

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208065Orig1s000**

**SUMMARY REVIEW**

## Division Director Summary Review

<b>Date</b>	November 10, 2015
<b>From</b>	Patricia Keegan
<b>Subject</b>	Division Director Summary Review
<b>NDA #</b>	NDA 208065
<b>Applicant Name</b>	AstraZeneca Pharmaceuticals, LP
<b>Date of Submission</b>	June 5, 2015
<b>PDUFA Goal Date</b>	February 5, 2016
<b>Proprietary Name / Established (USAN) Name</b>	Tagrisso/ osimertinib
<b>Dosage Forms / Strength</b>	Tablet for oral administration/ 40 mg and 80 mg tablets
<b>Proposed Indication(s)</b>	“for the treatment of patients with <span style="background-color: #cccccc; padding: 0 20px;">(b) (4)</span> metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.”
<b>Recommended Action for NME:</b>	<i>Approval under the provisions of 21 CFR 314.510</i>

<b>Material Reviewed/Consulted</b>	<b>Names of discipline reviewers</b>
OND Action Package, including:	
Regulatory Project Manager Review	Ingrid Fan
Medical Officer/Statistical Review	Sean Khozin, Chana Weinstock, & Joyce Cheng
Pharmacology Toxicology Review	Shawna Weis
CMC Review/OBP Review	Olen Stephens (Technical Lead); William M. Adams (Drug Product); Charles Jewell (Drug Substance); Ying Zhang (Process)
Biopharmaceutics	Gerlie Giesser & Okpo Eradiri
Microbiology & Process Review	Ying Zhang
Facility Review	Thuy Nguyen
Clinical Pharmacology Review	Jun Yang, Ada Zhuang, Ping Zhao, & Rosane Charlab Orbach
OSI	Lauren Iacono-Connors
OSE/DMEPA review	Otto Townsend
OSE/DRISK review	Carolyn L. Yancey
DPMH review	Carol H. Kasten
QT IRT	Huifang Chen
OPDP	Nazia Fatima
Patient Labeling Team Review	Nathan Caulk
CDTL Review	Gideon Blumenthal

OND=Office of New Drugs  
 OSI=Office of Scientific Investigations  
 OSE= Office of Surveillance and Epidemiology  
 DMEPA=Division of Medication Error Prevention and Analysis  
 DRISK=Division of Risk Management  
 DPMH=Division of Pediatric and Maternal Health  
 IRT=Interdisciplinary Review Team  
 OPDP=Office of Prescription Drug Products  
 CDTL=Cross-Discipline Team Leader

# Division Director Summary Review

## 1. Introduction

Tagrisso (osimertinib; Astra Zeneca Pharmaceuticals) is kinase inhibitor of both the wild-type and certain mutations of the epidermal growth factor receptor (EGFR); osimertinib also inhibits the activity of HER2, HER3, HER4, ACK1, and BLK.

This NDA relies on the results of two, open-label, fixed dose trials enrolling 411 patients with metastatic non-small cell lung cancer (NSCLC), evidence of disease progression while receiving a first-line EGFR tyrosine kinase inhibitor and documentation of EGFR T790M mutation-positive NSCLC as detected by the cobas® EGFR mutation test. All patients received osimertinib 80 mg once daily until disease progression or unacceptable toxicity. As agreed-upon with FDA, the primary endpoint was objective response rate (ORR) according to RECIST v1.1 as evaluated by Blinded Independent Central Review (BICR) and the key secondary endpoint was duration of response by BICR.

The data from the two trials were pooled to obtain more precise estimations of ORR, which were similar to the results in each trial alone. The patient characteristics were similar, with median ages of 62 and 64 years, 66% and 70% female; 58% and 63% Asian and 38% and 34% White; 66% and 60% WHO performance status 1; 67% and 76% never smokers; 70% and 68% had received prior chemotherapy as well as an EGFR TKI; somatic mutation in NSCLC with exon 19 deletion (71% and 65%), L858R (25% and 32%), G719X (2% and 2%), S768I (2% and 1%); CNS metastases (37% and 41%), in the AURA Extension and AURA2 trials, respectively.

Based on the BIRC determination, the confirmed overall response rate is 59% (95% confidence intervals (CI): 54, 64), with 96% of the 243 responders having ongoing responses ranging from 1.1 to 5.6 months. In order to better characterize duration of response, data were provided for a subgroup of 63 patients with T790M mutation-positive NSCLC, with disease progression on a prior EGFR TKI who received osimertinib at 80 mg daily in an earlier dose-escalation/dose expansion cohort of the AURA trial. In this subgroup, the BICR-confirmed objective response rate was 51% (32/63) and the median duration of response was 12.4 months.

The overall safety profile of osimertinib was primarily characterized in these 411 patients enrolled in AURA Extension and AURA2 who received osimertinib 80 mg daily, with evaluation of a larger patient experience of 813 patients receiving osimertinib 20 to 240 mg daily for uncommon, serious adverse reactions. The most serious adverse reactions of osimertinib identified across all clinical studies (n=813) were interstitial lung disease, cardiomyopathy, and QTc prolongation. Fatal ILD and fatal cardiomyopathy occurred in approximately 0.5% and 0.2% of patients, respectively. Across the 411 patients enrolled in AURA Extension and AURA2, 333 patients were exposed to osimertinib for at least 6 months,

97 patients were exposed for at least 9 months, and no patient was exposed to osimertinib for 12 months. In AURA Extension and AURA 2 studies (n=411), the most common (>20%) adverse reactions in osimertinib-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%).

There were no significant issues identified in the review of this NDA; however, the number of patients treated and the duration of exposure are relatively small and there is limited information on the durability of the response and on uncommon or late adverse reactions of osimertinib. A post-marketing requirement has been identified to verify the clinical benefit of osimertinib which will better characterize the toxicity profile and adverse reactions which may increase with cumulative exposure. In addition, studies to be conducted as either post-marketing requirements under 505(o) or 506B post-marketing commitments will provide additional information on the effects of intrinsic and extrinsic factors on the pharmacokinetics of osimertinib.

## 2. Background

### *Indicated Population and Available Therapy*

The NDA for osimertinib is intended to support the following proposed indication:

*For the treatment of patients with [REDACTED] <sup>(b) (4)</sup> metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. An improvement in survival or disease-related symptoms has not been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.*

Based on SEER, there will be an estimated 221,200 new cases (approximately 85% will be NSCLC) and 158,040 deaths due to lung cancer in the United States in 2015.<sup>1</sup> In the United States, approximately 15% of patients with adenocarcinoma of the lung harbor activating EGFR mutations.<sup>2</sup> Approximately half (57%) of new cases of lung cancer are metastatic at diagnosis; these patients have an estimated 5-year survival rate of 4.2%. While the SEER database does not provide information in genetically defined subgroups of NSCLC (i.e., those with EGFR mutations), the reported median overall survival times were 22.9 months and 28 months for EGFR TKI-treated patients in randomized trials of erlotinib and afatinib, respectively, which confirms the serious and life-threatening nature of EGFR mutation-positive NSCLC despite the availability of erlotinib, gefitinib, and afatinib.

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<sup>1</sup> <http://seer.cancer.gov/statfacts/html/lungb.html>. Accessed November 10, 2015.

<sup>2</sup> Keedy VL, Temin S, Somerfiled MR, Beasley MB, Johnson DH, McShane LM, et al. American Society of Clinical Oncology provisional clinical opinion: EGFR mutation testing for patients with advanced NSCLC considering 1st line EGFR TKI therapy. J Clin Oncol. 2011; 29: 2121-7.

Drugs which are FDA-approved for the treatment of patients with EGFR mutation-positive (exon 19 deletion or L858R substitution) metastatic NSCLC are erlotinib, afatinib, and gefitinib. There are no drugs which are FDA-approved for the treatment of patients with (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive-non-small-cell lung cancer (NSCLC), as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy, thus this is an unmet medical need.

FDA-approved drugs for the treatment of patients with NSCLC who have disease progression following platinum-based chemotherapy, (b) (4) are listed below with a summary of efficacy results. Based on the low overall response rates observed with these drugs, osimertinib appears to provide an advance (based on ORR) over these drugs.

**Docetaxel** is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of prior platinum-based chemotherapy. Approval was based on two randomized, open-label, active-controlled trials demonstrating an improvement in overall survival as compared to best supportive care [HR 0.56 (95% CI: 0.35, 0.88)], with median survival times of 7.5 months and 4.6 months, respectively; similar survival (5.7 months vs. 5.6 months) was observed for patients receiving docetaxel as compared to either vinorelbine or ifosfamide [HR: 0.82 (0.63, 1.06)]. In both trials, the ORR was relatively low: ORR 5.5% (95% CI: 1.1, 15.1) and ORR 5.7% (95% CI: 2.3, 11.3).

**Ramucirumab** is indicated, in combination with docetaxel, for the treatment of patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. Approval was based on randomized, double-blind, study of ramucirumab plus docetaxel versus placebo plus docetaxel, which demonstrated an improvement in overall survival [HR 0.86 (95% CI: 0.75, 0.98)] and progression-free survival [HR 0.76 (95% CI: 0.68, 0.86)]. The median survival was 10.5 months in patients randomized to ramucirumab plus docetaxel and 9.1 months for patients randomized to placebo plus docetaxel. The ORR was 23% (95% CI: 20, 26) for ramucirumab plus docetaxel.

**Pemetrexed** is indicated as a single-agent for the treatment of patients with locally advanced or metastatic **non-squamous** NSCLC after prior chemotherapy. Approval was based on a multi-center, randomized, open label, active-control study comparing pemetrexed to docetaxel in patients with NSCLC after prior chemotherapy which demonstrated a marginally significant improvement in overall survival [HR 0.78 (95% CI: 0.61, 1.0)]. The overall response rates were 8.5% (95% CI: 5.2-11.7) for those randomized to pemetrexed and 8.3% (95% CI: 5.1-11.5) for those randomized to docetaxel.

### *Presubmission Regulatory History*

On July 11, 2013, FDA issued a Safe May Proceed memo for the IND submitted June 11, 2013.

On November 6, 2013, FDA designated as a Fast Track development program the investigation of AZD9291 for the treatment of patients with metastatic NSCLC (b) (4) and have progressed following prior EGFR TKI therapy, based on the development program designed to demonstrate a clinically important increase in progression-free survival as compared to available therapy.

On January 13, 2014, FDA designated cobimetinib as an orphan drug for the treatment of (b) (4) melanoma with BRAF V600 mutation.

On January 14, 2014, a meeting was held to provide general advice on the adequacy of the development program (b) (4)

Key agreements and discussion were:

April 16, 2014: BTDR granted for the treatment of patients with metastatic, EGFR T790M mutation-positive, non-small cell lung cancer (NSCLC) whose NSCLC has progressed during treatment with an FDA-approved, EGFR tyrosine kinase inhibitor.

On September 4, 2014, FDA designated osimertinib (N-(2-{2-dimethylaminoethyl-methylamino}-4-methoxy-5-{[4-(1-methylindol-3-yl)pyrimidin-2-yl]amino}phenyl)prop-2-enamide mesylate salt) as an Orphan Drug for the treatment of epidermal growth factor receptor mutation-positive non-small cell lung cancer.

On July 8, 2014, AstraZeneca and Roche Molecular Systems (RMS) met with the Center for Devices and Radiologic Health (CDRH) regarding the development of a companion diagnostic for AZD9291. General agreement was reached regarding the PMA submission

for the RMS cobas® EGFR Mutation Test to serve as a companion diagnostic for AZD9291.

On August 15, 2014, FDA issued a memorandum, followed by a letter on September 11, 2014, providing general advice on the planned approach for drug product and drug substance stability data in the planned NDA.

On October 2, 2014, AstraZeneca met with FDA for Breakthrough Designation Type B Meeting to discuss the clinical and nonclinical components of a future NDA, respectively. On September 25, 2014, prior to the meeting, AstraZeneca communicated to FDA via email their intent to provide data from all the 175 patients in the AURA2 trial, with an assessment of efficacy in the proposed NDA based on approximately 350 subjects enrolled in the AURA extension and AURA2 trials, with all patients having at least 3-months of follow-up, supported by the results in approximately 50 patients enrolled in the Phase 1 portion of AURA 1 who were treated at the recommend Phase 2 dose with exposures up to approximately 20 months in order to provide additional data on durability of response. The summary results noted that the confirmed ORR was 61%; 95% CI (52% to 70%) in 127 evaluable, EGFR T790M mutation-positive patients treated with AZD9291. The following discussions and key agreements were:

- Inclusion of efficacy data from 431 patients with at least 3 months and maximum duration of follow-up of 7-8 months in the AURA extension and AURA2, with safety data from 511 patients treated at the proposed dose would support filing of the NDA.
- The proposed cardiac monitoring and analysis plan were adequate to characterize cardiac toxicity, however whether the information to be provided in the NDA is sufficient to identify and quantify a significant adverse effect on cardiac function will be determined during NDA review; post-marketing requirements to further assess the effect on LVEF may be required.
- The ECG monitoring and analysis plan were adequate to support an NDA filing.
- FDA generally agreed with the proposed pooling strategy for Studies D5160C00001 (AURA extension) and D5160C00002 (AURA2) in the ISS and ISE; the NDA should contain a detailed justification for combining the two studies and include tabulated summaries of key variables such as drug exposure and patients' baseline characteristics for each individual study. In addition, summarize and compare the major differences between the design and conduct of the studies, including the eligibility criteria. Provide the demographic and baseline tumor characteristics, and drug exposure for the pooled safety and efficacy populations.
- The primary analysis of ORR per BIRC assessment will be calculated based on all 350 patients enrolled in AURA extension and AURA2 trials.
- FDA agreed with the content, format, and proposed analyses of pooled datasets for efficacy and safety.
- FDA agreed with the proposal to submit a request for rolling NDA submission.
- The proposed clinical pharmacology package appeared generally acceptable to support the proposed NDA. The NDA should contain a description of the hepatic impairment, drug-drug interaction, and absolute bioavailability studies as post marketing requirements (PMRs) and AstraZeneca will need to provide adequate justification as to why the original NDA submission is complete without these study reports.

- With regard to the study intended to verify clinical benefit, the proposed study design intended to demonstrate superior PFS for osimertinib as compared to standard of care (gefitinib or erlotinib) in the first-line treatment of EGFR mutation-positive NSCLC (D5160C00007 [FLAURA]) was acceptable.

On October 7, 2014, AstraZeneca met with FDA for Breakthrough Designation Type B Meeting to discuss the CMC components of a future NDA, respectively. While FDA generally agreed with the proposed contents for a future NDA, FDA stated that AstraZeneca should request a formal Pre-NDA Meeting to reach final agreement on the NDA content and format in advance of submitting the NDA for review.

On October 28, 2014, FDA received a request for rolling submission and review of portions of the planned NDA.

On December 9, 2014, an interdisciplinary pre-NDA meeting was held to reach agreement on the content and format of the proposed NDA. Key agreements and discussions were:

- AstraZeneca's proposal to submit updated duration of response (DoR) data no later than July 31, 2015, more than 30 days after the submission of the final component of the NDA on June 5, 2015 was acceptable, however FDA may elect not to review the late submission. (b) (4)
- FDA generally agreed with AstraZeneca's approach for presentation of data on Adverse Effects of Special Interest; however other approaches (use of composite terms) may be considered based on FDA's review of the safety information.
- FDA requested that, in addition to the proposed safety analyses, the NDA contain analyses of adverse events leading to dose interruption and to dose reduction and median and ranges for time to first dose reduction, time to first dose interruption, and duration of dose interruption. Astra Zeneca agreed to provide this information for individual studies and for the pooled safety analysis.
- FDA agreed with the proposed exposure-response (E-R) analysis for efficacy (ORR) and for safety (diarrhea, rash) and Astra Zeneca agreed to provide an assessment for potential confounding factors for E-R relationships.
- FDA confirmed that agreement reached during the August 12, 2014, teleconference regarding data to be included in the NDA to support 12-month expiry dating.
- Based on AstraZeneca's description of the conduct (GLP-compliant) and results of the dose-finding, rat embryo-fetal development (EFD) study, FDA agreed that a formal EFD study was not required.
- Agreement was reached on the following late submissions (within 30 days of submission of the final portion of the NDA) of minor components: impurity qualification studies; updated DoR based on the data cut-off date of May 1, 2015, 9-month stability data on the commercial DP and DS batches.
- A REMS would not be required for filing the NDA based on the available data.

On January 16, 2015, FDA issued a letter accepting the amended request for rolling submission and review of the NDA. Based on this revised request, the NDA would be submitted in three components on January 26, April 7, and June 5, 2015.

On April 28, 2015, the Treatment Protocol D5160C00021 titled “A Multi-center, AZD9291 Expanded Access Program for the Treatment of Patients with Advanced/Metastatic EGFR T790M Mutation-Positive Non-small Cell Lung Cancer (NSCLC) Who Have Received Prior EGFR TKI Therapy,” submitted to IND 117879 on April 23, 2015, was allowed to proceed.

On May 12, 2015, FDA issued an Advice/Information request letter, which stated (b) (4)



On May 20, 2015, FDA issued an Advice/Information Request letter providing comments on the Dissolution Method Development Report and the information to be provided in the NDA regarding this aspect of CMC.

#### *Regulatory History of NDA*

- On January 26, 2015, the first portion of NDA 208065, containing a cover letter and form FDA 356h, Module 4, Module 5 (DMPK), and the summary for non-clinical data in module 2 was submitted for NDA 208065.
- On March 31, 2015, the proprietary name request was submitted to NDA 208065.
- On April 30, 2015, the second portion of NDA 208065 was submitted, containing a cover letter, Form FDA 356h and the datasets requested by the Office of Scientific Investigations (OSI) for use in selection of clinical study sites for bioresearch monitoring inspections.
- On June 5, 2015, the third and final portion of NDA 208065 was submitted, containing [the remaining information in Module 1, the remaining information in Module 2, all of Module 3 and the remaining information in Module 5 (all items except for the OSI datasets)].

### **3. CMC/ Biopharmaceutics**

I concur with the conclusions reached by the chemistry reviewer regarding the acceptability of the manufacturing of the drug product (osimertinib tablets) and drug substance (osimertinib mesylate). The drug product is not sensitive to light (b) (4). Microbial testing is not necessary for this drug substance or drug product as release specifications and will be monitored under stability testing. The proposed dissolution method and acceptance criteria were determined to be acceptable and data were provided in the application to bridge from the clinical trials product to the proposed commercial film-coated tablet formulation. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 12

months when at USP controlled temperature (20 °C to 25 °C (68 °F to 77 °F)) (b) (4)  
There are no outstanding issues.

In addition, the quality reviewers confirmed that the data provided support that the drug product is not degraded and absorption is not altered when prepared as an oral suspension for administration to patients who have difficulty swallowing, as described in agreed-upon product labeling.

No post-marketing commitments have been required however the following protocols are to be submitted to the NDA following approval:

- As described in the approval letter, “The comparability protocol to change the (b) (4) is acceptable, but this change must be reported as a CBE 30 and not a CBE 0.”
- A complete protocol to support the worst case scenario of (b) (4) will be provided, supported by the results of a long term stability study to generate the data necessary to establish the effect of an (b) (4) on the stability of the finished product, as a prior approval supplement.

## 4. Nonclinical Pharmacology/Toxicology

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharmacology/toxicology issues that preclude approval.

The NDA contained non-clinical pharmacology studies, 1-month and 13-week toxicology studies in rats and dogs, safety pharmacology studies (cardiovascular, CNS, respiratory and ocular, in vitro and in vivo genotoxicity studies, an in vitro phototoxicity study, and an assessment of embryofetal toxicity in GLP-compliant dose ranging study. FDA agreed that carcinogenicity studies were not required for the proposed indication.

Nonclinical pharmacology studies supported claims regarding inhibition of EGFR wild-type and EGFR T790M, L858R, exon 19 deletion mutations by osimertinib and of its active metabolites (AZ13575104 and AZ13597550) in in vitro studies and in tumor xenograft models, with greater activity against EGFR mutations than EGFR wild-type. In addition, inhibition was also observed against HER2, HER3, HER4, ACK1, and BLK at clinically relevant concentrations.

In 13- week non-clinical toxicology studies in rat and dogs, findings predicted by activity against wild type EGFR were observed in the GI tract (diarrhea, inappetence), skin (ulceration), cornea (corneal atrophy), and lungs (macrophage infiltration) were observed in both species at exposures approximating (rat) or 0.5 times (dog) that observed with the recommended human dose of 80 mg daily. The nonclinical toxicology studies in rats suggested impairment of male fertility based on increased pre-implantation losses in

unexposed females that had mated with males at exposures as low as 50% of that achievable with the recommended human dose.

Inhibition of cardiac ion channels, including hERG, was observed, however no effects on electrocardiology were observed in safety pharmacology studies. In safety pharmacology studies, there were equivocal findings of decreased contractility in dogs and guinea pigs.

Osimertinib was non-mutagenic in bacterial and mammalian cell assays and was negative for induction of structural chromosome aberrations in primary human peripheral blood mononuclear cells and the rat micronucleus assay. Therefore, product labeling does not recommend specific handling instructions (e.g., references to OSHA website).

In a GLP-compliant dose range-finding study in pregnant dams, administration of osimertinib on gestation days 2 through 20 resulted in increased post-implantation loss and early embryonic death at exposures 1.5 times that achievable with the recommended human dose. Administration of osimertinib on gestation days 6 through 20 at exposures achievable with the recommended human dose suggested an increase in the rate of fetal malformations (anencephaly and missing lung lobe) and variations as compared to controls.

## 5. Clinical Pharmacology/Pharmacogenomics

I concur with the conclusions reached by the clinical pharmacology and pharmacometrics reviewers that there are no outstanding clinical pharmacology issues that preclude approval.

The NDA contained the following studies and analyses addressing the clinical pharmacology of osimertinib: absorption, distribution, metabolism, and elimination (ADME) studies; single-dose studies in healthy volunteers; single- and multiple-dose (AURA Phase 1, AURA extension, and AURA2) studies conducted in patients with NSCLC; a food effects study with a high-fat meal, a study evaluating effects of pH-lowering agents on the absorption; exposure-response analyses for efficacy (response rate) and safety (diarrhea and rash); and a population pharmacokinetic (popPK) analysis evaluating for effects on intrinsic and extrinsic factors on osimertinib pharmacokinetics.

The recommended Phase 2 dose (RP2D) was based on the optimal biologic dose (OBD), which maximized clinical efficacy and minimized the incidence of adverse reactions arising from interaction with wild-type EGFR. The OBD was to be selected based on analysis of data obtained in Part 1 of the AURA trial, based on the following analysis:

- Dose vs. ORR, duration of response (DoR), depth of response and adverse events;
- Exposure of osimertinib and its active metabolites (AZ5104 and AZ7550) vs. ORR, DoR and depth of response and adverse event;
- Population PK exposure-response analyses for ORR, DoR, depth of response and adverse events.

Osimertinib is predominantly metabolized via CYP3A, with generation of two pharmacologically active metabolites (AZ7550 and AZ5104), which are present at

approximately 10% of the exposure of osimertinib. The median time to peak exposure (C<sub>max</sub>) is 6 hours and the median half-life is 48 hours. There was no evidence of a clinically important effect of a high-fat meal or of pH-lowering agents on the absorption of osimertinib. There is insufficient information to identify a safe and effective dose of osimertinib in patients with severe renal impairment or end-stage-renal disease or in patients with moderate or severe hepatic impairment.

There was no evidence of an exposure-response relationship for overall response rate. There were increasing risks of rash and diarrhea (all grades and  $\geq$  Grade 3) increasing osimertinib exposure. The relationship between ASZ9291 exposure and occurrence of interstitial lung disease (ILD) or ILD-like events was inconclusive.

There was no evidence of a large change in QTc (i.e., >20 ms) following single dose or multiple doses of osimertinib at the recommended dose, however a pharmacokinetic/pharmacodynamic (PK/PD) analysis suggested a concentration-dependent QTc interval prolongation at 80 mg (median increase of 14ms with 90% CI upper bound of 16ms). Based on the ECGs obtained in AURA2, 29% of patients had a QTc interval of >480 milliseconds (ms) and 0.5% of patients had an increase in QTc of >500ms.

In order to further characterize the safety, based on impact on the pharmacokinetic profile, of osimertinib, the following post-marketing requirements under 505(o) have been identified:

- Complete a pharmacokinetic study in patients to determine the pharmacokinetics and predict a reasonably safe dose, if any, of osimertinib when coadministered 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.*”
- Complete a pharmacokinetic study in patients to determine the pharmacokinetics and predict a reasonably safe dose, if any, of osimertinib when coadministered 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.*”
- Complete a pharmacokinetic study to evaluate the effect of repeated doses of osimertinib on the pharmacokinetics of a probe substrate of CYP3A4 to determine recommendations for coadministration of a CYP3A4 substrate with osimertinib in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.*”
- Complete a pharmacokinetic study to evaluate the effect of repeated doses of osimertinib on the pharmacokinetics of a probe substrate of BCRP to determine recommendations for coadministration of a BCRP substrate with osimertinib in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.*”
- Conduct a pharmacokinetic trial to determine the appropriate dose of osimertinib 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.*”

## 6. Clinical Microbiology

Not applicable. For microbiology and sterility issues relating to product quality, see Section 3 of this Summary Review.

## 7. Clinical/Statistical-Efficacy

The NDA relies on the pooled analyses of 411 patients enrolled in one clinical trial (AURA2) and a dose-expansion cohort of a larger trial (AURA Extension). Justification for pooling of the data is based on similar eligibility criteria and receiving the same treatment regimen (osimertinib 80 mg daily); it is noted that results are similar within each trial and when pooled. The number of patients evaluated provides a reasonable estimate of the overall response rate; however due to limited duration of follow-up, a reasonably precise estimation of the duration of response could not be obtained in these studies. Thus the application also relies on data in subgroup of patients enrolled in a dose-finding, activity estimating portion of the AURA trial, which has longer follow-up.

AURA Extension (also identified as Part 2 of Study D5160C00001 (AURA)) trial is designed as an open-label, non-randomized, non-comparative, multiple cohort trial. All patients received osimertinib at the recommended Phase 2 dose (80 mg once daily).

AURA2 protocol design is an open-label, non-randomized, non-comparative, multiple parallel cohort study to assess the safety and anti-tumor activity of osimertinib at the recommended Phase 2 dose.

Key eligibility criteria:

- Unresectable locally advanced or metastatic NSCLC
- Documentation of EGFR T790M mutation-positive NSCLC as detected by the cobas® EGFR mutation test
- Documentation of the presence one of the following EGFR mutations (G719X, exon 19 deletion, L858R, L861Q) or “clinical benefit” defined as complete or partial response or stable disease for  $\geq 6$  months while receiving following erlotinib or afatinib<sup>3</sup> ;
- Disease progression while receiving a first-line EGFR kinase inhibitor (e.g., gefitinib, erlotinib, afatinib).
- Prior treatment with a platinum-based regimen was permitted but not required in AURA Extension; patients who had received a platinum-based regimen were enrolled in a separate cohort of AURA2 ( $\geq$  third-line) from those who had received only a prior EGFR TKI (second-line cohort);

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<sup>3</sup> Jackman D, Pao W, Riely GJ, Engelman JA, Kris MG, Janne PA, Lynch T, Johnson BE, and Miller VA; Clinical Definition of Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Non-Small-Cell Lung Cancer. *J Clin Oncol* 28(2): 357-360, 2010.

- Prior treatment with a third-line EGFR TKI (e.g., CO-1686) was permitted in the AURA Extension study but not in AURA2.
- Patients with clinically important arrhythmias, QT prolongation, or taking medications likely to prolong QT were excluded; there were no eligibility criteria regarding baseline LVEF.

### Study Objectives

For regulatory purposes, as agreed upon during the January 14, 2014, meeting with FDA, the primary objective of the AURA Extension and AURA2 trials was determination of confirmed overall response rate (ORR), durable for at least 4 weeks, as determined by a blinded independent review committee (BIRC) (b) (4) masked to investigator assessment of response, in all patients who received at least one dose of osimertinib as of the data cut-off date. The key secondary endpoint was duration of response (DoR), as determined by the BIRC. Investigator-assessed ORR and DoR were additional efficacy endpoints. As per pre-submission communications and meetings, concordance between BIRC- and investigator-assessed ORR was also to be provided.

### Treatment plan:

All patients received osimertinib 80 mg orally, once daily, until disease progression or unacceptable toxicity.

Tumor assessments were obtained every 6 weeks; physical examination was performed pre-treatment, every 3 weeks Cycles 1-6, then every 6 weeks; ECGs were performed at screening visit, Cycles 1 - 6, and then every 6 weeks during treatment; an echocardiogram or MUGA scan was performed at screening and every 12 weeks thereafter; ophthalmologic examination was conducted pre-treatment and as clinically indicated.

### Statistical analysis plan:

The sample size for AURA2 was 175 patients total with 50 patients in the second-line cohort to allow the precision of the estimation of ORR within  $\pm 13\%$  and 125 patients in the third line or greater cohort to allow precision of the estimation of ORR within  $\pm 8\%$ . A similar sample size was applied to the AURA Extension 80 mg cohort for patients with prior EGFR TKI only (second-line) or those who had received an EGFR TKI and at least one other regimen (third-line or greater). Results were to be characterized using descriptive statistics only.

### *Bioresearch Monitoring Inspections*

Two clinical study sites were selected for inspection using CDER's Clinical Site Selection Tool (CSST). The CSST uses site specific data (e.g., enrollment, AE reporting, protocol violations, inspectional history) in a multi-attribute risk prioritization algorithm to display site level data for review, and use by the application review team to select clinical investigator sites for inspection. In addition, Astra Zeneca and the BIRC site (b) (4) were also inspected. Based on the review of preliminary inspectional findings for clinical study sites, the BIRC, and the sponsor, the data submitted to the Agency in support of NDA 208065, appeared reliable for use to support the application.

## Results

A total of 201 patients were enrolled between May 2014 and October 2014 across 40 clinical sites in 10 countries in Part 2 of the AURA trial (AURA Extension) and 210 patients were enrolled between June 2014 and October 2014 across 44 clinical sites in 8 countries in AURA 2. The database lock for clinical data provided in the NDA for both AURA Extension and AURA2 was January 9, 2015.

In AURA Extension, the baseline demographics and tumor characteristics were median age 62 years (range 37 to 89), female (66%), White (38%), Asian (58%), never smoker (67%), World Health Organization (WHO) performance status 0 (34%) or 1 (66%), adenocarcinoma histology, (97%), 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve] (30%), 2 or more prior lines of therapy (70%). Sites of metastasis were liver (32%), bone (51%), and brain (37%). Somatic EGFR mutations in addition to T790M were exon 19 deletion (71%), L858R (25%), G719X (2%), and S768I (2%).

In AURA 2, the baseline demographics and tumor characteristics were median age 64 years (range 35 to 88), female (70%), White (34%), Asian (63%), never smoker (76%), World Health Organization (WHO) performance status 0 (40%) or 1 (60%), adenocarcinoma histology (95%), 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve] (32%), 2 or more prior lines of therapy (68%). Sites of metastasis were liver (26%), bone (43%), and brain (41%). Somatic EGFR mutations in addition to T790M were exon 19 deletion (65%), L858R (32%), G719X (2%), and S768I (1%).

The median efficacy results for each study and pooled are summarized in the table below. Four percent of the patients with response have progressed, with a median duration of follow-up for the AURA Extension trial of 4.2 months and for AURA2 of 4.0 months. For the remaining 96% of the 243 responders, the duration of ongoing responses ranges from 1.1 to 5.6 months.

<b>Efficacy Measure (BICR)</b>	<b>Aura Extension (n=201)</b>	<b>AURA2 (n=210)</b>	<b>Pooled (n=411)</b>
Confirmed Objective Response Rate	57%	61%	59%
(95% CI)	(50, 64)	(54, 68)	(54, 64)
Complete Response	0	1%	0.5%
Partial Response	57%	60%	59%

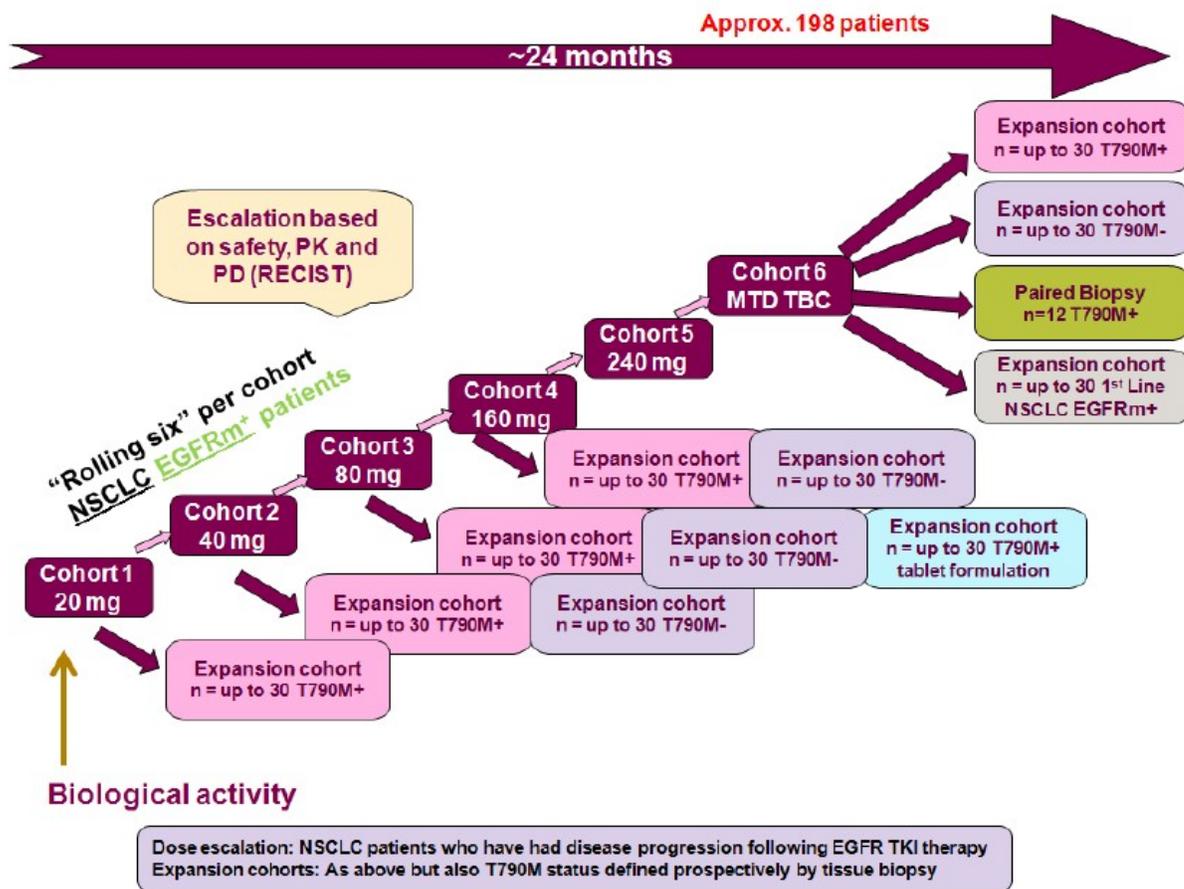
Exploratory analysis in demographic subgroups and in subgroups defined by tumor characteristics, most notably extent of prior treatment (first-line vs. second-line or greater) did not reveal any differences in anti-tumor activity.

### Supportive Efficacy Data

Study D5160C00001 (AURA), titled “A Phase 1, Open-Label, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumor Activity of Ascending Doses of AZD9291 in Patients with Advanced Non-Small Cell Lung Cancer who have

Progressed following Prior Therapy with an Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Agent.”

The general design of the dose-escalation and cohort expansion portion of that trial, which includes cohorts 1-5, is summarized in the figure below (abstracted from the briefing package for the January 14, 2014, meeting).



### Results

The database for Part 1 of the AURA trial was 355 patients; however efficacy analyses were limited to subset of 63 patients with T790M mutation-positive NSCLC, with disease progression on a prior EGFR TKI who received osimertinib at 80 mg daily. This subgroup was enrolled between September 2013 and November 2013, with a database lock of December 2, 2014. The median follow-up for this subgroup was 8.1 months (range: 0.5 to 14.3 months).

The median age of this subgroup was 60 years (range 40-81 years) with 30% age 65 years or older; 62% were female; 59% were Asian and 35% were White; 25% had WHO PS 0 and 75% WHO PS of 1; and two-thirds were “never smokers” and 32% were former smokers. At baseline, 98.4% had metastatic disease; 96.8% had adenocarcinoma, 1.6% large cell, and 1.6% “metastatic carcinoma” as the reported histologic subtype; all patients had T790M mutations alone (4.8%) or with other mutations, which included exon 19 deletions (65%), L858R substitutions (27%), and “other” (3.2%); the median number of prior treatment regimens was

4 (range 1-9), with a median of 2 prior EGFR TKI regimens with 75% having received prior erlotinib, 49% prior gefitinib, 30% prior afatinib, and 5% “other”. Two-thirds of patients received an EGFR TKI as their most recent prior therapy.

In this subgroup, the BICR-confirmed objective response rate was 51% (32/63) and the median duration of response was 12.4 months.

## 8. Safety

### *Size of the database,*

The safety database contained 766 patients with a data cut-off date of January 9, 2015 (January 16, 2015 for ILD) in the original NDA and was adequate to detect adverse reactions occurring at an incidence of 0.5%. Approximately 122 patients (16%) were exposed to osimertinib for more than 6 months. The original safety database was comprised of patients from AURA, AURA Extension, and AURA 2, as follows:

- AURA Part 1 (dose-escalation): 43 patients of whom 31 patients were dosed with the osimertinib capsule formulation and 12 patients with the 80 mg osimertinib tablet formulation;
- AURA Part 1 (dose-expansion): 312 patients dosed with osimertinib capsules (252 patients who had received prior therapy for NSCLC and 60 patients with no prior therapy for NSCLC);
- AURA Extension (AURA Part 2): 201 patients dosed with the osimertinib capsule formulation;
- AURA 2: 210 patients dosed with osimertinib capsules.

Updated safety information was provided for the 766 patients and new safety data from an additional 47 patients with a data cut-off date of May 1, 2015, were provided in the 90-day safety update, for a total safety dataset of 813 osimertinib-treated patients.

The overall safety profile of osimertinib was primarily characterized in these 411 patients enrolled in AURA Extension and AURA2 who received osimertinib 80 mg daily, with evaluation of a larger patient experience 813 patients receiving osimertinib 20 to 240 mg daily for uncommon, serious adverse reactions. The most serious adverse reactions of osimertinib identified across all clinical studies (n=813) were interstitial lung disease, cardiomyopathy, and QTc prolongation. Fatal ILD and fatal cardiomyopathy occurred in approximately 0.5% and 0.2% of patients, respectively.

Across the 411 patients enrolled in AURA Extension and AURA2, 333 patients were exposed to osimertinib for at least 6 months, 97 patients were exposed for at least 9 months, and no patient was exposed to osimertinib for 12 months. In AURA Extension and AURA 2 studies (n=411), the most common (>20%) adverse reactions in osimertinib-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%). Discontinuation of therapy due to adverse reactions occurred in 5.6% of patients; the most frequent adverse reactions leading permanent discontinuation of osimertinib were ILD and

cerebrovascular accidents/infarctions. Dose reductions occurred in 4.4% of patients; the most frequent adverse reactions that led to dose reductions or interruptions were prolongation of QTc (2.2%) and neutropenia (1.9%). Serious adverse reactions reported in  $\geq 2\%$  of patients were pneumonia and pulmonary embolus; fatal adverse events included ILD/pneumonitis, pneumonia, and CVA/cerebral hemorrhage

*Major safety concerns related to labeling*

The following items were identified as major safety concerns that should be included in the Warnings and Precautions section of Product labeling:

*Interstitial Lung Disease (ILD)/Interstitial Pneumonitis:* ILD is common to all EGFR tyrosine kinase inhibitors that inhibit EGFR wild type and EGFR activating mutations. Across all clinical studies of osimertinib, ILD in 3.3% (n=27) of osimertinib-treated patients (n=813); the incidence of fatal ILD was 0.5% (n=4).

*QTc Prolongation:* The heart rate-corrected QT (QTc) interval prolongation occurs in patients treated with TAGRISSO. The incidence of QTc greater than 500 milliseconds (ms) was 0.24%. Eleven (2.7%) of the 411 patients had an increase from baseline QTc greater than 60 ms. No cases of Torsades have been reported, however based on the limited safety experience, both in patient numbers and exposure, the risk of Torsade occurring at an incidence as high as 0.5% cannot be excluded.

*Cardiomyopathy:* Based on concerns regarding the potential for cardiomyopathy following a fatal case of cardiomyopathy observed in the dose-escalation, activity-estimating AURA trial and evidence that osimertinib inhibits the activity of HER2 in nonclinical studies, patients in the AURA Extension and AURA2 trials had assessment of LVEF by MUGA or echocardiogram at baseline and every 3 months. Across clinical trials, cardiomyopathy occurred in 1.4% (11/813) of osimertinib treated patients, with two deaths (0.2%) arising in patients with development of cardiomyopathy. Based on data provided in the 90-day safety update, among 176 patients with a baseline and at least one follow-up LVEF assessment in AURA Extension, 5 patients were identified with a 15% absolute decrease in LVEF; in two of these patients (1.1%) there was an absolute decrease in LVEF of 15% and an LVEF below 50%. Among 195 patients with a baseline and at least one follow-up LVEF assessment in the AURA2 study, 9 patients were identified with a 15% absolute decrease in LVEF and seven (3.3%) patients had an absolute decrease of 15% and an LVEF below 50%.

*REMS*

Both the clinical review team and the DRISK reviewer agreed that risk evaluation and mitigation strategies (REMS) are not required to ensure safe and effective use of osimertinib and that the serious risks of interstitial lung disease/interstitial pneumonitis and QTc prolongation can be mitigated through agreed-upon product labeling.

*PMRs and PMCs*

Two PMRs were required to further investigate the effects of hepatic impairment and strong CYP3A4 inhibitors on the pharmacokinetics of osimertinib due to the potential for increased

exposure leading to a potential increase in the incidence or severity of adverse reactions of osimertinib. The PMRs are described in Sections 5 and 13 of this Summary Review.

Three PMCs were required to evaluate the effects of extrinsic and intrinsic factors on the pharmacokinetics of osimertinib with the potential for lower than anticipated exposure and loss of or decrease in anti-tumor activity. The PMCs are described in Sections 5 and 13 of this Summary Review.

Finally, a PMR has been required to conduct adequate and well-controlled trials to verify the clinical benefit of osimertinib (b) (4). This PMR, under 21 CFR 314.510 is described in Section 13 of this Summary Review.

## 9. Advisory Committee Meeting

This NDA for a new molecular entity (osimertinib) was not referred for review to the Oncologic Drugs Advisory Committee (ODAC) because the safety profile is similar to that of other drugs approved for EGFR-mutation positive NSCLC; the clinical trial design is similar to that used to support previously approved products approved under 21 CFR 314.510 for the treatment of a genetically defined subgroup of NSCLC with disease progression following FDA-approved, genetically targeted therapy; and evaluation of the application did not raise significant safety or efficacy issues in the intended population. Therefore, outside expertise was not necessary; there were no controversial issues that would benefit from advisory committee discussion.

## 10. Pediatrics

On January 13, 2014, FDA designated cobimetinib as an orphan drug for the treatment of (b) (4) melanoma with BRAF V600 mutation. Therefore, cobimetinib for the approved indication is exempt from the requirements of the Pediatric Research Equity Act (PREA).

## 11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

## 12. Labeling

- Proprietary name: The proprietary name, Tagrisso, was identified as “conditionally acceptable” in correspondence dated June 2, 2015. The NDA review team, including the

OPDP reviewer, concurred with the DMEPA analysis that this name did not raise concerns regarding medication errors or promotional claims.

- Physician labeling

- Indications and Usage: Removed the phrase [REDACTED] (b) (4) of patients in AURA Extension and AURA2 had metastatic disease.
- Dosage Administration: edited for brevity; moved information [REDACTED] (b) (4) to a separate subsection for ease of identifying this information; removed statement that [REDACTED] (b) (4) [REDACTED] added dose modification for cardiomyopathy; modified language under 2.1 to reflect the need confirmation of genetic mutation [REDACTED] (b) (4)
- Dosage Forms and Strengths: edited for brevity/essential information
- Contraindications: no edits
- Warnings and Precautions: Added a new subsection on Cardiomyopathy for the reasons discussed in Section 8 of this Summary Review; edited subsection on embryofetal toxicity to include animal data; updated labeling to reflect risk of ILD across all clinical studies, reflect additional reports in 90-day safety update; and [REDACTED] (b) (4)
- Adverse Reactions: provided more detail on patient characteristics for safety population and described exposure data as per FDA Guidance on this section of product labeling; added information on most common adverse reactions, most common serious adverse reaction, incidence of dose modification (delay or reduction) and discontinuation for adverse reactions as well as most common adverse reactions resulting in dose modification or discontinuation. Expanded tabular listing of adverse reactions regardless of sponsor or investigator attribution, consistent with FDA Guidance on this section of product labeling; expanded tabular listing of laboratory abnormalities to include clinical chemistries, where Grade 3-4 laboratory abnormalities were identified; included cerebrovascular accident in the text as a clinically significant adverse reaction occurring at an incidence of greater than 2% but less than 10%.
- Drug Interactions: Revised for brevity, to clearly state that drug interaction studies with inhibitors, inducers or substrates of CYP enzymes and transporters have not been conducted, to provide advice on predicted interactions based on ADME studies.
- Use in Specific Populations: Sections 8.1-8.3 revised for conformance with the Pregnancy and Lactation Labeling Rule (PLLR); the basis for duration of contraception in females of [REDACTED] (b) (4) [REDACTED] 4 months in males [REDACTED] (b) (4) Subsection on geriatric patients edited for brevity; subsections on renal and hepatic impairment edited to briefly describe effects on PK in patients with hepatic or renal impairment based on population PK analyses

and state that there is no recommended dose in patients with moderate or severe hepatic impairment or severe renal impairment.

- [REDACTED] (b) (4)
- Description: Editorial changes.
- Clinical Pharmacology: Extensively edited subsection 12.3 for brevity and essential information; edited section 12.2 for brevity but retained description of results of pharmacokinetic analysis with predicted effects on QTc at the recommended dose of 80 mg; removed [REDACTED] (b) (4) in subsection 12.1 and included information on other targets (e.g. HER2) which may predict “off-target” toxicities.
- Nonclinical Pharmacology/Toxicology: Expanded information on study design, effects on fertility observed in nonclinical toxicology studies, and provide context on relative exposure as compared to that achieved with the recommended dose of 80 mg in humans.
- Clinical Studies: Edited to expand information on baseline demographic and tumor characteristics for AURA Extension and AURA 2, [REDACTED] (b) (4) [REDACTED] included information on duration of follow-up in AURA Extension and AURA2 to provide context; edited description of study design and population enrolled in the AURA trial for brevity and essential information necessary to support proposed indication.
- References: This section is not included in product labeling; references to the OSHA website for special handling instructions were not required because osimertinib is not genotoxic.
- How Supplied/Storage and Handling: Editorial changes; NCD number revised.
- Patient Counseling: Revised for consistency with format per FDA Guidance on this section of product labeling; added new subsections for QTc prolongation and Cardiomyopathy.
- Carton and immediate container labels: Container labeling for the 40-mg and 80-mg tablets are acceptable; changes were required to increase prominence of NDC on the label to avoid potential medication errors due to confusion between the 40-mg and 80-mg tablet.
- Patient labeling/Medication guide: Revised for consistency with USPI as revised, to ensure conformance with FDA’s Guidance for Useful Written Consumer Medication Information (2006) and current policy, written at no higher than 8<sup>th</sup> grade reading level [REDACTED] (b) (4) [REDACTED]

### 13. Decision/Action/Risk Benefit Assessment

- Regulatory Action: I concur with the recommendations of the review team and also recommend approval for this NDA under the provisions of 21 CFR 314.510 (accelerated approval).

- Risk Benefit Assessment

Metastatic, EGFR mutation-positive NSCLC is a serious and life-threatening disease with a median survival of approximately 2 years in two recently conducted randomized clinical trials. There are no drugs specifically approved for the treatment of patients who progress during first-line EGFR tyrosine kinase inhibitor (TKI) therapy (i.e., those with acquired resistance to an first-line EGFR TKI) and drugs approved for second-line treatment of NSCLC, following a platinum-based regimen (which includes two-thirds of those enrolled in AURA Extension and AURA 2, provided limited benefits and response rates ranging from 5% to 23%.

In the pooled analysis of AURA Extension and AURA 2, treatment with osimertinib resulted in an overall response rate of a 59% (95% CI: 54, 64). With a median duration of follow-up for the AURA Extension trial of 4.2 months and for AURA2 of 4.0 months, 4% of responding patients have progressed. For the remaining 96% of the 243 responders, the duration of ongoing responses ranges from 1.1 to 5.6 months. In a subgroup of patients enrolled in the AURA trial, who met the key eligibility criteria for the AURA Extension and AURA 2 trials who also received osimertinib 80 mg daily, the BICR-confirmed objective response rate was 51% (32/63) and the median duration of response was 12.4 months.

The most serious adverse reactions of osimertinib identified across all clinical studies (n=813) were interstitial lung disease, cardiomyopathy, and QTc prolongation. Fatal ILD and fatal cardiomyopathy occurred in approximately 0.5% and 0.2% of patients, respectively. Across the 411 patients enrolled in AURA Extension and AURA2, 333 patients were exposed to osimertinib for at least 6 months, 97 patients were exposed for at least 9 months, and no patient was exposed to osimertinib for 12 months. In AURA Extension and AURA 2 studies (n=411), the most common (>20%) adverse reactions in osimertinib-treated patients were diarrhea (42%), rash (41%), dry skin (31%), and nail toxicity (25%).

I agree with the recommendations of the review team, and concur this application should be granted accelerated approval based on the serious nature of the disease, unmet medical need, and demonstration of an overall response rate of 59% with a median duration of response that, based on the subgroup of patients treated in the AURA trial, of 12 months. The risk: benefit profile is favorable in that the durable ORR outweighs both the common and serious risks of osimertinib, which are similar to those already accepted by patients who have received a prior EGFR TKI and for there exists no satisfactory alternative therapy.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies  
Both the clinical review team and the DRISK reviewer agreed that risk evaluation and mitigation strategies (REMS) are not required to ensure safe and effective use of osimertinib and that the serious risks of interstitial lung disease/interstitial pneumonitis and QTc prolongation can be mitigated through agreed-upon product labeling. I concur with this assessment.

- Recommendation for other Postmarketing Requirements and Commitments

The following post-marketing requirement, under the provisions of 21 CFR 314.510, is required to verify the clinical benefit of osimertinib.

- 2978-1 Conduct and submit the results of at least one multicenter, randomized clinical trial establishing the superiority of osimertinib over available therapy as determined by progression-free or overall survival in patients with metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC)

The following post-marketing requirement trials were required under the provisions of the Food drug and Cosmetic Act 505(o) to conduct studies to assess for serious risks of osimertinib, which may result in an unintended increase in osimertinib exposure and increased risks of drug-related toxicity:

- 2978-2 Complete a pharmacokinetic trial to determine an appropriate dose of osimertinib in patients with mild to moderate 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.”
- 2978-3 Complete a clinical trial to evaluate the effect of a strong CYP3A4 inhibitor on the pharmacokinetics of osimertinib in accordance with the FDA draft Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

The following post-marketing commitments were agreed-upon between FDA and Astra Zeneca to further investigate factors that may result in decreased exposure to osimertinib, with the potential for effects on anti-tumor activity.

- 2978-4 Complete a clinical trial to evaluate the effect of a strong CYP3A4 inducer on the pharmacokinetics of osimertinib in accordance with the FDA draft Guidance for Industry entitled “Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.
- 2978-5 Complete a clinical trial to evaluate the effect of repeated doses of Tagrisso on the pharmacokinetics of a probe substrate 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.”
- 2978-6 Complete a clinical trial to evaluate the effect of repeated doses of Tagrisso on the pharmacokinetics of a probe substrate of breast cancer resistant protein (BCRP) in accordance with the FDA draft Guidance for Industry entitled “Drug Interaction

Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations.”

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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PATRICIA KEEGAN  
11/10/2015