC Section 4.8 (Undesirable effects) and PIL Section 4 (Possible side effects). **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations in EU SmPC Section 4.4 (Warnings and precautions for use) to consider monitoring LVEF in patients with cardiac risk factors or those who develop relevant cardiac signs/symptoms during treatment. • Guidance for patients to inform their HCP of any prior history of cardiac disorders prior to starting osimertinib treatment is provided in PIL Section 2 (What you need to know before you take TAGRISSO).
Important potential risks	
Rhabdomyolysis	**Routine risk communication:** • EU SmPC section 4.4 (Warnings and precautions for use) and PIL section 2 (What you need to know before you take TAGRISSO) **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendation in EU SmPC Section 4.4 (Warnings and precautions for use) to consider appropriate clinical evaluation and treatment in patients who develop relevant signs and symptoms of rhabdomyolysis. • PIL Section 2 (What you need to know before you take TAGRISSO) instructs patients to inform their HCP of any muscle pain or weakness and early signs and symptoms of rhabdomyolysis.

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Missing Information	None

Abbreviation: ADR, Adverse drug reaction; HCP, Healthcare professional; ILD, Interstitial lung disease; LVEF, Left ventricular ejection fraction; PIL, Patient Information Leaflet.

5.2 ADDITIONAL RISK MINIMISATION MEASURES

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

5.3 SUMMARY OF RISK MINIMISATION MEASURES

Table 5-2 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Interstitial lung disease	Routine risk minimisation measures: • EU SmPC Section 4.8 (Undesirable effects) • EU SmPC Section 4.2 (*Posology and method of administration*) and Section 4.4 (*Special warnings and special precautions for use*) • PIL Section 2 (*What you need to know before you take TAGRISSO*) • PIL Section 4 *(Possible side effects)*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up Questionnaire
Cardiac failure	Routine risk minimisation measures: • PTs cardiac failure and LVEF decreased: EU SmPC Section 4.8 *(Undesirable effects)* • EU SmPC Section 4.4 (Special warnings and special precautions for use) • PIL Section 2 (What you need to know before you take TAGRISSO) • PIL Section 4 (Possible side effects)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire
Important potential risks		
Rhabdomyolysis	Routine risk minimisation measures: • EU SmPC Section 4.4 (Special warnings and special precautions for use) • PIL Section 2 (What you need to know before you take TAGRISSO)	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted follow-up questionnaire

Abbreviations: ADR, Adverse Drug Reaction; EU, European Union; ILD, interstitial lung disease; PIL, Patient Information Leaflet; SmPC, Summary of Product Characteristics

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN FOR OSIMERTINIB

This is a summary of the Risk Management Plan (RMP) for TAGRISSO™ (osimertinib). The RMP details important risks of TAGRISSO, how these risks can be minimised, and how more information will be obtained about TAGRISSO risks and uncertainties (missing information).

The TAGRISSO™ Prescribing Information (PI) and patient information leaflet (PIL) give essential information to healthcare professionals and patients on how TAGRISSO™ should be used.

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

Important new concerns or changes to the current ones will be included in updates of the TAGRISSO™ RMP.

6.1 THE MEDICINE AND WHAT IT IS USED FOR

TAGRISSO™ is authorised for indications outlined – from Table 1-1 “Pharmaceutical forms and strengths” in the SmPC. It contains osimertinib as the active substance and it is given as a 40 mg or 80 mg once daily oral administration.

6.2 RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

Important risks of TAGRISSO™, together with measures to minimise such risks and the proposed studies for learning more about the risks of TAGRISSO™, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorised 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 (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

6.2.1 List of important risks and missing information

Important risks of TAGRISSO™ are risks that need special risk management activities to further investigate or minimise 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 <invented name>. 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 (e.g. on the long-term use of the medicine);

Table 6-1 List of important risks and missing information

Important identified risks	Interstitial lung disease Cardiac failure
Important potential risks	Rhabdomyolysis
Missing Information	None

6.2.2 Summary of important risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

This section presents a summary of important identified risks, important potential risks and missing information.

Table 6-2 Important identified risks

Interstitial lung disease (ILD)

Table 6-2 Important identified risks

Evidence for linking the risk to the medicine	Detailed case reports of pneumonitis have been received from clinical studies and post-marketing use. It is consistent with the known safety profile of EGFR TKIs. An imbalance was observed in the ADAURA study (DCO 11 April 2022): 11 patients (3.3%) receiving osimertinib experienced ILD/ pneumonitis compared to none in the placebo arm. Incidence and severity of ILD/pneumonitis was comparable across both arms in the FLAURA2 study (3.3% osimertinib plus chemotherapy vs 3.6% osimertinib monotherapy), indicating that there is no impact on this risk when osimertinib is combined with chemotherapy, such as pemetrexed and platinum-based chemotherapy. Overall, AEs of ILD/pneumonitis in the LAURA study were reported in a low but numerically higher proportion of patients in the osimertinib arm (11 [7.7%]) compared to the osimertinib monotherapy pooled safety dataset (73 [4.0%]). No safety signal in relation to an increase in the frequency and/or severity of these events was observed from a review of study data.
Risk factors and risk groups	Risk factors include previous chemotherapy treatment, previous radiation therapy to the lungs, pre-existing parenchymal lung disease, metastatic lung disease, concomitant pulmonary infection (Cataldo et al 2011) and previous or concurrent IO (immuno-oncology) therapy (Adderley et al 2021). Kudoh and colleagues report that other risk factors of ILD include older age, poor ECOG performance status (≥2), smoking, recent NSCLC diagnosis, reduced normal lung on CT scan, pre-existing chronic ILD, concurrent cardiac disease, and Japanese ethnicity (Kudoh et al 2008). In a case control study of 227 ILD patients from the Lung Tissue Research Consortium based in the US, an EGF mutation associated with EGF level changes and increased cancer risk, also demonstrated an elevated risk of ILD (OR=1.33, 95% CI=1.07–1.66, P=0.0099) with the A allele frequency being significantly higher in the cases (64%) than the controls (57%). The genotype association remained significant after adjusting for age and gender (P=0.0087) (Li et al 2014a).
Risk minimisation measures	Routine risk minimisation measures: EU SmPC Section 4.8 (Undesirable effects). Appropriate wording in Section 4.2 (Posology and method of administration) and Section 4.4 (Special warnings and special precautions for use) of the current SmPC relating to the importance of detection and subsequent management of this important identified risk. Advice to patients to report relevant medical history prior to starting treatment, and/or report any relevant symptoms during treatment is provided in the PIL.
Cardiac failure	

Table 6-2 Important identified risks

Evidence for linking the risk to the medicine	In the in vitro pharmacology studies, osimertinib and metabolites AZ5104 and AZ7550 were shown to inhibit HER2 (also known as erbB2) in the context of cancer cell lines. HER2 inhibition has previously been associated with a potential risk of a decrease in LVEF in some patients given trastuzumab following anthracycline-based therapy (Ewer and O'Shaughnessy 2007); however, analyses of LVEF in more recent HER2 small molecule inhibitors, including irreversible inhibitors, shows the link between HER2 inhibition and LVEF decrease is not conclusive (Ades et al 2014, Ewer et al 2014, Perez et al 2008). Additionally, more recent HER2 inhibitors (e.g. afatinib) have been shown not to be associated with this risk (Ewer et al 2015). Upon review of the data obtained in the AURA3 study, a numerical imbalance in the number of patients with an AE from the Cardiac failure or Cardiomyopathy SMQs, and in LVEF decreases between the 2 treatment arms (TAGRISSO™ versus chemotherapy) was noted. A similar numerical imbalance was also noted between treatment arms (TAGRISSO™ versus standard of care therapy [erlotinib or gefitinib]) in the FLAURA study. However, in a placebo-controlled trial (ADAURA), there was no difference between treatment arms in the number of patients who experienced LVEF decreases greater than or equal to 10 percentage points and a drop to less than 50% in either patients treated with TAGRISSO™ or patients treated with placebo, 1.5% (5/337); 1.5% (5/343), respectively. A numerical imbalance was observed in the incidence of cardiac effects events (cardiomyopathy or cardiac failure SMQs) in osimertinib plus chemotherapy (9.4%) when compared to osimertinib monotherapy (3.6%) in the FLAURA2 study. This difference was primarily driven by adverse events of ejection fraction decreased. Overall, a review of AEs indicative of cardiac failure was comparable with the type and frequency of AEs reported in the osimertinib monotherapy clinical development programme to date; no new safety signal for cardiac effects was identified. On a study population level, no notable changes in cardiac contractility (as measured by LVEF) over time were observed in either treatment arm. In the osimertinib + chemotherapy arm, median LVEF at baseline was 65.0%, which remained stable over time, with a lowest recorded median LVEF value of 64.0%. In the osimertinib arm, median LVEF was 66.0% at baseline, which remained stable over time, with a lowest recorded median LVEF value of 64.0%. Events of cardiac failure were observed in patients with underlying risk factors which could put patients at higher risk. The benefit risk profile of osimertinib and chemotherapy has not been impacted such that additional risk minimisation measures or further characterisation are warranted. In the LAURA study, no notable differences between treatment arms were observed in relation to cardiac contractility (as characterised by LVEF measurements). One patient (0.7%) in osimertinib arm and 0 patients in the placebo arm had an AE in the cardiac effects (cardiomyopathy or cardiac failure SMQs) grouped term.

Table 6-2 Important identified risks

Risk factors and risk groups	Risk factors for the development of cardiac failure (NHLBI, 2017) include: • Age (increased risk in patients over 65 years) and race (increased risk in Black patients compared to those from other races) • Other cardiac conditions such as arrhythmia, cardiomyopathy, congenital heart defects, or cardiac valve disease • Coronary heart disease • Previous cardiac damage from myocardial infarction • Diabetes or other metabolic diseases • Severe obesity • Long-term alcoholism or drug abuse • Long-term high blood pressure • Prior cancer treatments, e.g. anthracyclines or radiotherapy to the chest In order to facilitate the assessment of potential risks factors for change in LVEF measurements (as a precursor to the undesirable clinical outcome of cardiac failure) in osimertinib-treated patients, an exposure-response analysis, designed to explore a potential relationship between osimertinib PK exposure and decrease in minimum or maximum change from baseline LVEF measurement and LVEF events using data from the AURA, AURA2, AURA3 and FLAURA studies was performed. The analysis did not identify any covariates potentially confounding the exposure-to-LVEF event probability relationship, although there was an indication that patients of White ethnicity have a higher LVEF event risk than Asians or other ethnicities. Several covariates of medical history, i.e., hypertension, statin use, diabetes, ischemic heart disease, heart failure, coronary artery disease, hypothyroidism, and hypoalbuminemia were also tested. An indication for relationship with LVEF event probability was not identified for any of these covariates. Medical history of myocardial infarction, cardiomyopathy, and aortic stenosis were not considered as there were only very small numbers of occurrences.
Risk minimisation measures	Routine risk minimisation measures: EU SmPC Section 4.8 (Undesirable effects). Appropriate wording Section 4.4 (Special warnings and special precautions for use) of the current EU SmPC advising prescribers to consider monitoring of patients with cardiac risk factors or those who develop relevant cardiac signs/symptoms during treatment. Advice to patients to report relevant cardiac history prior to starting treatment and/or report any relevant symptoms during treatment is provided in the PIL.

Table 6-3 Important potential risks

Rhabdomyolysis	
Evidence for linking the risk to the medicine	Cases of rhabdomyolysis in patients that have been treated with osimertinib have been reported from post-marketing sources. sBlood CPK increase is a safety concern for a range of TKIs including third generation EGFR TKIs (Parafianowicz et al 2020, Sugimoto et al 2022, Zhang et al 2024). Reports of rhabdomyolysis and other clinical manifestations of muscle damage are much less common than reports of CPK increases with EGFR TKIs. These include a report of rhabdomyolysis following an overdose of a first-generation EGFR TKI (Obayashi et al 2022), reports of rhabdomyolysis following treatment with third generation EGFR TKIs (Lee et al 2025; Ishikawa et al 2016), and reports of rhabdomyolysis from interaction of first-generation EGFR TKI with statin / Oxycodone (Veeraputhiran et al 2008, Kahler and Hanna 2005, Korsic et al 2015).
Risk factors and risk groups	An analysis to identify specific risk factors and risk groups for rhabdomyolysis has not been conducted for osimertinib. **Risk factors for rhabdomyolysis include:** **Genetic:** metabolic disorders- long chain fatty acid oxidation, glycogen metabolism disorders; mitochondrial disorders; calcium influx disorders and caveolinopathy; muscular dystrophies; sickle cell trait **Acquired:** Crush injury, drugs, toxins and alcohol, strenuous exercise, infections including COVID-19, metabolic/dyselectrolytemias/ endocrine disorders; hyperthermia/ electric current; ischemia, idiopathic (Gupta et al 2021).
Risk minimisation measures	Routine risk minimisation measures: Appropriate wording Section 4.4 (Special warnings and special precautions for use) of the current EU SmPC advising prescribers to consider appropriate clinical evaluation and treatment in patients who develop relevant signs and symptoms of rhabdomyolysis.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies required for TAGRISSO.

6.2.3.2 Other studies in post-authorisation development plan

There are no studies required for TAGRISSO.

7 PART VII: ANNEXES

7.1 ANNEX 4: Specific adverse drug reaction follow-up forms

Targeted follow-up questionnaires (TFUQ) will be distributed for reported events of interstitial lung disease, cardiac failure and rhabdomyolysis (see Part III [*Pharmacovigilance Plan*] of the EU RMP for details).

The TFUQs for distribution are provided in this Annex below:

- Interstitial lung disease (named 'Questionnaire for events associated with Interstitial Lung Disease/Pneumonitis')
- Cardiac failure (named 'Questionnaire for events associated with heart failure')
- Rhabdomyolysis (named 'Questionnaire for events associated with rhabdomyolysis')

7.1.1 Questionnaire for events associated with Interstitial Lung Disease/Pneumonitis

Case ID: (For official use only)

Thank you for reporting an adverse event of/related to ILD/pneumonitis experienced by a patient under your care receiving TAGRISSO® (osimertinib). To better understand and effectively characterise ILD reports received from TAGRISSO® patients, we require some further information to make a full assessment. Please could you provide responses to the following questions. Where appropriate, you may indicate if you have already provided the information, or if you do not have this information. Any additional data we receive is useful for us to preserve the safety of patients and provide the best information for prescribers to preserve safety of our patients.

Patient medical history*

	Yes	No	**Start date** (DD/MMM/YYYY)	**Stop date**** (DD/MMM/YYYY)
Current or former smoker?				
Ever had pleurodesis performed?				
History of radiotherapy to the thorax? Please indicate radiotherapy type (e.g. IMRT, IGRT, SABR etc.) below if "Yes" has been selected				
Prior treatment with immuno-oncology (IO) agents? Please indicate name & dose below if "Yes" has been selected				

	Yes	No	**Start date** (DD/MMM/YYYY)	**Stop date**** (DD/MMM/YYYY)
Any immune-mediated AEs during treatment with a prior IO therapy? Please provide details below if "Yes" has been selected, and indicate the causative agent				
Ever experienced ILD/ pneumonitis due to any cause? Please complete next section if "Yes has been selected				

* Please provide details on another sheet if there is insufficient space to capture all of the patient's medical history in this table

** Please state ongoing/ unknown as applicable

Did the patient previously develop ILD during osimertinib therapy? Yes ☐ No ☐ Unknown ☐

If yes, and different from above, please provide further details below:

	Start date (DD/MMM/YYYY)	**Stop date (DD/MMM/YYYY / ongoing)**
Osimertinib therapy		
ILD/ pneumonitis event		

Action taken with osimertinib as a result of the previous episode of ILD:

Discontinued ☐ Continued ☐ Dose reduced ☐ (Date __/___/____) Not Applicable ☐ Other ☐ (please specify): _____

Severity of event (circle one): CTCAE Grade: 1 2 3 4 OR Mild Moderate Severe

Outcome of event (tick one): Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Ongoing ☐ Unknown ☐ Other ☐ (please specify): _____

Was the event confirmed via HRCT scan? Yes ☐ No ☐ Unknown ☐

Was the event treated with steroids? Yes ☐ No ☐ Unknown ☐

Has the patient previously experienced ILD/ Pneumonitis due to any cause?

Yes ☐ (If yes, please provide details below) No ☐ (If no, please proceed to next question)

Cause/Causative agent (if known): _____

	Start date (DD/MMM/YYYY)	**Stop date (DD/MMM/YYYY / ongoing)**
Cause/ causative agent		
ILD/ pneumonitis event		

If the previous event was drug-induced, please confirm the action taken with the causative agent:

Discontinued ☐ Continued ☐ Dose reduced ☐ (Date __/___/____) Not Applicable ☐ Other ☐ (please specify): _____

Severity of event (circle one): CTCAE Grade: 1 2 3 4 OR Mild Moderate Severe

Outcome of event (tick one): Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Ongoing ☐ Unknown ☐ Other ☐ (please specify): _____

Description of the CURRENT event of ILD/ Pneumonitis

	Start date (DD/MMM/YYYY)	Stop date (DD/MMM/YYYY / ongoing)
Osimertinib therapy		
ILD/ pneumonitis event		

Action taken with osimertinib as a result of the episode of ILD:

Discontinued ☐ Continued ☐ Dose reduced ☐ (Date __/___/____) Not Applicable ☐ Other ☐ (please specify): _____

Temporary stop ☐ (Stop date: ___/____/_____ Re-Start date: ___/____/_____)

Did the event recover/improve upon withdrawal of osimertinib? Yes ☐ No ☐ Unk ☐

Did the event re-occur upon re-start of osimertinib? Yes ☐ No ☐ Unk ☐

Other ☐ (please specify): _____

Severity of event (circle one): CTCAE Grade: 1 2 3 4 OR Mild Moderate Severe

Outcome of event (tick one): Recovered ☐ Recovered with sequelae ☐ Recovering ☐ Ongoing ☐ Unknown ☐ Fatal ☐ Other ☐ (please specify): _____

Was the event confirmed via HRCT scan? Yes ☐ No ☐ Unknown ☐

Was the event treated with steroids? Yes ☐ No ☐ Unknown ☐

Please provide a detailed clinical narrative of the event (symptoms, course):

How was the diagnosis of ILD/Pneumonitis made?

Diagnostic Test (e.g X-Ray, HRCT, MRI)	Test date (DD/MMM/YYYY)	Results/Findings

Were any other laboratory tests conducted to rule out alternate aetiologies (e.g. infection)?

Yes ☐ No ☐ Unknown ☐

If yes, please provide details of any relevant laboratory test results (e.g. infection testing. Broncho-alveolar lavage, white blood cell counts etc.) below or as an attachment to this questionnaire.

Was any specific treatment administered for the pulmonary event (e.g. steroids, other immunosuppressants, antibiotics etc.)?

Yes □ No □ (if yes, please provide details overleaf)

Medication	**Dosage**	**Start date (DD/MMM/YYYY)**	**Stop date (DD/MMM/YYYY)**

At the time of diagnosis of the pulmonary event was there any sign of cancer progression within the thorax? Yes □ No □ (if yes, please provide details):

Please complete the section below if the reported ILD/pneumonitis event was fatal:

Was an autopsy performed?	Yes ☐ No ☐
If yes, what were the results?	

Free text space for any additional information pertinent to the ILD/pneumonitis event

_____

_____

_____

_____

_____

_____

_____

_____

Reporter's Signature: _____Date: _____

7.1.2 Questionnaire for adverse events associated with heart failure (HF)

Case ID: (For official use only)

Thank you for reporting an adverse event of/related to Heart Failure (HF) experienced by a patient under your care receiving TAGRISSO® (osimertinib). To better understand and effectively characterise HF reports received from TAGRISSO® patients, we require some further information to make a full assessment. Please could you provide responses to the following questions. Where appropriate, you may indicate if you have already provided the information, or if you do not have this information. Any additional data we receive is useful for us to preserve the safety of patients and provide the best information for prescribers to preserve safety of our patients.

At the time of the diagnosis of the HF event, did the patient present with any recent history of the following risk factors (not including underlying cancer) for cardiovascular (CV) disease:

Yes ☐ **No** ☐ (if yes please provide details/select all applicable)

History of CV disease (please select any/all that apply and provide start/stop dates [DD/MMM/YYY])	
☐ Heart Failure Start date: _____ Stop date: _____	☐ Coronary artery disease with or without myocardial infarction Start date: _____ Stop date: _____
☐ Pulmonary oedema Start date: _____ Stop date: _____	☐ Prior use of potentially cardiotoxic therapy or radiotherapy to chest / mediastinum Start date: _____ Stop date: _____
☐ Cardiomyopathy Start date: _____ Stop date: _____	☐ Current or previous myocarditis, pulmonary hypertension, and /or pulmonary embolism Start date: _____ Stop date: _____

History of CV disease (please select any/all that apply and provide start/stop dates [DD/MMM/YYY])	
☐ Pericardial disease Start date: _____ Stop date: _____	☐ Family history of premature CV disease (<50 years) Start date: _____ Stop date: _____
☐ Valvular heart disease Start date: _____ Stop date: _____	☐ Congenital heart disease Start date: _____ Stop date: _____
☐ Hypertensive heart disease with left ventricular hypertrophy Start date: _____ Stop date: _____	☐ Arrhythmia (e.g. permanent AF, paroxysmal SVT/AF/A flutter, NSVT with structurally normal heart etc) Start date: _____ Stop date: _____
Other Condition: _____ Start date: _____ Stop date: _____ Other info: _____	Other Condition: _____ Start date: _____ Stop date: _____ Other info: _____

Other risk factors for CV disease (please select any/all that apply and provide start/stop dates [DD/MMM/YYY]):		
☐ Diabetes Start date: _____ Stop date: _____	☐ Obesity Start date: _____ Stop date: _____	☐ Hypertension Start date: _____ Stop date: _____
☐ Hyperlipidaemia Start date: _____ Stop date: _____	☐ Kidney dysfunction Start date: _____ Stop date: _____	☐ Smoking Start date: _____ Stop date: _____

History of CV disease (please select any/all that apply and provide start/stop dates [DD/MMM/YYY])		
☐ High alcohol intake/alcohol abuse Start date: _____ Stop date: _____	☐ Autoimmune/multisystem condition with potential for cardiac involvement Start date: _____ Stop date: _____	☐ Skeletal muscle disorder associated with cardiomyopathy (e.g. muscular dystrophy etc.) Start date: _____ Stop date: _____
Other Condition: _____ Start date: _____ Stop date: _____ Other info: _____	Other Condition: _____ Start date: _____ Stop date: _____ Other info: _____	

Prior to and/or at the time of the diagnosis of the HF event, was the patient receiving concomitant treatment with any medications (other than TAGRISSO®)?:

Yes ☐ No ☐ (if yes please provide details [below])

Medication Type	**Medication Name**	**Dose (Please give units and regimen)**	**Start Date (DD/MMM/YYYY)**	**Stop Date (DD/MMM/YYYY)**
☐ NSAIDS				
☐ Diabetes medications				
☐ Blood pressure and/or heart failure medications				
☐ Diuretics				
☐ ACE Inhibitors				
☐ Beta blockers				
☐ Diuretics				

Medication Type	**Medication Name**	**Dose** (Please give units and regimen)	**Start Date (DD/MMM/YYYY)**	**Stop Date (DD/MMM/YYYY)**
☐ Potentially cardiotoxic medicines (e.g. anthracyclines, HER2 etc.)				
☐ Any other medication relevant to the HF event				

Prior to and/or at the time of the diagnosis of the HF event, did the patient present with any of the following potential underlying cause(s):

Yes ☐ **No** ☐ (if yes please provide details/select all applicable)

Recent changes in Blood pressure or blood pressure and/or heart failure medication	Yes ☐ No ☐ (if yes please provide details) Change: _____ Start date: _____ Stop date: _____ Other info: _____
Recent I.V. fluid challenge	Yes ☐ No ☐ (if yes please provide details) Change: _____ Start date: _____ Stop date: _____ Other info: _____
C – acute Coronary syndrome H – Hypertension emergency A - Arrhythmia M – acute Mechanical cause P – Pulmonary embolism	Yes ☐ No ☐ (if yes please provide details) Condition: _____ Start date: _____ Stop date: _____ Other info: _____

Details of presenting symptoms:

Symptoms (Please select all applicable)

☐ Dyspnoea ☐ Chest pain/discomfort ☐ Palpitations ☐ Decreased Exercise Tolerance ☐ Fatigue
☐ Orthopnoea / Paroxysmal Nocturnal Dyspnoea ☐ Peripheral Oedema
☐ Altered Mental Status ☐ Other Symptoms of Heart Failure (Please specify below):

_____
_____

Physical examination (Please select all applicable)

☐ Peripheral Oedema	☐ Increased Abdominal Distension/Ascites
☐ Pulmonary Rales/Crackles/Crepitations	☐ Increased Jugular Venous Pressure
☐ Increased Hepatojugular Reflux	☐ S3 Gallop
☐ Clinically Significant Weight gain	☐ Rapid Weight Gain
☐ Cool Extremities	☐ Heart murmur (e.g. MR)
Heart Rate _____ (BPM)	Body temp _____ ºC/ºF (Please select units)
Blood Pressure _____ (mmHg)	Oxygen saturation _____ %

As part of the differential diagnosis, were any cardio-respiratory investigations conducted to confirm the HF event (e.g. Chest X-ray, Echocardiogram / MUGA / Cardiac MRI for evaluation of cardiac structure and function including Left Ventricular ejection Fraction (LVEF), ECG, BNP/NT-proBNP, Troponin, CKMB, Pulse oximetry/Blood gases)?

Yes ☐ No ☐ Unknown ☐

(if yes please provide the investigation results as an attachment to this completed questionnaire)

LABORATORY FINDINGS:

Were any laboratory test conducted to aid diagnosis or rule out an associated clinically significant abnormality (e.g. Blood counts [white cell count, haemoglobin level, haematocrit] and/or Liver Function Tests [ALT, AST, Bilirubin, serum creatinine, BUN, serum electrolytes, serum +/- urinary albumin (considering nephrotic syndrome)] and/or thyroid function tests)?

Yes ☐ No ☐ Unknown ☐

(if yes please provide the investigation results as an attachment to this completed questionnaire)

At the time of diagnosis of the HF event, were there any signs/symptoms of Cancer progression?

Yes ☐ (if yes please provide details) No ☐ Unknown ☐

OUTCOME OF THE CARDIAC EVENT (please select only ONE):

☐ Ongoing ☐ Fatal ☐ Recovering ☐ Recovered (Date of resolution ____/_____/_____) ☐ Recovered with sequalae (Date of resolution ____/_____/_____) ☐ Unknown

TREATMENT OF THE EVENT:

TAGRISSO® Start date: **Action taken with osimertinib:**
☐ None ☐ Dose reduced ☐ Permanently discontinued (Date of last dose: ___/____/_____) If discontinued, did the event recover/improve? Yes ☐ No ☐ ☐ Temporary stop (Stop date: ___/____/_____ Re-Start date: ___/____/_____) Did the event recover/improve upon withdrawal of osimertinib? Yes ☐ No ☐ Did the event re-occur upon re-start of osimertinib? Yes ☐ No ☐
What, if any, treatment was given to the patient for the reported event?
_____ _____ _____ _____ _____ _____ _____

Please complete the below section if the reported cardiac event was fatal:

Was an autopsy performed?	Yes ☐ No ☐
If yes, please provide the results and/or attach a copy of the autopsy report.	_____ _____ _____ _____ _____ _____

Reporter's Signature: _____Date: _____

Free text space for any additional details relevant to the heart failure event not captured above.

7.1.3 Questionnaire for adverse events associated with rhabdomyolysis

Case ID: (For official use only)

Thank you for reporting an adverse event of/related to rhabdomyolysis experienced by a patient under your care receiving TAGRISSO® (osimertinib). To better understand and effectively characterise rhabdomyolysis reports received from TAGRISSO® patients, we require some further information to make a full assessment. Please provide additional information below, if available to you. Any additional data we receive is useful for us to preserve the safety of patients and provide the best information for prescribers to preserve safety of our patients.

Endocrine conditions, metabolic and Genetic Disorders ☐ Metabolic or genetic disorders (e.g. disorders of muscle carbohydrate metabolism, carnitine palmitoyltransferase deficiency) ☐ Thyroid disorder (hypo-/hyperthyroidism) ☐ Other endocrine abnormality (e.g. diabetic ketoacidosis) **Temperature-Related Conditions** ☐ Hypothermia ☐ Hyperthermia ☐ Malignant hyperthermia ☐ Neuroleptic malignant syndrome **Physical Trauma and Injury** ☐ Exertional rhabdomyolysis ☐ Crush injury or trauma ☐ Electrical injuries ☐ Seizures/Epilepsy	**Renal impairment** ☐ Baseline renal impairment **Infectious Causes** ☐ Viral infection (e.g. EBV, CMV, HIV, Herpes virus) ☐ Bacterial infection **Substance-Related Conditions** ☐ Alcoholism or alcohol abuse (please specify) ☐ Drug or substance abuse (please specify) **Vascular Conditions** ☐ Arterial thrombosis **Envenomation** ☐ Snake or insect envenomation (please specify) **Other relevant:** ☐ Please specify: _____
☐ None of the above	

Was there any evidence of drug-drug-interactions leading up to this event?

☐ No

☐ Unknown

☐ Yes. Please specify medications/supplements and interactions:

_____

_____

_____

Description of the event

Details of presenting symptoms:

Did the patient present with any of the following signs or symptoms? Check all that apply:

Muscle-related symptoms ☐ Muscle tenderness ☐ Muscle stiffness ☐ Muscle aching (myalgia) ☐ Muscle weakness ☐ Muscle spasms ☐ Muscle hypotonicity ☐ Muscle hypertonicity ☐ Muscle swelling **Functional/mobility issues** ☐ Walking difficulty ☐ Frequent falls ☐ Poor balance ☐ Joint pain	**Systemic/general symptoms** ☐ Fatigue ☐ General weakness **Renal/urinary findings** ☐ Dark or red color urine ☐ Acute renal failure **Serious complications** ☐ Compartment syndrome ☐ Disseminated intravascular coagulation ☐ Respiratory difficulty ☐ Severe electrolyte disturbances
☐ None of the above	

Laboratory findings:

Please provide any laboratory results drawn at the time points below:

Diagnostic Test	Normal Range (with units)	Baseline level (prior to first dose)	Onset of symptoms / adverse event	Resolution of symptoms / adverse event	Peak value	Other – specify (Date __/__)
Serum Creatine Phosphokinase (CK / CPK)						
Serum Myoglobin						
Urine Myoglobin						
Serum Creatinine						
Creatinine Clearance Estimated with Cockroft-Gault formula or measured (timed urine collection)						
Serum Potassium						
Serum Calcium						
Other (e.g., muscle biopsy) – please specify:						

Treatment and outcome of the event

Action taken with osimertinib as a result of the event:

☐ Continued
☐ Dose reduced (Date __/___/____)
☐ Temporary stop (Stop date: ___/____/_____ Re-Start date: ___/____/_____)
☐ Permanently discontinued
☐ Not Applicable
☐ Other (please specify): _____

Did the event recover/improve upon withdrawal of osimertinib? Yes ☐ No ☐ Unknown ☐
Did the event re-occur upon re-start of osimertinib? Yes ☐ No ☐ Unknown ☐
☐ Other (please specify): _____

What, if any, treatment was given to the patient for the reported event?
_____

Free text space for any additional information pertinent to the Rhabdomyolysis event

Reporter's Signature: _____ Date: _____

7.2 ANNEX 8: Summary of changes to the risk management plan over time

7.2.1 Version History

Version	Approval date Procedure	Change
4.0	13 February 2016 EMEA/H/C/004124/0000	Version 4.0 of the EU-RMP was the first approved osimertinib EU RMP following the initial Marketing Authorisation Approval application.
5.0	27 January 2017 EMEA/H/C/004124/II/0004	Version 5.0 of the EU-RMP was created in order to update the document with the results of Study D5160C00020, which was conducted to address the area of missing information of 'TAGRISSO absolute oral bioavailability'. The following significant changes were therefore made in this EU RMP version: • 'TAGRISSO absolute oral bioavailability' was removed as an area of missing information. • Study D5160C00020, which had been listed as a Category 3 study in the previous osimertinib EU-RMP, was removed from the Pharmacovigilance Plan (Part III). Additional administrative changes to the EU RMP were also made to this version to reflect the current approval status of TAGRISSO.
6.0	25 April 2017 EMEA/H/C/004124/II/0009/G	Version 6.0 of the EU RMP was created in order to provide updated information pertaining to the overall safety profile of osimertinib following the interpretation of the primary analysis of data from the Phase III Study D5160C00003 (AURA3) study. During the interpretation of data from AURA3, the overall safety profile of osimertinib was also reassessed using pooled datasets comprising integrated safety data from cross-programme pivotal osimertinib Phase I to III studies. The following significant changes were therefore made in this EU RMP version: • The EU RMP was updated throughout with the results of the integrated analysis of study D5160C00003 (AURA3). • Study D5160C00003 (AURA3), which had been classified as a Category 2 study in the previous osimertinib EU-RMP, was removed from the Pharmacovigilance Plan (Part III). • The safety concern of 'Changes in cardiac contractility' was added as an important potential risk. • The previously described important potential risk of 'Ocular toxicity' was renamed 'Severe ocular effects'.

Version	Approval date Procedure	Change
7.0	06 July 2017 EMEA/H/C/004124/II/0015 EMEA/H/C/004124/II/0016	Version 7.0 of the EU-RMP was created in order to update the document with the results of nonclinical Study BS000760-92, which was conducted to address the area of missing information of 'Potential for transporter inhibition', and to report the results of Study D5160C00017. The following significant changes were therefore made in this EU RMP version: • 'Potential for transporter inhibition' was removed as an area of missing information. • Study BS000760-92, which had been listed as a Category 3 study in the previous osimertinib EU-RMP, was removed from the Pharmacovigilance Plan (Part III). • Study D5160C00017, which had been listed in the Pharmacovigilance Plan (Part III) of the previous osimertinib EU-RMP as a Category 3 study which had the potential to yield additional safety characterisation information on a number of existing safety concerns (namely interstitial lung disease, QT prolongation, severe skin reactions, severe diarrhoea, severe ocular effects, hepatotoxicity and long term exposure to osimertinib) was removed from the Pharmacovigilance Plan (Part III).

Version	Approval date Procedure	Change
8.0	Not approved. EMEA/H/C/04124/II/0019	Version 8.0 of the EU RMP was created in order to provide updated information pertaining to the overall safety profile of osimertinib following the interpretation of the primary analysis of data from the Phase III Study D5160C00007 (FLAURA) study. Furthermore, following the release of the revised 'Guideline on Good Pharmacovigilance Practices: Module V – Risk management systems (Rev. 2)', the format and contents of the EU RMP was updated to adopt the latest EU RMP template and to align the RMP with the updated principles on the classification of safety concerns. The following significant changes were therefore made in this EU RMP version: • Removal of the previously described important identified risk of 'QT prolongation', as no adverse clinical consequences of this effect have been observed with the use of osimertinib treatment. • Following a review of all available data, the previously described important potential risks of 'Developmental toxicity', 'Severe skin reactions', 'Severe diarrhoea', 'Severe ocular effects', and 'Hepatotoxicity' have been removed from the list of current safety concerns. • The previously described important potential risk of 'Changes in cardiac contractility' has been renamed 'Cardiac failure'. The rationale for the change in the name of this safety concern is the adoption of the revised principles introduced with the updated GVP V (Rev 2) guideline and the updated definition of a risk (as an undesirable clinical outcome) within the osimertinib EU RMP framework, and not as a result of any new data or safety signal. • Following a review of all available data, the previously described areas of missing information of 'Long term exposure to osimertinib', 'Use during lactation', 'Use in patients with ECOG performance status ≥2', 'Use in patients with symptomatic brain metastases', and 'Use in very elderly patients (≥75 years old)' have been removed from the list of current safety concerns. • Updates to all sections of the EU RMP to include data from the recently reported FLAURA study into the integrated safety analysis of osimertinib. • All section of the RMP have been updated to adopt the latest EU RMP template.

Version	Approval date Procedure	Change
9.0	Not approved. EMEA/H/C/004124/II/0021 EMEA/H/C/004124/II/0022 EMEA/H/C/004124/II/0023 EMEA/H/C/004124/II/0024	Version 9.0 of this EU RMP was created in order to provide updated information pertaining to the areas of missing information 'Use in patients with moderate or severe hepatic impairment', 'Potential for P-gp inhibition' and 'Potential for drug-drug interactions between osimertinib and non-CYP3A4 mediated PXR substrates' which became available following the primary analysis of data from the Category 3 Studies D5160C00008 and D5160C00036. Furthermore, the Category 3 ASTRIS and CAURAL studies were removed from the Pharmacovigilance (PV) Plan as they are no longer anticipated to provide additional meaningful data on the important identified risk of ILD. The following significant changes were therefore made in this EU RMP version: • PASS studies D5160C00008 and D6160C000036 completed and removed from the PV Plan. • Following the primary analysis of the PASS studies D5160C00008 and D5160C00036, missing information 'Use in patients with moderate or severe hepatic impairment', 'Potential for P-gp inhibition' and 'Potential for drug-drug interactions between osimertinib and non-CYP3A4 mediated PXR substrates' were removed from the RMP • PASS studies ASTRIS and CAURAL were removed from the PV Plan as they are no longer anticipated to provide additional meaningful data on the important identified risk of ILD and no longer meet the criteria for PASS.
10.0	07 June 2018 EMEA/H/C/04124/II/0019	Version 10.0 of the EU RMP was created in order to include the 2 items of missing information ('patients with ECOG performance status ≥2' and 'patients with symptomatic brain metastases') which were proposed for removal in version 8.0 (procedure number EMEA/H/C/04124/II/0019) but retained at the request of the EMA, pending data from the BLOOM study (D6030C00001).
11.0	13 July 2018 EMEA/H/C/004124/II/0021 EMEA/H/C/004124/II/0022 EMEA/H/C/004124/II/0023 EMEA/H/C/004124/II/0024	Version 11.0 of this EU-RMP has been created based on the recently approved v10.0 EU-RMP, as per an agreement with the European Medicines Agency (EMA), to submit a consolidated EU-RMP for Tagrisso which combines the changes from the review of EU-RMP v9.0 (procedure number: EMEA/H/C/004124/II/0021; EMEA/H/C/004124/II/0022; EMEA/H/C/004124/II/0023; EMEA/H/C/004124/II/0024) and EU-RMP v10.0 (procedure number: EMEA/H/C/04124/II/0019) in order to provide a final comprehensive RMP that reflects all pertinent changes.

Version	Approval date Procedure	Change
12.0 Succession 1	03 February 2019 EMEA/H/C/04124/II/0026	Version 12.0 of this EU-RMP has been created in order to update the document with newly available data following the completion of the BLOOM (D6030C00001) study. BLOOM has subsequently been removed from the PV Plan (Part III: 2) as an additional PV activity (Category 3 PASS) and the corresponding items of missing information 'use in patients with ECOG performance status ≥2' and 'use in patients with symptomatic brain metastases' have been removed as safety concerns (Part II: 7.2/7.3).
13	19 September 2019 (Succession 3) EMEA/H/C/004124/II/0029	The following significant changes were therefore made in this EU RMP version: • PASS study D5160C00035 completed and removed from the PV Plan. • missing information 'Use in patients with severe renal impairment' was removed from the RMP. • Administrative changes were made to further align the EU RMP with the GVP V rev 2 template
14	21 May 2021(Succession 3) EMEA/H/C/004124/II/0039/G	Version 14 of the EU-RMP was created in order to provide updated information to support the new indication for TAGRISSO following the interpretation of the primary analysis of data from the Phase III Study D5164C00001 (ADAURA) study. The EU-RMP has also been updated with new information arising from the completion of two animal carcinogenicity studies. No new safety concerns were identified and there were no significant changes to the existing safety concerns. Correction of typographical error in Table II-13 Inclusion of Post-Authorisation Efficacy study table in Part IV Addition of Annex 5
15	28 September 2023 (Succession 2) EMEA/H/C/004124/II/0052	Reclassification of cardiac failure from an important potential risk to an important identified risk following the EMA imposition (procedure EMEA/H/C/PSUSA/00010472/202111) to include cardiac failure as an ADR in section 4.8 of the EU SmPC. Removal of the completed D5164C00001 (ADAURA) study from list of ongoing post-authorisation efficacy studies as specific EU obligations. Addition of results from the rat carcinogenicity studies. Removal of Annex 5.

Version	Approval date Procedure	Change
16	28 June 2024 EMEA/H/C/004124/II/0053	Update to include the new indication TAGRISSOTM in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of adult patients with locally advanced or metastatic NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations (FLAURA2). Formatting/structure change to Annex 4 ILD TFuQ. No change in the content of the questionnaire.
17	19 December 2024 EMEA/H/C/004124/II/0056	• Update to include the new indication TAGRISSO™ as monotherapy for- the treatment of adult patients with locally advanced, unresectable (Stage III) NSCLC whose tumours have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations and whose disease has not progressed during or following platinum-based chemoradiation therapy, following completion of primary analysis from LAURA study in Part I and Part VI. • Updated epidemiology section with information regarding unresectable stage III NSCLC, addition of LAURA exposure data, updated post-authorization exposure data, and included data from LAURA for identified and potential risks in Part II.
18	Not applicable	Safety concerns Important Potential Risk: Rhabdomyolysis is added as new important potential risk

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