17 December 2015
EMA/CHMP/15445/20165
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

TAGRISSO

International non-proprietary name: OSIMERTINIB

Procedure No. EMEA/H/C/004124/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADME	Absorption Distribution Metabolism Elimination
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve (plasma concentration / time curve)
AUCss	Area under plasma concentration-time curve during any dosing interval at steady state
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics Classification System
BICR	Blinded independent central review
CAS	chemical abstract service
CEP	certificate European pharmacopoeia
CFU	colony-forming unit
CI	Confidence interval
Cmax	Maximum plasma concentration
Cmin	Minimum plasma concentration
CMC	Chemistry manufacturing and controls
c-QTc	Concentration-QTc
CR	Complete Response
Ct	Circulating tumour
CTCAE	Common terminology criteria for adverse events
CTD	common technical dossier
CYP	Cytochrome P450 isoenzyme
CV	Coefficient of variation
DCO	Data cut-off date
DDI	Drug-drug interaction
DLTs	Dose limiting toxicities
DMPK	Drug metabolism and pharmacokinetics
DNA	Deoxyribonucleic acid
DoE	Design of experiments
DP	drug product
DoR	Duration of response
DS	drug substance
DSC	differential scanning calorimetry
DSUR	Development Safety Update Report
EC	European Commission
ECG	Electrocardiogram
EEA	European Economic Area
EGFR	Epidermal Growth Factor Receptor
EGFRm	Tumour positive status for TKI-sensitivity conferring mutations in the tyrosine kinase domain of EGFR, which spans exons 18 to 21
EGFR TKI	Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor

EGFR T790M	EGFR mutation(s) resulting in threonine (T) replacement by methionine (M) at position 790 of EGFR
EMA	European Medicines Agency
EU	European Union
Ex19del	Deletion in exon 19
FAS	Full analysis population
FDA	Food & Drug Administration
FFPET	Formalin fixed, paraffin embedded tissue
FTIR	Fourrier transform IR
GC	gas chromatography
GI	Gastrointestinal
GMP	Good Manufacturing Practice
HPLC	High performance liquid chromatography
HR	Hazard ratio
IB	Investigator's Brochure
IC50	50% Inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICF	Informed consent form
ILD	Interstitial lung disease
IPC	in-process control
IR	infrared
KF	Karl Fischer titration
LC	Liquid chromatography
LDPE	Low density polyethylene
LVEF	Left Ventricular Ejection Fraction
MA	Material Attribute
MAA	Marketing Authorisation Applicant
MATE	Multidrug and toxin extrusion protein
MTD	Maximum tolerated dose
NA	Not applicable
NMR	nuclear magnetic resonance
NMT	not more than
NOEL	no observable effect level
NSCLC	non-small cell lung cancer
OAT	Organic anion transporter
OATP	Organic anion transporter protein
OCT	Organic cation transporter
ORR	Objective response rate
OS	Overall survival
PACMP	Post-approval change management plan
PAR	proven acceptable range
PD	Progressive Disease
PFS	Progression-free survival
Pgp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia

PK	Pharmacokinetics
PP	Process Parameter
ppm	parts per million
PR	Partial response
PSD	particle size distribution
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
QT	ECG interval measured from the onset of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QTc Fredericia corrected
QTPP	Quality target product profile
r	correlation coefficient
RECIST	Response Evaluation Criteria in Solid Tumours
RH	relative humidity
RSD	relative standard deviation
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable disease
SmPC	Summary of Product Characteristics
TAMC	total aerobic microbial count
THF	tetrahydrofuran
TKI	Tyrosine kinase inhibitor
tmax	Time to reach maximum concentration
TTC	threshold of toxicological concern
TYMC	total combined yeasts and moulds count
US	United States
USP	United States Pharmacopeia
UV	ultraviolet

1. Background information on the procedure

1.1. Submission of the dossier

The applicant AstraZeneca AB submitted on 5 June 2015 an application for Marketing Authorisation to the European Medicines Agency (EMA) for TAGRISSO, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 November 2014.

The applicant applied for the following indication: Treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Osimertinib was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claim(s): Medicinal product which aims at the treatment of a life-threatening disease in accordance with Article 2(1) of Commission Regulation No. 507/2006.

New active Substance status

The applicant requested the active substance Osimertinib (mesylate) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

A new application was filed in the following countries: United States.

The product was not licensed in any country at the time of submission of the application.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Karsten Bruins Slot

- The application was received by the EMA on 5 June 2015.
- Accelerated Assessment procedure was agreed-upon by CHMP on 21 May 2015.
- The procedure started on 25 June 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 September 2015. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 11 September 2015. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- The PRAC RMP Advice and assessment overview was adopted by PRAC on 08 October 2015.
- During the meeting on 19-22 October 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 October 2015.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 November 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 3 December 2015
- During the meeting on 14-17 December 2015, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional Marketing Authorisation for Tagrisso.
- The New Active Substance Report was adopted at the CHMP on 17 December 2015.

2. Scientific discussion

2.1. Introduction

Problem statement

Lung cancer is an aggressive, heterogeneous, and life-threatening disease. It has been one of the most common cancers in the world for several decades (1.8 million new cases in 2012, 12.9% of all new cancers worldwide (GLOBOCAN 2012). In the EU, lung cancer is ranked as the fourth most frequent cancer; approximately 313,000 new cases were diagnosed in 2012 (Ferlay et al. 2013). Furthermore, lung cancer incidence rates were two-fold higher in males compared to females (1,241,601 and 583,100, respectively). It is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly 1 in 5 cancer deaths (1.59 million deaths; 19.4% of all deaths from cancer) in 2012, including 168,000 deaths in the US and 268,000 deaths in Europe (GLOBOCAN 2012). NSCLC represents approximately 80 to 90% of all lung cancers (Cataldo et al 2011, Herbst et al 2008). For the minority of patients with NSCLC who have resectable disease, surgery offers the best chance of cure (Mountain 1997). Despite progress in early detection and treatment, NSCLC is most often diagnosed at an advanced stage and has a poor prognosis (Herbst et al 2008). Once NSCLC has progressed to a locally advanced or metastatic stage there is no cure and treatment is therefore focused on extending life, delaying disease progression, and improving symptoms and quality of life.

Progress in molecular biology has changed the therapeutic approach to NSCLC, and the treatment of advanced NSCLC can now be guided by the presence of certain mutations, e.g., epidermal growth factor receptor (EGFR), or anaplastic lymphoma kinase (ALK).

Since the discovery of the common somatic mutations in the kinase domain of EGFR in 2004 (Lynch et al 2004), NSCLC patients with activating EGFR mutations in exons 18-21 of EGFR (including L858R and exon 19 deletions [Ex19del], collectively described as EGFRm) are considered a subset of NSCLC in terms of pathogenesis, prognosis and treatment.

In recent years, studies have identified the presence of EGFR mutations in approximately 10% of patients with lung cancer in the European Economic Area (EEA) (Barlesi et al 2013, Esteban et al 2015, Gahr et al 2013, Rosell et al 2009). Overall, EGFR mutations have been found to be more frequent in never smokers, in patients with the adenocarcinoma histologic subtype, and in women. Their prevalence is also higher in East Asian patients than in Caucasian patients (ESMO clinical practice guidelines [Reck et al 2014]).

There is a large body of evidence showing consistent efficacy of EGFR TKIs in patients with sensitizing EGFR mutations and that these patients are more likely to benefit from initial treatment with an EGFR TKI in preference to doublet chemotherapy (Maemondo et al 2010, Mitsudomi et al 2010, Mok et al 2009, Rosell et al 2012, Zhou et al 2011, Wu et al 2014).

First- or second-generation EGFR TKIs (gefitinib, erlotinib, afatinib) would generally be considered first choice treatment for patients with activating mutations in EGFR, offering ORRs of approximately 60-70% and median PFS of 9 to 14 months (NCCN guidelines, ESMO clinical practice guidelines [Reck et al 2014], Sebastian et al 2014).

Despite achieving very good initial response rates and durable benefit following treatment with approved TKI drugs targeting EGFRm, these patients will eventually develop treatment resistant disease after 9-14 months (Jackman et al 2009, Mok et al 2009, Oxnard et al 2011, Maemondo et al 2010, Mitsudomi et al 2010, Rosell et al 2012, Sebastian et al 2014).

Survival rates of patients with advanced NSCLC who progress following treatment with EGFR-TKI remain very low, with a median overall survival of 1 to 2 years (Fukuoka et al 2011, Katakami et al 2013, Miller et al 2012, Mok et al 2014, Wang et al 2012, Wu et al 2010, Yu et al 2013).

Treatment following progression on EGFR TKI therapy is guided by patient performance status, symptoms, and extent of disease (NCCN Guidelines). Patients have traditionally been treated with chemotherapy.

Second-line platinum-based chemotherapy post EGFR TKI for EGFRm NSCLC generally provides response rates in the range of 20 to 30% (Gridelli et al 2012, Goldberg et al 2012, Maemondo et al 2010, Mok et al 2014, Wang et al 2012, Wu et al 2010).

Median PFS with platinum-containing doublet chemotherapy is generally reported to be in the range of 3 to 6 months (2nd-line), as was seen in the IMPRESS study (median 5.4 months).

Following progression on an EGFR TKI and doublet chemotherapy, the only remaining options are re-challenge with EGFR TKI, or salvage chemotherapy (usually single-agent), or investigational agents through clinical trials (Langer et al 2012).

Table 1: Overview of current treatments for EGFR mutation positive NSCLC after EGFR TKI

Treatment/N	ORR % (95% CI)	Median DoR, months (95% CI)	Median PFS/TTP, months (95% CI)	Median OS, months (95% CI)
Platinum Doublet Chemotherapy in EGFRm NSCLC after First Line EGFR TKI				
Placebo+Pemetrexed/Cisplatin (N=132)[1] In Metastatic EGFRm NSCLC after failure of first line gefitinib	*25.0 (17.9-33.3) [2]	NR	5.4 (4.6 to 5.5)	17.2 (15.6 -NC) -28.0% maturity
Single Agent Chemotherapy or EGFR TKI in Unselected NSCLC after prior Chemotherapy				
Docetaxel (N=55) vs BSC (N=49)[3]	5.5 (1.1-15.1) vs N/A	6.1 vs N/A[4]	TTP: 2.8 (2.1-4.2) vs 1.6 (1.4-2.1)	7.5 (5.5, 12.8) vs 4.6 (3.7, 6.1)
Docetaxel (N=125) vs Vinorelbine/Ifosfamide (N=123) [3]	5.7 (2.3-11.3) vs 0.8 (0.0-4.5)	9.1 vs 5.9 [5,a]	TTP: 2.0 (1.6 -2.7) vs 1.8 (1.5 -2.3)	5.7 (5.1, 7.1) vs 5.6 (4.4, 7.9)
Pemetrexed (N= 283) vs Docetaxel (N=288) [6] Nonsquamous subset: Pemetrexed (N= 205) vs Docetaxel (N=194)	8.5 (5.2-11.7) vs 8.3 (5.1-11.5)	4.6 v 5.3 [7]	2.9 (2.4—3.1) vs 2.9 (2.7-3.4)	8.3 (7.0-9.4) vs 7.9 (6.3-9.2) 9.3 (7.8-9.7) vs 8.0 (6.3-9.3)
Pemetrexed (N=54) vs Docetaxel (N=55)[8] In Metastatic NSCLC[b] after failure of EGFR TKI therapy	22.2 vs 25.5	NR	NR	8.5 vs 8.4
Erlotinib (n=488) vs Placebo (N=243)[9]	8.9 vs 0.9	7.9 vs 3.7	2.2 v 1.8[10]	6.7 vs 4.7[10]
Re-challenge with EGFR TKI in patient population enriched for EGFRm NSCLC				

Treatment/N	ORR % (95% CI)	Median DoR, months (95% CI)	Median PFS/TTP, months (95% CI)	Median OS, months (95% CI)
Erlotinib (N=125)[11] Retrospective review of EGFR TKI re-challenge after gefitinib failure in EGFRm-enriched[c] NSCLC	9 (5-15)	NR	2.0 (1.4-2.5)	11.8 (6.4-16.0)
Subset with PS 0,1, prior gefitinib benefit + cytotoxic chemotherapy between EGFR TKIs (N=32)[11]	25 (12–43)	NR	3.4 (2.4–4.9)	NR
Afatinib+BSC (N=390) vs Placebo+BSC (N=195)[12] In Metastatic EGFRm-enriched NSCLC after failure of EGFR TKI and Chemotherapy	*7% vs <1%	*5.6 (3.7-9.3) vs NR	*3.3 (2.79-4.40) vs 1.1 (0.95-1.68)	10.8 (10.0-12.0) vs 12.0 (10.2-14.3)

*assessment by independent central review; NC– not calculable; NR- not reported;
a one responder only; b EGFR mutation status not assessed; c 50% EGFRm, 23% EGFR WT, 27% EGFR status unknown; d 141 patients were tested for EGFRm, 96 (68%) were positive.
1.IMPRESS study: Mok et al 2014; 2. IMPRESS study: AstraZeneca data on file; 3. Taxotere PI; 4. Shepherd et al 2000; 5. Fossella et al 2000; 6. Alimta PI; 7. Hanna et al 2004; 8. Dong et al 2014; 9. Tarceva PI; 10. Shepherd et al 2005; 11. Hata et al 2011; 12.Miller et al 2012.

Patients with local or gradual disease progression may benefit from continued EGFR TKI therapy past objective disease progression, as a patient's tumour may have a meaningful population of cells still sensitive to an EGFR TKI. Many other novel agents and combinations have tried to overcome the acquired resistance to EGFR TKIs, but response rates were quite limited; with response rates generally lower than 10% (e.g., EGFR TKI+everolimus response rate 0% [Riely et al 2007]; neratinib response rate 3% [Sequist et al 2010a], IPI-504 response rate 4% [Sequist et al 2010b]). The combination of afatinib plus the anti-EGFR antibody cetuximab has shown an overall response rate of 29% and PFS <5 months, that is similar to that of chemotherapy in an unselected 2nd-line population (Janjigian et al 2014).

There are multiple mechanisms for acquired resistance, e.g.: amplification of the mesenchymal epithelial transition (MET) proto-oncogene, which activates an AKT-mediated signalling pathway, bypassing the EGFR; BRAF mutations; HER2 amplification; even histologic changes, i.e. transformation to small-cell or epithelial-mesenchymal transition.

However, the most common cause of acquired resistance (50-60%) is the EGFR T790M point mutation. Initially thought to simply exclude binding of EGFR-TKI drugs by steric hindrance, the substitution of methionine for threonine at position 790 in exon 20 is suggested to cause resistance by restoring the EGFR affinity for ATP, thus decreasing the binding of the reversible ATP-competitive TKIs, gefitinib and erlotinib (Herbst et al 2008, Kobayashi et al 2005, Pao et al 2005, Su et al 2012, Yu et al 2013).

Several studies showed that patients who acquired the T790M mutation after EGFR TKI therapy had longer post-progression survival than those without it, associated with less metastatic sites and a better performance status. In this sense, the acquired T790M mutation may be indicative of a more indolent disease (Oxnard et al 2011). There also is increasing evidence that a low level of the T790M mutation exists before treatment in many patients with EGFR-mutant NSCLC and may predict a worse PFS on e.g. erlotinib, compared to those without pre-treatment T790M (Inukai et al 2006). Currently there is no approved targeted therapy for the T790M 'gatekeeper' mutation.

About the product

Osimertinib is a TKI and an irreversible inhibitor of EGFRs harbouring sensitising-mutations (EGFRm) and TKI-resistance mutation T790M.

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 IC50s 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 IC50s 480 nM to 1.8 μM against phospho-EGFR). In vivo oral administration of osimertinib leads to tumour shrinkage in both EGFRm and T790M NSCLC xenograft and transgenic mouse lung tumour models.

The applicant applied for an accelerated procedure for the following indication:

TAGRISSO is indicated for the treatment of adult patients with locally advanced or metastatic EGFR T790M mutation-positive non-small-cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy.

The recommended indication is:

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).

Treatment with osimertinib should be initiated by a physician experienced in the use of anticancer therapies. The recommended dose of TAGRISSO is 80 mg osimertinib once a day until disease progression or unacceptable toxicity. When considering the use of osimertinib as a treatment for locally advanced or metastatic NSCLC, it is necessary that EGFR T790M mutation status is determined by a clinical laboratory using a validated test method

If 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 of TAGRISSO should be reduced to 40 mg taken once daily.

Dose reduction guidelines for adverse reactions toxicities are provided in Table 2.

Table 2: TAGRISSO dose adjustment information for adverse reactions

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.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 40 or 80 mg of osimertinib (as mesylate) as active substance.

Other ingredients are:

Tablet core: microcrystalline cellulose, mannitol, low-substituted hydroxpropyl cellulose, sodium stearyl fumarate

Tablet coating: polyvinyl alcohol, titanium dioxide (E 171), polyethylene glycol 3350, talc, yellow iron oxide (E 172), red iron oxide (E 172), black iron oxide (E 172)

The product is available in alu/alu blisters as described in section 6.5 of the SmPC.

2.2.2. Active substance

General information

The chemical name of osimertinib mesylate is *N*-(2-{[2-(dimethylamino)ethyl](methyl)amino}-4-methoxy-5-{[4-(1-methyl-1*H*-indol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide methansulfonate corresponding to the molecular formula $C_{29}H_{37}N_7O_5S$. It has a relative molecular mass of 595.7 g/mol and the following structure:

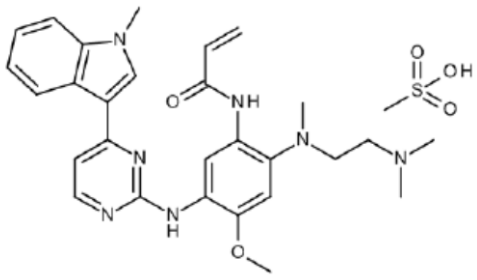


Figure 1: Structure of osimertinib mesylate

The structure of osimertinib was inferred from the route of synthesis and confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, UV spectroscopy, mass spectrometry and elemental analysis.

The active substance is a non-hygroscopic crystalline solid with pH dependent aqueous solubility: slightly soluble at pH 1.2, sparingly soluble in pH 4.5 buffer and very slightly soluble in pH 7 buffer. These properties are adequate for an oral solid dosage form. Only one polymorphic form is known despite extensive polymorph screening. Osimertinib is achiral.

Osimertinib is considered a new active substance from a quality perspective. The applicant compared its structure with active substances within authorised products in the EU and demonstrated that it is not a salt, ester, ether, isomer, mixtures of isomers, complex or derivative (e.g. pro-drug or metabolite) of any of them.

Manufacture, characterisation and process controls

Osimertinib is synthesized by a single manufacturer in four main steps using well-defined starting materials with acceptable specifications. The process was developed by the MAA before out-sourcing to the proposed commercial manufacturer.

A reworking procedure has been described to purify active substance which does not meet its specification. This is considered acceptable.

Critical steps have been defined and the in-process controls (IPCs) used to ensure the process performs as expected are described. Suitable specifications for isolated intermediates, starting materials and reagents have been presented.

The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. The synthetic route has remained the same with only minor changes to reagents and solvents which do not adversely impact the quality of the active substance.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The control strategy for a series of potentially mutagenic impurities has been devised in accordance with ICH M7 and ICH S9 since the product is intended to treat patients with advanced small cell lung cancer. Either suitable limits have been set in the active substance specification or efficient purge by the synthetic process has been demonstrated.

Critical quality attributes of the active substance have been defined as appearance, identity, assay and organic impurities. These properties are all controlled by tests in the active substance specification.

The active substance is packed in a container which complies with Commission Regulation (EU) No 10/2011.

Specification

The active substance specification includes tests for appearance, identity (active moiety and counter ion - FT-IR), assay (LC), impurities (LC), residual solvents (GC), residue on ignition (Ph. Eur.), particle size distribution (laser diffraction) and water content (KF).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. One mutagenic impurity has been identified and its level is set in line with ICH guidelines M7 (assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit genotoxic risk) and S9 (nonclinical evaluation for anticancer pharmaceuticals). The identification test is specific for the mesylate salt so no separate identification test for the counter ion is needed.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay testing has been presented.

Batch analysis data on 36 batches of the active substance were provided. The batches were all analysed according to the analytical methods and met with the specifications in place at the time they were manufactured and released. Of these, 11 were production scale batches analysed with the current analytical methods. The results were within the current specifications and consistent from batch to batch.

Stability

Stability data on three pilot scale batches manufactured by the MAA rather than the intended commercial supplier, but using the same process, and stored in the intended commercial package for up to 12 months under long term conditions (25 °C / 60% RH), up to 12 months under intermediate conditions (30 °C / 65% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) according to the ICH guidelines were provided. The following parameters were tested: description; assay; organic impurities; particle size distribution; polymorphic form; water content; microbiological quality. The analytical methods used were the same as for release and are stability indicating. All tested parameters were well within specification at all time-points and no significant trends were observed.

Supportive information from two earlier smaller scale batches manufactured using slightly modified routes (same sequence, different reagents) were also provided which also showed that the active substance is stable.

Photostability testing following the ICH guideline Q1B was performed on one batch (and one supportive batch) and the active substance shown not to be photosensitive.

Solid state stress testing was carried out up to 50 °C at ambient humidity. Solution state (or as a suspension if not soluble) degradation studies were carried out at pH 1, 7 and 13 or in the presence of an oxidant. Osimertinib is thermally and acid stable. Degradation is observed under basic, neutral and oxidative conditions.

The stability results indicate that the active substance is sufficiently stable. The stability results justify the proposed retest period of 12 months in the proposed container.

2.2.3. Finished medicinal product

Description of the product and Pharmaceutical development

The aim was to develop an immediate release dosage form containing either 40 or 80 mg of active substance. Film-coated tablets were chosen for the commercial presentation. Their cores are manufactured from a common granule blend and coated to form bioconvex, beige tablets of different sizes and debossed with their respective strengths in order to readily distinguish them. The quality target product profile (QTPP) was defined as immediate release dosage form containing osimertinib, that meets compendial and other relevant quality standards for appearance, identity, assay, impurities, uniformity of dosage units, dissolution, disintegration, hardness and friability.

Osimertinib is a non-hygroscopic solid with poor flow properties although other mechanical properties render it suitable for tableting. Only one polymorphic form is known and it exhibits pH dependent solubility in aqueous media with maximal solubility in weak acids. Permeability is formally low and so osimertinib is classed as BCS III although data suggested high enough permeability that it won't limit absorption. A series of different formulations was prepared during development including an oral solution used in early development, a powder in capsule formulation used in phase I, a film-coated tablet also used in phase I and the final commercial formulation used in phases I, II and III clinical trials. Sequential *in vivo* bioavailability studies were carried out in order to bridge between successive clinical trials. In parallel, *in vitro* dissolution studies demonstrated that differences in dissolution rate do not translate to differences in bioequivalence, further indicating that dissolution rate is not crucial to bioavailability. The phase I capsules contain the same excipients as those planned for commercialisation but in different proportions. Lower strength tablets were also used in phase I. The levels of lubricant, disintegrant and filler were optimised in order to improve product performance and manufacture. The amount of film coating mixture was also optimised to impart more consistent dissolution and appearance. A further *in vitro* dissolution study demonstrated the equivalence of tablets manufactured at the development and proposed commercial manufacturing sites.

Compatibility with the chosen core tablet and film coating excipients was shown using multi-variate design of experiments (DoE) under stressed conditions (high temperature/RH). Very little degradation was observed, indicating no compatibility issues. All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.2.1 of this report.

Risk assessment was used to guide development activities. The potential impact of individual formulation unit operations and the various input materials on quality attributes of the finished product was assessed and those deemed likely to be important were investigated experimentally. Material attributes (MAs) and process parameters (PPs) were set at appropriate levels to guarantee finished product quality and manufacturability based on these investigations. The overall control strategy is a combination input MAs, PPs, IPCs and finished product testing. No design space is applied for.

The discriminatory power of the dissolution method was investigated using batches manufactured with significant deviations in the most critical manufacturing parameters. In all instances, rapid release was achieved across the physiological pH range. Therefore, none of the manufacturing variables is considered critical to the dissolution behaviour of Tagrisso tablets. According to ICH Q6A, decision tree #7 (2), discriminatory power does not need to be demonstrated under such circumstances. The performance of the product is guaranteed by input material attributes, IPCs, and controlling the process under GMP within pre-determined limits.

The primary packaging is Alu/Alu blisters. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The applicant submitted a post-approval change management protocol (PACMP) for an additional primary packaging format, PVC/PVDC/Alu blisters. The Alu/Alu blister format was selected to provide a high barrier to water ingress. However, stability studies, including an open dish study at high humidity (40 ^{o}C / 75% RH) have shown that although an increase in water content is observed, this doesn't adversely impact the performance of the tablets with no change in assay, degradants or dissolution profile noticeable. Therefore, the medium moisture barrier provided by the PVC/PVDC/Alu format will provide sufficient protection. The PACMP is considered acceptable as is the reporting category IA_{IN} B.II.g.5.a.

Manufacture of the product and process controls

The manufacturing process consists of six main steps: blending of intra-granular excipients followed by lubrication; roller compaction and milling; lubrication of granules; compression; film-coating; packing. The process is considered to be a standard manufacturing process and as such, validation will be performed before the product is launched. An acceptable process validation scheme has been provided. Major steps of the manufacturing process have been validated by a number of studies. The critical steps are defined and suitable controls are applied. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release specifications are appropriate for this kind of dosage form and include tests for appearance, identification (UV, LC), assay (LC), degradation products (LC), dissolution (Ph. Eur.) and uniformity of dosage units (LC). The omission of a test for microbial quality was justified according to ICH Q6A (Decision Tree #8) in that evidence has been provided which indicates that the finished product has growth inhibitory properties. The water content of Tagrisso film-coated tablets is routinely low at release and after storage, and so no test for water content is needed.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standard used for assay testing has been presented.

Batch analysis results are provided for seven batches of 40 mg tablets and nineteen batches of 80 mg tablets, manufactured at pilot to production scale confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on three batches of each strength of tablet manufactured at ≥10% of commercial scale stored for up to 12 months under long term conditions (25 °C / 60% RH), up to 12 months under intermediate conditions (30 °C / 75% RH) and for up to 6 months under accelerated conditions (40 °C / 75% RH) in line with the ICH guidelines was provided. The batches of Tagrisso were manufactured by the proposed commercial process although two smaller scale 40 mg batches were made at a different site. Otherwise, the batches are identical to and packed in the same primary packaging as those proposed for marketing. Identical studies on samples stored in bulk packaging (aluminium bag in rigid container) were also carried out. Samples were tested for according to the release specifications with the omission of the dose uniformity and the inclusion of a test for microbial quality at some time-points. The analytical procedures used are the same as for release and were shown to be stability indicating.

No changes to any of the measured parameters were observed under any condition other than a small but notable increase in one specified degradation product. However, its level remained well within specification after 12 months and is predicted to do so, based on statistical analysis of the trends, over a 2 year period. Similar trends were observed for finished product stored in bulk packaging.

In addition, one batch of each strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant changes to any of the measured parameters were observed, indicating that Tagrisso is not photosensitive.

The batches were also stored under stressed conditions (50 ^{o}C / ambient RH and 40 ^{o}C / 75% RH / open container). The results indicate that Tagrisso is thermally stable but picks up up to 1 weight% water in a humid environment. However, this has no impact on other quality parameters or the product performance.

Based on available stability data, the proposed shelf-life of 18 months without special storage conditions as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

A PACMP for an additional packaging format was deemed acceptable, as was the variation classification which will be used to report the change.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The pivotal safety pharmacology, toxicology and toxicokinetic studies submitted to support this application were conducted in rats and dogs in compliance with GLP regulations. The dose range finding studies do not claim GLP compliance.

Osimertinib mesylate salt (the clinical form) was used for all of the GLP toxicology studies, except for the 1 month toxicity studies where the free base was used. In all studies, the dose levels are expressed as free base equivalent. The applicant did not seek scientific advice from the CHMP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vitro studies

Enzyme inhibition

The inhibition potency of osimertinib (AZD9291) and its pharmacologically active metabolites AZ5104 and AZ7550 were tested against three isolated mutant EGFR enzymes (L858R, L861Q and T790M/L858R) using a filter-binding radioactive ATP transferase assay.

Table 5 Summary of osimertinib, AZ5104 and AZ7550 inhibition against isolated EGFR enzymes (apparent IC_{50}, nM)

Compound	EGFR (T790M/ L858R)	EGFR (L858R)	EGFR (L861Q)	EGFR (wild-type)
osimertinib	1	12	5	184
AZ5104	<1	6	1	25
AZ7550	4	56	29	519

EGFRm sensitising mutants; L858R, L861Q

The selectivity of osimertinib, AZ5104 and AZ7550 was assessed using a panel of 244 isolated protein kinases and 21 lipid kinases.

Table 6: Percent of kinase inhibition at 1 µMm, and IC50 values (nM) for kinases significantly inhibited by osimertinib, AZ5104 or AZ7550

Kinase	osimertinib		AZ5104		AZ7550	
	% inhibition	IC_{50}	% inhibition	IC_{50}	% inhibition	IC_{50}
ACK1	100	71, 128	100	27, 66	76	156, 344
ALK	66	231, 1622	89	97, 175	58	420, 1804
BLK	**100**	**168, 442**	**100**	**27, 56**	**50**	**977, 1469**
BMX	**19**	**2425, 2381**	**68**	**505, 359**	**14**	**>10000, >10000**
BRK	87	255, 258	99	45, 57	56	843, 420
BTK	**64**	**699, 989**	**91**	**132, 451**	**12**	**5104, 4433**
ErbB2	**97**	**116**	**98**	**61**	**89**	**700**
ErbB4	**94**	**67, 46**	**97**	**7, 11**	**81**	**195, 222**
FAK	67	598, 774	95	136, 320	37	995, 1866
FES	39	389, 1985	83	127, 468	59	449, 1028
FGFR1	77	>10000	31	6018	12	>10000
FLT3	55	562, 2392	75	129, 911	39	302, 2128
FLT4	78	678, 983	82	142, 404	50	1784, 3190
IGF1-R	64	941, 1775	87	78, 395	38	1005, 4119
Ins R	66	432, 880	90	127, 226	39	1256, 1803
IRR	21	281, 2210	95	423, 342	19	840, 3510
ITK	**17**	**6956, 10000**	**81**	**925, 1529**	**23**	**>10000, >10000**
JAK3	**44**	**2640, 3436**	**49**	**1358, 2556**	**19**	**>10000, >10000**
LRRK2	75	375	65	993	35	3933
MLK1	88	85, 409	63	141, 1289	69	88, 448
MNK2	91	95, 155	91	62, 171	75	228, 585
PYK2	59	682, 1476	81	284, 536	28	2288, 4653
TEC	**79**	**420, 497**	**91**	**118, 219**	**43**	**1317, 2191**
TrkB	0	>10000	100	>10000	100	>10000
Txk	**66**	**1590, 2519**	**83**	**426, 621**	**29**	**2443, 5541**
YES	86	8193	22	4803	4	>10000

ND = Not determined
Kinases in bold have analogous reactive cysteine 797 residue in their catalytic site.
IC_{50} values from two independent studies are shown where tested. Single dose data is from single experiment that is representative of three independent studies.

Inhibition of EGFR phosphorylation in cells

In vitro cellular EGFR phosphorylation assays indicated that osimertinib has greater activity towards mutant EGFRs compared to wild-type in an *in vitro* cellular context.

Table 7: Summary of pEGFR IC50 inhibition in response to osimertinib, AZ5104 and AZ7550 across various cell lines following a 2 hour pre-incubation (Apparent IC50 Geomean, 95% confidence intervals when n>2, nM)

	H1975 (L858R/ T790M)	PC-9 VanR (ex19del/ T790M	PC-9 (ex19del)	H3255 (L858R)	H1650 (ex19del)	LoVo (WT)	A431 (WT)	NCI-H2073 (WT)
osimertinib	15 (10, 20)	6 (3, 13)	17 (13, 22)	60, 49	14, 12	480 (320, 720)	2376, 1193	1865 (872, 3988)
Decamitinib	40 (24, 65)	6 (2, 17)	0.7 (0.5, 1)	1.2, 1.3	0.04, 0.06	12 (8, 17)	51, 22	26 (7, 99)
Afatinib	22 (15, 31)	3 (2, 6)	0.6 (0.5, 0.8)	1, 0.8	0.6, 3	15 (10, 24)	27, 40	25 (5, 129)
Gefitinib	3102 (1603, 6001)	741 (484, 1136)	7 (5, 11)	11, 12	16, 19	59 (42, 82)	60, 88	61 (34, 110)
Erlotinib	6073 (3634, 10150)	1262 (588, 2711)	6 (4, 7)	8, 11	5, 8	91 (53, 156)	244, 260	108 (52, 223)
AZD5104	2 (2, 4)	1 (0.004, 8)	2 (2, 3)	ND	ND	33 (24, 45)	ND	53, 66
AZD7550	45 (34, 59)	29 (8, 108)	26 (10, 65)	ND	ND	786 (480, 1292)	ND	2356, 2367

ND: Not determined
EGFRm sensitising mutants: L858R, Ex19del
wt: wild-type

In vitro wash-out and time-dependent cellular kinetic studies supported the irreversible mechanism of action of osimertinib (data not shown).

Inhibition of *in vitro* cellular proliferation

Inhibition of proliferation has been studied in a panel of mutant and wild-type EGFR tumour cell lines.

Table 8: Anti-proliferative efficacy of osimertinib, AZ5104 and AZ7550 across mutant and wild-type EGFR cell lines (IC50 Geomean (nM), 95% CI where n>2) (pharmacology report 13)

Compound	H1975 (L858R/ T790M)	PC9VanR (Ex19del/ T790M)	PC9 (Ex19 del)	CALU3 (wt)	CALU6 (wt)[a]	H2073 (wt)
osimertinib	11 (6, 19) n=17	40 (30, 54) n=8	8 (7, 9) n=17	650 (457, 924) n=17	4089 (3551, 4708) n=15	461 (230, 924) n=12
AZ5104	3 (2, 5) n=11	7 (3, 17) n=3	3 (2, 3) n=11	80 (28, 231) n=11	2041 (1650, 2525) n=9	28 (7, 107) n=8
AZ7550	30 (ND) n=2	ND	16 (ND) n=2	954 (ND) n=2	3954 (ND) n=2	1361 (ND) n=1

ND = not determined
a: CALU6 is without wild-type EGFR proliferative drive

Acquired resistance to EGFR TKIs

T790M, as an acquired resistance mechanism across multiple independent populations of PC9 cells, was not detected following chronic treatment with osimertinib (see figure below).

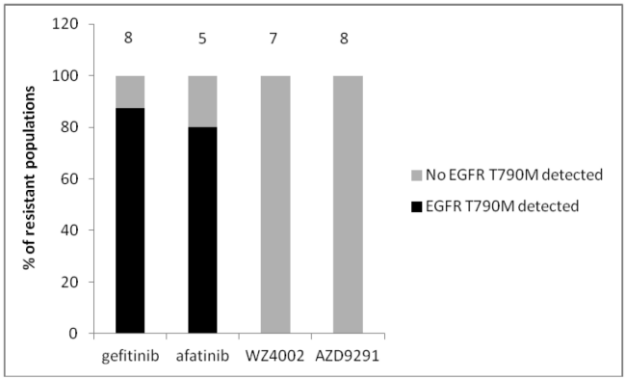


Figure 4: T790M acquired resistance to osimertinib in PC9 cells in vitro

In vivo studies

Tumour growth regression was investigated following oral treatment with daily doses of osimertinib of mice bearing EGFRm and EGFRm/T790M or wild-type EGFR xenograft tumours.

Table 9: Summary of xenograft % growth inhibition studies across models after 14 daily doses of osimertinib

Xenograft model	Mutation status	Dose mg/kg QD	% Tumor Growth Inhibition; Mean ± SEM (number of experiments where n>2)
H1975	L858R/T790M	25	120
		10	120
		5	119 ± 2 (n=9)
		2.5	116, 107
		1	81 ± 6 (n=3)
		0.5	39, 43
H3255	L858R	5	211
PC9VanR	Ex19del/T790M	5	171
PC9	Ex19del	25	212
		10	162
		5	178 ± 4 (n=8)
		2.5	165
		1	150, 154
		0.5	103
		0.25	39
		0.1	13
A431	wt	25	102
		10	94
		5	77 ± 3 (n=9)
		2.5	59
		1	43, 33
		0.5	36
		0.1	11
LOVO	wt	25	56
		5	7

Xenograft growth regression with osimertinib was accompanied by dose and time-dependent pharmacodynamic inhibition of phospho-EGFR (pEGFR) together with key downstream biomarkers phospho-AKT (pAKT) and phospho-ERK (pERK) across mutant and wild-type EGFR disease models in vivo (data not shown).

Osimertinib pharmacology caused tumour regression in transgenic disease models at low oral doses that align with clinical dose levels. Daily oral administration of 25 mg/kg of osimertinib resulted in profound and sustained growth regression in a PC9 brain metastasis model in vivo (data not shown).

Secondary pharmacodynamic studies

Osimertinib and its two metabolites, AZ5104 and AZ7550, were tested in a panel of *in vitro* radioligand binding, enzyme activity and functional assays covering a diverse range of receptors, ion channels, transporters and enzymes to explore their pharmacological profiles.

The table below shows those targets with <100 fold selectivity over primary target IC50 (osimertinib, AZ5104 and AZ7550 have IC50 values of ≤12, ≤6 and ≤56 nM, respectively, at isolated mutant EGF receptors).

Table 10: Effect of osimertinib, AZ5104 and AZ7550 in in vitro radioligand binding, enzyme activity and functional assays: summary of the targets where the IC50 or Ki (μM) is within 100-fold of primary target

Target[a]	AZD9291	AZ5104	AZ7550	Pharmacological Mode of Action
EGFR Kinase	0.014	<0.01	0.057	Inhibitor
5-HT_{2C} Receptor	0.018	0.014	0.098	Antagonist
Urotensin UT_2 Receptor	0.22	[b]	1.4	Antagonist
5-HT_{1D} Receptor (rat)	0.23	0.14	1.7	AZD9291= Partial Agonist, AZ5104=Agonist AZ7550=Antagonist
Dopamine D_2 Receptor	0.26	[b]	0.091	AZD9291 =agonist, AZ7550=ND[c]
α_{1B} Adrenoceptor	0.36	0.085	0.21	Antagonist
α_{1D} Adrenoceptor	0.27	0.072	0.30	ND
α_{2C} Adrenoceptor	0.38	[b]	0.83	Agonist
5-HT_{2B} Receptor	0.39	0.24	0.92	Antagonist
15 Lipoxygenase	0.40	[b]	0.47	Inhibitor
5-HT_7 Receptor	0.52	[b]	0.26	Antagonist
PDGFβ Receptor Kinase	0.54	[b]	0.51	Inhibitor
Dopamine D_1 Receptor	0.54	0.21	1.6	Antagonist
5-HT_{2A} Receptor	0.68	0.13	2.9	Antagonist
α_{1A} Adrenoceptor	0.78	[b]	2.8	Antagonist
KDR Kinase	0.81	0.30	0.81	Inhibitor
5-HT_{1A} Receptor	0.83	[b]	0.38	AZD9291=ND, AZ7550=Agonist
Somatostatin sst_4 Receptor	0.83	[b]	1.3	AZD9291=partial agonist AZ7550=ND
5-HT_{1B} Receptor (rat binding/hamster function)	0.98	[b]	1.6	Antagonist
Insulin Receptor Kinase	1.2	0.11	0.73	Inhibitor
Tachykinin NK_2 Receptor	1.2	[b]	2.8	Antagonist
Adenosine Transporter (guinea-pig)	[b]	0.041	5.5	ND
cKIT Kinase	[b]	0.55	0.54	Inhibitor

Melanocortin MC_5 Receptor	[b]	[b]	0.4	Antagonist
Dopamine D_3 Receptor	[b]	[b]	0.83	Agonist
Opioid μ Receptor	[b]	[b]	1.2	Agonist
Prostanoid EP_2 receptor	[b]	[b]	1.7	Antagonist
SRC Kinase	[b]	[b]	2.4	Inhibitor
Phosphodiesterase $PDE10_{A1}$	[b]	[b]	2.4	Inhibitor
5 Lipoxygenase	[b]	[b]	2.6	Inhibitor
Tachykinin NK_1 Receptor	[b]	[b]	2.8	Antagonist
Muscarinic M_1 Receptor	[b]	[b]	2.9	Antagonist
Neurotrophic Receptor Kinase 1	[b]	[b]	3.1	Inhibitor
Opioid κ Receptor (rat)	[b]	[b]	3.3	Antagonist
Muscarinic M_3 Receptor	[b]	[b]	3.7	Antagonist
Muscarinic M_5 Receptor	[b]	[b]	4.4	ND
Ghrelin Receptor	[b]	[b]	4.6	Antagonist
$5\text{-}HT_{5A}$ Receptor	[b]	[b]	4.6	ND
Translocator Protein (18kDa) (rat)	[b]	[b]	4.7	ND
Opioid δ Receptor	[b]	[b]	4.8	ND

[a] all human except where noted
[b] >100-fold selectivity vs. primary target (mutant EGFR, see Table 1).
[c] ND, not determined

Inhibition of Insulin-like Growth Factor-1 Receptor (IGF1R) and Insulin Receptor (InsR)

Table 11: IC50 inhibition for osimertinib, AZ5104 and AZ7550 against recombinant IGF1R and InsR enzyme assays (IC50 Geomean, 95% confidence intervals when n>2, nM)

	IGF1R	InsR
AZD9291	2360, 3460	1200 (620, 2290) (n=3)
AZ5104	238 (181, 313) (n=5)	90, 130
AZ7550	1710 (990, 2940) (n=4)	1020, 530

Safety pharmacology programme

Osimertinib has been evaluated in a panel of safety pharmacology studies to examine potential effects on the cardiovascular, gastrointestinal, respiratory and central nervous systems.

There were no notable effects of osimertinib on the respiratory, visual or central nervous systems in rats following administration of single doses up to 100 mg/kg in GLP safety pharmacology studies. (Study 3464SR, GLP).

Osimertinib inihibited the human ether-a-go-go related gene (hERG) encoded potassium channel in Chinese hamster ovary cells in vitro (study number VKS0795/0403SZ, GLP) with an IC50 of 0.69 μM indicating a potential to cause prolongation of the QT interval.

In the GLP dog cardiovascular study (Study 1352ZD), administration of single oral doses of osimertinib (0, 6, 20 and 60 mg/kg) to conscious telemetered dogs was associated with marginal differences in QTcR (up to 7 increase) and heart rate (up to 20% decrease) compared to the vehicle control in all three dosing groups. Group mean plasma concentrations at the lowest dose (6 mg/kg) were 0.516, 0.0150 and 0.0713 μM for osimertinib, AZ5104 and AZ7550, respectively.

In a non-GLP investigative study in the anaesthetized guinea pig (study 0264SG), intravenous infusion of osimertinib was associated with small decreases in heart rate (up to 7%) and +ve dP/dtmax (an index of cardiac contractility; up to 18%) and increases in left ventricular systolic pressure (up to 10%), PR interval (up to 7%), QTcB interval (up to 7%) and QRS duration (up to 26%). These findings were only seen at very high exposures (total plasma concentrations of 22.87 µM) and not at the lower dose of 5 mg/kg (total plasma concentrations of 4.76 µM).

Dose-dependent increases in blood pressure were seen in the rat telemetry study (study PH E 14191) at oral doses of 50 mg/kg and above (NOEL at 20 mg/kg). Exposure of osimertinib was based on extrapolation from other studies would be expected to be comparable to the human Cmax at the 80 mg dose (0.635 µM). There were no effects on blood pressure in the GLP dog telemetry study (osimertinib group mean Cmax up to 2.51 µM) or in the 1 month dog study. Some increases in blood pressure were noted during the 14 day dog dose range finding study, but these were confined to poorly tolerated doses (20 mg/kg) or above. The clinical relevance of the observed increased blood pressure is uncertain.

Osimertinib inhibited GI transit in the rat at clinically relevant plasma concentrations.

Pharmacodynamic drug interactions

No studies were submitted.

2.3.3. Pharmacokinetics

Non-clinical absorption, distribution, metabolism and excretion (ADME) studies were submitted. These studies used the same species and where possible the same strains of laboratory animal (mouse, rat, and dog) that were used in the pharmacology, general toxicology and reproductive toxicology studies. Tissue distribution was investigated in albino and partially pigmented rats. *In vitro* investigations were performed in isolated human tissue and in animal or insect derived tissue that expressed specific human drug metabolism and transport proteins. Metabolite identification was conducted following a single dose to human volunteers and on steady state plasma samples from patients.

The multi-analyte analytical methods used to assay osimertinib, and N-desmethyl metabolites AZ5104 and AZ7550 in preclinical pharmacokinetic and toxicology studies employed LC-MS/MS.

Absorption

Osimertinib absorption was moderate to high in preclinical species with bioavailabilities of 24-37% in rat (study 8308627) and 115% in dog (study 197725). Exposure increased approximately in proportion to increasing dose. Absorption was prolonged with Tmax typically being achieved at 2-4 h or later following higher doses in toxicology studies.

Osimertinib has a moderate to high volume of distribution in rat (12-13 L/kg) and dog (18 L/kg) which is consistent with the lipophilic and basic physico-chemical properties of the compound and with the observation that tissue concentrations were higher than blood in the rat QWBA study. Plasma clearances were 2.6 and1.8 L/h/kg in male and female rats and ~1.3 L/h/kg in the dog. The combination of moderate clearance and volume of distribution results in half lives of 2-5 h in rat and 5-13 h in dog. The half-life after oral dosing was longer than after IV which may indicate prolonged absorption of osimertinib. Half-lives in preclinical species were shorter than in humans where a half-life of 55.06 h was calculated after an 80 mg human capsule dose.

In rats, osimertinib exposure was up to 2 fold higher in female rats than males, which is consistent with the sex difference in clearance, and exposure increased approximately in proportion to dose in both sexes. Following daily dosing of between 4 and 40 mg/kg for 1 month to rats of both sexes, exposure was largely unchanged upon multiple dosing.

In male and female dogs, exposure was similar. Osimertinib exposure increased approximately in proportion to dose between 2 and 20 mg/kg. A slight accumulation was observed after 2 weeks and maintained at 4 weeks dosing in the 1 month toxicology study, consistent with the half-life in the dog (approximately 10 h).

Distribution

Tissue distribution

The tissue distribution of radiolabelled osimertinib was evaluated in study KMR002, in partially pigmented and albino rats.

In male partially pigmented rats, drug-related material was slowly absorbed and widely distributed at the early sampling times, with tissue concentrations typically higher than in blood. The highest concentrations of radioactivity were observed at 6 hours post-dose in uvea plus retinal pigment epithelium (RPE), inner renal cortex, bile ducts, pituitary, spleen, renal cortex, lung and Harderian gland. Radioactivity was still evident in 42% of tissues measured at 60 days after dosing.

The pattern of distribution in albino rats was, with the exception of melanin containing tissues, qualitatively similar to those observed in male partially pigmented rats at comparable times.

The central nervous system (i.e., brain and spinal cord) contained quantifiable radioactivity up to 21 days post-dose, suggesting that osimertinib drug-related radioactivity crosses the blood brain barrier to some extent. This was also supported by a study in SCID tumour bearing mice, with osimertinib brain to plasma AUC ratios up to 2.8.

Protein binding

The protein binding of osimertinib has not been determined due to instability in human plasma and non-specific binding issues.

However, a preliminary investigation of the plasma protein binding of osimertinib, AZ5104 and AZ13597550 at 100 µM (study ID VKS0890, see table below) indicated that the binding was high for each compound in all the species investigated, although a specific value could not be assigned for osimertinib and AZ7550 due to non-specific binding issues in the ultrafiltration collection tube. A computational model was used to predict the human protein binding. The prediction for AZ5104 was the same as that measured (98% bound) suggesting that the binding of osimertinib (99% predicted) and AZ7550 (98% predicted) were likely to be at least as high as for AZ5104.

Table 12: Preliminary binding of osimertinib incubated at 100 µM to mouse, rat, rabbit, dog, guinea pig and human plasma and human serum albumin (HSA) and α1-acid glycoprotein (AGP) in vitro by ultrafiltration

Species	AZD9291		AZ5104		AZ7550	
	Bound (%)	Unbound (%)	Bound (%)	Unbound (%)	Bound (%)	Unbound (%)
Mouse	NC	NC	97.9	2.1	NC	NC
Rat	NC	NC	96.4	3.6	NC	NC
Rabbit	NC	NC	98.0	2.0	NC	NC
Dog	NC	NC	98.6	1.4	NC	NC
Guinea pig	NC	NC	98.3	1.7	NC	NC
Human	NC	NC	98.0	2.0	NC	NC
HSA	82.3	17.7	69.0	31.0	83.7	16.3
AGP	15.9	84.1	29.5	70.5	21.5	78.5

NC Not calculated due to non-specific binding in the ultrafiltrate device

Blood/plasma ratio

osimertinib related material was mostly distributed into the blood cells. The distribution increased with time and was higher in male rats at all-time points.

In male dogs, after oral dosing the [^{14}C] blood/plasma ratio was approximately 1 at all time points. After intravenous dosing, the ratio decreased from 1.4 at the first time point (5 min) to approximately 1 after 6 hours where it remained constant up to 168 h.

Covalent binding

Osimertinib binds covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes (Studies 120118-CVB-KXZZ856, 111123-CVB-KXZZ856, KMN006).

Placental transfer

No studies have been conducted.

Metabolism

The metabolism of osimertinib has been investigated *in vitro* in mouse, rat, dog and human hepatocytes, in isolated recombinant cytochrome P450 (CYP) isozymes and in humans. No preclinical *in vivo* metabolism studies have been conducted.

Results from study ADME 025 showed that the metabolism of osimertinib was primarily to oxidative and dealkylated products with direct conjugation to a range of glutathione, cysteineglycine, glucuronide and sulphate conjugates. All metabolites formed in human hepatocytes were seen in incubations with rat and dog hepatocytes. Only 2 metabolites were detected between 1-10 % in human hepatocytes: the de-methylated M3 and the oxidated M4. The de-methylated plasma metabolites M3 (AZ7550) and M6 (AZ5104) are active metabolites.

In a panel of CYP isoforms, CYP3A4 was the principal CYP enzyme responsible for the metabolism of osimertinib although CYPs 1A2, 2A6, 2C9, 2E1 and 3A5 also contributed to a lesser extent. Similarly the metabolites AZ5104 and AZ7550 were extensively metabolized by CYP3A4 and/or CYP3A5. The extent of formation of AZ5104 and AZ7550 from osimertinib incubations also indicated that they were predominantly formed by CYPs 3A4 and 3A5.

Excretion

Following intravenous and oral administration of osimertinib, the major route of excretion was via faeces, with urinary elimination being a minor component. Excretion was rapid in rats (study KMR008), with the majority of dose recovered in the first 48h, and between 90.0 and 99.3% recovered within 168 h. In dogs (study 197725), excretion rate was variable between individuals, with the majority (85.2 to 86.4%) recovered within 168h. The constitution of the excreted radioactivity has not been further studied in animals. In humans, approximately 47.7% of osimertinib related components were excreted after 7 days, 68.9% after 21 days and 81.9% after 84 days with the majority of radioactivity excreted in faeces.

Pharmacokinetic drug interactions

Cytochrome P450 Inhibition

The direct and time-dependent CYP inhibitory potential of osimertinib, AZD5104 and AZD7550 (0.1-30 µM) were tested against a panel of CYP enzyme activities in vitro. Osimertinib showed to be an *in vitro* competitive inhibitor of CYP3A4/5 with an IC50 of 5.1 µM, but not CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6 and 2E1 at clinically relevant concentrations.

An *in vivo* study has been submitted to elucidate the CYP inhibition of osimertinib at the clinical doses. Modest inhibition was showed for CYPs 1A2 and 2C8. However, at clinical doses osimertinib did not result in DDI via inhibition of CYP1A2 or 2C8. At the highest osimertinib concentration (30 µM) no inhibition of CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 was observed. The metabolites AZ5104 and AZ7550 demonstrated modest inhibition against CYPs 1A2, 2C8, 3A4/5 with IC_{50} of >17.9 µM. Osimertinib was shown to be a weak time-dependent inhibitor of CYP3A4 in vitro (24% TDI at 50 µM) which was further analyzed where the kinetic time-dependent inhibition parameters kinact (maximal inactivation) and ki (concentration at 50% Kinact) for osimertinib against CYP3A4 were determined. The estimated values were 0.0617 min-1 and 1090 µM, respectively.

Cytochrome P450 Induction

The CYP induction potential of osimertinib was investigated using cultures of human hepatocytes. At the highest osimertinib concentration (3.3 µM), induction of CYP3A4 and CYP1A2 activity was observed (up to 45% and 16% of positive control respectively) with no induction of CYP2B6.

UGT inhibition

Based on in vitro studies, osimertinib is not an inhibitor of UGT2B7 and weak inhibitor of UGT1A1 and is unlikely to result in a clinically relevant hepatic DDI. However, due to higher concentrations observed in the intestine, intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown.

Transporter inhibition

The table below outlines results of studies that investigated the inhibition of efflux and uptake transporters by osimertinib.

Table 13: Inhibition of efflux and uptake transporters by osimertinib

Transporter	Apparent IC_{50} (µM) or inhibition (%) at highest concentration (µM)	Probe substrate
Pgp	No inhibition (30 µM)	digoxin
BCRP	2.0 µM	[^{3}H]-rosuvastatin
OATP1B1	22 µM	estradiol 17β glucuronide
OATP1B3	52.5 µM	atorvastatin
OAT1	No inhibition (100 µM)	para-aminohippurate
OAT3	No inhibition (100 µM)	furosemide
OCT2	7.98 µM	metformin
MATE1	4.63 µM	metformin
MATE2-K	23.0 µM	ASP

ASP: 4-Di-2-ASP (4-(4-(Diethylamino)styryl) -N-Methylpyridinium Iodide)

Transporter substrate

In vitro, osimertinib, AZ5104 and AZ7550 are substrates for the human drug efflux transporter MDR1 (P-gp) and BCRP. Osimertinib, AZ5104 and AZ7550 are not substrates for OATP1B1 and OATP1B3 (data not shown).

Protein binding

The human microsomal binding of osimertinib was observed to be 97.4% in a 4 hours incubation (fumics =0.0261, n=1). As this value indicated a high non-specific binding to human microsomes, the DDI assessment has been re-evaluated for CYPs 3A4, 2C8 and for other where the IC50 is >30 µM. Three situations were presented using a mechanistic static model: A) fumic = 1 and plasma protein binding (PPB) = 90%, B) fumic = 0.0261 and PPB = 90% and C) fumic = 0.0261 and PPB = 99%. In all situations the possibility of interaction with CYP3A4/5 was greater than with other CYPs.

Other pharmacokinetic studies

Metabolite pharmacokinetics

Two different N-desmethyl active metabolites of osimertinib (AZ5104 and AZ7550) were identified during incubations with rat or dog hepatocytes, and both were found to be pharmacologically active. The concentrations of metabolites AZ7550 and AZ5104 have been determined in mouse, rat and dog pharmacokinetic studies and 1 and 3 month rat and dog pivotal toxicology, safety pharmacology and rat embryofetal development studies following oral dosing of osimertinib.

Exposure to osimertinib and AZ7550 was quantified in all of these studies, but it was only possible to quantify exposure to AZ5104 in the 1 month dog study and dog cardiovascular study due to analytical issues (interfering component, failed ISR). Exposure to these metabolites achieved in rats and dogs at the highest doses tested in the pivotal repeat dose toxicity studies and in the rat embryofoetal development study were generally similar to or below that observed in humans at the 80 mg dose.

In rats (study 3416AR) both osimertinib and AZ7550 exposure on Day 28 increased approximately in proportion to increasing dose. AZ7550 maximal concentrations and AUC (0-24) were 5 to 13% and 6 to 14% of osimertinib

values. The exposure of osimertinib and AZ7550 on Day 91 of the rat 3 month toxicology study (study 526248) were similar to those from Day 28 of the 1 month toxicology studies.

In dogs (study 1351AD), osimertinib, AZ7550 and AZ5104 exposure on Day 28 increased approximately in proportion to increasing dose. AZ7550 maximal concentrations and AUC (0-24) ranged from 15 to 19% and 16 to 20% of osimertinib respectively. AZ5104 maximal concentrations and AUC (0-24) ranged from 4 to 5% and 5 to 8% of osimertinib, respectively. Exposure to osimertinib was consistently greater in females than males only in rats and there were no sex differences in exposure to AZD9191 and AZ7550 in dogs.

2.3.4. Toxicology

Toxicology studies submitted included repeat-dose toxicity studies in rats and dogs (up to 3 months duration), *in vitro* and *in vivo* genotoxicity, reproductive toxicity and phototoxic potential. Additional *in vitro* genetic toxicity studies were conducted on a number of potential impurities. All pivotal studies were conducted in compliance with GLP regulations and used the intended clinical route of administration (oral).

Single dose toxicity

Dedicated single dose toxicity studies were not submitted.

Repeat dose toxicity

Table 14: Repeat-dose toxicity studies with AZD 9291

Species/ strain/ Study ID (GLP)	Dose (mg/kg/day) Route (Vehicle)	n/sex /group	Duration	Major findings	NOAEL (mg/kg/day)
Rat / Wistar 3544KR (non-GLP)	100, 300, 1000 Oral (gavage) (0.5% w/v HPMC and methane sulphonic acid)	100, 1000 mg/kg:1M 300 mg/kg: 3M	2 days	≥100 mg/kg: ↓body weight 300 mg/kg: clinical signs, macroscopic findings in GI tract. 1000 mg/kg: Above MTD	<100
Rat / Wistar 3278DR (non-GLP)	0, 50, 100, 200 Oral (gavage) (0.5% w/v hydroxypropyl methylcellulose /0.1% w/v Polysorbate 80)	3M/ group	7 days	≥50 mg/kg: ↓body weight and food intake. Altered haematological parameters (↓reticulocytes, white blood cells and lymphocytes, ↑neutrophils) and clinical chemistry (↓triglycerides, sodium and total protein, and ↑phosphate and potassium). Histopathological findings in thymus (↓ lymphocytes and/or single cell lymphocyte necrosis) and stomach (crateriform depressions) ≥100 mg/kg: Above MTD. Histopathological findings in sternum (↓bone marrow cellularity), forestomach (inflammatory cell infiltration, gastric erosion/ulceration, ↑gastric weights), duodenum (inflammatory cell infiltration), and liver (↓glycogen, ↓weight)	<50
Rat / Wistar 3310DR (non-GLP)	0, 20, 40, 60 Oral (gavage) (0.5% w/v hydroxypropyl methylcellulose)	4/sex/ group	14 days	≥20 mg/kg: slight ↓food intake (F). Changes in haematological parameters (↓reticulocytes, ↑neutrophils, monocytes, lymphocytes). ↓ Urine total protein (M). Histopathological findings (F) in eye (corneal epithelial atrophy). ≥40 mg/kg: Above MTD (F). ↓Body	<20

				weight/body weight gain and food intake (M, F). Adverse clinical signs (F). ↓Visual acuity. Changes in clinical chemistry (↓ALP, triglycerides, total protein, albumin, globulin, calcium, cholesterol, phosphate, glucose. ↑urea, creatinine). Histopathological findings (M) in eye (corneal epithelial atrophy), thymus (hypocellularity, lymphocytolysis, ↓ weight), bone marrow (hypocellularity), small intestine (villous/epithelial atrophy, epithelial degeneration/necrosis/inflammation). ↓Liver glycogen (F). 60 mg/kg: Adverse clinical signs (M). ↓liver and spleen weight (M).	
Rat / Wistar 3416AR (GLP)	0, 4, 10, 20 (F), 40 (M) Oral (gavage) (0.5% w/v hydroxypropyl Methylcellulose)	10/sex/ group + 5/sex/ recovery group	28 days + 28 days recovery	≥4 mg/kg: ↓Body weight/body weight gain. Histopathological findings in eye (corneal atrophy) ≥10 mg/kg: Histopathological findings in tongue (F, atrophy), testes (tubular degeneration, spermatid retention), uterus and ovaries (anoestrus, degenerated corpora lutea). ↓RBC parameters (M), ↑WBC parameters (F) 20/40 mg/kg: ↓Food intake. ↓clinical chemistry parameters (triglycerides (M), cholesterol, total protein, albumin).↑WBC parameters. Histopathological findings in skin/muzzle (inflammatory cell infiltration), tongue (M, atrophy), epididymides (↓sperm, ↑cellular debris, ↓ weight), mesenteric lymph nodes (M, erythrocytes). ↓Weight of epididymides, liver, thymus and prostate. Recovery: No histopathological findings, except for minimal corneal epithelial atrophy (1F). Altered clinical chemistry	<4
Rat / Wistar 526248 (GLP)	0, 1, 10, 20 (F), 40/20 (M) Oral (gavage) (MilliQ water pH adjusted with methane sulfonic acid)	10/sex/group	92 days	≥10 mg/kg: ↓Body weight/body weight gain and food intake (M). Histopathological findings in skin (flaky, scabs, follicular inflammation), cornea (atrophy), oesophagus (atrophy), tongue (atrophy), testes (spermatid retention), uterus and vagina (epithelial thinning), Harderian gland (necrosis/degeneration and regeneration), lung (alveolar macrophage aggregation) and spleen (↑haematopoiesis). ↓Uterus-, prostate and epididymides weight. ≥20 mg/kg: Histopathological findings in stomach (atrophy, ulceration), mammary gland (M, atrophy), mesenteric lymph nodes (dark discolouration, erytrophagocytosis), ↑WBC parameters. Altered clinical chemistry (↓albumin, globulin and albumin/globulin ratio).↓Male fertility (↑preimplantation loss). 40/20 mg/kg: >MTD. Taken off-dose from Day 56, followed by a dose reduction to 20 mg/kg/day from Day 62.	1 (NOEL)
Dog / Beagle 1324DD (non-GLP)	MTD phase: single dose: 10, 30, 100, 200, 400, 5 days: 100 Repeat dose phase: 10, 20, 40, 60	1/sex/ dose	MTD: Single, ascending dose (2 days washout), 5 days repeat dose (100 mg/kg)	**MTD:** MTD ≥400 mg/kg (single dose) and <100 mg/kg (5 days). ≥10 mg/kg: ↓food intake. Sight to moderate ↑cholesterol. ≥30 mg/kg: ↑neutrophils, monocytes (F) ≥100 mg/kg: Emesis. ≥200 mg/kg: ↓body weight. ↑neutrophils (M). $\downarrow K^+$ 400 mg/kg: slight ↓RBC, HC and Hb (F)	<10

	Oral (gavage) (0.5% w/v hydroxypropyl methylcellulose)		Repeat dose: 14 days	100 mg/kg (5 days): ↑Large unstained cells (LUC) (M). ↑triglycerides. Sight ↑ALP. Slight ↓RBC, HC and Hb (M) **Repeat dose:** ≥10 mg/kg: ↑cholesterol. Histopathological findings in eyes (corneal atrophy, occasional ulceration/erosion), skin (epithelial degeneration) and tongue (epithelial atrophy, erosion and/or ulceration) ≥20 mg/kg: ↓RBC, HC, Hb (M). ↑neutrophils, monocytes and LUC (M). ↓Na^+ (M). ↑ALP (M), ↓creatinine. Histopathological findings in the intestine (inflammatory cell infiltration and/or epithelial degeneration) ≥40 mg/kg: Macrothrombocytes and ↓platelets (F). ↑triglycerides, total protein and globulin (F). ↑Phosphate. ↓ Na^+ (M). ↑ALP (F) 60 mg/kg: ↓RBC, HC, Hb (F). ↑ triglycerides, total protein and globulin (M).	
Dog / Beagle 1351AD (GLP)	0, 2, 6, 20/12 Oral (gavage) (0.5% w/v hydroxypropyl methylcellulose)	3/sex/ group	28 days + 28 days recovery	≥2 mg/kg: minor clinical signs, ↓food intake and body weight loss. Histopathological findings in testes (tubular atrophy) and epididymides (round germ cells), not seen at 20/12 mg/kg). ≥6 mg/kg: Histopathological findings in eye (corneal atrophy), tongue (atrophy) 20/12 mg/kg: >MTD (corneal epithelial erosion/ulceration detected by ophthalmology, ↑food consumption, ↓body weight and clinical signs). Taken off-dose from Days 8 to 10, dose reduced to 12 mg/kg from Day 11. Histopathological findings in duodenum (atrophy), ileum and skin (atrophy). Recovery: Corneal translucency (1F, 1M). No other findings.	<2
Dog / Beagle 526253 (GLP)	0, 1, 3, 10/6 Oral (gavage) (MilliQ water pH adjusted with methane sulfonic acid)	4/sex/ group	92 days	≥3 mg/kg: transient ocular findings (2M) 10/6 mg/kg: >MTD based on ocular clinical signs (conjunctival reddening, closed/partly closed eyes, discharge, corneal epithelial ulceration/erosion), and ↓food intake (F). Taken off-dose for short periods between Days 9 and 25, and reduced to 6 mg/kg/day from Day 23. ↑Neutrophils and fibrinogen. Histopathological findings in eyes (corneal opacity and atrophy), testes (atrophy) and epididymides (↓cellularity).	3

Genotoxicity

Table 15: Genotoxicity studies with osimertinib

Type of test (study ID)	Test system (strain)	S9	Concentration / Dose	Results	GLP
In vitro					
Ames test (793061)	*S.typhimurium* (TA1535, TA1537, TA98, TA100, *E.coli* (WP2 *uvr*A)	±	0.-333 µg/plate	Negative	Yes
Mouse lymphoma assay (793056)	L7178Y cells	±	-S9: 0-5 µM (0-4 µg/ml) +S9: 0-10 µM (0-6.5 µg/ml)	Negative	Yes
In vivo					
Micronucleus test (793538)	Rat	n.a.	0-300 mg/kg/day for 2 days (oral (gavage))	Negative	Yes

Carcinogenicity

As this application is for the use of osimertinib for the treatment of patients with advanced NSCLC no carcinogenicity studies were submitted, which was considered acceptable by the CHMP (see discussion on non-clinical aspects).

Reproduction Toxicity

Osimertinib has been evaluated in a modified rat embryo-foetal development study that included an assessment of pre-implantation pregnancy and a littering phase. Studies on male and female fertility, embryo-foetal development in rabbits and a pre-and postnatal development study in rats were not submitted.

Fertility and early embryonic development

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 rats and dogs, testicular findings comprising seminiferous tubular degeneration and/or spermatic retention accompanied by secondary epididymal changes (reduced sperm) and decreases in organ weights (prostate and epididymides in rats) have been seen in the 1 and 3 month studies (≥10 mg/kg/day in rats, ≥2 mg/kg/day in 1 month dog study and at 6/10 mg/kg/day in 3 month dog study). In the 1 month rat study these findings were not present following 1 month off-dose, indicating reversibility. In the 1 month dog study testicular pathology was present at the low and mid doses, but not at the high dose at the end of the dosing period.

Embryofoetal development

Effects on embryofoetal development and early postnatal survival/growth were assessed in a modified rat embryofoetal development study, which included a littering phase. Maternal toxicity was seen at doses of ≥ 20 mg/kg/day. Administration to rats prior to implantation until Day 20 of gestation resulted in an increase in post-implantation loss at 20 mg/kg/day. Dosing during the major period of embryonic organogenesis (Day 6 to 16 of gestation) was associated with reduced foetal weights at 20 and 30 mg/kg/day. Administration to dams during gestation and through early lactation (Day 6 of gestation until at least Day 6 of lactation) caused reduced pup survival (100% litter loss seen at 30 mg/kg/day) and reduced pup weights at ≥ 20 mg/kg/day. There were no compound-related external or visceral abnormalities in foetuses or pups (doses up to 30 mg/kg/day).

Exposure to osimertinib and AZ7550 was confirmed in suckling pups, which may indicate the potential for excretion of osimertinib and its metabolites in milk.

Toxicokinetic data

Plasma levels of osimertinib and metabolites AZ5105 and AZ7550 were evaluated in the pivotal repeat-dose toxicity studies.

Comparison of total osimertinib and AZ7550 exposures in rats, dogs and humans showed that the steady state C_{max} and AUC levels in humans at the proposed therapeutic dose of 80 mg was generally similar to or higher than that achieved at the high dose levels in the 3 month rat (5880 and 16200 nM.hr in males and females, respectively) and dog studies (5420 nM.hr), indicating lack of margins of safety. Due to failing incurrent sample reproducibility (ISR), TK parameters for metabolite AZ5104 are not available from the pivotal 3 month studies in rats and dogs, and margins of safety can therefore not be established for AZ5104.

Local Tolerance

No local tolerance studies were submitted as the drug will be administered orally.

Other toxicity studies

Antigenicity

Antigenicity studies were not submitted because there were was no evidence of immunological effects of osimertinib in the repeat dose toxicity studies.

Immunotoxicity

In accordance with ICH S8 and ICH S9, no dedicated immunotoxicity studies were submitted.

No relevant liver or immune-related signals have been identified in repeat dose toxicology studies up to 3 months duration. Increases in white blood cell counts and fibrinogen and decreases in red blood cell parameters were seen in rats and dogs. These findings were accompanied by increased haematopoiesis in the spleen in the 3-month rat study. They were considered to be secondary to the wild type EGFR-related degenerative and inflammatory changes seen in the skin and GI tract. These effects were reversible in the 1-month rat study (not seen in dogs at 1 month). The finding in the mesenteric lymph node (minimal to mild sinus erythrocytes and erythrophagocytosis) seen in rats at 1 and 3 months, which reversed following 1 month off-dose, was not associated with any other degenerative changes or pigment derived from red blood cell breakdown and is considered to be of limited toxicological significance.

Hypocellularity seen in the thymus and bone marrow were confined to non-tolerated or poorly tolerated doses (≥40 mg/kg) in the 7 and 14 day rat studies.

Limited assessments of other potential markers of immune activation (α-macroglobulin in the rat 7 day study and lymphocyte subsets in the dog 14 day study) were included in the dose range finding studies and there were no noteworthy changes. Marked decreases in platelets accompanied by macrothrombocytes on peripheral blood smears were seen in the 14 day dog study, but only at non tolerated doses (≥40 mg/kg); there were no histopathological correlates.

Dependence

Dependence studies were not submitted.

Metabolites

In addition to monitoring systemic exposure to AZ5104 and AZ7550 in the pivotal toxicology studies, an investigative study was conducted to evaluate the toxicology of AZ5104 following oral administration to female rats for 1 month. The in-life, clinical pathology and histopathological findings seen in AZ5104-treated rats were consistent with those observed with osimertinib in the rat with exception of the inflammatory changes in the skin (minimal to slight inflammatory cell infiltration) and adrenal gland (minimal cortical inflammatory cell infiltration) which showed partial recovery.

Impurities

Four potentially mutagenic impurities (based on structural alerts from commercial databases, DEREK and Leadscope, and/or an in-house database) were evaluated for bacterial mutagenicity *in vitro* using the Ames assay. Two impurities were negative in Ames assays, and are considered as non-mutagenic whilst the other two tested positive and are considered mutagenic.

Other studies

Osimertinib showed no evidence of phototoxic potential in an in vitro cytotoxicity assay conducted in the presence and absence of UV light.

2.3.5. Ecotoxicity/environmental risk assessment

An Environmental Risk Assessment (ERA) has been undertaken for osimertinib in accordance with the EMA Guidance (CHMP 2006). **Summary of main study results**

Substance (INN/Invented Name): osimertinib mesylate			
CAS-number (if available): 1421373-66-1			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	pH 4 log D_{ow} = 1.77 pH 7 log D_{ow} = 2.45 pH 9 log D_{ow} = 2.69	Potential PBT: No
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surfacewater}$, refined	0.0033	µg/L	> 0.01 threshold: No
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	Empingham (soil): K_d = 3702 L/kg; K_{oc} = 102830 L/kg Warsop (soil): K_d = 5384 L/kg; K_{oc} = 769189 L/kg Calwich Abbey (sediment): K_d = 9354 L/kg; K_{oc} = 190886 L/kg Swiss Lake (sediment): K_d = 6219 L/kg; K_{oc} = 1036439 L/kg Burley Menson (sludge): K_d = 4784 L/kg; K_{oc} = 16663 L/kg	The adsorption coefficient in sludge (Kd) is >3700 L/kg. The environmental fate and effects of osimertinib in the terrestrial compartment are therefore assessed in Tier B.
Ready Biodegradability Test	OECD 314B	Disappearance of the parent material from the activated sludge followed first-order kinetics with DT-50 values of 2.8 and 1.13 days in the biotic and abiotic sludge, respectively.	[^{14}C]osimertinib degraded rapidly in both biotic and abiotic sludge.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	Calwich Abbey $DT_{50,\ water}$ < 1 day $DT_{50,\ sediment}$ = 9 days $DT_{50,\ whole\ system}$ = 3 days % shifting to sediment = 94% at day 100	Greater than 10% of the applied radioactivity was associated with the sediment phase. The effect of osimertinib on the sediment dwelling organism

		Swiss Lake $DT_{50, water}$ < 1 day $DT_{50, sediment}$ = 13 days $DT_{50, whole\ system}$ = 1 day % shifting to sediment = 77% at day 100			*Chironomus riparius* is therefore investigated in Tier B. osimertinib is not expected to be persistent in the aquatic environment.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition green algae, *Pseudokirchneriella subcapitata*	OECD 201	NOEC EC_{50}	14 230	µg/L µg/L	
Daphnia sp. Reproduction Test					Ongoing
Fish, Early Life Stage Toxicity Test/*Species*					Ongoing
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} NOEC	>320 31.25	mg/L mg/L	$PNEC_{microorganism}$ = 3.1 mg/L PEC/PNEC ratio for microorganisms is <0.1: No expected risk to microorganisms.
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307				Ongoing
Soil Micro organisms: Nitrogen Transformation Test	OECD 216				Ongoing
Terrestrial Plants, Growth Test/*Species*	OECD 208				Ongoing
Earthworm, Acute Toxicity Tests	OECD 207				Ongoing
Collembola, Reproduction Test	OECD 232				Ongoing
Sediment dwelling organism *Chironomus riparius*	OECD 218	NOEC	100	mg/kg	No effect was observed on the emergence or development rate. The EC_{50} was determined to be greater than the highest tested concentration.

2.3.6. Discussion on non-clinical aspects

Pharmacology

In *in vitro* cellular EGFR phosphorylation assays, osimertinib showed potent inhibition of all single-activated (EGFRm) and double-T790M mutant (EGFRm/T790M) assays across different cell lines. Osimertinib has greater activity towards mutant EGFRs compared to wild-type in an *in vitro* cellular context. Furthermore, *in vitro* wash-out and time-dependent cellular kinetic studies supported the irreversible mechanism of action of osimertinib.

Two pharmacologically active metabolites, AZ5104 and AZ7550 have been identified. AZ5104 exhibited significantly greater potency than osimertinib across mutant and wild-type EGFR assays, and thus displayed a smaller margin of selectivity against wild-type EGFR compared to EGFRm/T790M and EGFRm *in vitro*.

Osimertinib and AZ7550 both showed low activity against IGF1R and InsR. In comparison, AZ5104 showed greater activity against IGF1R and InsR. Osimertinib and both metabolites were largely inactive against cellular pIGF1R with IC50s >1 µM, indicating that these agents do not potently inhibit IGF1R in cell context *in vitro*, and observed enzyme potency of AZ5104 did not appear to translate into significant cell activity.

Non-clinical data indicate that osimertinib and AZ5104 inhibit the hERG-channel, and QT-prolonging effect cannot be excluded. QTc interval prolongation has been observed in patients treated with osimertinib (see section 2.4.3).

Osimertinib inhibited GI transit in the rat at clinically relevant plasma concentrations. The mechanism underlying this finding in uncertain, but reductions in gastric emptying have been reported with other EGFR inhibitors in rats. The GI tract was identified as a target organ in the repeat dose toxicity studies in rats and dogs where there were histopathological findings (atrophic, degenerative and/or inflammatory changes associated with reductions in food consumption and body weight loss) that are considered to be a consequence of inhibition of the wild-type EGFR (see discussion on toxicology).

Pharmacokinetics

Exposure increased approximately in proportion to increasing dose. Absorption was prolonged with Tmax typically being achieved at 2-4h or later following higher doses in toxicology studies.

The plasma protein binding has not been determined due to instability of osimertinib in human plasma and non-specific binding. Based on computational algorithm, the prediction for AZ5104 was the same as measured (98% bound) suggesting that the binding of osimertinib (99% predicted) and AZ7550 (98% predicted) were likely to be at least as high as for AZ5104. For the purpose of DDI potential, a conservative value of 90% bound (10%) free has been used.

No metabolism studies in animals were provided. In general, non-clinical studies of *in vivo* metabolism should have been submitted. However, since no human metabolite comprises >8% of total osimertinib related material, and in view of the intended patient population, further characterization of metabolites and metabolite toxicity is not warranted.

Osimertinib was a substrate of P-gp and BCRP but is unlikely to result in clinically relevant drug interactions with active substances by osimertinib at the clinical doses. Osimertinib is not a substrate for OATP1B1 and OATP1B3.

Based on *in vitro* data, osimertinib is predicted to inhibit BCRP at clinically relevant concentrations. Therefore, osimertinib have the potential to increase plasma concentrations of co-administered medicinal products transported by this protein.

In in vitro studies osimertinib inhibited weakly transport via OATP1B1, OATP1B3, MATE1, MATE2K, and OCT2. Based on current scientific recommendation (ITC 2010), the inhibition of OATP1B1 would be unlikely to result in a clinically significant DDI. For OATP1B3, MATE2-K, OAT1, OAT3 a clinically meaningful DDI could be excluded but not with MATE1 and OCT2 substrates. However, as osimertinib has showed high covalent binding and the impact of the incubational binding fu_{inc} was not take into account in these in vitro study for drug transporters inhibition, the potential for transporter inhibition will be further addressed post authorisation (see RMP).

The osimertinib potential to inhibit the P-gp transporter cannot be predicted since the highest concentration studied (30 µM) is lower than the maximum expected concentrations in the intestine at clinical doses. The maximum expected concentrations in the intestine (64 µM) cannot be tested since it was cytotoxic. Based on solubility data and dissolution profiles provided, the gut concentrations did not seem to be highly limited by the solubility of the compound or by slow dissolution. Therefore, an in vivo clinical study on the potential of osimertinib for P-gp inhibition will be conducted and submitted by Q4 2017 (see RMP).Reversible inhibition of osimertinib was demonstrated in vitro for CYP2C8 and CYP3A4/5 and time-dependent inhibition for CYP3A4/5, while induction of mRNA was found for CYP1A2 and CYP3A4.

Osimertinib is not an inhibitor of UGT2B7 in vitro and is weak inhibitor of UGT1A1. It is therefore unlikely to result in a clinically relevant hepatic DDI. However, due to higher concentrations observed in the intestine, intestinal inhibition of UGT1A1 is possible but the clinical impact is unknown (see section 5.2 of the SmPC).

AZ5105 *in vitro* inhibited reversibly CYP1A2, CYP3A4/5, and CYP2C8, and time dependent CYP3A4/5, while induction of mRNA was found for CYP1A2 and CYP3A4. AZ7550 inhibited CYP3A4/5, CYP2C9, CYP2C19, and CYP2D6. Both AZ5105 and AZ7550 induced CYP3A5 and CYP1A2 mRNA, were substrates of P-gp and BCRP, but were not substrates for OATP1B1 and OATP1B3. AZ5104 and AZ7550 have not been included in the evaluation of interaction potential as the clinical plasma exposure of both metabolites is less than 25% of osimertinib.

Toxicology

The wild-type EGFR is widely expressed in tissues of epithelial, mesenchymal and neuronal origin where it plays an important role in many physiological processes including proliferation, regeneration, differentiation and development (Yano et al, 2003). While osimertinib is more potent towards mutant EGFR compared to wild-type EGFR, the active metabolite AZ5104 has significantly greater potency towards wild-type EGFR than osimertinib. Consequently, the repeat-dose toxicity findings are most likely related to inhibition of wild-type EGFR and are expected findings at higher doses of osimertinib, possibly related to AZ5104. This is further supported by similar findings with other EGFR inhibitors.

The majority of the findings in the toxicology studies were seen below clinical exposures and it was not possible to calculate safety margins.

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. The dose-limiting findings were reduced food consumption accompanied by body weight loss, and ocular clinical signs and ophthalmology findings. Increases in white cell counts, decreases in red cell parameters and increased haematopoiesis in the spleen are considered to be secondary to the degenerative and inflammatory changes in these tissues. Similar findings have been seen with other EGFR TKIs and these are considered to be class effects. The increased haematopoiesis in the spleen would be expected to be reversible once the inflammatory/degenerative pathology had resolved. Other target organs were the male reproductive tract, male mammary gland, mesenteric lymph nodes, harderian gland, lung, bone marrow and thymus.

An increased incidence of foamy alveolar macrophage aggregates was seen in the lung in the 3 month rat study (both sexes). Further characterisation of these macrophages by electron microscopy revealed changes consistent with early phospholipidosis in females and either lipofucinosis or multivesicular bodies in both sexes. Given the low severity of the findings and the lack of any associated degenerative or inflammatory changes in the lung alveoli or interstitial tissue, this small degree of phospholipid accumulation is considered likely to represent an adaptive response and is considered to be non-adverse. These changes would be expected to be reversible as no structural alterations were noted in the lungs and the changes were generally of minimal to mild severity (Chatman et al, 2009; Reasor et al 2006). Similar findings were not observed in the dog studies. Hence, the early phospholipidosis was considered unlikely to be of clinical relevance.

Marked decreases in platelets accompanied by macrothrombocytes on peripheral blood smears were seen in the 14 day dog study. Consequently, haematological parameters were monitored in patients with osimertinib.

However due to the lack of clinical consequences of the observed reductions, the identified risk was not categorised as important.

Recovery was assessed in the 1 month rat and dog studies where all findings were reversible, although partial recovery was seen for some of the corneal changes (corneal epithelial atrophy in rats and corneal translucencies in dogs) within the 1 month off-dose period. Based on preclinical experience with gefitinib, it is uncertain whether the corneal opacities would reverse (corneal opacities seen in the 6 month dog study with gefitinib did not fully reverse following 12 weeks off-dose; Yano et al 2003). The corneal findings seen in osimertinib-treated animals are considered to be a consequence of inhibition of the wild-type EGFR leading to a reduction in the production and migration of epithelial cells to replace those lost by normal exfoliation.

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.

A female fertility study has not been conducted. 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.

Post-implantation loss in rats was observed at an exposure equivalent to the human exposure at the recommended dose of 80 mg daily. Dosing during the major period of embryonic organogenesis was associated with reduced foetal weights. Administration to dams during gestation and through early lactation caused reduced pup survival and reduced pup weights. There were no compound-related external or visceral abnormalities in foetuses or pups. Exposure to osimertinib and AZ7550 was confirmed in suckling pups, which may indicate the potential for excretion of osimertinib and its metabolites in milk (see section 5.3 of the SmPC).

Carcinogenicity studies have not been performed with osimertinib which is considered acceptable in accordance with ICHS9. Osimertinib did not cause genetic damage in *in vitro* and *in vivo* assays.

Four impurities are considered adequately qualified based on the levels present in the batches used for the toxicity studies. The levels in the batches used for the genotoxicity studies are in principle too low to address potential genotoxicity of the four specified impurities. However, due to lack of structural alerts in two QSAR assays (DEREK and Leadscope), and due to negative genotoxicity studies with the structurally related osimertinib, are considered devoid of mutagenic potential. In addition, based on the intended patient population with life time expectancy less than 5 years, the proposed limit of intake is considered acceptable for the mutagenic impurities from a non-clinical point of view.

The lack of local tolerance and antigenicity studies were considered acceptable.

ERA

Osimertinib refined PECsurfacewater value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5. In addition, the risk of bioaccumulation is low. Osimertinib is therefore not expected to pose a risk to the environment.

However, if the applicant applies for a wider use of osimertinib in the future, bringing the refined PECsurfacewater value above the action limit, a thorough assessment of the phase II studies has to be performed.

2.3.7. Conclusion on the non-clinical aspects

Based on the submitted preclinical studies, osimertinib showed potent inhibition of all single-activated (EGFRm) and double-T790M mutant (EGFRm/T790M) assays.

The pharmacokinetic profile of osimertinib was well described. Protein binding has not been determined for osimertinib and AZ7550 but was predicted using computational models. The toxicity of osimertinib has been sufficiently well characterised, with adverse effects in study animals related to wild-type EGFR inhibition at higher doses. Most adverse effects seen were reversible.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study ID	Objectives of the study	Study design	Treatment details	Subjects receiving osimertinib	Subjects
D5160C 00005 (referred as Study 5)	BA for different oral formulations Safety	Phase I, single-centre, sequential design	Part A: Single dose osimertinib 20 mg administered as a **capsule** in Period 1, as a **solution** in Period 2, as a **tablet** in Period 3, all under fasted conditions Part B: Single dose osimertinib 20 mg administered as a **tablet** under fasted conditions in Period 1 and under fed conditions in Period 2	Part A: 16 Part B: 16	Healthy male adult subjects, age 21-53 years
D5160C 00010 (referred as Study 10)	Safety, PK, effect of omeprazole on osimertinib exposure	Phase I, multicentre, open-label, 2-period design	osimertinib 80 mg film-coated **tablet**, omeprazole 40 mg capsule, fasted state Period 1: Days 1 through 4, single oral dose of 40 mg omeprazole, day 5, single oral doses of 40 mg omeprazole and 80 mg osimertinib Period 2: Day 1, single oral dose of 80 mg osimertinib (minimum 21-day washout between periods)	68	Healthy male adult subjects, age 18-55 years
D5160C 00011 (referred as Study 11)	Absorption elimination	Phase I, single-centre, open-label design	[^{14}C]-osimertinib 20 mg **solution** formulation, single dose; administered orally in the fasted state	8	Healthy adult male subjects, age 30-65 years
D5160C 00001 AURA Phase I	Efficacy, safety, and PK	Phase I, open-label, multicentre, dose-escalation and dose-expansion	osimertinib 20 mg and 40 mg **capsule**; osimertinib 40 mg and 80 mg **tablet** Daily dosing starting at 20 mg once daily, escalating to 40 mg, 80 mg, 160 mg, and 240 mg once daily	312	NSCLC patients age 28-88 years, ± EGFR T790M mutation positive, who progressed following prior

		design	administered orally in the fasted state		therapy with an EGFR TKI agent ± chemotherapy
D5160C 00001 AURA extension	Efficacy and safety (and PK)	Phase II single-arm, multicentre, open-label, non-randomised extension to D5160C 00001 AURA	osimertinib 40 mg and 80 mg **tablet**; 80 mg once daily; administered orally in the fasted state	201	NSCLC patients age 37-89 years, EGFR T790M mutation positive, who progressed following prior therapy with an EGFR TKI agent ± chemotherapy
D5160C 00002 AURA2	Efficacy and safety (and PK in QTc analyses)	Phase II, single-arm, multicentre, open-label, non-randomised study	osimertinib 40 mg and 80 mg **tablet**; 80 mg once daily; administered orally in the fasted state	210	NSCLC patients age 35-88 years, EGFR T790M mutation positive, who progressed following prior therapy with an EGFR TKI agent ± chemotherapy

2.4.2. Pharmacokinetics

The pharmacokinetics of osimertinib have been characterized following single dosing in healthy volunteers (Study 5 – Comparative bioavailability and Food Effect; Study 10 – Effect of omeprazole [a proton pump inhibitor] on osimertinib exposure; Study 11 – Mass Balance) and after single and multiple dosing in patients with advanced NSCLC (Study 9 – Food effect; Study 12 – Effect of itraconazole [a CYP3A4 inhibitor]; Study 13 – Effect of rifampicin [a CYP3A4 inducer]; Study 14 – Effect on simvastatin [a sensitive CYP3A4 substrate]; Study 19 – Effect on rosuvastatin [a sensitive BCRP substrate]; AURA – Dose escalation; AURA extension – Pivotal and AURA 2 – Pivotal).

Different formulations

The final formulation is an immediate-release film-coated tablet. During the course of the development program, 4 different immediate release formulations were employed: capsule, oral solution, phase 1 tablet and film-coated tablet (see quality aspects).Film-coated tablets has been manufactured in two facilities.

Table 16: Description of osimertinib formulations dosed clinically

Formulation	Studies	Brief Description
osimertinib capsule	AURA Phase I and D5160C00005	osimertinib blend in capsule
osimertiniboral solution	D5160C00005 and D5160C00011	osimertinib powder for reconstitution
osimertinib Phase 1 tablet	AURA Phase I and D5160C00005	osimertinib beige film-coated tablet
osimertinib film-coated tablet	AURA extension, AURA2, D5160C00010	osimertinib beige film-coated tablet (proposed commercial formulation)

Capsule, oral solution and Phase I tablet: In a relative bioavailability study (Study 5 conducted with the lowest dose of 20 mg), the capsule formulation showed similar bioavailability to the solution and the Phase 1 tablet formulation. In AURA Phase I study, a statistical comparison of steady-state exposures after dosing 80 mg osimertinib daily as the capsule or Phase 1 tablet formulation showed that the exposures were similar, although were not bioequivalent according the standard criteria.

Phase I tablet and Film-coated tablet: The film-coated tablet was qualitatively identical to the Phase 1 tablet with small differences in the amounts of excipients. Both formulations showed similar dissolution profiles with release of greater than 85% within 30 minutes in pH 1.3 and pH 6.8 media.

Comparison of exposures from osimertinib clinical studies, in which either the capsule or Phase 1 tablet or film-coated tablets were dosed at 80 mg, indicated similar exposures across formulations. Of note, the variability of the tablet formulations appeared to be lower than that observed with the capsule formulation.

Table 17: Comparison of osimertinib geometric mean (%GCV) steady state PK parameters at 80 mg dose across clinical studies

Parameters	AURA Phase I		AURA extension (T790M+)	AURA2 (T790M+)
	All (T790M+ and T790M-)	Tablet (T790M+)		
Formulation	Capsule	Phase 1 tablet	Film-coated tablet	Film-coated tablet
Cycle/Day	C2/D1	C2/D1	C2/D1	C3/D1
N	111	10	183	192
T_{max}[a] (h)	4.08	5.89	6.00	5.92
	(0.97-12)	(3.95-8.12)	(1-23.97)	(0.97-23.37)
$C_{ss,max}$ (nM)	627 (54.0)	545 (45.7)	631 (44.9)	533 (42.9)
$C_{ss,min}$ (nM)	390 (57.0)	348 (54.8)	384 (51.0)	332 (48.7)
AUC_{ss} (nM*h)	12000 (52.2)	10360 (46.7)	11980 (46.2)	10180 (41.9)

a Median (min-max) shown

Film-coated tablet in two facilities: Equivalent release profiles were observed for tablets manufactured at both sites with both tablets showing release of greater than 85% within 15 minutes in pH 1.3 and pH 6.8 media and greater than 85% within 30 minutes in pH 4.5 medium (f_2 value in pH 4.5 medium was 52.6).

Dispersed tablet: For patients who are unable to swallow or where dosing via naso-gastric tube is required, tablets may also be administered as dispersion in water. The dissolution of osimertinib tablets dispersed in water was evaluated at pH 1.3 (QC media), 4.5 and 6.8 at both 40 and 80 mg. The release profiles for dispersed and intact tablets are similar, with comparable release being observed within 30 minutes, indicating that tablet pre-dispersion does not negatively affect extent of release. F2 values have not been provided.

Absorption

The absolute bioavailability of osimertinib in man has not been determined. Based on mass balance study (Study 11), absorption of osimertinib appears to be high with fraction absorbed greater than 0.8 based on less than 19% of the dose eliminated in faeces in the first 72 hours after dosing.

Following oral administration of osimertinib, peak plasma concentrations of osimertinib were achieved with a median (min-max) tmax of 6 (3 - 24) hours, with several peaks observed over the first 24 hours in some patients.

In healthy volunteers administered an 80 mg tablet where gastric pH was elevated by dosing of omeprazole for 5 days (Study 10), osimertinib exposure was not affected (AUC and Cmax increase by 7% and 2%, respectively) with the 90% CI for exposure ratio contained within the 80-125% limit.

In the Food effect study (Study 5) conducted with 20 mg using Phase I tablet, administration of the tablet with a high-fat meal increased osimertinib AUC and Cmax approximately 19% and 14%, respectively, compared to fasted conditions (see also elimination).

Table 18: Statistical comparison of PK parameters between fed and fasted at 20 mg using osimertinib Phase 1 tablet formulation (Study 5 Part B)

Analyte	PK parameter	N	Fasted Geometric LS Mean	Fed Geometric LS Mean[a]	Fed /Fasted ratio (90 % Confidence Interval)
osimertinib	AUC (nM*h)	16	1419	1691	119.1 (110.7, 128.2)
	C_{max} (nM)	16	29.29	33.36	113. 9 (102.4, 126.7)

[a] N=14

Fed conditions had no effect on the AUC and Cmax of the metabolites AZ5104 and the AUC of AZ7550 compared to fasted conditions. The Cmax of AZ7550 decreased by approximately 16% under fed conditions compared to fasted conditions. Based on a clinical pharmacokinetic study in patients at 80 mg (Study 9), food does not alter osimertinib bioavailability to a clinically meaningful extent (AUC increase by 6% (90%CI -5, 19) and Cmax decrease by 7% (90%CI -19, 6)). Food effect did not impact osimertinib median tmax (8 hours in fed vs 6 hours in fasted) or t1/2 (54 hours in fed vs 56 hours in fasted) (see sections 4.2 and 5.2 of the SmPC).

Distribution

Osimertinib appeared to be extensively distributed in healthy volunteers with mean (± SD) apparent volume of distribution (Vz/F) of 2495 (± 936) L after administration of 80 mg of the proposed commercial film-coated tablet in Study D5160C00010. In AURA Phase I, the mean (± SD) apparent volume of distribution (Vz/F) was 1216 (± 604) L in patients after the Phase 1 tablet dose at 80 mg. The volume of distribution was extensive in both populations and was approximately 2-fold greater in healthy volunteers than in patients. In a population pharmacokinetic modelling and simulation report for osimertinib typical value for apparent volume of distribution was 986 L. At steady-state, circulating plasma concentrations are typically maintained within a 1.6 fold range over the 24-hour dosing interval.

In vitro studies indicate that osimertinib is metabolized predominantly by CYP3A4, and CYP3A5. CYP3A4 mediated metabolism may be a minor pathway. Alternative metabolic pathways may exist which have not been fully characterized 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 (see sections 4.5 and 5.2 of the SmPC and also non-clinical section).

In the [^{14}C]-osimertinib human study (study D5160C00011), the whole blood to plasma ratio of total radioactivity was 0.917 in humans suggesting osimertinib and its metabolites distributed equally in whole blood and plasma.

Available *in vitro* non-clinical data suggest that osimertinib binds covalently to plasma proteins, serum albumin and hepatocytes.

The ability of osimertinib to enter the cerebrospinal fluid (CSF) was shown by the measurement of CSF concentration in one patient (in study AURA2). In that patient, the concentration of osimertinib measured in CSF was approximately 1% of the total osimertinib concentration in plasma

Elimination

Mean apparent clearance was low to moderate, after single dose in healthy male volunteers 27-30 L/h and in NSCLC patients 16.9 L/h. Osimertinib steady state clearance was 16.9 L/h after dosing with 80 mg osimertinib in NSCLC patients. In a population pharmacokinetic modelling & simulation report for osimertinib the typical value of clearance was 14.2 L/h.

According to Study D5160C00011 (in healthy volunteers), renal clearance (Cl_R) of osimertinib was low with mean Cl_R of 0.235 (± 0.116) L/h and 1.37 L/h and 1.77 L/h for AZ5104 y AZ7550, respectively.

Mean half-life of osimertinib after single dose tablet formulation was 53-64 hours in healthy male volunteers and 48 hours in NSCLC patients. In Study D5160C00011 (in healthy volunteers), the $t_{1/2}$ of osimertinib was calculated to 61 hours whereas the [^{14}C]-osimertinib equivalent in plasma was 472 hours in plasma and 556 hours in blood. It was only possible to extract approximately 8% and 65% of the radioactive material out of plasma and faeces respectively, likely due to irreversible binding of the osimertinib related material to plasma proteins.

The primary elimination pathway for osimertinib and metabolites was faecal.

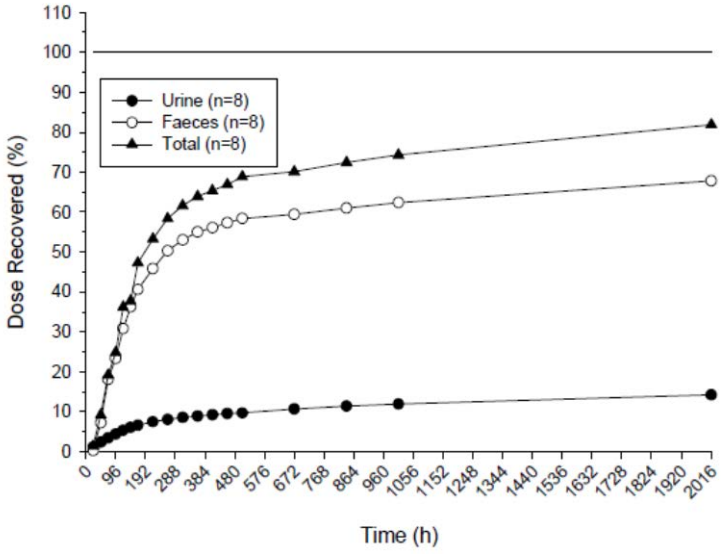
Table 19: Descriptive statistics for total radioactivity recovered (%dose) cumulatively by collection interval (both urine and faeces together) – Study 11

	0-168 hours			0-504 hours			0-2016 hours		
Parameter	Urine	Faeces	Total	Urine	Faeces	Total	Urine	Faeces	Total
N	8	8	8	6	8	6	8	8	8
Arithmetic mean	6.62	40.6	47.3	9.67	58.4	68.9	14.2	67.8	81.9
Standard deviation	1.12	6.71	7.08	1.75	4.18	3.54	2.08	4.35	4.41
Median	7.15	41.9	48.1	10.2	59.8	69.4	14.4	67.0	80.0
Minimum	4.86	29.4	35.8	7.09	50.8	64.5	10.5	62.9	77.2
Maximum	7.59	50.9	58.5	11.7	63.0	73.3	17.1	74.4	89.8

[a] Urine samples for two subjects were mixed at 480 to 504 hours; hence, recovery was calculated based on area under the rate curve

[b] 20 mg dose of [^{14}C]-AZD9291 = 40031nmolEq

Although total recovery of radioactivity was less than 90%, radioactivity was still being excreted at the end of the study (84 days). 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. Unchanged osimertinib accounted for approximately 2% of the elimination with 0.8% in urine and 1.2% in faeces (see section 5.2 of the SmPC).



Note: E10001004 and E10001016 were not included at 48 hours and E10001001 and E10001009 were not included at 504 hours due to urine collection errors at these time points.

Figure 5: Mean cumulative recovery of radioactivity in urine and faeces following oral dosing of [14C]-osimertinib in Study 11

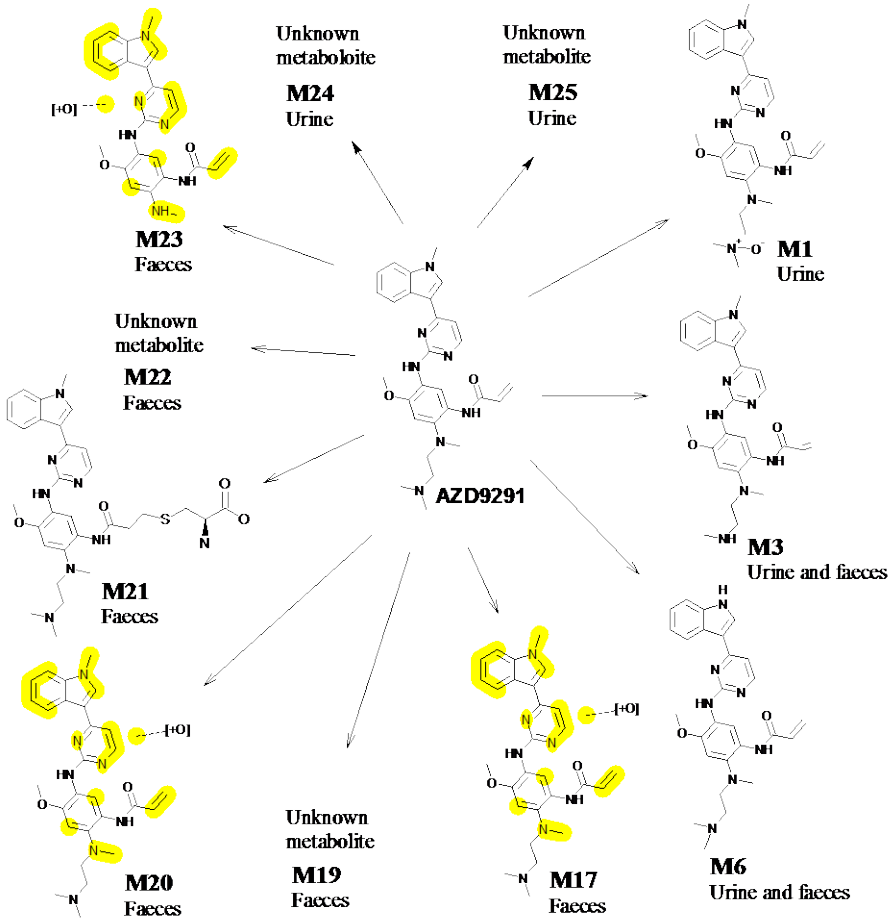


Figure 6: Proposed human metabolic pathway for osimertinib in human excreta

Table 20: Biotransformations and semi-quantitative estimates of metabolites in excreta up to 168 hours after a single oral administration of [14C]-osimertinib to healthy male volunteers at a 20 mg dose level

			% Administered dose	
Metabolite	**Description**	**Modification**	**Faeces**	**Urine**
AZD9291	Parent	NA	1.2	0.71
M1	AZ8420	+O	ND	0.13
M3	AZ7550	- CH_2	2.3	0.44
M6	AZ5104	- CH_2	5.6	0.96
M17	Oxidation	+O	0.33	ND
M19	Unknown	Unknown	0.80	ND
M20	Oxidation	+O	0.76	ND
M21	Cysteinyl adduct	+$C_3H_6O_2NS$	1.5	ND
M22	Unknown	Unknown	0.48	ND
M23	Dealkylation + Oxidation	-C_4H_9N, +O	0.47	ND
M24	Unknown	Unknown	ND[a]	0.25
M25	Unknown	Unknown	ND	1.9
Total			14	4.4

ND Not detected in AMS profile, NA not applicable
[a] Peak in AMS profile has similar retention to M20 in faeces AMS profile, no mass ion to confirm identity
Percentage radioactivity determined in pooled faeces (24-168 h) and pooled urine (0-168 h)

Dose proportionality and time dependencies

Osimertinib showed dose proportional increases in exposure (AUC and Cmax) both with increasing single and multiple doses. The PK for the 160 and 240 mg cohorts were time independent with a median temporal change parameter/linearity factor of 0.972 after dosing with osimertinib (capsule) and 0.901 after dosing with 80 mg osimertinib (Phase 1 tablet) after 22 days of dosing (with a value of 1 indicating that PK do not change with time).

Based on the mean osimertinib half-life of approximately 48 hours, steady-state is expected to be achieved after 10 to 11 days of once-daily dosing. Visual observation of trough levels of osimertinib, AZ5104 and AZ7550 indicates that steady-state is achieved by Day 15 for osimertinib and AZ5104 in AURA extension and by Day 22 for all of them in AURA2. As expected from the long half-life, accumulation of approximately 3 fold was observed after multiple once daily dosing of either the capsule or the Phase 1 tablet for 22 days.

Osimertinib induces and inhibits CYP3A4 in vitro, and osimertinib is meanly metabolized by this enzyme. However, the absence of auto-induction and auto-inhibition of osimertinib is supported by not only multiple PK parameters (temporal change parameter, predictable accumulation based on half-life, similar metabolite to parent exposure ratios, etc.) but also by the dose proportional PK observed after single dose (lack of auto-inhibition) and time independent PK after multiple dose (lack of auto-induction). Additionally, the analysis of 4β-hydroxycholesterol in study 14 and 19 indicated limited increase in the presence of multiple doses of osimertinib. Therefore, it is unlikely that significant auto induction of osimertinib is occurring.

Intra- and inter-individual variability

The overall inter-individual variability is considered moderate to high (%CV approximately 40-80%), being slightly lower in healthy volunteers (%CV approximately 30-50%). Inter-individual variability seems to be lower with film-coated tablets (40-50%) than with capsules. Intra-individual variability has not been studied.

Pharmacokinetic in target population

Exposure (AUC and C_{max}) was higher in NSCLC patients compared to healthy volunteers as a result of slower clearance and smaller volume of distribution. As consequence, the half-life was comparable between patients and healthy volunteers. Inter-individual variability seems to be slightly lower in healthy volunteer than in patients. Additionally, in the population PK analysis, a difference in clearance was observed between healthy subjects and patients with NSCLC, with healthy subjects having a higher clearance.

Mean PK parameters were obtained from patients. There were 3 single dose studies conducted in healthy volunteers to evaluate the relative bioavailability of different oral formulations (n=16) and preliminary food effect (Study 5; n=16), to evaluate the effect of gastric pH (Study 10; n=68) and to evaluate the rates and routes of absorption, metabolism and elimination ofosimertinib (Study 11; n=8). A definitive food effect study (Study 9; n=38) was conducted using the proposed commercial formulation (80 mg film-coated tablet formulation) in NSCLC patients. It was not considered appropriate to conduct the ^{14}C human ADME study in patients due to the slow elimination and need to characterize the excretion of osimertinib related material for approximately 85 days following a single oral dose. However, in the study about the co-administration with omeprazole differences detected in human were no relevant (increased osimertinib AUC by approximately 7% and Cmax by 2%). No higher differences than in healthy subjects are expected since the effect of gastric pH is mainly based on the drug properties.

Population PK model

A population PK model for osimertinib and AZ5104 was developed based on plasma concentrations of osimertinib and AZ5104 from Phase I/II studies in NSCLC patients (AURA extension and AURA2) and one study in healthy subjects (D5160C00005). The final population PK parent and metabolite model was comprised of first order oral absorption of osimertinib followed by two compartments in series: one-compartment for osimertinib followed by a compartment for AZ5104.

The impact of the following covariates on PK was evaluated: ethnicity, body weight (and/or body surface area, body mass index), formulation, sex, age, hepatic markers (albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin), creatinine clearance, and smoking status.

Table 21: Parameter estimates for the final osimertinib / AZ5104 PPK model

Parameter (units)	Estimate	%RSE	IIV% (%RSE)
NONMEM model estimates			
θ_1: CLparent/F (L/h)	14.2	1.8	45.6 (3.2)
θ_2: Vparent/F (L)	986	2.8	51.8 (3.3)
θ_3: ka (1/h)	0.24	4.9	89.4 (6.1)
θ_4: CLmetabolite/F (L/h)	31.5	2.7	52.3 (5.3)
θ_5: Vmetabolite/F (L)	207	4.4	51.8 (3.3)
θ_9: Healthy subject population effect (vs. NSCLC patients) on CLparent/F	0.44	19.4	--
θ_{10}: Effect of body weight on CLparent/F	0.56	14.0	--
θ_{12}: Ethnic Asian other population effect on CLmetabolite/F	0.21	16.4	--
θ_{13}: Ethnic Asian Chinese population effect on CLmetabolite/F	0.17	19.9	--
θ_{14}: Ethnic Asian Japanese population effect on CLmetabolite/F	0.20	18.7	--
θ_{15}: Ethnic non-Asian non-white population effect on CLmetabolite/F	0.10	33.9	--
θ_{16}: Healthy subject population effect (vs. NSCLC patients) on CLmetabolite/F	1.25	13.5	--
θ_{17}: Effect of body weight on CLmetabolite/F	0.99	9.3	--
θ_{20}: Effect of albumin on Vparent/F	1.33	17.7	--
θ_{21}: Effect of body weight on Vparent/F	0.65	16.5	--
			Shrinkage (%)
ηCLparent	0.46	3.2	2.2
ηCLparent-ηCLmetabolite covariance[a]	0.90	3.4	--
ηCLmetabolite	0.52	3.3	1.9
ηka	0.89	6.1	31.9
ηVparent	0.52	5.3	23.6
ηVmetabolite	0.62	6.5	39.0
Additive Error (g/L)	0.105	16.0	5.3
Proportional Error (%)	24.4	2.3	5.3

Source: \AZ\9291\Analysis\ dcov5.mod
Abbreviations: CLmetabolite = apparent clearance of AZ5104; CLparent = apparent clearance of AZD9291; F = relative bioavailability; IIV = inter-individual variability; NONMEM = non-linear mixed effects modelling software; NSCLC = non-small cell lung carcinoma/cancer; PPK = population pharmacokinetic; RSE = relative standard error; Vmetabolite = apparent AZ5104 volume of distribution; Vparent = apparent AZD9291 volume of distribution.
[a]Correlation coefficient (r) between random effects of CLparent and CLmetabolite = 0.90.

The primary predictors of variability in osimertinib and AZ5104 PK were disease state (i.e. NSCLC patient vs. healthy subjects), body weight and serum albumin. In addition there was an ethnicity effect observed for AZ5104 but not osimertinib. There were no factors identified that would require dose adjustment in patients.

The expected values of osimertinib AUC_{ss}, $C_{ss,max}$ and $C_{ss,min}$ for an 80-mg osimertinib dose in NSCLC patients are 11258 nM.h, 501 nM, and 417 nM, respectively. The expected values of AZ5104 AUC_{ss}, $C_{ss,max}$, and $C_{ss,min}$ for an 80-mg osimertinib dose in NSCLC patients are 1271 nM.h, 56 nM, and 52 nM, respectively.

Population PK estimated steady state AUC and C_{max} were similar to that observed across patient studies.

Special populations

Impairment renal function

A formal clinical study to investigate the impact of renal impairment on osimertinib PK was not conducted. In Study D5160C00011 (^{14}C-ADME) osimertinib, AZ5104 and AZ7550 were shown to undergo negligible renal clearance. However, as renal impairment can adversely affect some pathways of hepatic / gut metabolism, the impact of renal impairment was assessed in the population PK analysis. Based on a population pharmacokinetic analysis of 330 patients with mild renal impairment (CLcr 60 to less than 90 mL/min), 149 patients with moderate renal impairment (CLcr 30 to <than 60 mL/min), 3 patients with severe renal impairment (CLcr 15 to <than 30 mL/min) and 295 patients with normal renal function (≥90 mL/min), osimertinib exposures were similar. Patients with CLcr less than 15 mL/min were not included in the clinical trials.

Impairment hepatic function

In Study D5160C00011, osimertinib was shown to undergo significant metabolism mediated clearance presumably with the liver as a major site of biotransformation and hence, hepatic impairment might be expected to lead to increased exposure of osimertinib.

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. Based on the PK analysis (via NCA analysis) of patients from AURA2 and AURA extension, mild hepatic impairment had no impact on the apparent clearance of osimertinib.

Weight

After dosing with osimertinib at 80 mg daily, AZ5104 circulated at a mean of 10.44% and 9.78% of the osimertinib AUCss and Css,max, respectively, and AZ7550 circulated at 9.80% and 9.01% of osimertinib AUCss and Css,max, respectively. Based on the population pharmacokinetic analysis, body weight have an impact on apparent clearance and volume of distribution, indicating that within a body weight range of 43–90 kg, the AUCss for osimertinib may range from -20% to +30% compared to the median body weight of 62 kg, while for AZ5104 AUCss may range similarly from -40 to +50%. Across the 43-90 kg body weight range, AZ5104 and AZ7550 each circulated in plasma at a geometric mean AUCss (and Css,max) of approximately 10% of osimertinib AUCss (and Css,max). Taking the extremes of body weight into consideration, from <43 kg to >90 kg, AZ5104 metabolite ratios decreased from 11.8% to 9.6% while for AZ7550 it decreased from 12.8% to 9.9%, respectively. This decrease in exposure of both metabolites relative to osimertinib with increasing body weight is unlikely to be of clinical significance. The population PK analysis included 35 patients with baseline body weight >90 kg, with a maximum body weight of 122 kg. The mean AUCss in patients > 90 kg (11244.8 nM.h) was 17% lower than the mean AUCss in patients ≤90 kg (13547.7 nM.h).

Race

The population PK analysis included White (24%), non-Japanese or non-Chinese Asians (24%), Chinese (15%), Japanese (19%) and others (6%). There were some subjects who had missing ethnicity information (11.2%). The population PK analysis indicated there was no impact of race or ethnicity on osimertinib PK.

A small decrease in AZ5104 AUCss of approximately 10–23% may be expected in Chinese, Japanese, Asian other and non-Asian-non-white patients compared to white patients.

Smoking or use of other nicotine products

The population PK analysis did not identify smoking status (current smokers = 3%, former smokers = 30%, never smokers = 67%) as having a significant impact on osimertinib PK.

Age

The population PK analysis indicated that age had no impact on the PK of osimertinib (N=778, median (min-max) age = 61 (21 – 89) years.

Table 22: Number of NSCLC patients dosed with osimertinib 80 mg in the Clinical Pharmacology trials (multiple-dose patient studies)

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	61/214	28/214	2/214

Pharmacokinetic interaction studies

In vivo

Effects of other medicinal product on the pharmacokinetics of osimertinib

Considering the results of *in vitro* studies, it has been shown that the Phase I metabolism of osimertinib is predominantly via CYP3A4 and CYP3A5.

Strong CYP3A Inducer

Strong CYP3A4 inducers can decrease the exposure of osimertinib (see section 4.5 of the SmPC). In a clinical PK study in patients (Study 13), the steady-state AUC of AZD92941 was reduced by 78% (90% CI 81, 76) and of AZ5104 was reduced by 82% (90% CI 83, 79) when co-administered with rifampicin (600 mg daily for 21 days). The Cmax of AZ5104 was also reduced by 78%.

Strong CYP3A Inhibitor

In a clinical PK study in patients (Study 12), osimertinib co-administered with 200 mg itraconazole twice daily (a strong CYP3A4 inhibitor) had no clinically significant effect on the exposure of osimertinib [(AUC) increased by 24% (90% CI 15, 35) and C_{max} decreased by 20% (90% CI -27, -13)]. AZ5104 increased in AUC approximately 8% and decreased in Cmax approximately 24% and compared with the administration of osimertinib alone. Therefore, CYP3A4 inhibitors are not likely to affect the exposure of osimertinib.

In study 12 and 13, the results of metabolite AZ7550 are not in line with it were expected. Its behaviour is different from behaviour of metabolite AZ5104 and parent. The reason for this behaviour could be based on its long half-life or as consequence of the impact of the inductor or the inhibitor in the parent's metabolism. Nevertheless, considering that AZ7550 amounted to less than 8-10% of the exposure to osimertinib based on mean metabolite to parent ratios for AUC and Cmax, the fact that mean responsible for safety concerns is metabolite AZ5104 and the relevance of the observed modification in AUC and Cmax is low, this issue is not further persecuted.

P-glycoprotein and BCRP

Osimertinib is a substrate of P-glycoprotein and BCRP.

Gastric pH modifying agents

Based on the results of the clinical study with omeprazole, co-administration of omeprazole did not result in clinically relevant changes in osimertinib exposures.

Effects of osimertinib on the pharmacokinetics of other medicinal product

BCRP Substrate

Osimertinib is a competitive inhibitor of BCRP. In a clinical PK studying patients (Study 19), co-administration of osimertinib with rosuvastatin (sensitive BCRP substrate) increased the AUC and C_{max} of rosuvastatin by 35% (90% CI 15, 57) and 72% (90% CI 46, 103), respectively.

CYP3A Substrate

Osimertinib is a reversible and time-dependent inhibitor of CYP3A4/5 and inducer of CYP3A4 and CYP1A2. However, induction of CYP1A2 could be considered negative (due to sensitivity of the assay) since the increase in mRNA was less than 20% (16%) of the response of the positive control.

In a clinical PK study in patients (Study 14), co-administration of osimertinib with simvastatin (sensitive CYP3A4 substrate) decreased the AUC and C_{max} of simvastatin by 9% (90% CI -23, 8%) and 23% (90% CI -37, 6%) respectively. These changes are small and not likely to be of clinical significance. In this study osimertinib was dosed for 28 days. It should be noted that a new steady state level of CYP3A4 could be reached by 8-10 days and the steady-stated was achieved by Day 15 for osimertinib and AZ5104 in AURA extension and by Day 22 in AURA2. Although the duration of the study is slightly limited is acceptable to investigate whether an investigational drug is an inducer or a time-dependent inhibitor *in vivo*.

PBPK models

The impact of several interactions has been predicted using PBPK models using Simcyp (version 14). Simcyp model was created using a combination of in silico, in vitro and in vivo data. The final Simcyp model was checked with a clinical dataset to show that the model is predictive of the PK and the variability of osimertinib at the 80 mg dose. Using this final model, DDI simulations using oncology patient population administered with either itraconazole or ketoconazole (strong CYP3A4 inhibitor), or rifampicin (strong CYP3A inducer) was performed. Similarly, simulation of osimertinib as a perpetrator of DDI was conducted with either simvastatin (CYP3A4 substrate) or rosuvastatin (BCRP substrate) in the oncology patient population.

The initial PBPK model submitted was refined to include CYP3A inhibition and induction parameters for predicting the net effect of probe CYP3A substrates and validated against clinical DDI data.

The Simcyp PBPK model adequately predicted the plasma concentration-time profile for osimertinibosimertinib tablet monotherapy (AURA Phase I). The PK of osimertinib in a clinical DDI study with rifampicin, a strong inducer (Study 13) was used to verify the osimertinib DDI model. The Simcyp model was then used to predict the following interaction potential for the tablet formulation:

1. The effect of moderate CYP3A inducer (efavirenz) and a weak inducer (dexamethasone) on exposure of osimertinib. Additional simulations were performed to potentially define osimertinib dose adjustment when given in combination with CYP3A inducers.

2. The net effect of osimertinib on exposure to CYP3A probe substrate simvastatin.

3. A preliminary evaluation of the potential effect of co-administration of osimertinib on the BCRP substrate rosuvastatin was simulated using Simcyp. Although rosuvastatin is a substrate of OATP1B1, OATP1B3 and OCT2, based on static modelling, the potential effect of osimertinib on these transporters other than BCRP is unlikely. The model for rosuvastatin is not appropriately validated in Simcyp and hence, the simulations for this effect are preliminary and unvalidated and are shown for comparison only.

2.4.3. Pharmacodynamics

Mechanism of action

See non-clinical aspects.

Primary and Secondary pharmacology

Primary pharmacology

No pharmacodynamics biomarkers were collected from the studies provided.

Secondary pharmacology

A proper QT-study according to the ICH 14 guideline was not performed. The QTc interval prolongation potential of osimertinib was assessed in AURA2. Serial ECGs were collected following a single dose and at steady-state to evaluate the effect of osimertinib on QTc intervals. A PK-PD modelling of exposure related to QTc-intervals indicated a linear relationship between plasma concentration of osimertinib and prolongation of the QTcF-interval with increasing concentrations of osimertinib. The predicted a drug-related QTc interval prolongation at 80 mg of 14 msec with an upper bound of 16 msec (90% CI).

Relation between plasma concentration and effect

No relationship has been observed between probability of response, DoR, or best percentage change in tumour size from baseline and osimertinib or AZ5104 exposure in EGFR T790M mutation positive patients with advanced NSCLC who have progressed on or after EGFR TKI therapy.

2.4.4. Discussion on clinical pharmacology

Four different immediate release formulations were employed: capsule, oral solution, phase 1 tablet and film-coated tablet. Capsule and Phase 1 tablet formulation showed that the exposures were similar, although not bioequivalent according to the standard criteria. Considering the results on single-dose of study 5 and that osimertinib is a BCS class 3 compound, which has shown dose proportional PK between 20 mg and 80 mg and moderate-high inter-individual variability in NSCLC patients, this issue does not raise concern. In addition, pivotal studies (AURA Extension and AURA 2) are conducted with film-coated tablets. The modification of excipients between Phase 1 tablet and the film-coated tablet is not considered substantial. Similar exposures across different formulations used during the development program have been overall demonstrated.

The osimertinib volume of distribution indicate extensive distribution into tissue. Plasma protein binding could not be measured due to instability, but based on the physicochemical properties of osimertinib plasma protein binding is likely to be high. Osimertinib has also been demonstrated to bind covalently to rat and human plasma proteins, human serum albumin and rat and human hepatocytes.

Several issues in relation with covalent binding and the very limited identification of recovered radioactive material has been discussed since they produce uncertainties on exposure, identification of major elimination pathways, long term safety, bioanalytical assay, and results from *in vitro* experiments. At this time, there is no evidence of reversibility back to starting components once it is covalently bound, although it cannot be fully ruled out. The MAH will conduct a study investigating the potential for transporter inhibition taking into account the covalent binding and very limited identification of recovered radioactive material. In addition, more reliable estimation of plasmatic protein binding and binding to the transporters studies should be obtained from in vitro studies (see RMP).

According to non-clinical data, there were no toxicologically significant effects on the liver (e.g. plasma transaminases or histopathological changes) or effects indicative of immune-mediated toxicity. According to clinical safety data (median duration of treatment of 8.3 months with the longest being 24.9 months on treatment in AURA Phase I as of 01 May 2015 DCO), there are no long terms or late emerging effects from the covalent binding that could contribute to hepatic or immune mediated complications. With available data, no high impact on systemic exposure, bioanalytical method.

Considering that osimertinib and metabolite AZ7550 were not detectable at 648 hours in the plasma, it is recommended to use 30 days as washout period. As a consequence, it is proposed to recommend women of child-bearing potential to use effective contraception for at least 2 months (30 days PK washout and 4 weeks for completion of one menstrual cycle) and 4 months in male (30 days PK washout and 90 days for completion of one spermatogenic cycle) (see section 4.6 of the SmPC).

Relevant differences have been observed on PK parameters between NSCLC patients and healthy volunteers. It is not uncommon for oncology treatments to demonstrate different PK between healthy volunteers compared to cancer patients. The reasons for the differences in the PK are multi-factorial and covariates such as age, weight, metabolic capacity, renal function, plasma protein binding etc. may contribute to these differences (Cheeti et al 2013). Differences in age, creatinine clearance and body weight have been detected between healthy subjects and patients included in PK studies.

Population PK estimated steady state AUC and C_{max} were similar to those observed across patient studies. The PPK analysis was in general performed using well recognized model building techniques. The validity of the final model seems to be overall acceptable.

Regarding elimination of osimertinib, the DDI study with itraconazole suggests that CYP3A4 metabolism would not likely be a main pathway of osimertinib elimination. A clinical study (Study D5160C00020) to evaluate the absolute bioavailability of a single dose of osimertinib in healthy male subjects is planned and will be submitted by 30 June 2016 (see RMP). As bioavailability data will help understand the quantitative contribution of the different excretion routes/metabolism pathways, the MAH is requested to re-evaluate the elimination of osimertinib when these data is available and update the SmPC if needed.

Clinical studies investigating the impact of renal impairment on osimertinib have not been submitted. Number of patients included with severe renal impairment is low (n=3). Since severe renal impairment may influence the elimination of hepatically eliminated drugs, a reduced-design study in patients with severe renal impairment will be conducted post authorisation and the results will be submitted by 31 December 2018 (see RMP). No dose adjustment is recommended in patients with mild and moderate 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 sections 4.2, 4.4 and 5.2 of the SmPC)..

Considering that population with hepatic impairment included in the population PK analysis is limited and that serum albumin has been considered predictor of variability in osimertinib and AZ5104 PK, the effect of hepatic impairment on the PK of osimertinib cannot be ruled out in the population PK. Based on a pharmacokinetic analysis of 44 patients with mild hepatic impairment and 330 patients with normal hepatic function osimertinib exposures were similar. No dose adjustment is recommended in patients with mild hepatic impairment but caution should be used when administering osimertinib to these patients. The safety and efficacy of this medicinal product has not been established in patients with moderate or severe hepatic impairment. Until additional data become available, use in patients with moderate or severe hepatic impairment is not

recommended (see sections 4.2 and 5.2 of the SmPC).A clinical study investigating the impact of mild and moderate hepatic impairment (as assessed by Child-Pugh criteria) on osimertinib pharmacokinetics is currently ongoing and the results will be submitted by 30 November 2018 (see RMP).

The decrease in AUCss of AZ5104 expected in Chinese, Japanese, Asian other and non-Asian-non-white patients compared to white patients is unlikely to have clinically relevant impact. No dose adjustment based on patient race or ethnicity is needed (see sections 4.2 and 5.2 of the SmPC).

Number of current smokers (n=24; 3.1%) is low, limiting the possibility for a robust assessment of the PK in these patients. However, CYP1A2 (which is induced by smoking) is not a major enzyme involved in the metabolic clearance of osimertinib and it is therefore not expected a significant impact on osimertinib PK of smoking status (see section 5.2 of the SmPC).

Population PK analysis suggests that body weight has a greater impact on pharmacokinetics of the metabolites AZ5104 and AZ7550 than on pharmacokinetics of osimertinib. The exposures of the metabolites AZ5104 and AZ7550, compared to the exposures of osimertinib, have been described in the different body weight situations. The absence of dose adjustment in patients over 90 Kg has also been justified (see sections 4.2 and 5.2 of the SmPC).

Based on the results of a DDI study with rifampicin, it is recommended that concomitant use of strong CYP3A inducers (e.g. Phenytoin, rifampicin and carbamazepine) with osimertinib 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 osimertinib (see sections 4.5 of the SmPC). However use of St. John's wort is contraindicated with osimertinib (see section 4.3 of the SmPC).

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 osimertinib without any restrictions (see section 4.5 of the SmPC).

Based on clinical PK data, it is recommended that 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 osimertinib (see sections 4.5 and 5.2 of the SmPC).

In a clinical PK study with simvastatin (sensitive CYP3A4 substrate), the AUC and Cmax of simvastatin were decreased. The changes observed 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.

However, it is not the optimal study to extrapolate the results due to the net effect of osimertinib over CYP3A4/5 (reversible and time-dependent inhibition and induction). Simvastatin data is problematic to use to extrapolate the risk for enzyme induction of other PXR regulated enzymes but also to exclude the risk for inhibition of enzymes other than CYP3A4. Therefore, the applicant will conduct a new clinical study to assess the potential for DDI with a non-CYP3A4 mediated PXR substrate together with the potential for P-gp inhibition and submit the results by Q4 2017 (see RMP).

The study should investigate not only the net effect of induction and inhibition, but also the PK of the victim on the first day of co-administration to address the potential risk for enzyme inhibition. In the evaluation of the results from this trial, extrapolation to other enzymes both regarding induction and inhibition needs to be

discussed. In the meantime, the lack of knowledge regarding both enzyme inhibitory and inducing properties has been reflected in the product information (see sections 4.5 and 5.2 of the SmPC).

A risk for decreased exposure of hormonal contraceptives cannot be excluded.

No biomarker data were provided. Therefore, PD analysis provided focused on clinical markers of efficacy and safety (see discussion on clinical efficacy and safety).

Regarding the activity of osimertinib towards the T790M mutation in patients with advanced NSCLC, the ability of tumours to develop mechanisms against inhibitors of important signalling pathways may cause osimertinib resistance mutations to emerge. The Applicant is recommended to submit a proposal to investigate the mechanisms of resistance to osimertinib and identify potential treatment strategies.

The PK-PD modelling data on QT/QTc-interval are limited and biased as most patients in thecame from the 80 mg cohort. An influence on the QT/QTc-interval is also indicated by preclinical findings. The hERG-assay is e.g. blocked by relatively low concentrations of osimertinib (IC_{50} approx. 690 nM), and a study in dogs showed a 5-7 % increase in QT-prolongation. In addition, in Guinea pigs, a decrease in heart frequency and a 7 % increase in the QT-interval was seen. Based on available data, a concentration-dependent increase in QTc interval prolongation can be predicted with osimertinib.

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. It is not expected that differences in release rate observed between dispersed and intact tablets can affect osimertinib exposure.

2.4.5. Conclusions on clinical pharmacology

Basic pharmacokinetic properties for osimertinib are overall well characterized. An important feature of osimertinib is the covalent binding to proteins. This property is desirable form a pharmacodynamics point of view, however it causes a very long retention time of the drug in the body which could have impact on the long-term safety osimertinib treatment (see RMP).

Overall, the clinical pharmacology study package for osimertinib is considered sufficient for a conditional approval although relevant information is still missing in order to fully characterise the PK and PD profile of osimertinib.

The CHMP considers the following measures necessary to address the issues related to pharmacology:

- A clinical study to assess the absolute bioavailability of a single oral dose of osimertinib with respect to an intravenous microdose of [14C]osimertinib in healthy male subjects
- A clinical study to determine the PK, Safety and Tolerability of osimertinib following a single oral dose to patients with normal hepatic function or mild or moderate hepatic impairment

- A reduced-dosing clinical study in patients with severe renal impairment
- A clinical study to assess the potential for DDI with a non-CYP3A4 mediated PXR substrate and the potential for P-gp inhibition should be conducted.
- A study investigating the potential for transporter inhibition taking into account the covalent binding and very limited identification of recovered radioactive material. More reliable estimation of plasmatic protein binding and binding to the transporters studies should be obtained from in vitro studies.

2.5. Clinical efficacy

2.5.1. Dose response study

The AURA Phase I study was an open-label, multicentre study of osimertinib administered orally to 355 patients with advanced NSCLC designed to support a dose selection decision. The study included a substantial number of pre-treated patients with advanced NSCLC in the dose escalation (N=31) and dose expansion (n = 312, including 252 pre-treated patients, 12 pre-treated patients dosed with 80 mg Phase I tablet and 60 first-line patients) parts of the study, with a total of 283 pre-treated patients dosed with osimertinib capsule formulation across the range of doses tested (20, 40, 80, 160, and 240 mg). These 283 patients include 103 who were dosed with the capsule formulation at the recommended daily dose of 80 mg.

Expansion cohorts were included to investigate specific patient subgroups (according to tumour EGFR T790M mutation status) and to evaluate pharmacodynamic changes (paired biopsy cohorts in patients with EGFR T790M mutation tumours). In addition, 1 cohort of pre-treated EGFR patients (not selected by tumour EGFR T790M mutation status) received 80 mg of osimertinib as Phase 1 tablet formulation (n = 12; United States [US] only). One additional patient assigned to treatment died before receiving the first dose of osimertinib. Efficacy analyses were based on investigator assessment; a BICR assessment was also conducted in the subset of 63 pre-treated patients with T790M mutation-positive NSCLC who received osimertinib 80 mg. The study was ongoing at DCO (1 May 2015).

Table 23: Flow chart of study design

Dose escalation Not preselected by EGFR T790M mutation status	**Rolling six design**				
	Cohort 1 AZD9291 20 mg	**Cohort 2** AZD9291 40 mg	**Cohort 3** AZD9291 80 mg	**Cohort 4** AZD9291 160 mg	**Cohort 5** AZD9291 240 mg
Dose expansion[a] Enrolment by either: local laboratory testing followed by central laboratory confirmation (cobas® EGFR Mutation Test) or by central laboratory testing only	EGFR T790M mutation positive[a]	EGFR T790M mutation positive[a]	EGFR T790M mutation positive[a]	EGFR T790M mutation positive[a]	EGFR T790M mutation positive[a]
		EGFR T790M mutation negative[a]	EGFR T790M mutation negative[a]	EGFR T790M mutation negative[a]	
			EGFR T790M mutation positive paired biopsy cohort[a]	EGFR T790M mutation positive paired biopsy cohort[a]	
			EGFR T790M mutation positive extension cohort[a,b]	First-line EGFRm[c]	
			First-line EGFRm[c]		
			EGFR T790M mutation positive Japan cytology tablet cohort[a,b,d]		
			US only tablet cohort (EGFRm)[a,e]		

[a] Pre-treated patients who had received any prior number of lines of treatment, but including at least one prior EGFR TKI.
[b] The results for this cohort will not be reported in this clinical study report.
[c] Prior therapy for advanced non-small cell lung cancer not permitted.
[d] EGFR T790M mutation positive status derived from a cytology sample, included patients from Japan only.
[e] Not selected by tumour EGFR T790M mutation status, included patients from the US only. This expansion cohort included pharmacokinetic characterisation so all data for this cohort were collected on the dose escalation database.

Abbreviations: EGFR, epidermal growth factor receptor; EGFRm, EGFR-TKI sensitising mutation; TKI, tyrosine kinase inhibitor; T790M, mutation where threonine replaced by methionine at position 790 of EGFR

Clinical activity was observed across the 20- to 240-mg dose range.

Table 24: Pre-treated EGFR T790M mutation positive (by central testing) population: Objective response rate and best objective response (evaluable for response analysis set)

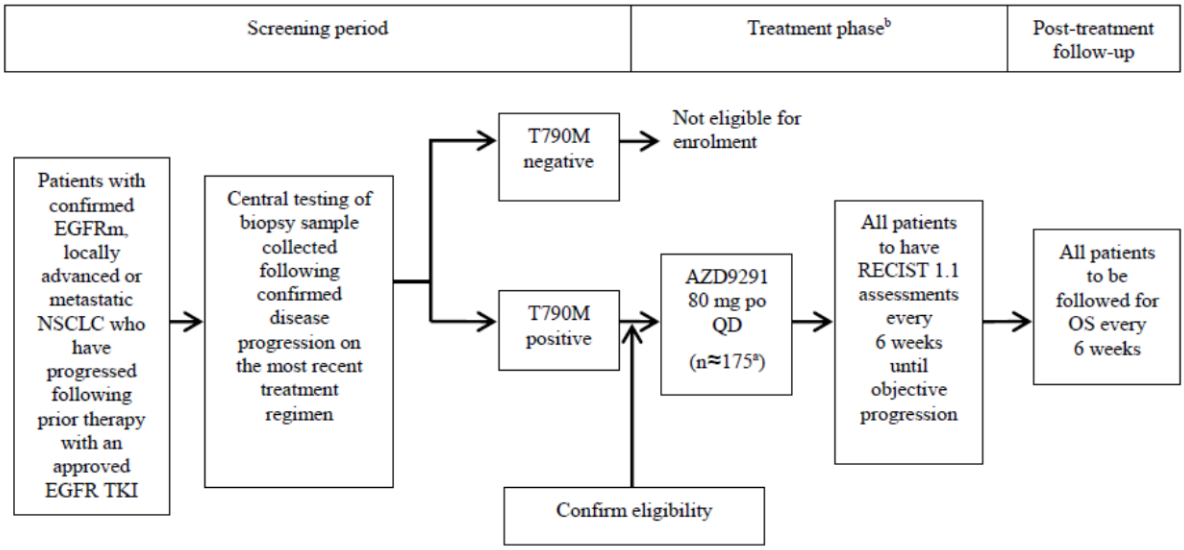
	Dose expansion population Centrally-tested EGFR T790M mutation positive at study entry					
	20 mg AZD9291 (N=10)	40 mg AZD9291 (N=32)	80 mg AZD9291 (N=61)	160 mg AZD9291 (N=41)	240 mg AZD9291 (N=13)	Total (N=157)
Complete response, n (%)	0	0	1 (1.6)	1 (2.4)	0	2 (1.3)
Partial response, n (%)	5 (50.0)	19 (59.4)	39 (63.9)	20 (48.8)	7 (53.8)	90 (57.3)
Confirmed ORR[a], n (%)	5 (50.0)	19 (59.4)	40 (65.6)	21 (51.2)	7 (53.8)	92 (58.6)
95% CI	18.7, 81.3	40.6, 76.3	52.3, 77.3	35.1, 67.1	25.1, 80.8	50.5, 66.4
Stable disease ≥6 weeks, n (%)	4 (40.0)	13 (40.6)	16 (26.2)	12 (29.3)	4 (30.8)	49 (31.2)
Progressive disease, n (%)	1 (10.0)	0	4 (6.6)	1 (2.4)	1 (7.7)	7 (4.5)
Not evaluable, n (%)	0	0	1 (1.6)	7 (17.1)	1 (7.7)	9 (5.7)

[a] Responses exclude unconfirmed responses
Abbreviation: CI, confidence interval; ORR, objective response rate

An approximate doubling in the incidence of skin disorders, nail effects and diarrhoea were observed at doses higher than 80 mg, with severe CTCAE ⩾grade 3 instances of these events happening more frequently at the 160- and 240-mg doses. A substantial increase in dose reductions due to adverse events was observed at doses of 160 mg (20.3%) and 240 mg (57.1%) compared to 80 mg (1.0%).

2.5.2. Main studies

A Phase I / II, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and anti-tumour activity of ascending doses of osimertinib in patients with advanced non-small-cell lung cancer who have progressed following prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor agent (AURA)

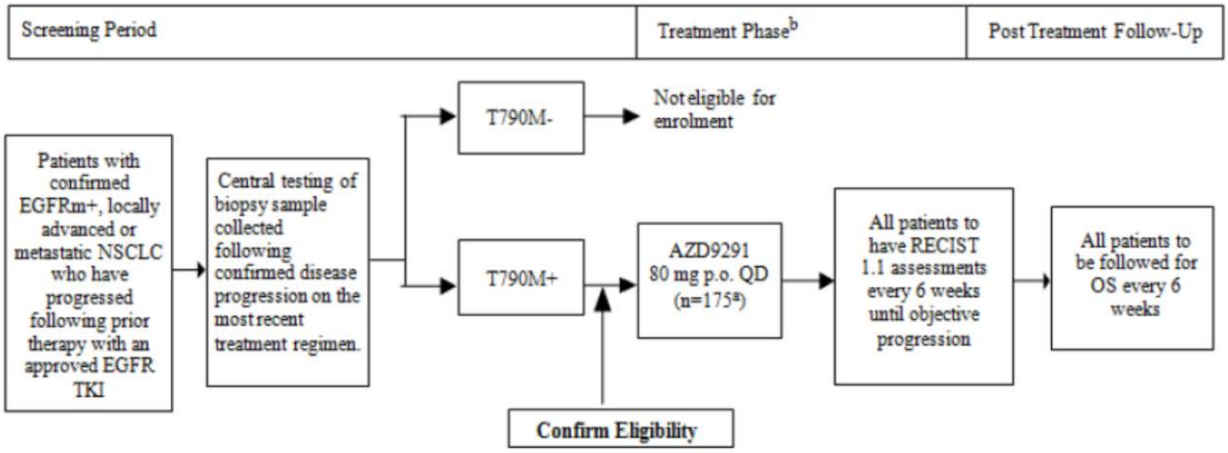


[a] A total of approximately 175 patients were planned to be dosed with AZD9291. Patient enrolment consisted of 2 cohorts: approximately 50 patients whose disease had progressed following either first-line therapy with an EGFR TKI (second-line; no additional lines of therapy, n≈50) or following treatment with at least 2 lines of prior therapy including at least 1 EGFR TKI (≥third-line, n≈125).

[b] Patients were considered enrolled at the time AZD9291 treatment was started. Patients continued to receive AZD9291 treatment until objective disease progression (according to RECIST 1.1), until a treatment discontinuation criterion was met, or for as long they were receiving clinical benefit in the opinion of the investigator. Patients who discontinued study treatment for reasons other than disease progression had to continue tumour assessments as per the protocol schedule until progression.

Figure 7: Study design – AURA

A Phase II, open-label, single-arm study to assess the safety and efficacy of osimertinib in patients with locally advanced / metastatic non-small-cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours are epidermal growth factor receptor mutation and T790M mutation positive (AURA2)



[a] A total of approximately 175 patients were planned to be dosed with AZD9291. Patient enrolment consisted of 2 cohorts: approximately 50 patients planned with EGFR T790M mutation positive whose disease had progressed following first-line therapy with 1 EGFR TKI agent but who had not received further treatment and approximately 125 patients planned with EGFR T790M mutation positive NSCLC whose disease had progressed following treatment with both EGFR TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment).

[b] Patients were considered enrolled at the time AZD9291 treatment was started. Patients continued to receive AZD9291 treatment until objective disease progression (according to RECIST 1.1) or for as long they were receiving clinical benefit in the opinion of the investigator. Patients who discontinued study treatment for reasons other than disease progression had to continue tumour assessments as per the protocol schedule until progression.

Figure 8: Study design – AURA2

Methods

Study Participants

Key inclusion criteria

1. Male or female at least 18 years in age (20 years in Japan);

2. Histological or cytological confirmation of the diagnosis of NSCLC;

3. *Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy* (**AURA2** only);

4. All patients had to have documented radiological progression on the last treatment administered prior to enrolling in the study (previous treatment with EGFR TKI and possibly other lines of therapy). In **AURA2**, this criterion was further defined as follows: radiological documentation of disease progression *either following first-line EGFR-TKI treatment but no further treatment OR following prior therapy with an EGFR TKI and a platinum-based doublet chemotherapy*.

5. *Confirmation that the tumour harboured an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, exon 19 deletion, L858R, and L861Q)* (mandatory in **AURA2**); in **AURA extension**, this criterion could be omitted if the patient had *experienced clinical benefit from EGFR TKI according to the Jackman criteria (Jackman et al 2010) followed by systemic objective progression (RECIST or WHO) while on continuous treatment with EGFR TKI*;

6. Central confirmation of the tumour T790M mutation-positive status from a biopsy sample taken after confirmation of disease progression on the most recent treatment regimen;

7. WHO performance status of 0-1;

8. At least 1 lesion, not previously irradiated and not chosen for biopsy during the study screening period, that could be accurately measured at baseline with computerised tomography (CT) or magnetic resonance imaging (MRI), which was suitable for accurate repeated measurements;

9. Females of child-bearing potential had to use adequate contraceptive measures, not to breast-feed, and to have a negative pregnancy test prior to the start of dosing;

10. Male patients had to be willing to use barrier contraception, ie, condoms;

11. *Patients from Japan were to be willing to remain in hospital from the first dosing day until Day 1 of Cycle 2* (**AURA extension** only);

12. For inclusion in the optional genetic research study, patients had to provide separate consent for genetic research.

Key exclusion criteria

1. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study sites);

2. Treatment with any of the following:

   - An EGFR TKI (eg, erlotinib, gefitinib, afatinib) within 8 days or approximately 5 half-lives, whichever was the longer, of the first dose of osimertinib;

   - Any cytotoxic chemotherapy, investigational agents or other anticancer drugs (in **AURA extension** only: *for the treatment of advanced NSCLC*) from a previous treatment regimen or clinical study within 14 days of the first dose of osimertinib;

   - Previous treatment with osimertinib *or* (in **AURA2** only) *with a third-generation EGFR TKI (eg, CO-1686);*

   - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of osimertinib;

   - Radiotherapy with a limited field of radiation for palliation within 1 week of the first dose of osimertinib (in **AURA extension** only), with the exception of patients receiving radiation to more

than 30% of the bone marrow or with a wide field of radiation, which had to be completed within 4 weeks of the first dose of osimertinib;

- 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 cytochrome P450 (CYP) 2C8 and potent inhibitors or inducers of CYP3A4;

- (In **AURA2** only) *Treatment with an investigational drug within 5 half-lives of the compound*;

3. Any unresolved toxicities from prior therapy greater than grade 1 in the CTCAE at the time of starting osimertinib, with the exception of alopecia and grade 2 prior-platinum-therapy-related neuropathy;

4. Spinal cord compression or brain metastases unless asymptomatic, stable, and not requiring steroids for at least 4 weeks prior to start of osimertinib treatment;

5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses, which, in the Investigator's opinion, made it undesirable for the patient to participate in the trial or which would jeopardise compliance with the protocol; or active infection including hepatitis B, hepatitis C, and human immunodeficiency virus. Screening for chronic conditions was not required;

6. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib;

7. Any of the following cardiac criteria:

   - Mean resting QTc >470 msec, obtained from 3 electrocardiograms (ECGs);

   - Any clinically important abnormalities in rhythm, conduction or morphology of resting ECG, eg, complete left bundle branch block, third-degree heart block, second-degree heart block, or PR interval >250 msec;

   - Any factors that increased the risk of QTc prolongation or risk of arrhythmic events;

8. Past medical history of ILD, drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD;

9. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:

   - Absolute neutrophil count $<1.5 \times 10^9$/L;

   - Platelet count $<100 \times 10^9$/L;

   - Haemoglobin <90 g/L;

- Alanine aminotransferase >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases;

- Aspartate aminotransferase >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases;

- Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's syndrome (unconjugated hyperbilirubinaemia) or liver metastases;

- Creatinine >1.5 times ULN concurrent with creatinine clearance <50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance was only required when creatinine >1.5 times ULN;

10. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib;

11. Women who were breast-feeding;

Judgement by the Investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions and requirements

Treatments

The recommended osimertinib oral daily dose of 80 mg was selected from a review of all available safety, tolerability, PK, and efficacy data from AURA Phase I

Patients (with the exception of patients with insulin-dependent diabetes) had to fast for ≥1 hour prior to taking a dose to ≥ 2 hours after dosing. Water was permitted during this fasting period.

Patients continued on treatment with osimertinib until RECIST v1.1-defined progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment as patients could continue to receive osimertinib beyond RECIST v1.1-defined progression as long as they continued to show clinical benefit, as judged by the investigator.

Objectives

AURA extension

Primary objective:
To investigate the safety, tolerability, and efficacy (ORR) of osimertinib when given orally to patients with locally advanced or metastatic NSCLC who had progressed following prior therapy with an EGFR-TKI agent.

Key secondary objectives:
To obtain additional assessments of the anti-tumour activity of osimertinib by evaluation of DoR, DCR, tumour shrinkage, PFS, using RECIST v1.1 as assessed by a BICR of radiological information, and OS; and to characterise the pharmacokinetics of osimertinib and its metabolites (AZ5104 and AZ7550) after multiple oral doses

AURA 2

Primary Objective:
To investigate the efficacy (ORR by BICR) of orally administered osimertinib.

Key Secondary Objectives:

To further assess the efficacy of osimertinib in terms of DoR, DCR, tumour shrinkage, and PFS as assessed by BICR; to investigate the safety and tolerability profile of osimertinib and to characterise the pharmacokinetics of osimertinib and its metabolites; to investigate the effect of osimertinib on QTc interval after oral dosing to NSCLC patients

Outcomes / endpoints

Primary endpoint

In both studies, the primary efficacy endpoint variable was the ORR according to RECIST 1.1 by BICR using the evaluable for response analysis set.

The ORR was defined as the percentage of patients with at least 1 visit response of CR or PR that was confirmed at least 4 weeks later (ie, a BOR of CR or PR). Data obtained up until progression, or the last evaluable assessment in the absence of progression, were included in the assessment of ORR. However, any CR or PR that occurred after a further anti-cancer therapy was received was not included in the numerator of the ORR calculation. Assessment were carried out every 6 weeks. For each patient, the BICR defined the overall visit response as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD) or not evaluable (NE) and the relevant scan dates for each time point (ie, for visits where response or progression was or was not identified).

From the investigators' review of the imaging scans, the RECIST tumour response data were used to determine each patient's visit response for TLs, NTLs) and new lesions. Patients with brain metastases, asymptomatic, stable and not requiring steroids for at least 4 weeks prior to start of study treatment, were included in the study; any brain metastases present at baseline were recorded as NTL.Sensitivity analyses of ORR were performed using the investigators' assessments of RECIST and the concordance between the ORR as assessed by BICR and as assessed by the investigator summarised using those patients evaluable for response by both investigator and BICR.

Patients with brain metastases (which had to be asymptomatic, stable and not requiring steroids for at least 4 weeks prior to the start of study treatment) were included in the study; any brain metastases present at baseline were recorded as non-target lesions (NTL)

Secondary endpoints

- Duration of response

The DoR was defined as the time from the date of first documented response, (that is subsequently confirmed) until the date of documented progression or death in the absence of disease progression. The end of response should coincide with the date of progression or death from any cause used for the PFS endpoint. The time of the initial response was defined as the latest of the dates contributing towards the first visit response of PR or CR.

- Disease control rate

The DCR was defined as the percentage of patients who had a BOR of CR or PR or SD for at least 6 weeks (allowing for a 1-week visit window)

- Tumour shrinkage

Tumour size is the sum of the longest diameters of the TLs. The best percentage change in tumour size from baseline was determined for each patient, ie, the maximum reduction from baseline or the minimum increase

from baseline in the absence of a reduction from baseline based on all post-baseline assessments prior to progression or the start of subsequent anticancer therapy.

- Progression-free survival

The PFS was defined as the time from date of first dose until the date of objective disease progression as defined by RECIST or death (by any cause in the absence of progression) regardless of whether the patient withdrew from osimertinib therapy or received another anti-cancer therapy prior to progression.

- Overall survival

Overall survival was defined as the time from the date of first dose until death due to any cause.

Exploratory endpoints

The following PROs were collected:

- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 items (EORTC QLQ-C30)
- The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Lung Cancer 13 items (EORTC QLQ-LC13)

Sample size

AURA extension Study

The primary endpoint of this Phase II extension part of the AURA study was ORR. The extension phase was to recruit approximately 175 patients with EGFR T790M mutation positive advanced NSCLC, whose disease had progressed following either 1 prior therapy with an EGFR TKI (2nd-line; no additional lines of therapy, n=50) or following treatment with at least 2 lines of prior therapy including at least 1 EGFR TKI and potentially other anticancer therapies (≥ 3rd-line, n=125).

With 175 patients, the precision of the estimation of ORR in the overall study population would be within ±8% (e.g. ORR 40%, 95% CI: 33.0%, 47.4%). The precision of the estimation of ORR would be within ±13% in the 50 patient cohort who have only received previous TKI treatment and within ±9% in the 125 patient cohort who have received previous TKI treatment and other anti-cancer therapy. The study also provided an adequate number of patients in which to assess the safety and tolerability of osimertinib; if zero events were observed in the 175 patients, there would be 95% confidence (2 sided) that the true event rate was less than 2.2%.

AURA 2 STUDY

The primary endpoint of this study was ORR. The study was to recruit approximately 175 patients with EGFR T790M mutation positive locally advanced NSCLC or metastatic NSCLC whose disease had progressed following either 1 prior therapy with an EGFR TKI (2nd-line, n=50) or following treatment with both EGFR TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment; ≥3rd-line, n=125).

With 175 patients, the precision of the estimation of ORR in the overall study population would be within ±8% (eg, ORR 40%, 95% CI 33.0%, 47.4%). The precision of the estimation of ORR would be within ±13% in the cohort who have only received previous TKI treatment and within ±9% in the cohort who have received previous TKI treatment and other anti-cancer therapy. The study also provided an adequate number of patients in which

to assess the safety and tolerability of osimertinib; if zero events were observed in the 175 patients, there would be 95% confidence (2 sided) that the true event rate was less than 2.2%.

Randomisation

Not applicable since both studies were not randomised

Blinding (masking)

Not applicable since both studies were single-arm and open-label studies.

Statistical methods

AURA extension and AURA2 studies

Descriptive statistics were used for all variables. Continuous variables were summarised by the number of observations, mean, standard deviation, median, minimum and maximum. Categorical variables were summarised by frequency counts and percentages for each category. Unless otherwise stated, percentages were calculated based on the full analysis set (FAS).

The FAS was defined as all patients enrolled who received at least 1 dose of study treatment.

Summaries of demography and all safety data summaries and analyses were produced based on the FAS.

The following efficacy analyses were conducted in the FAS:

- PFS by BICR
- Sensitivity analysis of ORR and best objective response (BOR) by BICR
- Investigator RECIST outcomes
- QoL

The evaluable for response analysis set was defined as all patients who received at least 1 dose of study treatment and had measurable disease at baseline according to the BICR of baseline imaging data.

The primary analysis of ORR, BOR, DoR, DCR and tumour shrinkage by BICR were produced based on the evaluable for response analysis set (patients evaluable for response by BICR).

Primary endpoint

The primary analysis of **ORR** will be presented together with 95% exact (Clopper-Pearson) confidence interval (CI) by study and overall. Overall ORR based on the pooled data will be calculated as the number (%) of patient with best objective response of confirmed CR or PR from both studies.

The similar analysis of ORR will also be presented by treatment cohort (2nd- versus ≥ 3rd-line) and overall. The ORR in each treatment cohort based on the pooled data will be calculated as the number (%) of patients with best objective response of confirmed CR or PR from each treatment cohort across two studies.

Secondary endpoints

In both studies the secondary outcomes variables were DoR, DCR, tumour shrinkage and PFS, according to RECIST 1.1 using assessments performed by a BICR. A further secondary variable was OS.

- Duration of response

If the response was not confirmed, it was not included. If a patient did not progress following a response, then their DoR used the PFS censoring time. DoR (months) in responding patients based on the BICR will be summarised using the median and 95% CI. The median will be calculated using the Kaplan-Meier method. The number and percentage of responding patients remaining in response at >3; >6; >9; >12 months will be summarised. The above analyses will be presented by study and overall. For overall DoR, the responding patients from both studies will be included in the analyses. A Kaplan-Meier plot will be presented for overall pooled population. The similar analysis of DoR will be presented by treatment cohort and overall. For DoR in each treatment cohort, the responding patients from each treatment cohort across two studies will be included in the analyses. A Kaplan-Meier plot will be presented for each treatment cohort.

- Tumour shrinkage

To assess the depth of tumour shrinkage, the proportion of patients who achieved >30%, >50% and >75% reduction in TL tumour size was summarised descriptively.The percentage change in TL tumour size from baseline was summarised using descriptive statistics and presented for each visit.

The best percentage change from baseline in TL tumour size was summarised descriptively and presented graphically using waterfall plots. In the following situations where patients' best percentage change data would have been missing, the value of +20% was imputed:

If a patient had no postbaseline assessments and had died

If a patient had new lesions or progression of NTLs

If a patient had withdrawn due to disease progression and had no evaluable TL data before or at progression

- Progression-free survival

PFS will be displayed using a Kaplan-Meier plot for overall pooled population. The total number of events, median PFS (calculated from the Kaplan-Meier plot, with 95% CIs), and the percentage PFS at 3, 6, 12 and 18 months will be summarised by study and overall. Similar analyses of PFS will be presented by treatment cohort and overall. A Kaplan-Meier plot will be presented for each treatment cohort.

- Overall survival

Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive.

Sensitivity analysis

Sensitivity analyses of ORR, DCR, DoR, tumour shrinkage and PFS using the investigators assessment of RECIST will be performed in an analogous manner to those using the BICR described above.

The concordance between ORR as assessed by BICR and by investigator will be presented by study and overall based on the FAS.

Subgroup analysis

The consistency of the ORR and DoR by BICR across the following key subgroups will also be evaluated based on pooled data across two studies. The analysis of ORR together with 95% exact (Clopper-Pearson) CI will be presented by treatment cohort and overall within each category of the key subgroups. DoR (months) in responding patients based on the BICR will be summarised using the median and 95% CI by treatment cohort

and overall within each category of the key subgroups. The median will be calculated using the Kaplan-Meier method. Kaplan-Meier plots will be presented for DoR within each category of the key subgroups for the overall pooled population to ensure that the median estimates within subgroups are not over-interpreted in these potentially small subgroups where the data may be limited and not mature at the primary analysis.

- Patients who received EGFR-TKI as last treatment prior to study start (further split into whether EGFR-TKI was <30 days or ≥30 days prior to first dose of osimertinib) and those whose treatment prior to study start was not an EGFR-TKI
- Ethnicity (Asian versus Non-Asian)
- Gender (Male versus Female)
- Age at screening (<65 versus ≥65)
- Mutation status prior to start of study (Exon 19 deletion/L858R/Other)
- Duration of most recent prior EGFR-TKI (<6 months versus ≥6 months)
- Smoking history
- Brain metastases at entry
- Patients with T790M+ detected in their baseline plasma sample (ctDNA) and patients that are T790M- by the plasma test
- Region (North America/Asia/Europe and rest of world)

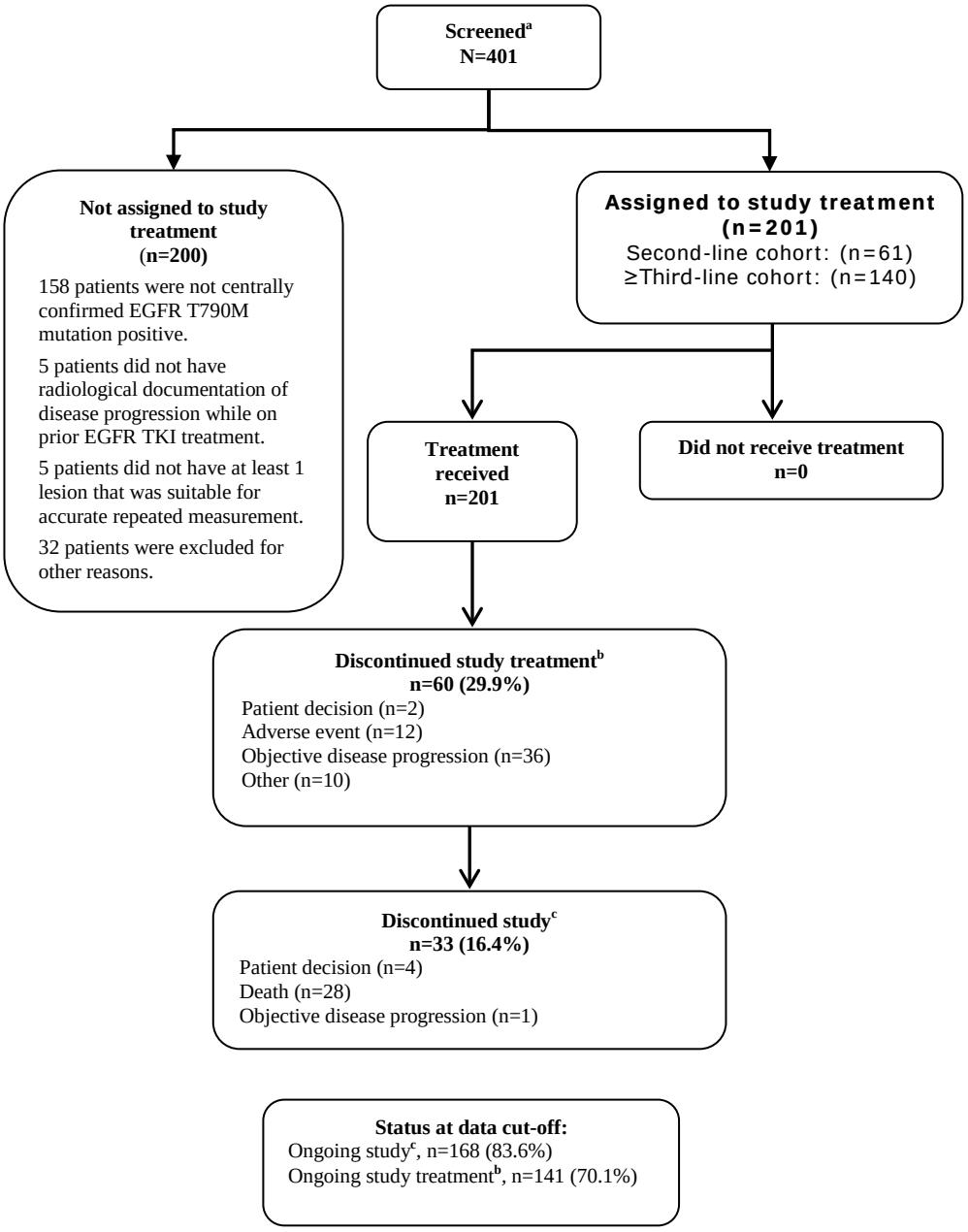
Forest plots of ORR by BICR for the above defined subgroups will be constructed for each treatment cohort and overall.

Interim analyses

There were no formal interim analyses planned for this study, but 2 DCO points were planned at approximately 3 months and 8 months after the last patient had been enrolled. This report covers analyses from the 8-month DCO. The final database will be locked at the end of the study, at 12 to 24 months after the last patient was enrolled.

Results

Participant flow



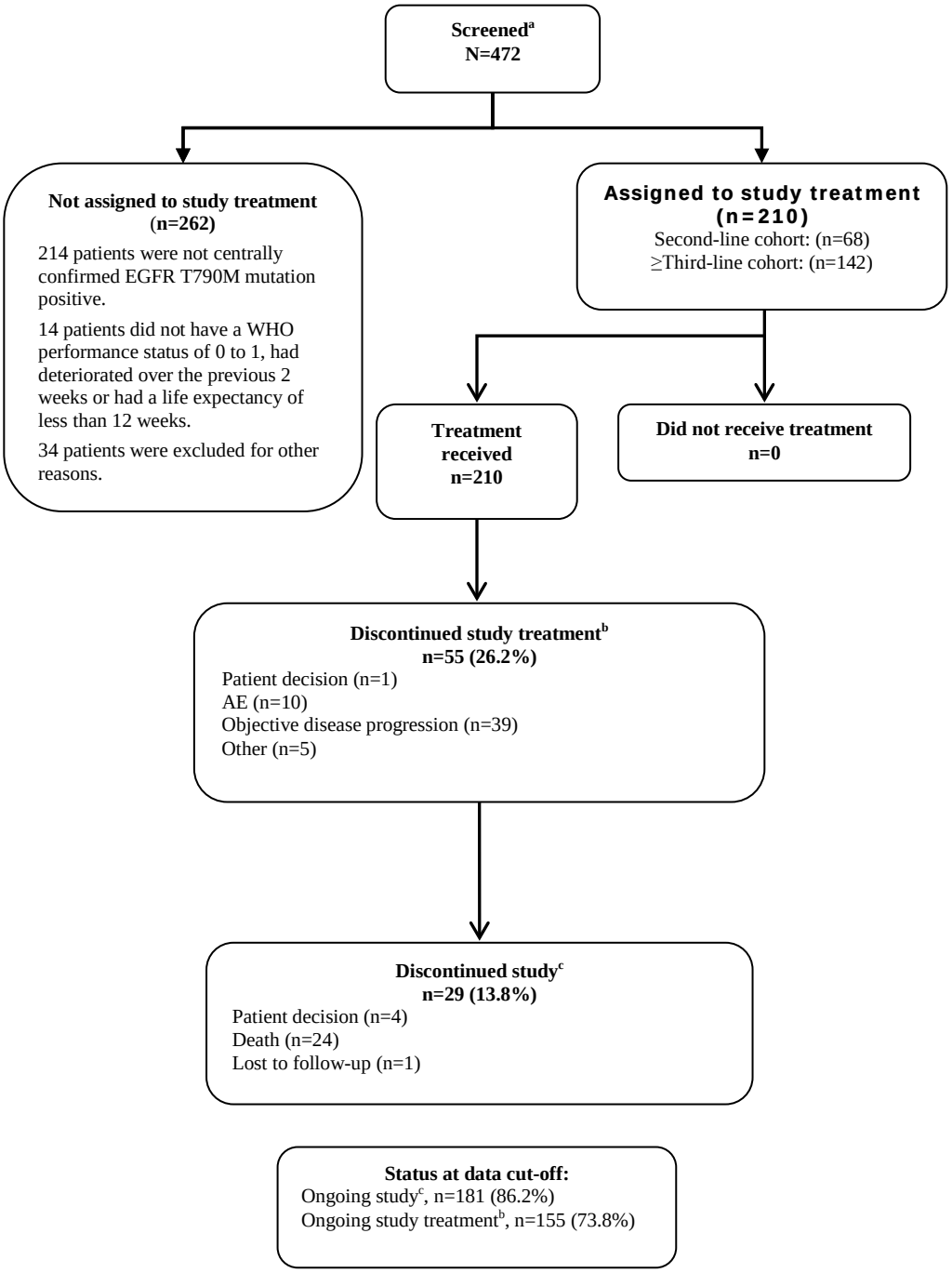
[a] Informed consent received. Patients could have had more than 1 reason for not being assigned to treatment and hence would be counted more than once.

[b] Percentages were calculated from the number of patients who received treatment.

[c] Percentages were calculated from the number of patients who were assigned to treatment.

Abbreviations: EGFR TKI, epidermal growth factor receptor tyrosine kinase inhibitor

Figure 9: AURA extension (the phase II component of the AURA study, D5160C00001)



[a] Informed consent received. Patients could have had more than 1 reason for not being assigned to treatment and hence would be counted more than once.

[b] Percentages were calculated from the number of patients who received treatment.

[c] Percentages were calculated from the number of patients who were assigned to treatment.

Abbreviations: AE, adverse event; Excl, exclusion criterion; Incl, inclusion criterion.

Figure 10: AURA2 (D5160C00002)

Recruitment

AURA extension

The first patient started treatment on 14 May 2014 and the last patient started treatment on 21 October 2014. The DCO for this report was 1 May 2015.

The study was open for enrolment at 46 study centres in Japan (16), the USA (7), South Korea (4), Australia (3), France (3), Germany (3), Spain (3), Italy (3), Taiwan (2) and the UK (2). Patients were both screened and recruited at 40 centres in 10 countries; 50.7% of patients were from Asia, 20.4% from North America, and 28.9% from Europe and rest of world.

AURA 2

The first patient started treatment on 13 June 2014 and the last patient started treatment on 27 October 2014. The DCO for this report was 1 May 2015.

The study was open for enrolment at 44 study centres in Canada (3), Hong Kong (2), Italy (5), Japan (14), South Korea (3), Spain (6), Taiwan (2) and the USA (9);51.9% of patients were from Asia, 31.9% were from North America and 16.2% were from Europe and rest of world.

Conduct of the study

AURA extension

There were 19 patients identified as having protocol deviations for review; 5 did not fulfil eligibility criteria, 9 protocol-required procedures were not adhered to, and 5 other reasons.

Key Protocol amendments (all the amendments were carried out before the start of patients recruitment):

a) Amendment 1 (29 March 2013): Additional clarifications regarding efficacy assessments such as PFS up to and beyond discontinuation of study treatment were included. Details of RECIST version 1.1 assessments and safety data requirements beyond discontinuation of study treatment but prior to disease progression were updated An option to enter patients into the study using local tumour EGFR T790M mutation status testing was added

b) Amendment 3 (27 February 2014): Amended to add a Phase II extension study (study title and all sections of this report). Addition of optional CSF sample collection

AURA 2

There were 25 patients identified as having protocol deviations for review; 12 did not fulfil eligibility criteria, 6 protocol-required procedures were not adhered to, and 5 other reasons. Of these deviations, there were 7 patients in the ≥3rd-line cohort who received 2 or more prior treatment regimens but did not have a platinum-containing doublet regimen as treatment for advanced NSCLC, as required in inclusion criterion 5. Two other protocol deviations were considered important protocol deviations with the potential to impact the primary assessment of efficacy:

Two patients had their tumour assessment performed more than 28 days before first dose

- Protocol amendments:

There were only two amendments, the first one was made prior to the start of patient recruitment (1 April 2014) and the second one after the start of patient recruitment (24 September 2014). None of the amendments was considered as major.

Baseline data

Table 25: Demographic characteristics by study (Full analysis set)

Demographic characteristic		AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Age (years)	n	201	210	411
	Mean	61.4	62.9	62.2
	SD	10.58	10.91	10.76
	Median	62.0	64.0	63.0
	Min	37	35	35
	Max	89	88	89
Age group (years) n (%)	<50	30 (14.9)	20 (9.5)	50 (12.2)
	≥50-<65	86 (42.8)	88 (41.9)	174 (42.3)
	≥65-<75	64 (31.8)	69 (32.9)	133 (32.4)
	≥75	21 (10.4)	33 (15.7)	54 (13.1)
	Total	201 (100)	210 (100)	411 (100)
Sex n (%)	Male	68 (33.8)	64 (30.5)	132 (32.1)
	Female	133 (66.2)	146 (69.5)	279 (67.9)
	Total	201 (100)	210 (100)	411 (100)
Race n (%)[a]	White	76 (38.2)	72 (34.3)	148 (36.2)
	Black or African American	1 (0.5)	3 (1.4)	4 (1.0)
	Asian	114 (57.3)	132 (62.9)	246 (60.1)
	Native Hawaiian or other Pacific Islander	0	1 (0.5)	1 (0.2)
	Other	4 (2.0)	2 (1.0)	6 (1.5)
	Not Reported	4 (2.0)	0	4 (1.0)
	Total	199 (100)	210 (100)	409 (100)
Ethnic group n (%)	Hispanic or Latino	16 (8.0)	5 (2.5)	21 (5.2)
	African-American	1 (0.5)	0	1 (0.2)
	Asian (other than Chinese and Japanese)	45 (22.4)	35 (17.2)	80 (19.8)
	Chinese	30 (14.9)	51 (25.0)	81 (20.0)
	Japanese	35 (17.4)	46 (22.5)	81 (20.0)
	Other	74 (36.8)	67 (32.8)	141 (34.8)
	Total	201 (100)	204 (100)	405 (100)

[a] Race not recorded for some patients due to local country regulations.

Table 26: Disease characteristics at baseline by study (Full analysis set)

	Number (%) of patients		
	AURA Extension osimertinib 80 mg (N=201)	**AURA2 osimertinib 80 mg (N=210)**	**Total osimertinib 80 mg (N=411)**
WHO performance status			
0 (Normal activity)	68 (33.8)	83 (39.5)	151 (36.7)
1 (Restricted activity)	132 (65.7)	127 (60.5)	259 (63.0)
2 (In bed less than or equal to 50% of the time)	1 (0.5)	0	1 (0.2)
Histology type			
Squamous cell carcinoma (NOS)	0	2 (1.0)	2 (0.5)
Adenocarcinoma (NOS)	171 (85.1)	170 (81.0)	341 (83.0)
Adenocarcinoma: acinar	11 (5.5)	10 (4.8)	21 (5.1)
Adenocarcinoma: papillary	10 (5.0)	17 (8.1)	27 (6.6)
Adenocarcinoma: bronchiolo-alveolar	3 (1.5)	1 (0.5)	4 (1.0)
Adenocarcinoma: solid with mucous formation	0	2 (1.0)	2 (0.5)
Adenosquamous carcinoma	1 (0.5)	1 (0.5)	2 (0.5)
Other	5 (2.5)	7 (3.3)	12 (2.9)
EGFR mutations by cobas® central test[d]			
T790M	197 (98.0)	208 (99.0)	405 (98.5)
Exon 19 deletion	142 (70.6)	137 (65.2)	279 (67.9)
L858R	51 (25.4)	67 (31.9)	118 (28.7)
G719X	4 (2.0)	4 (1.9)	8 (1.9)
S768I	3 (1.5)	3 (1.4)	6 (1.5)
Exon 20 insertion	2 (1.0)	1 (0.5)	3 (0.7)
T790M only	5 (2.5)	1 (0.5)	6 (1.5)
Overall disease classification			
Metastatic[a]	197 (98.0)	198 (94.3)	395 (96.1)
Locally advanced[b]	4 (2.0)	12 (5.7)	16 (3.9)
Brain metastases[c]	74 (36.8)	88 (41.9)	162 (39.4)
Visceral metastases[c]	173 (86.1)	168 (80.0)	341 (83.0)
Baseline sum of target lesions (mm), n	199	198	397
Mean	61.2	59.9	60.6
SD	36.90	40.50	38.69
Median	52.5	50.5	51.8
Min	12	10	10
Max	229	218	229
Baseline sum of target lesions tumour size category (mm)			
< 40	63 (31.3)	66 (31.4)	129 (31.4)
40 - 79	86 (42.8)	90 (42.9)	176 (42.8)
80 - 119	34 (16.9)	27 (12.9)	61 (14.8)
≥ 120	16 (8.0)	15 (7.1)	31 (7.5)

Table 27: Number of previous anti-cancer treatment regimens at baseline (Full analysis set)

	Number (%) of patients		
Number of regimens	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
1	61 (30.3)	69 (32.9)	130 (31.6)
2	49 (24.4)	45 (21.4)	94 (22.9)
3	33 (16.4)	38 (18.1)	71 (17.3)
4	22 (10.9)	22 (10.5)	44 (10.7)
5	14 (7.0)	7 (3.3)	21 (5.1)
> 5	22 (10.9)	29 (13.8)	51 (12.4)
n	201	210	411
Mean	2.8	3.0	2.9
SD	1.92	2.43	2.20
Median	2.0	2.0	2.0
Min	1	1	1
Max	11	14	14

Patients in the unknown category are not included in the calculation of n or the associated summary statistics.

Table 28: Number of previous EGFR-TKI regimens at baseline (Full analysis set)

	Number (%) of patients		
Number of regimens	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
1	111 (55.2)	131 (62.4)	242 (58.9)
2	47 (23.4)	42 (20.0)	89 (21.7)
3	33 (16.4)	18 (8.6)	51 (12.4)
4	7 (3.5)	9 (4.3)	16 (3.9)
5	2 (1.0)	4 (1.9)	6 (1.5)
> 5	1 (0.5)	6 (2.9)	7 (1.7)
n	201	210	411
Mean	1.7	1.8	1.7
SD	0.98	1.34	1.18
Median	1.0	1.0	1.0
Min	1	1	1
Max	6	9	9

Patients in the unknown category are not included in the calculation of n or the associated summary statistics. Patients may have more than one prior regimen.

Numbers analysed

Table 29: Analysis sets by study

	Number of patients		
	AURA Extension AZD9291 80 mg	AURA2 AZD9291 80 mg	Total AZD9291 80 mg
Patients assigned to treatment	201	210	411
Patients included in full analysis set	201	210	411
Patients excluded from full analysis set[a]	0	0	0
Did not receive at least one dose of treatment	0	0	0
Patients included in evaluable for response analysis set by BICR	199	198	397
Patients excluded from evaluable for response analysis set[a]	2	12	14
No measurable disease at baseline	2	12	14

[a] Patients could have been excluded for more than 1 reason.
Full analysis set - all patients enrolled who received at least one dose of study treatment.
Evaluable-for-response analysis set - all patients who received at least one dose of study treatment and have measurable disease at baseline according to the blinded independent central review (BICR) of baseline imaging data.

Outcomes and estimation

Primary endpoint: Objective response rate

As of the DCO of 1 May 2015, the median treatment exposure of patients treated in the ongoing AURA extension and AURA2 studies was 7.7 months (range: <0.1 month to 11.6 months). All patients had at least 6 months follow-up from first dose.

Table 30: Summary of objective response rate by BICR (evaluable-for-response set and FAS) and investigator (FAS) assessments per study

Analysis set Study	N	No. of patients with confirmed response[a]	ORR (%)	95% CI
BICR assessment of evaluable-for-response analysis set (primary efficacy analysis)				
AURA Extension AZD9291 80 mg	199	122	61.3	54.2, 68.1
AURA2 AZD9291 80 mg	199	141	70.9	64.0, 77.1
Total AZD9291 80 mg	398	263	66.1	61.2, 70.7
BICR assessment of FAS (sensitivity analysis)				
AURA Extension AZD9291 80 mg	201	122	60.7	53.6, 67.5
AURA2 AZD9291 80 mg	210	142	67.6	60.8, 73.9
Total AZD9291 80 mg	411	264	64.2	59.4, 68.9
Investigator assessment of FAS (sensitivity analysis)				
AURA Extension AZD9291 80 mg	201	142	70.6	63.8, 76.8
AURA2 AZD9291 80 mg	210	148	70.5	63.8, 76.6
Total AZD9291 80 mg	411	290	70.6	65.9, 74.9

BICR = blinded independent central review; FAS = full analysis set; ORR = objective response rate;
[a] Responses excluded unconfirmed responses.
Objective response rate was defined as the number (%) of patients with at least one visit response of CR or PR that was confirmed at least 4 weeks later.
The CIs were calculated using Clopper-Pearson exact method for binomial proportions.
Of note, by protocol and by BICR charter, brain metastases were considered to be non-target lesions. Therefore, in line with RECIST v1.1, brain metastases were not measured and were only assessed qualitatively at the time points specified in the protocols.

Table 31: Best objective response (BOR) by central review by study (Evaluable-for-response analysis set)

Response status	Best objective response	Number (%) of patients		
		AURA Extension AZD9291 80 mg (N=199)	AURA2 AZD9291 80 mg (N=199)	Total AZD9291 80 mg (N=398)
Response	Total	122 (61.3)	141 (70.9)	263 (66.1)
	Complete response[a]	0	2 (1.0)	2 (0.5)
	Partial response[a]	122 (61.3)	139 (69.8)	261 (65.6)
Non-response	Total	77 (38.7)	58 (29.1)	135 (33.9)
	Stable disease ≥6 weeks[b]	58 (29.1)	41 (20.6)	99 (24.9)
	Unconfirmed partial response[c]	14 (7.0)	12 (6.0)	26 (6.5)
	Stable disease	44 (22.1)	29 (14.6)	73 (18.3)
	Progression	19 (9.5)	15 (7.5)	34 (8.5)
	Unconfirmed partial response[c]	1 (0.5)	0	1 (0.3)
	RECIST progression	13 (6.5)	12 (6.0)	25 (6.3)
	Early death	5 (2.5)	3 (1.5)	8 (2.0)
	Not evaluable	0	2 (1.0)	2 (0.5)
	No evaluable follow-up assessments	0	1 (0.5)	1 (0.3)
	Unconfirmed partial response[c]	0	1 (0.5)	1 (0.3)

[a] Responses required confirmation after 4 weeks.
[b] SD ≥ 6 weeks included RECIST visit window (±7 days).
[c] PR or CR achieved but either no confirmation assessment performed or a confirmation assessment performed but response not confirmed.
RECIST version 1.1.

In the overall population, 86% (227/263) had documentation of response at the time of the first scan (6 weeks); 96% (253/263) had documentation of response at the time of the second scan (12 weeks).

Secondary efficacy endpoints:

Disease control rate

Table 32: Summary of disease control rate (DCR) by BICR assessment of the evaluable-for-response analysis set and by investigator assessment of the full analysis set

Analysis set Study	N	No. of patients with disease control	DCR (%)	95% CI
BICR assessment of evaluable-for-response set				
AURA Extension AZD9291 80 mg	199	180	90.5	85.5, 94.2
AURA2 AZD9291 80 mg	199	182	91.5	86.7, 94.9
Total AZD9291 80 mg	398	362	91.0	87.7, 93.6
BICR assessment of FAS				
AURA Extension AZD9291 80 mg	201	182	90.5	85.6, 94.2
AURA2 AZD9291 80 mg	210	192	91.4	86.8, 94.8
Total AZD9291 80 mg	411	374	91.0	87.8, 93.6
Investigator assessment of FAS				
AURA Extension AZD9291 80 mg	201	188	93.5	89.2, 96.5
AURA2 AZD9291 80 mg	210	197	93.8	89.7, 96.7
Total AZD9291 80 mg	411	385	93.7	90.9, 95.8

Disease control = best objective response of confirmed complete response, confirmed partial response or stable disease ≥6 weeks.
The CIs were calculated using Clopper-Pearson exact method for binomial proportions.
RECIST version 1.1.

Best change from baseline in target lesion size (tumour shrinkage)

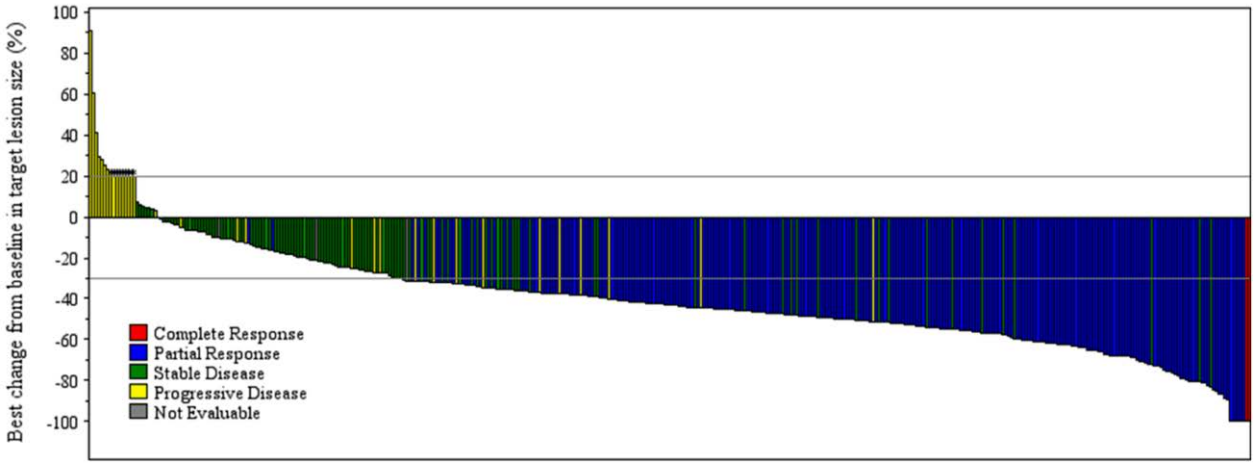


Figure 11: Target lesion size, best percentage change from baseline by central review - total, waterfall plot (Evaluable-for-response analysis set)

Best percentage change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
* represents imputed values: if it is known that the patient has died, has new lesions or progression of non-target lesions, has withdrawn due to PD and has no evaluable target lesion (before or at progression) assessments, best change will be imputed as 20%. RECIST version 1.1.

Duration of response

The median DoR based on BICR assessment had not been reached yet (22.8% maturity); however, the lower limit of the 95% CI was 8.3 months. The median DoR based on investigator assessment (27.6% maturity) was 8.5 months (95% CI: 8.5, NC).

Table 33: Duration and first documentation of objective response in patients with objective response by central review by study (Evaluable-for-response analysis set, patients with objective response)

	AURA Extension AZD9291 80 mg (N=122)	AURA2 AZD9291 80 mg (N=141)	Total AZD9291 80 mg (N=263)
Number of responders who subsequently progressed or died	22	38	60
Duration of response from onset of response (months)[a,b]			
25th percentile	7.0	5.6	6.9
Median	NC	7.8	NC
95% CI for median	NC, NC	7.1, NC	8.3, NC
75th percentile	NC	8.3	NC
Estimated Percentage remaining in response[b]			
at 3 Months (95% CI)	98.3 (93.4, 99.6)	91.9 (85.8, 95.4)	94.9 (91.3, 97.0)
at 6 Months (95% CI)	83.1 (73.7, 89.4)	74.5 (65.2, 81.6)	78.4 (72.1, 83.5)
at 9 Months (95% CI)	70.9 (57.7, 80.7)	NA	55.3 (40.6, 67.8)
Number and Percentage remaining in response			
> 3 Months	113 (92.6)	123 (87.2)	236 (89.7)
> 6 Months	55 (45.1)	43 (30.5)	98 (37.3)
> 9 Months	3 (2.5)	NA	3 (1.1)
Minimum duration of response (months)	1.4	1.3	1.3
Maximum duration of response (months)	9.7	8.4	9.7
Time to onset of response from first dose (weeks)			
25th percentile	5.4	5.6	5.4
Median	5.9	6.0	5.9
75th percentile	6.1	6.3	6.1
Time to onset of response from first dose (weeks)			
≤6 Weeks	104 (85.2)	123 (87.2)	227 (86.3)
≤12 Weeks	115 (94.3)	138 (97.9)	253 (96.2)
≤18 Weeks	119 (97.5)	141 (100)	260 (98.9)
≤24 Weeks	121 (99.2)	141 (100)	262 (99.6)

[a] Duration of response was the time from the first documentation of CR/PR (that was subsequently confirmed) until the date of progression or death in the absence of disease progression.
[b] Calculated using Kaplan-Meier technique.
RECIST version 1.1.
NA = not available

Progression free survival

Table 34: Median progression-free survival by BICR and investigator assessments by study (Full analysis set)

	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Median PFS based on BICR of FAS			
Total number of events[a]	80	79	159
Median progression free survival (months)[b]	NC	8.6	9.7
95% CI for median progression free survival	8.1, NC	8.3, 9.7	8.3, NC
Progression free at 3 months (%)	81.5	84.9	83.2
95% CI for PFS at 3 months	75.3, 86.2	79.2, 89.1	79.2, 86.5
Progression free at 6 months (%)	72.0	69.7	70.9
95% CI for PFS at 6 months	65.1, 77.8	62.8, 75.7	66.1, 75.1
Progression free at 9 months (%)	54.6	47.7	51.9
95% CI for PFS at 9 months	46.4, 62.1	36.2, 58.4	45.3, 58.1
Median follow-up for PFS (Months)	6.9	6.7	6.8
Median PFS based on investigator assessment of FAS			
Total number of events[a]	80	78	158
Median progression free survival (months)[b]	9.7	NC	9.7
95% CI for median progression free survival	8.2, NC	8.3, NC	8.3, NC
Progression free at 3 months (%)	89.5	89.4	89.4
95% CI for PFS at 3 months	84.3, 93.0	84.4, 92.9	86.0, 92.1
Progression free at 6 months (%)	75.1	71.1	73.0
95% CI for PFS at 6 months	68.4, 80.5	64.3, 76.8	68.4, 77.1
Progression free at 9 months (%)	54.2	52.7	53.5
95% CI for PFS at 9 months	45.7, 62.0	42.4, 61.9	47.2, 59.4
Median follow-up for PFS (Months)	6.9	6.8	6.8

[a] Progression events that did not occur at the time of analysis were censored and therefore excluded in the number of events.
[b] Calculated using the Kaplan-Meier technique.
Progression included deaths in the absence of RECIST progression.
RECIST version 1.1. NC = not calculable.

Fifty-seven of the 139 patients who progressed and were still alive at DCO (41.0%) subsequently received other anti-cancer therapies, the most frequent of which were platinum-based chemotherapy (27 patients, 19.4%) and non-platinum-based cytotoxic chemotherapy (22 patients, 15.8%); 11 patients (7.9%) received an EGFR-TKI.

Overall survival

Overall survival data are currently immature. At DCO, median follow-up for OS was 7.4 months.

Table 35: Survival status at the time of data cut-off and median overall survival by study (Full analysis set)

Status	Number (%) of patients AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Death	28 (13.9)	24 (11.4)	52 (12.7)
Still in survival follow up[a]	168 (83.6)	181 (86.2)	349 (84.9)
Terminated prior to death[b]	5 (2.5)	5 (2.4)	10 (2.4)
Voluntary Discontinuation by Subject	4 (2.0)	4 (1.9)	8 (1.9)
Subject Lost to Follow-up	0	1 (0.5)	1 (0.2)
Other	1 (0.5)	0	1 (0.2)
Total number of deaths	28	24	52
Median Overall survival (months)c	NC	NC	NC
95% CI for Median overall survival	NC, NC	NC, NC	NC, NC
Survival at 3 months (%)	96.5	97.1	96.8
95% CI for survival at 3 months	92.80, 98.32	93.72, 98.70	94.59, 98.14
Survival at 6 months (%)	93.0	91.7	92.3
95% CI for survival at 6 months	88.41, 95.77	86.97, 94.76	89.27, 94.54
Survival at 9 months (%)	84.0	87.1	85.3
95% CI for survival at 9 months	77.49, 88.74	80.83, 91.49	80.85, 88.71
Median follow-up for overall survival (months)	8.3	7.0	7.4

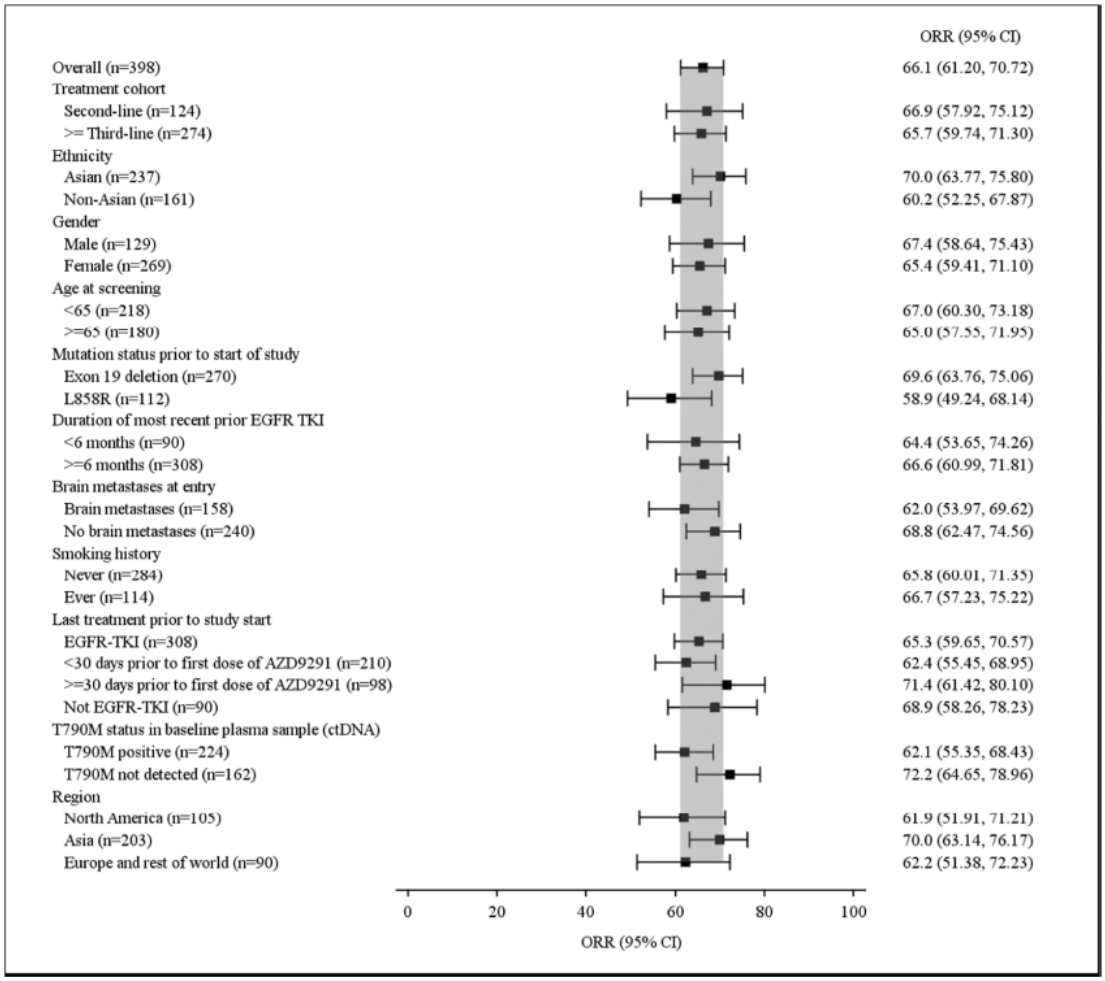
[a] Included patients known to be alive at data cut-off.
[b] Included patients with unknown survival status or patients who were lost to follow-up.
[c] Calculated using the Kaplan-Meier technique.

Patient reported outcome

The PRO data (EORTC LC13 and EORTC LC30) suggest that osimertinib does not cause deterioration of the patients quality of life compared to baseline.

Ancillary analyses

Objective response rate in subgroups of interest



Objective response rate (ORR) and 95% CI.
The CIs are calculated using Clopper-Pearson exact method for binomial proportions.
Dashed vertical lines represent the 95% confidence interval for the overall ORR.
Source: see Figure 2.1.4.1R from pooled efficacy figures in Module 5.3.5.3 Supportive efficacy data.

Figure 12: Objective response rate (ORR) by central review, Forest plot, by subgroup (Evaluable for response analysis set)

Assessment of EGFR T790M mutation status

In the phase I extension cohort of study D5160C00001 (AURA Extension), T790M+ patients were screened for enrollment using the cobas EGFR Mutation Test v1 using tissue. In AZ study D5160C00002 (AURA2), patients were screened for enrollment using the cobas EGFR Mutation Test v2 in tissue to identify those who harboured an EGFR sensitizing mutation and a T790M mutation. In both of these trials, plasma samples were collected at baseline and while on therapy for use in exploratory analyses.

Comparison of cobas plasma test vs cobas tissue test

In the method comparison 383 patients in AURA2 who provided adequate tissue for testing were prospectively screened for T790M mutation using the cobas tissue test. Of these patients, 344 (89.8%) also provided a plasma sample. EGFR T790M mutation status was compared in the tissue and plasma samples from these 344 patients

(Table 36). Not all patients who were tissue T790M mutation positive at screening were dosed in the studies, since some patients failed screening for reasons unrelated to mutation status.

Table 36: Summary of T790M detection rates in tissue and plasma samples from all screened patients in AURA2

cobas® EGFR Mutation Test v2 in Plasma	cobas® EGFR Mutation Test v1 in Tissue			
	T790M+	T790M-	Invalid	Total
T790M+	131	22	2	155
T790M-	92	89	6	187
Invalid	2	0	0	2
No Plasma Sample	8	29	2	39
Total	233	140	10	383
PPA (95% CI)	58.7% (52.2%, 65.0%)			
NPA (95% CI)	80.2% (71.8%, 86.5%)			
PPV (95% CI)	85.6% (79.2%, 90.3%)			
NPV (95% CI)	49.2% (42.0%, 56.4%)			

PPA: Positive percent agreement
NPA: Negative percent agreement
PPV: Positive predictive value
NPV: Negative predictive value

Comparison of cobas plasma test vs NGS plasma test

Comparison of the Roche cobas EGFR Mutation Test version 2 using plasma with a next generation sequencing (NGS) method (MiSeq, Illumina Inc.) was performed by Roche Molecular Systems (RMS) using plasma samples taken from patients during screening for the AURA2 study. The results for detection of the T790M mutation are detailed in Table 37.

Table 37: Agreement between cobas EGFR Mutation v2 in Plasma and the NGS Method for Detection of T790M

cobas EGFR Mutation Test v2 in Plasma	NGS				
	T790M+	T790M-	Invalid	No Plasma Sample	Total
T790M+	129	16	0	10	155
T790M-	12	163	0	12	187
Invalid	2	0	0	0	2
Total	143	179	0	22	344
PPA (95% CI)	91.5% (85.7%, 95.1%)				
NPA (95% CI)	91.1% (86.0%, 94.4%)				
PPV (95% CI)	89.0% (82.8%, 93.1%)				
NPV (95% CI)	93.1% (88.4%, 96.0%)				

PPA: Positive percent agreement
NPA: Negative percent agreement
PPV: Positive predictive value
NPV: Negative predictive value

Summary of main study(ies)

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 38: Summary of Efficacy for trials AURA Extension and AURA 2 (pooled analysis)

<table>
<tr><td colspan="4"><u>Title:</u> AURA extension and AURA 2 (pooled studies)</td></tr>
<tr><td>Studiy identifiers</td><td colspan="3">Study code: D5160C00001 (Phase II extension; AURA)
Study code: D5160C00002 (AURA2)</td></tr>
<tr><td rowspan="2">Design</td><td colspan="3">AURA Extension: Phase II single-arm, open label non-randomized study extension to AURA
AURA 2: Phase II, single-arm, open label non-randomized study to replicate the efficacy and safety data observed in the AURA extension</td></tr>
<tr><td colspan="2">Duration of main phase:
Duration of Run-in phase:
Duration of Extension phase:</td><td>Studies ongoing.
N/A
N/A</td></tr>
<tr><td>Hypothesis</td><td colspan="3">To investigate the safety, tolerability, and efficacy (ORR) of osimertinib when given orally to patients with locally advanced or metastatic NSCLC who had progressed following prior therapy with an EGFR-TKI agent</td></tr>
<tr><td>Treatment group</td><td colspan="2">Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC</td><td>osimertinib 80 mg. Duration of treatment no yet confirmed. Population FAS 201+210 (AURA extension + AURA 2)</td></tr>
<tr><td>Endpoints and definitions</td><td>Primary endpoint: Confirmed objective response rate at DCO</td><td>Confirmed ORR at DCO</td><td>Percentage of patients who had at least 1 best objective response of CR or PR.
ORR evaluation was conducted through BICR on the evaluable for response population using RECIST v1.1. Objective response had to be confirmed at a follow-up scan performed at least 4 weeks after the scan identifying the initial response.</td></tr>
</table>

	Secondary endpoint: Disease control rate	DCR	Percentage of patients who had a BOR of confirmed CR, confirmed PR or confirmed SD ≥6 weeks
	Secondary endpoint: Duration of response	DoR	DoR measured from date of first documented response (which had to be subsequently confirmed) until the date of documented progression or death in the absence of disease progression.
	Secondary endpoint: Tumour shrinkage	-	Best change from baseline in size of TL using RECIST v1.1, ie, maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction.
	Secondary endpoint: Progression-free survival	PFS	Time from date of first dose until the date of objective disease progression as defined by RECIST v1.1 or death by any cause in the absence of progression, regardless of whether the patient withdrew from osimertinib therapy or received another cancer therapy prior to progression.
	Secondary endpoint: Overall survival	OS	Time from the date of first dose until death from any cause.
Database lock	DCO (ongoing study): 1 May 2015.		

Results and Analysis

Analysis description	**Primary Analysis ORR:**	
Analysis population and time point description	Evaluable for response analysis set by blinded independent central review	
Descriptive statistics and estimate variability	Treatment group	Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC
	Number of patients	398
	Confirmed ORR: n/N, ORR%	263/398, 66.1%
	95% CI	61.2–70.7
Effect estimate per comparison	N/A. Single arm studies	

Analysis description	**Secondary endpoint: DCR**	
Analysis population and time point description	Evaluable for response based on BICR assessment of baseline imaging data DCR	
Descriptive statistics and estimate variability	Treatment group	Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC
	Number of patients	398
	DCR: n/N, DCR%	362/398, 91
	95% CI	87.7-93.6
Effect estimate per comparison	N/A. Single arm studies	
Analysis description	**Secondary analysis: DoR**	
Analysis population and time point description	Evaluable for response based on BICR assessment of baseline imaging data Median DoR for responders	
Descriptive statistics and estimate variability	Treatment group	Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC
	Number of patients	263
	Median DoR	Not yet Confirmed
	95% CI	8.3-NC
Effect estimate per comparison	NA	
Analysis description	**Secondary analysis: Best percentage change from baseline in TL size.**	
Analysis population and time point description	Evaluable for response based on BICR assessment of baseline imaging data Best percent change from baseline in TL size	
Descriptive statistics and estimate variability	Treatment group	Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC
	Number of patients	397
	Mean best % change from baseline in TL size	−45.01
	SD	28.010
Effect estimate per comparison	NA	
Analysis description	**Secondary analysis: PFS**	

Analysis population and time point description	FAS based on BICR assessment Median PFS	
Descriptive statistics and estimate variability	Treatment group	Pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC
	Number of patients	411
	n PFS events/N, Median PFS	159/411 9.7
	95% CI	8.3-NC
Effect estimate per comparison	N/A	

Clinical studies in special populations

No clinical studies have been submitted in special populations.

The numbers of elderly patients dosed with osimertinib 80 mg from AURA Phase I, AURA extension and AURA2 are provided in the table below.

Table 39: Number of patients dosed with osimertinib 80 mg in the non-controlled AURA Phase I, AURA extension and AURA2 trials

Full Analysis Set	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
AURA Phase I dose expansion	14/63	5/63	0/63
AURA extension	64/201	19/201	2/201
AURA2	69/210	31/210	2/210

Supportive study(ies)

Data from AURA phase I (dose-escalation and dose expansion parts) provides some information on the duration of response to be expected with osimertinib in the current indication. Investigator-based efficacy data from all pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC who received osimertinib at doses ranging from 20 mg to 240 mg in AURA phase I dose-expansion (n = 163), with particular focus on the subset of 63 pre-treated EGFR T790M mutation-positive patients who received the 80 mg dose of osimertinib, has been presented. Response assessment based on confirmed objective responses as determined by BICR was available for the 80 mg T790M mutation-positive subset of patients. Sixty of the 63 pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC treated with osimertinib 80 mg were evaluable for response based on BICR assessment of baseline imaging data.

The demographics and disease characteristics at baseline are quite similar between the patients in the phase II pooled population and the 163 patients in AURA phase I dose-expansion study.

In the 37 pre-treated patients with EGFR T790M mutation-positive NSCLC who had a confirmed response by BICR in the 80 mg cohort (ORR 61.7% 95%CI 48.2-73.9) the median DoR from first documentation of objective response by Kaplan-Meier method, based on BICR data, was 9.7 months (95% CI: 8.3, NC).

In the subset of 63 pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC who received 80 mg osimertinib, the median PFS based on BICR was 11.0 months (95% CI: 7.0, 15.2).

2.5.3. Discussion on clinical efficacy

EGFR-mutant NSCLC is characterised by exhibiting sensitivity to EGFR TKIs such as erlotinib and gefitinib; nevertheless, usually acquired resistance develops after a median of 9–14 months (N. Engl. J. Med. 361, 947–957; 2009). The most common mechanism of TKI resistance is a second-site mutation (T790M) in the EGFR kinase domain, which could be found in 50-60% of biopsies carried out (Clin. Cancer Res. 17, 1169–1180; 2011). In these patients, the therapeutic alternatives are scarce, with chemotherapy and TKI re-challenge, as the preferred options.

The recommended daily dose of 80 mg for osimertinib was established during the AURA phase I study has demonstrated a positive benefit/risk profile that maximises clinical activity in patients with EGFR T790M mutation-positive NSCLC, while simultaneously minimising the incidence and severity of adverse reactions as well as dose modifications. Importantly, this dose ensures that patients will receive a clinically active dose regardless of inter-patient variability and allows prescribers to reduce the dose should this be necessary. Additionally, preclinical modelling indicates that the 80 mg dose is likely to provide better activity than the 40 mg dose in brain metastases. The doses of 160 mg and 240 mg were clearly less tolerable than the 80-mg dose, with no perceivable benefit in efficacy.

Design and conduct of clinical studies

The overall goal of the single-arm trials was to show clinically meaningful benefit in the proposed indication, with prospective replication of data across 2 studies. Both studies had very similar designs in terms of the patient population (i.e. similar inclusion criteria, similar proportion of 2nd-line and ≥ 3d-line), conduct, and outcome measures (same schedule of radiological assessments).

Patients were either 2nd-line patients (i.e. after one EGFR TKI) or ≥3rd-line patients (after EGFR TKI and at least one other regimen). The presence of mutations known to be associated with EGFR TKI sensitivity was only introduced in the AURA 2 study. Patients with brain metastases were included in the study; any brain metastases present at baseline were recorded as non-target lesions (NTL).

Mutation status was determined using Roche cobas EGFR mutation test based on biopsies from the patients after progression on their most recent line of therapy. 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 osimertinib. 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 (see section 4.4

of the SmPC).. With the proposed testing strategy, 50-60% of all patients potentially eligible for osimertinib treatment could avoid an invasive procedure.

In both studies, the primary efficacy endpoint variable was the ORR according to RECIST 1.1 by BICR using the evaluable for response analysis set. Even though the use of ORR as primary endpoint would not be the recommended primary endpoint, however given the design of the studies and the unmet medical need, this could be acceptable, in particular considering the request for conditional approval.

In both studies the secondary outcomes variables were DoR, DCR, tumour shrinkage and PFS, according to RECIST 1.1 using assessments performed by a BICR. A further secondary variable was OS.

Even though no formal interim analysis has been pre-planned, the results submitted for both studies are based on the DCO 1st May 2015, approximately 6 months after the last patient was enrolled, to allow for at least a 6 month follow-up after the first dose.

A total of 873 patients signed informed consent and started screening in AURA extension (401) and AURA2 (472). In both studies a high proportion of patients was not assigned to study treatment because of the absence of confirmatory T790M mutation in the majority of the cases.

The percentage of discontinuations of study drug is low in both studies (16% and 14%) probably as a consequence of the duration of the study (DCO: 1st May 2015)

Overall, the included patients appear to represent the target population, i.e. relatively young (63 years as the median age), non-smoking (71.5%) female patients (67.9%) with tumours of adenocarcinoma histology (83%). The demographics and baseline characteristics are very similar for the patients in the two phase II studies and also across lines of therapy. The vast majority of the patients included in the studies are Asian (60.1%) reflecting the higher incidence of EGFR mutation-positive NSCLC in Asian patients. A sufficient number of white patients (36.2%) is also included in the two studies in order to ensure an assessment which is representative of a European population as well.

The cohorts in both studies seem to be reasonably balanced. In the AURA extension study, there were almost 37% of patients with brain metastases. In the AURA 2 study, the presence of brain metastases was reported in 42% of subjects and there seem to be more brain metastases in the 3rd-line cohort (46% vs 34%).

Efficacy data and additional analyses

Results based on the primary endpoint are considered clinically meaningful. Confirmed ORR in the pooled evaluable population according to the BICR assessment was 66%. The proportion of patients in AURA extension study that obtained antitumor activity from osimertinib was 60.7% and 61.6% (2nd and 3rd-line cohorts respectively). All the responses were partials. In the AURA 2 study the ORR was 73% and 69.9% (2nd and 3rd-line cohorts respectively), with only two patients in complete response. Results according to the assessment of the investigators were similar to those obtained by the BICR. Of note, among the proportion of patients with non-response, the percentage of subjects with stable disease ≥6 weeks ranged from 20.6% to 29.1%, which is of clinical value and will likely have an impact on the PFS data.

Focusing on the analysis of subgroups in the pooled data, this analysis reveals differences in ORRs between patients with different EGFR mutations (69.6% in patients with Exon 19 deletion versus 58.9% in patients with L858R mutation), and also between Asian (70.0%) and non-Asian patients (60.2%). Differences in efficacy between different EGFR-mutation types have been observed in earlier reports which suggests that the exon 19 deletion might have a higher sensitivity to EGFR TKIs compared with L858R (Riely et al 2006, Fukuoka et al 2011, Kim et al 2011, Sequist et al 2013, Karachaliou et al 2015). However, after the review of baseline

demographics, weight/exposure and efficacy data provided, there is no clear explanation to the observed differences in response between subgroups of patients with different ethnicity. No differences were noted between the two cohorts of both studies (2nd and 3rd-line)

The median duration of the response according to the BICR has not been achieved yet (95% CI 8.3-NC) which can be expected given the low maturity of the data (22.8%). However, data from investigator assessment provide a median DoR of 8.5 months, with 96.2% of responders showing a documented objective response at their second scheduled follow-up scan (Week 12 ± 1 week; according BICR). The DoR based on investigator assessment seems to be in line with the data from the phase I study, with a percentage of maturity for DoR of 46% (% progressed or died by BICR) the median DoR being 9.7 months (BICR; 95% CI 8.3-NC).

Most of the studied patients had confirmed **tumour shrinkage**, which suggest that osimertinib is active in most of the NSCLC patients with T790M mutation-positive tumours.

Data on PFS from the pooled phase II studies and phase I trial, show a median PFS around 10-11 months, with 39% and 52% of events respectively. Analyses of subgroups based on PFS do not suggest any subsets of patients where the efficacy of osimertinib could be worse than in the whole population, even though these data should be taken very cautiously due to the immaturity and sample size of the some subgroups.

OS data are not mature enough so as to reach any conclusion

The absence of comparator represents an uncertainty in this application, however the historical ORR obtained by chemotherapy, or TKI re-challenge, are considerably lower than those seen in the AURA studies. Even in the worst-case scenario of a response rate of 50% and DoR of 6 months (lower 95%CI for the AURA extension study is 54.2%), this seems superior to that described in the literature for alternative treatments. The objective response rate with 2nd line chemotherapy agents has been described around 25-30% at best (Dong et al 2014; J Int Med Res. 2014 Feb;42(1):191-7.), whereas the proportion of patients previously treated with TKI and achieving a response when re-challenged with another TKI hardly exceed 10-20%. In fact the re-challenge with TKI after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy, was tested in the LUX-Lung 1 study with afatinib, obtaining response rates of 7.4% (Lancet Oncol. 2012 May;13(5):528-38). Furthermore, the recent results from the IMPRESS trial (Mok et al 2014) where patients who had progressed on first-line gefitinib, were treated with cisplatin/pemetrexed or cisplatin/pemetrexed with continuation of gefitinib showed no differences in terms of PFS and ORR (median PFS was 5.4 months, and 25% of patients had response). These results have been recently supported by Halmos et al (The Oncologist 2015; 20: 1298–1303).

Therefore, it is highly plausible that the response seen in the AURA studies can be deemed superior to the different alternatives usually offered to these patients, indicating a new valuable option for patients with presence of T790M mutation

Although no clinical studies have been conducted, osimertinib is expected to be effective in first line treatment in the presence of the T790M mutation. The applicant is currently conducting a “Phase III, Double-blind, Randomised Study to Assess the Safety and Efficacy of osimertinib versus a Standard of Care EGFR TKI as First Line Treatment in Patients with EGFR Mutation Positive, Locally Advanced or Metastatic NSCLC”. This study will explore the efficacy of osimertinib in first line, including patients with the presence of the T790M mutation, if any is ultimately included. The contribution of the study results to provide supportive evidence for the use of osimertinib in first line patients harbouring the T790M could be relevant as long as there are enough patients with the T790M mutation. However, given the very low prevalence of this mutation in first line (Mok et al 2009; Inukai et al 2006; Sequist et al 2008), the real contribution of this phase 3 trial is expected to be limited.

From a mechanistic point of view, there is no foreseen impact of previous treatment on the expected benefit from treatment with osimertinib in patients with T790M mutation. Nevertheless, the consequence of moving the chemotherapy to 2nd-line is unknown in terms of life expectancy. As explaining by Yun et al (Proc Natl Acad Sci U S A. 2008 Feb 12;105 (6):2070-5), substitution of threonine 790 with methionine (T790M) has been thought to cause resistance by steric interference with binding of TKIs, including gefitinib and erlotinib. Osimertinib is therefore considered the optimal treatment alternative over available EGFR TKI therapies in patients with advanced EGFR positive NSCLC in the presence of T790M, regardless of the line of therapy.

Taking as a reference the most recent study of chemotherapy in first line in EGFR mutation positive patients, the LUX-Lung 3 study (afatinib vs cisplatin plus pemetrexed chemotherapy) it can be observed that the ORR for chemotherapy was 23% and 44% (independent and investigator assessment respectively) with a median duration of response of 5.5 months. In the EURTAC study, the best overall response rate for chemotherapy was 10.5%, whereas in the IPASS study, ORR for chemotherapy was 47% (EGFR+). In all of them the use of TKIs offered better results in response rate and PFS. It is therefore reasonable to expect that osimertinib in first line treatment of patients with T790M mutation will have a higher activity than chemotherapy as well. But in the worst case scenario, where osimertinib had a similar efficacy than chemotherapy, the better safety profile of this drug would make it a more suitable treatment option.

Therefore, based on the above efficacy and safety considerations, a broad indication in patients with T790M mutation can reasonably be recommended.

It is expected that the use of osimertinib in first line will be limited since the testing for the presence of T790M in EGFR positive NSCLC (first line) is not routinely performed because of the low prevalence of this mutation in patients not previously exposed to TKIs therapies.

Although the PRO data do not suggest deterioration of the patient's quality of life, the design of the two phase II studies (open-label, uncontrolled) makes it difficult to conclude on the clinical relevance of symptomatic improvement in patients treated with osimertinib.

Additional efficacy data needed in the context of a conditional MA

The AURA3 study (D5160C00003) is a phase III, open label randomised study of osimertinib vs. platinum-based doublet chemotherapy for patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour an EGFR T790M mutation within the EGFR gene. The primary endpoint is PFS and the secondary endpoints include ORR, DoR, DCR and OS. The results from AURA3 are expected to be submitted by 30 June 2017.

2.5.4. Conclusions on the clinical efficacy

The high antitumor activity shown by osimertinib in the two phase II studies carried out is considered of clinical value. Osimertinib is a new alternative before chemotherapy, with outstanding response rates. It is expected this will be translated into clinical benefit for patients, although the magnitude of such benefit in terms of OS and/or PFS remains unknown. Results from the ongoing phase III study (AURA 3) will need to be provided to address this uncertainty.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to further confirm the efficacy of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, the applicant should submit the final results of the phase III

study AURA3 comparing osimertinib to platinum-based doublet chemotherapy by 30 June 2017.

2.6. Clinical safety

The safety assessment was limited to the population of enrolled patients who received at least one dose of study drug (the safety population) which is also the defined full analysis set (FAS). Adverse events and SAEs were collected from the time of informed consent, throughout the treatment period and including the safety follow-up period (defined as 28 days after study drug was discontinued).

Patient exposure

Overall extent of exposure: Clinical program

Based on an informal DCO of 01 June 2015 at least 1221 subjects have been exposed to study treatment (osimertinib alone or in combination). Dose levels ranged from 20 mg to 240 mg.

Seventy (70) subjects were exposed to osimertinib in combination with another treatment.

Overall subject exposure included 591 subjects who participated in Phase I studies, 411 subjects who participated in the Phase II programme and 149 subjects who participated in the Phase III programme.

In the Phase II studies 333 (81.0%) patients received osimertinib for longer than 6 months and 97 patients (23.6%) received osimertinib for longer than 9 months. In AURA Phase I, the pre-treated dose expansion population (n=271) provides the main contribution to additional safety information. In this population the median exposure to osimertinib is 8.2 months (251.0 days) and 162 (59.8%) patients received osimertinib for longer than 6 months. These patients with longer exposure provide additional safety information for the potential use of osimertinib in the longer term. At the DCO date for this study (01 May 2015), the longest duration of exposure to osimertinib across the clinical programme is from patients enrolled in AURA Phase I, in which patients have received up to 24.9 months (759 days) treatment with osimertinib to date (median 8.3 months [253 days]).

The main contributory safety data from AURA Phase I are from the pre-treated capsule expansion cohort.

Overall extent of exposure: Phase II studies (AURA ext and AURA2)

Given the almost identical study designs of AURA extension and AURA2, safety data were pooled to provide increased sensitivity and precision towards the evaluation of the safety and tolerability profile of osimertinib in the proposed indication, compared to each individual trial using the same testing methodology. Data from AURA Phase I are presented as additional information towards the primary safety assessment provided by the Phase II pooled dataset.

The median total treatment duration was longer in the AURA extension study than in AURA2 due to an earlier recruitment period (8.2 months versus 7.4 months).

At the time of DCO for these clinical studies, 01 May 2015, 296 patients (72.0%) in the Phase II studies remained on study drug treatment (141 patients (70.1%) in AURA extension, and 155 patients [73.8%] in AURA2) so exposure will increase with longer follow up.

The majority of common AEs (ie, rash, diarrhoea) occur within the first few weeks of treatment.

Table 40: Duration of exposure in Phase II studies - total and categorical (Full analysis set)

Treatment duration (months)		AURA Extension 80 mg AZD9291 (N=201) n (%)	AURA2 80 mg AZD9291 (N=210) n (%)	Total (N=411) n (%)
Total treatment duration (months)[a]	Median	8.2	7.4	7.7
	Min	0.1	0.0	0.0
	Max	11.6	10.6	11.6
Total treatment duration (months)[a]	<3 months	19 (9.5)	18 (8.6)	37 (9.0)
	3 – 6 months	17 (8.5)	24 (11.4)	41 (10.0)
	6 – 9 months	102 (50.7)	134 (63.8)	236 (57.4)
	9 – 12 months	63 (31.3)	34 (16.2)	97 (23.6)
Actual treatment duration (months)[b]	<3 months	19 (9.5)	19 (9.0)	38 (9.2)
	3 – 6 months	19 (9.5)	26 (12.4)	45 (10.9)
	6 – 9 months	103 (51.2)	133 (63.3)	236 (57.4)
	9 – 12 months	60 (29.9)	32 (15.2)	92 (22.4)
Relative dose intensity (RDI)[c]	Mean	97.7	97.8	97.7
	Median	100.0	100.0	100.0
	Min	45.0	48.4	45.0
	Max	100.0	100.8	100.8
Percentage intended dose (PID)[d]	Mean	96.1	96.4	96.3
	Median	100.0	100.0	100.0
	Min	45.0	19.0	19.0
	Max	100.0	100.8	100.8

[a] Total treatment duration=(last dose date - first dose date +1)/(365.25/12).
[b] Actual treatment duration=total treatment duration, excluding dose interruptions.
[c] RDI is the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation.
[d] PID is the percentage of the actual dose delivered relative to the intended dose through progression.
If a patient had not discontinued then the DCO date was used in place of last dose date.

Table 41: Treatment interruptions and dose reductions for osimertinib (Full analysis set)

		Number (%) of patients		
		AURA Extension 80 mg AZD9291 (N=201)	AURA2 80 mg AZD9291 (N=210)	Total (N=411)
Received planned starting dose:	Yes	201(100)	210 (100)	411 (100)
Number of patients with a dose modification[c]	Any	52 (25.9)	72 (34.3)	124 (30.2)
Number of patients with an interruption	Any	52 (25.9)	72 (34.3)	124 (30.2)
	1 interruption	34 (16.9)	43 (20.5)	77 (18.7)
	2 interruptions	9 (4.5)	21 (10.0)	30 (7.3)
	>2 interruptions	9 (4.5)	8 (3.8)	17 (4.1)
Reason for interruption:	Adverse Event	36 (17.9)	39 (18.6)	75 (18.2)
	Surgery	1 (0.5)	3 (1.4)	4 (1.0)
	Laboratory Abnormality	1 (0.5)	3 (1.4)	4 (1.0)
	Patient Forgot	12 (6.0)	20 (9.5)	32 (7.8)
	Patient Decision	2 (1.0)	0	2 (0.5)
	Other Reason	13 (6.5)	15 (7.1)	28 (6.8)
Number of patients with a dose reduction	Any	11 (5.5)	7 (3.3)	18 (4.4)
Reason for dose reduction[b]:	Adverse Event	11 (5.5)	7 (3.3)	18 (4.4)

[a] Reasons for interruptions are not mutually exclusive for patients with multiple interruptions although will be counted only once per category.
[b] Reasons for dose reductions are not mutually exclusive for patients with multiple reductions although will be counted only once per category.
[c] Number of patients with either an interruption and/or a dose reduction.
[d] Reasons for dose modifications are not mutually exclusive for patients with multiple modifications although will be counted only once per category.

The median length of a dose interruption, excluding dose interruptions where the patient forgot to take their dose, was 7 days and ranged from 1 to 170 days. The maximum period for a dose interruption (170 days) appears to be as a result of a data entry error.

In AURA extension, two additional patients who had AEs leading to interruptions were identified but are not included in the table above since they had not been entered in the dosing eCRF. Therefore, the total number of patients with interruptions caused by AEs in AURA extension is 38 (18.9%). In the total Phase II population, 77 (18.7%) patients had dose interruptions due to AEs.

Adverse events

A categorical overview of the AE safety profile from the pooled Phase II data is presented in the table below.

Table 42: Categories of adverse events: Number (%) of patients who had at least 1 adverse event in any category (Full analysis set)

	Number (%) of patients[a]		
	DCO 01 May 2015		
AE category	AURA extension osimertinib 80 mg (N=201)	AURA2 osimertinib 80 mg (N=210)	Total osimertinib 80 mg (N=411)
Patients with any AE	198 (98.5)	203 (96.7)	401 (97.6)
CTCAE ≥grade 3 AEs	60 (29.9)	61 (29.0)	121 (29.4)
SAEs	41 (20.4)	42 (20.0)	83 (20.2)
Fatal SAEs	8 (4.0)	5 (2.4)	13 (3.2)
AEs leading to discontinuation	12 (6.0)	11 (5.2)	23 (5.6)
AEs leading to dose modification	41 (20.4)	41 (19.5)	82 (20.0)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
Abbreviations: AE = adverse event, CTCAE = Common Terminology Criteria for Adverse Events (version 4.0), DCO = data cut-off, SAE = serious adverse event. MedDRA version 17/18.

In 86.4% (355/411) of patients, AEs were considered to be possibly causally related to osimertinib by the investigator.

In the pooled analysis of the Phase II studies, the majority of patients (68.1%) experienced AEs of mild (Grade 1: 30.4%) to moderate (Grade 2: 37.7%) severity. the most commonly reported EGFR-associated AEs by Medical Dictionary for Regulatory Activities [MedDRA] PT) were diarrhoea, rash, dry skin and paronychia; these AEs were mostly mild to moderate in severity. AEs were most frequently reported in the SOCs of GI disorders (287/411; 69.8%), Skin disorders (264/411; 64.2%), and Infections (212/411; 51.6%).

Dose interruptions, dose reductions and treatment discontinuations with osimertinib 80 mg due to AEs were reported for 18.7%, 4.4%, and 5.6% of patients respectively; the mean and median relative dose intensity (RDI) was 97.7% and 100.0% respectively.

The most common AEs (occurring in ≥10% of patients in the phase II studies) are provided in the table below.

Table 43: Adverse events, most common (frequency of ≥10%) (Full analysis set)

	Number (%) of patients[a]					
	DCO 09 January 2015			DCO 01 May 2015		
AE category	AURA extension osimertinib 80 mg (N=201)	AURA2 osimertinib 80 mg (N=210)	Total osimertinib 80 mg (N=411)	AURA extension osimertinib 80 mg (N=201)	AURA2 osimertinib 80 mg (N=210)	Total osimertinib 80 mg (N=411)
Patients with any AE	195 (97.0)	200 (95.2)	395 (96.1)	198 (98.5)	203 (96.7)	401 (97.6)
Diarrhoea	83 (41.3)	72 (34.3)	155 (37.7)	93 (46.3)	81 (38.6)	174 (42.3)
Rash	48 (23.9)	48 (22.9)	96 (23.4)	49 (24.4)	49 (23.3)	98 (23.8)
Dry skin	35 (17.4)	47 (22.4)	82 (20.0)	43 (21.4)	52 (24.8)	95 (23.1)
Paronychia	36 (17.9)	28 (13.3)	64 (15.6)	40 (19.9)	32 (15.2)	72 (17.5)
Nausea	26 (12.9)	20 (9.5)	46 (11.2)	35 (17.4)	34 (16.2)	69 (16.8)
Decreased appetite	28 (13.9)	21 (10.0)	49 (11.9)	36 (17.9)	29 (13.8)	65 (15.8)
Constipation			37 (9.0)[b]	30 (14.9)	32 (15.2)	62 (15.1)
Cough			36 (8.8)[b]	32 (15.9)	25 (11.9)	57 (13.9)
Fatigue	24 (11.9)	22 (10.5)	46 (11.2)	25 (12.4)	32 (15.2)	57 (13.9)
Pruritus	23 (11.4)	29 (13.8)	52 (12.7)	25 (12.4)	32 (15.2)	57 (13.9)
Back pain			36 (8.8)[b]	27 (13.4)	25 (11.9)	52 (12.7)
Stomatitis			39 (9.5)[b]	27 (13.4)	22 (10.5)	49 (11.9)
Platelet count decreased	24 (11.9)	18 (8.6)	42 (10.2)	27 (13.4)	20 (9.5)	47 (11.4)
Headache			32 (7.8)[b]	22 (10.9)	20 (9.5)	42 (10.2)

[a] Number (%) of patients with AEs, sorted in descending frequency of preferred term (total).
Most common is defined as a total frequency of >10% (in total group).
Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
[b] PTs were <10% at the DCO date of 09 January 2015.
Abbreviations: DCO = data cut-off MedDRA version 17.1/18

CTCAE ≥Grade 3 events

Severe AEs (CTCAE ≥Grade 3) were reported for 29.4% (121/411) of patients and were considered by the investigator to be possibly causally related to osimertinib in 11.7% (48/411) of patients.

AEs of CTCAE Grades 3 and 4 were reported for 25.5% (105/411) and 1.2% (5/411) of patients, respectively.

The most common SOCs with reported AEs of CTCAE Grade ≥3 were Respiratory disorders (8.3%; 34/411), Investigations (5.8%; 24/411), Infections (5.8%; 24/411), and Blood and lymphatic system disorders (3.9%; 16/411).

Table 44: Adverse events of CTCAE Grade 3 or higher by preferred term (reported in ≥2 patients) (Full analysis set)

	Number (%) of patients[a]		
	AURA Extension	AURA2	
	osimertinib 80 mg	osimertinib 80 mg	Total osimertinib 80 mg
System organ class / Preferred term	(N=201)	(N=210)	(N=411)
Patients with AE of CTCAE Grade 3 or higher	60 (29.9)	61 (29.0)	121 (29.4)
Pneumonia	7 (3.5)	4 (1.9)	11 (2.7)
Pulmonary embolism	3 (1.5)	6 (2.9)	9 (2.2)
Dyspnoea	5 (2.5)	2 (1.0)	7 (1.7)
Neutrophil count decreased	4 (2.0)	3 (1.4)	7 (1.7)
Anaemia	4 (2.0)	2 (1.0)	6 (1.5)
Alanine aminotransferase increased	3 (1.5)	2 (1.0)	5 (1.2)
Electrocardiogram QT prolonged	0	5 (2.4)	5 (1.2)
Diarrhoea	2 (1.0)	2 (1.0)	4 (1.0)
Hyponatraemia	2 (1.0)	2 (1.0)	4 (1.0)
Pneumonitis	3 (1.5)	1 (0.5)	4 (1.0)
Thrombocytopenia	1 (0.5)	3 (1.4)	4 (1.0)
Asthenia	3 (1.5)	0	3 (0.7)
Back pain	1 (0.5)	2 (1.0)	3 (0.7)
Decreased appetite	2 (1.0)	1 (0.5)	3 (0.7)
Hypoxia	3 (1.5)	0	3 (0.7)
Interstitial lung disease	2 (1.0)	1 (0.5)	3 (0.7)
Leukopenia	2 (1.0)	1 (0.5)	3 (0.7)
White blood cell decreased	2 (1.0)	1 (0.5)	3 (0.7)
Blood creatine phosphokinase increased	0	2 (1.0)	2 (0.5)
Cerebral haemorrhage	1 (0.5)	1 (0.5)	2 (0.5)
Cerebral infarction	0	2 (1.0)	2 (0.5)
Cerebrovascular accident	2 (1.0)	0	2 (0.5)
Ejection fraction decreased	1 (0.5)	1 (0.5)	2 (0.5)
Fatigue	2 (1.0)	0	2 (0.5)
Hypokalaemia	2 (1.0)	0	2 (0.5)
Influenza	2 (1.0)	0	2 (0.5)
Nausea	2 (1.0)	0	2 (0.5)
Neutropenia	1 (0.5)	1 (0.5)	2 (0.5)
Platelet count decreased	1 (0.5)	1 (0.5)	2 (0.5)
Pleural effusion	2 (1.0)	0	2 (0.5)
Pneumonia aspiration	1 (0.5)	1 (0.5)	2 (0.5)

System organ class / Preferred term	Number (%) of patients[a] AURA Extension osimertinib 80 mg (N=201)	AURA2 osimertinib 80 mg (N=210)	Total osimertinib 80 mg (N=411)
Presyncope	0	2 (1.0)	2 (0.5)
Supraventricular tachycardia	0	2 (1.0)	2 (0.5)
Traumatic fracture	1 (0.5)	1 (0.5)	2 (0.5)
Urinary tract infection bacterial	1 (0.5)	1 (0.5)	2 (0.5)
Vomiting	2 (1.0)	0	2 (0.5)

[a] Patients with multiple AEs of CTCAE Grade 3 or higher are counted once for each preferred term.
Number (%) of patients with AEs of CTCAE Grade 3 or higher, sorted in decreasing frequency of PT (total).
Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
CTCAE = Common Terminology Criteria for Adverse Events version 4.0.
MedDRA version 18.

Compared to the Phase II studies, the overall incidence of AEs of CTCAE ≥Grade 3 events in the Phase I study was numerically higher (43.9%; 119/271) of pre-treated patients who received the osimertinib capsule formulation in the dose expansion part of the study. The AEs of ≥CTCAE Grade 3 reported in ≥5 patients were pulmonary embolism (3.7%; 10/271 patients), pneumonia (3.7%; 10/271 patients), anaemia (3.0%; 8/271 patients), dyspnoea (2.6%; 7/271 patients), paronychia and diarrhoea (2.2% each reported in 6/271 patients), and neutrophil count decreased (1.8%; 5/271 patients).

AEs of special interest

A number of AESI have been identified based on pre-clinical findings, emerging data from clinical studies of osimertinib and pharmacological effects of approved EGFR TKIs.

Pneumonia, pulmonary embolism and dyspnoea are the most common AEs of CTCAE Grade ≥3 in the Phase I and Phase II studies. These 3 AEs are described here in a more detailed assessment since they have not been identified as AESIs.

Interstitial lung disease (ILD)

ILD-like events

In the pooled Phase II studies, at the DCO date of 01 May 2015 ILD (grouped terms) was reported in 2.7% (11/411) of patients during treatment with osimertinib 80 mg. The median time to onset for ILD grouped term events was 83 days (range 17 to 230 days). The distribution of patients is as follows: 7 Asian patients, 4 non-Asian patients, 8 reports were serious, while 3 reports were non-serious, 4 patients with CTCAE Grade 1 AEs; 3 patients with CTCAE Grade 3 AEs, and 4 patients with fatal AEs (0.7%), 5 patients recovered, 1 patient was recovering, 1 patient had not recovered.

Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) were reported in 2.9% and were fatal in 0.3% of the 1221 patients who received osimertinib across clinical trials. ILD or ILD-like adverse reactions were reported in 11/411 (2.7%) of patients who received osimertinib in the two Phase II studies, of which 0.7% were Grade 3 or 4 and 1% were fatal. The incidence of ILD was 6.2% in patients of Japanese ethnicity, 1.2% in patients of Asian ethnicity and 2.4% in non-Asian patients. The median time to onset of ILD or ILD-like adverse reactions was 2.7 months (See Sections 4.4 and 4.8 of the SmPC).

Referring the recovery from the AEs, 11 (0.9%) patients recovered from the AE, 5 (0.4%) patients were recovering, 15 (1.2%) patients had not recovered.

Treatment with the study drug was discontinued in 33 out of 35 patients with reported ILD, as per protocol. The majority of these patients were treated according to local clinical practice, with corticosteroids and often in association with antibiotics to treat the differential diagnosis of respiratory infection.

Cardiac effects

Following a review of preclinical and EGFR TKI and HER2 class data, the applicant identified two cardiac topics of special interest to assess potential risks of cardiac toxicity. These are QT prolongation and reduction in cardiac contractility (including LVEF decreases).

In the Phase II studies there were 19 (4.6%) patients with AEs in the Cardiac disorder SOC outside of the SMQs shows 20 [4.9%] patients with AEs, however, an AE of cardiac failure congestive reported in the AURA extension study was captured within the grouped terms SMQ of Cardiac failure.

Adverse events with PTs in cardiac failure or cardiomyopathy SMQs were reported in 5 patients (1.2%) in the phase II studies.

Left ventricular ejection fraction analysis

No clinically significant change was observed in median LVEF from the baseline of 63% in the 195/210 patients (90.9%) who had at least one post-baseline echocardiograph assessment in Aura 2 study.

QT prolongation

In both Phase II studies an increase from baseline in median QTcF was observed, which reached a plateau by Cycle 3 Day 1.

In AURA2 the mean time-matched change from baseline in QTcF at Week 6 across all time points was14.5 ms (90% CI 14.0, 15.0), with the maximum upper 90% CI limit at any time point being 17.5 ms.

Data on QTcF intervals are summarised in the table below

Table 45: QTcF intervals at any observation on treatment (QTc analysis set) AURA2

	Number (%) of patients		
	Second-line (N=68)	≥Third-line (N=142)	Total (N=210)
QTcF value above xxx ms at any time during treatment			
>450[b] (ms)	22 (32.4)	41 (28.9)	63 (30.0)
>480[b] (ms)	2 (2.9)	7 (4.9)	9 (4.3)
>500[b] (ms)	0	1 (0.7)	1 (0.5)
QTcF increase[a] by more than yy ms at any time during treatment			
>30[b] (ms)	33 (48.5)	54 (38.0)	87 (41.4)
>60[b] (ms)	3 (4.4)	3 (2.1)	6 (2.9)
>90[b] (ms)	0	2 (1.4)	2 (1.0)
QTcF value above xxx ms and QTcF increase[a] by more than yy ms at any time during treatment			
Value >450(ms) and increase >30(ms)[b]	15 (22.1)	26 (18.3)	41 (19.5)
Value >500(ms) and increase >60(ms)[b]	0	1 (0.7)	1 (0.5)
QTcF decrease[a] by more than yy ms at any time during treatment			
>30[b] (ms)	4 (5.9)	6 (4.2)	10 (4.8)
>60[b] (ms)	0	0	0
>90[b] (ms)	0	0	0

[a] Change from time-matched baseline to any observation on treatment.
[b] The number of patients was a cumulative count for each category.
Baseline was the screening visit.
Fridericia's correction was used for QTc.
On treatment was defined as assessments between the start of treatment and 28 days following the date of last dose of study medication.

In the AURA extension, the median change from baseline in QTcF at Cycle 3 Day 1 was 14.71 msec.

Table 46: QT intervals, any observation on treatment (Full analysis set) AURA extension

	Number (%) of patients Total (N=201)
QTcF value above xxx ms at any time during treatment	
>450[b] (ms)	55 (27.4)
>480[b] (ms)	7 (3.5)
>500[b] (ms)	0
QTcF increase[a] by more than yy ms at any time during treatment	
>30[b] (ms)	83 (41.3)
>60[b] (ms)	5 (2.5)
>90[b] (ms)	0
QTcF value above xxx ms and QTcF increase[a] by more than yy ms at any time during treatment	
Value >450(ms) and increase >30 (ms)[b]	32 (15.9)
Value >500(ms) and increase >60 (ms)[b]	0
QTcF decrease[a] by more than yy ms at any time during treatment	
>30[b] (ms)	13 (6.5)
>60[b] (ms)	1 (0.5)
>90[b] (ms)	0

[a] Change from baseline to any observation on treatment.
[b] The number of patients is a cumulative count for each category.
Baseline is the average of permissible baseline assessments.
Fridericia's correction has been used for QTc.
On treatment is defined as assessments between the start of treatment and 28 days following the date of last dose of study medication.

Of the 411 Phase II patients, one patient was found to have a QTc greater than 500 msec, and 11 patients (2.7%) had an increase from baseline QTc greater than 60 msec

AURA2 provided the primary assessment of the pro-arrhythmic risk of osimertinib in line with ICH E14, according to the applicant. The effect of both single and multiple dosing of osimertinib on QT/QTc interval was evaluated using extensive ECG sampling.

Based on a c-QTc analysis, a drug-related QTc interval prolongation was observed in the AURA2 study. The mean (90% CI) increase in ΔQTcF interval (based on time-matched change from baseline) was estimated to be 0.271 (0.241 – 0.301) ms per 10 nM increase in osimertinib plasma levels, based on a linear mixed effects model, with gender not having a significant effect in the model. This resulted in a predicted mean drug-related QTcF interval prolongation at the proposed osimertinib therapeutic dose (80 mg) of 14.2 msec with an upper bound of the associated two-sided 90% CI of 15.8 msec.

In AURA Phase I an increase from baseline in median QTcF was observed, which reached a plateau by Day 1of Cycle 3. The median change from baseline in QTcF on Day 1 of Cycle 3 was 12.3 msec when considering all doses. There appeared to be an increase of the QTcF effect with dose, with a median increase of 4.0 msec and 9.0 msec on Day 1 of Cycle 3 (week 6) at the 20 mg and 40 mg dose levels respectively, while median increases of 12.7 msec, 16.3 msec and 14.5 msec were reported at the 80 mg, 160 mg and 240 mg dose levels, respectively. At the 160 mg and 240 mg dose levels, there were isolated occurrences where the median interval increase per cycle was greater than 20 msec. A total of 26.2% (71/271) of patients had a QTcF interval >450 msec at any time during treatment. Six (2.2%) patients had a QTcF interval >480 msec and 1 (0.4%) patient had a QTcF interval >500 msec (522 msec). One fatal AE was reported in a patient treated with the 240 mg dose in this in the AURA1 study (Grade 5 Pulseless Electrical Activity).

QT interval relevant cardiac AEs:

Across the Phase II studies, there were no events of Torsade de Pointes (TdP) reported or of Sudden death; Ventricular tachycardia; Ventricular fibrillation and flutter.

There was one CTCAE Grade 2 AE of syncope reported in a patient with a maximum QTcF 454 msec and a medical history of dizziness. This event was considered by the investigator not to be possibly causally related to osimertinib and resolved in 1 day.

There were no reported AEs with PTs in the Arrhythmias standardised MedDRA queries (SMQ). In the Phase II studies, adverse events with PTs in the QT prolongation SMQ category were reported in 17 patients (4.1%); all reported PTs were Electrocardiogram QT Prolonged. Nine (2.2%) patients reported maximum Grade 1 events; 3 (0.7%) reported maximum CTCAE Grade 2 events and 5 (1.2%) patients reported maximum CTCAE Grade 3 events. Per protocol requirement, CTCAE Grade 3 QT prolongation events led to a dose interruption.

One fatal AE was reported in a patient treated with the 240 mg dose in AURA Phase I (Grade 5 Pulseless Electrical Activity).

EGFR TKI class effects:

- Skin Effects

Skin disorders comprise 4 subgroups of rashes/acnes, pruritus, dry skin, and exfoliative rash.

Table 47: Skin effects as reported in the pooled Phase II studies (AURA Extension and AURA2)

Grouped term / Preferred term	Number (%) of patients[a] AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Skin Effects	119 (59.2)	127 (60.5)	246 (59.9)
Dry Skin	63 (31.3)	64 (30.5)	127 (30.9)
Dry skin	43 (21.4)	52 (24.8)	95 (23.1)
Eczema	2 (1.0)	1 (0.5)	3 (0.7)
Skin fissures	12 (6.0)	12 (5.7)	24 (5.8)
Xerosis	8 (4.0)	2 (1.0)	10 (2.4)
Exfoliative Rash	2 (1.0)	4 (1.9)	6 (1.5)
Skin exfoliation	2 (1.0)	4 (1.9)	6 (1.5)
Pruritus	25 (12.4)	32 (15.2)	57 (13.9)
Pruritus	25 (12.4)	32 (15.2)	57 (13.9)
Pruritus generalised	1 (0.5)	0	1 (0.2)
Rashes And Acnes	82 (40.8)	88 (41.9)	170 (41.4)
Acne	2 (1.0)	7 (3.3)	9 (2.2)
Dermatitis	3 (1.5)	0	3 (0.7)
Dermatitis acneiform	12 (6.0)	16 (7.6)	28 (6.8)
Erythema	7 (3.5)	4 (1.9)	11 (2.7)
Folliculitis	3 (1.5)	1 (0.5)	4 (1.0)
Rash	49 (24.4)	49 (23.3)	98 (23.8)
Rash generalised	1 (0.5)	0	1 (0.2)
Rash macular	0	3 (1.4)	3 (0.7)
Rash maculo-papular	9 (4.5)	14 (6.7)	23 (5.6)
Rash papular	2 (1.0)	2 (1.0)	4 (1.0)
Rash pustular	5 (2.5)	1 (0.5)	6 (1.5)

[a] Number (%) of patients with AEs of special interest, sorted on alphabetical grouped term, subgrouped term and preferred term.
Specific adverse events of interest may either be grouped MedDRA preferred terms or individual MedDRA preferred terms.
Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
MedDRA version 18.

A total of 51.8% (213/411) patients had maximum reported Grade 1 (mild) AEs of skin effects (grouped terms). Adverse events of maximum reported Grade 2 (moderate) or Grade 3 (severe) were reported for 7.5% (31/411) and 0.5% (2/411) of patients respectively. One Grade 3 event was maculo-papular rash. The other Grade 3 event was for the PT of erythema. There were no SAEs. No skin-related AE led to hospitalisation.

The most common anatomical locations for skin effects (grouped terms) AEs were the face (115/411; 43.2% patients) and hands (110/411; 41.4% patients).

AEs leading to dose modifications were reported for 0.5% (2/411) patients (erythema and rash each reported for 1 patient) and 1 patient (0.2%) had an AE (rash maculo-papular) leading to permanent discontinuation. Adverse events of maximum reported Grade 2 (moderate) or Grade 3 (severe) were reported for 4.4% (18/411) and 0.5% (2/411) of patients respectively. The median time to onset of Rashes and Acnes was 20.5 days (range 1 to 266) with a median duration of 122.0 days. After one month of treatment with osimertinib, the prevalence

of rashes and acnes (grouped term) remains relatively constant over the duration of treatment, with approximately 20% to 30% patients experiencing AEs in this grouped term at any one time point. Medication was administered for 37.4% of patients with rashes and acnes AEs, typically consisting of topical steroids. Treatments did not increase the resolution or decrease the duration of rash/acne.

A total of 28.2% (116/411) patients had maximum reported Grade 1 (mild) AEs of dry skin (grouped term). Adverse events of maximum reported Grade 2 (moderate) were reported for 2.4% (10/411) of patients. There were no Grade ≥3 AEs, no SAEs, and no AEs that led to dose modifications or permanent discontinuations. Median time to onset of dry skin AEs was 26 days (range 1 to 255).

- Diarrhoea

Diarrhoea was reported in 42.3% (174/411) patients during treatment with osimertinib 80 mg. The majority of reported AEs of diarrhoea were considered mild in severity. A total of 35.8% (147/411) patients had maximum Grade 1 AEs of diarrhoea. Adverse events of maximum Grade 2 or 3 were reported for 5.1% (21/411) and 1.0% (4/411) patients respectively. No fatal AEs of diarrhoea were reported. Out of the 263 events of diarrhoea there was a single event that led to discontinuation of osimertinib. There were 4 patients with AEs that led to dose interruption.

The overall median time to onset of first event of diarrhoea was 18.0 days (n=174; mean 43.0, range 1 to 251 days), with a median total duration of all episodes of diarrhoea of 81.0 days (range 1 to 310 days).

There were no events reported of GI perforation or haemorrhagic diarrhoea.

At the DCO date, 183/263 (69.6%) events were reported to have resolved, 22/263 (8.4%) events were reported to be resolving, one event was reported to be resolved with sequelae, and 57/263 (21.7%) were reported to be ongoing.

Less than half of all events of diarrhoea were treated (95/263 events; 36.1%). Antipropulsives (eg, loperamide) were administered for 77 events. Of the 95 treated events, 57 (21.7% of all events) events were reported to have resolved (4 of these patients also had a dose modification) and 34 (12.9% of all events) were reported to be ongoing at the DCO date of this data. For the 168 events where no treatment was given, 123 (46.8% of all events) were reported to have resolved and 44 (16.7% of all events) events were reported to be ongoing without any dose modification at the DCO date of this analysis.

The median total duration of all episodes of diarrhoea was 81.0 days (range 1 to 310 days) this calculation includes AEs of intermittent, sporadic, or occasional diarrhoea and therefore may overestimate the median continuous duration due to the inclusion of days/periods without diarrhoea.

Events were typically of low clinical significance with no requirement for medical intervention to prevent the development of complications such as dehydration or electrolyte disturbance.

In the Phase II studies, three patients experienced diarrhoea concurrently with renal failure and/or dehydration (high level term).

After one month of treatment with osimertinib the prevalence of diarrhoea remains relatively constant over the duration of treatment, with approximately 20% patients experiencing diarrhoea at any one point.

In AURA Phase I: dose expansion cohort, diarrhoea was reported in 53.5% (145/271) of patients. Diarrhoea was reported in 42.3 % (41/97) of patients in the 80 mg cohort and the incidence increased in the 160 mg and 240 mgdose levels (69.9%; 65/93 patients and 85.7%; 12/14 patients, respectively).

- Upper GI Inflammation [and nasal mucosal] effects

Upper GI inflammatory adverse events (grouped term) were reported in 22.6% (93/411) patients in the Phase II studies (during treatment with osimertinib 80 mg), including 11.9% (49/411) patients reporting stomatitis, 3.2% (13/411) patients reporting oropharyngeal pain, 2.9% (12/411) patients reporting epistaxis and 2.4% (10/411) patients reporting dysphagia. All other PTs were reported in ≤2% of patients. All AEs of upper GI inflammatory events were Grade 1 (19.0%) or Grade 2 (3.4%) in severity. One grade 3 event of gastritis was reported in one patient (0.2%) which led to dose modification but was not considered related to osimertinib. There were no permanent discontinuations. The median time to onset of first event of upper GI inflammatory AE was 63.0 days (mean 77.3 days; range 1 to 263 days). A total of 125 events were reported for 93 patients. Less than half of the 125 events required treatment (57 events; 45.6 %). Of these 125 events, 69 (55.2 %) were reported to have resolved, 12 (9.6%) were reported to be resolving and 43 (34.4%) were reported to be ongoing at the DCO date of this analysis.

Stomatitis was reported in 11.9% (49 of 411) patients during treatment with osimertinib 80 mg, with a similar frequency in both Phase II studies. The overall median time to onset of first event of stomatitis was 43 days (range 3 to 252 days). All reported AEs of stomatitis were considered Grade 1 (10.0%) or Grade 2 (1.9%) in severity. None of the 49 reported events of stomatitis required osimertinib discontinuation, dose interruption or dose modification.

- Nail Effects

Nail effects AEs were reported by 25.1% (103/411) of the patients across the Phase II studies during treatment with osimertinib 80 mg. The most commonly reported nail effect PT was paronychia 17.5%. The next most frequently reported nail effect PTs were nail disorders (3.2%) and onychoclasis (2.7%). All reported AEs of nail effects were Grade 1 (19.7%) or Grade 2 (5.4%) in severity. No patients reported Grade ≥3 events of nail effects and no SAEs of nail effects were reported. The overall median time to onset of first event of nail effects was 70 days (range 1 to 296 days).

No patients discontinued osimertinib due to a nail effect AE. One patient had a dose modification due to the nail effect AE paronychia. Less than half of all events of nail effects were treated (54 events; 42.5%). Of these 127 events, 38 (29.9%) were reported to have resolved, 14 (11.0%) were reported to be resolving and 74 (58.3%) were reported to be ongoing at the DCO date of this analysis.

A similar pattern of nail effect AEs was reported in AURA Phase I dose expansion cohort (29.5%), with the most commonly reported PT being paronychia (23.6%).

- Ocular effects

Osimertinib has not been associated with clinically significant ocular surface effects such as ulcerative keratitis, or severe or serious ocular AEs.

Ocular effect (grouped term) AEs were reported by 11.2% (46/411) patients with a similar distribution between both Phase II studies. Ocular effects of conjunctival disorders were reported in 9.5% (39/411), corneal disorders in 0.7% (3/411), lacrimal disorder in 6.6% (27/411) and periorbital/eyelid disorders in 1.7% (7/411) of patients.

The most common PTs reported in the Ocular effects grouped terms were Dry Eye in 5.6% (23/411) patients and conjunctivitis in 2.9% (12/411) patients. No other PT was reported at a frequency ≥2%. Twenty-six patients (6.3%) with ocular effects AEs received treatment, but no ocular effects AEs led to permanent discontinuation of osimertinib 80 mg. Three (1.1%) patients had a dose modification due to an ocular event and 1 (0.4%)

patient had a dose interruption due to an ocular event. Median time to first onset of events in the ocular effects grouped terms was 36.5 days (range 1 to 249 days).

Ocular effects AEs were predominantly Grade 1 (8.8%) with Grade 2 events reported in 2.4% patients. There were no SAEs, no Grade ≥ 3 events, and no events of corneal erosion or corneal ulceration.

The findings in the Phase II studies were consistent with the observations in Phase I, where no dose-related toxicity was observed in the ocular effects for AESI or eye disorder SOC/PT.

In AURA Phase I: first-line capsule cohort a CTCAE Grade 3 event of corneal erosion was reported as an SAE in 1 patient at the 80 mg dose level; this patient also had a dose interruption. The corneal erosion was attributed to the patient's underlying Sjögren's syndrome and was not considered by the investigator to be possibly causally related to treatment with osimertinib.

Cardiac contractility

A causal association between osimertinib and cardiac failure adverse events cannot be fully excluded due to the temporal relationship between receiving study drug and onset/recovery of events. Based on available data, There is no evidence of a causal relationship between osimertinib and decrease in cardiac function or cardiac contractility.

Elevations AST or ALT

Osimertinib is eliminated mainly via the liver. Evaluation for liver toxicity has shown no apparent association of osimertinib with drug induced liver injury. Hepatic parameters were unchanged from baseline in the majority of patients during treatment with osimertinib. The majority of maximum CTCAE grade shifts from baseline were mild (to moderate in severity. Grade 3 changes in ALT elevations were reported for 1.2% of patients and Grade 3 changes in AST elevations were reported for 0.2% of patients. No Hy's Law cases were identified.

Adverse drug reactions (ADRs)

The list of ADRs has been established by the applicant taking into account the following criteria: pre-clinical findings, class effects, plausibility in light of the drug's pharmacology (e.g. wild-type EGFR inhibition), incidence rates in light of epidemiological data in the NSCLC population (indirect comparisons to placebo data from trials in NSCLC patients), dose response relationship in AURA Phase I, time to onset of events and/or re-challenge data where available, confounding factors, the presence or absence of single events which are strongly indicative of a drug reaction.

Table 48: Adverse drug reactions reported in AURA Extension and AURA2 studiesa

MedDRA SOC	MedDRA term	CIOMS descriptor / overall frequency (all CTCAE grades)[b]	Frequency of CTCAE grade 3-4
Respiratory, thoracic and mediastinal disorders	Interstitial lung disease[c]	Common (2.7%)[d]	0.7%
Gastrointestinal disorders	Diarrhoea	Very common (42%)	1%
	Stomatitis	Very common (12%)	0%
Skin and subcutaneous tissue disorders	Rash[e]	Very common (41%)	0.5%
	Dry skin[f]	Very common (31%)	0%
	Paronychia[g]	Very common (25%)	0%
	Pruritus	Very common (14%)	0%
Investigations (findings based on test results presented as CTCAE grade shifts)	Platelet count decreased[h]	Very common (54%)	1.2%
	Leucocytes decreased[h]	Very common (67%)	1.2%
	Neutrophils decreased[h]	Very common (33%)	3.4%

[a] Only events for patients receiving at least one dose of TAGRISSO are summarized.
[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 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 bed disorder, nail bed inflammation, nail bed tenderness, nail discoloration, nail disorder, nail dystrophy, nail infection, nail ridging, onychoclasis, onycholysis, onychomadesis, paronychia.
[h] Represents the incidence of laboratory findings, not of reported adverse events.

Serious adverse event / deaths / other significant events

Serious adverse events

Serious adverse events were reported for a total of 20.2% (83/411) of patients in the osimertinib Phase II studies with no notable differences between the two studies. Respiratory disorders (7.3%) and Infections (6.1%) were the most common SOCs for SAE reporting. The most commonly reported SAEs were pneumonia and pulmonary embolism (see Table 49).

SAEs were considered by the investigator to be possibly causally related to osimertinib in 5.1% (21/411) of patients. The SAEs considered by the investigator to be possibly causally related to treatment with osimertinib that occurred in >1 patients were pneumonitis, ILD and thrombocytopenia.

Table 49: Serious adverse events, by preferred term in ≥2 patients (Full analysis set)

	Number (%) of patients[a]		
Preferred term	AURA Extension AZD9291 80 mg (N=201)	AURA2 AZD9291 80 mg (N=210)	Total AZD9291 80 mg (N=411)
Patients with any SAE	41 (20.4)	42 (20.0)	83 (20.2)
Pneumonia	7 (3.5)	4 (1.9)	11 (2.7)
Pulmonary embolism	3 (1.5)	8 (3.8)	11 (2.7)
Interstitial lung disease	2 (1.0)	2 (1.0)	4 (1.0)
Pneumonitis	3 (1.5)	1 (0.5)	4 (1.0)
Anaemia	2 (1.0)	1 (0.5)	3 (0.7)
Dyspnoea	2 (1.0)	1 (0.5)	3 (0.7)
Influenza	2 (1.0)	1 (0.5)	3 (0.7)
Cerebral haemorrhage	1 (0.5)	1 (0.5)	2 (0.5)
Cerebral infarction	0	2 (1.0)	2 (0.5)
Cerebrovascular accident	2 (1.0)	0	2 (0.5)
Deep vein thrombosis	0	2 (1.0)	2 (0.5)
Fatigue	1 (0.5)	1 (0.5)	2 (0.5)
Pleural effusion	2 (1.0)	0	2 (0.5)
Pneumonia aspiration	1 (0.5)	1 (0.5)	2 (0.5)
Respiratory failure	2 (1.0)	0	2 (0.5)
Supraventricular tachycardia	0	2 (1.0)	2 (0.5)
Thrombocytopenia	1 (0.5)	1 (0.5)	2 (0.5)
Urinary tract infection	1 (0.5)	1 (0.5)	2 (0.5)

[a] Number (%) of patients with SAEs, sorted in decreasing frequency of PT (total).
Includes adverse events with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.
MedDRA version 18.

In the Phase II studies a total of 18.5% of patients had an AE that led to hospitalisation. The most common SOCs for AEs leading to hospitalisation were Respiratory disorders (7.1%; 29/411 patients) and Infections (5.8%; 24/411 patients). Only the PTs of pneumonia (2.7%) and pulmonary embolism (2.4%) led to hospitalisation in more than 5 patients.

Deaths

In the osimertinib Phase II studies to date, there were 52 (12.7%) deaths reported in the 28 day follow-up period and post follow-up. The majority of the patients died due to the disease under investigation only. The most common fatal AE across the clinical programme was pneumonia.

In total, 13 patients (3.2%) died due to AEs. Of these 13 patients, 4 experienced AEs leading to death that were considered by the investigator to be possibly causally related to treatment with osimertinib (3 patients had AEs of ILD, and 1 patient had an AE of pneumonitis).

Table 50: All deaths (Full analysis set)

Category	Number (%) of patients AURA Extension 80 mg osimertinib (N=201)	AURA2 80 mg osimertinib (N=210)	Total (N=411)
Total number of deaths	28 (13.9)	24 (11.4)	52 (12.7)
Death related to disease under investigation only	20 (10.0)	19 (9.0)	39 (9.5)
AE with outcome of death only	2 (1.0)	3 (1.4)	5 (1.2)
AE with outcome of death only (AE start date falling after 28 day follow up period)	0	0	0
Number of patients with death related to disease and an AE with outcome of death	6 (3.0)	2 (1.0)	8 (1.9)
Other deaths[a]	0	0	0

[a] Patients who died and are not captured in the earlier categories.
Death related to disease under investigation is determined by the investigator.
Rows are mutually exclusive; patients are only reported in one category.

In AURA Phase I dose expansion cohort in total, 40 deaths (40/271 patients; 14.8%) were reported by the DCO date of 01 May 2015. Twenty-eight (10.3%) of these deaths were considered to be related to the disease under investigation only. Nine (3.3%) deaths were attributed to an AE only and 3 (1.1%) patients had their death reported as being related to the disease under investigation and also as an AE with the outcome of death. Of the 12 patients who died due to an AE the most frequently reported AE that led to death was pneumonia (6 patients). No other AE that led to death was reported in more than 1 patient. None of the AEs leading to death were considered by the investigator to be possibly causally related to treatment with osimertinib.

In AURA Phase I remaining cohorts, one death (3.2%) occurred in the pre-treated capsule formulation dose escalation cohort. In total, 2 deaths (2/12 patients; 16.7%) occurred. One death (8.3%) was considered to be related to the disease under investigation. One death (8.3%) was considered to be secondary to the AE of renal failure. The death was not considered by the investigator to be possibly causally related to treatment with osimertinib.

Laboratory findings

Hepatobiliary disorders or clinical chemistry for hepatic function

In the phase II studies, 6.6% of patients had reports of any specific hepatobiliary AE in the Investigations SOC or the hepatobiliary disorder SOC and <20% of patients had abnormal hepatic biochemistry values for any individual parameter. Adverse events in the hepatobiliary disorders SOC were reported in 10/411 (2.4%) of patients, six patients (1.5%) had AEs that were mild (CTCAE Grade 1), one patient (0.2%) had an AE that was moderate (CTCAE Grade 2).

Based on the Investigations SOC (hepatic-related), AEs of ALT elevation were reported for 6.6% (27/411) of patients, AEs of AST elevation were reported for 6.3% (26/411) of patients, and AEs of blood bilirubin increased were reported for 1.5% (6/411) of patients.

Two patients were hospitalised due to hepatic-related AEs. Two patients had a dose interruption due to increased ALT and AST. One (0.2%) patient experienced a dose discontinuation due to drug-induced liver injury. Seven patients experienced a dose interruption due to hepatic-related AEs.

No Hy's law cases were identified in the AURA Phase II studies. Three patients with combined ALT or AST, and bilirubin were identified (patients who have ALT or AST ≥3 × ULN and total bilirubin ≥2 × ULN at any time during the study, ie, not necessarily at the same time, elevations at any time during the study). Each case has confounding factors.

Adverse events reported in the AURA Phase I dose expansion cohort relevant to hepatic function were reported under both the hepatobiliary disorders SOC and the investigations SOC; frequencies and severities of AEs in the Phase I study were similar to those in the Phase II studies.

Renal disorders or clinical chemistry for renal function

In the phase II studies, Adverse events were reported in 27/411 patients (6.6%) under the Renal and urinary disorders SOC of which most events were mild in severity (5.1% of Grade 1, 1.0% of Grade 2 and 0.5% AE of Grade 3). One AE of renal impairment leading to a dose interruption, one Grade 3 AE of urinary incontinence and one SAE of Grade 3 renal failure leading to hospitalisation were reported. No discontinuations due to AEs were reported. For the overall patient population, there was a slight rise in median serum creatinine during treatment with osimertinib, with a corresponding fall in median creatinine clearance which stabilised early in the first cycle. Based on the Investigations SOC (renal-related), blood creatinine increased was reported in 3.2% of patients (grade 1 in 1.7% of the patients and grade 2 in 1.5% of the patients). One patient had an AE of blood creatinine increased that led to a dose interruption. One patient had a grade 1 AE of increased blood urea nitrogen (BUN).

Adverse events reported in the AURA Phase I dose expansion cohort in the renal and urinary disorders SOC, AEs were reported in 11.8% (32/271) of patients; 7.7% (21/271) patients had AEs of Grade 1, 2.6% (7/271) patients had AEs of Grade 2. The Grade ≥3 AEs were: nephrolithiasis (grade 3: 0.4%), renal failure (grade 3: 0.4%), chronic renal failure (Grade 4: 0.4%), chronic kidney disease (Grade 4: 0.4%), and renal failure acute (Grade 4: 0.4%). A dose reduction due to an AE of chronic renal failure was reported in 1 (0.4%) patient. One (0.4%) patient discontinued osimertinib due to an AE of renal failure. In the pre-treated, tablet formulation cohort in AURA phase I study 1 death (8.3%; 1/12) was considered to be secondary to an AE of renal failure.

Platelets, leucocytes and neutrophils

Haematological related AEs were reported under the blood and lymphatic disorders SOC and under the investigations SOC. Grade 3 events were reported by <2% of patients per PT and there were two patients with Grade 4 toxicities. There was one patient with an AE of pancytopenia, which was reported as mild by the investigator. The investigator considered the event to be possibly causally related. No patient discontinued osimertinib due to changes in haemoglobin or RBC count.

Decreases from baseline in median values for platelets, neutrophils and leucocytes were observed early in treatment with osimertinib. Median values appear to stabilise after the initial drop with the majority of patients experiencing no change in CTCAE grade, or a single grade change. As would be expected with the small magnitude of these changes, no clinically significant sequelae in the population have been observed.

Platelets: At a population level, a decrease in median platelet count was seen over time in early cycles which stabilised towards the lower limit of normal (LLN). In total 56.7% of patients had a platelet count below the LLN at any point during the treatment period mainly Grade 1 (41/47 patients), this includes patients who had a value below the LLN at baseline. Platelet count decreased was reported in 11.4%of the patients and only one SAE related to a decrease in platelets was reported. Thrombocytopenia was reported in 5.4% (22/411) of patients with the majority of patients having Grade 1 events (14/22 patients).

Leucocytes: AEs of white blood cell count decreased were reported in a total of 7.5% of patients. Grade 1 AEs were reported in 1.9% of patients, CTCAE Grade 2 AEs in 4.9% of patients and CTCAE Grade 3 in 0.7% of patients. All were considered non serious. Two patients had dose interruptions due to an AE were reported. No patients who had WBC count decreased were treated for the event. AEs of leukopenia were reported in a total of 2.9% of patients. Grade 1 AEs were reported in 0.5% patients, Grade 2 AEs in 1.7% of patients and Grade 3 in 0.7% of patients. All were considered non serious. Two patients had dose interruptions due to AEs reported. In total 3 patients received granulocyte-colony stimulating factor for WBC count decrease and leucopenia.

Neutrophils: AEs of neutrophil count decreased were reported in a total of 6.1% of patients. Grade 1 AEs were reported in 1.0% of patients, Grade 2 AEs in 3.4% of patients and Grade 3 in 1.5% of patients. One SAE was reported. There was one (0.2%) patient with a discontinuation due to changes in neutrophil count over time. AEs of neutropenia were reported in a total of 4.1% of patients. Grade 1 AEs were reported in 1.7% of patients, Grade 2 AEs in 1.9% of patients and Grade 3 in 0.5% of patients. All were considered non serious and there were two patients with dose interruptions and one dose reduction. No events of febrile neutropenia were reported. Four patients received colony-stimulating factor treatment for neutropenia in the Phase II studies whilst on osimertinib.

Anaemia

AEs of anaemia were reported for 9.7% (40/411) of patients. Three patients had SAEs of anaemia (CTCAE Grade 2): One patient had an SAE due to hospitalisation, with a time to onset at Day 156; One patient is described in the platelet section; and one patient reported a CTCAE Grade 3 SAE of anaemia, starting on Day 202 which led to dose interruption and administration of concomitant treatment. Anaemia AEs of CTCAE Grade 1 were reported for 4.6% of patients (19/411 patients), with Grade 2 AEs reported for 3.6% (15/411) of patients and CTCAE Grade 3 AEs reported for 1.5% (6/411) of patients. A total of 7 patients had blood transfusions and 1 patient had Darbepoetin alfa whilst on osimertinib. Two AEs of anaemia led to dose interruption.

Clinical chemistry laboratory values

In the majority of patients, there were no clinically significant changes in albumin, creatinine, calcium, glucose, magnesium, potassium or sodium observed during treatment. A small percentage of patients developed 3-grade shifts in magnesium (hyper), potassium (hyper and hypo), sodium (hypo) and creatinine (hyper) in the Phase II studies.

In the Phase II studies, AEs relevant to clinical biochemistry parameters were reported in no more than 3.2% of patients for any specific PT. The most commonly reported AEs were blood creatinine increased in 3.2% of patients, hypocalcaemia in 2.4% of patients and hyponatraemia in 2.2% of patients. The majority of AEs were Grade 1 or 2 in severity. Four patients experienced Grade 3 AEs of hyponatraemia, 2 patients experienced Grade 3 AEs of hypokalaemia, and Grade 3 AEs of hyperglycaemia and hypocalcaemia were experienced by 1 patient each.

Safety in special populations

Race

An assessment of the safety profile of osimertinib was performed for patients, split by race: White (n=148); Black/African American (n=4); Asian (n=246); Other (n=7). As the number of Black/African American patients and the number of Other patients is low, the interpretation has concentrated mainly on any differences seen between White and Asian patients.

The incidence of AEs was similar across all 4 groups (all >95%). However, the frequency of AEs considered by the investigator to be possibly causally related to osimertinib was higher in Asian patients (89.4%) versus White patients (80.4%). A similar pattern was observed for Grade ≥3 AEs considered by the investigator to be possibly causally related to osimertinib (Asian patients 14.6%; versus White patients 7.4%).

Serious adverse events were reported less frequently for Asian patients (15.0%) compared to White patients (27.7%). Serious adverse events were reported for two Black/African American patients (50.0%) and no SAEs were reported for 'Other' patients.

Dose interruption as a result of an AE occurred at a slightly higher rate in the Asian population (20.3%) than in the White population (15.5%). Some differences between Asians and White patients were identified.

Age

An assessment of the safety profile of osimertinib was performed in patients aged <65 years (n=224), ≥65 - <75 years (n=133) and ≥75 years (n=54).

The incidence of adverse events was similar across all 3 groups, however AEs of Grade≥ 3 were more frequent for the older populations, i.e. 27.7% of patients aged <65 years, 28.6% of patients aged ≥65 - <75 years and 38.9% of patients aged ≥75 years experienced AEs of Grade≥ 3.

The frequency of osimertinib dose interruption due to an AE or SAE was numerically higher in the highest age group; 16.5% of patients aged <65 years, 18.0% of patients aged ≥65 to <75 years and 29.6% of patients aged ≥75 years.

The incidence of rash, decreased appetite, constipation, platelet count decreased, upper respiratory tract infection and rashes and acnes (group term) was numerically higher in the highest age group.

Table 51: Adverse events by age group in the pooled phase II studies (AURA Extension and AURA2)

MedDRA Terms **N**	**Age <65** **Number (%)** **224**	**Age 65-74** **Number (%)** **133**	**Age 75-84** **Number (%)** **50**	**Age 85+[a]** **Number (%)** **4**
Total AEs	218(97.3)	129(96.0)	50(100)	4(100)
Serious AEs – Total	48(21.4)	25(18.8)	10(20.0)	0
- Fatal	9(4.0)	2(1.5)	2(4.0)	0
- Hospitalization / prolong existing hospitalization	N/A	N/A	N/A	N/A
- Life-threatening	N/A	N/A	N/A	N/A
- Disability / incapacity	N/A	N/A	N/A	N/A
- Other (medically significant)	N/A	N/A	N/A	N/A
AE leading to drop-out	12(5.4)	7(5.3)	4(8.0)	0
Psychiatric disorders	27(12.1)	15(11.3)	6(12.0)	0
Nervous system disorders	65(29.0)	33(24.8)	15(30.0)	0

Accidents and injuries	11(4.9)	5(3.8)	1(2.0)	1(25.0)
Cardiac disorders	11(4.9)	8(6.0)	0	1(25.0)
Vascular disorders	19(8.5)	14(10.5)	3(6.0)	2(50.0)
Cerebrovascular disorders	6(2.7)	4(3.0)	6(12.0)	0
Infections and infestations	118(52.7)	65(48.9)	26(52.0)	3(75.0)
Anticholinergic syndrome	59(26.3)	35(26.3)	10(20.0)	2(50.0)
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	17(7.6)	9(6.8)	4(8.0)	0
-Adverse events more common in older patients (AE appearing at > 10% in the age 75-84 group and / or in more than 2 patients in the 85+ age group)				
Decreased appetite	28 (12.5)	1 (15.8)	13 (26.0)	3 (75.0)
Diarrhea	101 (45.1)	50 (37.6)	21 (42.0)	2 (50.0)
Platelet count decreased	22 (9.8)	15 (11.3)	8 (16.0)	2 (50.0)
Constipation	36 (16.1)	16 (12.0)	9 (18.0)	1 (25.0)
Cough	34 (15.2)	16 (12.0)	6 (12.0)	1 (25.0)
Pruritus	30 (13.4)	20 (15.0)	6 (12.0)	1 (25.0)
Stomatitis	25 (11.2)	18 (13.5)	5 (10.0)	1 (25.0)
Fatigue	34 (15.2)	16 (12.0)	7 (14.0)	0
Headache	24 (10.7)	13 (9.8)	5 (10.0)	0
Adverse events of special interest, by grouped term[b]				
Cardiac effects (QT)	8 (3.6)	5 (3.8)	2 (4.0)	2 (50.0)
Cardiac effects (cardiac failure)	1 (0.4)	3 (2.3)	1 (2.0)	0
Diarrhea	101 (45.1)	50 (37.6)	21 (42.0)	2 (50.0)
ILD and pneumonitis	5 (2.2)	5 (3.8)	1 (2.0)	0
Nail Effects	62 (27.7)	33 (24.8)	8 (16.0)	0
Ocular effects	24 (10.7)	15 (11.3)	7 (14.0)	0
Skin Effects	136 (60.7)	77 (57.9)	31 (62.0)	2 (50.0)
Upper GI tract inflammatory events	54 (24.1)	29 (21.8)	9 (18.0)	1 (25.0)

N/A- data not available

[a] please note that interpretation of incidence in the 85+ age group needs to be done in context of the small number of patients in this subgroup . For example; a change in 1 patient would change the percentage by 25%.

[b] grouped as specified in the 90 day safety update

Gender

Overall, the safety profile of osimertinib was similar for male (n=132) and female patients (n=279). No meaningful differences were observed between males and females in the incidence of AEs in any category, and no specific AEs with a difference of ≥10% were seen. There was double the incidence of 'upper respiratory tract infection' (PT) in males compared with females (11.4% vs 5.4%). There were no other AEs (when considering PTs with a frequency of >10%) with a doubling incidence.

Effect of baseline BSA

An assessment of the safety profile of osimertinib at the AE category level was performed for patients, split by BSA, ie <1.73 m2 (n=267) and ≥1.73 m2 (n=137).

The incidence of AEs was similar across both groups. Patients with a baseline BSA of ≥1.73 m2 had a numerically higher incidence of SAEs (22.6% vs 18.4%).

An assessment of the safety profile was also conducted for the most common AEs (>10% frequency) at PT level and at grouped term level (for AESIs), split by baseline BSA. The incidence of 'cough' (PT) (23.4% vs 9.0%), 'dyspnoea' (PT) (15.3% vs 4.1%) and 'asthenia' (PT) (12.4% vs 4.1%) was at least numerically double the

≥1.73 m2 group and the incidence of 'stomatitis' (PT) (15.7% vs 5.1%) was at least numerically double the <1.73 m2 group. No other notable differences between the AE profiles were observed.

Baseline WHO performance status

An assessment of the safety profile of osimertinib at the AE category level was performed in patients with WHO performance status at baseline of 0 (n=152) and ≥1 (n=259). Patients who had WHO PS ≥1 at baseline experienced higher frequencies of CTCAE Grade 3 or higher adverse events (32.8% vs 23.7%) and causally related CTCAE Grade ≥3 events (15.1% vs 5.9%). Serious adverse events (22.0% vs. 17.1%) and adverse events leading to dose interruptions (21.2% vs 14.5%) were also higher in patients with a WHO PS ≥1 at baseline.

The most common (>10% frequency) AEs were similar across WHO PS at baseline categories.

Comorbidity of hypertension

Overall, the safety profile of osimertinib was similar patients with hypertension (n=145) or without hypertension (n=266). There was no difference in the incidence of AEs for patients with hypertension or without hypertension (hypertension: 99.3%; no hypertension: 96.6%). AEs of CTCAE Grade 3 or higher were more frequent for patients with hypertension than for patients without hypertension (33.8% vs. 27.1%); this was also true for AEs leading to dose modifications (28.3% vs. 15.4%).

The most common (>10% frequency) AEs were similar for patients with hypertension or without hypertension at baseline.

Treatment line (2nd-line, ≥ 3rd-line)

In general there was no difference in the incidence of AEs for patients with 2nd-line (125/129; 96.9%) and 3rd-line (276/282; 97.9%). However, 3rd-line patients reported more AEs with CTCAE 3 or higher (93/282; 33%) compared to 2nd-line patients (28/129; 21.7%). This was also true for causally related CTCAE Grade 3 or higher (3rd-line: 43/282; 15.2%; 2nd-line: 5/129; 3.9%). Serious AEs (22.3% vs 15.5%) and AEs leading to dose modifications (22.0% vs 15.5%) were also higher for 3rd-line patients.

An assessment of the safety profile was also conducted for the most common (>10% frequency) AEs both at the PT level and at the group term level (for AESIs) for 2nd-line and 3rd-line. Adverse events more commonly associated with 3rd-line treatment compared to patients in 2nd-line, with a numerical difference of 5% or more, were observed for pruritus (15.6% vs 10.1% of patients), vomiting (12.1% vs 3.9% of patients), and WBC decreased (10.3% vs 1.6% of patients).

Analysis of the sub-group of patients outlined above has indicated no increase in safety risk in case of prior treatment with 2nd/3rd or later lines of TKIs. Overall, the osimertinib safety profile appears acceptable, irrespective of the number of priorEGFR TKIs that had been received.

Renal function

SAP-defined subgroup analysis was not performed for patients with renal impairment. Study exclusion criteria mandated that patients with creatinine >1.5 times ULN concurrent with creatinine clearance <50 ml/min were to be excluded from taking part.

Hepatic function

SAP-defined subgroup analysis was not performed for patients with hepatic impairment. Study exclusion criteria mandated that patients with ALT >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the

presence of liver metastases, or, AST >2.5 times ULN if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases, or, Total bilirubin >1.5 times ULN if no liver metastases or >3 times ULN in the presence of documented Gilbert's syndrome or liver metastases, were to be excluded from taking part.

Effect of smoking status

An assessment of the safety profile of osimertinib at the AE category level was performed for patients smoking status split by Ever (n=117) and Never (n=294).

Overall there was no notable difference between the ever and never smoking statuses.

An assessment of the safety profile was also conducted for the most common AEs (>10% frequency) at PT level and at grouped term level (for AESIs), split by smoking status. No notable difference between the AE profile was observed. Adverse events with a numerical difference of 5% or more were observed for nausea (11.1% vs 19.0%), platelet count decreased (19.7% vs 8.2%), dry skin (grouped term) (35.0% vs 29.3%) and rashes and acnes (grouped term) (45.3% vs 39.8%) for Ever versus Never smokers respectively.

Since osimertinib PK exposure is unaffected by smoking status, it is unlikely that smoking status would impact the safety profile of osimertinib. The small numerical differences in the AEs leading to dose modifications for ever smokers vs. Never smokers that are seen are most likely an artefact of natural variability. Overall, irrespective of smoking status osimertinib is a tolerable treatment for ever smokers and neversmokers.

The overall PK and safety data, also does not suggest a relationship between being a smoker and an impact of osimertinib on the safety profile.

Safety related to drug-drug interactions and other interactions

An analysis of relevant AEs in the Phase II studies was conducted, focusing on patients concomitantly using a statin. In total, 47 patients were on a statin and 364 patients had no statin use. No notable differences between the profiles were observed.

In the pivotal Phase II clinical trials, 67.9% (279/411) of patients recruited were female with a median age of 63 years old (mean 61.9 years). The age of the recruited population of female patients is broadly characteristic of a NSCLC population and represents a group of patients where the use of contraceptives is likely to be minimal. Based on the pharmacokinetic characteristics of osimertinib, it is the Applicant's position that the exposure of osimertinib is unlikely to be affected by previous contraceptive treatments and thereby, the safety and/or efficacy of osimertinib in these patients is not expected to be any different compared to others who have not used contraceptives.

Discontinuation due to adverse events

Adverse events leading to discontinuation

The frequency of adverse events leading to discontinuation was low across the osimertinib pooled Phase II studies (5.6%; 23/411). The common AEs that characterise the osimertinib safety profile (diarrhoea, rash) did not generally lead to discontinuation of treatment.

Across the Phase II studies, the reported discontinuations due to AEs in ≥2 patients were ILD and pneumonitis (each reported in 5 patients; 1.2%), and cerebrovascular accident (CVA) and pulmonary embolism (each reported in 2 patients; 0.5%). Nineteen events leading to discontinuations in 15 patients were considered by the investigator to be possibly causally related to treatment with osimertinib. For ILD or ILD-like events it was mandated in the study protocols that the patients discontinue.

The low rate of discontinuation from osimertinib 80 mg therapy in both the Phase II studies and the AURA Phase I study indicates osimertinib at the recommended daily dose is tolerated by this advanced NSCLC patient population.

In study the dose expansion cohort of the AURA Phase I, in total, 10.0% (27/271) of patients across all doses of osimertinib discontinued due to an AE**.** 4/271 patients; 1.5%) and pneumonia (3/71 patients; 1.1%). The events of pneumonitis were all reported for patients at the 160 mg dose level. No single PT drove the incidence of AEs leading to discontinuation of osimertinib. osimertinib was discontinued due to AEs that were considered by the investigator to be possibly causally related to treatment with osimertinib in 3.3% (9/271) of patients. An increase in the incidence of AEs leading to discontinuation of osimertinib that were considered by the investigator to be possibly causally related to treatment with osimertinib was apparent from 80 mg to 160 mg (1/97 patient; 1.0% and 7/93 patients; 7.5%, respectively). At the 80 mg dose level 8.2% (8/97) of patients discontinued due to an AE. No individual PT leading to discontinuation was reported for more than one patient. The PTs of pulmonary embolism, AST increased, intestinal obstruction, atrial fibrillation, pneumonitis, renal failure and cardiac failure acute were considered by the investigator to be possibly causally related to treatment with osimertinib.

Dose reductions due to adverse events

Adverse events leading to a dose reduction of osimertinib to 40 mg occurred in 18 patients (4.4%) in the Phase II studies suggesting good tolerability of osimertinib.

In 14 patients with dose reductions due to AEs, there was no evidence of any single type of toxicity driving the dose reductions. Fourteen PTs leading to dose reduction were reported for these 14 patients, with some patients having more than one AE reported. The PT of electrocardiogram QT prolonged was reported for 3 patients and the PT of nausea was reported for 2 patients, all other PTs were reported for only one patient each. Four additional patients with dose reductions due to AEs were recorded on the exposure CRF and not linked to a particular AE on the AE CRF.

In the Phase II clinical trials with osimertinib, patients who had a dose reduction to 40 mg were rarely discontinued at a later time point due to an AE. Of the 18 (4.4%) patients who had a dose reduction to 40 mg osimertinib, 16 patients (3.9%) continued treatment with osimertinib. Two patients (0.5%) subsequently discontinued osimertinib due to an AE: one due to rash maculo-papular; one due to drug induced liver injury.

Adverse events that led to a dose reduction were reported in 10.7% (29/271) of pre-treated patients who received the osimertinib capsule formulation.

The main reasons for dose reductions were related to the SOCs of GI disorders (8/271 patients; 3.0%), infections (7/271 patients; 2.6%), skin effects (6/271 patients; 2.2%) and investigations (5/271 patients; 1.8%). The most commonly reported PTs were diarrhoea (5/271 patients; 1.8%), paronychia (4/271 patients; 1.5%) and nausea (3/271 patients; 1.1%). With the exception of dizziness and chronic renal failure (1 patient each at the 40 mg dose level) and blood creatine phosphokinase increased (1 patient at the 80 mg dose level), AEs that led to a dose reduction were only reported at the 160 mg and 240 mg dose levels, suggesting a relationship of dose reductions with dose.

Dose interruptions due to adverse events

AEs led to dose interruptions in 18.7% (77/411) of patients in the Phase II studies, with a total of 115 dose interruptions in 77 patients. In the majority of the 115 events, only 1 PT contributed to the dose interruption per

event (84.3%; 97/115), with a maximum of 3 PTs contributing to a dose interruption for one event. This observation further supports the tolerability of osimertinib at 80 mg.

The most common SOCs with AEs leading to dose interruptions were Investigations (5.8%; 24/411) and Infections (4.4%; 18/411). The most common PTs leading to dose interruptions were electrocardiogram QT prolonged (8/411; 1.9%), neutrophil count decreased (6/411; 1.5%), and ALT increased (5/411; 1.2%). All other PTs were reported in no more than 4 patients each.

Of the 77 patients who had a temporary interruption for an AE, subsequent dose reduction or dose discontinuation was infrequent. A total of 56/77 (72.7%) patients continued osimertinib at the same dose with no dose reduction or discontinuation due to an AE and 17/41 (41.5%) patients were dose reduced. Six patients later discontinued due to an AE (two of whom, also had a dose reduction after previous dose interruptions due to AE).

In AURA Phase I dose expansion cohort the Dose interruptions due to AEs were reported in 22.9% (62/271) of pre-treated patients who received the osimertinib capsule formulation in the dose expansion part of the study. The reasons driving dose interruptions were distributed across different SOCs. The major reasons were related to the SOCs of GI disorders (16/271 patients; 5.9%), investigations(13/271 patients; 4.8%), and infections (12/271 patients; 4.4%). The most commonly reported PTs were diarrhoea (6/271 patients; 2.2%), pulmonary embolism (5/271 patients; 1.8%), paronychia (5/271 patients; 1.8%), neutrophil count decreased (4/271 patients; 1.5%), and ALT increased, nausea and vomiting (each reported 3/271 patients; 1.1%).Generally, there was no clear association with the incidence of AEs leading to dose interruption and osimertinib dose level.

Post marketing experience

There is no post-marketing data available for osimertinib

2.6.1. Discussion on clinical safety

The established safety/tolerability profile of approved small molecule EGFR TKI agents (gefitinib, erlotinib, afatinib), derived from clinical experience, consists mostly of gastrointestinal disturbances (diarrhoea, nausea and vomiting) and skin reactions (rash, acne, dry skin and pruritus, and rarely, severe bullous and exfoliative reactions). The aetiology of these events is thought to be related to inhibition of non-mutated EGFR by these agents in target tissues. These events are well characterised and are considered to be mostly mild or moderate in severity and reversible with supportive care or a short cessation of therapy. Typical onset is within the first month of treatment and there is considered to be a dose relationship.

Other types of adverse event (AE) reported commonly or very commonly with these agents in patients with advanced NSCLC include anorexia, stomatitis, asthenia, keratitis, conjunctivitis and alopecia.

Less common toxicities that have been associated with EGFR TKIs include Interstitial lung disease (ILD); the frequency of ILD documented in this patient population is 1.3% with gefitinib and between <1/100 and ≥1/1000 (i.e. 0.1-1.0%) with erlotinib, including fatalities. From the currently approved SmPC for afatinib, it is stated that ILD-like AEs are reported in 0.7% amongst more than 3800 patients. Furthermore, gefitinib, erlotinib and afatinib have all been associated with hepatotoxicity (Spraggs et al 2013). EGFR TKI agents have also demonstrated an increase in embryolethality and abortion in non-clinical reproductive toxicity studies. The applicant claims that the non-clinical toxicology profile of osimertinib largely reflects the pharmacological action of this compound, and is generally consistent with that reported for other EGFR TKIs such as erlotinib, gefitinib and afatinib.

The safety evaluation is mainly based on data from two phase II studies, AURA extension (N=201) and AURA2 (N=210), including a total of 411 patients.

Due to the single arm design of the studies submitted, lack of control arm hampers the (direct) comparison to other treatment regimens.

The median exposure for patients in the two Phase II studies (411 patients), 7.7 months with 236 (57.4%) of the patients received osimertinib for longer than 6 months. In AURA Phase I study population the median exposure to osimertinib is 8.2 months and 102 (50.7%) patients received osimertinib for longer than 6 months.

In summary, in the pooled analysis of the Phase II studies, AEs were reported for almost all, in 97.6% of patients in the study; casually related to osimertinib in 86.4% of the patients. Most adverse reactions were Grade 1 or 2 in severity.

Common AEs: For the pooled phase II studies, AEs were most frequently reported in the SOCs of GI disorders (69.8%), Skin disorders (64.2%), and Infections (51.6%). The most common PTs were diarrhoea (42.3%), rash (23.8%), dry skin (23.1%) and paronychia (17.5%)

Fatal AEs were reported for 3.2% (13/411) of patients, 4 of which were considered by the investigator to be possibly causally related to osimertinib. The most common fatal AE across the clinical program was pneumonia, which is not unexpected in an advanced NSCLC population.

Serious adverse events were reported in 20.2% (83/411) of patients; 5.1% (21/411) of patients had an SAE considered by the investigator to be possibly causally related to osimertinib. In general, the SAEs reported are commonly reported in patients with advanced lung cancer and are not unexpected.

Dose interruptions due to AEs were reported for 18.7% of patients, dose reductions due to AEs were reported for 3.4% of patients, and discontinuations due to AEs were reported for 5.6% of patients. Dose reductions due to ADRs occurred in 2.2% of the patients. Discontinuation due to adverse reactions or abnormal laboratory parameters was 3.2%.

The most common reasons for permanent discontinuation of treatment are related to the respiratory system, being pneumonitis and pneumonia, which is not unexpected in this patient population.

AESI: The adverse events of special interest (AESI) topics includes skin effects, diarrhoea, upper GI inflammation, stomatitis, Interstitial Lung Disease (ILD) or ILD-like effects, nail effects, ocular effects, and cardiac effects (including QT prolongation and cardiac contractility) as well as other safety topics (hepatobiliary disorders, renal disorders, upper GI tract effects including stomatitis).

Severe, life-threatening or fatal Interstitial Lung Disease (ILD) or ILD-like adverse reactions (e.g. pneumonitis) have been observed in patients treated with osimertinib 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.

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, osimertinib should be permanently discontinued and appropriate treatment initiated as necessary (see sections 4.4 and 4.8 of the SmPC).

The development of ILD is a potential risk associated with advanced NSCLC and treatments used for NSCLC, including chemotherapy and EGFR TKIs. Interstitial lung disease (ILD) is considered an important identified risk for osimertinib based on the nature of the signal and number of reported events.

The risk of developing ILD in Japanese Asian patients appears higher than for patients of non-Asian ethnicity in the rest of world. The reason for this observed difference is currently not known. Despite the low number of ILD events, the data suggest as a risk factor belonging to the Asian ethnic group.

No clear risk factors have been identified in the ongoing investigations into ILD events reported across the osimertinib program.

The frequency reported should be considered in the context of the underlying disease and previous cancer therapies received by trial participants. NSCLC and its treatment are factors which are known to pre-dispose patients to occurrence of ILD. The incidence of ILD with EGFR TKIs is variable, reported in up to 5.7% of treated patients, with severe ILD reported in up to 2.6% of treated patients. Rates of acute ILD events up to and exceeding10% have been reported in patients receiving chemotherapy and radiotherapy. In many cases for currently approved EGFR TKIs, ILD can be fatal, with more than 30% of ILD events with a fatal outcome reported in some studies (Shi et al, 2014). Based on the limited available data on irreversible EGFR inhibitors, there is no evidence of an increased level of risk associated with irreversible inhibition of EGFR inhibitors. Afatinib reports a 1.5% incidence rate of ILD, with a 0.4% fatality rate, which is in line with other EGFR inhibitors (afatinib USPI).

Time to onset of ILD with EGFR-TKIs is often very rapid with a risk of ILD with gefitinib mainly in the first 4 weeks of treatment, whereas with osimertinib the majority of ILD reports were between 4 and 12 weeks (median time to onset 83 days; range 17 days to 230 days across the osimertinib program).

The AURA2 study included an intensive assessment of electrocardiogram (ECG) parameters, addressing key aspects of a conventional thorough QT/QT interval corrected for heart rate (QTc) study, including time-matched ECG assessments.

QTc interval prolongation occurs in patients treated with osimertinib. 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. 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 sections 4.4 and 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 conducted 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 osimertinib 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 (see sections 4.4 and 4.8 of the SmPC).

It is acknowledged that no evidence of any clinical consequences of QT prolongation has been observed in clinical studies to date, hence, a contraindication is not warranted. However, the risk for such events are at present unknown, and the proposed product information (PI) from the company will hopefully facilitate an informed decision regarding the administration of osimertinib to patients that may be at higher risk of QTc interval prolongation and provide appropriate guidance regarding any modification to treatment that might be needed should an event of QTc interval prolongation occur. No safety signal with regards to cardiac events was observed, other than the already described drug-related QTc interval prolongation. QT prolongation is classified

as an important identified risk in the proposed RMP.

Cardiac contractility: A causal association between osimertinib and cardiac failure adverse events cannot be fully excluded due to the temporal relationship between receiving study drug and onset/recovery of events. Based on available data, osimertinib has no detrimental effect upon cardiac contractility.

Diarrhoea was the most commonly reported AE across the osimertinib Phase II studies and Phase I study.

The severity of diarrhoea seen in clinical trials reflects the margin of selectivity against wild-type EGFR displayed by osimertinib when compared to other EGFR TKIs. In particular severe events such as haemorrhagic diarrhoea or GI perforation have not been seen.

At the event level, the diarrhoea experienced during treatment with osimertinib has not required dose reduction, and has rarely led to dose interruption, or permanent discontinuation. Less than half of all events of diarrhoea received treatment and irrespective of whether treatment had been received, were reported to have resolved.

Events were typically of low clinical significance with no requirement for medical intervention to prevent the development of complications such as dehydration or electrolyte disturbance.

In the pooled phase II studies, skin effect grouped term AEs were reported in 59.9% of patients, Rash (23.8%) and dry skin (23.1) were the most common skin effect PTs in the skin effects grouped terms.

There were no SAEs .No skin-related AE led to hospitalisation. Across the studies there were no severe bullous, severe blistering, or severe exfoliative rash events, no events suggestive of hypersensitivity reactions, including SJS or TEN (Lyell's syndrome), and no events of phototoxicity.

The company claims that the low severity of the safety profile of skin effects seen in the osimertinib clinical trials reflects the margin of selectivity against wild-type EGFR displayed by osimertinib when compared to other EGF TKIs, however, these severe events are reported as rare with treatment of other TKIs and it may not have been possible to detect them at this stage. Based on current knowledge, skin effects seem to be very frequently occurring, but manageable and seldom require dose reduction or discontinuation, and hence, do not seem to significantly contribute to the tolerability burden in this advanced NSCLC population.

Events in any of the ocular effects grouped terms were reported in a total of 11.2% of patients with a similar distribution between both Phase II studies. The most common PTs reported in the Ocular effects grouped terms were dry eye in 5.6% (23/411) of patients and conjunctivitis in 2.9% (12/411) of patients. No other PT was reported at a frequency ≥2%. There were no SAEs, no events of CTCAE Grade 3 or greater and no events of corneal erosion or corneal ulceration. Twenty-six patients (6.3%) with ocular effects AEs received treatment, but no ocular effects AEs led to permanent discontinuation of osimertinib 80 mg.

With regards to renal disorders or clinical chemistry for renal function the data shows a slight rise in serum median creatinine (and corresponding fall in median creatinine clearance) which stabilises within the first cycle. Less than 5% of patients reported renal AEs across the Phase II studies, most of which were mild in severity.

Decreases from baseline in median values for platelets, neutrophils and leucocytes were observed early in treatment with osimertinib. Median values appear to stabilise after the initial drop with the majority of patients experiencing no change in CTCAE grade, or a single grade change. As would be expected with the small magnitude of these changes, no clinically significant sequelae in the population have been observed.

CTCAE grade changes from baseline were observed in other haematological (e.g. haemoglobin, lymphocytes) and biochemical parameters (e.g. creatinine, sodium, potassium, magnesium), but no pattern in time to onset

or clinical course of events was identified. These changes in laboratory parameters have not been identified as adverse drug reactions (ADRs) associated with osimertinib and were not considered to be of clinical consequence.

Osimertinib is eliminated mainly via the liver. A small number of patients reported AEs of elevations in AST (6.3%) or ALT (6.6%) and the majority of these elevations were Grade 1 or Grade 2 changes. Grade 3 changes in ALT elevations were reported for 1.2% of patients and Grade 3 changes in AST elevations were reported for 0.2% of patients. No Hy's Law cases were identified however the patient population is too limited at the time (3 cases were considered but finally not lead to a definitive conclusion).

The overall assessment did not identify an increased risk of drug-induced liver injury (DILI).

Any differences seen between different ethnicities were thought not to be of clinical significance. The difference observed in SAE incidence (higher in Whites) and AE incidence (higher in Asians) is reflective of variability in data with no relationship with the product.

The safety profile for osimertinib is broadly similar across age groups in terms of nature, severity and impact of adverse events. However as expected among the elderly ($\geqslant$65 years) the incidences were numerically higher for at least some AEs and also (S)AEs that led to dose modifications (interruptions or reductions) as compared to the younger (23 % versus 17 %). Older patients experienced more Grade 3 or higher adverse reactions compared to younger patients (32% versus 28%). No overall differences in efficacy were observed between these subjects and younger subjects. No dosage adjustment is required due to patient age, body weight, gender, ethnicity and smoking status.

In phase I/II clinical trials a limited number of patients were treated with osimertinib daily doses of up to 240 mg without dose limiting toxicities. In these studies, patients who were treated with osimertinib daily doses of 160 mg and 240 mg experienced an increase in the frequency and severity of a number of typical EGFR-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 osimertinib in error, without any resulting clinical consequences.

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

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. Based on its mechanism of action and preclinical data, osimertinib may cause foetal harm when administered to a pregnant woman. Osimertinib should not be used during pregnancy unless the clinical condition of the woman requires treatment with osimertinib. In addition, women of childbearing potential should be advised to avoid becoming pregnant while receiving osimertinib. 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. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with osimertinib. There are no data on the effect of osimertinib on human fertility. Results from animal studies have shown that osimertinib has effects on male and female reproductive organs and could impair fertility (see sections 4.6 and 5.3 of the SmPC).

Osimertinib has no or negligible influence on the ability to drive and use machines (see section 4.7 of the SmPC).

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

The phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy will provide additional data to confirm the safety profile of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive

2.6.2. Conclusions on the clinical safety

Overall, the osimertinib safety profile was as expected for a population of patients with advanced NSCLC treated with an EGFR TKI agent with an improved margin of selectivity against wild-type EGFR. The most commonly reported AEs being low-grade gastrointestinal disturbances (primarily diarrhoea) and skin effects (mainly rash, acne, and dry skin) which are consistent with some degree of inhibition of wild-type EGFR.A total of 2.9% (35/1221) patients have reported ILD or suspected ILD-like events

Adverse events of maximum CTCAE Grades 3, 4 and 5 have been experienced in 25.5% (105/411) 1.2% (5/411) and 2.7% (11/411) of patients, respectively. Serious adverse events were reported in 20.2% (83/411) of patients; 5.1% (21/411) of patients had an SAE considered by the investigator to be possibly causally related to osimertinib. Fatal AEs were reported for 3.2% (13/411) of patients, 4 of which were considered by the investigator to be possibly causally related to osimertinib.

The lack of comparator in the studies hampers to properly contextualise the tolerability and toxicity. The long term safety profile is not totally known. Nevertheless, despite these uncertainties, the overall safety profile of osimertinib is considered acceptable and manageable, with a likely better tolerability than the traditional chemotherapy

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA

In order to confirm the safety profile of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive the applicant should submit the final results of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy by 30 June 2017.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP).

The PRAC considered that the RMP version 1.0 (dated May 2015) could be acceptable if the applicant implements all the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur RMP assessment report dated 08 October 2015.

The CHMP endorsed this advice.

The Applicant implemented all the changes to the RMP as requested by PRAC and CHMP.

The CHMP approved the RMP version 4.0 (dated December 2015) with the following contents:

Safety concerns

Table 52 – Summary of the safety concerns

Important Identified Risks	• Interstitial lung disease • QT prolongation
Important Potential Risks	• Developmental toxicity • Severe skin reactions • Severe diarrhoea • Ocular toxicity • Hepatotoxicity
Missing Information	• Long term exposure to osimertinib • Use during lactation • Use in patients with severe renal impairment • Use in patients with moderate or severe hepatic impairment • Use in patients with ECOG performance status ≥2 • Use in patients with symptomatic brain metastases • Potential for drug-drug interactions between osimertinib and non-CYP3A4 mediated PXR substrates • Potential for transporter inhibition • Potential for P-gp inhibition • osimertinib absolute oral bioavailability • Use in very elderly patients (≥75 years old)
Abbreviation: ADR, adverse drug reaction; DDI, drug-drug interaction; ECOG: Eastern Co-operative Group; QT, ECG interval measured from the beginning of the QRS complex to the end of the T wave.	

Pharmacovigilance plan

Table 53 – Ongoing and planned additional pharmacovigilance studies / activities in the Pharmacovigilance Plan

Study number (Category [1-3]), Title and design	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports (planned or actual)
D5160C00003 (AURA3) (Category 2) A Phase III, open label, randomised study of osimertinib vs. platinum-based doublet chemotherapy for patients with locally advanced or metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour an EGFR T790M mutation within the EGFR gene.	*Primary Objective:* To assess the efficacy of osimertinib compared with platinum-based doublet chemotherapy by assessment of PFS. *Secondary Objectives:* - To further assess the efficacy of osimertinib compared with platinum-based doublet chemotherapy in terms of ORR, DoR, DCR, tumour shrinkage, and OS. - To assess the effect of osimertinib compared to platinum-based doublet chemotherapy on subjects' disease-related symptoms and HRQoL. - To characterise the PK of osimertinib and metabolites in subjects receiving osimertinib. *Safety objective:* - To assess the safety and tolerability profile of osimertinib compared with platinum based doublet chemotherapy.	ILD QT prolongation Severe skin reactions Severe diarrhoea Ocular toxicity Hepatotoxicity Long term exposure to osimertinib	Started	Final CSR due May 2018 (planned)
D5165C00001 (CAURAL) (Category 3) A phase III, multi-centre, open label, randomized study to assess the efficacy and safety of osimertinib in combination with MEDI4736 versus osimertinib monotherapy in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have received Prior EGFR TKI therapy.	*Primary Objective:* To assess the efficacy of osimertinib in combination with MEDI4736 versus osimertinib monotherapy in terms of PFS as 2nd line or higher treatment for patients who have progressed following an approved EGFR-TKI therapy. *Secondary Objectives:* - To further assess the efficacy of osimertinib in combination with MEDI4736 versus osimertinib monotherapy in terms of ORR, DoR, DCR, tumour shrinkage, OS and PFS landmark analyses. - To assess the impact of osimertinib in combination with MEDI4736 versus osimertinib monotherapy on disease-related symptoms and HRQoL in NSCLC patients. - To assess the PK of osimertinib as a single agent and in combination with MEDI4736. - To characterise the PK, immunogenicity and pharmacodynamics of MEDI4736 after single dosing and at steady state after multiple dosing when given intravenously to patients with EGFRm NSCLC in combination with osimertinib. To assess the safety and tolerability profile of osimertinib as a single agent	ILD QT prolongation Severe skin reactions Severe diarrhoea Ocular toxicity Hepatotoxicity Long term exposure to osimertinib	Started	Final CSR due Feb 2019 (planned)

	and in combination with MEDI4736.			
D5160C00017 (Category 3) A Phase II, open label, single-arm study to assess the safety and efficacy of osimertinib in Asia Pacific patients with locally advanced/metastatic NSCLC whose disease has progressed with previous EGFR TKI therapy and whose tumours harbour a EGFR T790M mutation within the EGFR gene.	*Primary Objective:* To assess the efficacy of osimertinib by assessment of ORR. *Secondary Objectives:* To further assess the efficacy of osimertinib in terms of PFS, DoR, DCR, tumour shrinkage, and OS. To assess the safety and tolerability profile of osimertinib. To assess the impact of osimertinib on patients' disease-related symptoms and HRQoL.	ILD QT prolongation Severe skin reactions Severe diarrhoea Ocular toxicity Hepatotoxicity Long term exposure to osimertinib	Started	Final CSR due Nov 2016 (planned)
D5160C00022 (Category 3) Open label, multinational, multicenter, real world treatment study of single agent osimertinib for patients with advanced/ metastatic EGFR T790M mutation positive NSCLC who have received prior therapy with an EGFR TKI.	The primary objective of this study is to assess the efficacy and safety of single agent osimertinib in a real world setting in adult patients with advanced or metastatic, EGFR T790M mutation positive NSCLC, who have received prior EGFR TKI therapy.	ILD QT prolongation Severe skin reactions Severe diarrhoea Ocular toxicity Hepatotoxicity Long term exposure to osimertinib Use in patients with ECOG PS ≥2 Use in patients with symptomatic brain metastases	Started	Final report due May 2019 (planned)
D5160C00007 (FLAURA) (Category 3) A Phase III, double-blind, randomised study to assess the efficacy and safety of osimertinib vs. a SoC EGFR TKI as first-line treatment in patients with EGFRm, locally advanced or metastatic NSCLC**.**	*Primary Objective:* To assess the efficacy of single agent osimertinib compared with SoC EGFR TKI therapy as measured by PFS. *Secondary objectives:* - To assess the efficacy of osimertinib compared with SoC EGFR TKI therapy by assessment of PFS in patients with positive (or negative) pre-treatment, EGFR T790M (amino acid substitution at position 790 in EGFR, from a threonine to a methionine) mutation; EGFR Ex19del or L858R mutation; or EGFRm (Ex19del or L858R) detectable in plasma-derived ctDNA. - To further assess the efficacy of osimertinib compared with SoC EGFR TKI therapy. - To characterise the PK of osimertinib and its metabolites (AZ5104 and AZ7550). - To assess the impact of osimertinib	ILD QT prolongation Severe skin reactions Severe diarrhoea Ocular toxicity Hepatotoxicity Long term exposure to osimertinib	Started	Final CSR due Jan 2019 (planned)

	compared to SoC EGFR TKI therapy on patients' disease-related symptoms and HRQoL. - To assess patient satisfaction with treatment when receiving osimertinib compared with SoC EGFR TKI therapy. *Safety Objective:* To assess the safety and tolerability profile of osimertinib compared with SoC EGFR TKI therapy.			
D6030C00001 (BLOOM) (Category 3) A Phase I, open-label, multicentre study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumour activity of AZD3759 or osimertinib in patients with EGFRm advanced stage NSCLC.	*Primary Objective:* To investigate the safety and tolerability of AZD3759 (both Part A and Part B) when given orally to patients with advanced stage EGFRm NSCLC who have progressed following prior therapy, including Maximum Tolerated Dose determination, if possible (Part A only) *Secondary Objectives (osimertinib specific only):* To evaluate anti-tumour efficacy and safety in patients treated with osimertinib (only for patients with brain metastasis [BM] and/or leptomeningeal metastasis [LM])). To determine the pharmacokinetics of osimertinib and metabolites in blood and CSF following multiple oral dosing (only for patients with LM and/or BM). To evaluate the changes from baseline in CNS symptoms (analyzed from BN20) in patients with LM treated with AZD3759/osimertinib.	Use in patients with ECOG PS ≥2 Use in patients with symptomatic brain metastases	Started	Final CSR due May 2017 (planned)
D5160C00008 (Category 3) A Phase I, open-label, non-randomised study designed to determine the PK profile, safety and tolerability of osimertinib following a single oral dose in patients with advanced solid tumours and normal hepatic function or mild or moderate hepatic impairment. This is a 2-part study: - Part A will investigate the PK of osimertinib in patients with mild or moderate hepatic impairment compared to patients with normal hepatic function; - Part B will allow any patient with mild or moderate hepatic impairment or normal hepatic function, who completes Part A, continued access to osimertinib after the PK phase and will provide additional safety data.	*Primary Objective:* To characterise the effect of hepatic impairment on the PK of osimertinib after a single oral dose of 80 mg to patients with advanced solid tumours and mild or moderate hepatic impairment or normal hepatic function. *Secondary Objectives:* - To characterise the effect of hepatic impairment on the PK of osimertinib metabolites AZ5104 and AZ7550 after a single oral dose of 80 mg to patients with advanced solid tumours and mild or moderate hepatic impairment or normal hepatic function. - To investigate the safety and tolerability of single and multiple oral doses of osimertinib in advanced solid tumour patients with mild or moderate hepatic impairment and in those with normal hepatic function.	Exposure of osimertinib in patients with hepatic impairment Hepatotoxicity	Started	CSR (Part A): Nov 2018 (planned) CSR Addendum (Part B): Mar 2019 (planned)
D5160C00020 (Category 3) A study to assess the absolute bioavailability of a single oral dose	*Primary objective:* To assess the absolute bioavailability of osimertinib in healthy male	osimertinib absolute oral bioavailability	Ongoing	30 June 2016 (planned)

of osimertinib with respect to an intravenous microdose of [14C]osimertinib in healthy male subjects	subjects. *Secondary objectives:* To evaluate the pharmacokinetic parameters of osimertinib in plasma following a single oral dose of osimertinib and a radiolabelled intravenous (IV) microdose of [14C] osimertinib in healthy male subjects. *Safety Objectives:* To examine the safety and tolerability of osimertinib. *Exploratory objectives:* - To evaluate the pharmacokinetic parameters of metabolites AZ5104 and AZ7550 in plasma following a single oral dose of osimertinib and a radiolabelled IV microdose of [14C] osimertinib in healthy male subjects. - To collect and store deoxyribonucleic acid (DNA) for future pharmacogenetic exploratory research into genes or genetic variation that may influence on PK, metabolism or safety and tolerability to osimertinib.			
Study number to be determined (Category 3) Study title and design to be determined	Clinical pharmacology reduced-dosing study in patients with severe renal impairment	Use in patients with moderate or severe hepatic impairment	Planned	Q4 2018 (planned)
Study number to be determined (Category 3) Study title and design to be determined	Clinical pharmacology study assessing the potential of transporter inhibition	Potential for transporter inhibition	Planned	To be determined
Study number to be determined (Category 3) Study title and design to be determined	Drug-drug interaction study with a substrate for another PXR regulated enzyme (different to CYP3A4), incorporating an *in vivo* assessment of the potential of osimertinib to inhibit P-gp	Potential for drug-drug interactions between osimertinib and non-CYP3A4 mediated PXR substrates Potential for P-gp inhibition	Planned	Q4 2017 (planned)

Abbreviations: ADR, adverse drug reaction; AUC, area under the plasma concentration-time curve; AUC_{tau}, AUC between doses at steady state; BCRP, breast cancer resistance protein; C_{max}, maximum plasma concentration; CSR, Clinical Study Report; $C_{ss,max}$, maximum plasma concentration at steady state; ctDNA, circulating tumour deoxyribonucleic acid; DCR, disease control rate; DDI, drug-drug interaction; DoR, duration of response; 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 TKI, epidermal growth factor receptor tyrosine kinase inhibitor; HRQoL, health related quality of life; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; QT, ECG interval measured from the beginning of the QRS complex to the end of the T wave; SoC, standard of care.

[a] A full CSR will be produced for Part A of this study (PK analysis). Part B (safety follow-up) will be reported as a CSR addendum.

Risk minimisation measures

Table 54: Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
ILD	SmPC wording in Section 4.2, 4.4, 4.8.	None
QT prolongation	SmPC wording in Section 4.2, 4.4, 4.8, 5.1.	None
Important potential risks		
Developmental toxicity	SmPC wording in Section 4.6, 5.2.	None
Severe skin reactions	SmPC wording in Section 4.2.	None
Severe diarrhoea	SmPC wording in Section 4.2.	None
Ocular toxicity	None	None
Hepatotoxicity	None	None
Missing information		
Long term exposure to osimertinib	None	None
Use during lactation	SmPC wording in Section 4.6.	None
Use in patients severe renal impairment	SmPC wording in Section 4.2, 5.2.	None
Use in patients with moderate or severe hepatic impairment	SmPC wording in Section 4.2, 5.2.	None
Use in patients with ECOG performance status ≥2	None	None
Use in patients with symptomatic brain metastases	None	None
Potential for drug-drug interactions between osimertinib and non-CYP3A4 mediated PXR substrates	None	None
Potential for transporter inhibition	None	None
Potential for P-gp inhibition	None	None
osimertinib absolute oral bioavailability	None	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Use in very elderly patients (≥75 years old)	None	None
Abbreviations: ADR, adverse drug reaction; DDI, drug-drug interaction; ECOG, Eastern Co-operative Oncology Group; ILD, interstitial lung disease; QT, electrocardiogram interval measured from the beginning of the QRS complex to the end of the T wave; SmPC, Summary of Product Characteristics; PL, Package leaflet		

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, osimertinib is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is approved under a conditional marketing authorisation [REG Art 14(7)].

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Pooled results from the two phase II studies have shown that the administration of 80 mg of osimertinib in the treatment of EGFR T790M mutation positive advanced NSCLC patients who had progressed following prior therapy with an EGFR TKI, lead to an objective response rate by BICR of around 66%. The ORR was similar between 2nd and 3rd-line cohorts in both phase II studies. All the responses were partials in the AURA extension, whereas two patients had complete response in the AURA 2 study. Results according to the assessment of the investigators were similar to those obtained by the BICR. The analysis of subgroups shows similar results among the different populations studied.

The median duration of the response according to the BICR has not been achieved yet (95% CI 8.3-NC). However, data from investigator assessment provide a median of DoR of 8.5 months, with 96.2% of responders showing a documented objective response at their second scheduled follow-up scan (Week 12 ± 1 week; according BICR). The other secondary variables, support the efficacy of osimertinib in this population: tumour shrinkage in approximately 94% of patients and a proportion of patients estimated to be alive and progression free around 71% and 52% at 6 and 9 months, respectively.

These results are also supported by those obtained in the AURA phase I study, where in the subset of 37 patients in the 80 mg cohort (ORR 61.7% 95%CI 48.2-73.9) the median DoR from first documentation of objective response by Kaplan-Meier method, based on BICR data, was 9.7 months (95% CI: 8.3, NC).

Uncertainty in the knowledge about the beneficial effects.

The design of the studies could be considered the most important uncertainty, as there was no control group, which makes it difficult to drawn firm conclusions on the added benefit from treatment. .

Despite ORR is a commonly used endpoint in oncology studies, its use is usually limited to exploratory studies since it is not able to reliably estimate the ultimate benefit for patients in terms of life expectancy. Furthermore, data in terms of PFS and OS are too immature to reflect the real benefit of osimertinib.

Even though ORR results seem promising and outstanding, duration of the response has not yet been totally estimated in the main studies supporting this application. Moreover, it is very likely that mechanisms of resistance are developed by the tumour, decreasing the activity of osimertinib and leading to the failure of treatment. Some of these resistances have already been described (Ann Oncol. 2015 Aug 12; Thress et al., Nature Medicine, 2015).

The subgroup analyses of ORR by demographics and disease characteristics reveal differences in ORRs between patients that possess different EGFR mutations (69.6% in patients with Exon 19 deletion versus 58.9% in patients with L858R mutation), and also between patients of Asian (70.0%) and non-Asian ethnicity (60.2%).

There are no data in patients harbouring the T790 mutation in the absence of previous exposure to TKIs. Theoretically, osimertinib is expected to be as effective in first as well as in 2nd line in the presence of T790M. From a mechanistic point of view, the expected benefit from treatment with osimertinib should not be related to previous treatment. Furthermore, dedicated studies are hardly feasible since the prevalence of the mutation in patients naïve to EGFR TKIs is estimated to be around 1%. An ongoing study will explore the efficacy of osimertinib in first line, including patients with the presence of the T790M mutation. Nevertheless, given the low prevalence of the mutation in patients not previously exposed to TKIs the evidence that will be generated is expected to be limited (osimertinib versus TKI Inhibitors as First-Line Treatment in Patients with EGFR Mutation Positive).

Risks

Unfavourable effects

According to the data from the phase II studies, the administration of osimertinib is mainly characterised by the following AEs: diarrhoea (42.3%), rash (23.8%), dry skin (23.1%) and paronychia (17.5%).

Adverse events Grade ≥3 were reported for 29.4% (121/411) patients. Of them 1.2% (5/411) were grade 4. Around 11.7% (48/411) of patients had an AE Grade ≥ 3 considered by the investigator to be possibly causally related to osimertinib. The most frequent AEs grade ≥ 3 were pneumonia, pulmonary embolism, dyspnoea and neutrophil count decreased., alanine aminotransferase increased.

In the osimertinib Phase II studies to date, most deaths were considered to be due to the underlying disease only (39 of the 52 deaths). The most common fatal AE across the clinical programme was pneumonia. In the phase II studies, Fatal AEs were reported for 3.2% (13/411) of patients, 4 of which were considered by the investigator to be possibly causally related to osimertinib (3 patients had AEs of ILD, and 1 patient had an AE of pneumonitis).

Serious adverse events (SAEs) were reported in 20.2% (83/411) patients; 5.1% (21/411) of patients had an SAE considered by the investigator to be possibly causally related to osimertinib.

Among the AEs of special interest, it should be noted the ILD/pneumonitis and the QT Interval Prolongation. The former was reported in 2.9% and was fatal in 0.3% of the 1221 patients who received osimertinib across clinical trials. Regarding the QT interval prolongation, of the 411 patients in AURAex and AURA2, one patient (less than 1%) was found to have a QTc greater than 500 msec, and 11 patients (2.7%) had an increase from baseline QTc greater than 60 msec.

Uncertainty in the knowledge about the unfavourable effects

The size of the safety database and the few data in the long run, are the most important uncertainties related to toxicity and tolerability of this drug. Again the lack of comparator hampers to contextualise the actual safety profile.

In fact, severe skin reactions, diarrhoea, ocular toxicity and hepatotoxicity have been reported for similar TKI medicinal products and although few severe cases were seen with AZD, the limitations of the safety database may well explain it. So, at the present time these are considered relevant potential safety concerns.

Relevant potential DDI interactions should be considered missing information for prescribing physician until further clinical data become available

Considering that the median age at diagnosis for NSCL is around 70 years, available data in very elderly patients (>75 years old) is limited and considered relevant missing information.

Osimertinib was shown to undergo significant metabolism mediated clearance presumably with the liver as a major site of biotransformation and hence, hepatic impairment might be expected to lead to increased exposure of osimertinib. A clinical study investigating the impact of mild and moderate hepatic impairment (as assessed by Child-Pugh criteria) on osimertinib pharmacokinetics is currently ongoing.

Unfortunately, no clear risk factors have been identified in the ongoing investigations into ILD events reported across the osimertinib program, except the general knowledge that a previous history of ILD is a significant risk factor for the development of a subsequent episode. Japanese patients experienced a higher incidence of ILD in the clinical studies with osimertinib compared to non-Japanese [the incidence of ILD was 3.5% in patients of Asian ethnicity (2.3% in Japanese patients) and 2.0% in patients of non-Asian ethnicity]. The reason for this observed difference is currently not known. Published data have noted that ILD is more common in Asia than the rest of the world, although reports are inconsistent.

As patients with clinically important cardiac abnormalities in rhythm and conduction were excluded from the AURA studies, it is not certain what effect osimertinib will have in these patients with baseline risk factors. Therefore, the careful selection and close monitoring of patients may avert the development of QT prolongation.

Effects table

Table 55:. Effects Table for [osimertinib in EGFR T790M + NSCLC)] (data cut-off: May 1st 2015…).

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
ORR (BICR)	Anti-tumour activity (CR+PR)	%	66	N/A	Pooled data from two phase II single arm open label studies / Only 2 CR	Efficacy section of ARs
DoR	Duration of the response (local evaluation)	Median (months)	8.5	N/A	Short follow-up. Data from phase I study (n=37), median DoR = 9.7 months	
PFS	Progression free survival	Median (months)	9.7	N/A	Pooled data from two phase II single arm open label studies	
Unfavourable Effects						
AEs	Adverse events regardless causality	%	97.6	N/A	Absence of comparative data. Short follow-up	Safety section of ARs
AEs grade ≥3	Adverse events grade 3-4 regardless causality	%	29.4	N/A		
SAEs	Serious AEs regardless causality	%	20.2	N/A		
Deaths	Number of deaths	Absolute value	39	N/A		
Diarrhoea	AE most commonly reported	%	42.3	N/A		
Rash	AE most commonly reported	%	23.8	N/A		
Dry skin	AE most commonly reported	%	23.1	N/A		
Paronychia	AE most commonly reported	%	17.5	N/A		
ILD	AE of special interest	%	2.7	N/A		
QT prolongation	AE of special interest	%	2.7%	N/A		

Abbreviations: AE (adverse event); AR (assessment report); BICR (blinded independent committee review); CR (complete response); DCR (disease control rate); DoR (duration of the response); ILD (Interstitial lung disease); N/A (not applicable); N/C (not yet calculable); ORR (objective response rate); PFS (progression free survival); PR (partial response)

Notes: Efficacy and safety data are taken from the pooled results from the two phase II studies (AURA extension and AURA 2). Data from the phase I study (AURA) are indicated when applicable.

Benefit-risk balance

Importance of favourable and unfavourable effects

The historical ORR obtained by chemotherapy, or TKI re-challenge, are considerably lower than those seen in the AURA studies. Even assuming that the response rate could be overestimated and in the worst-case scenario of a response rate 50 % and DoR of 6 months (lower 95%CI for AURA extension study is 54.2%). Thus, tumour responses associated to osimertinib treatment are expected to be superior to the different alternatives usually offered to patients T790M+, which is expected to be translated into benefit in terms of relevant endpoint, although of uncertain magnitude.

Despite the lack of long term data on the duration of responses, data from investigator assessment give a median of DoR of 8.5 months.

Regarding the safety profile, the majority of the AEs identified in the safety database were mostly mild (maximum AEs Grade 1– diarrhoea 35.8%, rash 21.7%, dry skin 21.4%, paronychia 12.7%) to moderate (maximum AEs Grade 2 – diarrhoea 5.1%, rash 2.2%, dry skin 1.7%, paronychia 4.9%) in severity. Grade ≥3 AEs for the PTs above were reported only for the PT of diarrhoea (1.0%), no AEs Grade 3 AEs were reported for the PTs of rash, dry skin or paronychia. The percentages of severe AEs and deaths are not deemed too high if we consider the context of the disease and the usually associated to chemotherapy. Even comparing osimertinib with other TKIs and the class-effects related to those like skin-effect, diarrhoea, upper GI inflammatory adverse events, nail and ocular effects, osimertinib appears to have an improved margin of selectivity against wild-type EGFR

Despite the limited database, available data are partially in line with the already known safety profile for this class of medicinal products and considered overall acceptable in the current context.

Benefit-risk balance

Despite the remaining uncertainties on the true magnitude of the benefit, the observed benefits are considered to outweigh the expected risks associated with osimertinib treatment in the initially claimed: “the treatment of adult patients with locally advanced or metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy”.

Furthermore, it is noted that T790M may be present in a small subset of patients not previously exposed to TKIs, i.e. first line. For these patients, neither chemotherapy nor available TKIs constitute optimal treatment alternatives. By contrary, similar rates of response as in 2nd line would be expected with osimertinib and thus, this could be a suitable treatment option for those patients with metastatic EGRF T790 mutation-positive NSCLC not previously exposed to EGFR TKIs. Therefore, benefits are considered to outweigh risks also in this small subset of patients.

Data available are not considered sufficiently comprehensive to grant a full marketing authorization however they are of sufficient relevance in the context of a life-threatening disease where an unmet medical need exists. Therefore, a conditional approval is supported subject to presentation submission of comprehensive data within reasonable timelines.

Discussion on the benefit-risk balance

A conditional approval has been applied, besides an accelerated assessment. The latter was adopted on May 2015. Regarding the former, the CHMP is of the opinion that, although comprehensive clinical data referring to

the safety and efficacy of the medicinal product have not been supplied, all the following requirements for a conditional marketing are met:

- the risk-benefit balance of the medicinal product, as defined in Article 1(28a) of Directive 2001/83/EC, is positive;

The benefit risk balance is considered positive by the CHMP. Osimertinib has shown an outstanding and very promising ORR, which appears long-lasting and thus, deemed of clinical value. This tumour response appears quite superior to that seen with any of the available treatment options in the current context, where those are limited. Despite the limitations of the evidence provided, it is noted that results have been replicated in two phase II clinical studies besides a phase I study. In addition, the antitumour effect was associated with some improvement in tumour related symptoms and is expected to translate into a gain in PFS and eventually in OS. However, it is recognised that a reliable estimation of the benefits in terms of PFS and/or survival cannot be done at the present time.
In addition to that, the tolerability of this new treatment seems to be adequate and manageable, with a frequency of AEs leading to discontinuation and dose modification of around 5.6% and 20% respectively, which is clearly lower than those reported for the chemotherapy.

- it is likely that the applicant will be in a position to provide the comprehensive clinical data;

It seems likely that the applicant can provide comprehensive clinical data from the AURA3 study, since full enrolment is projected to be completed within the third quarter (Q3) of 2015 and completion is expected in a reasonable timeframe i.e. 30 June 2017.

- unmet medical needs will be fulfilled;

There is currently an unmet medical need for more active treatments in those patients with NSCLC harbouring the T790M mutation. Osimertinib has shown promising ORR in these patients that has not been observed with currently available therapies.

- the benefit to public health of the immediate availability on the market of the medicinal product concerned outweighs the risk inherent in the fact that additional data are still required

In this context, taking into account the poor prognosis of these patients, the substantial increment in tumour responses and expected DoR over available treatment options, as well as the consistency in ORRs among the studies submitted, a benefit in terms of clinical outcomes can be reasonably expected subject to presentation of comprehensive efficacy and safety clinical data within reasonable timelines (the results from the phase III trial AURA3 will be submitted by 30 June 2017).

Thus on the basis of the above criteria being met, a conditional approval can be supported.
In conclusion, “TAGRISSO is indicated for the treatment of adult patients with locally advanced or metastatic EGRF T790 mutation-positive non-small cell lung cancer (NSCLC).”

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Tagrisso in the treatment of adult patients with locally advanced or metastatic epidermal

growth factor receptor (EGFR) T790M mutation-positive non-small-cell lung cancer (NSCLC) is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

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.

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.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of osimertinib in the treatment of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC, the applicant should submit the clinical study report of the phase III study AURA3 comparing osimertinib to platinum-based doublet chemotherapy.	30 June 2017

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that osimertinib is qualified as a new active substance.