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 the risks and uncertainties (missing information) of TAGRISSO™.

The TAGRISSO™ summary of product characteristics (SmPC) and its package leaflet (PL) 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 which is part of the European Public Assessment Report (EPAR).

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

I: THE MEDICINE AND WHAT IT IS USED FOR

TAGRISSO™ is authorised for the 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 adult patients with locally advanced or metastatic NSCLC with activating epidermal growth factor receptor (EGFR) mutations or the adjuvant treatment after complete tumour resection in adult patients with non-small cell lung cancer (NSCLC) whose tumours have epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) substitution mutations. It contains osimertinib as the active substance and it is given as a 40mg or 80mg tablet for once daily oral administration.

Further information about the evaluation of the benefits of TAGRISSO can be found in the TAGRISSO EPAR, including in its plain-language summary, available on the EMA website (http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004124/human_med_001961.jsp&mid=WC0b01ac058001d124).

II: 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.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

II: 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 TAGRISSO™. 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 1 List of important risks and missing information

Important identified risks	• Interstitial lung disease
Important potential risks	• Cardiac failure
Missing information	• None

II: 2 SUMMARY OF IMPORTANT RISKS

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

Table 2 Important identified risks

Interstitial lung disease (ILD)	
Evidence for linking the risk to the medicine	The development of ILD-like events was prospectively identified as a potential safety concern from a review of the use of other EGFR TKI medications and was therefore considered a topic of special interest in the osimertinib clinical development programme. Following evaluation of all available data, ILD was added as a listed ADR in Section 4.8 (*Undesirable effects*) of the osimertinib SmPC, and wording relating to the detection and management of potential/confirmed events of ILD was implemented in Section 4.4 *(Special warnings and precautions for use)* and Section 4.2 *(Posology and method of administration).* The recent ADAURA placebo-controlled trial provides conclusive evidence of the osimertinib-related nature of ILD observed in these patients. No patients in the placebo arm were diagnosed with ILD, as opposed to 10 patients in the osimertinib arm who were diagnosed with ILD. All reported events were considered to be either mild or moderate in severity (6 patients [1.8%] with maximum CTCAE Grade 1 events, and 4 patients [1.2%] with maximum CTCAE Grade 2 events), and all patients were reported to have recovered. Only 1 event was reported as an SAE (due to hospitalisation).

Table 2 Important identified risks

Interstitial lung disease (ILD)	
Risk factors and risk groups	ILD has been noted as a potentially life-threatening complication of treatment with other EGFR TKI medications (erlotinib, gefitinib and afatinib), and is typically observed within the first month of therapy. Risk factors include previous chemotherapy treatment, previous radiation therapy to the lungs, pre-existing parenchymal lung disease, metastatic lung disease, and concomitant pulmonary infection (Cataldo et al 2011). 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 EGFR mutation associated with EGFR 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). The relationship between potential risk factors for developing ILD in patients who receive TAGRISSO™ treatment has been explored using simple univariate analyses for specific risk factors (as identified from literature) presenting the ILD rate in each level of the factor with unadjusted Odds Ratios (OR) and corresponding 95% CIs comparing the ILD rate between levels of the factor. Due to the low number of ILD events it is difficult to discern any clear differences. Variability in the risk of ILD is observed across potential risk factors but all confidence intervals are wide and overlapping. The only factor that demonstrated an Odds Ratio (OR) with a lower bound 95% CI above 1 was ethnicity, with the risk of developing ILD in Japanese Asian patients being somewhat higher than for patients of non-Asian ethnicity in rest of world (ROW): OR 3.50, 95% CI (1.48, 8.28).
Risk minimisation measures	<u>*Routine risk minimisation measures*</u>*:* • SmPC Section 4.8 (*Undesirable effects*). • SmPC Section 4.2 (*Posology and method of administration*) and Section 4.4 (*Special warnings and special precautions for use*).

Table 3 Important potential risks

Cardiac failure	
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

Table 3	Important potential risks
Cardiac failure	
	HER2 inhibitors (e.g. afatinib) have been shown not to be associated with this risk (Ewer et al 2015). Whilst there is no direct evidence that inhibition of erbB2 is linked with cardiac failure or LVEF decreases, the understanding of the role of erbB2 inhibitors in cardiac function is not fully elucidated, and there is therefore a potential risk of a role for erbB2 in the stress/recovery response to cardiac damage (e.g. myocardial infarction). In consideration of this mechanistic hypothesis, AstraZeneca, in consultation with internal and external experts, put in place a clinical cardiac monitoring plan in order to evaluate the potential impact of osimertinib on LVEF. Routine monitoring of AEs, including external cardiologist review, assess a potential drug involvement in the aetiology and recovery of cardiac events. 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. Based on the complete body of evidence available, the overall interpretation does not support a causal relationship between osimertinib and changes in cardiac contractility manifesting as either LVEF decreases or heart failure. Nevertheless, considering the potential impact of LVEF decreases on individual patients with concurrent cardiac risk factors, and as a drug effect cannot be ruled out completely, the potential risk of cardiac failure (so named to reflect a potential adverse clinical outcome measure of changes in cardiac contractility) remains under evaluation as an important potential risk.
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

Table 3	Important potential risks
Cardiac failure	
	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:* • SmPC Section 4.4 (*Special warnings and special precautions for use*).

Table 4	Missing information
There are currently no outstanding items of missing information for TAGRISSO.	

II: 3 POST AUTHORISATION DEVELOPMENT PLAN

II: 3.1 Studies which are conditions of the marketing authorisation

The following study is a condition of the marketing authorisation for TAGRISSO in the EU.

D5164C00001 (ADAURA): A Phase III, Double-blind, Randomized, Placebo-Controlled Multi-centre, study to assess the efficacy and safety of AZD9291 versus Placebo, in Patients with Epidermal Growth Factor Receptor Mutation Positive Stage IB-IIIA Non-small Cell Lung Carcinoma, following Complete Tumour Resection With or Without Adjuvant Chemotherapy.

Purpose of study:

Primary objective:

To assess the efficacy of AZD9291 compared to placebo as measured by disease free survival (DFS). (Primary outcome measure includes DFS by investigator assessment).

Secondary objectives:

To further assess the efficacy of AZD9291 compared with placebo. (Secondary outcome measures include DFS rate at 2, 3, 4 & 5 years, Overall Survival (OS), and OS rate at 2,3,4 and 5 years at the time of primary analysis).

Exploratory objectives:

To further assess the efficacy of AZD9291 compared with placebo (Exploratory outcome measures included OS and OS rate at 2, 3, 4, and 5 years).

To assess the efficacy of AZD9291 in patients with confirmed baseline T790M status (positive / negative) using a high sensitivity method yet to be determined (retrospective). Exploratory outcome measures included DFS by investigator assessment and OS.

II: 3.2 Other studies in post-authorisation development plan

There are no other studies planned or ongoing in the post-authorisation development plan.