ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 40 mg film-coated tablets
TAGRISSO 80 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

TAGRISSO 40 mg tablets
Each tablet contains 40 mg osimertinib (as mesylate).

TAGRISSO 80 mg tablets
Each tablet contains 80 mg osimertinib (as mesylate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

TAGRISSO 40 mg tablets
Beige, 9 mm, round, biconvex tablet, debossed with “AZ” and “40” on one side and plain on the reverse.

TAGRISSO 80 mg tablets
Beige, 7.25 x 14.5 mm, oval, biconvex tablet, debossed with “AZ” and “80” on one side and plain on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

TAGRISSO is indicated 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).

4.2 Posology and method of administration

Treatment with TAGRISSO should be initiated by a physician experienced in the use of anticancer therapies.

When considering the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC, it is necessary that EGFR T790M mutation status is determined. EGFR T790M mutation status should be determined by using a validated test method (see section 4.4).

Posology
The recommended dose is 80 mg osimertinib once a day until disease progression or unacceptable toxicity.

If a dose of TAGRISSO is missed, the dose should be made up unless the next dose is due within 12 hours.

TAGRISSO can be taken with or without food at the same time each day.

Dose adjustments
Dosing interruption and/or dose reduction may be required based on individual safety and tolerability. If dose reduction is necessary, then the dose should be reduced to 40 mg taken once daily.

Dose reduction guidelines for adverse reactions toxicities are provided in Table 1.

Table 1. Recommended dose modifications for TAGRISSO

Target organ	**Adverse reaction**[a]	**Dose modification**
Pulmonary	ILD/Pneumonitis	Permanently discontinue TAGRISSO
Cardiac	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold TAGRISSO until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of serious arrhythmia	Permanently discontinue TAGRISSO
Other	Grade 3 or higher adverse reaction	Withhold TAGRISSO for up to 3 weeks
	If Grade 3 or higher adverse reaction improves to Grade 0-2 after withholding of TAGRISSO for up to 3 weeks	TAGRISSO may be restarted at the same dose (80 mg) or a lower dose (40 mg)
	Grade 3 or higher adverse reaction that does not improve to Grade 0-2 after withholding for up to 3 weeks	Permanently discontinue TAGRISSO

[a] Note: The intensity of clinical adverse events graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.
ECGs: Electrocardiograms; QTc: QT interval corrected for heart rate

Special populations
No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status (see section 5.2).

Hepatic impairment
No clinical studies have been conducted to specifically evaluate the effect of hepatic impairment on the pharmacokinetics of osimertinib. No dose adjustment is recommended in patients with mild hepatic impairment (total bilirubin ≤upper limit of normal (ULN) and aspartate aminotransferase (AST) >ULN or total bilirubin >1.0 to 1.5x ULN and any AST) or moderate hepatic impairment (total bilirubin between 1.5 to 3 times ULN and any AST) but caution should be used when administering TAGRISSO to these patients. The safety and efficacy of this medicinal product has not been established in patients with severe hepatic impairment. Until additional data become available, use in patients with severe hepatic impairment is not recommended (see section 5.2).

Renal impairment
No clinical studies have been conducted to specifically evaluate the effect of renal impairment on the pharmacokinetics of osimertinib. No dose adjustment is recommended in patients with mild, moderate, or severe renal impairment. Limited data are available in patients with severe renal impairment. The safety and efficacy of this medicinal product has not been established in patients with end-stage renal disease [creatinine clearance (CLcr) <15 mL/min, calculated by the Cockcroft and Gault equation], or on dialysis. Caution should be exercised when treating patients with severe and end-stage renal impairment (see section 5.2).

Paediatric population
The safety and efficacy of TAGRISSO in children or adolescents aged less than 18 years have not been established. No data are available.

Method of administration
This medicinal product is for oral use. The tablet should be swallowed whole with water and it should not be crushed, split or chewed.

If the patient is unable to swallow the tablet, the tablet may first be dispersed in 50 mL of non-carbonated water. It should be dropped in the water, without crushing, stirred until dispersed and immediately swallowed. An additional half a glass of water should be added to ensure that no residue remains and then immediately swallowed. No other liquids should be added.

If administration via nasogastric tube is required, the same process as above should be followed but using volumes of 15 mL for the initial dispersion and 15 mL for the residue rinses. The resulting 30 mL of liquid should be administered as per the naso-gastric tube manufacturer's instructions with appropriate water flushes. The dispersion and residues should be administered within 30 minutes of the addition of the tablets to water.

4.3 Contraindications

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

St. John's Wort should not be used together with TAGRISSO (see section 4.5).

4.4 Special warnings and precautions for use

Assessment of EGFR T790M mutation status
When considering the use of TAGRISSO as a treatment for locally advanced or metastatic NSCLC, it is important that the EGFR T790M mutation status is determined. A validated test should be performed using either tumour DNA derived from a tissue sample or circulating tumour DNA (ctDNA) obtained from a plasma sample.

Only robust, reliable and sensitive tests with demonstrated utility for the determination of T790M mutation status of tumour derived DNA (from a tissue or a plasma sample) should be used.

Positive determination of T790M mutation status using either a tissue-based or plasma-based test indicates eligibility for treatment with TAGRISSO. However, if a plasma-based ctDNA test is used and the result is negative, it is advisable to follow-up with a tissue test wherever possible due to the potential for false negative results using a plasma-based test.

Interstitial Lung Disease (ILD)
Severe, life-threatening or fatal Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) have been observed in patients treated with TAGRISSO in clinical studies. Most cases improved or resolved with interruption of treatment. Patients with a past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies (see section 4.8).

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 3.5% and were fatal in 0.6% of the 833 patients who received TAGRISSO in AURA studies. The incidence of ILD was 8.2% in patients of Japanese ethnicity, 1.9% in patients of Asian ethnicity and 2.9% in non-Asian patients (see section 4.8).

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. Treatment with this medicinal product should be interrupted pending investigation of these symptoms. If ILD is diagnosed, TAGRISSO should be permanently discontinued and appropriate treatment initiated as necessary.

QTc interval prolongation
QTc interval prolongation occurs in patients treated with TAGRISSO. QTc interval prolongation may lead to an increased risk for ventricular tachyarrhythmias (e.g. torsade de pointes) or sudden death. No arrhythmic events were reported in AURAex or AURA2 (see section 4.8). Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 ms) were excluded from these studies (see section 4.8).

When possible, the use of osimertinib in patients with congenital long QT syndrome should be avoided. Periodic monitoring with electrocardiograms (ECGs) and electrolytes should be considered in patients with congestive heart failure, electrolyte abnormalities, or those who are taking medicinal products that are known to prolong the QTc interval. Treatment should be withheld in patients who develop a QTc interval greater than 500 msec on at least 2 separate ECGs until the QTc interval is less than 481 msec or recovery to baseline if the QTc interval is greater than or equal to 481 msec, then resume TAGRISSO at a reduced dose as described in Table 1. Osimertinib should be permanently discontinued in patients who develop QTc interval prolongation in combination with any of the following: Torsade de pointes, polymorphic ventricular tachycardia, signs/symptoms of serious arrhythmia.

Changes in cardiac contractility
Across clinical trials, Left Ventricular Ejection Fraction (LVEF) decreases greater than or equal to 10% and a drop to less than 50% occurred in 4.0% (26/655) of patients treated with TAGRISSO who had baseline and at least one follow-up LVEF assessment. Based on the available clinical trial data, it is not possible to determine a causal relationship between effects on changes in cardiac contractility and TAGRISSO. In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.

Keratitis
Keratitis was reported in 0.7% (n=6) of the 833 patients treated with TAGRISSO in the AURA studies. Patients presenting with signs and symptoms suggestive of keratitis such as acute or worsening: eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist (see section 4.2 Table 1).

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Strong CYP3A4 inducers can decrease the exposure of osimertinib. Osimertinib may increase the exposure of BCRP substrates.

Active substances that may increase osimertinib plasma concentrations
In vitro studies have demonstrated that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5. In a clinical pharmacokinetic study in patients, co-administration with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure of osimertinib (area under the curve (AUC) increased by 24% and C_{max} decreased by 20%). Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib. Further catalyzing enzymes have not been identified.

Active substances that may decrease osimertinib plasma concentrations
In a clinical pharmacokinetic study in patients, the steady-state AUC of osimertinib was reduced by 78% when co-administered with rifampicin (600 mg daily for 21 days). Similarly, the exposure to metabolite, AZ5104 decreased by 82% for the AUC and 78% for C_{max}. It is recommended that concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin and carbamazepine) with TAGRISSO should be avoided. Moderate CYP3A4 inducers (e.g. bosentan, efavirenz, etravirine, modafinil) may also decrease osimertinib exposure and should be used with caution, or avoided when possible. There are no clinical data available to recommend a dose adjustment of TAGRISSO. Concomitant use of St. John's Wort is contraindicated (see section 4.3).

Effect of gastric acid reducing active substances on osimertinib
In a clinical pharmacokinetic study, co-administration of omeprazole did not result in clinically relevant changes in osimertinib exposures. Gastric pH modifying agents can be concomitantly used with TAGRISSO without any restrictions.

Active substances whose plasma concentrations may be altered by TAGRISSO
Based on *in vitro* studies, osimertinib is a competitive inhibitor of BCRP transporters.

In a clinical PK study, co-administration of TAGRISSO with rosuvastatin (sensitive BCRP substrate) increased the AUC and C_{max} of rosuvastatin by 35% and 72%, respectively. Patients taking concomitant medications with disposition dependent upon BCRP and with narrow therapeutic index should be closely monitored for signs of changed tolerability of the concomitant medication as a result of increased exposure whilst receiving TAGRISSO (see section 5.2).

In a clinical PK study, co-administration of TAGRISSO with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and C_{max} of simvastatin by 9% and 23% respectively. These changes are small and not likely to be of clinical significance. Clinical PK interactions with CYP3A4 substrates are unlikely. Pregnane X Receptor (PXR) regulated enzyme interactions other than CYP3A4 have not been studied. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

4.6 Fertility, pregnancy and lactation

Contraception in males and females
Women of childbearing potential should be advised to avoid becoming pregnant while receiving TAGRISSO. Patients should be advised to use effective contraception for the following periods after completion of treatment with this medicinal product: at least 2 months for females and 4 months for males. A risk for decreased exposure of hormonal contraceptives cannot be excluded.

Pregnancy
There are no or limited amount of data from the use of osimertinib in pregnant women. Studies in animals have shown reproductive toxicity (embryolethality, reduced foetal growth, and neonatal death, see section 5.3). Based on its mechanism of action and preclinical data, osimertinib may cause foetal harm when administered to a pregnant woman. TAGRISSO should not be used during pregnancy unless the clinical condition of the woman requires treatment with osimertinib.

Breast-feeding
It is not known whether osimertinib or its metabolites are excreted in human milk. There is insufficient information on the excretion of osimertinib or its metabolites in animal milk. However, osimertinib and its metabolites were detected in the suckling pups and there were adverse effects on pup growth and survival (see section 5.3). A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with TAGRISSO.

Fertility
There are no data on the effect of TAGRISSO on human fertility. Results from animal studies have shown that osimertinib has effects on male and female reproductive organs and could impair fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

TAGRISSO has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Studies in EGFR T790M mutation-positive NSCLC patients previously treated with an EGFR TKI
The data described below reflect exposure to TAGRISSO in 690 patients with EGFR T790M mutation-positive non-small cell lung cancer who received prior EGFR TKI therapy. These patients received TAGRISSO at a dose of 80 mg daily in one randomised Phase 3 study (AURA3-second line only) and 2 single-arm studies (AURAex and AURA2-second line or greater) (see section 5.1). In AURA3, the median duration of study treatment was 8.1 months for patients in the TAGRISSO arm (n=279) and 4.2 months for patients in the chemotherapy arm (n=136). The majority of patients in the pooled Phase 2 studies were heavily pre-treated: 68% had received at least 2 prior treatment regimens and 46% had received 3 or more prior lines of therapy. In addition to EGFR-TKI therapy, approximately two thirds (63%) of patients had received prior platinum-based chemotherapy. The overall median duration of study treatment in AURAex and AURA2 was 13 months (N=411). Most adverse reactions were Grade 1 or 2 in severity. The most commonly reported adverse drug reactions (ADRs) were diarrhoea (44%) and rash (41%). Grade 3 and Grade 4 adverse events across both studies were 26% and 2%, respectively. In patients treated with TAGRISSO 80 mg once daily, dose reductions due to adverse reactions occurred in 2.3% of the patients. Discontinuation due to adverse reactions or abnormal laboratory parameters was 6.5%.

Patients with a past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD were excluded from clinical studies. Patients with clinically important abnormalities in rhythm and conduction as measured by resting electrocardiogram (ECG) (e.g. QTc interval greater than 470 ms) were excluded from these studies. Patients were evaluated for LVEF at screening and every 12 weeks thereafter.

Tabulated list of adverse reactions
Adverse reactions have been assigned to the frequency categories in Table 2 where possible based on the incidence of comparable adverse event reports in a pooled dataset from the of 690 previously treated EGFR T790M mutation positive patients who received TAGRISSO at a dose of 80 mg daily in the AURA3, AURAex and AURA 2 studies.

Adverse reactions are listed according to system organ class (SOC) in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category for each adverse reaction is based on the CIOMS III convention and is defined as: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from available data). Table 2 summarises the adverse reactions from AURAex (Phase 2), AURA 2 and AURA3 studies for patients receiving at least one dose of TAGRISSO.

Table 2. Adverse reactions reported in AURA[a] studies

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3 or higher
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[c]	Common (3.2%)[d]	1.3%
Gastrointestinal disorders	Diarrhoea	Very common (44%)	1.0%
	Stomatitis	Very common (15%)	0%
Eye disorders	Keratitis[e]	Uncommon (0.9%)	0%

MedDRA SOC	MedDRA term	CIOMS descriptor/ overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3 or higher
Skin and subcutaneous tissue disorders	Rash[f]	Very common (41%)	0.7%
	Dry skin[g]	Very common (29%)	0%
	Paronychia[h]	Very common (27%)	0%
	Pruritus[i]	Very common (15%)	0%
Investigations	QTc interval prolongation[j]	Uncommon (0.7%)	
(Findings based on test results presented as CTCAE grade shifts)	Platelet count decreased[k]	Very common (54%)	2.1%
	Leucocytes decreased[k]	Very common (66%)	2.4%
	Neutrophils decreased[k]	Very common (32%)	4.3%

[a] Data is cumulative from Phase 3 (AURA3) and Phase 2 (AURAex and AURA 2) studies; only events for patients receiving at least one dose of TAGRISSO are summarised.
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0.
[c] Includes cases reported within the clustered terms: Interstitial lung disease and pneumonitis.
[d] 4 CTCAE grade 5 events (fatal) were reported.
[e] Includes cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect, corneal defect.
[f] Includes cases reported within the clustered terms for rash AEs: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and dermatitis acneiform.
[g] Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema.
[h] Includes cases reported within the clustered terms: Nail bed disorder, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail toxicity, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, paronychia.
[i] Includes cases reported within the clustered terms: pruritus, pruritus generalised, eyelid pruritus.
[j] Represents the incidence of patients who had a QTcF prolongation >500msec.
[k] Represents the incidence of laboratory findings, not of reported adverse events.

Table 3. ADRs in AURA3[a] study

MedDRA SOC	TAGRISSO overall frequency (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)	
NCI Grade	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
MedDRA Preferred Term				
Respiratory, thoracic and mediastinal disorders				
Interstitial Lung Disease[b,c]	3.6	0.4	0.7	0.7
Eye disorders				
Keratitis[d]	1.1	0	0.7	0
Gastrointestinal disorders				
Diarrhoea	41	1.1	11	1.5
Stomatitis	15	0	15	1.5

MedDRA SOC	TAGRISSO overall frequency (N=279)		Chemotherapy (Pemetrexed/Cisplatin or Pemetrexed/Carboplatin) overall frequency (N=136)	
NCI Grade	Any Grade (%)	Grade 3 or higher (%)	Any Grade (%)	Grade 3 or higher (%)
Skin and subcutaneous tissue disorders				
Rash[e]	34	0.7	5.9	0
Dry skin[f]	23	0	4.4	0
Paronychia[g]	22	0	1.5	0
Pruritus[h]	13	0	5.1	0
Investigations				
QTc interval prolongation[i]	1.4	0	0.7	0
(Findings based on test results presented as CTCAE grade shifts)				
Platelet count decreased[j]	46	0.7	48	7.4
Leukocytes decreased[j]	61	1.1	75	5.3
Neutrophils decreased[j]	27	2.2	49	12

[a] Data is cumulative from AURA3 study; only events for patients receiving at least one dose of TAGRISSO are summarised.
[b] Includes cases reported within the clustered terms: Interstitial lung disease and pneumonitis.
[c] 1 CTCAE grade 5 event (fatal) was reported.
[d] Includes cases reported within the clustered terms: Keratitis, punctate keratitis, corneal erosion, corneal epithelium defect, corneal defect.
[e] Includes cases reported within the clustered terms for rash AEs: Rash, rash generalised, rash erythematous, rash macular, rash maculo-papular, rash papular, rash pustular, erythema, folliculitis, acne, dermatitis and dermatitis acneiform.
[f] Includes cases reported within the clustered terms: Dry skin, skin fissures, xerosis, eczema.
[g] Includes cases reported within the clustered terms: Nail disorders, nail bed disorders, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, paronychia.
[h] Includes cases reported within the clustered terms: pruritus, pruritus generalised, eyelid pruritus.
[i] Represents the incidence of patients who had a QTcF prolongation >500msec.
[j] Represents the incidence of laboratory findings, not of reported adverse events.

Safety findings in the single-arm Phase 2 AURAex and AURA2 studies were generally consistent with those observed in the AURA3 TAGRISSO arm. No additional or unexpected toxicity has been observed and adverse events have been aligned in type, severity and frequency.

Description of selected adverse reactions

Interstitial lung disease (ILD)
In the AURA studies, the incidence of ILD was 8.2% in patients of Japanese ethnicity, 1.9% in patients of non-Japanese Asian ethnicity and 2.9% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.8 months (see section 4.4).

QTc interval prolongation
Of the 833 patients in AURA studies treated with TAGRISSO 80 mg, 0.7% of patients (n=6) were found to have a QTc greater than 500 msec, and 2.9% of patients (n=24) had an increase from baseline QTc greater than 60 msec. A pharmacokinetic analysis with TAGRISSO predicted a concentration-dependent increase in QTc interval prolongation. No QTc-related arrhythmias were reported in the AURA studies (see sections 4.4 and 5.1).

Gastrointestinal effects
In the AURA studies, diarrhoea was reported in 43.5% of patients of which 36.8% were Grade 1 events, 5.5% Grade 2 and 1.0% were Grade 3; no Grade 4 or 5 events were reported. Dose reduction was required in 0.3% of patients and dose interruption in 0.7%. One event (0.1%) led to discontinuation. In AURA3 the median time to onset was 22 days and the median duration of the Grade 2 events was 5.5 days.

Elderly
In AURA3 (N=279), 41% of patients were 65 years of age and older, of whom 15% were 75 years of age and older. Compared with younger subjects (<65), more subjects ≥65 years old had reported adverse reactions that led to study drug dose modifications (interruptions or reductions) (5.3% versus 4.2%). The types of adverse events reported were similar regardless of age. Older patients reported more Grade 3 or higher adverse reactions compared to younger patients (5.3% versus 2.4%). No overall differences in efficacy were observed between these subjects and younger subjects. A consistent pattern in safety and efficacy results was observed in the analysis of AURA Phase 2 studies.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In TAGRISSO clinical trials a limited number of patients were treated with daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with TAGRISSO daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR TKI-induced AEs (primarily diarrhoea and skin rash) compared to the 80 mg dose. There is limited experience with accidental overdoses in humans. All cases were isolated incidents of patients taking an additional daily dose of TAGRISSO in error, without any resulting clinical consequences.

There is no specific treatment in the event of TAGRISSO overdose. In case of suspected overdose, TAGRISSO should be withheld and symptomatic treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, protein kinase inhibitors; ATC code: L01XE35.

Mechanism of action
Osimertinib is a Tyrosine Kinase Inhibitor (TKI). It is an irreversible inhibitor of Epidermal Growth Factor Receptors (EGFRs) harboring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M.

Pharmacodynamic effects

In vitro studies have demonstrated that osimertinib has high potency and inhibitory activity against EGFR across a range of all clinically relevant EGFR sensitising-mutant and T790M mutant non-small cell lung cancer (NSCLC) cell lines (apparent IC_{50}s from 6 nM to 54 nM against phospho-EGFR). This leads to inhibition of cell growth, while showing significantly less activity against EGFR in wild-type cell lines (apparent IC_{50}s from 480 nM to 1.8 μM against phospho-EGFR). *In vivo* oral administration of osimertinib lead to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

Cardiac electrophysiology

The QTc interval prolongation potential of TAGRISSO was assessed in 210 patients who received osimertinib 80 mg daily in AURA2. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of osimertinib on QTc intervals. A pharmacokinetic analysis predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

Clinical efficacy and safety

Pre-treated T790M positive NSCLC patients-AURA3

The efficacy and safety of TAGRISSO for the treatment of patients with locally advanced or metastatic T790M NSCLC whose disease has progressed on or after EGFR TKI therapy, was demonstrated in a randomised, open-label, active-controlled Phase 3 study (AURA3). All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to randomisation. The T790M mutation status was also assessed using ctDNA extracted from a plasma sample taken during screening. The primary efficacy outcome was progression-free survival (PFS) as assessed by investigator. Additional efficacy outcome measures included ORR, DoR and overall survival (OS) as assessed by investigator.

Patients were randomised in a 2:1 (TAGRISSO: platinum-based doublet chemotherapy) ratio to receive TAGRISSO (n=279) or platinum-based doublet chemotherapy (n=140). Randomisation was stratified by ethnicity (Asian and non-Asian). Patients in the TAGRISSO arm received TAGRISSO 80 mg orally once daily until intolerance to therapy, or the investigator determined that the patient was no longer experiencing clinical benefit. Chemotherapy consisted of pemetrexed 500 mg/m^2 with carboplatin AUC5 or pemetrexed 500 mg/m^2 with cisplatin 75 mg/m^2 on Day 1 of every 21-day cycle for up to 6 cycles. Patients whose disease has not progressed after four cycles of platinum-based chemotherapy may receive pemetrexed maintenance therapy (pemetrexed 500 mg/m^2 on Day 1 of every 21-day cycle). Subjects on the chemotherapy arm who had objective radiological progression (by the investigator and confirmed by independent central imaging review) were given the opportunity to begin treatment with TAGRISSO.

The baseline demographic and disease characteristics of the overall study population were: median age 62, ≥75 years old (15%), female (64%), white (32%), Asian (65%), never smoker (68%), WHO performance status 0 or 1 (100%). Fifty-four percent (54%) of patients had extra-thoracic visceral metastases, including 34% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery, and/or prior radiotherapy to CNS metastases) and 23% with liver metastases. Forty-two percent (42%) of patients had metastatic bone disease.

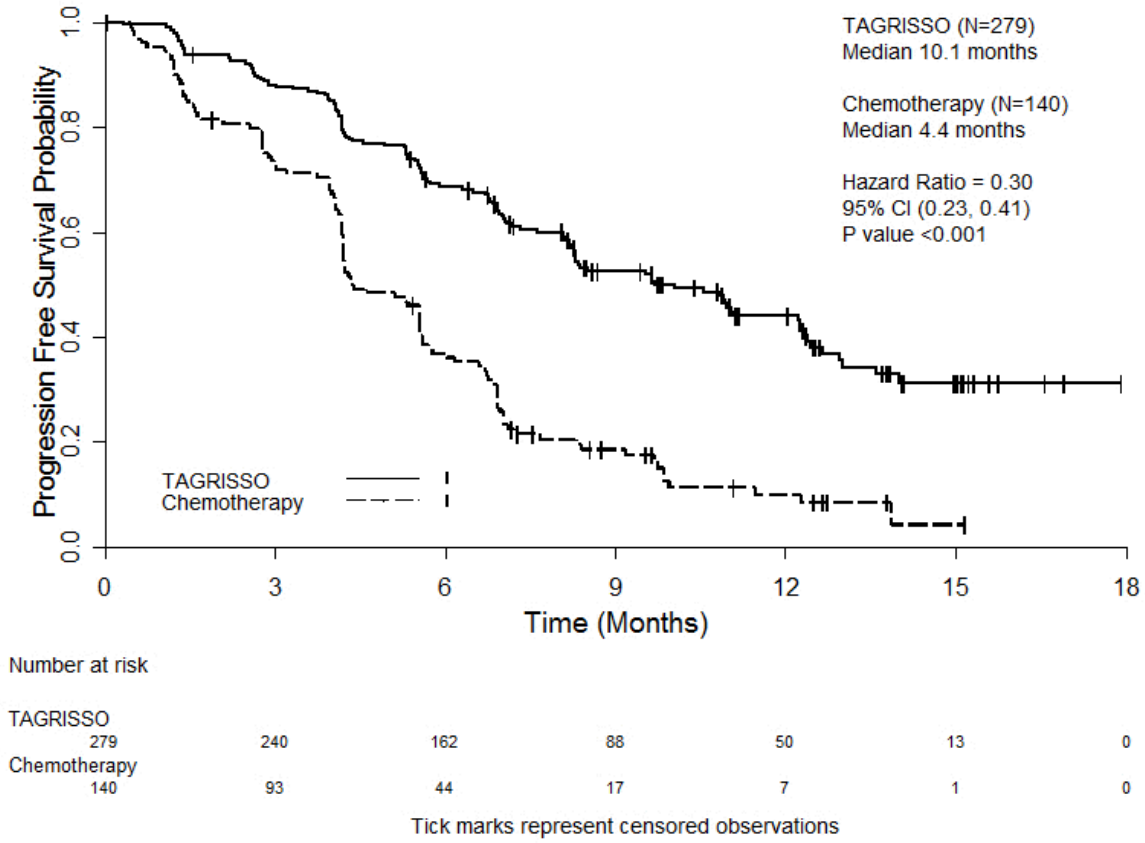
AURA3 demonstrated a statistically significant improvement in PFS in the patients treated with TAGRISSO compared to chemotherapy. Efficacy results from AURA3 by investigator assessment are summarised in Table 4, and the Kaplan-Meier curve for PFS is shown in Figure 1. Overall survival data were not mature at the time of this initial OS analysis.

Table 4. Efficacy results from AURA3 by investigator assessment

Efficacy Parameter	**TAGRISSO (N=279)**	**Chemotherapy (N=140)**
Progression-Free Survival		
Number of Events (% maturity)	140 (50)	110 (79)
Median, Months (95% CI)	10.1 (8.3, 12.3)	4.4 (4.2, 5.6)
HR (95% CI); P-value	0.30 (0.23,0.41); P-value <0.001	
Overall Survival[1]		
Number of Deaths (% maturity)	69 (24.7)	40 (28.6)
Median OS, Months (95% CI)	NC (20.5, NC)	NC (20.5, NC)
HR (95% CI); P-value	0.72 (0.48, 1.09); P-value = 0.121	
Objective Response Rate[2]		
Number of responses, Response Rate (95% CI)	197 71% (65, 76)	44 31% (24, 40)
Odds ratio (95% CI); P-value	5.4 (3.5, 8.5); P-value <0.001	
Duration of Response (DoR)[2]		
Median, Months (95% CI)	9.7 (8.3, 11.6)	4.1 (3.0, 5.6)

HR=Hazard Ratio; CI=confidence interval; NC=non-calculable
All efficacy results based on RECIST investigator assessment
[1]The first analysis of OS was performed approximately 4 months after the primary analysis of PFS. The OS analysis was not adjusted for the potentially confounding effects of crossover (94 [67%] patients on the chemotherapy arm received subsequent osimertinib treatment).
[2] ORR and DoR results by investigator assessment are consistent with those reported via Blinded Independent Central Review (BICR); ORR by BICR assessment was 64.9% [95% CI: 59.0, 70.5] on osimertinib and 34.3 % [95% CI: 26.5, 42.8] on chemotherapy; DoR by BICR assessment was 11.2 months (95% CI: 8.3, NC) on osimertinib and 3.1 months (95% CI: 2.9, 4.3) on chemotherapy.

Figure 1. Kaplan-Meier curves of Progression-Free Survival as assessed by investigator in AURA3



A sensitivity analysis of PFS was conducted by a Blinded Independent Central Review (BICR) and showed a median PFS of 11.0 months with TAGRISSO compared with 4.2 months with chemotherapy. This analysis demonstrated a consistent treatment effect (HR 0.28; 95% CI: 0.20, 0.38) with that observed by investigator assessment.

Clinically meaningful improvements in PFS with HRs less than 0.50 in favour of patients receiving TAGRISSO compared to those receiving chemotherapy were consistently observed in all predefined subgroups analysed, including ethnicity, age, gender, smoking history and EGFR mutation (Exon 19 deletion and L858R).

CNS metastases efficacy data in AURA3 study

Patients with asymptomatic, stable brain metastases not requiring steroids for at least 4 weeks prior to the start of study treatment were eligible to be randomised in the study. A BICR assessment of CNS efficacy by RECIST v1.1 in the subgroup of 116/419 (28%) patients identified to have CNS metastases on a baseline brain scan are summarised in Table 5.

Table 5. CNS efficacy by BICR in patients with CNS metastases on a baseline brain scan in AURA3

Efficacy Parameter	TAGRISSO	Chemotherapy
CNS Objective Response Rate[1]		
CNS response rate % (n/N) (95% CI)	70% (21/30) (51, 85)	31% (5/16) (11%, 59%)
Odds ratio (95% CI); P-value	5.1 (1.4, 21); 0.015	
CNS Duration of Response[2]		
Median, Months (95% CI)	8.9 (4.3, NC)	5.7 (NC, NC)
CNS Disease control rate		
CNS disease control rate	87% (65/75) (77, 93)	68% (28/41) (52, 82)
Odds ratio (95% CI); P-value	3 (1.2, 7.9); 0.021	
CNS Progression-free survival[3]	N=75	N=41
Number of Events (% maturity)	19 (25)	16 (39)
Median, Months (95% CI)	11.7 (10, NC)	5.6 (4.2, 9.7)
HR (95% CI); P-value	0.32 (0.15, 0.69); 0.004	

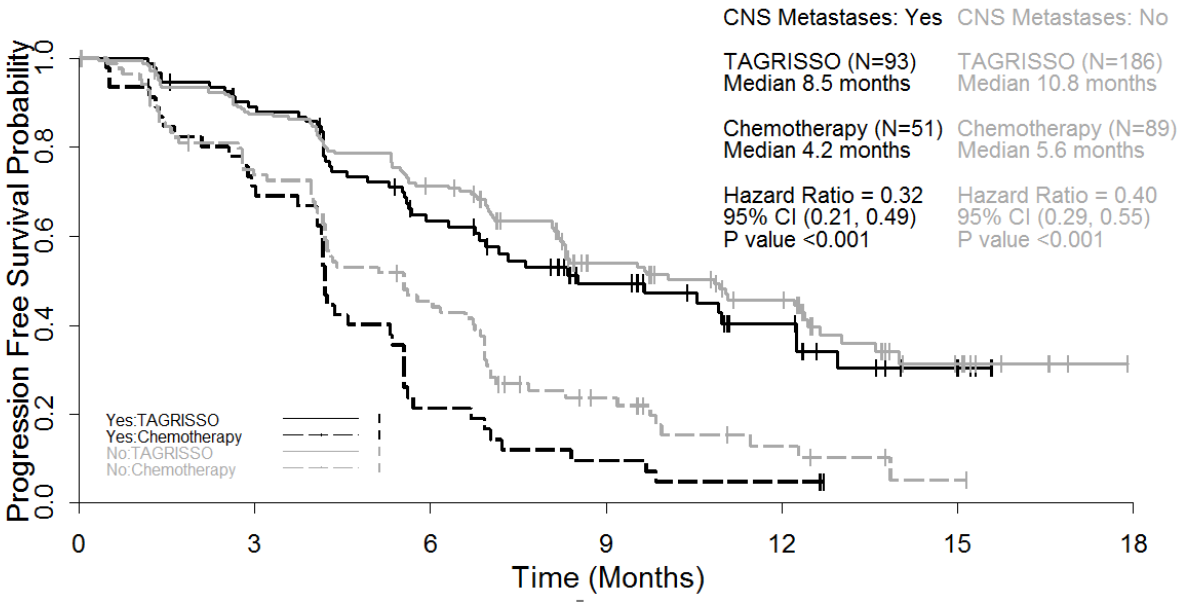
[1] CNS Objective Response Rate and Duration of Response determined by RECIST v1.1 by CNS BICR in the evaluable for response population (CNS measurable lesions at baseline by BICR) n=30 for TAGRISSO and n=16 for Chemotherapy

[2] Based on patients with response only; DoR defined as the time from the date of first documented response (complete response or partial response) until progression or death event; DCR defined as the proportion of patients with response (complete response or partial response), or stable disease ≥ 6 weeks

[3] CNS Progression Free Survival determined by RECIST v1.1 by CNS BICR in the full analysis set population (CNS measurable and non-measurable lesions at baseline by BICR) n=75 for TAGRISSO and n=41 for Chemotherapy
A HR<1 favours TAGRISSO

A pre-specified PFS subgroup based on CNS metastases status at study entry was performed in AURA3 and is shown in Figure 2.

Figure 2. Overall PFS by investigator assessment by CNS metastases status at study entry, Kaplan-Meier plot (full analysis set) in AURA3



AURA3 demonstrated a statistically significant improvement in PFS for patients receiving TAGRISSO compared to those receiving chemotherapy irrespective of CNS metastases status at study entry.

Patient Reported Outcomes

Patient-reported symptoms and health-related quality of life (HRQL) were electronically collected using the EORTC QLQ-C30 and its lung cancer module (EORTC QLQ-LC13). The LC13 was initially administered once a week for the first 6 weeks, then every 3 weeks before and after progression. The C30 was assessed every 6 weeks before and after progression.

Key lung cancer symptoms analysis

TAGRISSO improved patient-reported lung cancer symptoms compared to chemotherapy by demonstrating a statistically significant difference in mean change from baseline versus chemotherapy during the overall time period from randomisation until 6 months for 5 pre-specified primary PRO symptoms (appetite loss, cough, chest pain, dyspnoea, and fatigue) as shown in Table 6.

Table 6. Mixed Model Repeated Measures – Key lung cancer symptoms - mean change from baseline in TAGRISSO patients compared with chemotherapy

	Appetite Loss		**Cough**		**Chest Pain**		**Dyspnoea**		**Fatigue**	
Arms	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)	TAGRISSO (279)	Chemo-therapy (140)
N	239	97	228	113	228	113	228	113	239	97
Adj Mean	-5.51	2.73	-12.22	-6.69	-5.15	0.22	-5.61	1.48	-5.68	4.71
Estimated Difference (95%CI)	-8.24 (-12.88, 3.60)		-5.53 (-8.89, -2.17)		-5.36 (-8.20, -2.53)		-7.09 (-9.86, -4.33)		-10.39 (-14.55, -6.23)	
p-value	p <0.001		p=0.001		p<0.001		p<0.001		p<0.001	

Adjusted mean and estimated differences obtained from a Mixed Model Repeated Measures (MMRM) analysis. The model included patient, treatment, visit, treatment-by-visit interaction, baseline symptom score, and baseline symptom score-by-visit interaction and used an unstructured covariance matrix.

HRQL and physical functioning improvement analysis
Patients on TAGRISSO had significantly greater chances of achieving a clinically meaningful improvement of greater than or equal to 10 points on the global health status and physical functioning of the EORTC-C30 questionnaire compared with chemotherapy during the study period Odds Ratio (OR) global health status: 2.11, (95% CI 1.24, 3.67, p=0.007); OR physical functioning 2.79 (95% CI 1.50, 5.46, p=0.002).

Pre-treated T790M positive NSCLC patients - AURAex and AURA2
Two single-arm, open-label clinical studies, AURAex (Phase 2 Extension cohort, (n=201)) and AURA2 (n=210) were conducted in patients with EGFR T790M mutation-positive lung cancer who have progressed on one or more prior systemic therapies, including an EGFR TKI. All patients were required to have EGFR T790M mutation-positive NSCLC identified by the cobas EGFR mutation test performed in a central laboratory prior to treatment. The T790M mutation status was also assessed retrospectively using ctDNA extracted from a plasma sample taken during screening. All patients received TAGRISSO at a dose of 80 mg once daily. The primary efficacy outcome measure of these two trials was ORR according to RECIST v1.1 as evaluated by a Blinded Independent Central Review (BICR). Secondary efficacy outcome measures included Duration of Response (DoR) and Progression-Free Survival (PFS).

Baseline characteristics of the overall study population (AURAex and AURA2) were as follows: median age 63 years, 13% of patients were ≥75 years old, female (68%), White (36%), Asian (60%). All patients received at least one prior line of therapy. Thirty-one percent (31%) (N=129) had received 1 prior line of therapy (EGFR-TKI treatment only), 69% (N=282) had received 2 or more prior lines. Seventy-two percent (72%) of patients were never smokers, 100% of patients had a World Health Organization (WHO) performance status of 0 or 1. Fifty-nine percent (59%) of patients had extra-thoracic visceral metastasis including 39% with CNS metastases (identified by CNS lesion site at baseline, medical history, and/or prior surgery and/or prior radiotherapy to CNS metastases) and 29% with liver metastases. Forty-seven percent (47%) of patients had metastatic bone disease. The median duration of follow up for PFS was 12.6 months.

In the 411 pre-treated EGFR T790M mutation-positive patients, the total ORR by Blinded Independent Central Review (BICR) was 66% (95% CI: 61, 71). In patients with a confirmed response by BICR, the median DoR was 12.5 months (95% CI: 11.1, NE). The ORR by BICR in AURAex was 62% (95% CI: 55, 68) and 70% (95% CI: 63, 77) in AURA2. The median PFS was 11.0 months 95% CI (9.6, 12.4).

Objective response rates by BICR above 50% were observed in all predefined subgroups analysed, including line of therapy, ethnicity, age and region.

In the evaluable for response population, 85% (223/262) had documentation of response at the time of the first scan (6 weeks); 94% (247/262) had documentation of response at the time of the second scan (12 weeks).

<u>*CNS metastases efficacy data in Phase 2 studies (AURAex and AURA2)*</u>
A BICR assessment of CNS efficacy by RECISTv 1.1 was performed in a subgroup of 50 (out of 411) patients identified to have measurable CNS metastases on a baseline brain scan. A CNS ORR of 54% (27/50 patients; 95% CI: 39.3, 68.2) was observed with 12% of these responses being complete responses.

Clinical studies have not been conducted in patients with de novo EGFR T790M mutation-positive NSCLC.

<u>Paediatric population</u>
The European Medicines Agency has waived the obligation to submit the results of studies with TAGRISSO in all subsets of the paediatric population in NSCLC (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Osimertinib pharmacokinetic parameters have been characterised in healthy subjects and NSCLC patients. Based on population pharmacokinetic analysis, osimertinib apparent plasma clearance is 14.2 L/h, apparent volume of distribution is 997 L and terminal half-life of approximately 48 hours. The AUC and C_{max} increased dose proportionally over 20 to 240 mg dose range. Administration of osimertinib once daily results in approximately 3 fold accumulation with steady-state exposures achieved by 15 days of dosing. At steady-state, circulating plasma concentrations are typically maintained within a 1.6 fold range over the 24-hour dosing interval.

Absorption
Following oral administration of TAGRISSO, peak plasma concentrations of osimertinib were achieved with a median (min-max) t_{max} of 6 (3-24) hours, with several peaks observed over the first 24 hours in some patients. The absolute bioavailability of TAGRISSO is 70% (90% CI 67, 73). Based on a clinical pharmacokinetic study in patients at 80 mg, food does not alter osimertinib bioavailability to a clinically meaningful extent. (AUC increase by 6% (90% CI -5, 19) and C_{max} decrease by 7% (90% CI -19, 6)). In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days, osimertinib exposure was not affected (AUC and C_{max} increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit.

Distribution
Population estimated mean volume of distribution at steady-state (V_{ss}/F) of osimertinib is 997 L indicating extensive distribution into tissue. *In vitro*, plasma protein binding of osimertinib is 94.7% (5.3% free). Osimertinib has also been demonstrated to bind covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes.

Biotransformation
In vitro studies indicate that osimertinib is metabolised predominantly by CYP3A4, and CYP3A5. However, with current available data, alternative metabolic pathways cannot be fully ruled out. Based on *in vitro* studies, 2 pharmacologically active metabolites (AZ7550 and AZ5104) have subsequently been identified in the plasma of preclinical species and in humans after oral dosing with osimertinib; AZ7550 showed a similar pharmacological profile to TAGRISSO while AZ5104 showed greater potency across both mutant and wild-type EGFR. Both metabolites appeared slowly in plasma after administration of TAGRISSO to patients, with a median (min-max) t_{max} of 24 (4-72) and 24 (6-72) hours, respectively. In human plasma, parent osimertinib accounted for 0.8%, with the 2 metabolites contributing 0.08% and 0.07% of the total radioactivity with the majority of the radioactivity being covalently bound to plasma proteins. The geometric mean exposure of both AZ5104 and AZ7550, based on AUC, was approximately 10% each of the exposure of osimertinib at steady-state.

The main metabolic pathway of osimertinib was oxidation and dealkylation. At least 12 components were observed in the pooled urine and faecal samples in humans with 5 components accounting for >1% of the dose of which unchanged osimertinib, AZ5104 and AZ7550, accounted for approximately 1.9, 6.6 and 2.7% of the dose while a cysteinyl adduct (M21) and an unknown metabolite (M25) accounted for 1.5% and 1.9% of the dose, respectively.

Based on *in vitro* studies, osimertinib is a competitive inhibitor of CYP 3A4/5 but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations. Based on *in vitro* studies, osimertinib is not an inhibitor of UGT1A1 and UGT2B7 at clinically relevant concentrations hepatically. Intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Elimination
Following a single oral dose of 20 mg, 67.8% of the dose was recovered in faeces (1.2% as parent) while 14.2% of the administered dose (0.8% as parent) was found in urine by 84 days of sample collection. Unchanged osimertinib accounted for approximately 2% of the elimination with 0.8% in urine and 1.2% in faeces.

Interactions with transport proteins
In vitro studies have shown that osimertinib is not a substrate of OATP1B1 and OATP1B3. *In vitro*, osimertinib does not inhibit OAT1, OAT3, OATP1B1, OATP1B3, MATE1, OCT2 and MATE2K at clinically relevant concentrations.

Effects of osimertinib on P-gp and BCRP
Based on *in vitro* studies, osimertinib is a substrate of P-glycoprotein and breast cancer resistant protein (BCRP), but is unlikely to result in clinically relevant drug interactions with active substances by osimertinib at the clinical doses. Based on *in vitro* data, osimertinib is an inhibitor of BCRP and P-gp. PXR regulated enzyme interactions other than CYP3A4 have not been studied (see section 4.5).

Special populations
In a population based pharmacokinetic analyses (n=1088), no clinically significant relationships were identified between predicted steady-state exposure (AUC_{ss}) and patient's age (range: 25 to 91 years), gender (65% female), ethnicity (including White, Asian, Japanese, Chinese and non-Asian-non-White patients) and smoking status (n=27 current smokers, n=329 former smokers). Population PK analysis indicated that body weight was a significant covariate with a less than 20% change in osimertinib AUC_{ss} expected across a body weight range of 89 kg to 43 kg respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median body weight of 60 kg. Taking the extremes of body weight into consideration, from <43 kg to >89 kg, AZ5104 metabolite ratios ranged from 11.8% to 9.6% while for AZ7550 it ranged from 12.8% to 8.1%, respectively. Based on population PK analysis, serum albumin was identified as a significant covariate with a -15% to +30% change in osimertinib AUC_{ss} expected across the albumin range of 29 to 46 g/L respectively (95% to 5% quantiles) when compared to the AUC_{ss} for the median baseline albumin of 39 g/L. These exposure changes due to body weight or baseline albumin differences are not considered clinically relevant.

Hepatic impairment
Osimertinib is eliminated mainly via the liver, and hence, patients with hepatic impairment may have increased exposure. A pharmacokinetic trial in subjects with hepatic impairment has not been conducted. Based on population PK analysis, there was no relationship between markers of hepatic function (ALT, AST, bilirubin) and osimertinib exposure. The hepatic impairment marker serum albumin showed an effect on the PK of osimertinib. Clinical studies that were conducted excluded patients with AST or ALT >2.5x upper limit of normal (ULN), or if due to underlying malignancy, >5.0x ULN or with total bilirubin >1.5x ULN. Based on a pharmacokinetic analysis of 104 patients with mild hepatic impairment, 8 patients with moderate hepatic impairment and 972 patients with normal hepatic function osimertinib exposures were similar. There are no data available on patients with severe hepatic impairment (see section 4.2).

Renal impairment
A pharmacokinetic study in patients with renal impairment has not been conducted. Based on a population pharmacokinetic analysis of 471 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 208 patients with moderate renal impairment (CLcr 30 to <than 60 mL/min), 5 patients with severe renal impairment (CLcr 15 to <than 30 mL/min) and 402 patients with normal renal function (greater than or equal to 90 mL/min), osimertinib exposures were similar. Severe renal impairment may influence the elimination of hepatically eliminated medicinal products. Patients with CLcr less than 15 mL/min were not included in the clinical trials.

5.3 Preclinical safety data

The main findings observed in repeat dose toxicity studies in rats and dogs comprised atrophic, inflammatory and/or degenerative changes affecting the epithelia of the cornea (accompanied by corneal translucencies and opacities in dogs at ophthalmology examination), GI tract (including tongue), skin, and male and female reproductive tracts with secondary changes in spleen. These findings occurred at plasma concentrations that were below those seen in patients at the 80 mg therapeutic dose. The findings present following 1 month of dosing were largely reversible within 1 month of cessation of dosing with the exception of partial recovery for some of the corneal changes.

Osimertinib penetrated the intact blood-brain barrier of the cynomolgus monkey (i.v. dosing), rat and mouse (oral administration).

Non-clinical data indicate that osimertinib and its metabolite (AZ5104) inhibit the h-ERG channel, and QTc prolonging effect cannot be excluded.

Carcinogenesis and mutagenesis
Carcinogenicity studies have not been performed with osimertinib. Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays.

Reproductive toxicity
Degenerative changes were present in the testes in rats and dogs exposed to osimertinib for ≥1 month and there was a reduction in male fertility in rats following exposure to osimertinib for 3 months. These findings were seen at clinically relevant plasma concentrations. Pathology findings in the testes seen following 1 month dosing were reversible in rats; however, a definitive statement on reversibility of these lesions in dogs cannot be made.

Based on studies in animals, female fertility may be impaired by treatment with osimertinib. In repeat dose toxicity studies, an increased incidence of anoestrus, corpora lutea degeneration in the ovaries and epithelial thinning in the uterus and vagina were seen in rats exposed to osimertinib for ≥1 month at clinically relevant plasma concentrations. Findings in the ovaries seen following 1 month dosing were reversible. In a female fertility study in rats, administration of osimertinib at 20 mg/kg/day (approximately equal to the recommended daily clinical dose of 80 mg) had no effects on oestrus cycling or the number of females becoming pregnant, but caused early embryonic deaths. These findings showed evidence of reversibility following a 1 month off-dose.

In a modified embryofoetal development study in the rat, osimertinib caused embryolethality when administered to pregnant rats prior to embryonic implantation. These effects were seen at a maternally tolerated dose of 20 mg/kg where exposure was equivalent to the human exposure at the recommended dose of 80 mg daily (based on total AUC). Exposure at doses of 20 mg/kg and above during organogenesis caused reduced foetal weights but no adverse effects on external or visceral foetal morphology. When osimertinib was administered to pregnant female rats throughout gestation and then through early lactation, there was demonstrable exposure to osimertinib and its metabolites in suckling pups plus a reduction in pup survival and poor pup growth (at doses of 20 mg/kg and above).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol
Microcrystalline cellulose
Low-substituted hydroxypropyl cellulose
Sodium stearyl fumarate

Tablet coating
Polyvinyl alcohol
Titanium dioxide (E 171)
Macrogol 3350
Talc
Yellow iron oxide (E 172)
Red iron oxide (E 172)
Black iron oxide (E 172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Al/Al perforated unit dose blisters. Cartons of 30 x 1 tablets (3 blisters).

Al/Al perforated unit dose blisters. Cartons of 28 x 1 tablets (4 blisters).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1086/001
EU/1/16/1086/002
EU/1/16/1086/003
EU/1/16/1086/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2 February 2016
Date of latest renewal: 12 December 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)
Lonza AG
Walliser Werke
Postfach
CH-3930 Visp
Switzerland

Name and address of the manufacturer(s) responsible for batch release
AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
SWEDEN

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 40 mg film-coated tablets
osimertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 40 mg osimertinib (as mesylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1086/001
EU/1/16/1086/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tagrisso 40 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 80 mg film-coated tablets
osimertinib

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 80 mg osimertinib (as mesylate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

30 x 1 film-coated tablets
28 x 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/16/1086/002
EU/1/16/1086/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

tagrisso 80 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

10 FILM-COATED TABLET BLISTERS (PERFORATED)
7 FILM-COATED TABLET BLISTERS (PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 40 mg tablets
osimertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

10 FILM-COATED TABLET BLISTERS (PERFORATED)
7 FILM-COATED TABLET BLISTERS (PERFORATED)

1. NAME OF THE MEDICINAL PRODUCT

TAGRISSO 80 mg tablets
osimertinib

2. NAME OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

TAGRISSO 40 mg film-coated tablets
TAGRISSO 80 mg film-coated tablets
osimertinib

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What TAGRISSO is and what it is used for

TAGRISSO contains the active substance osimertinib which belongs to the protein kinase inhibitor class of anticancer medicines. TAGRISSO is used to treat adults with a type of lung cancer called 'non-small cell lung cancer.' It is used when:
- You test positive for a 'T790M mutation' – see 'How TAGRISSO works.'
- Your cancer is advanced and is worsening despite previous treatments, which may have included a medicine which worked to block 'EGFR' (epidermal growth factor receptor).

How TAGRISSO works
- A test has shown that your cancer is linked to a specific change in the EGFR gene called 'T790M.' This is known as a T790M mutation.
- Because of this T790M mutation, medicines that block EGFR may no longer work.
- TAGRISSO affects T790M and may help to slow or stop your lung cancer growing. It may also help to shrink the tumour.

If you have any questions about how this medicine works or why this medicine has been prescribed for you, ask your doctor.

2. What you need to know before you take TAGRISSO

Do not take TAGRISSO if:
- you are allergic (hypersensitive) to osimertinib or any of the other ingredients of this medicine (listed in section 6).
- you are taking St. John's Wort (Hypericum perforatum).

If you are not sure, talk to your doctor, pharmacist or nurse before taking TAGRISSO.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking TAGRISSO if:
- you have suffered from inflamation of your lungs (a condition called 'interstitial lung disease').
- you have ever had heart problems – your doctor may want to keep a close eye on you.
- you have a history of eye problems.

If any of the above apply to you (or you are not sure), talk to your doctor, pharmacist or nurse before taking this medicine.

Tell your doctor straight away while taking this medicine if:
- you have sudden difficulty in breathing together with a cough or fever. See 'Serious side effects' in section 4 for more information.

Children and adolescents
TAGRISSO has not been studied in children or adolescents. Do not give this medicine to children or adolescents under the age of 18 years.

Other medicines and TAGRISSO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This includes herbal medicines and medicines obtained without a prescription. This is because TAGRISSO can affect the way some other medicines work. Also some other medicines can affect the way TAGRISSO works.

Tell your doctor before taking TAGRISSO if you are taking any of the following medicines:

The following medicines may reduce how well TAGRISSO works:
- Phenytoin, carbamazepine or phenobarbital – used for seizures or fits.
- Rifabutin or rifampicin – used for tuberculosis (TB).
- St. John's Wort (Hypericum perforatum) – an herbal medicine used for depression.

TAGRISSO may affect how well the following medicine works and/or increase side effects of these medicines:
- Warfarin – used for blood clots.
- Phenytoin and S-mephenytoin – used for seizures or fits.
- Alfentanil, fentanyl and other painkillers used for operations.
- Rosuvastatin – used to lower cholesterol.
- Oral hormonal contraceptive pill– used to prevent pregnancy.
- Bosentan – used for high blood pressure in the lungs.
- Efavirenz and etravirine – used to treat HIV infections/AIDS.
- Modafinil – used for sleep disorders.

If you are taking any of the medicines listed above, tell your doctor before taking TAGRISSO.
Your doctor will discuss appropriate treatment options with you.

Pregnancy – information for women
- If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. If you do become pregnant during treatment, tell your doctor straight away. Your doctor will decide with you whether you should carry on taking TAGRISSO.
- You should not become pregnant while taking this medicine. If you are able to become pregnant, you must use effective contraception. See 'Contraception - information for women and men' below.
- If you plan to become pregnant after taking the last dose of this medicine, ask your doctor for advice. This is because some medicine may remain in your body, (see advice on contraception below).

Pregnancy – information for men
- If your partner becomes pregnant while you are taking this medicine, tell your doctor straight away.

Contraception – information for women and men
You must use effective contraception during treatment.
- TAGRISSO may interfere with how well oral hormonal contraceptives work. Discuss with your doctor the most appropriate methods of contraception.
- TAGRISSO may pass into semen. Therefore, it is important that men also use effective contraception.

You must also do this after completing treatment with TAGRISSO:
- **Women** – keep using contraception for 2 months after.
- **Men** – keep using contraception for 4 months after.

Breast-feeding
Do not breast-feed while taking this medicine. This is because it is not known if there is a risk to your baby.

Driving and using machines
TAGRISSO has no or no marked influence on the ability to drive and use machines.

3. How to take TAGRISSO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
- The recommended dose is one 80 mg tablet each day.
- If necessary, your doctor may reduce your dose to one 40 mg tablet each day.

How to take
- TAGRISSO is taken by mouth. Swallow the tablet whole with water. Do not crush, split or chew the tablet.
- Take TAGRISSO every day at the same time.
- You can take this medicine with or without food.

If you have trouble swallowing the tablet, you can mix it in water:
- Put the tablet in a glass.
- Add 50 mL (about two-thirds of a tumblerful) of still (non-fizzy) water – do not use any other liquids.
- Stir the water until the tablet breaks up into very small pieces - the tablet will not completely dissolve.
- Drink the liquid straight away.
- To make sure you have taken all of the medicine, rinse the glass thoroughly with another 50 mL of water and drink it.

If you take more TAGRISSO than you should
If you take more than your normal dose, contact your doctor or nearest hospital straight away.

If you forget to take TAGRISSO
If you forget a dose, take it as soon as you remember it. However, if it is less than 12 hours until your next dose is due, skip the missed dose. Take your next normal dose at its scheduled time.

If you stop taking TAGRISSO
Do not stop taking this medicine - talk to your doctor first. It is important to take this medicine every day, for as long as your doctor prescribes it for you.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor straight away if you notice the following serious side effects:
- Sudden difficulty in breathing together with a cough or fever - this may be a sign of inflamed lungs (a condition called 'interstitial lung disease') and can be fatal in some cases. Your doctor may wish to stop TAGRISSO if you get this side effect. This side effect is common: it may affect up to 1 in 10 people.
- If you develop watery eyes, sensitivity to light, eye pain, eye redness, or vision changes. This side effect is uncommon: it may affect up to 1 in 100 people.

Tell your doctor straight away if you notice the serious side effects listed above.

Other side effects
Very common (may affect more than 1 in 10 people)
- Diarrhoea - this may come and go during treatment. Tell your doctor if your diarrhoea does not go away or becomes severe.
- Skin and nail problems - signs may include itching, dry skin, rash, redness around the fingernails. This is more likely in areas exposed to the sun. Using moisturisers regularly on your skin and nails can help with this. Tell your doctor if your skin or nail problems get worse.
- Stomatitis - inflammation of the inner lining of the mouth.
- Reduction in the number of white blood cells (leukocytes or neutrophils).
- Reduction in the number of platelets in the blood.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse.
This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store TAGRISSO

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date (EXP) which is stated on the blister foil and carton. The expiry date refers to the last day of that month.
- This medicine does not require any special storage conditions.
- Do not use any pack that is damaged or shows signs of tampering.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What TAGRISSO contains
- The active substance is osimertinib (as mesylate). Each 40 mg film-coated tablet contains 40 mg of osimertinib. Each 80 mg film-coated tablet contains 80 mg of osimertinib.

- The other ingredient(s) are mannitol, microcrystalline cellulose, low-substituted hydroxypropyl cellulose, sodium stearyl fumarate, polyvinyl alcohol, titanium dioxide, macrogol 3350, talc, yellow iron oxide, red iron oxide, black iron oxide.

What TAGRISSO looks like and contents of the pack
TAGRISSO 40 mg is supplied as beige, film-coated, round and biconvex tablets, marked with “AZ” and “40” on one side, and plain on the other.

TAGRISSO 80 mg is supplied as beige, film-coated, oval and biconvex tablets, marked with “AZ” and “80” on one side, and plain on the other.

TAGRISSO is supplied in blisters containing 30 x 1 film-coated tablets, packed in cartons containing 3 blisters of 10 tablets each.

TAGRISSO is supplied in blisters containing 28 x 1 film-coated tablets, packed in cartons containing 4 blisters of 7 tablets each.

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Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.