CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208065Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology NDA Review	
NDA	208,065
Submission Type	Original NDA; 505(b)(1); New Molecular Entity
Submission Date	6/5/2015
Review Classification	Priority
PDUFA Due Date	11/15/2015
Brand Name	Tagrisso®
Generic Name	Osimertinib (AZD9291)
Proposed Indication	(b) (4) metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR TKI therapy
Formulation	40 mg and 80 mg Tablets
Dosing Regimen	80 mg daily (QD)
Related IND	117,879
Sponsor	AstraZeneca Pharmaceuticals
OCP Reviewer/TL	Jun Yang, Ph.D./Hong Zhao, Ph.D.
Pharmacometrics Reviewer/TL	Ada Zhuang, Ph.D./Yaning Wang, Ph.D.
PBPK Reviewer	Ping Zhao, Ph.D.
Genomics Reviewer/TL	Rosane Charlab Orbach, Ph.D./Michael Pacanowski, Pharm.D., M.P.H.
QT-IRT Reviewer	Ada Zhuang, Ph.D.
OCP Division	Division of Clinical Pharmacology V (DCPV)
Clinical Division	Division of Oncology Products 2 (DOP2)

EXECUTIVE SUMMARY

Clinical efficacy of oral Tagrisso 80 mg film-coated tablet once daily for treatment of patients with (b) (4) metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR Tyrosine Kinase Inhibitor (TKI) therapy was demonstrated in two ongoing single-arm, open-label Phase 2 studies, AURA extension (n = 201) and AURA2 (n = 210). The objective response rate (ORR, complete response [CR] + partial response [PR]) according to RECIST v1.1 was the major efficacy endpoint. The ORR was evaluated by a Blinded Independent Central Review Committee (BICR) and the ORR was 57.8% for AURA extension study and 64.1% for AURA2 study.

Tagrisso 80 mg once daily demonstrated acceptable tolerability and safety with relatively low rate of treatment discontinuations (3.9%), dose reductions (1.9%), and dose interruptions (13.4%). In the pooled analysis of the Phase II studies comprising 411 patients, adverse events (AEs) were reported for 96.1% of patients. A total of 19.5% AEs were grade 3 or higher. Serious Adverse Reactions (SAEs) rate was reported for 12.7% and 7 (1.7%) patients died because of adverse events. The recommended dose of Tagrisso is 80 mg once daily taken without regard to food. Administration of 20 mg osimertinib Phase 1 tablet with a high-fat breakfast showed a minimal increase in C_{max} (14%) and AUC (19%). Pre-dosing of 40 mg omeprazole tablets for 5 days had no clinically meaningful impact on the exposure of osimertinib at a single 80 mg dose. The appropriate dose of Tagrisso has not been established in patients with severe renal impairment or end-stage-renal disease. The appropriate dose of Tagrisso has not been determined in patients with moderate or severe hepatic impairment.

No exposure-response (E-R) relationship between osimertinib exposure (steady-state AUC) and efficacy (probability of response) was identified following a daily dose of 80 mg using data from studies AURA Phase 1, AURA extension, and AURA2. The probability of patient experiencing all grades of rash or diarrhea increased with exposure. However, the incidences of grade 3 or higher rash or diarrhea were less than 1%.

1.1 RECOMMENDATIONS

This NDA is acceptable from a clinical pharmacology perspective, provided that the Applicant and the Agency come to an agreement regarding the labeling language. The Office of Clinical Pharmacology recommends granting approval of this NDA.

Decision	Sufficiently Supported?	Recommendations and Comments
Evidence of Effectiveness	☒ Yes ☐ No ☐ NA	Registration trials
Proposed dose for general population	☒ Yes ☐ No ☐ NA	Both non-clinical and clinical studies demonstrated optimal activity at 80 mg daily dose. Clinical tolerability was decreased at doses of 160 mg and higher. The proposed dose has been demonstrated

		to be efficacious and safe in the proposed patient population. Please refer to the clinical reviews for safety and efficacy.
Proposed dose adjustment in specific patients or patients with comedications	☐ Yes ☒ No ☐ NA	Labeling Recommendations: Not provided. See section 1.2 for PMRs.
Pivotal bioequivalence studies	☐ Yes ☐ No ☒ NA	A formal bioequivalence trial was not performed since the to-be-marketed formulation is the same as that used in the clinical trials.
Labeling	☒ Yes ☐ No ☐ NA	

1.2 POST-MARKETING REQUIREMENTS (PMRS)

The Applicant is required to conduct the following post-marketing requirement trials:

1. Complete a pharmacokinetic study in patients [redacted] (b) (4) Tagrisso with inhibitors of CYP3A4 in accordance with the FDA draft Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations"* found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf. Submit the final study report as PMR under the NDA.

2. Complete a pharmacokinetic study in patients [redacted] (b) (4) Tagrisso with inducers of CYP3A4 in accordance with the FDA draft Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations"* found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf. Submit the final study report as PMR under the NDA.

3. Complete a pharmacokinetic study to evaluate the effect of repeated doses of Tagrisso on the pharmacokinetics of a probe substrate of CYP3A4 [redacted] (b) (4) in accordance with the FDA draft Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations"* found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf. Submit the final study report as PMR under the NDA.

4. Complete a pharmacokinetic study to evaluate the effect of repeated doses of Tagrisso on the pharmacokinetics of a probe substrate of BCRP [redacted] (b) (4)

[redacted] (b) (4) in accordance with the FDA draft Guidance for Industry entitled "*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations"* found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf. Submit the final study report as PMR under the NDA.

5. Conduct a pharmacokinetic trial to determine the appropriate dose of Tagrisso in patients with hepatic impairment in accordance with the FDA Guidance for Industry entitled "Pharmacokinetics in Patients with Impaired Hepatic Function: Study Design, Data Analysis, and Impact on Dosing and Labeling" found at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072123.pdf. Submit the final study report as PMR under the NDA.

ADDITIONAL COMMENTS

The applicant is requested to submit the final study reports of the following studies to the IND:

[redacted] (b) (4)

[redacted] (b) (4)

Signatures:

Jun Yang, Ph.D. Clinical Pharmacology Reviewer Division of Clinical Pharmacology V	Hong Zhao, Ph.D. Team Leader Division of Clinical Pharmacology V
Ada Zhuang, Ph.D. Pharmacometrics Reviewer Division of Pharmacometrics	Yaning Wang, Ph. D. Pharmacometrics Team Leader Division of Pharmacometrics
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Vikram Sinha, Ph.D. Director, Division of Pharmacometrics	NAM Atiqur Rahman, Ph.D. Director, Division of Clinical Pharmacology V

Cc: DOP2: CSO – **I Fan**; MTL – **G Blumenthal**; MO – **S Khozin;**
DCP5: Reviewers – **J Yang**; PM reviewers: **A Zhuang**; TL – **H Zhao**; PMTL – **Y Wang;** GG reviewers: **R C Orbach;** GGTL: **M A Pacanowski;**
Division Deputy Director – **B Booth**; Division Director - **A Rahman**

A combination of abbreviated Office of Clinical Pharmacology (OCP) Briefing and pre-midcycle meeting was held on August 28, 2015.

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Registration Trial: Clinical efficacy of oral Tagrisso 80 mg once daily (QD) for patients with [redacted] (b) (4) metastatic EGFR T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy was demonstrated in two ongoing single-arm, open-label Phase 2 studies, AURA extension (n = 201) and AURA2 (n = 210). The major efficacy endpoint, objective response rate (ORR, complete response [CR]+partial response [PR]) according to RECIST v1.1 as evaluated by a Blinded Independent Central Review Committee (BICR), was 57.8% and 64.1%, for AURA extension and AURA2 Studies, respectively.

In the pooled analysis of the Phase II studies comprising 411 patients who received Tagrisso 80 mg QD, adverse events (AEs) were reported for 96.1% of patients. A total of 19.5% AEs were CTCAE grade 3 or higher. Severe AEs were reported for 12.7% and fatal AEs were reported for 1.7% of patients. Dose interruptions, dose reductions and treatment discontinuations with Tagrisso 80 mg due to AEs were reported for 13.4%, 1.9%, and 3.9% of patients, respectively; the mean and median relative dose intensity (RDI) was 98.1% and 100.0%, respectively.

Pharmacokinetics (PK): The pharmacokinetics (PK) of osimertinib have been characterized following single dosing in healthy volunteers and in patients with advanced NSCLC following single and multiple dosing. The PK properties of osimertinib were dose and time independent across the 20-240 mg dose range. The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (C_{max}) of osimertinib increased dose proportionally over 20 to 240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) and exhibited linear PK. Administration of Tagrisso QD resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. The ratio of C_{max} to C_{min} (minimal concentration) was 1.6 at steady-state.

Absorption: In cancer patients, the median time to C_{max} (T_{max}) of osimertinib was 6 (range: 3-24) hours. The C_{max} and AUC of osimertinib increased by 14% and 19%, respectively, following administration of a 20 mg Phase 1 tablets with a high-fat, high-calorie meal (containing approximately 58 grams of fat and 1000 calories) compared to fasting conditions. [redacted] (b) (4) . No bioequivalence (BE) studies were conducted because the commercial film-coated tablet formulation was used in the Phase 2 registration trials.

Distribution: The mean volume of distribution at steady-state (Vss/F) of osimertinib was 986 L. Plasma protein binding could not be measured due to instability. However, the plasma protein binding of osimertinib is likely high based on its physicochemical properties.

Metabolism: The main metabolic pathways of osimertinib were oxidation (predominantly CYP3A) and dealkylation in vitro. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after oral osimertinib dosing. AZ7550 showed a similar potency to osimertinib, while AZ5104 showed greater against the exon 19 deletion and

T790M mutants (approximately 8-fold) and wild-type (approximately 15-fold) EGFR. The geometric mean exposure (AUC) of each metabolites was approximately 10% of the exposure of osimertinib at steady-state.

Elimination and Excretion: In a mass balance study after administration of single 20 mg oral solution dose of [^{14}C]-osimertinib, 67.8% and 14.2% of radioactivities were recovered in feces and urine over 84 days, respectively. Unchanged osimertinib accounted for approximately 2% of the elimination. Osimertinib plasma concentrations decreased with time and a population estimated mean half-life was 48 hours and oral CL/F was 14.2 (L/h).

Drug-Drug Interaction: Osimertinib is predominantly metabolized via CYP3A. Drug interaction studies have not been conducted with Tagrisso. In the absence of any clinical drug-drug interactions (DDI) data, predictions using applicant's PBPK model cannot be used to generate Tagrisso dose recommendations in the presence of CYP3A modulators. The following dosage recommendations are based on that osimertinib is a CYP3A substrate in vitro. Avoid concurrent administration of strong CYP3A inhibitors with TAGRISSO. If no other alternative exists, the patient should be closely monitored for signs of toxicity. Avoid strong CYP3A inducers if possible because concomitant use may decrease osimertinib plasma concentrations.

In vitro data indicate that osimertinib is likely to be a perpetrator of DDI through inhibition of CYP3A and breast cancer resistance protein (BCRP) transporter and induction of CYP3A4, CYP2C, P-glycoprotein (P-gp) and CYP1A2 enzymes. Based on in vitro studies, osimertinib is a substrate of P-gp and BCRP and is not a substrate of OATP1B1 and OATP1B3 in vitro. Osimertinib is a competitive inhibitor of CYP 3A, but not CYP2C8, 1A2, 2A6, 2B6, 2C9, 2D6 and 2E1 in vitro. Osimertinib induced CYP3A4 (Pregnane X dependent) and CYP1A2 enzymes. Osimertinib is an inhibitor of BCRP and does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2 in vitro.

Gastric Acid Reducing Agents: The exposure of osimertinib was not affected by concurrent administration of a single 80 mg Tagrisso dose following 40 mg omeprazole administration for 5 days.

PK in Specific Populations:

Renal Impairment: No dedicated clinical study has been conducted to evaluate the effect of renal impairment on the PK of osimertinib. Based on population PK (PopPK) analysis, no dose adjustment is recommended in patients with mild [creatinine clearance (CLcr) 60 - 89 mL/min], and moderate (CLcr 30- 59 mL/min) renal impairment. As patients with CLcr less than 15 mL/min or end-stage-renal disease with or without hemodialysis were not included in the clinical trials, the appropriate dose of Tagrisso has not been established in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage-renal disease.

Hepatic Impairment: No dedicated clinical study has been conducted to evaluate the effect of hepatic impairment on the PK of osimertinib. Based on PopPK analysis, no dose adjustment is recommended in patients with mild hepatic impairment (NCI organ dysfunction working group criteria: total bilirubin < upper limit of normal [ULN] and Aspartate aminotransferase [AST]

between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5 x ULN and any AST). The appropriate dose of Tagrisso has not been determined in patients with moderate (Child Pugh B) or severe (Child Pugh C) hepatic impairment. A clinical study to evaluate the impact of mild and moderate hepatic impairment on osimertinib exposure is ongoing and the final study report will be submitted under the post-marketing requirement (PMR).

No dose adjustment for age, sex, body weight, race or smoking status is recommended based on the results of a PopPK analysis.

Exposure-Response (E-R) Relationship: Logistic regression model was used to access the relationship between osimertinib exposure (AUCss) and efficacy/safety endpoints using data from the patient studies AURA Phase 1, AURA extension, and AURA2. There was no evidence of a relationship between exposure and probability of response in EGFR T790M mutation positive patients with advanced NSCLC who have progressed on or after EGFR TKI therapy. The probability of patient experiencing rash and diarrhea (all grades) increased with osimertinib exposure. However, the incidence of experiencing grade 3 or higher rash or diarrhea was less than 1%. The relationship between ASZ9291 exposure and occurrence of interstitial lung disease (ILD) or ILD-like events was inconclusive.

QT/QTc: A large change in QTc (i.e., >20 ms) was not detected in AURA2 following single dose or multiple doses of osimertinib. Significant QT prolongation at steady-state was observed with the maximum mean change from baseline (with the upper bound of the two-sided 90% CI) in QTcF of 16.2 (17.6) ms. A pharmacokinetic/pharmacodynamic (PK/PD) analysis suggested a concentration-dependent QTc interval prolongation at 80 mg of 14 ms with an upper bound of 16 ms (90% CI).

Conclusion: Overall, the clinical pharmacology information presented in this NDA application is acceptable. Below are the ongoing studies with planned submission dates.

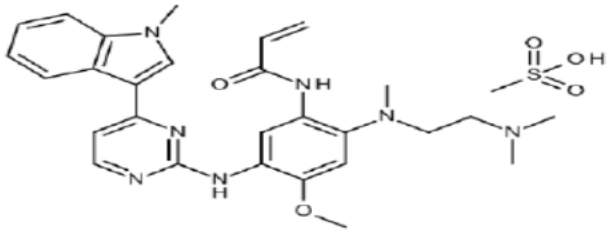
Study/Data Update	**Final CSR available**
DDI - Effect of CYP3A4 Inhibitor (Study D5160C00012)	Dec 2015
DDI - Effect of CYP3A4 Inducer (Study D5160C00013)	Jan 2016
DDI - Effect of CYP3A4 Substrate (Study D5160C00014)	Feb 2016
DDI - Effect of BCRP Substrate (Study D5160C00019)	Feb 2016
Hepatic Impairment (Study D5160C00008)	Aug 2016
[redacted] (b) (4)	
Fed/Fasted Study (Study D5160C00009)	Dec 2015

QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTITES

2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they related to clinical pharmacology and biopharmaceutics review?

Osimertinib (AZD9291) mesylate (Molecular formula; $C_{28}H_{33}N_7O_2 \bullet CH_4O_3S$) (b) (4) (b) (4) with molecular weight of (b) (4) (mesylate). (b) (4) (free base). The proposed commercial formulation of osimertinib has been developed as an 80 mg oval, biconvex, beige film-coated tablets and a 40 mg round, biconvex, beige film-coated tablets (referred to as the film-coated tablet), for oral administration containing 95.4 mg or 47.7 mg of osimertinib mesylate, respectively.



The solubility of osimertinib mesylate was measured in various media and the data presented in Table 1.

Table 1. Osimertinib mesylate solubility in various media (37°C, 24 hours)

Medium	Solution pH [a]	Solubility, as AZD9291 (mg/mL) [b, c]	Descriptive term
pH 1.2 HCl/KCl	1.24	>3	Slightly soluble
pH 4.5 acetate buffer	4.60	>11	Sparingly soluble
pH 6.8 phosphate buffer	6.73	>5	Slightly soluble
pH 7.0 phosphate buffer	7.00	0.60	Very slightly soluble
pH 7.25 phosphate buffer	7.25	0.26	Very slightly soluble
pH 7.5 phosphate buffer	7.49	0.07	Practically insoluble
FaSSIF (pH 6.5)	6.47	>5	Slightly soluble
Water	NT	3.1	Slightly soluble
Ethanol (99.5%)	NT	0.9	Very slightly soluble
Diluent [d]	NT	111	Freely soluble
DMSO	NT	18.9	Sparingly soluble
(b) (4)			

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Osimertinib is a kinase inhibitor that is an irreversible inhibitor of epidermal growth factor receptors harboring sensitizing-mutations (EGFRm; exon 19 deletion and L858R) or resistance T790M mutations (T790M).

The proposed indication is for the treatment of patients with (b) (4) metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR Tyrosine Kinase Inhibitor (TKI) therapy.

2.1.3 What are the proposed dosage and route of administration?

The recommended dose of Tagrisso is 80 mg orally taken once daily (QD) with or without food.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical trials used to support dosing or claims?

Efficacy evidence to support the claim in the proposed indication is based on a total of 411 patients enrolled in 2 ongoing single-arm Phase 2 studies, AURA extension (n = 201) and AURA2 (n = 210). The primary efficacy objective of both studies was the objective response rate (ORR) in the evaluable-for-response population (N = 397) based on blinded independent central review (BICR) of imaging data, using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1). Secondary efficacy objectives included disease control rate (DCR), duration of response (DoR), time to first documentation of objective response, best change from baseline in size of target lesion (TL; i.e., tumor shrinkage), progression-free survival (PFS), overall survival (OS), and health-related quality of life (HRQoL) through patient reported outcomes (PRO).

The majority of pharmacokinetics (PK) data has been generated in the advanced NSCLC patients with extensive single dose PK data being obtained in the escalation phase of AURA Phase 1 study. Multiple dose PK data were obtained from the safety and efficacy studies (AURA Phase 1, AURA extension, and AURA2) in which the collection of PK was mandatory in all patients. PK data in Western and Asian (including Japanese) subjects have been collected throughout development. Key features of studies are summarized below.

- D5160C00001 (AURA Phase 1): Phase 1 component (dose-escalation and dose expansion) of Study D5160C00001conducted in patients with advanced EGFRm NSCLC.

- D5160C00001 (AURA extension): Phase 2 component of Study D5160C00001 (AURA) conducted in pre-treated patients with advanced EGFR T790M mutation-positive NSCLC who progressed following either one prior therapy with an EGFR-TKI agent or treatment with both EGFR-TKI and at least one other prior line of therapy.

- D5160C00002 (AURA2): Phase 2 study conducted in pre-treated patients with advanced EGFR T790M mutation-positive NSCLC who progressed following either 1 prior therapy with an EGFR-TKI agent or treatment with at least 1 EGFR TKI and 1 regimen of platinum-based doublet chemotherapy.

2.2.2 What is the basis for selecting the clinical endpoint or surrogate and how are they used to assess efficacy in the pivotal clinical study? What is the clinical outcome in terms of efficacy and safety?

Primary Efficacy Endpoint: Clinical efficacy and safety of oral Tagrisso (80 mg) QD treatment for patients with locally advanced or metastatic EGFR T790M mutation-positive non- NSCLC who have progressed on or after EGFR TKI therapy was demonstrated in two ongoing single-arm, open-label Phase 2 studies, AURA extension and AURA2.. The major efficacy endpoint, ORR (CR+PR) according to RECIST v1.1 as evaluated by BICR, was 58% and 64%, for AURA extension and AURA2 Studies, respectively (Table 2).

Table 2. Key efficacy results in AURA extension and AURA2, in patients with T790M mutation-positive NSCLC who received osimertinib

Efficacy Parameter	**AURA Extension (n=199)**	**AURA 2 (n=198)**	**Overall (n=397)**
ORR by BICR% (95% CI)	58% (51%, 65%)	64% (57%, 71%)	61% (56 %, 66%)
CR n (%)	0 (0%)	2 (1%)	2 (0.5%)
PR n (%)	115 (58%)	125 (63%)	240 (61%)

Safety:
Osimertinib 80 mg QD has demonstrated acceptable tolerability and safety with respect to treatment discontinuations, dose reductions, or dose interruptions. In the pooled analysis of the Phase II studies comprising 411 patients who received Tagrisso 80 mg QD, adverse events (AEs) were reported for 96.1% of patients. A total of 19.5% AEs were CTCAE grade 3 or higher. Severe AEs were reported for 12.7% and fatal AEs were reported for 1.7% of patients. Dose interruptions, dose reductions and treatment discontinuations with Tagrisso 80 mg due to AEs were reported for 13.4%, 1.9%, and 3.9% of patients, respectively; the mean and median relative dose intensity (RDI) was 98.1% and 100.0%, respectively.

The most commonly reported EGFR-associated AEs (by MedDRA preferred term) were diarrhea (37.7%), rash (23.4%), dry skin (20.0%) and paronychia (15.6%); these AEs were mostly mild (maximum CTCAE Grade 1 – diarrhea 34.3%, rash 21.2%, dry skin 19.0%, paronychia 11.9%) to moderate (maximum CTCAE Grade 2 – diarrhea 2.7%, rash 2.2%, dry skin 1.0%, paronychia 3.6%) in severity. CTCAE Grade ≥3 AEs for the preferred term above were reported to be less than 1%.

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately

identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. Osimertinib and its active metabolites, AZ5104 and AZ7550, are the main circulating moieties in human blood. The performance of the bioanalytical methods is reviewed in Section 2.6.

2.2.4 Exposure-response (E-R)

2.2.4.1 Is the dose adjustment necessary based on any intrinsic factors (e.g., body weight, sex, race, and renal/hepatic function)?

No. Although body weight was a significant covariate on osimertinib and its metabolite AZ5104 CL/F and osimertinib Vc/F, a 20-30% difference in osimertinib AUCss and a 40-50% difference for AZ5104 AUCss from the AUCss for the median body weight of 62 kg would be expected across a body weight range of 43-90 kg. For all ethnic classes, as a significant covariate of AZ5104 CL/F, a 10-23% lower in AZ5104 AUCss than that in white patients would be expected. None of the effect of covariates was considered clinical relevant. The creatinine clearance was not a significant covariate and the AUCss of osimertinib was similar among patients with normal renal function and mild/moderate renal impairment. There were only 3 patients with severe renal impairment enrolled in the clinical trials, providing inadequate information for dose adjustment. Alanine aminotransferase (ALT) levels (4-277 U/L) were considered not clinical relevant and other makers of liver function such as Aspartate aminotransferase (AST) (6-258 U/L) was not significant covariate. However, no dedicated clinical study has been conducted to evaluate the effect of hepatic impairment on the PK of osimertinib. Based on available data, the fixed dose approach appears appropriate for osimertinib. Dose adjustment is not necessary based on body weight, sex or race. The effects of (b) (4) and hepatic impairment on the osimertinib systemic exposure are required to be further evaluated in dedicated clinical studies. See Pharmacometrics review in Appendix for more information.

2.2.4.2 Dose the exposure-response relationship for efficacy support the proposed dose of 80 mg once daily?

Yes. There was no evidence of a relationship between exposure and probability of response in EGFR T790M mutation positive patients with advanced NSCLC who have progressed on or after EGFR TKI therapy across the dose range of 20 to 240 mg. In dose finding study (AURA I), the 80 mg dose provides substantial clinical efficacy as demonstrated across Phase 1 and Phase 2 studies by higher objective response rate (ORR) as shown in Table 3. Doses of 160 mg and higher appear unlikely to provide any additional efficacy benefit. Similar conclusion could be drawn for other efficacy endpoints including duration of response (DoR) and tumor shrinkage. In addition, although 40 mg dose also provided relatively high ORR (Table 3), some patients would have similar exposure to the 20 mg dose group, which is the lowest studied dose showing clinical activity. There would be limited dose reduction space for dose of 40 mg. Therefore, the exposure-response relationship for efficacy supports the proposed dose of 80 mg once daily in EGFR mutation positive advanced NSCLC patients. See Pharmacometrics review attached to this review for more information.

Table 3. Observed response rates in AURA Phase I study*

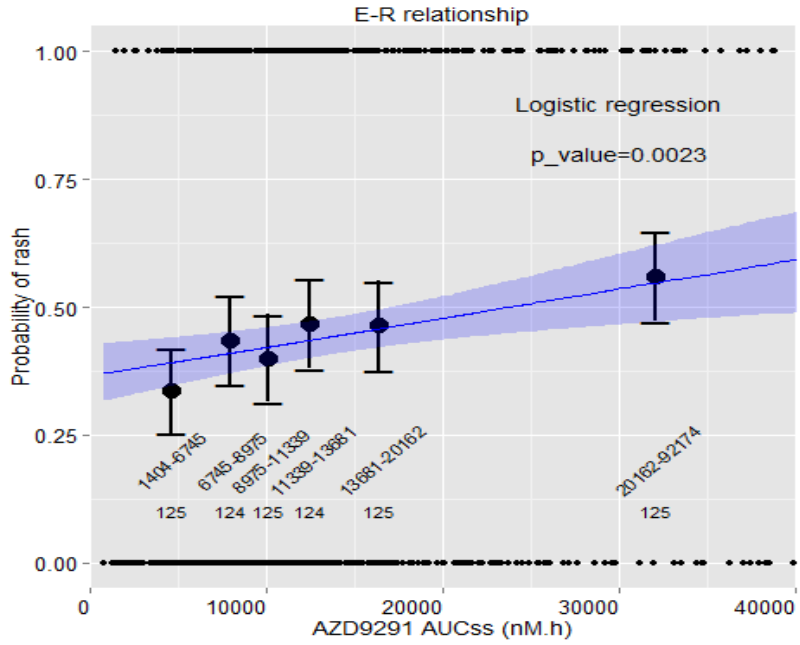
Dose (mg)	AUCss 95% quantile (nM·h)	n/N	Observed rate (95% CI)
20	1061-4985	5/10	50% (19-81)
40	2185-12663	19/32	59% (41-76)
80	4451-23086	40/61	66% (52-77)
160	10132-46690	21/41	51% (35-67)
240	12250-75267	7/13	54% (25-81)

**Only include the patients who were EGFR T790M mutation-positive by central testing and evaluable for response by investigator assessment*
Source: Applicant's dose justification report, Page 10, Table 1

2.2.4.3 Dose the exposure-response relationship for safety support the proposed dose of 80 mg once daily?

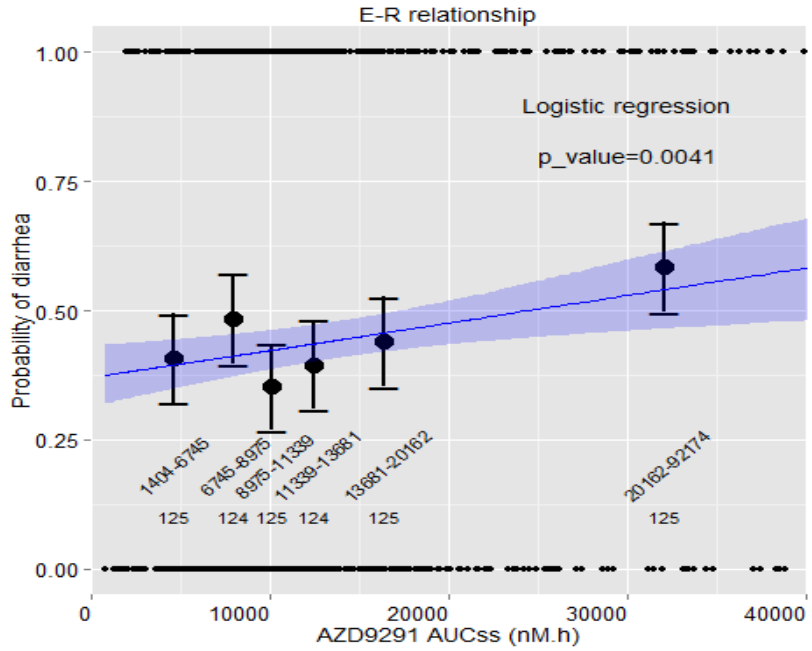
Yes. There was a significant relationship between exposure and probability of rash or diarrhea as shown in Figure 1 and 2. An increase in the incidence of skin disorders, nail effects and diarrhea were observed at doses higher than 80 mg. A substantive increase in dose reductions due to adverse events (AEs) was observed at dose of 160 mg or higher compared to 80 mg. It is worth noticing that the safety events in the exposure-response relationship analysis included all grade rash and diarrhea with low incidence of Grad 3 and 4 AEs. The exposure-response analysis for safety supports the proposed dose of 80 mg once daily in EGFR mutation positive advanced NSCLC patients.

Figure 1. E-R relationship between osimertinib AUCss and probability of rash



Source: Review's independent analysis

Figure 2. E-R relationship between osimertinib AUCss and probability of diarrhea



Source: Review's independent analysis

See Pharmacometrics review attached to this review for more information.

2.2.4.4 Does this drug prolong the QT or QTc interval?

A large change in QTc (i.e., >20 ms) was not detected in AURA2 trial following single dose or multiple doses of osimertinib. Significant QT prolongation at steady-state was observed with the maximum mean change from baseline (with the upper bound of the two-sided 90% CI) in QTcF of 16.2 (17.6) ms. A pharmacokinetic/pharmacodynamic (PK/PD) analysis suggested a concentration-dependent QTc interval prolongation at 80 mg of 14 ms with an upper bound of 16 ms (90% CI). Overall summary of findings is presented in Table 4.

Table 4: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for osimertinib 80 mg (FDA Analysis)

Treatment	Day	Time (hour)	ΔQTcF (ms)	90% CI (ms)
AZD9291 80 mg	Cycle 1 Day 1 (Single Dose)	2	2.1	(0.8, 3.3)
AZD9291 80 mg	Cycle 3 Day 1	0	16.2	(14.8, 17.6)

See QT-IRT review for more information.

2.2.5 *Pharmacokinetic (PK) characteristics of the drug and its major metabolites*

2.2.5.1 *What are the PK characteristics of the drug?*

The PK of osimertinib have been characterized following single dose administration in healthy volunteers and in patients with advanced NSCLC following single and multiple dose administration. Healthy volunteers showed higher apparent clearance (CL/F) and an approximately 35% lower osimertinib exposure (AUC_{ss}) compared to NSCLC patients. The PK properties of osimertinib were dose and time independent across the 20-240 mg dose range. The AUC and C_{max} of AXD9291 increased dose proportionally over 20 to 240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) and exhibited linear PK. Administration of Tagrisso QD resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. The ratio of C_{max} to C_{min} (minimal concentration) was 1.6 at steady-state.

Absorption and Distribution: In cancer patients, the median time to C_{max} (T_{max}) of osimertinib was 6 (range: 3-24) hours. The C_{max} and AUC of osimertinib increased by 14% and 19%, respectively, following administration of a 20 mg osimertinib Phase 1 tablet with a high-fat, high-calorie meal (containing approximately 58 grams of fat and 1000 calories) compared to fasting conditions. (b) (4) No bioequivalence (BE) studies have been conducted because the commercial film-coated tablet formulation was used in the Phase 2 registration trials. The mean volume of distribution at steady-state (Vss/F) of osimertinib was 986 L. Plasma protein binding could not be measured due to instability (See detail under QBR 2.6.2). However, the plasma protein binding of osimertinib is likely high based on its physicochemical properties.

Metabolism and Elimination: The main metabolic pathways of osimertinib were oxidation (predominantly CYP3A) and dealkylation in vitro. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after oral Tagrisso dosing. AZ7550 showed a similar potency to osimertinib, while AZ5104 showed greater potency against the exon 19 deletion and T790M mutants (approximately 8-fold) and wild-type (approximately 15-fold) EGFR. The geometric mean exposure (AUC) of both AZ5104 and AZ7550 was approximately 10% each of the exposure of osimertinib at steady-state. Based on a population PK analysis, the estimated mean half-life of osimertinib was 48 hours and oral CL/F was 14.2 (L/h).

In a mass balance study after administration of single 20 mg oral solution dose of [^{14}C]-osimertinib, 67.8% and 14.2% of radioactivities were recovered in feces and urine over 84 days, respectively. Unchanged osimertinib accounted for approximately 2% of the elimination.

2.2.5.2 *Does the mass balance trial suggest renal or hepatic as the major route of elimination?*

The mass balance trial suggests that hepatic elimination is the major route for osimertinib clearance. See QBR 2.2.5.1.

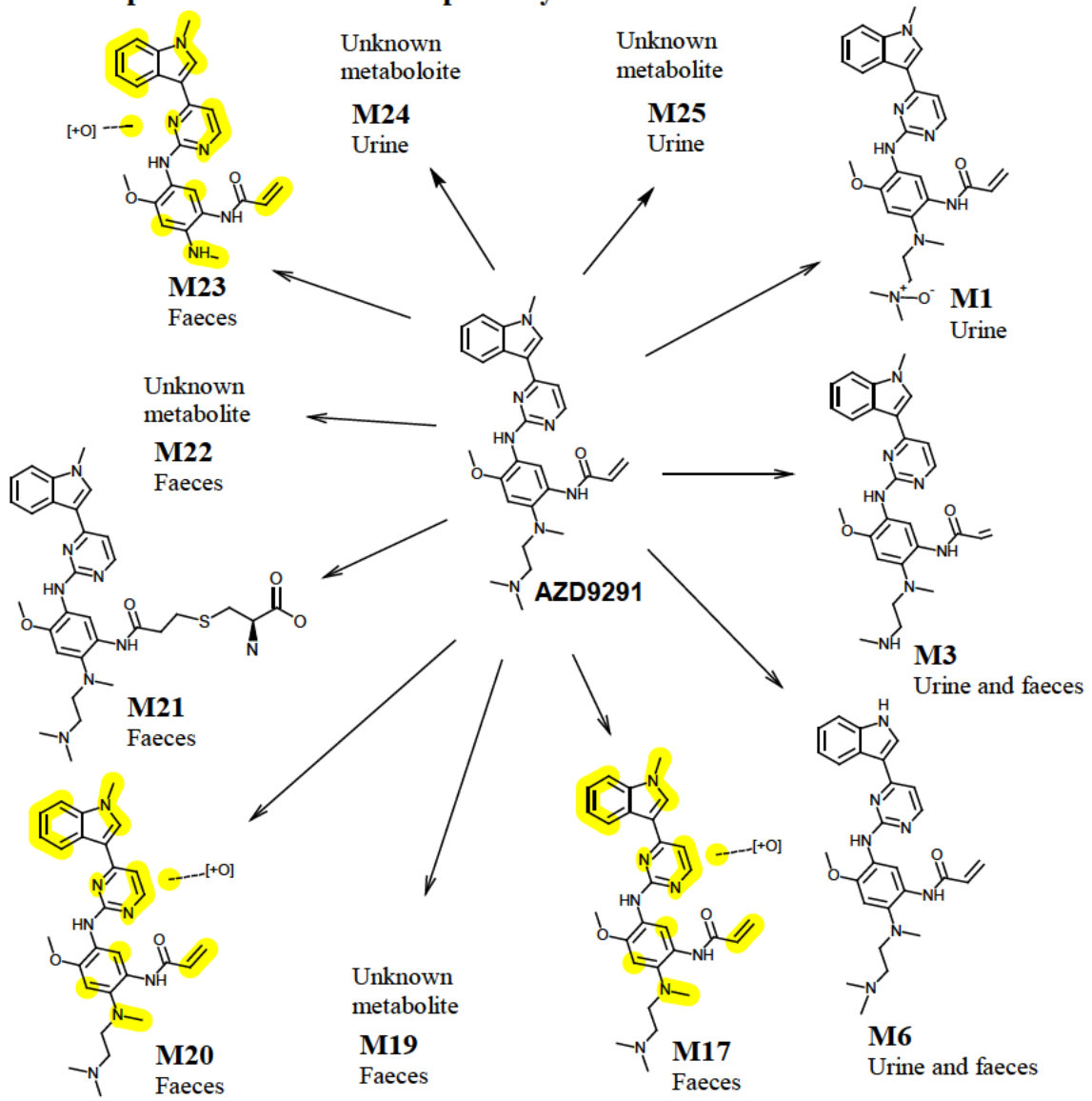
2.2.5.3 *What are the characteristics of drug metabolism?*

The main metabolic pathway of osimertinib was oxidation (predominantly CYP3A) and dealkylation in vitro. The in vivo metabolic profile in plasma at steady state after the 80 mg dose was determined by HPLC-UV-MSn analysis of plasma samples from the AURA Phase 1 study.

Additionally, the human metabolic fate was determined by HPLC-MSn analysis of samples of plasma, urine and feces collected from the mass balance study.

Majority of the radioactivity eliminated in urine was an unknown early eluting peak in the LC-AMS analysis (M25) with osimertinib, AZ5104 and AZ7550 accounting for a mean (± SD) of 0.8% (± 0.3%), 0.4% (± 0.2%) and 0.5% (± 0.2%) of the radiochemical dose, respectively in human urine during the collection interval. At least 12 components were observed in the pooled urine and fecal samples with 5 components accounting for >1% of the dose. The major components were unchanged osimertinib, AZ5104 and AZ7550, accounting 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. The proposed human metabolic pathway for osimertinib is shown in Figure 3.

Figure 3. Proposed human metabolic pathways for osimertinib in human excreta.



2.2.5.4 What is the degree for linearity or non-linearity based on dose-concentration relationship?

Dose proportionality assessments of $AUC_{(0\text{-}72h)}$ and C_{max} in cancer patients after single-dose and multiple dose administration of 20 mg to 240 mg of osimertinib was conducted using a power model. The slope from the power model was 1.00 for $AUC_{(0\text{-}72h)}$ and 1.05 for C_{max} after a single dose; and was 1.03 for AUC_{ss} and 1.01 for $C_{ss,max}$ after multiple doses indicating that the PK of osimertinib is dose proportional (Tables 5 & 6).

Table 5. Statistical analysis of dose proportionality for single dosing (Cycle 0) of osimertinib in AURA Phase I

PK Parameter	Slope Parameter	90% Confidence Interval
C_{max} (nM))	1.05	0.84, 1.26
$AUC_{0\text{-}72}$ (nM*h)	1.00	0.80, 1.21

Table 6. Statistical analysis of dose proportionality for multiple dosing (Cycle 2, Day 1) of osimertinib in AURA Phase 1

PK Parameter	Slope Parameters	90% Confidence Interval
$C_{ss,max}$ (nM)	1.01	0.93, 1.09
AUC_{ss} (nM*h)	1.03	0.94, 1.11

Comparison of PK parameters from the healthy volunteer studies indicates that the exposures (AUC and C_{max}) increased dose proportionally from 20 to 80 mg (Table 7).

Table 7. Comparison of osimertinib PK parameters in healthy volunteer studies

Parameters	Study 5	Study 5	Study 11	Study 10
Formulation	Capsule	Phase 1 tablet	Solution	Film-coated tablet
Dose (mg)	20	20	20	80
N	16	16	8	47
T_{max} [a] (h)	6 (6-10)	6 (4-10)	6 (6-8.12)	6 (3-12)
C_{max} [b] (nM)	31.6 (42.9)	31.6 (27.8)	29.9 (21.5)	126.1 (31.0)
$AUC_{(0\text{-}72)}$ [b] (nM*h)	1060 (47.0)	1060 (24.0)	1010 (27.5)	4106 (32.3)
AUC[b] (nM*h)	1520 (50.5)	1580 (32.6)	1590 (36.2)	6269 (37.0)
$t_{1/2}$ [c] (h)	52.6 (± 11.2)	59.7 (± 15.6)	61.2 (± 10.8)	64.0 (± 7.3)
CL/F [c] (L/h)	29.9 (± 18.3)	26.7 (± 10.0)	26.7 (± 10.6)	27.3 (± 10.5)
V_z/F [c] (L)[b]	2170 (± 1230)	2230 (± 526)	2260 (± 618)	2495 (± 936)

a Median (min-max shown)
b Geometric mean (GCV%) shown
c Mean (±SD) shown

2.2.5.5 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

Following administration on Cycle 1, Day 1, C_{max} and $AUC_{0-\tau}$ estimates exhibited moderate to high variability, with inter-subject variability (%CV) ranged from 36% to 78%. On Cycle 2, Day 1, C_{max} and $AUC_{0-\tau}$ estimates exhibited variability ranging from 19% to 54 %. The population estimated mean $C_{ss,max}$ and AUC_{ss} at 80 mg dose in NSCLC patients is 501 nM and 11258 nM*h, respectively.

2.3 INTRINSIC FACTORS

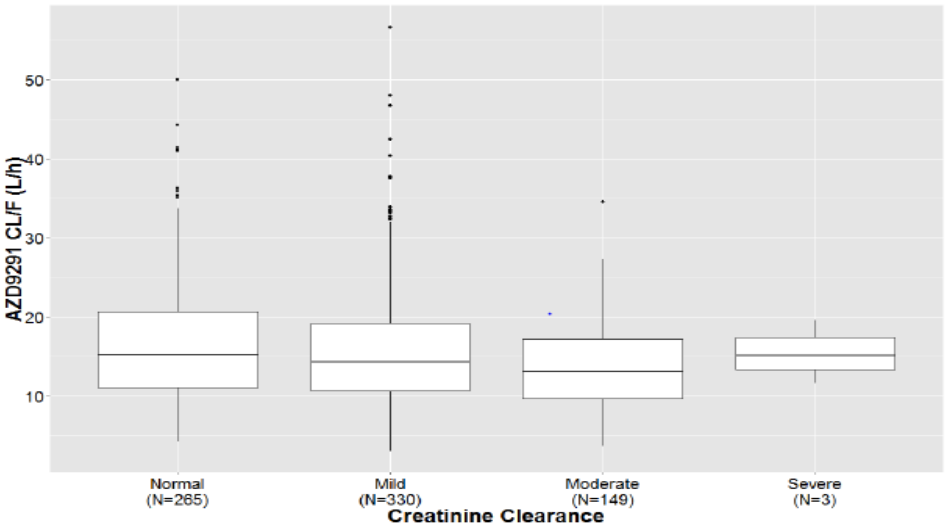
2.3.1 What intrinsic factors (age, gender, race, weight, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No dose adjustment for age, sex, body weight, race or smoking status is recommended based on the results of a population PK analysis. See attached Pharmacometrics review for more information.

2.3.2 Renal Impairment

The impact of renal impairment on the PK of osimertinib was assessed in the population PK analysis. Figure 4 shows a boxplot of osimertinib AUC_{ss} by varying degrees of renal impairment. Based on a population PK analysis of 330 patients with mild renal impairment (CLcr 60 to 89 mL/min), 149 patients with moderate renal impairment (CLcr 30 to 59 mL/min), 3 patients with severe renal impairment (CLcr <30 mL/min) and 295 patients with normal renal function (≥ 90 mL/min), osimertinib apparent clearance were similar among the four groups. As patients with CLcr less than 15 mL/min or end-stage-renal disease with or without hemodialysis were not included in the clinical trials, the appropriate dose of Tagrisso has not been established in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage-renal disease.

Figure 4. Box plot of osimertinib apparent clearance (CL/F) versus baseline creatinine clearance in patients



Normal ≥ 90 mL/min; mild 60-89 mL/min; moderate 30-59 mL/min; severe 15-29 mL/min

2.3.3 Hepatic Impairment

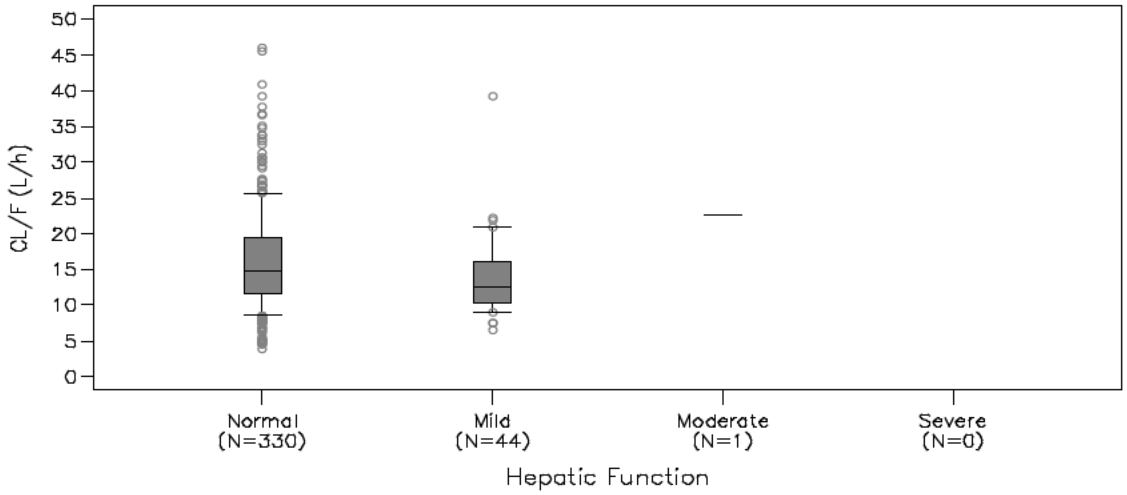
In AURA Phase 1, AURA extension and AURA2 Studies, patients were excluded if they had:

- ALT> 2.5 x the upper limit of normal (ULN) if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
- AST > 2.5 x ULN if no demonstrable liver metastases or > 5 times ULN in the presence of liver metastases
- Total bilirubin > 1.5 x ULN if no liver metastases or > 3 x ULN in the presence of documented Gilbert's Syndrome (unconjugated hyperbilirubinaemia) or liver metastases

Based on the population PK analysis, markers of hepatic function (baseline AST, ALT, bilirubin levels) did not have a clinically important impact on PK of osimertinib and were not included in the final population PK model. In a PK analysis of patients from AURA2 and AURA extension, where the criteria for hepatic dysfunction as defined by National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria for hepatic dysfunction was applied, mild hepatic impairment had no impact on the apparent clearance of osimertinib (Figure 5). This was based on an analysis of 44 patients with mild hepatic impairment (total bilirubin < ULN and AST between 1 to 1.5x ULN or total bilirubin between 1.0 to 1.5 times ULN and any AST), and 1 patient with moderate hepatic impairment (total bilirubin between 1.5x to 3.0x ULN and any AST) and 330 patients with normal hepatic function (total bilirubin $\leq$ ULN and AST $\leq$ ULN), osimertinib apparent clearance were similar among the three groups. No dose adjustment is necessary for mild hepatic impairment. Dose recommendation cannot be made for patients with moderate or severely impaired hepatic function due to lack of data.

Figure 5. Osimertinib clearance as a function of hepatic dysfunction as defined by NCI-ODWG criteria in Phase II studies (based on NCA analysis)

Study Code: D5160C00001 Phase II Extension and D5160C00002 (Pooled)
Box plot of steady state apparent clearance and hepatic impairment based on NCI classification
(PK analysis set)



Horizontal line: median, box Q1–Q3
Whiskers extend to the 10th and 90th percentiles
Program: S:\D9291\FILEST\MT\MT004AL Executed: 2015–05–13 at 17:38 Data Extraction Date: 09JAN2015

A clinical study investigating the impact of mild to moderate hepatic impairment (as assessed by Child-Pugh criteria) on osimertinib PK is currently ongoing and the final study report will be submitted under the post-marketing requirement (PMR).

2.3.4 Genetics

The clinical efficacy of osimertinib, as assessed by ORR, is based on data from two Phase 2 studies, AURA extension and AURA2, and on supportive data from Phase 1, in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. Consistent with early Phase 1 results, significant objective response rates were observed in the Phase 2 studies, therefore supporting the use of T790M mutation-positive status to define the responder population in the EGFR TKI resistance setting. No relevant differences in ORR were observed as a function of primary EGFR mutations (exon 19 deletions, L858R), prior EGFR TKI history or TKI timing, or race (Asian or non-Asian), although a trend appeared to favor Asian (vs. non-Asian) and patients with tumors positive for EGFR exon 19 deletions (vs. L858R). This trend suggests that the type of baseline EGFR mutation and race (Asian vs. non-Asian) may contribute to differential sensitivity to osimertinib. In contrast, pre-treated EGFR T790M mutation-negative NSCLC patients appeared to derive less benefit, and the marginal activity observed in Phase 1 may be driven by patients who did not have an EGFR TKI as the most recent therapy prior to study entry. In addition to the proposed population, first-line patients with locally advanced or metastatic NSCLC, the majority (76.7%) with T790M-negative tumors, appeared to derive benefit from osimertinib based on Phase 1 data, regardless of the presence or absence of a T790M mutation in the tumor. The impact of a T790M mutation-selective inhibitor on tumor evolution in treatment- naive patients with T790M-negative tumors is not clear. Limited data are available in first-line with T790M-positive NSCLC patients, who are less likely to benefit from available EGFR TKIs, to draw conclusions. The

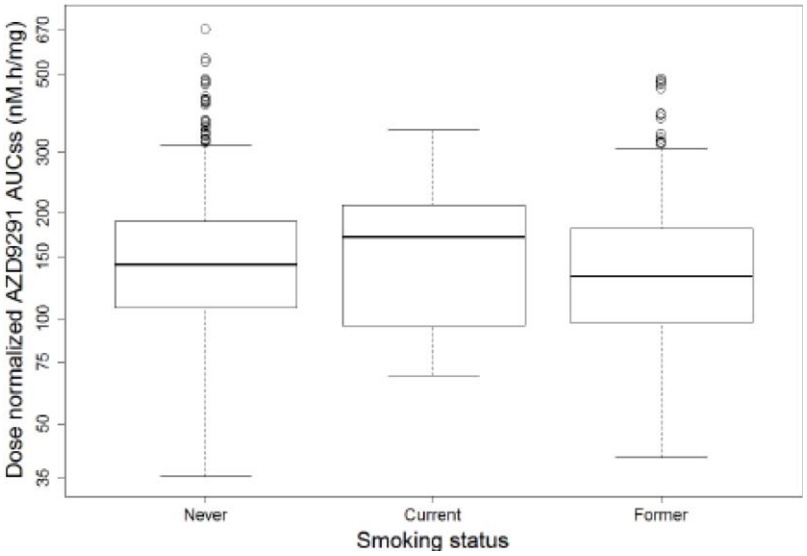
clinical results are in agreement with non-clinical osimertinib activity against TKI-sensitizing and the T790M mutated forms of EGFR.

2.4 EXTRINSIC FACTORS

1.1.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or –response and what is the impact of any differences in exposure on response?

Smoking Status: The population PK analysis of 778 patients did not identify smoking status (current smokers =3%, former smokers = 30%, never smokers = 67%) having a significant impact on osimertinib PK. Figure 6 shows box plot of a dose normalized osimertinib AUCss as a function of smoking status. The analysis results suggest that CYP1A2 (which is induced by smoking) is not a major enzyme involved in the metabolism of osimertinib.

Figure 6. Box plot of dose normalized patient Osimertinib AUCss versus smoking status



Gastric pH modifiers: osimertinib C_{max} and AUC were 2% and 7% higher when osimertinib 80 mg film-coated tablet was administered to healthy volunteers with prior dosing of 40 mg omeprazole tablets for 5 days to elevate the gastric pH (Table 8).

Table 8. Statistical comparisons of PK parameters with and without omeprazole dosing at 80 mg osimertinib film-coated tablet formulation

Analyte	PK parameter	N	AZD9291 + omeprazole Geometric LS Mean	AZD9291 alone Geometric LS Mean[a]	AZD9291/AZD9291 +omeprazole %ratio (90 % Confidence Interval)
AZD9291	AUC (nM*h)	53	6690	6273	106.7 (100.3, 113.5)
	AUC_{0-72} (nM*h)	54	4404	4105	107.3 (100.3, 114.8)
	C_{max} (nM)	57	127.8	125.8	101.7 (94.7, 109.2)

[a] N=47

1.1.2 Drug-drug interactions

In vivo drug interaction studies have not been conducted with Tagrisso.

3.4.2.1 Is there an in vitro basis to suspect in-vivo drug-drug interactions?

Osimertinib as a victim of DDI: There is a potential DDI when co-administration of Tagrisso with inhibitors or inducers of CYP3A. The *in vitro* metabolic fate of osimertinib in hepatocytes and isolated recombinant CYP enzymes has demonstrated that metabolic clearance appears to be mainly dependent on CYP 3A4 and 3A5. 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). In reversible inhibition assays, osimertinib had limited inhibitory effect against CYP 3A4, 2C8 and 1A2 (Table 9).

Table 9. Interpretation of CYP inhibition data

Parameter	Potential DDI if value greater than	1A2	2C8	3A4/5 (Nf)
IC_{50}	NA	>25.7	22.8	5.1
K_i[a]	NA	>12.8	11.4	2.55
R	10	NA	NA	251
R_1	11	NA	NA	251
R_h	1.1	1.06	1.07	1.30
R_{infree}	1.25	1.09	1.10	1.45
R_{imax}	0.02	<0.006	0.007	0.030

NA – not applicable, [a] – Ki = IC_{50}/2 as probe substrates at K_m, R = $[I_2]/K_i$, R_1 = 1+$[I_2]/K_i$, R_h = 1+$[I]/K_i$, R_{infree} = 1+ $[I_{in\ free}]/K_i$, R_{imax} = [unbound C_{max}]/K_i,

Based on in vitro studies, osimertinib and its two active metabolites, AZ5104 and AZ7550 are substrates of P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) and are not a substrate of OATP1B1 and OATP1B3.

Osimertinib as a perpetrator of DDI: In vitro, osimertinib is a competitive inhibitor of CYP3A, but not CYP2C8, 1A2, 2A6, 2B6, 2C9, 2D6 and 2E1 at clinical concentrations. Osimertinib is an inhibitor of BCRP and does not inhibit P-gp, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2 in vitro (Table 10). Osimertinib is likely to be a perpetrator of DDI through inhibition of CYP3A and BCRP transporter and induction of CYP3A4 (Pregnane X dependent), and CYP1A2 enzymes.

Table 10. Interpretation of osimertinib transporter inhibition data

Transporter	IC_{50} (= K_i) (µM)	R	$R_{in\ free}$ [a]	$R_{in\ free}$ [b]	R_{imax}	Potential for DDI
Potential DDI if value greater than	NA	10	1.25	0.04	0.1 (FDA 2012) 0.02 (EMA 2012)	NA
P-gp	No inhibition	ND	NA	NA	ND	Unlikely
BCRP	2.0	320	NA	NA	0.039	Yes (intestinal)
OATP1B1	22.0	NA	1.05	0.05	NA	Unlikely
OATP1B3	52.5	NA	1.02	0.02	NA	Unlikely
OCT2	7.98	NA	NA	NA	0.0097	Unlikely
MATE1	4.63	NA	NA	NA	0.017	Unlikely
MATE2K	23.0	NA	NA	NA	0.003	Unlikely
OAT1	No inhibition	NA	NA	NA	ND	Unlikely
OAT3	No inhibition	NA	NA	NA	ND	Unlikely

NA – not applicable, ND – not determined, $R = [I_2]/K_i$, [a] $R_{in\ free} = 1 + [I_{in\ free}]/Ki$, [b] $R_{in\ free} = [I_{in\ free}]/Ki$, $R_{imax} = [\text{unbound } C_{max}]/K_i$.

3.4.2.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro data indicate that osimertinib is likely to be a perpetrator of DDI through inhibition of CYP3A and induction of CYP3A4, and CYP1A2 enzymes.

3.4.2.3 Is the drug a substrate of and/or an inhibitor of P-glycoprotein transport processes?

Based on in vitro studies, osimertinib and its two active metabolites, AZ5104 and AZ7550 are substrates of P-gp and BCRP and are not a substrate of OATP1B1 and OATP1B3 in vitro.

3.4.2.4 Are there any other metabolic/transporter pathways that may be important?

Other CYPs may be involved to a minor extent and direct conjugation was detected with glutathione and cysteineglycine in human hepatocyte incubations.

3.4.2.5 Dose the label specify co-administration of another drug and if so, has the interaction potential between these drugs been evaluated?

No co-administration of other drugs is specified in the label since Tagrisso is used as monotherapy for the proposed indication.

3.4.2.6 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administrated?

In vivo drug interaction studies have not been conducted with Tagrisso. See Appendix for the Physiological-based Pharmacokinetic (PBPK) Modeling Review for more information.

2.5 *GENERAL BIOPHARMACEUTICS*

1.2.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

The Applicant considered osimertinib tablet as BCS class (b) (4) drug based on the solubility data (See QBR 2.1.1, Table 1) and the physiological properties of osimertinib (e.g., calculated LogP = 4.8).

1.2.2 What moieties should be assessed in bioequivalence studies?

Osimertinib is the primary active moiety and AZ5104 may also contribute to efficacy and safety due to its greater potency against the exon 19 deletion and T790M mutants (approximately 8-fold) and wild-type (approximately 15-fold) EGFR. No BE study was conducted during osimertinib development as the to-be-marketed film-coated tablet formulation was used in the registration trials.

1.2.3 What is the composition of the to-be-marketed formulation?

The components and compositions of osimertinib tablets are shown in Table 11.

Table 11. Qualitative and quantitative composition of osimertinib film-coated tablets

Components	Quantity (mg per unit)		Function	Standard
	40 mg	80 mg		
Tablet core				
AZD9291 mesylate[a]	47.7	95.4	Active	AstraZeneca
Mannitol	(b) (4)			NF
Microcrystalline cellulose				NF
Low-substituted hydroxypropyl cellulose				NF
Sodium stearyl fumarate				NF
Nominal core tablet weight				
Tablet coating[b, c]				
Polyvinyl alcohol				USP
Titanium dioxide				USP
(b) (4) 3350				NF
Talc				USP
Yellow ferric oxide				NF
Red ferric oxide				NF
Black ferric oxide				NF
(b) (4)				USP

[a] (b) (4)

[b] The tablet coating ingredients listed may be included as a propriety composite, eg. (b) (4)

[c] (b) (4)

1.2.4 What is the absolute bioavailability of this drug?

(b) (4)

[redacted]

1.2.5 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trial?

The to-be-marketed film-coated tablet formulation was used in the Phase 2 registration studies, no BE studies are required.

1.2.6 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The recommended dose of Tagrisso is 80 mg QD without regard to food. osimertinib AUC and C_{max} increased approximately 19% and 14%, respectively, following administration of osimertinib 20 mg Phase 1 tablet to healthy volunteers with a high-fat meal (800 to 1000 calories) compared to fasted conditions (Table 12). Food had no effect on the AUC and C_{max} of AZ5104 (an active metabolite of osimertinib), compared to fasted conditions. (b) (4)

[redacted]

Table 12. Statistical comparison of PK parameters between fed and fasted conditions at 20 mg osimertinib Phase 1 tablet formulation

Analyte	PK parameter	N	Fasted Geometric LS Mean	Fed Geometric LS Mean[a]	Fed /Fasted ratio (90 % Confidence Interval)
AZD9291	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

2.6 *ANALYTICAL SECTION*

1.3.1 Was the active moiety identified and measured in the clinical trial?

Yes. osimertinib and two other pharmacologically active metabolites, AZ5104 and AZ7550 were measured in the clinical trials.

1.3.2 For all moieties measured, is free, bound or total measured? What is the basis for that decision, if any, and is it appropriate?

Total plasma concentration was measured in the studies included in this NDA submission. The plasma protein binding of osimertinib has not yet been determined due to plasma instability.

According to the applicant, osimertinib is [redacted] (b) (4) (calculated LogP = [redacted] (b) (4) and is expected to be highly bound to human plasma protein (99% bound).

The stability studies of osimertinib at between 0.1 and 100 μM across multiple species after incubation (6 hours) at 37°C indicated that osimertinib was not stable in mouse, rat and human plasma or HSA, but was stable in dog plasma and in human α1-acid glycoprotein solution (AGP) at 0.1, 1 and 100 μM (Table 13). Further investigation of osimertinib stability in human plasma at 1 μM and 37°C was undertaken with inhibitors (sodium fluoride, phenylmethylsulfonyl fluoride, ethylenediaminetetraacetic acid), none of which markedly improved the percentage osimertinib remaining at the end of the incubation.

Table 13. Mean (n = 3) osimertinib remaining after incubation at 37°C for 6h in mouse, rat, dog and human plasma, human serum albumin (HSA) solution and human α1-acid glycoprotein solution (AGP)

AZD9291 concentration (μM)	% AZD9291 remaining after 6h					
	Mouse	Rat	Dog	Human	HSA	AGP
0.1	15	36	90	< 1	11	101
1	25	43	88	< 0.1	11	108
10	43	34	83	< 0.1	9.7	105
100	30	32	98	0.09	14	104

In vitro plasma bindings of osimertinib and its active metabolites, AZ5104 and AZ7550, for untreated male mice (CD-1 strain), male rats (Han Wistar), female rabbits (New Zealand White strain), male dogs (Beagle), male guinea pigs (Dunkin Hartley) and male humans and in HSA and AGP solutions over an original target concentration range 0.1, 1, 10 and 100 μM were determined by ultrafiltration. The sponsor states that non-specific binding of each compound in the ultrafiltrate restricted the protein binding experiment to a single 100 μM concentration.

1.3.3 What bioanalytical procedures are method were used to determine drug concentrations? Are they acceptable for this NDA?

Bioanalytical methods for the determination of osimertinib and its metabolites AZ7550 and AZ5104 in human EDTA plasma were developed and validated at [redacted] (b) (4)

For all methods, calibration, quality control (QC) and clinical study samples (40 μL) were spiked with ($^{13}C,^{2}H3$) osimertinib as an internal standard, processed by either protein precipitation or dilution and then simultaneously assayed for osimertinib, AZ7550 and AZ5104 using reversed-phase high performance liquid chromatography (RP-HPLC) with Turbo Ion Spray® tandem mass spectrometric (MS/MS) detection. During validation of all the assays, no analytically significant interferences from endogenous matrix components were observed at the retention times of each analyte in the matrix samples screened. All analytes were found to demonstrate acceptable stability in all matrices for up to four cycles of freeze/thaw (at nominal -

20 and -80°C). Validation accuracy and precision summary data and additional stability data, are presented in Table 14 below.

Table 14. Validation accuracy and precision summary data and additional stability data for bioanalytical methods for osimertinib, AZ7550 and AZ5104 in human biological samples.

	Method HB-12-128	Method HB-13-050	Method HB-14-001	Method HB-14-002	Method HB-13-081
Between-run accuracy (%)	AZD9291=97.6–105.0 AZ7550=101.5–108.4 AZ5104=99.2-103.2	AZD9291=97.1–101.7 AZ7550=99.7–106.1 AZ5104=96.2–100.6	AZD9291=95.6-102 AZ7550=98.0-105 AZ5104=94.7–106	AZD9291=93.6-100 AZ7550=96.7–111 AZ5104=95.6–101	AZD9291=99.5-110 AZ7550=97.1-109 AZ5104=99.5-103
Between-run precision (%)	AZD9291=3.0–6.8 AZ7550=3.3–11.0 AZ5104=4.5–6.9	AZD9291=2.1–6.7 AZ7550=2.7–7.9 AZ5104=2.4–6.0	AZD9291=2.0–11.5 AZ7550=2.2-7.8 AZ5104=5.2–9.5	AZD9291=2.1–7.1 AZ7550=2.9–9.7 AZ5104=1.6–5.6	AZD9291=4.8–9.0 AZ7550=5.4–9.0 AZ5104=5.5–8.0
Within-run accuracy (%)	AZD9291=96.0–108.0 AZ7550=100.0–119.6 AZ5104=97.8–109.6	AZD9291=95.0–104.4 AZ7550=98.3–106.8 AZ5104=95.6–103.2	AZD9291=94.4-106 AZ7550=94.7-112 AZ5104=88.0–109	AZD9291=90.4-101 AZ7550=96.1-117 AZ5104=92.8–101	AZD9291=93.3-114 AZ7550=91.9-113 AZ5104=97.0-106
Within-run precision (%)	AZD9291=1.5–10.7 AZ7550=2.4–10.3 AZ5104=2.5–6.1	AZD9291=1.1–6.9 AZ7550=1.4–10.5 AZ5104 =1.8–9.0	AZD9291=0.9–12.8 AZ7550=1.8–7.6 AZ5104=1.7–11.3	AZD9291=1.4–8.2 AZ7550=2.3–12.5 AZ5104=1.0–6.1	AZD9291=2.9–9.8 AZ7550=3.8–10.8 AZ5104=2.0–12.2
a Stability in whole blood, acceptable up to:	2 hours	2 hours	N/A	N/A	N/A
Stability at room temperature acceptable up to:	6 hours	24 hours	24 hours	24 hours	24 hours
*Long term stability acceptable up to:	62 days	39 days	62 days	99 days	95 days

[a] at 37°C left to cool at room temperature & on wet ice

N/A = Not applicable

* Ongoing plasma stability experiment data, part of the validation but not yet reported, demonstrate stability within acceptable limits for AZD9291 and AZ5104 for up to 400 days storage at a nominal -80°C. For AZ7550, stability within acceptable limits has so far been demonstrated for concentrations > 100 ng/ml for up to 169 days at a nominal -80°C..

DETAILED LABELING RECOMMENDATIONS

FDA recommended clinical pharmacology labeling modifications on the Applicant proposed labeling are presented below. The modifications made by the Agency are in BLUE.

FULL PRESCRIBING INFORMATION

Proposed Labeling	Agency Suggestion
7. DRUG INTERACTION (b) (4)	7. DRUG INTERACTION Drug interaction studies have not been conducted with TAGRISSO.

7.1 Effect of Other Drugs on Osimertinib

Strong CYP3A Inhibitors

(b) (4)

Strong CYP3A Inducers

(b) (4)

7.2 Effect of Osimertinib on Other Drugs

Agents whose plasma concentrations may be increased by concomitant treatment with TRADENAME

(b) (4)

(b) (4)

7.1 Effect of Other Drugs on Osimertinib

Strong CYP3A Inhibitors

Avoid concomitant administration of TAGRISSO with strong CYP3A inhibitors, including macrolide antibiotics (e.g., telithromycin), antifungals (e.g., itraconazole), antivirals (e.g., ritonavir) and nefazodone, as concomitant use of CYP3A inhibitors with osimertinib may increase osimertinib plasma concentrations. If no other alternative exists, monitor patients more closely for adverse reactions of TAGRISSO [see Dosage and Administrations (2.4)].

Strong CYP3A Inducers

Avoid concomitant administration of TAGRISSO with strong CYP3A inducers (e.g., phenytoin, rifampicin, carbamazepine, St. John's Wort) as CYP3A inducers may decrease osimertinib plasma concentrations.

7.2 Effect of Osimertinib on Other Drugs

Avoid concomitant administration of TAGRISSO with drugs that are sensitive substrates of CYP3A, BCRP, or CYP1A2 with narrow therapeutic indices, including but not limited to fentanyl, cyclosporine, quinidine, ergot alkaloids phenytoin, rifampicin, carbamazepine, as osimertinib may increase or decrease plasma concentrations of these drugs.

[redacted] (b) (4)	
8. USE IN SPECIFIC POPULATION	
8.6 Renal Impairment No clinical study has been conducted to [redacted] (b) (4) evaluate the effect of renal impairment on the pharmacokinetics of [redacted] (b) (4) Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild [redacted] (b) (4) [redacted] (b) (4) [redacted] *[see Clinical Pharmacology (12.3)]*. *8.7 Hepatic Impairment* No clinical studies have been conducted to [redacted] (b) (4) evaluate the effect of hepatic impairment on the pharmacokinetics of [redacted] (b) (4) Based on population pharmacokinetic (PK) analysis, no dose adjustment is recommended in patients with mild hepatic impairment. [redacted] (b) (4) [redacted] *[see Clinical Pharmacology (12.3)]*.	***8.6 Renal Impairment*** No dedicated clinical study has been conducted to evaluate the effect of renal impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild [creatinine clearance (CLcr) 60 - 89 mL/min], and moderate (CLcr 30- 59 mL/min) renal impairment [redacted] (b) (4) there is no recommended dose for TAGRISSO for patients with severe renal impairment (CLcr < 30 mL/min) or end-stage-renal disease *[see Clinical Pharmacology (12.3)]*. ***8.7 Hepatic Impairment*** No dedicated clinical study has been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of osimertinib. Based on population pharmacokinetic (PK) analysis, no dose adjustment is recommended in patients with mild hepatic impairment [NCI organ dysfunction working group (NCI-ODWG)]. There is no recommended dose for TAGRISSO for patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.
12. CLINICAL PHARMACOLOGY	
12.2 Pharmacodynamics *Cardiac Electrophysiology* The QT interval prolongation potential of TRADENAME was assessed in 210 patients who received [redacted] (b) (4) 80 mg daily in Study 2. [redacted] (b) (4) (b) (4)	***12.2 Pharmacodynamics*** *Cardiac Electrophysiology* The QT interval prolongation potential of TAGRISSO was assessed in 210 patients who received TAGRISSO 80 mg daily in Study 2. A central tendency analysis of the QTcF data at steady-state demonstrated that the maximum mean change from baseline was 16.2 (upper bound of two-sided 90% CI: 17.6) msec. A pharmacokinetic/pharmacodynamic analysis with osimertinib suggested a concentration-dependent QTc interval prolongation at TAGRISSO 80 mg of 14 msec with an upper bound of 16 msec (90% CI).
12.3 Pharmacokinetics ***Absorption*** [redacted] (b) (4)	***12.3 Pharmacokinetics*** The area under the plasma concentration-time curve (AUC) and maximal plasma concentration (C_{max}) of osimertinib increased dose proportionally over 20 to

(b) (4)

Distribution

(b) (4)

(b) (4)

plasma protein binding is likely to be high.

Elimination

(b) (4)

Metabolism

(b) (4)

The main metabolic pathway of (b) (4) was oxidation and dealkylation.

(b) (4)

(b) (4)

240 mg dose range (i.e., 0.25 to 3 times the recommended dosage) after oral administration and exhibited linear pharmacokinetics (PK). Administration of TAGRISSO orally once daily resulted in approximately 3-fold accumulation with steady state exposures achieved after 15 days of dosing. At steady state, the Cmax to Cmin (minimal concentration) ratio was 1.6-fold.

Absorption

(b) (4), the median time to C_{max} of osimertinib was 6 hours (range 3-24 hours). Following administration of a 20 mg TAGRISSO tablets with a high-fat, high-calorie meal (containing approximately 58 grams of fat and 1000 calories), the Cmax and AUC of osimertinib increased by 14% and 19% respectively, compared to fasting conditions.

Distribution

The mean volume of distribution at steady-state (V_{ss}/F) of osimertinib was 986 L. Plasma protein binding of osimertinib is likely high based on its physiochemical properties.

Elimination

Osimertinib plasma concentrations decreased with time and a population estimated mean half-life of osimertinib was 48 hours, and oral clearance (CL/F) was 14.2 (L/h).

Metabolism

The main metabolic pathways of osimertinib were oxidation (predominantly CYP3A) and dealkylation in vitro. Two pharmacologically active metabolites (AZ7550 and AZ5104) have been identified in the plasma after TAGRISSO oral administration. The geometric mean exposure (AUC) of each metabolite (AZ5104 and AZ7550) was approximately 10% of the exposure of osimertinib at steady-state.

Excretion

Osimertinib is primarily eliminated in the feces (68%) and to a lesser extent in the urine (14%). Unchanged osimertinib accounted for approximately 2% of the elimination.

Specific Populations

No clinically significant differences in the pharmacokinetics of osimertinib were observed based on age, sex, ethnicity, body weight, smoking status, mild (CLcr 60-89 mL/min) and moderate (CLcr 30-59 mL/min) renal impairment, and mild hepatic impairment. (b) (4)

(b) (4)

Excretion

(b) (4)

Unchanged (b) (4) accounted for approximately 2% of the elimination (b) (4)

Special populations

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Drug Interactions

***Effect of Other Drugs on* TAGRISSO:**

Strong CYP3A Inhibitor: Clinical studies evaluating TAGRISSO in the presence of strong CYP3A inhibitors have not been conducted *[see Drug Interactions (7.1)]*.

Strong CYP3A Inducers: Clinical studies evaluating TAGRISSO in the presence of strong CYP3A inducers have not been conducted *[see Drug Interactions (7.1)]*.

Gastric Acid Reducing Agents: The exposure of osimertinib was not affected by concurrent administration of a single 80 mg TAGRISSO tablet following 40 mg omeprazole administration for 5 days.

Effect of Osimertinib on Other Drugs:

CYP450 Metabolic Pathways: Osimertinib is a competitive inhibitor of CYP3A, but not CYP2C8, 1A2, 2A6, 2B6, 2C9, 2D6 and 2E1 in vitro. Osimertinib induced CYP3A4 (Pregnane X dependent) and CYP1A2 enzymes.

(b) (4) ***Transporter Systems:*** Based on in vitro studies, osimertinib is a substrate of P-glycoprotein and breast cancer resistant protein (BCRP) and is not a substrate of OATP1B1 and OATP1B3 in vitro.

(b) (4) Osimertinib is an inhibitor of BCRP and does not inhibit P-glycoprotein, OAT1, OAT3, OATP1B1, OATP1B3, MATE1, MATE2K and OCT2 in vitro.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

concentrations.

(b) (4)

APPENDIX 1: PHARMACOMETRICS REVIEW

Pharmacometric review

1. Summary of findings

The population pharmacokinetic (PPK) model developed by the Applicant is capable of characterizing the pharmacokinetics of osimertinib (osimertinib) based on dataset consisting of 1 clinical trial (Study 5) in healthy volunteer and 3 clinical trials (AURA I, AURA extension, and AURA2) in epidermal growth factor receptor (EGFR) mutation positive advanced non-small cell lung carcinoma/cancer (NSCLC) patients.

The structural model that best described the pharmacokinetics of osimertinib was first order absorption followed by 2 compartments for osimertinib and its metabolite, AZ5104, respectively. Patient population (vs. healthy subjects), body weight, serum albumin, and Asian ethnicity population effects (vs. white subjects) were significant covariates.

Logistic regression model was used to access the relationship between drug exposure (AUCss) and efficacy/safety endpoints using data from the patient studies AURA I, AURA extension, and AUR2. There was no evidence of a relationship between exposure and probability of response in EGFR T790M mutation positive patients with (b) (4) NSCLC who have progressed on or after EGFR TKI therapy. The probability of patient experiencing rash and diarrhea increased with exposure. The relationship between ASZ9291 exposure and occurrence of interstitial lung disease (ILD) or ILD-like events was inconclusive.

1.1 Key Review Questions

The purpose of this review is to address the following key questions:

1.1.1 Is the dose adjustment necessary based on any intrinsic factors (e.g., body weight, sex, race, and renal/hepatic function)?

No. Although body weight was a significant covariate on osimertinib and its metabolite AZ5104 CL/F and osimertinib Vc/F, a 20-30% difference in osimertinib AUCss and a 40-50% difference for AZ5104 AUCss from the AUCss for the median body weight of 62 kg would be expected across a body weight range of 43-90 kg. For all ethnic classes, as a significant covariate of AZ5104 CL/F, 10-23% lower in AZ5104 AUCss than that in white patients would be expected. None of the effect of covariates was considered clinical relevant. The creatinine clearance was not a significant covariate, the AUCss of osimertinib was similar among patients with normal renal function and mild/moderate renal impairment. There were only 3 patients with severe renal impairment enrolled in the clinical trials, providing inadequate information for dose adjustment. ALT levels (4-277 U/L) were considered not clinical relevant and other makers of liver function such as AST (6-258 U/L) was not significant covariate. However, no dedicated clinical study has been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of osimertinib. Based on available data, the fixed dose approach appears appropriate for osimertinib. Dose adjustment is not necessary based on body weight, sex, and race. The effects of (b) (4) /hepatic impairment are required to be further evaluated in dedicated clinical studies.

1.1.2 Does the exposure-response relationship for efficacy support the proposed dose of 80 mg once daily?

Yes. There was no evidence of a relationship between exposure and probability of response in EGFR T790M mutation positive patients with (b) (4) NSCLC who have progressed on or after EGFR TKI therapy across the dose range of 20 to 240 mg. In dose finding study (AURA I), the 80 mg dose provides substantial clinical efficacy as demonstrated across Phase 1 and Phase 2 studies by higher objective response rate (ORR) as shown in Table 3. Doses of 160 mg and higher appear unlikely to provide any additional efficacy benefit. Similar conclusion could be drawn for other efficacy endpoints including duration of response (DoR) and tumor shrinkage. In addition, although 40 mg dose also provided relatively high ORR (Table 3), some patients would have similar exposure to the 20 mg dose group, which is the lowest studied dose showing clinical activity. There

would be limited dose reduction space for dose of 40 mg. Therefore, the exposure-response relationship for efficacy supports the proposed dose of 80 mg once daily in EGFR mutation positive (b) (4) NSCLC patients.

Table 1 Observed response rates in AURA Phase I study*

Dose (mg)	AUCss 95% quantile (nM·h)	n/N	Observed rate (95% CI)
20	1061-4985	5/10	50% (19-81)
40	2185-12663	19/32	59% (41-76)
80	4451-23086	40/61	66% (52-77)
160	10132-46690	21/41	51% (35-67)
240	12250-75267	7/13	54% (25-81)

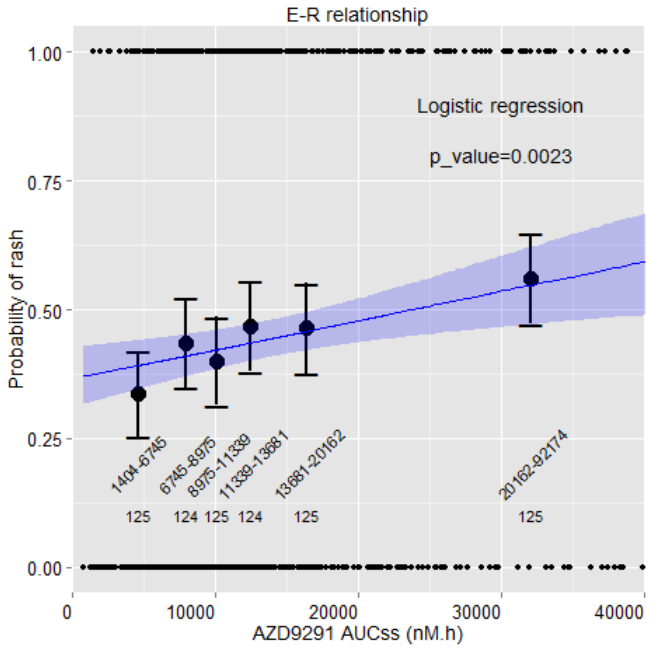
*Only include the patients who were EGFR T790M mutation-positive by central testing and evaluable for response by investigator assessment

Source: Applicant's dose justification report, Page 10, Table 1

1.1.3 Does the exposure-response relationship for safety support the proposed dose of 80 mg once daily?

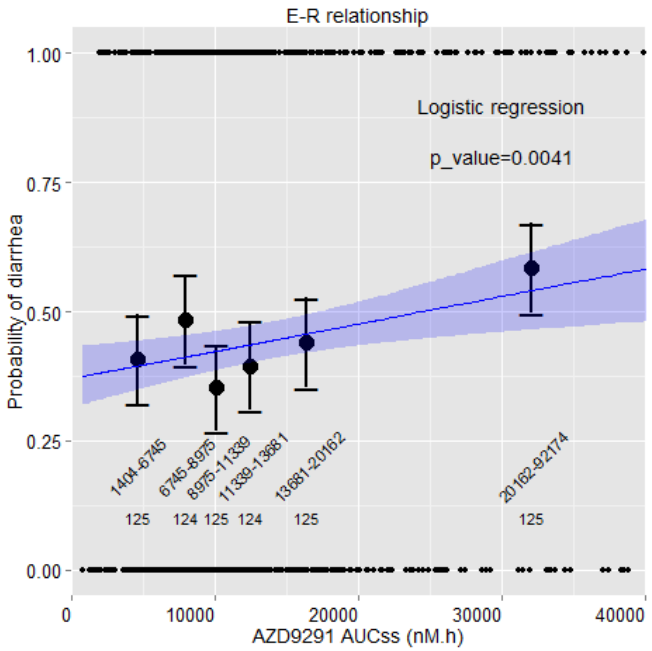
Yes. There was a significant relationship between exposure and probability of rash or diarrhea as shown in Figure 1 and 2. An increase in the incidence of skin disorders, nail effects and diarrhea were observed at doses higher than 80 mg. A substantive increase in dose reductions due to adverse events (AEs) was observed at dose of 160 mg or higher compared to 80 mg. It is worth noticing that the safety events in the exposure-response relationship analysis included all grade rash and diarrhea with low incidence of Grad 3 and 4 AEs. The exposure-response analysis for safety supports the proposed dose of 80 mg once daily in EGFR mutation positive (b) (4) NSCLC patients.

Figure 1 Exposure-response relationship between osimertinib AUCss and probability of rash



Source: Review's independent analysis

Figure 2 Exposure-response relationship between osimertinib AUCss and probability of diarrhea



Source: Review's independent analysis

1.2 Recommendations

The Division of Pharmacometrics (Office of Clinical Pharmacology) has reviewed this application and recommends approval of 80 mg osimertinib administered once daily. The reviewer agrees with the Applicant's conclusion from the population PK analysis that no dose adjustments are necessary for osimertinib based on body weight, sex, race in adult patients. The effects of hepatic (b) (4) impairment need to be further evaluated. The exposure-response relationship for efficacy and safety support the proposed dose of 80 mg once daily in EGFR mutation positive (b) (4) NSCLC patients.

2. Pertinent regulatory background

NSCLC represents approximately 80 to 90% of all lung cancer, which has been one of the most common cancers in the world for several decades. Currently, there are limited options available for patients with metastatic NSCLC who have progressed on or after a currently approved EGFR TKI. In a high proportion (approximately 60%) of patients, the EGFR T790M mutation has been identified as the major mechanism of resistance to EGFR TKI therapy. There are no approved therapies that effectively address this mechanism of acquired resistance. Applicant is seeking a market approval for the use of osimertinib tablets (80 mg once daily) for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.

3. Results of Applicant's analysis

The pharmacometric analyses in this review cover the Applicant's population PK analysis and exposure-response analysis for efficacy and safety.

3.1 Population PK analysis

3.1.1 Objectives

- To characterize the PPK of osimertinib in healthy subjects and patients with NSCLC

- To identify and quantify covariate effects which describe inter-subject variability for selected PK parameters
- To obtain individual exposure estimates of osimertinib in patients with NSCLC for use in subsequent exposure-response evaluations.

3.1.2 Trial included in the population PK model

The PPK analysis used data from the patient studies AURA I, AURA extension, AURA2, and 1 study in healthy subjects (Study 5) as shown in Table 2.

Table 2 Summary Table of Studies to be Included in the PPK Analysis

Study	Dose(mg)	No. of patients	Sampling
AURA I	Capsule: 20, 40, 80, 160 and 240 Tablet: 80	Capsule: 30 (SD); 225 (MD) Table: 12 (SD); 12 (MD)	Intensive
AURA extension	Film-coated tablet: 80	175 (MD)	Intensive
AURA2	Film-coated tablet: 80	175 (SD and MD)	Intensive
Study 5	Solution: 20 Capsule: 20 Tablet: 20	Capsule vs solution vs tablet fasted: 16 (SD) Tablet fasted vs fed: 16 (SD)	Intensive

*SD means single dose and MD means multiple doses.
Source: Applicant's population PK report, Page 9, Table 1.

There were a total of 24028 concentration observation records from 780 individuals. Of 780 individuals, 32 were healthy subjects (Study 5), 337 were Phase I patients (AURA), and 411 were Phase II patients (AURA extension and AURA2). Figure 2 display osimertinib concentrations vs time for all patients and observations in the full dataset.

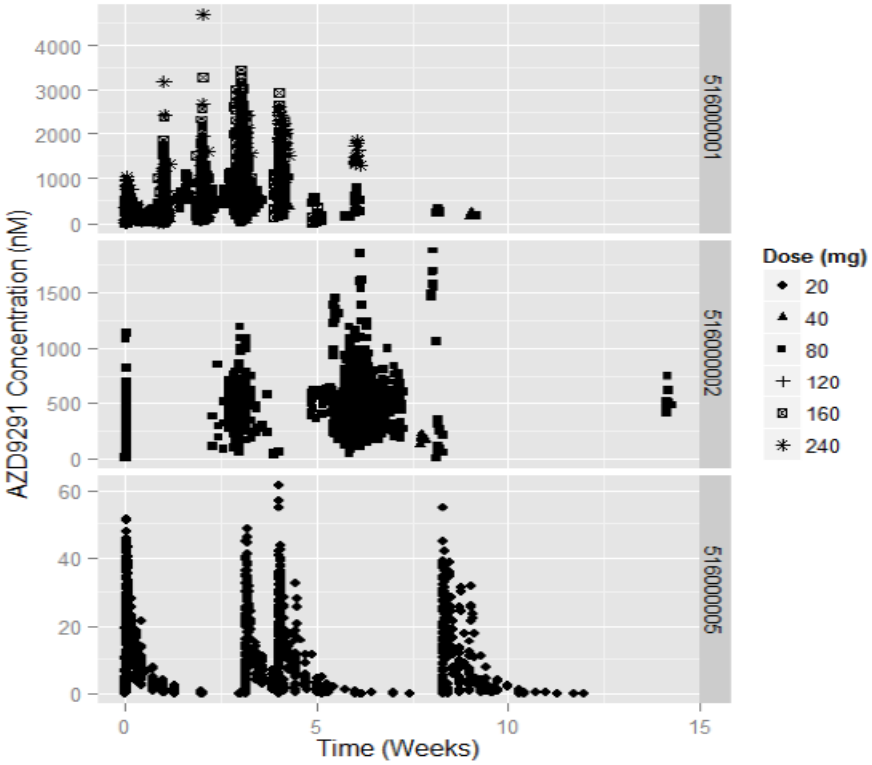


Figure 1 osimertinib time since first dose by study

Source: Applicant's population PK report, Page 29, Figure 2.

Demographic data are summarized in Table 3 and Table 4 (continuous and categorical data, respectively).

Table 3 Summary of baseline demographic data: continuous variables

Covariate (units)	Mean	SD	Median	Range	N	Missing
Body weight (kg)	63.3	14.3	62	33–122	777	1 (0.1%)
Age (years)	60.2	11.9	61	21–89	778	0 (0.0%)
Body mass index (kg/m^2)	23.7	4.1	23.1	14.9–42.6	769	9 (1.2%)
Body surface area (m^2)	1.7	0.2	1.7	1.1–2.5	769	9 (1.2%)
Estimated creatinine clearance (mL/min)[a]	85	28.2	82	22.4–192.4	777[a]	1 (0.1%)
Albumin (g/L)	38.4	5.3	39	2.8–53.3	773	5 (0.6%)
ALT (U/L)	21.8	18.5	17	4–277	778	0 (0.0%)
AST (U/L)	26.7	16.7	23	6–258	777	1 (0.1%)
Alkaline phosphatase (U/L)	142	145.8	94	18–1935	777	1 (0.1%)
Bilirubin (µmol/L)[b]	9.6	4.8	8.6	0.3–49	776[b]	2 (0.3%)

Source: Applicant's population PK report, Page 31, Table 3.

Table 4 Summary of baseline demographic data: categorical variables

Covariate	Category	N	%
Sex	Female	287	36.9
	Male	491	63.1
Study	AURA1[a]	538	68.9
	AURA2	210	27
	Study 5	32	4.1
Smoking status	Never	522	67.1
	Current	24	3.1
	Former	232	29.8
Ethnicity	White	188	24.2
	Asian (not Japanese or Chinese)	188	24.2
	Japanese	146	18.8
	Chinese	119	15.3
	Other	50	6.4
	Missing	87	11.2
Population	Healthy subjects	32	4.1
	Non-small cell lung cancer patients	746	95.9

Source: Applicant's population PK report, Page 31, Table 4.

3.1.3 Base model

The base model comprised 2 compartments: one for osimertinib followed by a second compartment for its metabolite AZD5104. Oral absorption of osimertinib from the depot site into the central compartment was modeled as a first-order process with absorption rate constant (ka, hr^{-1}). Apparent clearance (L/hr) and volume of distribution (L) parameters were also estimated for osimertinib and AZ5104. There was little time delay (<1 h) for the appearance of the metabolite, AZ5104, from the parent in plasma. The parameter estimates for the base model are presented in Table 5.

Table 5 Parameter estimates for the base model

Parameter (units)	Estimate	%RSE	IIV% (%RSE)
NONMEM model estimates			
θ_1: CLparent/F (L/h)	14.4	1.9	48.7 (3.0)
θ_2: Vparent/F (L)	955	3.0	59.6 (2.9)
θ_3: ka (1/h)	0.24	5.0	89.6 (6.2)
θ_4: CLmetabolite/F (L/h)	36.6	2.2	60.3 (4.4)
θ_5: Vmetabolite/F (L)	205	4.3	62.1 (5.6)
			Shrinkage (%)
ηCLparent	0.49	3.0	2.1
ηCLparent-ηCLmetabolite covariance[1]	0.90	3.1	-
ηCLmetabolite	0.60	2.9	1.7
ηka	0.90	6.2	32.8
ηVparent	0.60	4.4	20.1
ηVmetabolite	0.62	5.6	38.9
Additive Error (g/L)	0.099	16.2	5.4
Proportional Error (%)	24.5	2.3	5.4

Source: Applicant's population PK report, Page 149, Appendix 9.6.

3.1.4 Covariate model development

To evaluate if any of the covariates impact on osimertinib and AZ5104 exposure, univariate covariate analysis was performed. In the forward search, the following effects were accepted (P<0.01):

- body weight on CLparent (ΔOFV -63.9)
- body weight on CLmetabolite (ΔOFV -113.2)
- body weight on Vparent (ΔOFV -24.5)
- albumin on Vparent (ΔOFV -75.9)
- dose on CLparent (ΔOFV -19.5)
- dose on F1 (ΔOFV -15.0)
- fed/fasted state on CLparent (ΔOFV -37.1)
- fed/fasted state on F1 (ΔOFV -13.7)
- age on CLparent (ΔOFV -11.1)
- ethnic group on CLparent (ΔOFV -12.0)
- ethnic group on CLmetabolite (ΔOFV -29.5)
- Healthy subject population on CLparent (ΔOFV -10.4)
- Healthy subject population on CLmetabolite (ΔOFV -145.3)
- ALT on CLmetabolite (ΔOFV -14.5)

Ethnic group on CLparent, which was added in the forward search, was removed in the backward elimination step. All other covariates were retained from the backward search.
During model finalization process, the covariates having less than 20% impacts within the 90% percentile of their distributions on PK parameters were removed: ATL, age, dose, and fed state. All Asian race covariates were in the 20% range. However, as understanding the difference between various Asian race categories and white/non-white non-Asian was of clinical interest, race was retained in the final model (Table 6, 7 and 8).

Table 6 Impact of continuous covariates taken from the covariate search from given percentiles

Covariate (units)	Percentiles of covariates or impact of covariates at a given percentile from the reference value				
	5%	25%	50%	75%	95%
Age (yr)	40	53	61[a]	68	78
Percent difference of reference CLparent at given age percentile[b]	6%	2%	0%	-1%	-3%
Weight (kg)	43	53	62[a]	72	90
Percent difference of reference CLparent at given body weight percentile	-18%	-8%	0%	9%	23%
Percent difference of reference CLmetabolite at given body weight percentile	-30%	-14%	0%	16	43%
Percent difference of reference Vparent at given body weight percentile	-21%	-9%	0%	10%	27%
ALT (IU/L)	8	12	17[a]	26	46
Percent difference of reference CLmetabolite at given alanine aminotransferase percentile[b]	-5%	-2%	0%	3%	7%
Albumin (g/L)	29	35	39[a]	42	46
Percent difference of reference Vparent at given albumin percentile	-31%	-11%	0%	8%	20%

Source: Applicant's population PK report, Page 35, Table 5.

Table 7 Impact of dose from the covariate search relative to an 80-mg dose

Covariate (units)	Covariate values of interest or impact of covariates at given reference value				
AZD9291 dose (mg) (percent of AURA2 dose)	20 (25%)	40 (50%)	80[a] (100%)	160 (200%)	240 (300%)
Percent difference of reference CLparent at given dose[b]	-7%	-4%	0	4%	6%
Percent difference of F at given dose[a]	-14%	-8%	0%	8%	13%

Source: Applicant's population PK report, Page 36, Table 6.

Table 8 Impact of categorical covariates taken from the covariate search

Covariate	Patients (n)	Patients (%)	Impact
Fed state on CLparent[a]	14	1.8	-10%
Fed state on F[a]	14	1.8	8%
Healthy subject population on CLparent	32	4.1	28%
Healthy subject population on CLmetabolite	32	4.1	92%
Ethnic Asian other on CLmetabolite	188	24.1	23%
Ethnic Asian Chinese on CLmetabolite	146	18.7	18%
Ethnic Asian Japanese on CLmetabolite	120	15.4	22%
Ethnic non-Asian non-white on CLmetabolite	138	17.7	10%

Source: Applicant's population PK report, Page 36, Table 7.

3.1.5 Final population PK model

The final osimertinib/AZ5104 Population PK model includes the following parameter-covariate relationships (body weight and albumin are normalized by their median values in the analysis dataset of 62 kg and 39 g/L, respectively):

$$CL_{parent,i}/F = \theta_1 \cdot \left(\frac{Body\ weight}{62}\right)^{\theta_{10}} \cdot (1 + Healthy\ Subject \cdot \theta_9) \cdot exp(\eta_{CLparent,i})$$

$$CL_{metabolite,i}/F = \theta_4 \cdot \left(\frac{Body\ weight}{62}\right)^{\theta_{17}} \cdot (1 + Healthy\ Subject \cdot \theta_{16}) \cdot (1 + Ethnic\ Asian\ Other \cdot \theta_{12}) \cdot (1 + Ethnic\ Asian\ Chinese \cdot \theta_{13}) \cdot (1 + Ethnic\ Asian\ Japanese \cdot \theta_{14}) \cdot (1 + Ethnic\ Non - Asian\ Non - White \cdot \theta_{15}) \cdot \exp(\eta_{CLmetabolite,i})$$

$$V_{parent,i}/F = \theta_2 \cdot \left(\frac{Body\ weight}{62}\right)^{\theta_{21}} \cdot \left(\frac{Albumin}{39}\right)^{\theta_{20}} \cdot exp(\eta_{Vparent,i})$$

$$V_{metabolite,i}/F = \theta_5 \cdot exp(\eta_{Vmetabolite,i})$$

$$ka = \theta_3 \cdot exp(\eta_{ka,i})$$

In the model shown above, “healthy subject” is an indicator variable with value “0” for AURA I and AURA2 studies and “1” Study 5 healthy subjects. Ethnic Asian (other, Chinese, or Japanese) and ethnic non-Asian non-white are indicator variables with value “1” when true and “0” otherwise. Final population PK model parameter estimates are presented in Table 9. Overall, the parameters of the model, including the covariate effects, are estimated with good precision.

Table 9 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: Applicant's population PK report, Page 43, Table 8.

3.1.6 Model assessment

Figure 3 and Figure 4 present osimertinib goodness-of-fit plots for the final population PK model. Lines of identity, zero lines, and trend lines were overlaid. The individual predictions fit well along the identity line, and the conditionally weighted residuals were relatively low and well distributed along the zero line relative to population predictions.

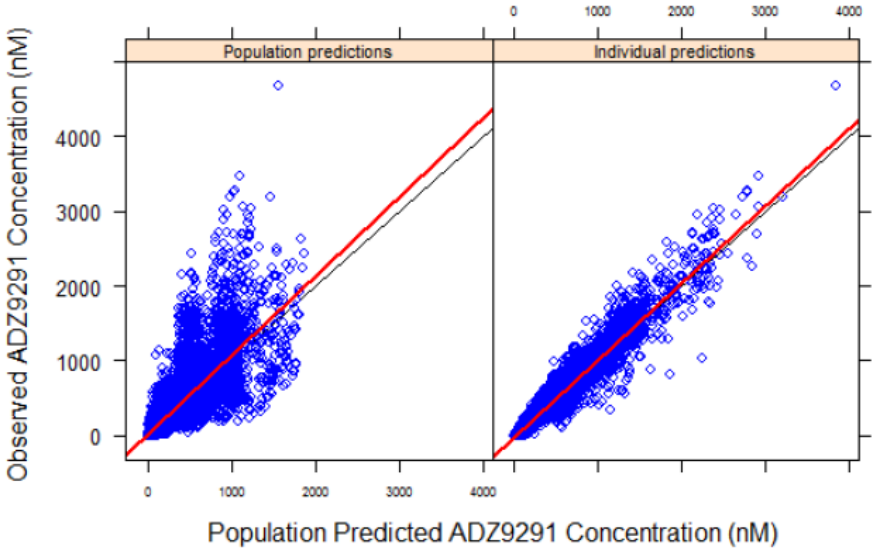


Figure 3 General goodness-of-fit for osimertinib from the final population PK model (loess smoothing line in red)

Source: Applicant's population PK report, Page 44, Figure 9.

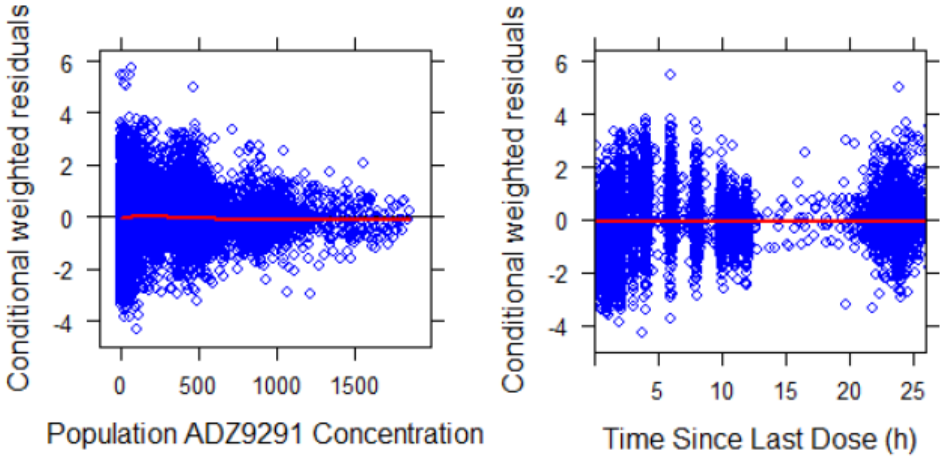


Figure 4 Residual goodness-of-fit for osimertinib from the final population PK model (loess smoothing line in red)

Source: Applicant's population PK report, Page 45, Figure 10.

There is a misspecification of residuals related to times greater than the 24-hour dosing interval (Figure 5). This was not considered critical as the main objective of this population PK model was to estimate steady-state exposures for the 24-hour dosing period.

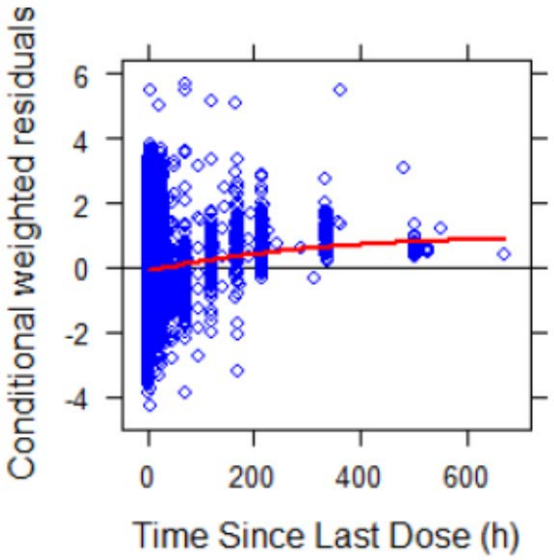


Figure 5 Full time since last dose conditionally weighted residuals for osimertinib for the final population PK model

Source: Applicant's population PK report, Page 281, Figure 9.17.

The goodness-of-fit plots for AZ5104 also support the final model fit is reasonable. However, the concentration profile of AZ5104 is slightly under predicted.

Due to different dosing schedules between and within dosing cohorts, a prediction-corrected VPC (pcVPC) was created to standardize observations within pcVPC bins. The pcVPC of the final population PK model are shown in Figure 6. The model describes the observed data well, and model predictions were also generally within the 90% prediction intervals. Similar plot could be observed for AZ5104.

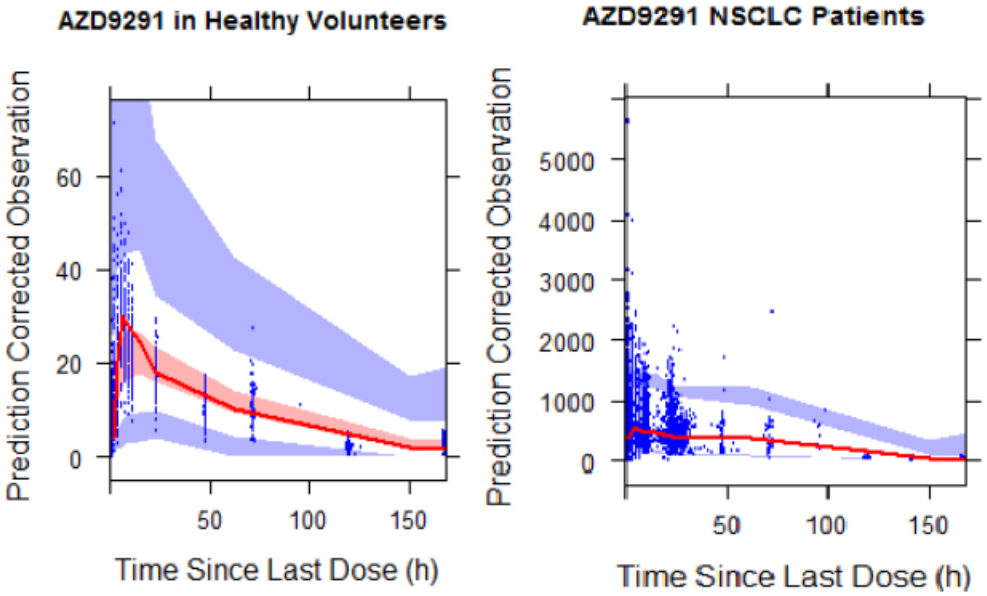


Figure 6 Prediction-corrected visual predictive checks for the final PPK model

Source: Applicant's population PK report, Page 48, Figure 13.

3.1.7 Applicant's conclusion

An integrated PPK model has been developed that characterizes the time course of osimertinib and AZ5104 concentrations in plasma in a joint manner and has been based on data from both NSCLC patients (single dose, multiple-dose and steady state) and healthy subjects (single dose, washout data). A one-compartmental disposition model for both osimertinib and AZ5104, with first order

oral absorption of osimertinib into the central compartment and the formation of AZ5104 from osimertinib, was identified that best described the time course of the plasma concentration-time course of osimertinib and AZ5104 in an adequate manner.
The following covariates had no impact on PK:

- Age, gender, smoking status
- Renal/hepatic function is not expected to impact the AUCss for both osimertinib and AZ5104, although an effect for ALT on apparent clearance of AZ5104 was identified

The following significant patient covariates were identified:

- Body weight on osimertinib CL/F and Vc/F: a -20% to +30% change in osimertinib AUCss (compared to the AUCss for the median body weight of 62 kg) would be expected across a body weight range of 43–90 kg
- Body weight on AZ5104 CL/F: a -40% to +50% change for AZ5104 AUCss (compared to the AUCss for the median body weight of 62 kg) would be expected across a body weight range of 43–90 kg
- For all ethnic classes (Chinese, Japanese, Asian other and non-Asian-non-white), a decrease in AZ5104 AUCss of 10–23% vs white patients may be expected.

There was no difference in PK between the 4 formulations used during the development program (solution, capsule, Phase I tablet, film-coated tablet).
Reviewer's comment: The reviewer verified the Applicant's population PK analysis for osimertinib. The goodness-of-fit plots indicate that the model reasonably describes the data. As mentioned by Applicant, there was misspecification of residuals related to times greater than the 24 h dosing interval. Based on Figure 5, there is a clear trend that the concentration was underestimated after 150 h. However, the VPC plot provided by Applicant only includes the concentration profile within 150 h. In addition, the reviewer agrees that no clinically significant impact of age, body weight, race, were identified from the available data, thus, a fixed dose approach appears to be appropriate forosimertinib.However, further clinical studies should be conducted to evaluate the effects of hepatic/renal impairment on PK of osimertinib.
Osimertinibosimertinib

3.2 Exposure-response analyses for efficacy and safety
3.2.1 Objective

1. To assess the potential relationships between osimertinib and AZ5104 exposure (AUCss) and Response Evaluation Criteria in Solid Tumors (RECIST)-based efficacy parameters: objective response rate (ORR), duration of response (DoR), and best percentage change in tumor size from baseline
2. To assess the potential relationships between osimertinib and AZ5104 exposure (AUCss) and occurrence of EGFR-related adverse events (AEs) of rash and diarrhea.
3. To provide a descriptive relationship between osimertinib and AZ5104 exposure (AUCss) and occurrence of ILD

3.2.2 Trial included in the exposure-response analyses
The exposure response analyses included data from various components of 2 clinical studies with osimertinib as shown in Table 10. Table 11 summarizes the number of patients included in the efficacy and safety exposure response analyses by study and by dose.

Table 10 Summary of studies included in the current analysis

Study ID	Phase	Study type	N
AURA	I	Study D5160C00001 Phase I component in EGFR mutation positive advanced NSCLC patients	337
AURA extension	II	Study D5160C00001 Phase II component in EGFR T790M positive advanced NSCLC patients who have progressed following either 1 prior therapy with an EGFR TKI agent or following treatment with both EGFR TKI and at least 1 other prior line of therapy, such as cytotoxic doublet chemotherapy or immunotherapy	201
AURA2	II	Study D5160C00002 Phase II in EGFR T790M positive advanced NSCLC patients who have progressed following either 1 prior therapy with an EGFR TKI agent or following treatment with at least 1 EGFR TKI and at least 1 prior platinum-based doublet chemotherapy	210

Source: Applicant's PK-PD modeling and simulation report, Page 17, Table 1.

Table 11 Summary of the number of patients by study and by dose

Study	Dose (mg), number of patients (%)					Total number of patients (n = 748)
	20 (n = 21)	40 (n = 58)	80 (n = 552)	160 (n = 96)	240 (n = 21)	
AURA Escalation	6 (28.6%)	6 (10.3%)	18 (3.3%)	6 (6.3%)	7 (33.3%)	43 (5.7%)
AURA Expansion	15 (71.4%)	52 (89.7%)	123 (22.3%)	90 (93.8%)	14 (66.7%)	294 (39.3%)
AURA Extension	0 (0.0%)	0 (0.0%)	201 (36.4%)	0 (0.0%)	0 (0.0%)	201 (26.9%)
AURA2	0 (0.0%)	0 (0.0%)	210 (38.0%)	0 (0.0%)	0 (0.0%)	210 (28.1%)

Source: Applicant's PK-PD modeling and simulation report, Page 26, Table 2.

3.2.3 The relationship between osimertinib AUCss and AZ5104 AUCss

Figure 7 shows a scatterplot of osimertinib AUCss versus AZ5104 AUCss values. The plot suggests a strong relationship with an estimated correlation of 0.94. Therefore, osimertinib and AZ5104 AUCss values were not included in the same models to avoid collinearity problems due to this high correlation. Instead, separate models were developed for each of these 2 exposure metrics.

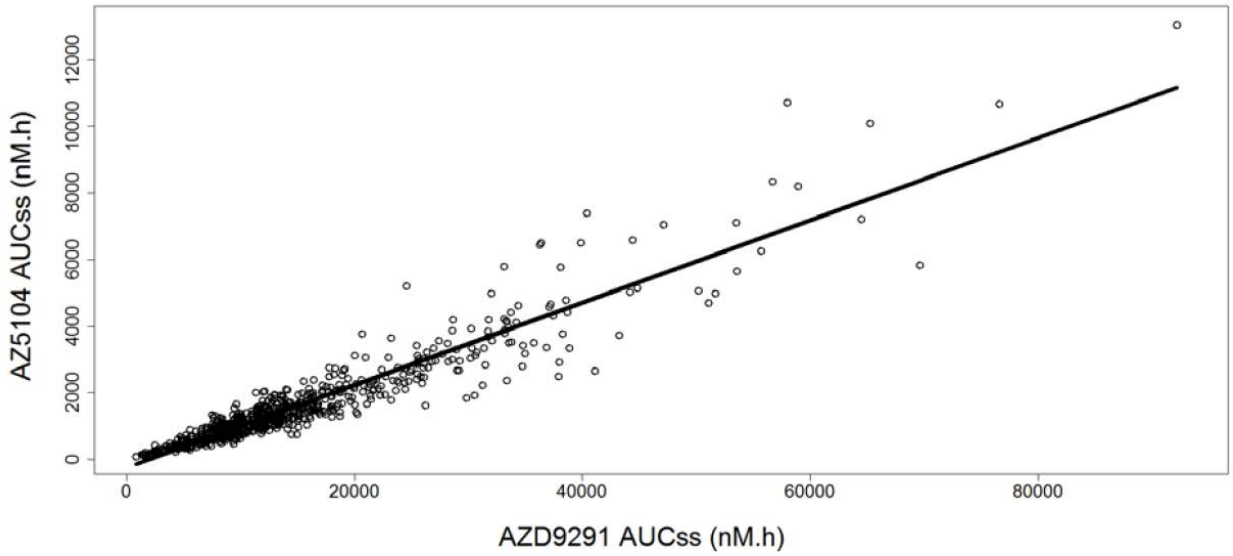


Figure 7 Scatterplot showing the strong relationship between individual osimertinib AUCss with individual AZ5104 AUCss values

Source: Applicant's PK-PD modeling and simulation report, Page 28, Figure 1.

3.2.4 Logistic regression model for response rate

The constant probability model was selected as the best describing the data and the predicted probability of response (95% CI) from this model was 0.60 (0.56–0.65).

To provide idea about the "trend" (although not statistically significant) in the relationship of the probability of response and exposure, linear effect of log AUCss was evaluated using logistic mode. The estimated slope (95% CI) for log osimertinib AUCss was -0.18 (-0.49; 0.14), demonstrating no statistical significance. For AZ5104, the estimated slope (95% CI) for log AUCss was -0.21 (-0.48; 0.07), again demonstrating no statistical significance. The left panel of Figure 8 shows the model-predicted fit based on linear osimertinib AUCss in comparison to the observed probability of response calculated in bins created from quantiles of osimertinib AUCss. The panel suggests a slight decrease in probability of response with increasing exposure and it shows that the model generally describes the data well. The right panel shows the model fit together with the 95% CI on the prediction.

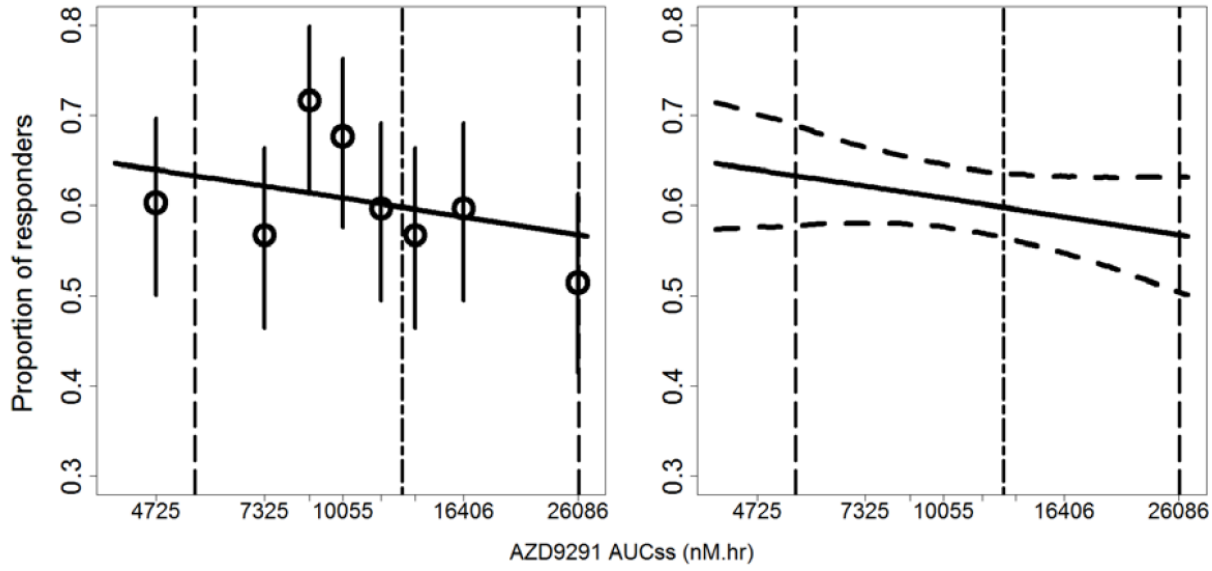


Figure 8 Observed response probabilities (with 95% CI as vertical bars) and model prediction based on osimertinib AUCss

Source: Applicant's PK-PD modeling and simulation report, Page 34, Figure 7.
Reviewer's comment: The reviewer verified the relationship between osimertinib exposure and ORR (Figure 9). The result confirms there was no significant exposure-response relationship for ORR with P value higher than 0.05. The response rate is relative flat across wide exposure range, indicating that higher dose would not provide further benefit.

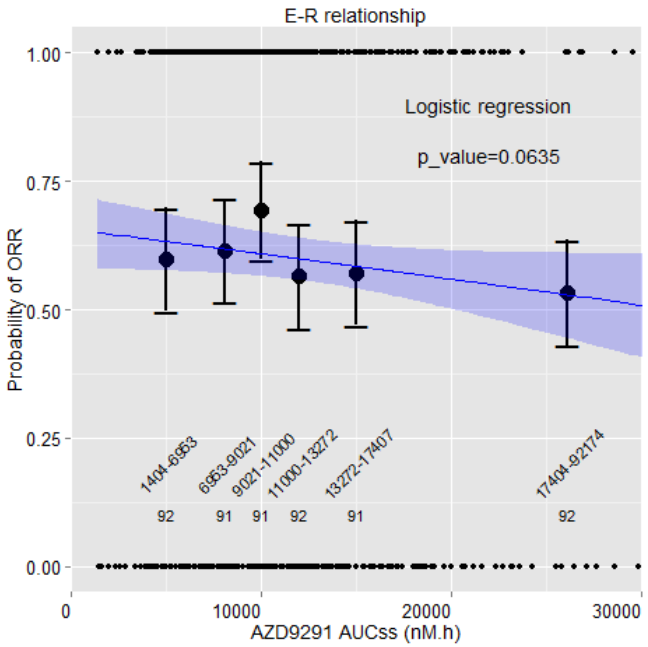


Figure 9 Relationship between osimertinib exposure and probability of objective response rate

Source: Review's independent analysis

3.2.5 Duration of response

An exploratory Kaplan-Meier (KM) analysis evaluated the DoR as function of osimertinib AUCss bins. Figure 10 (left panel) suggests that there is no clear trend in the relationship between DoR and exposure. Figure 10 (right panel) also appears to show no clear relationship between time to onset of response and DoR. There was no relationship between DoR and AZ5104 AUCss as well. Hence, the evaluation of this exposure-response relationship was not pursued further. It should be noted that DoR data is immature for patients in AURA extension and AURA2 therefore results should be interpreted with caution.

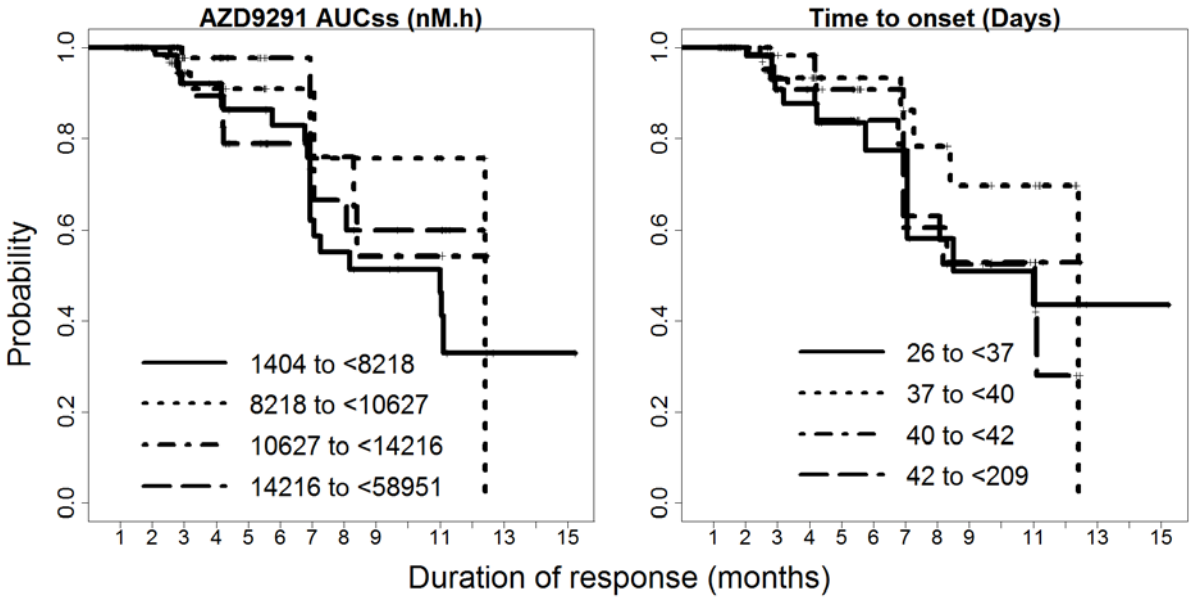


Figure 10 Kaplan-Meier representation of DoR in quartiles of osimertinib AUCss and stratified by time to onset of response

Source: Applicant's PK-PD modeling and simulation report, Page 35, Figure 8.

3.2.6 Best percent change in tumor size from baseline

The scatterplots of the best percent change from baseline in tumor size with osimertinib AUCss in Figure 11 with the corresponding LOESS smoother suggest that there is no relationship between exposure and the best percent change in tumor size from baseline.

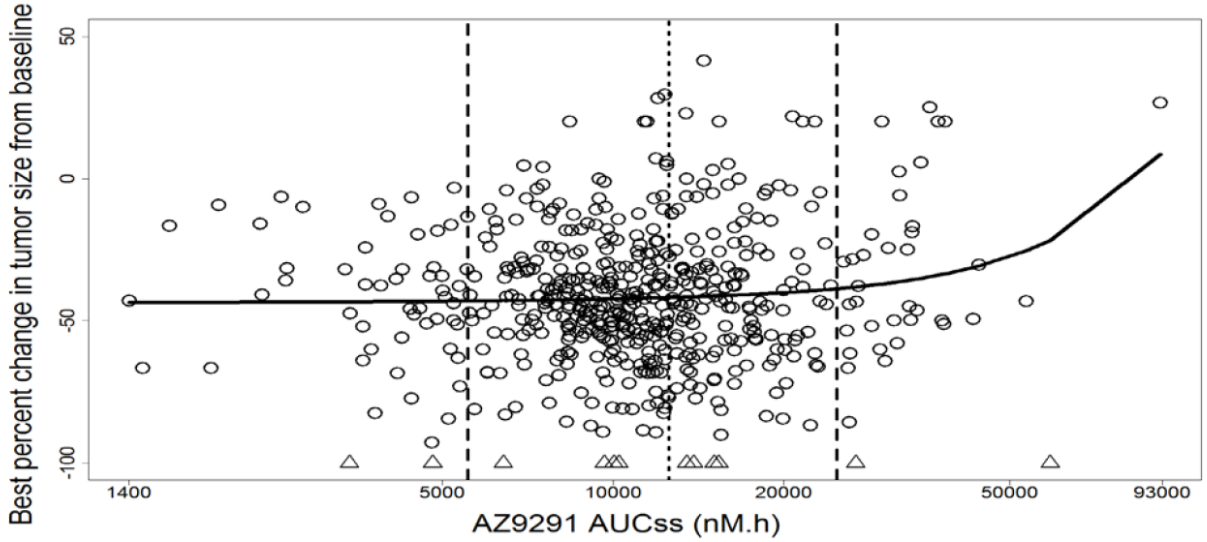


Figure 10 Best percent change in tumor size from baseline in relation to osimertinib AUCss

Source: Applicant's PK-PD modeling and simulation report, Page 37, Figure 10.

3.2.7 Logistic model for rash

The results from analyses of both osimertinib and AZ5104 indicate that of all evaluated models, a linear model best describes the relationship between log AUCss and probability of rash. For osimertinib, a linear relationship between log AUCss and probability of rash led to a statistically significant improvement in model fit (P = 0.0001) relative to a constant probability model. The value of the positive slope (95% CI) for this linear relationship of osimertinib AUCss was 0.50 [0.27–0.73]. A similar trend was observed for AZ5104.

Based on the mean osimertinib AUCss in each dose group, the predicted probabilities of having rash (95% CI) for patients who received 20, 40, 80, 160, and 240 mg osimertinib were 0.28 (0.21–0.36), 0.36 (0.31–0.42), 0.46 (0.43–0.50), 0.55 (0.50–0.61), and 0.60 (0.53–0.67), respectively. Based on AZ5104, the respective probabilities were 0.29 (0.22–0.38), 0.38 (0.33–0.43), 0.46 (0.43–0.50), 0.55 (0.49–0.61), and 0.59 (0.52–0.66).

The parameter estimates and standard errors for the linear model for log osimertinib AUCss model are given in Table 12. The %RSE values in Table 12 suggest that the parameters are generally well estimated. The left panel of Figure 16 shows the model prediction in relation to observed probabilities; the plot suggests that the model captures the pattern in the data well. The right panel of Figure 11 shows the model prediction with 90% CI as well as the exposure range for 80-mg osimertinib.

Table 12 Parameters estimates for the probability of rash model

Parameter description	Parameter	Estimate (SE)	%RSE
Intercept	α_0	-4.88 (1.10)	23%
Linear effect (log) AZD9291 AUC_{ss}	α_1	0.50 (0.12)	23%

Source: Applicant's PK-PD modeling and simulation report, Page 41, Table 5.

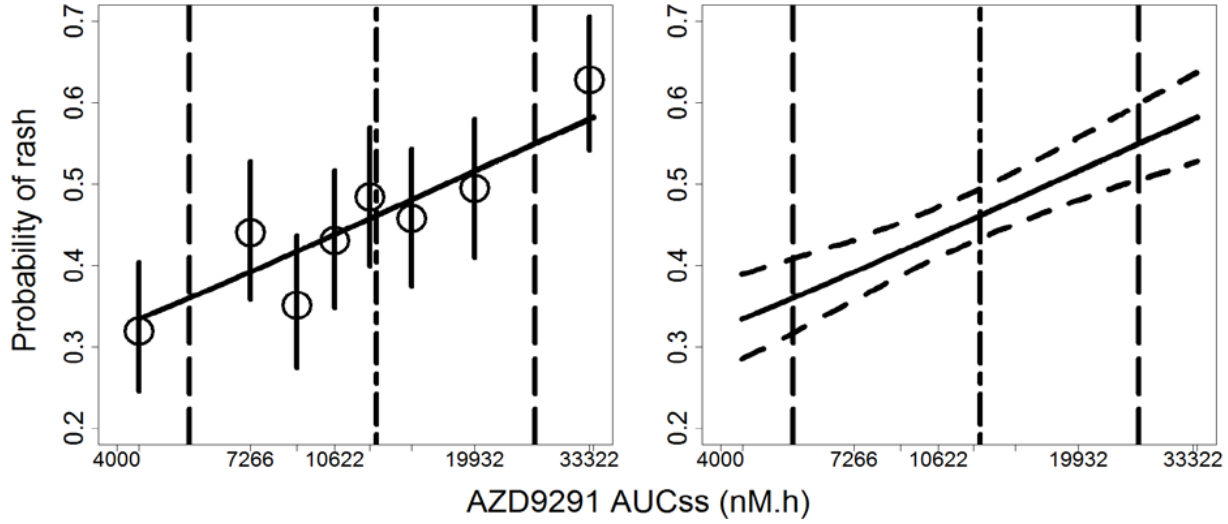


Figure 11 Observed probabilities and model prediction of rash

Source: Applicant's PK-PD modeling and simulation report, Page 42, Figure 16.

Reviewer's comment: The review conducted an independent logistic analysis for rash as shown in Figure 2, confirming the significant relationship between osimertinib AUCss and probability of rash. This relationship supports lower dose selection without considering efficacy. However, the analysis includes all Grades safety event with only few Grade 3-4 events.

3.2.8 Logistic model for diarrhea

For osimertinib AUCss, a linear log AUCss effect led to a statistically significant improvement in the model fit (P = 0.0001) when compared with a constant probability model. A similar trend was observed for AZ5104, where addition of a linear log AUCss effect significantly improved the model fit in relation to a constant probability model (P =0.001). The estimated slope (95% CI) for log osimertinib AUCss was 0.45 (0.23–0.68).

Evaluated at the mean osimertinib AUCss in each dose group, the predicted probabilities of having diarrhoea (95% CI) for patients who received 20, 40, 80, 160, and 240 mg osimertinib were 0.29 (0.22–0.37), 0.37 (0.32–0.42), 0.45 (0.42–0.49), 0.54 (0.48–0.60), and 0.58 (0.51–0.65), respectively. Based on AZ5104, the respective probabilities were 0.30 (0.24–0.38), 0.38 (0.34–0.43), 0.46 (0.43–0.50), 0.54 (0.49–0.59), and 0.57 (0.51–0.65).

The observed probabilities of diarrhea as a function of osimertinib AUCss, together with the model-predicted probabilities, are shown in Figure 12. The left panel suggests that the model captures the trend in the data well and the right panel gives an indication about the uncertainty around the estimated probability profile. Both panels also show the mean (90% CI) of osimertinib AUCss in the patients who received 80-mg osimertinib. The parameter estimates for osimertinib model are given in Table 13 and the associated %RSE values suggest that the estimates are estimated with acceptable precision.

Table 13 Parameters estimates for the probability of diarrhea model

Parameter description	Parameter	Estimate (SE)	%RSE
Intercept	α_0	-4.47 (1.09)	24%
Linear effect (log) AZD9291 AUC_{ss}	α_1	0.45 (0.12)	26%

Source: Applicant's PK-PD modeling and simulation report, Page 44, Table 6.

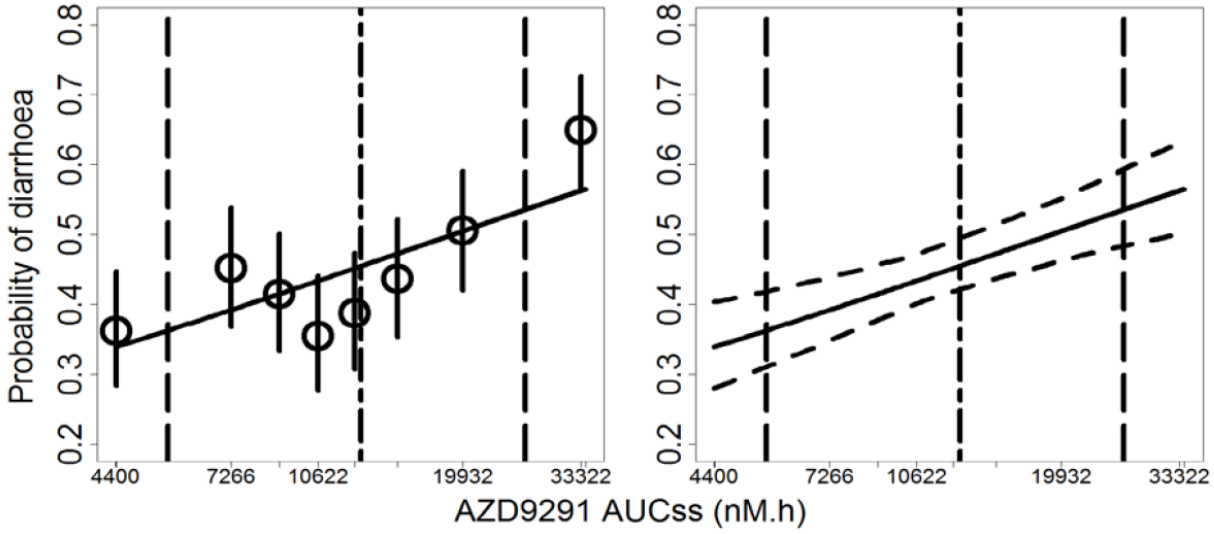


Figure 12 Observed probabilities and model prediction of diarrhea

Source: Applicant's PK-PD modeling and simulation report, Page 43, Figure 17.
Reviewer's comment: The review conducted an independent logistic analysis for diarrhea as shown in Figure 3. The significant relationship between osimertinib AUCss and probability of diarrhea supports lower dose selection without considering efficacy. However, the analysis includes all Grades safety event with only few Grade 3-4 events.

3.2.9 Relationship between exposure and occurrence of ILD or ILD-like events

Of the 748 patients, 21 patients, constituting a percentage of 2.8%, had ILD or ILD-like events. The distribution according to the first dose received was 20 mg (0), 40 mg (0), 80 mg (16), 160 mg (5), and 240 mg (0). Figure 13 shows the relationship between the first dose a patient received and individual osimertinib AUCss and AZ5104 AUCss values, respectively. The triangles signify patients who had ILD or ILD-like events. There appears to be no clear trend in the relationship between exposure and occurrence of ILD or ILD-like events from these exploratory plots. It can therefore be considered that the graphical exploration of the relationship between osimertinib and AZ5104 exposure with the occurrence of ILD or ILD-like events was inconclusive.

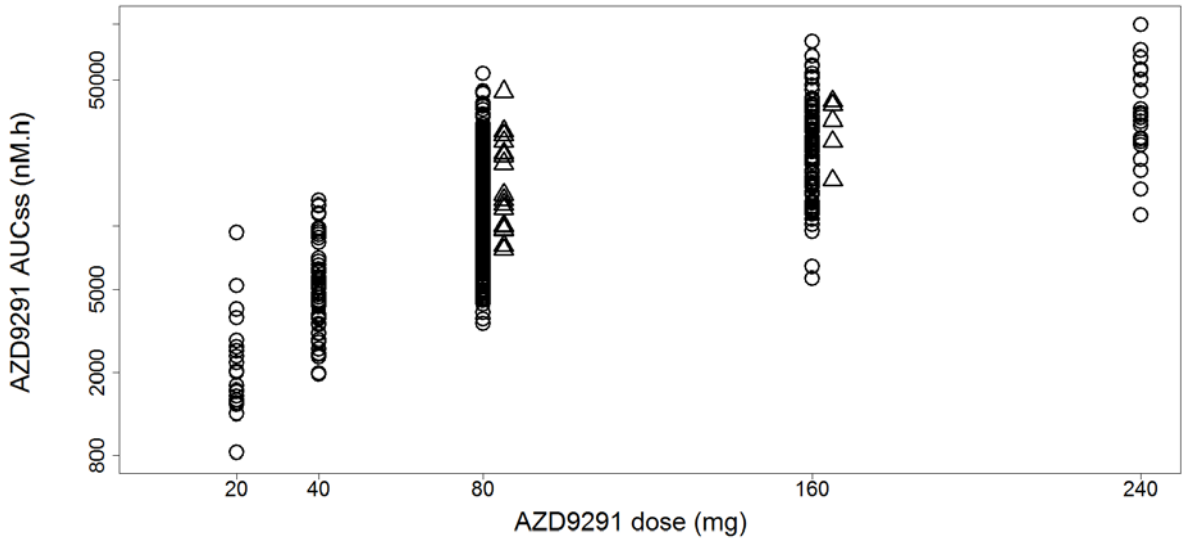


Figure 13 Relationship between occurrence of ILD or ILD-like events and osimertinib AUCss
Source: Applicant's PK-PD modeling and simulation report, Page 52, Figure 29.

3.2.10 Applicant's conclusion

Over the 20- to 240-mg dose range studied (where the majority of data comes from 80-mg), there was no evidence of a relationship between exposure and probability of response in EGFR T790M mutation positive patients with (b) (4) NSCLC who have progressed on or after EGFR TKI therapy. There was no evidence of a relationship between exposure and DoR in EGFR T790M mutation positive patients with (b) (4) NSCLC who have progressed on or after EGFR TKI therapy. There was no evidence of a relationship between exposure and best percent change in tumor in EGFR T790M mutation positive patients with (b) (4) NSCLC who have progressed on or after EGFR TKI therapy.

The probability of a patient experiencing rash increased with exposure. Evaluated at the mean osimertinib AUCss in each dose group, predicted probabilities of having rash (95% CI) for patients who received 20, 40, 80, 160, and 240 mg osimertinib were 0.28 (0.21–0.36), 0.36 (0.31–0.42), 0.46 (0.43–0.50), 0.55 (0.50–0.61), and 0.60 (0.53–0.67), respectively. The probability of a patient experiencing diarrhea increased with exposure. For osimertinib AUCss, the predicted probabilities of having diarrhea (95% CI) for patients who received 20, 40, 80, 160, and 240 mg osimertinib were 0.29 (0.22–0.37), 0.37 (0.32–0.42), 0.45 (0.42–0.49), 0.54 (0.48–0.60), and 0.58 (0.51–0.65), respectively. The probability of a patient experiencing both rash and diarrhoea increased with increasing exposure. Based on osimertinib AUCss , the predicted probabilities of having both rash and diarrhea (95% CI) for patients who received 20, 40, 80, 160, and 240 mg osimertinib were 0.08 (0.05–0.12), 0.14 (0.10–0.18), 0.23 (0.20–0.26), 0.34 (0.29–0.40), and 0.41 (0.34–0.50), respectively.

Graphical exploration of the relationship between osimertinib and/or AZ5104 plasma exposure and occurrence of ILD or ILD-like events was inconclusive.

Reviewer's comment: The exposure-response relationship for efficacy and safety support the proposed dose of 80 mg once daily, providing high response rate as well as acceptable safety profile. The result of reviewer's analyses is consistent with that of Applicant's analyses.

APPENDIX 2: PBPK REVIEW

Physiological-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	NDA208065
Drug Name	Osimertinib
Proposed Indication	Treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy
Clinical Division	DDOP
PBPK Consult request	Jun Yang, Ph.D.
Primary PBPK Reviewer	Ping Zhao, Ph.D.
Secondary PBPK Reviewer	Hong Zhao, Ph.D.
Applicant	AstraZeneca

1. Objectives

The objective of this review is to evaluate the submitted physiologically-based pharmacokinetic (PBPK) modeling information [1] that predicted the potential drug-drug interaction (DDI) for osimertinib.

2. Background

2.1. Regulatory history on PBPK submission

Osimertinib is for the treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy [2]. Osimertinib has a high oral absorption (>80%).

In vitro, osimertinib is predominantly metabolized by hepatic CYP3A, and has a potential to inhibit CYP3A and breast cancer resistance protein (BCRP). Dedicated drug interaction trials are planned or are ongoing to assess osimertinib's DDI potential. (b) (4)


(b) (4)


(b) (4)

3. Methods

A population based PBPK software SimCYP® (Version 14.0.102.0, Sheffield, UK) was used by the applicant to develop osimertinib PBPK model and to conduct simulations to predict potential DDIs. The concept and construct of SimCYP have been described by Jamei et al [4] and the software is updated on an annual basis. Parameter values and sources for osimertinib are summarized in **Appendix Table 1**. Models of CYP3A modulators (itraconazole, "sim-Itraconazole" and "sim-OH-Itraconazole"; ketoconazole, "sim-Ketoconazole 200 mg" BD; rifampicin, "SV-Rifampicin-MD") and enzyme/transporter substrates (simvastatin, "sim-Simvastatin"; rosuvastatin, "SV-Rosuvastatin") from software's built-in models were directly used.

The applicant conducted simulations using a population expected to be representative of oncology patients (Oncology Patients in simcyp V14) according to Cheeti et al [5]. Generally, subjects were under fasted condition, with an age range of 23-92 years, and a fraction of female of 0.51. Details of DDI simulations can be found in **Appendix Table 2**.

4. Results

4.1. Can PBPK model describe osimertinib plasma concentration-time profiles observed in NSCLC patients?

The applicant's osimertinib model considered detailed elimination mechanisms based on in vitro findings, with overall apparent clearance (CL/F) and absorption kinetics (e.g., effective passive permeability in man $P_{eff,man}$) optimized according to pharmacokinetic data in patients after single and multiple doses (**Appendix Table 1**). PBPK simulated osimertinib plasma concentration time profile appears to describe that observed in patients (**Appendix Figure 1**).

(b) (4)

Table 3 summarizes suggested changes in applicant's draft label related to osimertinib dosing in the presence of CYP3A modulators. Relevant labeling language should be updated when results of ongoing DDI studies become available.

Table 3. Suggested changes in applicant's draft label - dosing recommendations of osimertinib in the presence of CYP3A modulators

Sections	From	To
Highlight under "DRUG INTERACTIONS"	Strong CYP3A Inhibitors (b) (4) If no other alternative exists, the patient should be closely monitored for signs of toxicity. (7.1)	Strong CYP3A Inhibitors: Avoid. May increase TRADENAME plasma concentrations
Section 7.1 Effect of Other Drugs on (b) (4)	(b) (4) Strong CYP3A Inducers (b) (4)	Clinical studies evaluating TRADENAME in the presence of strong CYP3A inhibitors or strong CYP3A inducers have not been conducted. Avoid co-administration of TRADENAME with strong CYP3A inhibitors or strong CYP3A inducers
Section 12.3 under "Drug Interaction"	(b) (4)	*Strong CYP3A Inhibitor:* Clinical studies evaluating TAGRISSO in the presence of strong CYP3A inhibitors have not been conducted *[see Drug Interactions (7.1)]*. *Strong CYP3A Inducers:* Clinical studies evaluating TAGRISSO in the presence of strong CYP3A inducers have not been conducted *[see Drug Interactions (7.1)]*.

4.3. Can PBPK prediction be used to (b) (4)

(b) (4)

According to FDA's draft guidance for industry [6], a clinical DDI trial should be conducted to evaluate the effect of osimertinib on the PK of a sensitive CYP3A substrate.

Table 4 summarizes suggested changes in applicant's draft label related to drugs whose exposure may be affected by osimertinib. Relevant labeling language should be updated when results of ongoing DDI studies become available.

Table 4. Suggested changes in applicant's draft label - dosing recommendations of drugs whose exposure may be affected by osimertinib [3]

Sections	From	To
Section 7.2 Effect of Osimertinib on Other Drugs	(b) (4)	Avoid concomitant administration of TAGRISSO with drugs that are sensitive substrates of CYP3A, breast cancer resistance protein (BCRP), or CYP1A2 with narrow therapeutic indices, including but not limited to fentanyl, cyclosporine, quinidine, ergot alkaloids phenytoin, rifampicin, carbamazepine, as osimertinib may increase or decrease plasma concentrations of these drugs.
Section 12.3 under "Drug Interactions" Effect of (b) (4)	(b) (4)	*CYP450 Metabolic Pathways:* Osimertinib is a competitive inhibitor of CYP3A, but not CYP2C8, 1A2, 2A6, 2B6, 2C9, 2D6 and 2E1 in vitro. Osimertinib induced CYP3A4 (Pregnane X dependent) and CYP1A2 enzymes.

4.4. Can PBPK prediction be used [redacted]

[redacted]

Changes relevant to BCRP inhibition [redacted] are suggested in **Table 4**. Relevant labeling language should be updated when results of ongoing DDI studies become available.

5. Conclusion

[redacted] Several changes have been suggested in draft label regarding dose recommendations for substrate drugs of CYP3A or BCRP when co-administered with osimertinib.

6. Appendices

6.1. Abbreviations

AUC, area under the concentration-time profile; AUCR, the ratio of the area under the curve of the substrate drug in the presence and absence of the perpetrator; BCRP, breast cancer resistance protein; b.i.d., twice daily dosing; B/P, blood to plasma ratio; Cmax, maximal concentration in plasma; CmaxR, the ratio of the maximum plasma concentration of the substrate drug in the presence or absence of the perpetrator; CL, clearance; CL_{int}, intrinsic clearance; CLpo, oral clearance; CL/F, apparent clearance; DDI: drug-drug interaction; EGFR, epidermal growth factor receptor; F, bioavailability; f_a, fraction absorbed; F_g, fraction that escapes intestinal metabolism; f_{mj}, fraction of total clearance mediated by j CYP isoform or renal elimination; $f_{u,p}$, fraction unbound in plasma; $f_{u,gut}$, apparent unbound fraction in enterocytes; $f_{u,mic}$, microsomal free fraction; k_a, first order absorption rate constant; K_i, reversible inhibition constant; K_I, inactivator concentration that supports half maximal rate of inactivation; k_{inact}, maximal inactivation rate; $LogP_{o:w}$, logarithm of the octanol-water partition coefficient; MATEs, Multidrug and toxin extrusion protein; NA, not applicable; NDA: new drug application; NSCLC, non-small cell lung cancer; OATP, organic anion-transporting polypeptide; OCT, organic cation transporter; PBPK: Physiological-based Pharmacokinetic; $P_{eff,man}$, effective passive permeability in man; P-gp, P-glycoprotein; q.d., once daily dosing; Q_{gut}, a hypothetical flow term for the intestine absorption model; TKI, tyrosine kinase

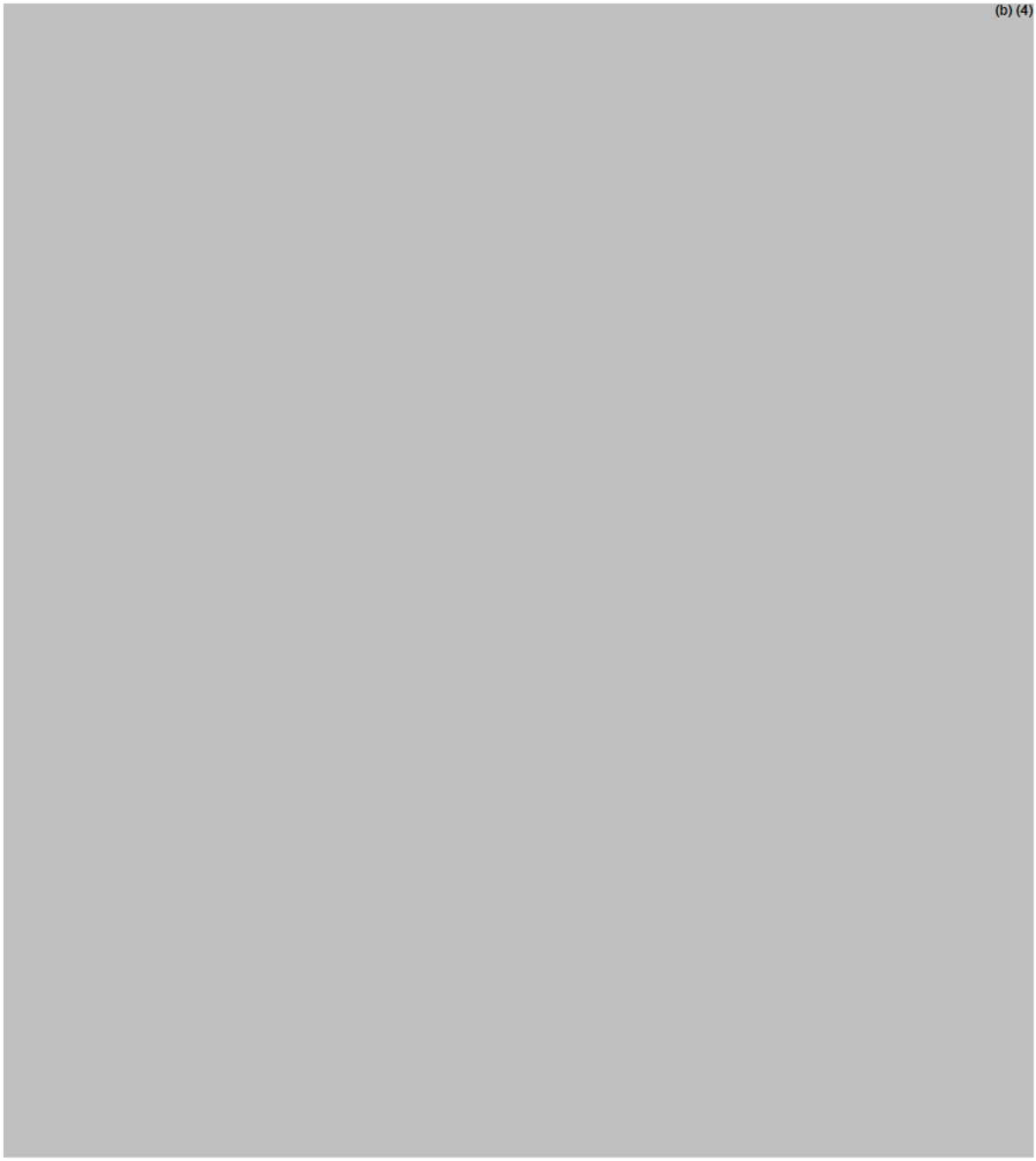
inhibitor; T_{max}: time at maximal concentration in plasma; $V_{d,ss}$, volume of distribution at steady state.

6.2. Information Request

NA.

Appendix Tables and Figures

Appendix Table 1. Input parameters of osimertinib using SimCYP (V14.1). (modified from Appendix A1 of ref [1])



Appendix Table 2. Simulation study design for DDI predictions

(b) (4)

(b) (4)

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APPENDIX 3: Genomics and Targeted Therapy Group Review

OFFICE OF CLINICAL PHARMACOLOGY GENOMICS GROUP REVIEW

NDA Number	208065
Submission Date	June 05, 2015
Applicant Name	AstraZeneca
Generic Name	Osimertinib (AZD9291)
Proposed Indication	Treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have progressed on or after EGFR tyrosine kinase inhibitor (TKI) therapy.
Primary Reviewer	Rosane Charlab Orbach, Ph.D.
Secondary Reviewer	Michael Pacanowski, Pharm.D., M.P.H.

1 BACKGROUND

Osimertinib is an irreversible EGFR TKI proposed for the treatment of patients with (b) (4) metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy.

The presence of sensitizing mutations in the EGFR tyrosine kinase domain defines a molecular subset of NSCLC tumors with a better prognosis and sensitivity to EGFR TKIs in the metastatic setting [PMID: 20966921, 23401451]. The best documented EGFR TKI-sensitizing mutations are exon 19 deletions and L858R in exon 21, representing about 90% of reported EGFR mutations in NSCLC. Between these two mutation types, patients with exon 19 deletions appear to have higher response rates to EGFR TKIs and longer survival compared to those with L858R [PMID: 16818686], illustrating the complexity of this molecular subset. The remaining 10% to 15% of EGFR mutations represent an even more diverse and phenotypically heterogeneous group, for which the clinical significance is not well established [PMID: 23403632].

First-generation (gefitinib, erlotinib) and second-generation (afatinib) EGFR TKIs are approved as first-line therapy in patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or L858R. However, despite initial clinical benefit, acquired resistance to EGFR TKI therapy invariably develops, with an average progression-free survival (PFS) of around 10 to 16 months [PMID: 25477325, 23401451]. The most commonly reported mechanism of acquired resistance to gefitinib and erlotinib (in approximately 50% of the cases) is the T790M second site mutation occurring within EGFR exon 20. This mutation, often referred to as “gatekeeper”, is believed to affect the binding ability of reversible TKIs such as erlotinib and gefitinib by both steric hindrance [PMID: 20103621] and by increasing the affinity of the mutant EGFR for ATP [PMID: 18227510]. Afatinib, an irreversible EGFR TKI, showed non-clinical activity against the EGFR T790M mutation at higher concentrations compared to drug-sensitive mutants, and therefore may still select for T790M clones [PMID: 26364032]. The EGFR T790M mutation has also been reported in <5% of untreated NSCLC using conventional methods.

Osimertinib is an irreversible EGFR TKI that targets the T790M resistance mutation and other EGFR TKI-sensitizing mutations, while having a reduced affinity for wild-type EGFR relative to

the mutant forms of EGFR. In accordance with its mechanism of action, non-clinical and early Phase 1 data showed that osimertinib would be most effective in pre-treated EGFR T790M mutation-positive NSCLC patients, with EGFR T790M mutation-negative patients deriving less benefit. Therefore, the Phase 2 trials of osimertinib supporting this NDA, AURA extension and AURA 2, were enriched for an EGFR T790M mutation-positive NSCLC population. The purpose of this review is to evaluate whether the EGFR T790M mutation status adequately defines the responder population in pre-treated metastatic NSCLC, and whether there is heterogeneity in treatment response based on the baseline EGFR mutation status (or other genetic factors). This review will also explore whether there is evidence of osimertinib activity beyond the proposed EGFR T790M mutation-positive population who have progressed on or after EGFR TKI therapy.

2 SUBMISSION CONTENTS RELATED TO GENOMICS

2.1 Non-Clinical Studies

The results of the following non-clinical studies were used to assess the apparent IC50s of osimertinib (AZD9291) in different mutations.

- Pharmacology Report-12: In Vitro Enzyme and Cellular primary pharmacology for AZD9291 and metabolites AZ13575104 and AZ13597550.

- Pharmacology Report-01: AZD9291, AZ13575104 and AZ13597550 Secondary Kinase Selectivity.

2.2 Clinical Studies

The clinical efficacy of osimertinib supporting NDA 208065 is based a total of 411 patients enrolled in 2 ongoing Phase 2 studies, AURA extension (n = 201) and AURA2 (n = 210). Both studies were open-label, single-arm studies of the safety, PK, and efficacy of once-daily osimertinib 80 mg tablet in pre-treated patients with locally advanced/metastatic NSCLC who had progressed on or after receiving at least 1 prior regimen of EGFR TKI therapy, and whose tumors were positive for the EGFR T790M mutation. Supportive efficacy data from the AURA Phase 1 study in pre-treated (second line or greater) EGFR T790M mutation-positive patients (80 mg dose) was used to provide further characterization of the clinical activity of osimertinib.

2.2.1 EGFR mutation status: AURA extension/AURA2

In both studies, patients were assigned to treatment after central confirmation of the EGFR T790M-positive status using the cobas® EGFR mutation test. The cobas assay is designed to identify exon19 deletions, L858R, T790M, G719X, S768I, exon 20 insertions, and L861Q. For confirmation, a tissue biopsy after progression on the most recent line of therapy was used. A pre-market approval (PMA) supplement has been submitted in the US for approval of the in vitro diagnostic (IVD) as a companion diagnostic for osimertinib.

In addition to EGFR T790M mutation-positive tumors, in AURA extension, eligible patients had either a confirmed EGFR mutation associated with EGFR TKI sensitivity (G719X, exon 19 deletions, L858R, L861Q) or they had experienced clinical benefit from EGFR TKI according to Jackman criteria [PMID:19949011] followed by objective progression while on continuous treatment with an EGFR TKI, while in AURA2, all patients had to have central confirmation of an EGFR TKI-sensitizing mutation to be enrolled.

The primary efficacy endpoint in both AURA extension and AURA2 studies was objective response rate (ORR), defined as the number of patients in the evaluable for response population (n = 397) who had a best objective response of complete or partial response (CR or PR) based on response evaluation criteria in solid tumors (RECIST) v1.1 by blinded independent central review (BICR). Secondary efficacy endpoints included disease control rate (DCR), duration of response (DoR), time to first documentation of objective response, best change from baseline in size of the target lesion (tumor shrinkage), PFS, and overall survival (OS).

2.2.2 EGFR mutation status: AURA Phase 1

The Phase 1 component of the AURA study was a first-in-human study that included various cohorts of EGFR mutation-positive advanced NSCLC patients (with or without the T790M mutation) following an initial dose escalation phase. The overall study included 355 patients: 31≥second-line patients in the dose escalation phase, 252 ≥second-line patients at various doses (20 mg to 240 mg) and with EGFR T790M mutation status centrally confirmed, 12 ≥second-line patients treated with the 80 mg Phase 1 tablet formulation, and 60 first-line EGFR TKI treatment-naive patients treated at 2 dose levels (80 mg and 160 mg). Of the 252 patients in the dose expansion, 163 (64.7%) had EGFR T790M mutation-positive tumors (157 evaluable for response; 59 treated with osimertinib 80 mg were evaluable for response based on BICR assessment of baseline imaging data), 69 (27.4%) had EGFR T790M mutation-negative tumors and 20 (7.9%) had tumors with an unknown EGFR T970M status. Patients in the expansion cohorts were permitted to enter based upon local assessment of EGFR TKI-sensitizing and T790M mutations, but with retrospective central confirmation of the mutation status.

Reviewer comment: (b) (4) *the reviewer evaluated ORR results in the first-line EGFR TKI treatment-naive and in the EGFR T790M mutation-negative cohorts included in AURA Phase 1 dose expansion.*

3 KEY QUESTIONS AND SUMMARY OF FINDINGS

3.1 Does EGFR T790M mutation status adequately define the responder population in pre-treated metastatic NSCLC?

The clinical efficacy of osimertinib, as assessed by ORR, is based on data from two Phase 2 studies, AURA extension and AURA2, and on supportive data from Phase 1, in patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy. Consistent with early Phase 1 results, significant objective response rates were observed in the Phase 2 studies, therefore

supporting the use of T790M mutation-positive status to define the responder population in the EGFR TKI resistance setting. No relevant differences in ORR were observed as a function of primary EGFR mutations (exon 19 deletions, L858R), prior EGFR TKI history or TKI timing, or race (Asian or non-Asian), although a trend appeared to favor Asian (vs. non-Asian) and patients with tumors positive for EGFR exon 19 deletions (vs. L858R). This trend suggests that the type of baseline EGFR mutation and race (Asian vs. non-Asian) may contribute to differential sensitivity to osimertinib. In contrast, pre-treated EGFR T790M mutation-negative NSCLC patients appeared to derive less benefit, and the marginal activity observed in Phase 1 may be driven by patients who did not have an EGFR TKI as the most recent therapy prior to study entry. In addition to the proposed population, first-line patients with locally advanced or metastatic NSCLC, the majority (76.7%) with T790M-negative tumors, appeared to derive benefit from osimertinib based on Phase 1 data, regardless of the presence or absence of a T790M mutation in the tumor. The impact of a T790M mutation-selective inhibitor on tumor evolution in treatment-naive patients with T790M-negative tumors is not clear. Limited data are available in first-line with T790M-positive NSCLC patients, who are less likely to benefit from available EGFR TKIs, to draw conclusions. The clinical results are in agreement with non-clinical osimertinib activity against TKI-sensitizing and the T790M mutated forms of EGFR.

3.1.1 EGFR mutations of interest (based on published literature)

The frequencies and characteristics of mutations relevant to this review are summarized below. The frequencies reported in this section may not reflect geographic and ethnic variations related to EGFR-mutated NSCLC, and/or differences in the patient populations and in the assays used to detect mutations in various studies. EGFR mutations can co-occur increasing the degree of complexity of tumor genotypes and potentially leading to differential sensitivity to EGFR TKIs [PMID: 20966921; 21531810; 23242437; 25994105].

Table 1: Location and frequency of EGFR mutations of interest based on literature

Mutation type	Location within EGFR tyrosine kinase domain	Estimated frequency in EGFR-mutated NSCLC [a]	Sensitivity to EGFR TKIs [a, c]
Exon 19 deletions	Exon 19	48%	increased
L858R	Exon 21	43%	increased
T790M	**Exon 20**	**<5% naive / 50% acquired resistance** [b]	**decreased**
Exon 20 insertions	Exon 20	4-10%	mostly decreased [d]
G719X	Exon 18	2-3%	possibly increased
S768I	Exon 20	2%	mixed-response
L861Q	Exon 21	2%	possibly increased

Source: www.mycancergenome.org; [PMID: 15886310, 25994105, 23485129]. [a] Results are controversial for uncommon mutations; [b] <5% of untreated EGFR-mutated tumors / 50% of EGFR-mutated tumors with acquired resistance to erlotinib/gefitinib; [c] Refers to non-T790M selective EGFR TKIs; [d] Although a few sensitive variants have been suggested, most exon 20 insertion variants are reported to be resistant to EGFR TKIs.

3.1.2 Non-clinical studies submitted by the applicant

3.1.2.1 Osimertinib selectivity against EGFR TKI-sensitizing and T790M resistance mutations

Please refer to the Pharmacology/Toxicology review for details on the referred studies. The following summary is based on results provided by the applicant.

Osimertinib (AZD9291) inhibited EGFR phosphorylation across cell lines harboring EGFR TKI-sensitizing [exon 19 deletions or L858R (PC-9, H3255, H1650)] or T790M resistance mutations (H1975, PC-9VanR), while having less activity against wild-type EGFR (LOVO, A431, H2073; apparent mean IC50s from 6 nM to 54 nM for mutant vs. 480 nM to 1.8 μM for wild-type). However, an osimertinib metabolite, AZ5104, demonstrated greater activity towards EGFR mutant and wild-type compared to osimertinib, displaying a smaller margin of selectivity between mutant and wild-type enzymes (Table 2), the potential impact of which has not been established. The applicant also reports that osimertinib and its metabolites (AZD5104, AZ7550) inhibited isolated mutant EGFR L861Q enzyme with apparent IC50s of 5, 1 and 29 nM, respectively (data generated at (b) (4). Of note, plasma levels of the AZ5104 and AZ7550 metabolites in humans were less than 10% of total circulating drug exposure. For details, please refer to the Clinical Pharmacology review (Dr. Jun Yang).

Table 2: Inhibition of EGFR phosphorylation in response to osimertinib (AZD9291) and its metabolites

	H1975 (L858R/ T790M)	PC9 VanR (Ex19del/ T790M)	PC9 (Ex19 del)	H3255 (L858R)	H1650 (Ex19 del)	LOVO (wt)	A431 (wt)	H2073 (wt)
AZD9291	15 (10, 20) n=16	6 (3, 13) n=5	17 (13, 22) n=16	60, 49	14, 12	480 (320, 720) n=16	2376, 1193	1865 (872, 3988) n=4
AZ5104	2 (2, 4) n=9	1 (0.004, 8) n=3	2 (2, 3) n=8	ND	ND	33 (24, 45) n=8	ND	53, 66
AZ7550	45 (34, 59) n=9	29 (8, 108) n=3	26 (10, 65) n=6	ND	ND	786 (480, 1292) n=7	ND	2356, 2367

Source: Applicant's table 3 - Nonclinical Written Summary-Pharmacology. pEGFR IC50 inhibition in response to compound following a 2 hour pre-incubation (apparent IC50 geomean, 95% confidence intervals when n>2, nM); ND=not determined.

In addition to EGFR, osimertinib and AZ5104 may also target ERBB2 (HER2) in vivo, but the extent of inhibition achieved at clinical exposures is uncertain. Other possible osimertinib targets based on biochemical assays may include ERBB4 (HER4), TEC and BLK.

3.1.3 Clinical studies submitted by the applicant

3.1.3.1 AURA2 and AURA Extension Phase 2 Studies

Baseline Demographics and EGFR mutation distribution

Of 873 patients that signed inform consent for AURA2 and AURA Extension, 462 (52.9%) failed screening. Of these, 372 (80.5%) failed screening because the EGFR T790M mutation-positive status was not confirmed by central testing. The 411 patients in the pooled AURA2/AURA extension population (full analysis set; FAS) had a median age of 63 years at study entry (range: 35-89), 67.9% of patients were female, 60.1% were of Asian racial origin (White, 36.2%), and 71.5% were never-smokers. The vast majority (96.1%) had metastatic NSCLC, and adenocarcinoma histology (96.1%). About one third (31.4%) received osimertinib as second-line therapy and 68.6% received osimertinib as ≥third-line therapy. The most common EGFR sensitizing mutations were exon 19 deletions (67.9%) and L858R (28.7%). Demographic characteristics were similar across studies and lines of therapy. The distribution of EGFR mutations at study entry is listed in Table 3.

Reviewer comment: The demographic characteristics are consistent with the fact that EGFR mutations are more common in (unselected) NSCLC tumors from East Asians (30% vs.10 % in Western Europeans), never-smokers and in tumors with adenocarcinoma histology [PMID: 23401451].

Table 3: EGFR mutation distribution in AURA extension and AURA2 (full analysis set)

EGFR mutation by central test, N	AURA extension N= 201	AURA2 N= 210	Total N=411
Exon 19 del / L858R / Other* / None	142 / 51 / 9 / 5	137 / 67 / 8 / 1	279 / 118 / 17 / 6
T790M: Positive / Negative / Unknown	197 / 3 / 1	208** / 0 / 0	405 / 3/ 1

Source: Applicant's presentation, June 19, 2015. * "Other" refers to uncommon EGFR mutations (G719X, S768I, exon 20 insertions). Co-occurrence is counted in more than one category. ** Although confirmed T790M-positive, the central mutation data for 2 patients in AURA2 is not associated with their final patient identifier. Exon 19 del= exon 19 deletions

Topline efficacy results

Based on the applicant's analyses, as of the data cut-off (DCO) for the Phase 2 studies of 9 January 2015, the confirmed ORR by BICR in the pooled evaluable for response population (N = 397) was 61.0%. ORR rates per study are indicated in Table 4. Of 242 patients with confirmed objective response (2 CR, 240 PR), 232 (95.9%) were ongoing in response at DCO, with DoR ranging from 1.1 months to 5.6 months. Median PFS has not yet been reached and OS data is immature. Phase 1 supportive data is presented in section 3.1.3.2 of this review. For full efficacy analyses of NDA 208065, please refer to Clinical review (Dr. Sean Khozin).

Table 4: Summary of ORR by BICR (evaluable for response analysis set) per study

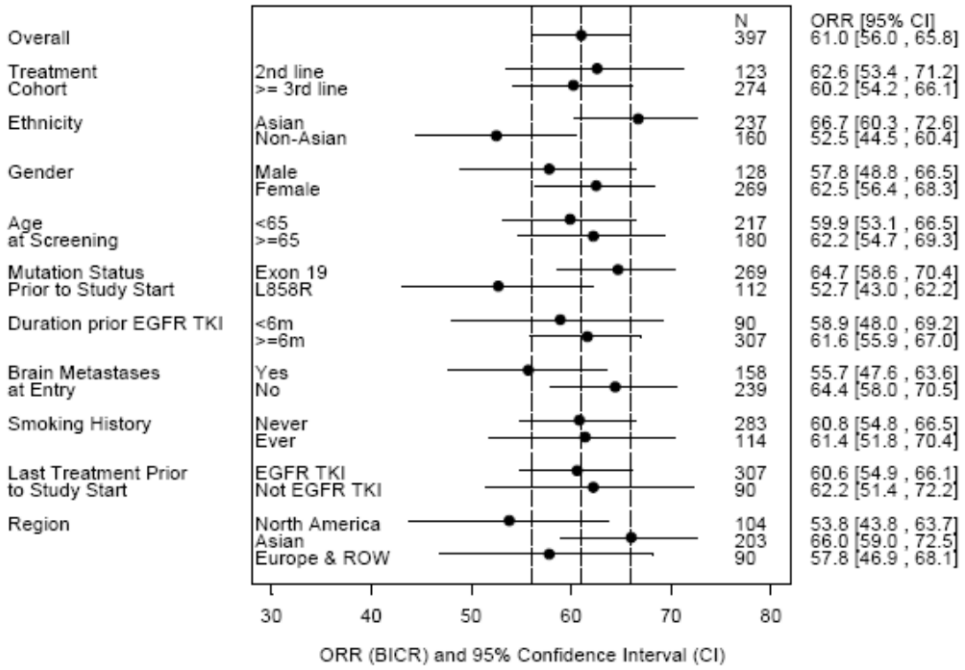
Analysis set Study	N	No. of patients with confirmed response[a]	ORR (%)	95% CI
BICR assessment of evaluable-for-response analysis set (primary efficacy analysis)				
AURA Extension AZD9291 80 mg	199	115	57.8	50.6, 64.7
AURA2 AZD9291 80 mg	198	127	64.1	57.0, 70.8
Total AZD9291 80 mg	397	242	61.0	56.0, 65.8

Source: Applicant's table 12 - Summary of Clinical Efficacy. BICR = blinded independent central review; ORR = objective response rate; [a] Responses exclude unconfirmed responses.

ORR according to subgroups

Based on the applicant's analyses, ORRs of 52.5% to 66.7% were observed across subgroups of interest (Figure 1). Numerical differences in ORR were observed for patients with tumors positive for exon 19 deletions (64.7%) vs. L858R (52.7%), with a trend favoring exon 19 deletions. Numerical differences in ORR were also observed for Asian (66.7%) vs. non-Asian patients (52.5%), and North American (53.8%) vs. Asian (66.0%) regions. Of four African-Americans in the evaluable for response population (1 in AURA extension and 3 in AURA2), all had PR as best objective response. ORR with osimertinib did not vary as a function of immediate treatment prior to study entry, including the time from prior EGFR TKI.

Figure 1: ORR by BICR, Forest plot by subgroup (evaluable for response analysis set)



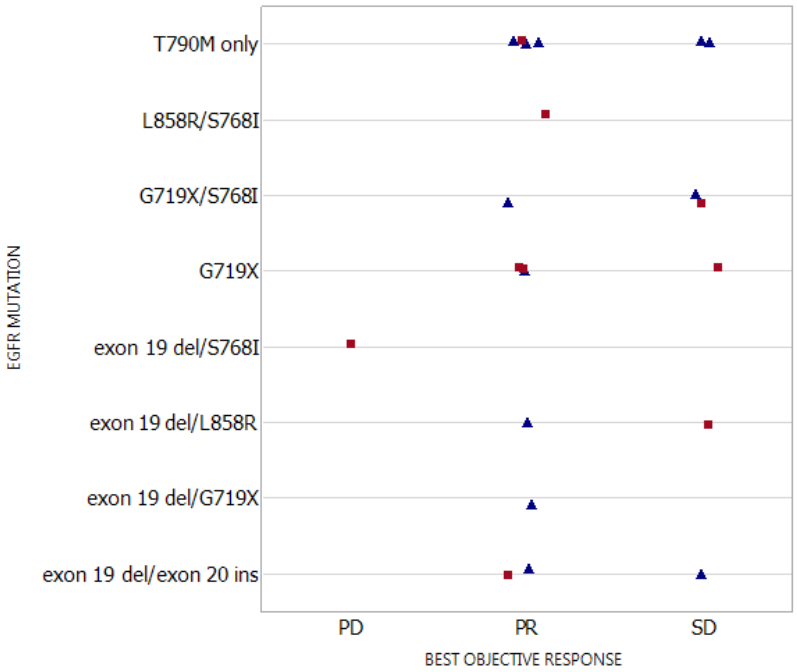
Source: Applicant's Figure 4- Summary of Clinical Efficacy. Two patients with both exon 19 deletions and L858R were grouped under exon 19 deletions. Objective response rate (ORR) and 95% CI. Dashed vertical lines represent the 95% confidence interval for the overall ORR.

Reviewer comment: ORRs of similar magnitude were observed irrespective of baseline EGFR mutation status (exon 19 deletions, L858R), prior EGFR TKI history or TKI timing, or race (Asian or non-Asian). The type of baseline EGFR mutation and race (Asian vs. non-Asian) may contribute to differential sensitivity to osimertinib, a pattern that has been observed with other EGFR TKIs.

Fifteen patients had tumors positive for uncommon EGFR mutation genotypes along with the T790M mutation. Six patients had tumors positive for EGFR T790M only. L861Q mutation was not reported in either study. Although limited by the small number of patients and heterogeneity of genotypes to determine whether uncommon EGFR mutation genotypes confer differential sensitivity to osimertinib, objective responses (PR: 13/21) were observed regardless of the uncommon EGFR mutation type (Figure 2) in both studies. Of note, 3 patients (2 in AURA extension and 1 in AURA2) had tumors positive for exon 20 insertions and exon 19 deletions along with the T790M mutation.

Reviewer comment: Exon 20 insertions are mostly associated with decreased sensitivity to EGFR TKIs and are not commonly reported to co-occur with other EGFR mutations. Due to potential cut-off issues in an early version of the mutation detection assay, it is possible that these 3 cases correspond to false positive results and should be interpreted with caution (for details, please refer to CDRH Summary of Safety and Effectiveness (SSED) for P120019/S007).

Figure 2: Best objective response by EGFR uncommon mutation category per study (evaluable for response analysis set)



Source: Reviewer analyses; AURA 2 (■) and AURA extension (▲). All represented patients had T790M-positive tumors. Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), Exon 20 ins = exon 20 insertions; exon 19 del= exon 19 deletions. Two patients with co-occurring common EGFR mutations (exon 19 deletion/L858R) were also included. One patient (exon 19 del/S768I) in AURA extension was not confirmed T790M positive. Exon 20 insertions cases may represent false positives.

Reviewer comment: Patients may actually have additional uncommon EGFR mutations in conjunction with the ones interrogated by the trial assay. It is also not clear whether osimertinib will be effective in patients whose primary EGFR mutation is an exon 20 insertion (an EGFR TKI resistance mutation), as the reported exon 20 insertion cases in AURA extension and AURA2 may be false positives.

3.1.3.2 AURA Phase 1 Component: Dose Expansion Population

Topline efficacy results

Phase 1 results were consistent with Phase 2 data. Based on the applicant analyses, the ORR in the 157 evaluable for response pre-treated patients with centrally-confirmed T790M mutation-positive NSCLC across all doses (20 mg to 240 mg) based on investigator assessment was 58.6% (95% CI: 50.5, 66.4): 92 of 157 patients had confirmed objective responses (2 CR and 90 PR). DCR was 89.8% (141/157). As of the DCO, the ORR by BICR in the 59 evaluable for response patients in the pre-treated 80 mg T790M mutation-positive subset (supportive data) was 54.2% (32/59 patients; 95% CI: 40.8, 67.3).

ORR according to subgroups

Pre-treated EGFR T790M mutation-negative cohorts: There were 69 centrally-tested EGFR T790M mutation-negative patients in the evaluable for response analysis set (Table 5). As of the DCO of 02 December 2014, the confirmed ORR across all doses based on investigator assessment was 23.2%. In total, 44 of the 69 evaluable patients had a PR or SD (DCR of 63.8%). Compared with pre-treated, centrally-tested EGFR T790M mutation-positive patients, the response rate and DCR in T790M mutation-negative patients were lower (58.6% and 89.8%, respectively).

Table 5: Pre-treated EGFR T790M mutation-negative (by central testing) population: Objective response rate and best objective response (evaluable for response analysis set)

	Dose expansion population Centrally-tested EGFR T790M mutation negative at study entry				
	20 mg AZD9291 (N=3)	40 mg AZD9291 (N=17)	80 mg AZD9291 (N=29)	160 mg AZD9291(N=20)	Total (N=69)
Partial response, n (%)	2 (66.7)	2 (11.8)	6 (20.7)	6 (30.0)	16 (23.2)
Confirmed ORR[a], n (%)	2 (66.7)	2 (11.8)	6 (20.7)	6 (30.0)	16 (23.2)
95% CI	9.4, 99.2	1.5, 36.4	8.0, 39.7	11.9, 54.3	13.9, 34.9
Stable disease ≥6 weeks, n (%)	1 (33.3)	5 (29.4)	14 (48.3)	8 (40.0)	28 (40.6)
Progressive disease, n (%)	0	10 (58.8)	9 (31.0)	6 (30.0)	25 (36.2)
Not evaluable, n (%)	0	0	0	0	0

Source: Applicant's table 24-D5160C00001 (Phase 1 component) Clinical Study Report.
Responses exclude unconfirmed responses; CI=confidence interval; ORR=objective response rate.

Although results are exploratory and limited by the small sample size, ORR in the pre-treated EGFR T790M-negative population appeared to be driven by the subgroup of patients whose most recent therapy prior to study entry was not an EGFR TKI (40.7 % vs. 11.9%; Table 6). This trend persists when time of EGFR TKI treatment (< 30 days vs. ≥30 days) is compared. These differences were not observed in the pre-treated T790M-positive cohorts or in Phase 2 data (Figure 1).

Table 6: Pre-treated EGFR T790M mutation-negative and T790M mutation-positive (by central testing) population: ORR by most recent prior treatment

EGFR TKI prior to study entry	T790M mutation-negative population N (%)		T790M mutation-positive population N (%)	
	Yes	No	Yes	No
EGFR TKI as most recent therapy prior to study	5/42 (11.9%)	11/27 (40.7%)	57/103 (55.3%)	35/54 (64.8%)
EGFR TKI <30 days before osimertinib *	3/32 (9.4%)	2/10 (20%)	37/64 (57.8%)	18/37 (48.6%)

Source: Applicant's D5160C00001 (Phase 1 Component) Clinical Study Report (tables 11.2.1.3 and 11.2.1.7) and reviewer analyses. * Information on EGFR TKI timing was not available for two patients with T790M mutation-positive tumors.

Reviewer comment: *Based on non-clinical data, osimertinib has activity against TKI-sensitizing mutations. The observed responses in tumors lacking T790M mutation may be explained by the presence (or re-emergence) of EGFR TKI-sensitizing clones, especially in tumors of patients whose most recent therapy prior to study entry was not an EGFR TKI (i.e., had intervening chemotherapy). Although tumor heterogeneity or mutation detection assay issues leading to false positives cannot be ruled out, the apparent higher activity noted in T790M-negative patients whose most recent therapy was not an EGFR TKI (and which was not observed in the T790M- positive population) would argue against tumor heterogeneity or detection issues as predominant reasons for the observed responses.*

About one third of patients (36%) with T790M-negative tumors had PD as best objective response based on investigator assessment (vs. 4.5% in the pre-treated T790M-positive population). Mechanisms implicated in resistance to EGFR TKIs other than the T790M mutation may have contributed to this result. These may include MET and ERBB2 gene amplification, PIK3CA or BRAF mutations, reduced neurofibromin expression, bypass through IGF-1R signaling, increased AXL kinase activation and phenotypic/histological changes (e.g., development of small-cell lung cancer (SCLC) features and epithelial-to-mesenchymal transition) [PMID: 19632948; 25477325]

First-line cohorts: According to the applicant, the protocol was amended (amendment 1, March 29, 2013) to include first-line cohorts based on non-clinical in vitro data suggesting that osimertinib may delay the development of EGFR TKI resistance through the EGFR T790M mutation. All 60 patients in the first-line cohorts were evaluable for response (80 mg n=30 and 160 mg n=30). EGFR TKI-sensitizing mutation-positive NSCLC and no prior therapy for advanced disease were inclusion criteria. EGFR mutation status (including T790M) was centrally confirmed; 36.7% and 40% had tumors harboring exon 19 deletions and L858R (one patient with L858R/S768I), respectively. The majority of patients (76.7%) had T790M-negative tumors as anticipated, but 8.3% (5 patients) had EGFR T790M mutation-positive tumors at baseline and 15% had unknown T790M status. Most patients were female (75%), Asian (71.7%), never-smokers (66.7%), presented with metastatic NSCLC (93.3%), and had

adenocarcinoma histology (100%). Based on the applicant, the overall ORR was 70.0% (95% CI: 56.8, 81.2), with a 60% ORR at the 80 mg dose level (95% CI: 40.6, 77.3) and an 80% ORR at the 160 mg dose level (95% CI: 61.4, 92.3).

Reviewer comment: As supported by osimertinib non-clinical activity against EGFR TKI-sensitizing mutations, the observed response rates in the first-line cohorts with the majority of patients having tumors positive for EGFR TKI-sensitizing mutations without detectable T790M are similar to those reported for other EGFR TKIs in the first-line setting. It has been suggested that (undetectable) T790M-positive and wild-type clones may coexist at baseline [PMID: 26269204]. The potential effect of an EGFR TKI-sensitizing and T790M mutant-selective inhibitor on tumor evolution and acquired resistance in the first-line setting is not known.

Of the 5 patients with T790M-positive tumors at baseline, 4 patients had PR and one patient had SD as best objective response.

Reviewer comment: Based on limited data from early-phase exploratory study, treatment-naive patients with T790M-positive tumors appear to respond to osimertinib.

3 SUMMARY AND CONCLUSIONS

- Osimertinib is an irreversible EGFR TKI that targets the T790M resistance mutation and other EGFR TKI-sensitizing mutations, while having a relatively lower affinity for wild-type EGFR.

- Non-clinical and clinical data support the proposed population of patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on or after EGFR TKI therapy.

- Based on AURA phase 1 component data; dose expansion cohorts:

    - Pre-treated patients who had T790M-negative tumors appeared to derive less benefit as compared to those with T790M-positive tumors, and the marginal activity observed in Phase 1 may be driven by patients who did not have an EGFR TKI as the most recent therapy prior to study entry.

    - First-line patients with locally advanced or metastatic NSCLC, the majority (76.7%) with T790M-negative tumors, appeared to derive benefit from osimertinib based on Phase 1 data, regardless of the presence or absence of a T790M mutation in the tumor. The impact of a T790M mutation-selective inhibitor on tumor evolution in treatment-naive patients with T790M-negative tumors is not clear.

    - Although supported by osimertinib mechanism of action, limited data are available in first-line T790M-positive NSCLC patients, who are less likely to benefit from available EGFR TKIs (i.e., 5 patients in AURA Phase 1 component), to draw conclusions.

- A Phase 3 trial of osimertinib vs. erlotinib or gefitinib as first-line treatment in patients with EGFR mutation-positive (exon 19 deletions, L858R), locally advanced or metastatic NSCLC is ongoing.

- The EGFR C797S mutation is reported to be a potential mechanism of resistance to osimertinib in T790M-positive NSCLC [PMID: 25939061]. Additional proposed mechanisms include a by-pass pathway activating either HER2 or MET [PMID: 26269204]. The exploration of resistance mechanisms may help to determine the best sequence among available EGFR TKIs and inform potential combination treatment strategies.

5 RECOMMENDATIONS

The submission is acceptable from a Genomics and Targeted Therapy Group perspective.

5.1 Labeling Recommendations

Please see integrated labeling recommendations in Section 3 of the Clinical Pharmacology review and final labeling language.

5.2 Post-marketing studies

No post-marketing commitments or requirements are recommended at this time.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUN YANG
10/05/2015

ROSANE CHARLAB ORBACH
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10/05/2015

VIKRAM P SINHA
10/05/2015

HONG ZHAO
10/05/2015
I concur.

NAM ATIQUR RAHMAN
10/05/2015
I concur.

November 12, 2015

This review references the incorrect NDA 206947 in the title. The review is actually related to NDA 208065.

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206947

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	208065/0	**Brand Name**	Not determined
OCP Division (I, II, III, IV, V)	OCP Division V	**Generic Name**	Osimertinib
Medical Division	DOP2	**Drug Class**	Small molecular
OCP Reviewer	Jun Yang, Ph.D. Luning Zhuang, Ph.D. Sarah Dorff, Ph.D.	**Indication(s)**	(b) (4) metastatic EGFR T790M mutation-positive NSCLC
OCP Team Leader	Hong Zhao, Ph.D. (CP); Yaning Wang, Ph.D. (PM) Rosane, Charlab Orbach, Ph.D. (GG)	**Dosage Form**	40 mg and 80 mg tablet
Pharmacometrics Reviewer	Luning Zhuang, Ph.D.	**Dosing Regimen**	80 mg daily (QD)
Date of Submission	6/5/2015	**Route of Administration**	Oral
Estimated Due Date of OCP Review	10/5/2015	**Sponsor**	AstraZeneca
Medical Division Due Date	10/28/2015	**Priority Classification**	Priority
PDUFA Due Date	11/15/2015		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	x			
Tabular Listing of All Human Studies	x			
HPK Summary	x			
Labeling	x			
Reference Bioanalytical and Analytical Methods	x	4		
I. Clinical Pharmacology				
Mass balance:	x	1		Study 11, 20 mg solution
Isozyme characterization:	x	2		
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -	x			
Healthy Volunteers-				
single dose:	x	3		Studies 5 and 10
multiple dose:				
Patients-				
single dose:				
multiple dose:	x	2		AURA1 and AURA2
Dose proportionality -	x			**AURA Phase 1 and cross study comparison**
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				Ongoing DDIs
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206947

Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				**waiver**
geriatrics:				
renal impairment:				Determined not to conduct
hepatic impairment:				ongoing
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:	**x**	**1**		
II. Biopharmaceutics				
Absolute bioavailability				**Ongoing**
Relative bioavailability -	**x**	**1**		
solution as reference:				
alternate formulation as reference:		**1**		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**x**	**1**		**20mg in HVs,** (b) (4)
Bio-waiver request based on BCS				
BCS class				**Not determined**
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Immunogenicity assessment				
Genotype/phenotype studies	**x**	**2**		**AURA and AURA 2**
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**6**		

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements

No	Content Parameter	Yes	No	N/A	Comment
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		x		Phase 2 used the final tablet formulation, no BE study is needed
2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	x			DDI with gastric pH modifying drugs were evaluated. Ongoing for DDI of CYP3A and BCRP
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or	x			

	submit a waiver request?				
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?		x		
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	x			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	x			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	x			
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	x			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	x			
	Complete Application				
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	x			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA 206947

	Content Parameter	Yes	No	N/A	Comment
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
1	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	x			
2	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	x			EGFR Mutation Status: EGFR-TKI "sensitizing" mutations and EGFR T790M.
	Studies and Analyses				
3	Is the appropriate pharmacokinetic information submitted?	x			
4	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	x			
5	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	x			
6	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	x			
7	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			x	Granted orphan drug designation; Pediatric disease-specific waiver is submitted.
8	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			x	In the United States, approximately 0.0% of incident patients were diagnosed under age 20;
9	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	x			
	General				
10	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	x			
11	Was the translation (of study reports or other study information) from another			x	

	language needed and provided in this submission?				

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
YES

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

Jun Yang — July 27, 2015
Reviewing Clinical Pharmacologist — Date

Hong Zhao — July 27, 2015
Team Leader/Supervisor — Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JUN YANG
08/12/2015

HONG ZHAO
08/12/2015
I concur.