CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategy (REMS) Review

Date:	October 29, 2015
Reviewer:	Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)
Acting Team Leader:	Naomi Redd, Pharm. D., DRISK
Division Director:	Cynthia LaCivita, Pharm. D., DRISK
Subject:	Evaluation to determine whether REMS is necessary to ensure that the benefits of osimertinib outweigh its risks
Drug Name:	TAGRISSO (osimertinib)
Therapeutic Category:	Kinase Inhibitor
Dosage, Form, Strength:	40 mg, 80 mg oral tablets
Office of New Drugs:	Division of Oncology Products-2 (DOP-2)
Application Type/Number:	Rolling Original NDA 208-065 received on June 5, 2015
Applicant:	AstraZeneca Pharmaceuticals, LP
PDUFA Deadline :	February 5, 2016
OSE RCM #:	2015-452 NME, Rolling NDA, PDUFA V Program, Risk Management Plan, Priority Review

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EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for AZD9291[1] (osimertinib), a new molecular entity (NME), kinase inhibitor (KI) proposed for the treatment of patients with 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 tyrosine KI (TKI) therapy. This Rolling Original New Drug Application (NDA) 208-065[2], submitted by Astra Zeneca to the Division of Oncology Drug Products-2 (DOP-2), includes a Core Patient Risk Management Plan that does not include a REMS proposal.

The DRISK and the DOP-2 concurred that osimertinib does not require a REMS to ensure that its benefits outweigh its risks of Interstitial Lung Disease (ILD), QT prolongation, and embryofetal toxicity. The DOP-2 and the DRISK concluded that oncology and hematology healthcare providers are informed on the clinical management of the serious risks associated with use of oral EGFR TKI products. Currently marketed oral TKIs [e. g., Iressa (gefitinib) approved May 2003; Tarceva (erlotinib) approved November 2004; and Gilotrif (afatinib) approved November 2013] are associated with similar risks as those reported with osimertinib and do not have a REMS to ensure that the benefits outweigh the risks associated with each product. See **Table 1**, in this review that includes the labeled safety risks with each product compared to osimertinib.

The prescription drug user fee act (PDUFA) goal date is February 5, 2016. This NDA is a Priority Review with accelerated approval based on tumor response rate and duration of response.

1 INTRODUCTION

The AZD9291 clinical development program was initially submitted on June 11, 2013 in the Investigational New Drug (IND) 117-879 for NSCLC. The FDA agreed to a rolling NDA submission on October 2, 2014[3] as AZD9291 was concurrently granted breakthrough therapy designation for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.

The AZD9291 clinical development program consists of two, Phase (P) 2, single-arm trials (AURA extension and AURA2) that include data from 411 patients (with a median of 4.4 months exposure to AZD9291 treatment) in the pooled P2 studies. These patients represent locally advanced and/or metastatic EGFR T790M mutation-positive NSCLC patients (129 patients [31%] 2nd-line [i.e., treated with prior EGFR TKI only], and 282

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[1] The laboratory code of the pharmacologically active parent drug, AZD9291, is used throughout the clinical description of the studies in this review.

[2] Rolling Original NDA 208-065 was received over 3 submissions: Part 1, Non-Clinical Sections submitted on January 26, 2015; Part 2, Clinical OSI datasets submitted on April 7, 2015; Part 3, Regional Information as Clinical and Quality Sections submitted on June 5, 2015

[3] In accordance with the *Guidance for Industry Expedited Programs for Serious Conditions - Drugs and Biologics (May 2014)*

patients [69%] greater than or equal to 3rd-line patients who had progressed on or after prior EGFR TKI plus additional therapies, 91% of whom had been treated with platinum-based doublet chemotherapy).[4] The AZD9291 is not marketed in any country at this time. The AZD9291 studies submitted in this application are:

- **AURA** is study D5160C00001, P1 component including dose-escalation, dose-expansion to determine safety, tolerability, biologically effective dose, and to determine the preliminary anti-tumor activity of AZD9291.
- **AURA extension** is study D5160C00001, P2 component, in EGFR mutation positive advanced NSCLC patients.
- **AURA2** is study D5160C00002, P2 in EGFR T790M mutation positive advanced NSCLC patients who have progressed following either one prior therapy with an EGFR TKI agent of following treatment with both EGFR TKI and, at least, one prior platinum-based doublet chemotherapy.
- The **AURA P3** study (D5160C00003) of AZD9291 versus (vs) platinum-based doublet chemotherapy in 410 patients with advanced NSCLC who have progressed on a prior EGFR TKI (b) (4) that is ongoing. Complete enrollment is projected in 3 quarter 2015. The primary analysis of profession free survival (PFS) is expected to be submitted in the 2nd half of 2016.[5]

The primary efficacy endpoint reported as the objective response rate (ORR) by blinded independent central review (BICR) was 61%, 95% Confidence Interval (CI) 56% to 65.8%, based on 242 responses from 397 evaluable EGFR T907M mutation positive patients in both P2 studies.[4]

2 BACKGROUND

2.1 PRODUCT BACKGROUND

As explained by the applicant, AZD9291 is an oral, irreversible EGFR-KI that is claimed to be effective against both EGFRm (KI sensitivity-conferring mutations) and EGFR T790M mutation- positive (KI resistance-conferring mutation). AZD9291is designed to have limited activity against the wild-type EGFR.[6]

AZD9291 is in a structural class with a differentiated KI profile for treatment of patients with advanced NSCLC who develop the T790M resistance mutation following progression on currently approved EGFR TKI therapy. As cited earlier in this review, AZD9291 is proposed for the treatment of patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy.[2]

2.2 PROPOSED FORMULATION AND DOSAGE

[4] NDA 208-065 AZD9291, Global Submit (GS), Module 2. Section 2.5 Clinical Overview, page 10 of 89

[5] NDA 208-065 AZD9291, GS, Module 2, subsection 2.5 Clinical Overview, page 20 of 89

[6] NDA 20-065 AZD9291, GS, Module 2, Section 2.5 Clinical Overview, subsection Product Development, page13 of 89

The proposed AZD9291 formulation is an oral tablet, 80 mg orally once daily, until disease progression or unacceptable toxicity. A 40 mg tablet is proposed to provide a dose reduction option for patients unable to tolerate the 80 mg dose.[2]

2.3 DISEASE CONDITION - LUNG CANCER AS ADVANCED EGFR T790M MUTATION-POSITIVE NON-SMALL CELL LUNG CANCER PATIENTS

Lung cancer is largely a disease of modern man and was considered rare before 1900 with fewer than 400 cases described in the medical literature. By mid-twentieth century, lung cancer has become epidemic and established as the leading cancer related deaths in North America and Europe, killing more than three times as many men as prostate cancer and nearly twice as many women as breast cancer.[7]

Lung cancer has been one of the most common cancers in the world for several decades (1.8 million new cases in 2012, 12.9% of all new cancers worldwide with an estimated 214,000 new cases in 2012 in the United States (US) [GLOBOCAN 2012].[8] It is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly 1 in 5 cancer deaths (1.59 million deaths; 19.4% of all deaths from cancer) in 2012,including 168,000 deaths in the US and 388,000 deaths in Europe (GLOBOCAN 2012).[4]

The largest majority (80 to 90%) of lung cancers is caused by cigarette smoking. Cigarette smokers have a 10-fold or greater increase risk of this cancer compared to those who have never smoked.[3] Other risk factors identified include occupational exposures to asbestos, arsenic, bischloromethyl ether, hexavalent chromium, mustard gas, nickel and polycyclic aromatic hydrocarbons.[3]

Exposure to environmental carcinogens, such as those found in tobacco smoke, induce or facilitate the transformation from bronchoepithelial cells to the malignant phenotype. The contribution of carcinogens on transformation is modulated by polymorphic variations in genes that affect aspects of carcinogen metabolism.[9]

Certain genetic polymorphisms of the P450 enzyme system, specifically CYP1A1, or chromosome fragility are associated with development of lung cancer. For example, first degree relatives of lung cancer probands have a 2- to 3-fold higher excess risk of lung cancer and other cancers, many of which are not smoking-related. These data suggest that specific genes and/or genetic variants may contribute to susceptibility to lung cancer. A rare germline mutation (T790M) involving the epidermal growth factor receptor (EGFR) may be linked to lung cancer susceptibility in never-smokers.[5]

The NSCLC represents approximately 80 to 90% of all lung cancers.[10] For the minority of patients with NSCLC who have resectable disease, surgery offers the best chance of

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[7] Horn L, Pao W, Johnson DH. Chapter 89, Neoplasms of the Lung, page 737 - 753

[8] NDA 208-065 AZD9291 (osimertinib), GS, Module 2.5 Clinical Overview, Subsection 1.2.1 Unmet medical need, page 13 of 89

[9] Horn L, Pao W, Johnson DH. Chapter 89 Neoplasms of the Lung, Subsection Inherited Predisposition to Lung Cancer, page 739

[10] Cataldo VD, Gibbons DL, Perez-Soler R, Quintas-Cardama A. Treatment of non-small cell lung cancer with erlotinib or gefitinib, *N Engl J* Med 2011;364(10):947-55

cure.[11] NSCLC is most often diagnosed at an advanced stage and has a poor prognosis.[12] Once NSCLC has progressed to a locally advanced or metastatic stage, there is no cure and treatment is focused on extending life, delaying disease progression and improving quality of life.

Since discovery of the common somatic mutations in the kinase domain of EGFR in 2004[13], it is confirmed that NSCLC patients with activating EGFR mutations in exons 18 through 21 of EGFR (including L858R and exon 19 deletions (Ex19del), collectively described as EGFRm) are a distinct subset of NSCLC in terms of pathogenesis, prognosis and treatment.[2]

Studies have identified EGFR mutations in approximately 10% of patients with lung cancer in the European Economic Area[14], 15% of patients with lung cancer in the US (American Society of Clinical Oncology provisional clinical opinion)[15], and 30% to 50% of patients with lung cancer in Asia[8]. EGFR mutations have been found more frequently in never smokers, in patients with the adenocarcinoma histologic subtype, and in women.[2]

2.4 ARMAMENTARIUM OF THERAPY FOR PATIENTS WITH NSCLC

Per the applicant's description, progress in molecular biology has changed the therapeutic approach to NSCLC and treatment of advanced NSCLC that can be guided by detection of mutations, e.g., EGFR, or anaplastic lymphoma kinase (ALK).[7] The National Comprehensive Cancer Network (NCCN) Guidelines for NSCLC recommend that the drug regimen with the highest likelihood of benefit and an acceptable toxicity profile for the prescriber and patient should be given as initial therapy, with NSCLC histology, EGFR mutation status, and ALK translocation status considered important factors in the selection of systemic therapy.[16]

According to the applicant and discussed in the BLA Team Meetings, at this time, there are no approved therapies that address acquired resistance to EGFR TKI therapy as a result of the EGFR T790 mutation, the most common mechanism of resistance to this class of drug.[17] Advanced EGFR T790M mutation-positive NSCLC patients who have progressed on EGFR TKI have a limited life expectancy, and are frequently symptomatic

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[11] Mountain CF. Revisions in the International System for Staging Lung cancer. *Chest* 1997; 111:1710-17

[12] Herbst RS, Heymach JV, Lippman SM. Lung Cancer *N Engl J Med*. 2008;359:1367-80

[13] Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, BRannigan BW, et al. Activating mutations in the EGFR underlying responsiveness of NSCLC to gefitinib. N Engl J Med 2004;350:2129-39

[14] Barlesi F, Blons H, Beau-Faller M, Rouquette I, Ouafik L, Mosser J, et al. Results of routine EGFR, HER2, KRAS, BRAF,P13KCA mutations detection and EML4-ALK gene fusion assessment on the first 10,000 NSCLC patients. J Clin Oncol 2013;31 [suppl; abstr 8000]

[15] Keedy VL, Temin S, somerfiled MR, Beasley MB, Johnson DH, McShane LM, et al. American Society of Clincial Onolocy proviionsla clinical opinion: EGFR mutation testing for patients with advanced NSCLC considering f1st line EGFR TKI therapy. J Clin Oncol. 2011;29:2121-7

[16] NDA 208-065 AZD9291 (osimertinib), GS, Module 2.5 Clinical Overview, Subsection 1.2.2 Current Treatment of Patients with EGFR Mutation Positive NSCLC, page 14 to17

[17] NDA 208-065 AZD929, GS, Module 2, Section 2.5 Clinical Overview, page 10 of 89

and debilitated by the disease. The EGFR is expressed in the epithelium which helps to preserve mucosal integrity, promote mucosal repair in the gut, and maintain the protective barrier of the skin.

- *1st Line Treatment of EGFR Mutation-Positive NSCLC*

Efficacy of EGFR KIs as gefitinib (Iressa™), erlotinib (Tarceva™), and afatinib (Gilotrif™) in patients with sensitizing EGFR mutations show that these patients are more likely to benefit from initial treatment with an EGFR KI in preference to doublet chemotherapy.[18, 19] Erlotinib and gefitinib are oral small-molecule kinase inhibitors that inhibit signaling via EGFR. They were the first EGFR inhibitors to be approved for the treatment of patients with NSCLC.

Xalkori (crizotinib) and Zykadia (ceritinib) are FDA-approved oral KIs with the indication for treatment of patients with metastatic NSCLC with anaplastic lymphoma kinase (ALK)-positive tumors as detected by an FDA-approved test. Neither product has a Boxed Warning or requirement for additional risk management measures, such as REMS.

– Xalkori (crizotinib) labeled safety risks (*Section 5 Warnings and Precaution*s) include hepatotoxicity, ILD, QT prolongation, (b) (4), and bradycardia.

– Zykadia (ceritinib) labeled safety risks (*Section 5. Warnings and Precautions*) include gastrointestinal (GI) toxicity, hepatotoxicity, ILD, QT prolongation, hyperglycemia, bradycardia, and pancreatitis.

The EGFR KI safety profile is considered favorable in comparison to the cytotoxic effects of chemotherapy.[13] See the Appendix, Table 1 with labeled safety risks across three approved oral EGFR TKI drugs compared to AZD9291. The most common treatment-emergent adverse events with EGFR KIs are GI and cutaneous effects, specifically, diarrhea and rash. Though most toxicity associated with EGFR KIs are similar for gefitinib and erlotinib, more diarrhea, rash, and paronychia have been seen with afatinib.[20] Most of these common adverse events tend to be mild to moderate; however, labeling for these drugs includes warnings of severe bullous/blistering/exfoliative events, hypersensitivity reactions (e.g., Stevens-Johnson syndrome), warnings about more serious clinical sequelae of diarrhea (e.g., dehydration, renal effects), and severe GI effects (e.g., GI perforation, hemorrhagic diarrhea). Some clinically significant ocular surface effects include keratitis and ulcerative events. Labeling for these drugs includes interstitial lung disease.[2] See the **Appendix**, in this review, **Table 1,** with labeled risks associated with approved oral EGFR TKI drugs compared to AZD9291.

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[18] Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isobe H, et al. Gefitinib or Chemotherapy for NSCLC with mutated EGFR. *New Engl J Me*d 2010;362:2380-8

[19] Wu Y-L, Liam C-K, Zhou C, Wu G, Liu X, Zhong Z, et al. First-line erlotinib versus cisplatin/gemcitabine in patients with advanced EGFR mutation-positive NSCLC: Interim Analysis form the Phase 3, Open-Label, ENSURE Study; Abstract P1.11-021. *J Thoracic Oncol* 2013: 8(Suppl 2) Presented at WCLC November 2013

[20] Burotto M, Manasanch EE, Wilkerson J, Fojo T, Gefitinib and Erlotinib in Metastatic NSCLC: A Meta-analysis of Toxicity and Efficacy of Randomized Clinical Trails. *The Oncologist* 2015;20:400-410

- *2nd Line Treatment of EGFR Mutation-Positive NSCLC*

Second-line platinum-based chemotherapy post EGFR TKI for EGFRm NSCLC generally provides response rates in the range of 20 to 30%.[11]

– *3rd Line Treatment of EGFR Mutation-Positive NSCLC*

Following progression on an EGFR KI and doublet chemotherapy, the only remaining options are re-challenge with EGFR KI, or salvage chemotherapy (usually a single agent), or an investigational agent through clinical trials.[21]

2.5 REGULATORY HISTORY

The regulatory history specific to NDA 208-065 for AZD9291 (osimertinib) follows:

- **June 11, 2013**: First-in-human studies with AZD9291 in patients with NSCLC (IND 117-879).
- **November 6, 2013**: The FDA granted Fast Track Designation for AZD9291for treatment of patients with metastatic NSCLC whose tumors harbor the T790M mutation and have progressed following prior EGFR TKI therapy. The clinical program was initially designed to demonstrate a clinically important increase in progression free survival (PFS) compared to available therapy.
- **April 16, 2014**: The FDA granted Breakthrough Designation (See the Introduction, in this review, for details).
- **July 1, 2014**: The applicant submitted an Initial Pediatric Study Plan that described plans to submit a waiver for pediatric requirements in NDA 208-065.
- **September 4, 2014**: The Office of Orphan Products Development granted Orphan Drug Designation for AZD9291 in the treatment of EGFR mutation-positive NSCLC.
- **December 9, 2014**: The FDA held an Interdisciplinary Pre-NDA, Type B Meeting with AstraZeneca to reach agreement on the content and format of the proposed NDA for AZD9291. The to-be-marketed formulation will be an 80 mg and 40 mg oral tablet. The applicant discussed the following results (dated August 1, 2014):
  - The confirmed ORR is 61%; 95% Confidence Interval (52% to 70%), across 78 responding patients among 127 evaluable, EGFR T790M+ patients treated with AZD9291. In more than 80% of the confirmed responses observed, the response has been sustained for more than 24 weeks. The median duration of response among approximately 50 patients with objective responses who were treated with the recommended Phase 2 dose of AZD9291 in the Phase 1 portion of the AURA trial is estimated to be 8.2 months with a lower 95% CI of 6.9 months based on the Kaplan Meier method.[22]

[21] Langer CJ, Mok T, Postmus PE. Targeted agents in the 3rd/4th-line treatment of patients with advanced (Stage III/IV) NSCLC. *Cancer Treatment Reviews* 2012;05:

[22] Pre-NDA, Type B Meeting Minutes, under IND 117,879 dated December 9, 2014.

- The intended NDA will include final and interim results of the AURA extension and the AURA2 trial, respectively.
- The sponsor planned to submit assessment of efficacy based on ~ 350 patients from AURA extension and AURA2, with all patients having had at least 3-months of follow-up. Supplemental information will provide characterization of the durability of response from ~ 50 patients enrolled in the dose-escalating portion of the AURA-1 trial who were treated with the 80 mg dose.

- **December 16, 2014**: The sponsor submitted request for a proprietary name for AZD9291 (under IND 117,879) and amended this request on January 14, 2015.
- **January 16, 2015**: The FDA granted a rolling NDA status to NDA 208-065.
- **January 26, 2015**: The applicant submitted Part 1 of NDA 208-06 to the DOP-2.
- **February 24, 2015**: The applicant submitted Request for Proposed Proprietary Name Review as (b) (4) to the Division of Medication Error Prevention and Analysis (DMEPA).
- **March 31, 2015**: The applicant submitted Request for Proprietary Name Review for an alternate proprietary name, Tagrisso. The proposed established name, (b) (4), remained unchanged.
- **April 13, 2015**: The applicant *submitted Proprietary Name Safety Evaluation Report.* Both proposed names, (b) (4) and Tagrisso, were evaluated. Based on the Med-ERRS staff performing a Failure Mode and Effects Analysis for the proposed trademark candidates and considering the clinical criteria that can increase or decrease the risk of medication confusion with another product, both proposed names scored a 5, with 1 being the "poorest" and 5 being the "best".
- **April 30, 2015**: The applicant submitted Part 2 of NDA 208-065 to DOP-2.
- **May 29, 2015**: The applicant submitted Proprietary Name Review Amendment to the DMEPA for the *new* trade name, Tagrisso, and *new* established name, osimertinib.
- **June 5, 2015**: The applicant submitted Part 3 of NDA 208-065 to DOP-2 and requested Priority Review for this NDA.
- **June 16, 2015**: The DOP-2 held the Filing Meeting for NDA 208-065. Priority Review status was granted. There were no filing issues for discussion.

  Preliminary discussion occurred with DOP-2 Division Director, Cross-Disciplinary Team Leader, and DOP-2 Clinical Efficacy and Safety Reviewers regarding the serious risks of ILD, QT prolongation, and embryofetal toxicity associated with use of osimertinib and the potential need for a REMS program. The DOP-2 stated that hematology and oncology healthcare providers are familiar with clinical management of the known serious risks associated with use of oral EGFR TKI therapies. The reported ILD as well as QT prolongation associated with AZD9291 appear to be mild to moderate compared to approved oral EGFR TKIs with worse safety profiles. The QT prolongation is not among the serious risks associated with afatinib, erlotinib or

gefitinib (See the **Appendix**, in this review, **Table 1,** which shows labeled risks across approved oral EGFR TKIs in NSCLC).

- **August 12, 2015**: The Office of Surveillance and Epidemiology (OSE) and the DRISK held an OSE Pre-Mid-Cycle Safety Meeting. The QT prolongation appears to be mild and manageable with labeling. The DPV reviewer noted that the proposed formulation for osimertinib is targeted differently (metastatic EGFR T790M mutation-positive NSCLC) and appears to offer a more favorable safety profile compared to other oral TKIs (targeted for tumors with EGFR exon 19 deletions or exon 21 substitutions).
- **August 19, 2015**: The applicant submitted requested clinical information, in response to concerns about patients [a total of 381 patients (92.9%)] who experienced increases in creatinine while on the study treatment, AZD9291.
- **September 1, 2015**: The applicant submitted a response to an Information Request from the DOP-02 for historical control comparison study statistical analysis plan (See NDA 208-065/Sequence 002). These data were requested via Drs. Pazdur, Keegan, Blumenthal, and Khozin on July 9, 2015 and in subsequent teleconference discussions.

  The purpose of this submission was to provide background and details regarding a proposal to convert from Accelerated Approval to Full Approval based on an analysis of the AZD9291 P2 data compared to historical patient-level data from a separate study with a similar patient population.
- **September 2, 2015**: The Mid-Cycle Meeting for AZD9291 was held. The Clinical Review Team agreed that the applicant achieved the primary efficacy endpoint, ORR of 59.9% for the single-arm, 80 mg once daily dose (AURA extension and AURA 2 study) per the DOP-2 Clinical Efficacy Reviewer, Sean Khozin, M. D. Asian patients appear to be more responsive to AZD9291 compared to non-Asian patients. Patients with central nervous system metastases need further investigation as underscored by Richard Pazdur, MD. The DOP-2 Clinical Safety Reviewer, Chana Weinstock, M. D., concluded that the major serious risk with exposure to AZD9291 is ILD/pneumonitis that may be potentially fatal. The most common reported adverse events were rash including dry skin, diarrhea, and nail disorders.

  Based on the clinical safety data available at this meeting, the DOP-2 and the DRISK agreed that, at that time, REMS was not needed for osimertinib to ensure the benefits out weight the risks. The serious risks in proposed labeling, *Section 5. Warnings and Precautions* are ILD, QT prolongation, and embryofetal toxicity.
- **September 11, 2015**: Mid-Cycle Communication Meeting (via teleconference) with the applicant. There were no significant issues regarding Clinical, Statistics, Clinical Pharmacology, and Non-clinical. Chemistry Manufacturing and Controls (CMC) discussed outstanding issues (e.g., calculation of unspecified impurities, preparation of an oral suspension for patients who have difficulty swallowing (evaluation of the data to support commercial launch of the proposed clinical batches), and evaluation of the bulk product storage and shipping studies) with plans to resolve these concerns. There are no plans to convene an Advisory Committee Meeting for AZD9291.

Postmarketing Requirements (PMR) and/or Commitments (PMC) were discussed:

- Clinical PMR
  1. Conduct and submit results of at least one multicenter, randomized clinical trial establishing the superiority of osimertinib over available therapy in patients with metastatic EGFR T790M mutation-positive NSCLC.
- Clinical Pharmacology PMRs
  2. Complete a pharmacokinetic (PK) study in patients to determine how to dose AZD9291 with inhibitors of CYP3A4.
  3. Complete a PK study in patients to [redacted] (b) (4) with inducers of CYP3A4.
  4. Complete a PK study to evaluate the effect of repeated doses of AZD9291 on the PK of a probe substrate of CYP3A4 [redacted] (b) (4)
  5. Complete a PK study to evaluate the effect of repeated doses of AZD9291 on the PK study of a probe substrate of Breast Cancer Resistance Protein (BCRP) [redacted] (b) (4)
  6. Conduct a PK trial to determine the appropriate dose of AZD9291 in patients with hepatic impairment.

- **October 13, 2015:** The DOP-2 held the Late-Cycle Meeting for NDA 208-065. The applicant agreed with the 6 proposed postmarketing requirements. The DOP-2 agreed to send the substantially complete proposed osimertinib labeling to the applicant by October 16, 2015 for the applicant's agreement and/or comments and/or questions.

2.2 Materials Reviewed

- **June 5, 2015**: Original NDA 208-065 Tagrisso (AZD9291/osimertinib) proposed for the treatment of [redacted] (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TK therapy. A Core Patient Risk Management Plan was submitted in Module 1.16, Risk Management Plan.
- **September 2, 2015**: NDA 208-065, DOP-2 Mid-Cycle Review Slide Deck per Sean Khozin, M. D., Clinical Efficacy Reviewer, DOP-2; Chana Weinstock, M. D., Clinical Safety Reviewer, DOP-2; and Joyce Cheng, DOP-2 Biostatistics Reviewer, Ph.D.
- **September 2, 2015**: NDA 208-065, 90-Day Safety Update Report (data cut-off on June 1, 2015).
- **September 8, 2015**: Label and Labeling Review written by Otto L. Townsend, Pharm. D., DMEPA; Chi-Ming "Alice" Tu, Pharm. D., Team Leader, DMEPA
- **September 24, 2015:** Mid-Cycle Communication Meeting Minutes written by Ingrid Fan, RPM, DOP-2

- **October 5, 2015***:* Clinical Pharmacology Review written by Jun Yang, Ph. D.; Hong Zhao, Ph. D.; Ada Zhuang, PH. D., Division of Clinical Pharmacology, DOP-2.
- **October 15, 2015**: Clinical Efficacy Review for Osimertinib written by Sean Khozin, M. D., Clinical Reviewer, DOP-2
- **October 20, 2015**: Secondary Review for Osimertinib written by Gideon Blumenthal, M. D., DOP-2 Team Leader
- **October 22, 2015**: Comments from the applicant on the DOP-2 proposed revisions to the substantially complete labeling for osimertinib (labeling is under negotiation)
- ***Pending*** **October, 20**15: Clinical Safety Review for Osimertinib written by Chana Weinstock, M. D., Clinical Reviewer, DOP-2

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The clinical development program in NDA 208-065 for AZD9291, proposed to treat patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy, is based on clinical data from AURA, Phase (P)1 component, AURA extension (P2 component), and AURA 2 (P2 component). All patients received prior EGFR TKI therapy. A mandatory biopsy after progression on the most recent treatment regimen was required for central testing of T790M mutation status, prior to enrollment, to ensure a molecularly characterized patient population.[23] Brief description of these trials follows:

- **AURA** (D5160C00001, P1 component): a multi-center, open-label (OL), dose-escalation, and dose-expansion study to determine safety and tolerability, maximum tolerated dose (MTD), effective dose, pharmacokinetic (PK), and preliminary anti-tumor activity of AZD9291 (n = 355 patients).
- **AURA extension** (D5160C00001, P2 component): a single-arm, OL, non-randomized study extension to AURA (n = 201 ≥ 2nd-line patients treated with AZD9291, 80 mg per day).
- **AURA 2** (D5160C00002, P2 component): a single-arm, OL, non-randomized study to replicate efficacy and safety data observed in the AURA extension study (n = 210 ≥ 2nd-line patients treated with AZD9291, 80 mg per day).

Follow-up on the P2 studies is insufficient to estimate the median duration of response (DOR) for this NDA (Mid-cycle Meeting, per DOP-2 Clinical Review Team).

The confirmatory trial, **AURA3,** is an ongoing randomized P3 study (D5160C00003) for AZD9291 versus (vs) platinum-based doublet chemotherapy in 410 patients with advanced NSCLC who have progressed on a prior EGFR TKI (b) (4) (b) (4) The complete enrollment is projected by the end of 3rd quarter 2015.

[23] Abbreviations used in Section 3, of this review, follow: BICR-blinded independent central review; DoR-duration of response; MTD-maximum tolerated dose; n-number; PK-pharmacokinetic; P-Phase; OL-Open-Label; ORR-objective response rate; OS-overall survival; PFS-progression free survival; vs-versus.

[24] Cut-off date for P1 (AURA) study was December 2, 2014 and for both P2 studies (AURA extension and AURA2) the cut-off date was January 9, 2015. The formal cut-off date of January 16, 2015 was used in the

Clinical Efficacy

The primary endpoint of both studies (AURA and AURA Extension) was the objective response rate (ORR), defined as the percentage of patients with confirmed complete response or partial response to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and assess by blinded independent central review (BICR). Patients were scanned at baseline and every 6 weeks until objective disease progression. The ORR was analyzed at approximately 3 and 8 months after the last patients were enrolled, and patients were followed for duration of response (DOR), progression-free survival (PFS), and overall survival (OS). The ORR, supported by the DOR, was considered a surrogate endpoint likely to predict clinical benefit in pre-treated patients that can be used in single-arm studies because it is a direct measure of the drug's anti-tumor activity (Pazdur, 2008)[25].

Results of Clinical Efficacy

Primary Efficacy Endpoint - Objective Response Rate

As of the data cut-off for the P-2 studies (January 9, 2015), AURA extension and the AURA2, the confirmed ORR by BICR was 61%; 95% confidence interval (CI) (56% to 65.8%), based on 242 of 397 evaluable EGFR T790M mutation-positive patients with confirmed objective responses to ACD9291. There were a total of 2 patients (0.5%) with a best objective response of complete response, and 240 (60.5%) had a best objective response of partial response. These results were confirmed by the DOP-2 Clinical Efficacy Reviewer in the Mid-cycle Meeting.

The AURA extension and AURA2 studies demonstrated consistent ORR by both the BICR and the investigator assessment, and for both the primary evaluable for response analysis set and the full analysis set. The investigator-assessed pooled confirmed ORR in the full analysis population was 66.2% (95% CI: 61.4, 70.7), with 272 patients with confirmed objective responses to AZD9291. See the DOP-2 Clinical Efficacy Review by Sean Khozin, M. D.

Secondary Efficacy Endpoint - Onset of Response

Time to first documentation of objective response from the first AZD9291 dose demonstrated 91.7% of responders had a first documented response at their first scheduled follow-up RECIST scan at Week 12 $\pm$ 1 week.

Secondary Endpoint – Change from Baseline in Target Lesion Size

Evidence of tumor shrinkage was observed in 94% of patients and the mean percentage change in the target lesion size by BICR in the pooled P2 evaluable for response population was -40.4%, standard deviation 25.9.

Secondary Efficacy Endpoint - Duration of Response

Drug Safety Update Report and the Investigator's Brochure. To provide additional safety data given the seriousness and lower frequency of ILD grouped term events, preliminary ongoing invalidated safety data relating to ILD in the clinical program is based on an informal cut-off date of April 7, 2015.

[25] Pazdur R. "Endpoints for assessing drug activity in clinical trials", *Oncologist* 2008;13:19-21

Of the 63 patients with EGFR T790M mutation-positive NSCLC treated with 80 mg/day, 59 were evaluable for response by BICR. The response rate in these 59 patients was 54.2% (32 of 59 patients) with a median DOR of 12.4 months, with a lower 95% CI of 8.3 months.

Of the 32 patients with confirmed responses by BICR, 22 patients (68.8%) had ongoing responses, with durations ranging from 1.4 to 12.5 months. Based on the Kaplan-Meier estimate, 89.6% of responding patients are estimated to have duration of response beyond 3 months; 77.8% for > 6 months; 57.1% for > 9 months.

Secondary Efficacy Endpoint - Progression-free Survival

Median PFS has not yet been reached in the pooled P2 studies. Of the 411 EGFR T790M mutation-positive patients in the full analysis population by BICR, 84 patients had progressed or died (20.4% maturity); 327 patients (79.6%) remained alive and PFS at the time of analysis.

See the DOP-2 Clinical Efficacy Review by Sean Khozin, M. D. for additional details on efficacy results.

Study Population and Demographics

Patient demographic and baseline characteristics were similar in the pooled P2 studies. Sixty-eight percent were female and most were never smokers (71.5%) vs former smokers (26.8%). The median age was 63 years (range 35 to 89 years). These were global studies: 51.3% of patients were recruited from Asia (19.7% from Japan), 26.3% from North American, and 22.4% from Europe and the rest of the world.

The majority of patients had metastatic NSCLC (96.1%) and adenocarcinoma histology (96.1%). The majority of patients were World Health Organization Performance Status 1 (63%). Eighty-three percent of all patients had visceral metastases at baseline, and 39.4% had previously treated, stable brain metastases.

Patient Disposition

The 411 patients in the pooled population (201 patients from AURA extension and 210 from AURA2) consisted of patients with locally advanced or metastatic EGFR T790M mutation-positive NSCLC who had progressed on or after EGFR TKI therapy. Of the 411 patients, 129 (31.4%) received AZD9291 as 2nd line therapy and 282 (68.6%) as ≥ 3rd line therapy from pooled efficacy.

As of the data-cutoff, 381 of 411 patients (92.7%) were ongoing in the studies, including 351 patients (85.4%) who were still receiving AZD9291 treatment. The proportion of patients who discontinued AZD9291 therapy [60 patients (14.6%) was low: 33patients (8%) discontinued due to objective disease progression, 16 patients (3.9%) due to AEs, 3 patients (0.7%) per patient decision, and 8 patients (1.9%) for other reasons]. Of the 30 patients (7.3%) who withdrew from the study, 24 (5.8%) had died.

3.1 CLINICAL SAFETY

Clinical safety data is from the pooled dataset in 411 patients (AURA extension and AURA2). Safety data from 252 patients in the AURA P1 expansion provides context to the P2 safety data, with longer follow-up.

3.1.1 Extent of Exposure

The median exposure to AZD9291 in the P2 studies was 4.4 months (range 0.1 month to 7.9 months). Safety data from 252 patients in the AURA P1 expansion includes 7.7 months median exposure (range < 1 to 18 months). Though the median exposure in the P2 studies is shorter than the duration of therapy predicted for NSCLC patients treated with AZD9291, the majority of common adverse events (AEs) e. g., rash, diarrhea) occurred within the first weeks of treatment (80 mg/day).

3.1.2 Deaths

Pooled P2 Studies

Using the cutoff date of January 9, 2015, there were a total of 24 (5.8%) deaths reported in the pooled P2 studies, during treatment, through the 28-day follow-up period. One death in the AURA2 trial had limited information reported by the data cutoff date and this death did not appear in the applicant's disposition table. After the dataset cutoff date, the applicant was able to report that the cause of death was disease progression.

A total of 7 patients (1.7%) died due to an adverse event (see **Table** 2, below):

- In 4 patients, the investigator considered the death to be causally attributed to NSCLC *and* a fatal AE.
- In 3 other patients, death was causally attributed to the AE alone. In 2 of these 3 deaths (shaded rows in Table 2), the AE of ILD was causally attributed to study treatment, AZD9291.

Table 2 - Patients treated with AZD9291 who experienced an outcome of death

Treatment	Age/Sex	AE (PT) Primary/ Secondary	Time to Onset of AE (days)	Death related to NSCLC	Investigator Causality
AZD9291					
As above	F/83 yrs	Cerebrovascular Accident	33 days	No	No
As above	F/74 yrs	CHF/Hepatic impairment	122 days	No	No
As above	F/66 yrs	ILD	47 days	Yes	Yes
As above	M/60 yrs	Pneumonia	45 days	Yes	No
As above	F/50 yrs	Pneumonia	33 days	Yes	No
As above	F/42 yrs	Pneumonia Aspiration/Lung neoplasm malignant	14 days	Yes	No
As above	F/63 yrs	ILD	59 days	No	Yes

Table reference, see NDA 208-065 AZD9291, GS, Module 2, Subsection 2.7.4 Summary of Clinical Safety, Table 16, page 68 of 171

There were 2 additional deaths not initially submitted in the January 9, 2015 cutoff date report that were with causality attributed to Intestinal Lung Disease. Therefore, there were a total of 9 deaths in the pooled P2 studies and a total of 4 cases of ILD causally attributed to study treatment, AZD9291. Chana Weinstock, MD, the DOP-2 Clinical Safety Reviewer, clarified these two additional deaths causally attributed to AZD9291

AURA P1 Dose Expansion Cohort

A total of 27 deaths (27 of 252 patients; 10.7%) were reported by the data cutoff date of December 2, 2014 from the AURA, P1 dose expansion cohort. A total of 18 deaths (7.1%) of these deaths were considered to be related to NSCLC. A total of 7 (2.8%) of these deaths were causally attributed to an AE only and 2 deaths (0.8%) in these patients were reported as being related to the NSCLC and an AE with the outcome of death. Of the 9 patients who died due to an AE, the most frequently reported AE causally attributed to death was pneumonia (5 patients). No other AE causally attributed to death was reported in more than one patient. See **Table 3** below.

Table 3 - Dose Expansion Part: All Deaths

Number (%) of patients treated with AZD9291, Pre-Treated, Oral Capsule						
Category	**20 mg N=15**	**40 mg N=52**	**80 mg N=97**	**160 mg N=74**	**240 mg N=14**	**Total N=252**
Total # of deaths	1 (6.7)	7 (13.5)	15 (15.5)	3 (4.1)	1 (7.1)	27 (10.7)
Death related to NSCLC	0	5 (9.6)	10 (10.3)	3 (4.1)	0	18 (7.1)
AE w/outcome of death only	0	2 (3.8)	4 (4.1)	0	1 (7.1)	7 (2.8)
# pts w/death related to NSCLC and an AE w/death outcome	1 (6.7)	0	1(1.0)	0	0	2 (0.8)
Table reference: see NDA 208-065 AZD9291, GS, Module 2, subsection 2.7.4 Summary of Clinical Safety, Table 17, page 71 or 171						

See DOP-2 Clinical Safety Review by Chana Weinstock, M. D., for additional details on these fatal cases.

3.1.3 Drop-Outs/Discontinuations

There were 16 (3.9%) discontinuations in the pooled studies. The most common AE leading to a discontinuation was ILD/pneumonitis that led to study discontinuation in 8 patients (2%). Cerebrovascular accident (CVA) was the only other AE leading to discontinuation of study treatment in 4 patients (1%).

3.1.4 Non-Fatal Serious Adverse Events

Per the DOP-2 Clinical Safety Reviewer, Chana Weinstock, M. D., non-fatal serious adverse events (SAEs) occurred in 11.4% of patients (see **Table 4** below).

Table 4 - Non-fatal Serious Adverse Events

Preferred Term	**Event**	**# Patients**	**Proportion (%)**
Pneumonia	6	5	1.22
Pulmonary Embolism	5	5	1.22
Pneumonitis	3	3	0.73
Abdominal Pain	2	2	0.49
Dyspnea	2	2	0.49
Fatigue	2	2	0.49
Pharyngeal abscess	2	1	0.24

Thrombocytopenia	2	2	0.49
Table per Chana Weinstock, M. D., DOP-2 Clinical Safety Reviewer			

Grade 3 to 4 AEs

The Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 to 4 adverse events were reported in 77 patients (19%). Among these 77 patients, 35 patients (8.5%) had events of Grade 3 to 4 that were attributed by the clinical investigator to study treatment AZD9291. The Grade 3 to 4 AEs were neutrophil count decreased in 6 patients (1.46%); dyspnea and pneumonia, each in 5 patients (1.22%); Alanine aminotransferase increased and pulmonary embolism, each in 4 patients (each, 0.97%); anemia , diarrhea, electrocardiogram QT prolonged, hypoxia, leukopenia, pneumonitis, and thrombocytopenia were each reported in 3 patients (each, 0.73%)

3.1.5 Common Adverse Events

The most frequently reported common AEs were reported in 96.1% (395/411) patients across the pooled P2 studies. The most frequently reported system organ classes (SOC) were: skin disorders (248/411 patients; 60.3%), Gastrointestinal (GI) disorders (243/411 patients; 59.1%), and Infections and Infestations (166/411patients: 40.4%). By the preferred term (PT), the most frequent AEs were: diarrhea (37.7%), rash (23.4%), dry skin (20%), and paronychia (15.6%).

There were no reported events of GI perforation or hemorrhagic diarrhea. There were no CTCAE Grade 3 events of exfoliative rash. The commonly reported AEs in the AURA1 cohort were consistent with those reported in the pooled P2 studies.

Laboratory Abnormalities

Laboratory abnormalities were also among the most common AEs reported in between 10% to 20% of patients in the pooled P2 studies. The laboratory AE, all Grades (%), were: thrombocytopenia (14.6%; Grade 3 to 4, 1%) and white blood cell decreased (12.7%; Grade 3 to 4, 2/7%).

3.2 ADVERSE EVENTS OF SPECIAL INTEREST

Interstitial Lung Disease (ILD)/Pneumonitis, Pneumonia

At the time of the initial data cutoff (on January 9, 2015), 21 patients were reported with ILD/pneumonitis. There were 12 patients in the AURA P1 cohorts, 5 patients in the AURA extension P2 component, and 4 patients in the AURA2, P2 component who experienced ILD/pneumonitis. Following the data cutoff date of April 7, 2015, an additional 10 patients were reported with ILD/pneumonitis. There are a total of 31 patients reported to experience ILD/pneumonitis among 1,185 patients exposed to AZD9291 treatment. The rate of ILD/pneumonitis is 2.7% (per the DOP-2 Clinical Safety Reviewer) in the AZD9291 clinical development program and the substantially complete proposed osimertinib labeling.

– The mean patient age was 62.8 years (range 39 years to 82 years); median day of AZD9291 treatment was 54 days (range 14 days to 240 days); 16 patients (52%) were reported as Grade 3 or higher ILD; 68% were Asian and 71% were female patients.

In the pooled P2 studies, pneumonia was reported in 10 of 411 patients; 2.4% .Severity ranged from moderate (CTCAE Grade 2) to fatal (CTCAE Grade 5). Grade 2, pneumonia was reported in 3 patients (0.7%) and Grade 3 pneumonia was reported in 5 patients (1.2%). Grade 5 pneumonia was reported in 2 patients (0.5%). Pneumonia as a SAE was reported in 7 of 411 patients (1.7%).

As cited earlier in this review, there were a total of 3 fatal events, 2 deaths possibly, causally attributed to pneumonitis. See the DOP-2 Clinical Safety Review for additional details. See the substantially complete proposed osimertinib labeling *Section 5.1 Warnings and Precautions, Interstitial Lung Disease.*

Cardiac Contractility and QT Prolongation

The applicant reported on two cardiac events of special interest, specifically, QT prolongation and reduction in cardiac contractility, including left ventricular ejection fraction (LVEF) decreases.

In the pooled P2 studies, there were no clinically significant changes reported in LVEF from baseline in 176 patients (88%) who had a post-baseline echocardiogram assessment. A total of 3 patients (1.5%) were reported to experience an LVEF decrease of ≥ 15 percentage points from baseline to an LVEF ≥ 50%. Of these 3 patients, 1 patient had further LVEF decrease of ≥ 10 percentage points from baseline to an LVEF value < 50%.

In the pooled P2 studies, AEs by the PT cardiac failure or cardiomyopathy were reported in 2 patients: 1 patient with Grade 5 Congestive Heart Failure (CHF) and 1 patient with Grade 3 AE of ejection fraction decreased in AURA extension. See the DOP-2 Clinical Safety Review for additional details.

A total of 61 (29%) of patients had a QT interval corrected for heart rate (QTc) Fredericia corrected (QTcF) heart-rate corrected QTcF value > 450 msec at any time during AZD9291 treatment: 8 patients (3.8%) had a QTcF > 480 msec, and 1 patient (0.5%) had a QTcF > 500 msec. The mean time-matched change from baseline in QTcF at week 6 across all item points was 14.5 milliseconds (msec) (90% CI 14, 15) [with the upper 90% CI limit at any time point being 17.5 msec]. See the substantially complete proposed osimertinib labeling *Section 5.2 Warnings and Precautions, QT Interval Prolongation.*

Embryofetal Toxicity

The Pharmacology Toxicology Reviewer recommends a pregnancy warning in Physician Labeling Rule format (formerly, Category D) for osimertinib based on post-implantation loss and post natal death/decreased pup weight when administered drug, organogenesis through Lactation Day 6 (exposed to AZD9291 treatment). There are no adequate and well-controlled studies in pregnant women using AZD9291. Based on its mechanism of action, AZD9291 may cause fetal harm when administered to a pregnant woman. The substantially complete proposed osimertinib labeling includes embryofetal toxicity.

3.3 90-DAY SAFETY UPDATE REPORT

The 90-day safety update report (SUR) on AZD9291 (received on September 2, 2015) reported on clinical data from the cut-off date of May 1, 2015 which is 4 months after the previous data cutoff date for the pooled P2 studies (on January 9, 2015). The pooled P2

studies provided exposures up to 11.6 months and the P1 component of AURA provides longer treatment exposures up to 24.9 months (759 days).

As reported by the applicant, and agreed with by the DOP-2 Clinical Review Team, the incidence of AEs leading to AZD9291 dose reduction and permanent discontinuation has remained low (3.4 and 5.6%, respectively). The mean and median dose intensity (percentage intended dose) has remained high (96.3% and 100%, respectively).

The discontinuations due to AEs in ≥ 2 patients were ILD and pneumonitis (each reported in 5 patients; 1.2%) and CVA and pulmonary embolism (each reported in 2 patients; 0.5%).

There were 52 (12.7%) deaths reported in the pooled P2 studies. A total of 39 of these 52 patients were reported to have died due to their underlying disease, NSCLC. There were a total of 13 patients (3.2%) whose death is possibly causally attributed to the study treatment, AZD9291. Of these 13 patients, 4 deaths were considered by the clinical investigator to be possible causally related to AZD9291 exposure: 3 patients had AEs of ILD and 1 patient had an AE of pneumonitis. [26]

The number of patients with an AE of CTCAE Grade ≥ 3 or a SAE increased with longer follow-up of NSCLC. The most common reported AEs of CTCAE Grade ≥ 3 were pneumonia and pulmonary embolism, 2.7% and 2.2%, respectively, in the pooled P2 studies.

Diarrhea (42.3%), rash (23.8%), dry skin (23.1%), and paronychia (17.5%) remain the most commonly reported AEs and were mostly mild (maximum CTCAE Grade 1). There were no reports of significant AEs such as severe bullous, severe blistering or severe exfoliative skin events, hypersensivity reaction including Stevens-Johnson syndrome or toxic epidermal necrolysis, gastrointestinal perforation, or hemorrhagic diarrhea.

The AEs reported were consistent with the known clinical safety reported from the P2 studies. There were no new AEs reported in the 90-Day SUR and no AE prompted revisions to the proposed labeling. See the DOP-2 Clinical Safety Review for additional details.

4 DISCUSSION

Osimertinib (Tagrisso), a new molecular entity, is an oral, irreversible EGFR-KI that claims efficacy against EGFRm, a KI sensitivity conferring mutation, and EGFR T790M mutation-positive, a KI resistance-conferring mutation. Osimertinib is proposed for the treatment of patients with metastatic EGFR tumor positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. The recommended dose is 80 mg orally once daily and proposed labeling recommends that the presence of T790M mutation in the tumor specimen be confirmed prior to imitation of treatment with Tagrisso.

The AZD9291(osimertinib) achieved statistical significance on the primary efficacy endpoint of an objective response rate, by blinded independent central review, of 61% (95% CI 56% to 65.8%) based on 242 responses from 397 evaluable EGFR T790M

[26] NDA 208-056 AZD9291, GS, 90 Day SUR, pages 20 through 195 (received on September 2, 2015).

mutation-positive in both phase 2 studies (AURA extension and AURA2). See **Section 3**, in this review, for brief summary on the primary and secondary endpoint results in the pooled Phase 2 studies.

The most important safety risks associated with use of osimertinib are Interstitial Lung Disease (ILD), QT prolongation, and embryofetal toxicity. As discussed by the DOP-2 Clinical Review Team, the reported ILD as well as QT prolongation associated with AZD9291 appear to be mild to moderate compared to the approved oral EGFR TKIs with worse safety profiles (see **Table 1**). The diagnosis of ILD was reported in 2.7% of patients. Pulmonary embolism was among the most commonly reported PTs of CTCAE ≥ Grade 3 (9/411; 2.2%). The proposed substantially complete osimertinib labeling recommends permanently discontinuing treatment with Tagrisso in patients diagnosed with ILD/pneumonitis. See the proposed substantially complete osimertinib labeling Section 2.4, Dose Modification for Adverse Reactions, Pulmonary, ILD/pneumonitis.

Abnormal electrocardiogram QT prolongation prompted dose reduction or interruption in 2.2% of patients. A total of 61 (29%) of patients had a QT interval corrected QTcF value > 450 msec: 8 of these patients had QTcF > 480 msec and 1 patient had QTcF > 500 msec. Regarding the risk of QT prolongation, proposed labeling recommends monitoring electrocardiograms and electrolytes in patients who have a history or predisposition for QTc prolongation, or those who are taking medications that are known to prolong the QTc interval. It is recommended to withhold, then restart osimertinib at a reduced dose or permanently discontinue osimertinib with evidence of abnormal QTcF.

Osimertinib can cause fetal harm (embryofetal toxicity) though there are no clinical studies with AZD9291 in pregnant patients. It is recommended to advise females of reproductive potential of the potential risk to the fetus and to use effective non-hormonal contraception during treatment with osimertinib and for 6 weeks after the final dose. In the osimertinib clinical development program, the median patient age was 63 years (range 35 years to 89 years).

In the proposed substantially complete osimertinib labeling, withholding osimertinib is recommended until the QTc interval is less than 481 msec or recovery to baseline QTc is greater than or equal to 481 msec, then restart at a 40 mg dose. .

Fatal adverse reactions occurring in more than 1 patient included: ILD/pneumonitis (4 patients), pneumonia (4 patients), and cerebrovascular accident/cerebral hemorrhage (2 patients). Discontinuation of osimertinib due to adverse reactions was reported in 5.6% of patients treated with osimertinib. The proposed substantially complete osimertinib labeling, Section 2.4 Dose Modification for Adverse Reactions, includes target organ adverse reactions and recommendations on dose modification to withholding osimertinib. In labeling Section 5.1 Warnings and Precautions, it is recommended to withhold osimertinib and promptly investigate for ILD in any patient who presents with worsening of respiratory symptoms which may be indicative of ILD (e. g., dyspnea, cough and fever). Permanently discontinue osimertinib if ILD is confirmed. See the proposed substantially complete osimertinib labeling *Section 5 Warnings and Precautions, Section 6 Adverse Reactions,* and *Section 6.1 Clinical Trials Experience).* There is no Boxed Warning in the proposed osimertinib labeling.

In the pooled P2 studies, the most common adverse reactions (all grades) observed in osimertinib-treated patients (> 20% all grades) were diarrhea and rash (42%), and nail toxicity (26%). Dose reductions occurred in 4.4% of patients treated with osimertinib. The most frequent adverse reactions leading to dose reductions or interruptions were: electrocardiogram QT prolongation (2.2%) and neutropenia (1.9%).

The applicant's proposed Core Patent Risk Management Plan (PRMP) for AZD9291 identifies the important safety concerns (as cited above) and proposes a Pharmacovigilance Plan, implementation of risk-minimizing measures in proposed labeling, and does not include a REMS proposal or non-REMS education materials. At this time, the reported safety profile of osimertinib appears to be consistent with known risks reported with approved oral EGFR KIs.

The DOP-2 Clinical Review Team concluded that oncology and hematology healthcare providers are informed on similar adverse reactions associated with use of approved oral EGFR KI products in patients with NSCLC (See **Table 1**, and Section 2.4 Armamentarium of Treatment, in this review). In the AZD9291 Mid-cycle Communication Meeting (held on September 2, 2015), the DOP-2 Clinical Review Team agreed with the DRISK that a REMS is not needed to ensure that the benefits of osimertinib outweigh its risks. The proposed labeling includes Patient Counseling Information but does not include a Medication Guide (see **Table 1**, with comparison of EGFR TKI product labeling/risks. Osimertinib is proposed for oral use. The DOP-2 Clinical Safety Reviewer confirms that the most likely setting for use will be as an outpatient.

In the Late-Cycle Meeting held on October 13, 2015, there were no discipline review letters issued or substantive review issues identified to- date. The 6 postmarketing requirement studies were listed per title, study completion date and the final report. The DOP-2 plans to require: one clinical postmarketing requirement (PMR) to conduct and submit results of at least one multi-center, randomized clinical trial establishing the superiority of osimertinib over available therapy in patients with metastatic EGFR T790M mutation-positive NSCLC, and 5 Clinical Pharmacology PMRs for NDA 208-065 Tagrisso (osimertinib) oral tablet (see the Regulatory History entry dated September 11, 2015 for brief description of the proposed PMRs). The substantially complete proposed osimertinib labeling remains under negotiation with the applicant.

5 CONCLUSION

The DRISK and DOP-2 concur that the reported risks of Interstitial Lung Disease, QT prolongation, and embryofetal toxicity associated with use of osimertinib are familiar to oncology and hematology healthcare providers, the most likely prescribers of EGFR KI therapies in patients with NSCLC.

The DRISK and the DOP-2 concur that, if osimertinib were to be approved, a REMS is not necessary for osimertinib to ensure that the benefits outweigh the risks of Interstitial Lung Disease, QT prolongation, and embryofetal toxicity. These risks will be communicated through labeling. The DOP-2 should consult the DRISK if additional safety information is identified that warrants re-evaluation of the risk management measures for AZD9291 (osimertinib).

APPENDIX: See the next page

Table 1 – Approved Kinase Inhibitor Products for the Treatment of NSCLC

Approved Kinase Inhibitor Products for Treatment of Non-Small Cell Lung Cancer				
Trade/Est Name	**TAGRISSO (osimertinib)**	**GILOTRIF (afatinib)**	**TARCEVA (erlotinib)**	**IRESSA (gefitinib)**
NDA/Approved	208-065 (*under review*)	201-292 (Jul-13)	021-743 (Nov-04)	021-399 (May-03)
Indication	Tx pts (b) (4) positive NSCLC, detected by FDA approv test, who have progressed on or after EGFR TKI therapy.	1st-line tx of pts w metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitutions mutations as detected by an FDA-approved test. Limitation of use: safety and efficacy of GILOTRIF have not been established in pts whose tumors have other EGFR	1st-line tx pts w NSCLC whose tumors have EGEGFR exon 19 deletions or exon 21 (L858R) substitution mutations as detected by FDA-approved test. Maintenance tx pts locally adva or metastatic NSCLC whose disease has not progressed after 4 cycles of platinum-based 1st-line chemo. Tx locally adva or metastatic NSCLC after failure of at least 1 prior chemotherapy regi. 1st-line tx of pts w locally adva or metastatic pancreatic cancer, in combo w gemcitabine.	Monotherapy for continued tx of metastatic NSCLC after failure of both platinum based and docetaxel chemotherapy who are benefiting or have benefited from IRESSA
Boxed Warning	None proposed	None	None	None
Warning & Precautions	1. Interstitial Lung Disease (ILD) 2. QT Prolongation 3. Embryofetal Toxicity	1. Diarrhea (may cause dehydration renal failure) 2. Bullous and Exfoliative Skin Disorder (discontinue for life-threatening cutaneous reactions) 3. ILD 4. Hepatic toxicity 5. Keratitis 6. Embryofetal Toxicity	1. ILD 2. Renal Failure 3. Hepatotoxicity w or w/o Hepatic Impairmt 4. Gastrointestinal Perforation 5. Bullous & Exfoliative Skin Disorders 6. Myocardial Infarction/Ischemia 7. Cerebrovascular Accident 8. Microangiopathic Hemolytic Anemia w/ Thrombocytopenia 9. Ocular Disorders 10. Hemorrhage in Pts Taking Warfarin 11. Embryofetal Toxicity	1. Pulmonary Toxicity - ILD

Adverse Reactions	Diarrhea, rash, dry skin	Diarrhea, rash/dermatitis acneiform, stomatitis, paronychia, dry skin, decreased appetite, pruritus	Rash, diarrhea, anorexia, fatigue, dyspnea, cough, nausea, and vomiting	Hepatotoxicity, diarrhea, rash, acne, dry skin, nausea, vomiting
Pregn Category	PLR labeling	Category D	Category D	Category D
Med Guide	No	No	No	No
Pt Coun Inform	Yes	Yes	Yes	No
REMS	None proposed	No	No	No

Abbreviations: Adv-advanced; Adver-adverse; Assoc-associated; Chemo-chemotherapy; Coun.-Counseling; Inform-Information; EFGR-epidermal growth factor receptor; Inform-Information; ILD-Interstitial Lung disease; Impairmt-impairment; Med Guide-Medication Guide; New Drug Application-NDA; NSCLC-non small cell lung cancer; PLR-Physician Labeling Rule; Pregn-pregnancy; REMS-risk evaluation and mitigation strategy; TKI-tyrosine kinase inhibitor

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/s/

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10/29/2015

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