

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208065Orig1s000**

**OTHER REVIEW(S)**

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** November 13, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 208065  
**Product Name and Strength:** Tagrisso (osimertinib) Tablets, 40 mg and 80 mg  
**Submission Date:** November 12, 2015  
**Applicant/Sponsor Name:** AstraZeneca  
**OSE RCM #:** 2015-450-2  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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#### 1 PURPOSE OF MEMORANDUM

DOP2 requested that we review the revised container label for Tagrisso (Appendix A) to determine if it is acceptable from a medication error perspective. The revision is in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSION

The revised container label for the Tagrisso 40 mg tablet is acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>1</sup> Townsend, O. Label and Labeling Review for Tagrisso (NDA 208065). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 NOV 05. 3 p. OSE RCM No.: 2015-450-1.

APPENDIX A. LABEL AND LABELING SUBMITTED ON NOVEMBER 12, 2015

Each tablet contains 40 mg osimertinib.  
**USUAL ADULT DOSAGE:** See Prescribing Information.  
**WARNING:** As with all medications, keep out of the reach of children.  
 Store at room temperature between 68°F to 77°F (20°C to 25°C).

NDC 0310-1349-30 **30 Tablets**



**40 mg tablets**

Rx only



37395-01

LOT  
EXP

3 0310-1349-30 7

N

TAGRISSO is a trademark of the AstraZeneca group of companies. © AstraZeneca 2015  
 Manufactured for: AstraZeneca Pharmaceuticals LP  
 Wilmington, DE 19850  
 By: AstraZeneca AB, SE-151 85 Södertälje, Sweden  
 Product of Switzerland

Each tablet contains 80 mg osimertinib.  
**USUAL ADULT DOSAGE:** See Prescribing Information.  
**WARNING:** As with all medications, keep out of the reach of children.  
 Store at room temperature between 68°F to 77°F (20°C to 25°C).

NDC 0310-1350-30 **30 Tablets**



**80 mg tablets**

Rx only



37397-01

LOT  
EXP

3 0310-1350-30 3

N

TAGRISSO is a trademark of the AstraZeneca group of companies. © AstraZeneca 2015  
 Manufactured for: AstraZeneca Pharmaceuticals LP  
 Wilmington, DE 19850  
 By: AstraZeneca AB, SE-151 85 Södertälje, Sweden  
 Product of Switzerland

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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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OTTO L TOWNSEND  
11/13/2015

CHI-MING TU  
11/13/2015

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

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NDA/BLA #                      208-065 Osimertinib (Tagrisso)  
Product Name: \_\_\_\_\_

PMR/PMC Description:   Hepatic Impairment Pharmacokinetic Trial  

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>12/31/2018</u>
	Final Report Submission:	<u>5/31/2019</u>
	Other: _____	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

(b) (4)



2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of the clinical pharmacokinetic trial is to determine an appropriate osimertinib dose in patients with hepatic impairment.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a pharmacokinetic trial to determine an appropriate dose of Tagrisso 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."

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for NDAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for *each* PMR/PMC in the Action Package.

NDA/BLA # 208-065 Osimertinib (Tagrisso)  
Product Name: \_\_\_\_\_

PMR/PMC Description: Drug Interaction

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>4/30/2015</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Osimertinib is a substrate of CYP3A. Trial to (b) (4) the effect of CYP3A4 inhibitor on the pharmacokinetics of osimertinib is ongoing and the applicant proposes to submit the final study report in December 2015.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this clinical trial is to (b) (4) of CYP3A4 inhibitors with osimertinib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a clinical trial to evaluate the effect of a strong CYP3A4 inhibitor on the pharmacokinetics of Tagrisso (osimertinib) in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for NDAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208-065 Osimertinib (Tagrisso)  
Product Name: \_\_\_\_\_

PMR/PMC Description: Drug Interaction

PMR/PMC Schedule Milestones:	Final Protocol Submission:	<u>Submitted</u>
	Study/Trial Completion:	<u>7/31/2015</u>
	Final Report Submission:	<u>12/31/2015</u>
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Osimertinib is a substrate of CYP3A. Trial to (b) (4) the effect of CYP3A4 inducers on the pharmacokinetics of osimertinib is ongoing and the applicant proposes to submit the final study report in December 2015.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this clinical trial is to (b) (4) of CYP3A4 inducers with osimertinib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a clinical trial to evaluate the effect of a strong CYP3A4 inducer on the pharmacokinetics of Tagrisso (osimertinib) in accordance with the FDA draft Guidance for Industry entitled “*Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

Continuation of Question 4

- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
  - Pharmacokinetic studies or clinical trials
  - Drug interaction or bioavailability studies or clinical trials
  - Dosing trials
  - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
- 
- Meta-analysis or pooled analysis of previous studies/clinical trials
  - Immunogenicity as a marker of safety
  - Other (provide explanation)
- 

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
  - Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
  - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
  - Dose-response study or clinical trial performed for effectiveness
  - Nonclinical study, not safety-related (specify)
- 
- Other
- 

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
  - Are the objectives clear from the description of the PMR/PMC?
  - Has the applicant adequately justified the choice of schedule milestone dates?
  - Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
- 

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for NDAs)

## PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for ***each*** PMR/PMC in the Action Package.

NDA/BLA # 208-065 Osimertinib (Tagrisso)  
Product Name:

PMR/PMC Description: Drug Interaction

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Submitted
	Study/Trial Completion:	4/30/2015
	Final Report Submission:	12/31/2015
	Other:	

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Osimertinib is an inhibitor and an inducer of CYP3A. Trial to (b) (4) the effects of osimertinib on the pharmacokinetics of a sensitive substrate of CYP3A4 is ongoing and the applicant proposes to submit the final study report in December 2015.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this clinical trial is to (b) (4) of sensitive substrates of CYP3A4 with osimertinib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a clinical trial to evaluate the effect of repeated doses of Tagrisso (osimertinib) 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*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

*Continuation of Question 4*

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

---

Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

---

5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

Has the applicant adequately justified the choice of schedule milestone dates?

Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for NDAs)

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NDA/BLA # 208-065 Osimertinib (Tagrisso)  
Product Name: \_\_\_\_\_

PMR/PMC Description: Drug Interaction \_\_\_\_\_

PMR/PMC Schedule Milestones:	Final Protocol Submission:	Submitted
	Study/Trial Completion:	7/31/2015
	Final Report Submission:	12/31/2015
	Other:	_____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

Osimertinib is an inhibitor of breast cancer resistant protein (BCRP). Trial to (b) (4) the effects of osimertinib on the pharmacokinetics of a sensitive substrate of BCRP is ongoing and the applicant proposes to submit the final study report in December 2015.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The goal of this clinical trial is to (b) (4) of sensitive substrates of BCRP with osimertinib.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

- **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

- **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
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- **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
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4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

Complete a clinical trial to evaluate the effect of repeated doses of Tagrisso (osimertinib) 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*” found at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf>.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)

*Continuation of Question 4*

Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)

Pharmacokinetic studies or clinical trials

Drug interaction or bioavailability studies or clinical trials

Dosing trials

Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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Meta-analysis or pooled analysis of previous studies/clinical trials

Immunogenicity as a marker of safety

Other (provide explanation)

---

Agreed upon:

Quality study without a safety endpoint (e.g., manufacturing, stability)

Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)

Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E

Dose-response study or clinical trial performed for effectiveness

Nonclinical study, not safety-related (specify)

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Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

Does the study/clinical trial meet criteria for PMRs or PMCs?

Are the objectives clear from the description of the PMR/PMC?

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Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

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**PMR/PMC Development Coordinator:**

*This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for NDAs)

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/s/  
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JUN YANG  
11/12/2015

HONG ZHAO  
11/12/2015  
I concur.

JEFFERY L SUMMERS  
11/13/2015

NDA/BLA # NDA  
Product Name: Osimertinib (Tagrisso)/ AZD9291

PMR/PMC Description: Randomized clinical trial evaluating Osimertinib versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy (b) (4)

PMR/PMC Schedule Milestones: Final Protocol Submission: May 28, 2014  
Study/Trial Completion: December 2016  
Final Report Submission: April 2017  
Other: n/a

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The proposed PMR is the submission of the clinical study report for a planned open label, randomized study of Osimertinib versus platinum-based doublet chemotherapy for patients with locally advanced or metastatic non-small cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy (b) (4)

(b) (4)

This was the basis for granting breakthrough therapy designation to Osimertinib, and the basis for the accelerated approval of Osimertinib.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the “new safety information.”

The accelerated approval of Osimertinib was based on single-arm study information. Efficacy and safety data was not compared to a randomized control arm and this has implications for interpretation of the data. Regular approval is contingent on demonstration of efficacy and safety in this population against a control arm of available therapy in this setting.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

***If not a PMR, skip to 4.***

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?  
***Do not select the above study/clinical trial type if:*** such an analysis will not be sufficient to assess or identify a serious risk
- Analysis using pharmacovigilance system?  
***Do not select the above study/clinical trial type if:*** the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?  
***Do not select the above study type if:*** a study will not be sufficient to identify or assess a serious risk
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

At least one 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).

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial

- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

*Continuation of Question 4*

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

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- Meta-analysis or pooled analysis of previous studies/clinical trials
- Immunogenicity as a marker of safety
- Other (provide explanation)

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Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

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- Other

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5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

***If so, does the clinical trial meet the following criteria?***

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

---

**PMR/PMC Development Coordinator:**

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

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(signature line for BLAs)

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/s/  
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CHANA WEINSTOCK  
11/12/2015

JEFFERY L SUMMERS  
11/12/2015

GIDEON M BLUMENTHAL  
11/12/2015

# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

Device Generic Name: Real-time PCR test

Device Trade Name: **cobas**<sup>®</sup> EGFR Mutation Test v2

Device Procode: OWD

Applicant's Name and Address: Roche Molecular Systems, Inc. (RMS)  
4300 Hacienda Drive  
Pleasanton, CA 94588-2722

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P120019/S007

Date of FDA Notice of Approval: November 13, 2015

Expedited: Granted priority review status on June 2, 2015 because the device addresses an unmet medical need, as demonstrated by significant clinically meaningful advantage.

The original PMA (P120019) for the **cobas**<sup>®</sup> EGFR Mutation Test (v1) was approved on May 14, 2013. This device is a real-time PCR test for the qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the epidermal growth factor receptor (EGFR) gene in DNA derived from formalin-fixed paraffin-embedded (FFPET) human non-small cell lung cancer (NSCLC) tumor tissue. The test is intended to be used as an aid in selecting patients with NSCLC for whom Tarceva<sup>®</sup> (erlotinib), an EGFR tyrosine kinase inhibitor (TKI), is indicated. The SSED to support the previously approved indication is available on the CDRH website and is incorporated by reference here.

The current panel-track supplement was submitted to expand the intended use and indication for use of the **cobas**<sup>®</sup> EGFR Mutation Test v2 for the detection of the exon 20 (T790M) substitution mutation in NSCLC patients for whom Tagrisso<sup>®</sup> (osimertinib) treatment is indicated.

## II. INDICATIONS FOR USE

The **cobas**<sup>®</sup> EGFR Mutation Test v2 is a real-time PCR test for the qualitative detection of defined mutations of the epidermal growth factor receptor (EGFR) gene in DNA derived from formalin-fixed paraffin-embedded tumor tissue (FFPET) from non-small

cell lung cancer (NSCLC) patients. The test is intended to aid in identifying patients with NSCLC whose tumors have defined EGFR mutations and for whom safety and efficacy of a drug have been established as follows:

Tarceva <sup>®</sup> (erlotinib)	Exon 19 deletions and L858R
Tagrisso <sup>®</sup> (osimertinib)	T790M

Drug safety and efficacy have not been established for the following EGFR mutations also detected by the **cobas**<sup>®</sup> EGFR Mutation Test v2:

Tarceva <sup>®</sup> (erlotinib)	G719X, exon 20 insertions, T790M, S768I and L861Q
Tagrisso <sup>®</sup> (osimertinib)	G719X, exon 19 deletions, L858R, exon 20 insertions, S768I, and L861Q

For manual sample preparation, FFPET specimens are processed using the **cobas**<sup>®</sup> DNA Sample Preparation Kit and the **cobas z 480** analyzer is used for automated amplification and detection.

### III. CONTRAINDICATIONS

None.

### IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the **cobas**<sup>®</sup> EGFR Mutation Test v2 labeling.

### V. DEVICE DESCRIPTION

The **cobas**<sup>®</sup> EGFR Mutation Test v2 is based on two processes:

1. The **cobas**<sup>®</sup> DNA Sample Preparation Kit provides reagents for manual specimen preparation to obtain genomic DNA from formalin-fixed, paraffin-embedded tissue (FFPET).
2. The **cobas**<sup>®</sup> EGFR Mutation Test v2 kit provides reagents for automated real-time PCR amplification and detection of the EGFR mutations.

Two external run controls are provided and the EGFR exon 28 wild-type allele serves as an internal, full process control.

#### A. Specimen Preparation

FFPET specimens are processed and genomic DNA is isolated using the **cobas**<sup>®</sup> DNA Sample Preparation Kit. A deparaffinized 5- $\mu$ m section of an FFPET specimen is lysed by incubation at an elevated temperature with a protease and chaotropic lysis/binding buffer that releases nucleic acids and protects the released genomic DNA from DNases. Subsequently, isopropanol is added to the lysis mixture that is

then centrifuged through a column with a glass fiber filter insert. During centrifugation, the genomic DNA is bound to the surface of the glass fiber filter. Unbound substances, such as salts, proteins and other cellular impurities, are removed by centrifugation. The adsorbed nucleic acids are washed and then eluted with an aqueous solution. The amount of genomic DNA is spectrophotometrically determined and adjusted to a fixed concentration of 5 ng/ $\mu$ L with 25  $\mu$ L used in the amplification and detection mixture.

## **B. PCR Amplification and Detection**

### **Target Selection and Amplification**

The **cobas**<sup>®</sup> EGFR Mutation Test v2 kit uses primers that define specific base-pair sequences for each of the targeted mutations. For the exon 19 deletion mutations, sequences ranging from 125 to 141 base pairs are targeted; for the L858R substitution mutation in exon 21, a 138 base pair sequence is targeted; for the T790M substitution mutation in exon 20, a 118 base pair sequence is targeted; for the G719X substitution mutation in exon 18, sequences ranging from 104 to 106 base pairs are targeted; for the S768I substitution mutation in exon 20, a 133 base pair sequence is targeted; for the exon 20 insertion mutations, sequences ranging from 125 to 143 base pairs are targeted; for the L861Q substitution mutation in exon 21, a 129 base pair sequence is targeted; for the internal control in exon 28, an 87 base pair sequence is targeted. Amplification occurs only in the regions of the EGFR gene between the primers; the entire EGFR gene is not amplified.

The **cobas**<sup>®</sup> EGFR Mutation Test v2 uses allele-specific PCR (AS-PCR) chemistry for amplification and detection. The selected AS-PCR primers specifically amplify the targeted mutant sequences over the wild-type sequences and/or other human genomic DNA. The **cobas**<sup>®</sup> EGFR Mutation Test v2 is designed to use three master mix (MMx) reagents which are run in three separate wells. The number and types of primers and probes differ based on the particular target(s). The **cobas**<sup>®</sup> EGFR Mutation Test v2 detects the following EGFR mutations in exons 18, 19, 20, and 21:

**Table 1. EGFR Mutations Detected by the cobas<sup>®</sup> EGFR Mutation Test v2**

<b>Exon</b>	<b>EGFR Mutation</b>	<b>EGFR Nucleic Acid Sequence</b>	<b>COSMIC ID<sup>1</sup></b>
Exon 18	G719X	2156G>C	6239
		2155G>A	6252
		2155G>T	6253
Exon 19	Ex19Del	2240_2251del12	6210
		2239_2247del9	6218
		2238_2255del18	6220
		2235_2249del15	6223
		2236_2250del15	6225
		2239_2253del15	6254
		2239_2256del18	6255

Exon	EGFR Mutation	EGFR Nucleic Acid Sequence	COSMIC ID <sup>1</sup>
		2237_2254del18	12367
		2240_2254del15	12369
		2240_2257del18	12370
		2239_2248TTAAGAGAAG>C	12382
		2239_2251>C	12383
		2237_2255>T	12384
		2235_2255>AAT	12385
		2237_2252>T	12386
		2239_2258>CA	12387
		2239_2256>CAA	12403
		2237_2253>TTGCT	12416
		2238_2252>GCA	12419
		2238_2248>GC	12422
		2237_2251del15	12678
		2236_2253del18	12728
		2235_2248>AATTC	13550
		2235_2252>AAT	13551
		2235_2251>AATTC	13552
		2253_2276del24	13556
		2237_2257>TCT	18427
2238_2252del15	23571		
2233_2247del15	26038		
Exon 20	S768I	2303G>T	6241
	T790M	2369C>T	6240
	Ex20Ins	2307_2308ins9GCCAGCGTG	12376
		2319_2320insCAC	12377
		2310_2311insGGT	12378
		2311_2312ins9GCGTGGACA	13428
2309_2310AC>CCAGCGTGGAT	13558		
Exon 21	L858R	2573T>G	6224
		2573_2574TG>GT	12429
	L861Q	2582T>A	6213

<sup>1</sup>Catalogue of Somatic Mutations in Cancer (COSMIC), 2011, v.51.  
<http://www.sanger.ac.uk/genetics/CGP/cosmic>.

MMx1 (first amplification reaction) contains:

- Fourteen AS-PCR primers, one common primer, and one common probe are used to detect the Exon 19 deletion and complex mutations.
- One AS-PCR primer, one common primer, and one common probe are used to detect the S768I mutation.

MMx2 (second amplification reaction) contains:

- One AS-PCR primer, one common primer, and one common probe are used to detect the L858R mutation.
- One AS-PCR primer, one common primer, and one common probe are used to detect the T790M mutation.

MMx3 v2 (third amplification reaction) contains:

- Three AS-PCR primers, one common primer, and one common probe are used to detect G719X mutations.
- Three AS-PCR primers, one common primer, and one common probe are used to detect Exon 20 insertion mutations.
- One AS-PCR primer, one common primer, and one common probe are used to detect the L861Q mutation.

A derivative of *Thermus* species Z05-AS1 DNA polymerase is utilized for target amplification. Briefly, the PCR reaction mixture is heated to denature the genomic DNA and expose the primer target sequences. As the mixture cools, the upstream and downstream primers anneal to the target DNA sequences. The Z05-AS1 DNA polymerase, in the presence of divalent metal ion and excess dNTPs, extends each annealed primer, thus synthesizing a second DNA strand. This completes the first cycle of PCR, yielding a double-stranded DNA copy, which includes the targeted base-pair regions of the EGFR gene. This process is repeated for a number of cycles, with each cycle effectively doubling the amount of amplicon DNA.

Selective amplification of target nucleic acid from the specimen is achieved in the **cobas**<sup>®</sup> EGFR Mutation Test v2 by the use of AmpErase<sup>®</sup> (uracil-N-glycosylase) enzyme and deoxyuridine triphosphate (dUTP), which are included in the Master Mix reagents. The AmpErase enzyme recognizes and catalyzes the destruction of DNA strands containing deoxyuridine, but not DNA containing thymidine. Deoxyuridine is always present in the amplicons due to the use of dUTP as one of the nucleotide triphosphates in the Reaction Mix reagent; therefore, only amplicon contains deoxyuridine. The AmpErase<sup>®</sup> enzyme is inactive at temperatures above 55°C, i.e., throughout the thermal cycling steps, and therefore does not destroy target amplicon.

### **Automated Real-time Detection**

The **cobas**<sup>®</sup> EGFR Mutation Test v2 utilizes real-time PCR technology. Each target-specific, oligonucleotide probe in the reaction is labeled with a fluorescent dye that serves as a reporter, and with a quencher molecule that absorbs (quenches) fluorescent emissions from the reporter dye within an intact probe. During each cycle of amplification, a probe complementary to the single-stranded DNA sequence in the amplicon binds and is subsequently cleaved by the 5' to 3' nuclease activity of the Z05-AS1 DNA polymerase. Once the reporter dye is separated from the quencher by this nuclease activity, fluorescence of a characteristic wavelength can be measured when the reporter dye is excited by the appropriate spectrum of light. Two different reporter dyes are used to label the mutations targeted by the test. Amplification of the

targeted EGFR sequences are detected independently across three reactions by measuring fluorescence at the two characteristic wavelengths in dedicated optical channels.

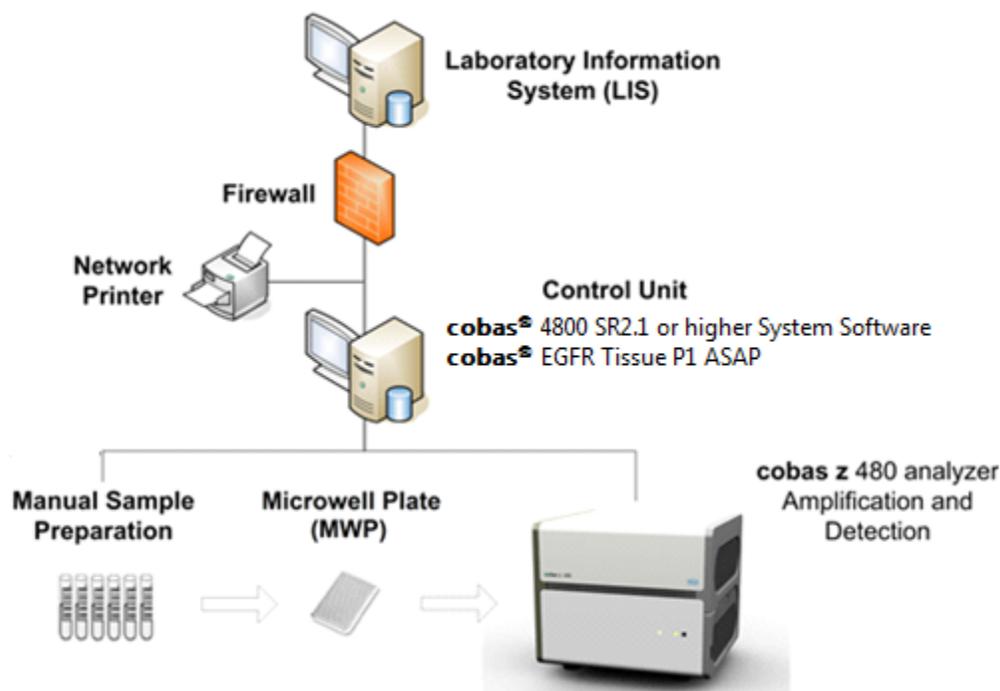
### **Instrument and Software**

The **cobas**<sup>®</sup> 4800 system is controlled by the **cobas**<sup>®</sup> 4800 system software, which provides the core software engines and user interfaces. This core system software was designed to allow multiple assays to be performed on the system using assay specific analysis package software (ASAP). The **cobas z 480** analyzer component of the test system also has its own internal instrument control software, which is driven by the core software.

A dedicated Control Unit computer runs the **cobas**<sup>®</sup> 4800 system software and provides an interface to the **cobas z 480** and Laboratory Information System (LIS). The computer also processes the fluorescent signals with the analyte specific analysis package and stores the test results in a controlled database. The complete system allows a user to create a test work order for each specimen either manually or automatically when connected to a LIS. A software wizard guides the user through the necessary steps to perform a run, which includes **cobas z 480** maintenance handling, test selection, specimen ID entry, reagent and microwell plate barcode entry, microwell plate loading and run start.

The **cobas**<sup>®</sup> 4800 system tracks each specimen during processing and analysis on the **cobas z 480** analyzer. Once the thermal run is complete the ASAP software processes the fluorescence data using data analysis algorithms, assesses the validity of the controls and determines the results using the assay specific result interpretation logic. The software then provides the results to the user in three formats: a printable PDF results report, a GUI based result viewer and a result export file that can be exported to the LIS.

The **cobas**<sup>®</sup> 4800 system software includes the **cobas**<sup>®</sup> 4800 EGFR Analysis Package (AP) software, which contains an algorithm to determine sample results and run validity. The overall **cobas**<sup>®</sup> 4800 system components are shown in the diagram below:



The final version of the ASAP software used to analyze all studies in this panel-track supplement is EGFR Tissue P1 AP v1.0.0.1560.

### Interpretation of Results

If the run is valid, then the cycle threshold (Ct) and CtR (relative cycle threshold) values for each sample will be evaluated against acceptable ranges for each channel. The CtR value is determined by calculating the difference between the mutation's observed Ct and the corresponding Internal Control (IC) Ct value from the same Master Mix. Ct values are not available to the user. Tables 2 and 3 summarize how the individual amplification Master Mix results are combined to provide an overall result.

**Table 2. Individual Amplification Master Mix Results to Overall Results.**

Master Mix 1 Result	Master Mix 2 Result	Master Mix 3 v2 Result	Reported Result
Valid, No Mutation Detected	Valid, No Mutation Detected	Valid, No Mutation Detected	Valid, No Mutation Detected
Valid, No Mutation Detected	Valid, No Mutation Detected	Valid, Mutation Detected	Valid, Mutation Detected
Valid, No Mutation Detected	Valid, No Mutation Detected	Invalid	Invalid
Valid, No Mutation Detected	Valid, Mutation Detected	Valid, No Mutation Detected	Valid, Mutation Detected
Valid, No Mutation Detected	Valid, Mutation Detected	Valid, Mutation Detected	Valid, Mutation Detected

<b>Master Mix 1 Result</b>	<b>Master Mix 2 Result</b>	<b>Master Mix 3 v2 Result</b>	<b>Reported Result</b>
Valid, No Mutation Detected	Valid, Mutation Detected	Invalid	Invalid
Valid, No Mutation Detected	Invalid	Valid, No Mutation Detected	Invalid
Valid, No Mutation Detected	Invalid	Valid, Mutation Detected	Invalid
Valid, No Mutation Detected	Invalid	Invalid	Invalid
Valid, Mutation Detected	No Mutation Detected	Valid, No Mutation Detected	Valid, Mutation Detected
Valid, Mutation Detected	No Mutation Detected	Valid, Mutation Detected	Valid, Mutation Detected
Valid, Mutation Detected	Valid, No Mutation Detected	Invalid	Invalid
Valid, Mutation Detected	Valid, Mutation Detected	Valid, No Mutation Detected	Valid, Mutation Detected
Valid, Mutation Detected	Valid, Mutation Detected	Valid, Mutation Detected	Valid, Mutation Detected
Valid, Mutation Detected	Valid, Mutation Detected	Invalid	Invalid
Valid, Mutation Detected	Invalid	Valid, No Mutation Detected	Invalid
Valid, Mutation Detected	Invalid	Valid, Mutation Detected	Invalid
Valid, Mutation Detected	Invalid	Invalid	Invalid
Invalid	Valid, No Mutation Detected	Valid, No Mutation Detected	Invalid
Invalid	Valid, No Mutation Detected	Valid, Mutation Detected	Invalid
Invalid	Valid, No Mutation Detected	Invalid	Invalid
Invalid	Valid, Mutation Detected	Valid, No Mutation Detected	Invalid
Invalid	Valid, Mutation Detected	Valid, Mutation Detected	Invalid
Invalid	Valid, Mutation Detected	Invalid	Invalid
Invalid	Invalid	Valid, No Mutation Detected	Invalid
Invalid	Invalid	Valid, Mutation Detected	Invalid
Invalid	Invalid	Invalid	Invalid

**Table 3. Result Interpretation of the cobas® EGFR Mutation Test v2**

<b>Test Result</b>	<b>Mutation Result**</b>	<b>Interpretation</b>
Mutation Detected (MD)	<i>G719X</i> Ex19Del <i>S768I</i> <i>T790M</i> <i>Ex20Ins</i> L858R <i>L861Q</i> (More than one mutation may be present)	Mutation detected in specified targeted EGFR region.
No Mutation Detected* (NMD)	N/A	No mutation detected in targeted EGFR regions
Invalid	N/A	Specimen result is invalid. Repeat the testing of specimens with invalid results following the instructions outlined in the “Retesting of Specimens with Invalid Results” section.
Failed	N/A	Failed run due to hardware or software failure. Contact your local Roche office for technical assistance

\*A No Mutation Detected (NMD) result does not preclude the presence of a mutation in the targeted EGFR regions, because results depend on percent mutant sequences, adequate specimen integrity, absence of inhibitors, and sufficient DNA to be detected.

\*\*Italicized mutation results consist of new mutations included in this device version based on data in this submission. Mutations other than one exon 19 deletions (Ex19Del), L858R, and T790M will be intended for analytical detection only.

### **Test Controls**

One EGFR mutant control and one EGFR negative control are provided. The EGFR wild-type allele on exon 28 serves as an internal, full process control.

1. *EGFR Mutant Control*: The Mutant Control is a blend of six DNA plasmids containing specified EGFR mutation sequences and cell line DNA that is wild-type for EGFR. The Mutant Control is composed of plasmids representing the most frequently observed mutation for each mutation class detected by the test. The Mutant Control will be included in every run and will serve as a process control for amplification and detection. The Mutant Control must yield Cycle threshold (Ct) values for the Internal Control (IC), exon 19 deletion mutations, and L858R mutation within the respective acceptable ranges for the run to be considered valid.
2. *EGFR Negative Control*: The Negative Control is a full process contamination control for a given test batch of specimens. The Negative Control consists of a blank vial containing no specimen (specimen diluent only) is processed through specimen preparation and the resulting eluate is subsequently diluted, amplified and detected. The Negative Control Ct values must be either not detected or

greater than the pre-established Ct maximum value for the exon 19 deletion and L858R mutation groups and the IC for the run to be considered valid.

3. *EGFR WT Internal Control (IC)*: The Internal Control in EGFR exon 28 from test specimens serves as a full process control. This control ensures that every step of the process from specimen preparation to amplification and detection has been completed successfully.

## **VI. ALTERNATIVE PRACTICES AND PROCEDURES**

There are no other FDA-cleared or -approved alternatives for the testing of formalin-fixed, paraffin-embedded NSCLC tissue for EGFR mutation status in the selection of patients who are eligible for first-line treatment with Tarceva<sup>®</sup> (erlotinib) or second-line or later treatment with Tagrisso<sup>®</sup> (osimertinib).

## **VII. MARKETING HISTORY**

The **cobas**<sup>®</sup> EGFR Mutation Test (v1) was introduced into the United States and globally starting on May 14, 2013. The **cobas**<sup>®</sup> EGFR Mutation Test (v1) is commercially available in the following countries: Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Croatia, Cyprus, Czech Republic, Denmark, Ecuador, Estonia, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, Iceland, India, Indonesia, Ireland, Italy, Japan, Korea, Latvia, Liechtenstein, Lithuania, Luxembourg, Malaysia, Malta, Mexico, Netherlands, New Zealand, Nicaragua, Norway, Pakistan, Panama, Peru, Philippines, Poland, Portugal, Romania, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, Turkey, United Arab Emirates, United Kingdom, United States, Uruguay, Venezuela, Vietnam.

The **cobas**<sup>®</sup> EGFR Mutation Test v2 has not been marketed in the United States or any foreign country.

## **VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH**

Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect **cobas**<sup>®</sup> EGFR Mutation Test v2 results and subsequently improper patient management decisions in NSCLC treatment. For the specific adverse events that occurred in the clinical studies, please see Section X below.

## **IX. SUMMARY OF PRECLINICAL STUDIES**

### **A. Laboratory Studies**

For the non-clinical studies described below, percentage of tumor was assessed by pathology review. Bi-directional Sanger sequencing and next generation sequencing (NGS) methods were used to select the specimens for testing. Percentage of mutation of NSCLC FFPET specimen was determined using an NGS method.

Software changes occurred after completion of testing of the AURA2 clinical specimens. The revised software changes were appropriately validated with regression testing and the data from all studies were reanalyzed with the revised software versions.

During performance of the clinical studies on patient samples from the AURA2 study, a 3.1% (12/383) discordant rate was observed between the **cobas**<sup>®</sup> EGFR Mutation Test v2 and the NGS reference method. As a result of this and similar inquiries from customers outside the US, the algorithm for detection of the exon 20 insertion mutations was reassessed. The new cut-off was validated using an independent cohort of specimens and validated against the analytical and clinical study specimens. As a result of the change the ASAP software was updated to EGFR Tissue P1 AP v1.0.0.1560 and the results of all studies were reanalyzed. Upon reanalysis of the study data, the only studies affected by the change were the Limit of Detection, Slide vs. Curl Equivalency, and Reproducibility studies. The changes in these studies are noted in their descriptions below.

## **1. Correlation with Reference Method**

The analytical performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2 was assessed by comparing it to a validated quantitative NGS method. Percent mutation present in specimens was determined for all specimens used to demonstrate analytical and clinical performance.

Patients were enrolled into the AURA2 study using an Investigative Use Only (IUO) version (v1) of the **cobas**<sup>®</sup> EGFR Mutation Test which reported results for the additional five mutations which were masked in the version of the test approved under P120019. All specimens subsequently retested using version 2 of the test and the percent of EGFR mutation was identified using a validated NGS method. Table 4 summarizes the calculated positive percent agreement (PPA) and negative percent agreement (NPA) and overall percent agreement (OPA). Thirteen specimens were determined to be invalid upon comparison with NGS and thirty (30) of the 383 samples were identified as T790M+ by NGS but were negative by the **cobas**<sup>®</sup> EGFR Mutation Test v2. In 11 of the 30 discordant samples, the percent T790M mutation as determined by NGS was below the LoD of the **cobas**<sup>®</sup> EGFR Mutation Test v2 (2.0%). Of the remaining 19 samples, the T790M mutation was detected by the v1 test in seven samples ( $7/383 = 1.8\%$ ), but the mutation was not detected by the v2 test, because the Internal Control Ct values were outside of the acceptable range, indicating poor amplifiability of the DNA template. The remaining 12 samples in which T790M was not detected by either version of the test, each of the Internal Control Ct values were moderately delayed, again suggesting poor amplifiability of the DNA template.

**Table 4. cobas® EGFR Mutation Test v2 vs. NGS Using AURA2 Specimens**

		NGS			
		Exon T790M Deletion			
		MD	MND	Invalid	Total
cobas® EGFR Mutation Test v2 Result	MD	226	3	2	231
	MND	30	109	0	139
	Invalid	5	6	2	13
	Total	261	118	4	383
Without Invalid Results	PPA (95% CI)	226/256 = 88.3% (95% CI: 83.8%, 91.7%)			
	NPA (95% CI)	109/112 = 97.3% (95% CI: 92.4%, 99.1%)			
	OPA (95% CI)	(226+109)/368 = 91.0% (95% CI: 87.7%, 93.5%)			
With Invalid Result	PPA (95% CI)	226/263 = 85.9% (81.2%, 89.6%)			
	NPA (95% CI)	109/122 = 89.3% (82.6%, 93.7%)			
	OPA (95% CI)	(226+109)/383 = 87.5% (83.8%, 90.4%)			

Note: Estimates with invalid results assume that the results invalid by both methods are discordant with the reference method (worst case scenario).

Table 5 below summarizes the ability of the cobas® EGFR Mutation Test v2 to accurately identify the four rare EGFR mutations was also established by comparison to the NGS reference method. Diagonal cells (shaded) represent concordance between NGS and the cobas® EGFR Mutation Test v2 test results, while the off-diagonal cells represent discordance between NGS and the cobas® EGFR Mutation Test v2. Specimens included in the “Other Mutations” column due to the identification of other mutations detected by NGS and the cobas® EGFR Mutation Test v2.

**Table 5. cobas® EGFR Mutation Test v2 vs. NGS for Rare Mutations**

cobas® EGFR Mutation Test v2	NGS							Total
	G719X	S768I	G719X & S768I	Ex20Ins	L861Q & G719X	Other Mutations <sup>1</sup>	WT	
G719X	9	0	0	0	0	1	1	11
S768I	0	4	0	0	0	0	0	4
G719X & S768I	0	0	2	0	0	0	0	2
<i>Ex20Ins</i>	0	0	0	0	0	4	0	4
L861Q & G719X	0	0	0	0	1	0	0	1
Other Mutations <sup>1</sup>	1	1	0	1	0	326	2	331
Wild type	0	0	0	0	0	3	14	17
Total	10	5	2	1	1	334	17	370

<sup>1</sup> Other mutations include any mutation result that does not contain G719X, S768I, Ex20ins, or L861Q. Italicized text indicates change in the number of Ex20Ins from the original 12 after cut-off recalculation.

## 2. Analytical Sensitivity

### a. Analytical Sensitivity - Limit of Blank (LoB)

To assess performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2 in the absence of template and to ensure that a blank sample or a sample with wild-type DNA does not generate an analytical signal that might indicate a low concentration of mutation, samples with no template and NSCLC FFPET EGFR wild-type specimens were evaluated.

- i. Limit of Blank (LoB) no template – DNA Specimen Diluent reagent was run as the sample with no template. None of the replicates tested across each sample panel and reagent lot yielded a “Mutation Detected” result. Ct values can be measured out to 55 cycles and results reported as “NaN” for “Not a Number”, indicating no growth curve was observed and no Ct value was determined.
- ii. Limit of Blank (LoB) FFPET Specimens – NSCLC FFPET EGFR wild-type specimens were tested. Specifically, 30 wild-type specimens were tested using 50 ng DNA per amplification. There were no detectable Ct values in the EGFR mutation channels in the presence of EGFR wild-type DNA isolated from NSCLC FFPET specimens. Using the analysis prescribed in the CLSI EP17-A2 guideline, the LoB was determined to be zero for all mutations.
- iii. The study data were reanalyzed to assess the impact of the cut-off change for the Exon 20 insertion mutations. No change in the established LoB was identified.

**b. Analytical Sensitivity - Limit of Detection (LoD)**

Replicate **cobas**<sup>®</sup> EGFR Mutation Test v2 measurements were performed on dilution panel members that contained various amounts of genomic DNA and various percentages of the EGFR mutation, which bracketed the expected analytical sensitivity of the **cobas**<sup>®</sup> EGFR Mutation Test v2. Several studies were performed by testing dilution panels prepared from FFPET specimen blends.

**Specimen FFPET blends** – Multiple FFPET specimen DNA extracts representing each of the mutations detected by the test were blended with EGFR wild-type FFPET specimen extracts to generate samples targeting 10, 5.0, 2.5, and 1.25% mutation levels as determined by an NGS method, that was validated for detecting the EGFR mutations in exons 18, 19, 20, and 21. Serial dilutions of each specimen blend were prepared and eight (8) replicates of each panel member were run using each of three **cobas**<sup>®</sup> EGFR Mutation Test v2 kit lots (n=24/panel member). The sensitivity of each sample was determined by the lowest amount of DNA that produced an EGFR “Mutation Detected” rate of at least 95% for the targeted mutation. The study results are summarized in Table 6.

**Table 6. Sensitivity of the cobas® EGFR Mutation Test v2 using FFPET Specimen Blends**

Exon	EGFR Mutation	Mutation Sequence	Percent Mutation in the Panel Member to achieve ≥95% “Mutation Detected” Rate with 50 ng DNA input per reaction well (n=24 replicates)	COSMIC ID
18	G719X	2155 G>T	5.6	6253
		2155 G>A	3.2	6252
		2156 G>C	4.7	6239
		2156 G>C	2.5	6239
19	Exon 19 Deletion	2235_2249del15	1.4	6223
		2236_2250del15	2.5	6225
		2238_2252del15	2.4 <sup>c</sup>	23571
		2239_2248>C	2.2	12382
		2240_2254del15	7.2	12369
		2240_2257del18	13.4 <sup>b</sup>	12370
		2237_2253>TTGCT <sup>a</sup>	6.32	12416
		2237_2255>T <sup>a</sup>	4.08	12384
		2239_2256del18 <sup>a</sup>	4.74	6255
		2238_2252del15 <sup>a</sup>	5.45	23571
2239_2257>GT <sup>a</sup>	6.02	Not Found		
20	T790M	2369 C>T	2.4	6240
		2369 C>T	3.0	6240
	S768I	2303 G>T	2.4	6241
		2303 G>T	1.3	6241
	Exon 20 Insertion	2307_2308insGCCAGC GTG	1.7	12376
		2310_2311insGGT	1.3	12378
2319_2320insCAC	6.81 <sup>e</sup>	12377		
21	L858R <sup>d</sup>	2573 T>G	4.0	6224
		2573 T>G	4.2	6224
		2573 T>G	4.3	6224
		2573 T>G	4.3	6224
		2573 T>G	5.3	6224
	L861Q	2582T>A	2.1	6213

<sup>a</sup> Only a single level targeting approximately 5% mutation was tested for these non-predominant exon 19 deletion mutations present in the EURTAC cohort. Specimen DNA blends were tested across 3 study sites. Data is included for completeness.

<sup>b</sup> Analytical sensitivity of the cobas® EGFR Mutation Test v2 for detecting this mutation is greater than 10% mutation level using the standard input of 50 ng per reaction well.

<sup>c</sup> Two independent specimens for the exon 19 deletion (2238\_2252del15) were tested.

<sup>d</sup> Five independent specimens for the exon 21 L858R mutation were tested.

<sup>e</sup> Analytical sensitivity of the cobas® EGFR Mutation Test v2 for detecting this mutation is greater than 5% mutation level using a standard input of 50 ng per reaction well after reanalysis using the revised exon 20 insertion cut-off.

The studies support the claim that the **cobas**<sup>®</sup> EGFR Mutation Test v2 can detect 5% EGFR mutant alleles in a background of 95% wild-type alleles in formalin-fixed, paraffin-embedded tumor samples when using 50 ng DNA per amplification reaction (50 µL), with the exception of five mutations: the 2240\_2257del18 exon 19 deletion mutation, which is detected at a sensitivity of >10%, and 2319\_2320insCAC exon 20 insertion and three exon 19 deletions (2237\_2253>TTGCT, 2240\_2254del15, and 2239\_2257>GT) determined from a prior approval which were detected at >6% upon reanalysis of the data after the exon 20 insertion cut-off was changed.

### **3. Analytical Sensitivity – Genomic DNA Input Range**

Various genomic DNA input amounts may result from DNA quantitation errors and/or variation in the amount of degraded DNA. To evaluate the effects of various genomic DNA input amounts, genomic DNA of five DNA input concentrations of 50, 12.5, 3.1, 0.8 and 0.2 ng per amplification reaction were evaluated as part of the LoD - Specimen FFPE blends study. The study results supported the recommended DNA input of 50 ng per PCR reaction for the **cobas**<sup>®</sup> EGFR Mutation Test v2.

### **4. Analytical Sensitivity – Minimum Tumor Content**

Twenty (20) NSCLC FFPE specimens (ten wild-type and ten EGFR mutants) mounted on slides with tumor content data were tested in single replicates for macro-dissected vs. neat conditions to determine the impact of tumor content on the performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2. The mutations represented in the study consisted of five L861Q mutations; two Ex19Del and T790M dual mutations, one L858R and T790M dual mutation, and one T790M and G719X dual mutation. The percent tumor content was determined by pathologist assessment and spanned 8 - 95% tumor content by area (1 sample ≤ 10% and 9 samples > 10%) for mutant specimens and spanned 1-90% tumor content by area (3 samples ≤ 10% and 7 samples > 10%) for wild-type specimens. EGFR mutation status was determined by NGS. Each specimen pair consisted of adjacent sections and macro-dissection was performed as described in the package insert. Macro-dissection did not affect the detectability of EGFR mutations in FFPE specimens with <10% tumor content by the **cobas**<sup>®</sup> EGFR Mutation Test v2. However macro-dissection is still considered necessary for NSCLC FFPE sections with less than 10% tumor content prior to testing with the **cobas**<sup>®</sup> EGFR Mutation Test v2.

### **5. Analytical Specificity**

#### **a. Primer and Probe Specificity**

Sequence information and alignment of the primers and probes with the EGFR gene was provided. A traditional Basic Local Alignment Search Tool (BLAST) search was performed for all of the oligonucleotides (primers and probes) as well as the target EGFR exons and amplicons using the human reference genome GRCh37. The traditional BLAST search was conducted using BLASTN 2.2.10 to assess short matches between the query (i.e., oligonucleotides and target sequences) and the database sequences. Based on two threshold parameters, T and S, sequences are reported as potential matches. A ThermoBLAST analysis (BLASTN 2.2.17, version 1.2.2.4.0) was also conducted to assess potential mismatches in hybridization, including stabilizing G-T mismatches. Based on the combined results of the BLAST searches, no potentially cross-reacting sequences other than the targeted sequences were identified.

**b. Cross Reactivity**

Cross-reactivity of the **cobas**<sup>®</sup> EGFR Mutation Test v2 to other EGFR exon 19 mutations were evaluated using the Phase II AURA2 clinical trial specimens and EGFR plasmids. While the **cobas**<sup>®</sup> EGFR Mutation Test v2 demonstrated cross-reactivity to the mutations listed in Table 7 below, analytical performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2 in detecting these mutations has not been evaluated.

**Table 7. Mutations Observed in the Phase II AURA2 Study Determined to Cross-React with the **cobas**<sup>®</sup> EGFR Mutation Test v2**

Exon	Mutation Sequence	Amino Acid Change	COSMIC ID
19	2253_2276del24	S752_I759delSPKANKEI	13556
	2236_2256>ATC	E746_S752>I	133190
21	2572_2573CT>AG	L858R	13553

Plasmid constructs containing the non-predominant mutations for exons 18, 19, 20, and 21 were blended with wild-type genomic DNA to create 5% mutant sample with 50 ng DNA input per PCR. Results demonstrated that the **cobas**<sup>®</sup> EGFR Mutation Test v2 cross-reacts to the following mutations at a  $\geq$  86% hit rate. Independently, the EGFR exon 19 substitution mutation L747S was also tested at a genomic copy number equivalent to 50 ng/PCR input and confirmed to be cross-reactive.

**c. Microorganisms and EGFR Homologs**

Specificity of the **cobas**<sup>®</sup> EGFR Mutation Test v2 was evaluated by testing lung-related microorganisms, and plasmids of EGFR homologs, i.e., plasmids containing the sequences from each of the HER2, HER3, and HER4 genomic regions analogous to the sequences in EGFR exons 18, 19, 20, and 21 amplified by the **cobas**<sup>®</sup> EGFR Mutation Test v2.

- i. EGFR Homolog Panels – Structurally related epidermal receptor tyrosine kinase protein analog sequences (EGFR/HER1, HER2, HER3 and HER4) were shown to not cross-react with the **cobas**<sup>®</sup> EGFR Mutation Test v2 when the potential cross-reactive sequence was added at a genomic copy number equivalent to 50 ng/PCR input to the isolated pooled EGFR mutation positive DNA stock prior to the amplification/detection procedure. A control condition without plasmid DNA was included. Results indicated that the observed mutations for all tested FFPET specimens matched the expected mutation as determined by sequencing, in the presence and absence of the added HER gene plasmid DNA.
- ii. Testing of Lung-Related Microorganisms – *Streptococcus pneumoniae* and *Haemophilus influenzae* at  $4 \times 10^5$  colony forming units (CFU) were found not to cross react or interfere with the **cobas**<sup>®</sup> EGFR Mutation Test v2 when added to specimens containing wild-type and mutant EGFR sequences during the tissue lysis step. Presence of *Pseudomonas aeruginosa* and *Aspergillus Niger* at approximately 100 CFU/mL in EGFR MMx1, EGFR MMx2, and EGFR MMx3 were found not to cross react or interfere with the performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2.

## 6. Interference – Effects of Necrotic Tissue

To evaluate the potential interference of high necrotic tissue content in NSCLC FFPET specimens using the **cobas**<sup>®</sup> EGFR Mutation Test v2, 41 NSCLC FFPET specimens, including 18 mutant specimens (four with exon 19 deletion mutations, three with the L858R mutation, one with both the S768I and L858R mutations, two with the S768I and G719X mutations, two with the L861Q mutation, five with the G719X mutation, and one with the exon 20 insertion mutation) and 23 wild-type specimens, were evaluated. Percent necrosis, as identified by a pathologist, varied from 0-60% for mutant FFPET specimens and 5-85% for wild-type FFPET specimens.

Eighteen (18) mutant and 23 wild-type specimens with tumor content of 35-80% and 14-82% mutation were used in this study to assess the impact of the necrotic tissues. All observed results matched the expected results for all the specimens tested. Data supported that necrotic tissue content up to 85% in NSCLC FFPET specimens do not interfere with the call results for the **cobas**<sup>®</sup> EGFR Mutation Test v2.

An additional review of the data from the AURA2 study showed the percent necrosis present in specimens with the T790M mutation ranged from 0-70%, percent tumor ranged from 5-95% and the presence of necrosis did not appear to interfere with detection of the mutation. Up to 30% necrosis was observed in specimens that tested positive for Ex20Ins after the cut-off was revised in those specimens that were identified as positive.

## 7. Interference – Triglycerides or Hemoglobin

To evaluate the potential interference of triglycerides and hemoglobin on the performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2, five conditions were tested for each of 13 NSCLC FFPE specimens across two studies:

- Hemoglobin (2 mg/mL)
- Buffer Control for Hemoglobin
- Triglycerides (37 mM)
- Buffer Control for Triglycerides
- Neat (No Substance)

Five 5- $\mu$ m sections were obtained from each of the NSCLC EGFR FFPE specimens. Each section was deparaffinized and spiked with one of the five potential interfering materials in tissue pellet suspension prior to DNA extraction. The levels of triglycerides (37 mM) and hemoglobin (2 mg/mL) were equal to the levels recommended to be tested by CLSI guideline EP7-A2, Appendix D. Following deparaffinization and the spiking of potential interfering substances, genomic DNA was isolated from each of the spiked tissue specimens using the **cobas**<sup>®</sup> EGFR Mutation Test v2.

Seven mutant specimens with tumor content of approximately 13-41% mutation were used in this study to assess the impact of the interference at approximately 3-fold to 4-fold analytical sensitivity. All observed results matched the expected results at the levels of triglycerides and hemoglobin tested, indicating that triglycerides and hemoglobin do not interfere with the performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2.

## 8. Interference – Drugs

To evaluate the potential interference of therapeutic drugs which may be present in NSCLC FFPE specimens that could be tested with the **cobas**<sup>®</sup> EGFR Mutation Test v2, 13 NSCLC FFPE specimens were tested with drugs (i.e., albuterol, ipratropium, fluticasone, ceftazidime, imipenem, cilastin, piperacillin, tazobactam, betadine, and lidocaine) and the solvents used to dissolve each drug. Five (5)  $\mu$ m sections were obtained from each NSCLC EGFR FFPE specimen. Each of the sections was deparaffinized and spiked with tested drugs or solvent in tissue pellet suspension prior to DNA extraction. The levels of potential interfering substance were equal to the levels recommended to be tested by CLSI guideline EP7-A2 or at 3x  $C_{max}$  value as recommended by the drug's package insert with the exception of betadine, which is a topical solution that was tested as 10  $\mu$ L of a 10% (w/v) solution. Genomic DNA was isolated and tested from each of the spiked tissue specimens using the **cobas**<sup>®</sup> EGFR Mutation Test v2. Seven mutant specimens with tumor content of 15-40% mutation were used in this study to assess the impact of the interference. All observed results matched the expected

results for all conditions tested, indicating the tested drugs do not interfere with the performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2.

## 9. **Repeatability**

Repeatability was demonstrated across two studies.

The first study included five NSCLC FFPET specimens with mutations for each of the four (one Ex20Ins mutation, one L858R and T790M dual mutation, and one S768I and G719X dual mutation) out of the seven mutations detected by the **cobas**<sup>®</sup> EGFR Mutation Test v2. Each sample was tested in duplicate by two operators using two different **cobas**<sup>®</sup> DNA Sample Preparation and **cobas**<sup>®</sup> EGFR Mutation Test kit reagent lot combinations across four days; the testing was split between two **cobas z** 480 analyzers. Six incorrect or invalid calls were observed in the study due to either contaminated replicates (n = 4) or the presence of an additional mutation at very low levels resulting in intermittent calls (n=2). Therefore, 154/160 calls were correct, demonstrating a repeatability rate of 96.25%.

A second study was conducted which included three EGFR mutant NSCLC FFPET specimens (one L861Q, one G719X, one exon 20 insertion), each representing a different mutation, and one EGFR wild-type FFPET specimen. The study was conducted as described above but was conducted across eight days due to several invalid runs over three days. The invalid runs were due to user error, internal control (IC) Ct value being above the IC Ct<sub>max</sub> cut-off, and contamination of a negative control and a single sample replicate. Overall, 127/128 (99.2%) results were accurately identified by the assay after resolution of the invalid results.

## 10. **Reproducibility**

A reproducibility study was performed to assess the reproducibility of the **cobas**<sup>®</sup> EGFR Mutation Test v2 across three external testing sites with two operators per site, three reagent lots (two lots per site), and five non-consecutive testing days (per operator), with an 11-member panel of DNA samples extracted from FFPET sections of wild-type (WT) and mutant NSCLC specimens. The panel included specimens representing the G719X mutation, T790M mutation, S768I mutation, exon 20 insertion mutations, and L861Q mutation. Each mutation-positive specimen was represented at two concentrations, near the mutation's LoD and 2X LoD, prepared from genomic DNA (gDNA) blends (mutation positive with WT gDNA). Each sample at each concentration was run in duplicate. Of 91 runs, 90 (98.9%) were valid. A total of 1,980 tests were performed with 11 panel members tested in duplicate in 90 valid runs; all test results were valid. There were no Mutation Detected results in 180 valid tests of WT panel members, producing 100% agreement. Agreements were 100% for all mutant panel members. Results by overall agreement are presented in Table 8. The coefficient of variation (CV)

was <9.2% in all mutant panel members. For the external control, the overall CV was ≤1.3%. The CV was ≤0.6% between lots and ≤ 1.1% within-lot.

**Table 8. Overall Agreement Estimates by Panel Member**

Panel Member	Mutation	Number of Valid Tests	Agreement (N)	
			n	% (95% CI) <sup>a</sup>
1	Wild-Type	180	180	100 (98.0, 100.0)
2	G719X - LoD	180	180	100 (98.0, 100.0)
3	T790M - LoD	180	180	100 (98.0, 100.0)
4	S768I - LoD	180	180	100 (98.0, 100.0)
5	Ex20Ins – LoD <sup>b</sup>	180	166	92.2 (87.3, 95.7)
6	L861Q - LoD	180	180	100 (98.0, 100.0)
7	G719X - 2X LoD	180	180	100 (98.0, 100.0)
8	T790M - 2X LoD	180	180	100 (98.0, 100.0)
9	S768I - 2X LoD	180	180	100 (98.0, 100.0)
10	Ex20Ins - 2X LoD	180	180	100 (98.0, 100.0)
11	L861Q - 2X LoD	180	180	100 (98.0, 100.0)

Note: Results were in agreement when a mutant panel member had a valid result of MD for the target mutation or when a wild-type panel member had a valid result of NMD.

<sup>a</sup> 95% CI = 95% exact binomial confidence interval.

<sup>b</sup> The overall agreement was revised from 100% for Ex. 20 insertions at the LoD to 92.2% after the mutation cut-off was changed and the data re-analyzed.

CI = confidence interval; LoD = limit of detection; NMD = No Mutation Detected

The total CV % ranged from 2.2% to 9.1% across all panel members. Within each component, CV% ranged from 0.0% to 8.0% across all panel members. Within-run accounted for the major percentage of the variance (from 29.1% to 79.0%) for the mutation panel members. Percentage of total variance attributed to lot varied from 0.0% to 26.3%; attributed to site/instrument varied from 0.0% to 16.1%; attributed to day varied from 11.8% to 55.7%; and attributed to operator varied from 0.0% to 13.6% to across mutant panel members. The summary results are shown in Tables 9 and 10 below for the mutant positive panel members and for Ex20Ins after cut-off revision. Panel member 1 consisted of an EGFR wild-type specimen.

**Table 9. Overall Mean, Standard Deviation, and %CV for CtR from Valid Results of Mutant Panel Members and Ct from Valid Results for Ex20Ins Panel Members**

		Standard Deviation (SD) and Percent Coefficient of Variation (CV)											
		Lot		Site/Inst.		Operator		Day		Within-Run		Total	
Panel Member	Mean CtR (95% CI)	SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV %
2	8.41 (8.2, 8.6)	0.09	1.0	0.00	0.0	0.00	0.0	0.09	1.0	0.14	1.7	0.19	2.2
3	6.80 (6.6, 7.0)	0.00	0.0	0.03	0.4	0.07	1.0	0.15	2.2	0.14	2.0	0.22	3.2
4	3.21 (3.0, 3.4)	0.00	0.0	0.07	2.2	0.05	1.5	0.12	3.6	0.16	4.9	0.21	6.7
6	4.20 (4.0, 4.4)	0.10	2.4	0.06	1.4	0.04	0.9	0.09	2.1	0.12	2.9	0.19	4.6
7	7.46 (7.3, 7.6)	0.07	0.9	0.03	0.4	0.00	0.0	0.08	1.1	0.13	1.7	0.17	2.3

		Standard Deviation (SD) and Percent Coefficient of Variation (CV)											
		Lot		Site/Inst.		Operator		Day		Within-Run		Total	
Panel Member	Mean CtR (95% CI)	SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV %	SD	CV %
8	5.78 (5.7, 5.9)	0.02	0.4	0.00	0.0	0.07	1.3	0.15	2.5	0.11	1.8	0.20	3.4
9	2.30 (2.1, 2.5)	0.00	0.0	0.06	2.7	0.00	0.0	0.07	3.1	0.19	8.0	0.21	9.1
11	3.39 (3.2, 3.6)	0.07	2.2	0.01	0.4	0.04	1.2	0.08	2.5	0.11	3.3	0.16	4.8
	Mean Ct (95% CI)												
5	32.41 (32, 32.9)	0.17	0.5	0.20	0.6	0.5	0.1	0.18	0.5	0.32	1.0	0.45	1.4
10	31.63 (31.3, 32)	0.16	0.5	0.06	0.2	0.09	0.3	0.19	0.6	0.26	0.8	0.37	1.2

**Table 10. Total Precision, Standard Deviation and Percentage of Total Variance of CtR Attributed to Lot, Site/Instrument, Operator, Day, and Within-Run by Mutant Type Panel Members**

Panel Member	N	Total SD	Percentage of Total Variance [CV(%)]					Total CV
			Lot	Site/Instrument	Operator	Day	Within-Run	
2	180	0.19	21.17 (1.02)	0.00 (0.00)	0.00 (0.00)	21.00 (1.01)	57.84 (1.68)	2.2
3	180	0.22	0.00 (0.00)	1.69 (0.42)	10.15 (1.02)	47.81 (2.22)	40.36 (2.04)	3.2
4	180	0.21	0.00 (0.00)	11.03 (2.22)	4.82 (1.47)	29.45 (3.63)	54.71 (4.95)	6.7
5	180	0.45	14.09 (0.53)	19.4 (0.62)	1.02 (0.14)	15.41 (0.55)	50.08 (0.99)	1.4
6	180	0.19	26.35 (2.38)	9.19 (1.40)	3.55 (0.87)	20.78 (2.11)	40.13 (2.93)	4.6
7	180	0.17	15.62 (0.90)	2.82 (0.38)	0.00 (0.00)	23.47 (1.10)	58.09 (1.74)	2.3
8	180	0.20	1.51 (0.42)	0.00 (0.00)	13.62 (1.26)	55.72 (2.54)	29.14 (1.84)	3.4
9	180	0.21	0.00 (0.00)	9.16 (2.74)	0.00 (0.00)	11.83 (3.11)	79.01 (8.05)	9.1
10	180	0.37	18.84 (0.51)	2.67 (0.19)	5.47 (0.27)	25.52 (0.59)	47.50 (0.81)	1.2
11	180	0.16	20.02 (2.16)	0.62 (0.38)	6.11 (1.19)	25.75 (2.45)	47.50 (3.33)	4.8

### 11. Lot-to-Lot Reproducibility

The **cobas**<sup>®</sup> EGFR Mutation Test v2 utilizes two separate kits: (1) The **cobas**<sup>®</sup> DNA Sample Preparation kit for isolation of DNA from NSCLC FFPET specimens, and (2) the **cobas**<sup>®</sup> EGFR Mutation Test v2 for the amplification and detection of the isolated DNA for EGFR mutation status. Over two studies eight NSCLC FFPET specimens were tested with nine combinations of 3 lots of the **cobas**<sup>®</sup> DNA Sample Preparation Kit and 3 lots of the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit. The eight NSCLC FFPET specimens included two L858R and T790M dual mutant specimens; one S768I and G719X dual mutation specimen; one L861Q specimen; one exon 20 insertion specimen; one G719X specimen; one L861Q specimen; and two EGFR wild-type specimens. The percent tumor content in EGFR mutant specimens ranged from 14% to 22.7%. The observed results matched the expected results for eight of the nine lot combinations. One EGFR wild-type specimen replicate yielded a G719X result. There was insufficient eluate remaining in that replicate to perform repeat testing and confirm the result using NGS. NGS testing was performed on the remaining replicate which resulted in a NMD result. A root cause for the incorrect result was not identified; however, overall the results demonstrated that different lots of the two kits can be used interchangeably. The mean Ct and % CV values for each channel were summarized across lots and no trend in Ct values was observed.

## **12. Specimen Handling – Curl Versus Slide Equivalency**

To evaluate the equivalence of using DNA extracted from 5- $\mu$ m unmounted NSCLC FFPET sections (FFPET “curls”) and DNA extracted from NSCLC FFPET sections mounted on slides (FFPET “slides”), specimens were tested across two studies. The specimens from both studies represented a total of 81 NSCLC FFPET specimens (45 wild-type and 36 mutant specimens). The mutant specimens included 13 exon 20 insertions; six G719X; four L861Q; one exon 19 deletion and S768I dual mutation; five T790M and L858R dual mutations; two T790M and exon 19 deletion dual mutation; one T790M and G719X dual mutation; three S768I and G719X dual mutations; and one S768I and L858R dual mutation.

Two sections were sliced from each NSCLC FFPET specimen; one section was mounted on a slide and the other “curl” section placed into a microfuge tube, and prepared according to directions. Both the slide and curl sections for each specimen were tested using one lot combination of the **cobas**<sup>®</sup> DNA Sample Preparation Kit and **cobas**<sup>®</sup> EGFR Mutation Test v2 kit.

Thirty-one (31) specimens were included in the first study and were comprised of 11 mutation-positive specimens and 20 wild-type specimens. The mutant-positive specimens consisted of five exon 20 insertions; one G719X; one exon 19 deletion and S768I dual mutation; one T790M and L858R dual mutation; two S768I and G719X dual mutation; and one S768I and L858R dual mutation specimen. Tumor content ranged from 25% to 80% for mutant specimens and from 1% to 85% for wild-type specimens. The results demonstrated 97% (30/31) agreement between unmounted FFPET curls and FFPET slides.

The second study included 50 NSCLC FFPET specimens (25 wild-type and 25 mutant specimens). The mutant specimens included five G719X specimens, one G719X and S768I specimen, eight exon 20 insertion specimens, one G719X and T790M specimen, four L861Q specimens, two exon 19 deletion and T790M specimens, and four L858R and T790M specimens. Two sections were sliced from each NSCLC FFPET specimen; one section was mounted on a slide and the other “curl” section placed into a microfuge tube, and prepared according to directions. Both the slide and curl sections for each specimen were tested using one lot combination of the **cobas**<sup>®</sup> DNA Sample Preparation Kit and **cobas**<sup>®</sup> EGFR Mutation Test v2 kit. Tumor content ranged from 8% to 95% for mutant specimens and from 1% to 90% for wild-type specimens. Two specimens demonstrated discordant results between the slides and curls with reporting the presence of an extra mutation in the slide specimen (one L768I and one Ex19Del). In both specimens, the discordant sample demonstrated an additional mutation than expected. Upon investigating the cause for the discordant results, one slide sample did not demonstrate the extra mutation result after the same eluate was

reamplified. For the second specimen, when the DNA eluates were reamplified the slide demonstrated another mutation result in addition to the previous extra mutation. After DNA was isolated from fresh samples the expected results were observed. While contamination was deemed the reason for the discordances, the study demonstrated a 98% (49/50) agreement between the FFPET curls and FFPET slides specimens.

The results from the curl vs. slide equivalency study were reanalyzed after the exon 20 insertion mutation was changed using the software containing the new algorithm. Only one specimen was impacted in which one sample, a exon 20 insertion mutation curl, was affected where the result changed from mutation detected to no mutation detected. An investigation of the data showed that the Ct of the exon 20 insertion channel was 34.6, which is beyond the newly established cut-off of 33.1.

### **13. Specimen Handling – Macro-dissection**

The accuracy of samples following macro-dissection was evaluated with AURA2 clinical trial specimens that had less than 10% tumor content. Refer to Section 4 on “Analytical Sensitivity - Minimum Tumor Content” above for more details.

### **14. Guard banding**

The objective of the guard banding studies was to establish the robustness of the PCR conditions for the **cobas**<sup>®</sup> EGFR Mutation Test v2. Guard banding studies were performed on the **cobas**<sup>®</sup> EGFR Mutation Test v2 Thermal Cycling Profile and Proteinase K concentration (for DNA isolation procedure).

Six FFPET NSCLC specimens consisting of one T790M and G719X dual mutation; one S768I and G719X dual mutation; one L861Q mutation, one G719X mutation; one exon 20 insertion mutation; and one wild-type specimen were used. At least ten 5- $\mu$ m sections were obtained from each of the specimens and processed to isolate DNA using a single lot of the **cobas**<sup>®</sup> DNA Specimen Preparation Kit according to the **cobas**<sup>®</sup> EGFR Mutation Test v2 Instructions for Use. After processing, all replicates of each specimen were combined to make a pool of extracted DNA. Three replicates of each specimen pool were tested for each condition using a single reagent lot of the **cobas**<sup>®</sup> EGFR Mutation Test v2.

#### **a. Thermal Cycling Profile**

The thermal cycling profile was guard banded by varying both the denaturation and annealing temperatures by  $\pm 1^\circ\text{C}$ . All replicates of each specimen pool produced their expected results. For each specimen tested, the average Ct for each guard band condition was within 1 Ct of the average Ct of the control condition. The Ct difference from control condition for all specimens combined ranged from -0.19 to 0.52. The results showed that the

**cobas**<sup>®</sup> EGFR Mutation Test v2 is able to tolerate variations of  $\pm 1^{\circ}\text{C}$  of the thermal cycling profile in denaturation and annealing temperatures.

**b. Proteinase K (PK)**

During sample preparation, the NSCLC FFPET specimen is lysed by incubation at an elevated temperature with a proteinase and chaotropic lysis/binding buffer that release nucleic acids and protect the released genomic DNA from DNases. For each specimen processed by the **cobas**<sup>®</sup> DNA Sample Preparation kit, 70  $\mu\text{L}$  of PK and 180  $\mu\text{L}$  of DNA Tissue Lysis Buffer are added. The mixture is first incubated at  $56^{\circ}\text{C}$  for 60 minutes and then at  $90^{\circ}\text{C}$  for 60 minutes.

PK was guard banded by varying the PK volume ( $\pm 20\%$ ), the first incubation temperature ( $\pm 2^{\circ}\text{C}$ ), and the first incubation time ( $\pm 25\%$ ) using the **cobas**<sup>®</sup> DNA Sample Preparation kit. Following the **cobas**<sup>®</sup> EGFR Mutation Test v2 Instructions for Use, three operators each processed one replicate of three NSCLC FFPET specimens for nine PK conditions. A single reagent lot was used in this study and a total of three runs were performed. All replicates of each specimen produced their expected results. For each PK condition tested, the average Ct for each guard band condition was within 1 Ct of the average Ct of the control condition. The Ct difference from control condition for all specimens combined ranged from -0.26 to 0.32. The results showed that the **cobas**<sup>®</sup> EGFR Mutation Test v2 is able to tolerate differences of  $\pm 20\%$  for PK volume,  $\pm 2^{\circ}\text{C}$  for the first incubation temperature, and  $\pm 25\%$  for the first incubation time.

**15. Stability Studies**

**a. Clinical Specimen, Slide-Mounted and Slide Curl**

To demonstrate the stability of sections from NSCLC FFPET clinical specimens when mounted on a slide (“slide”) or when not mounted on a slide (“curl”), three NSCLC FFPET specimens, representing three EGFR mutations and one EGFR wild-type specimens were evaluated. The three EGFR mutations were represented by two specimens and consisted of one T790M and L858R dual mutation (17.48% and 16.38% mutation) and one L861Q mutation (14% mutation) specimens. Ten 5- $\mu\text{m}$  sections were obtained from each of the three NSCLC FFPET specimens, mounted or not mounted on slides (one section per slide). The slides and curls were stored at  $2-8^{\circ}\text{C}$  and  $32^{\circ}\text{C}$  and tested after 0 and 61 days. At each time point, two slides and two curls for each specimen and storage temperature were processed using one lot of the reagent. Results from the three specimens matched the expected results (based on sequencing results) at both time points. These results indicated that sections stored as slides or curls are stable at least 61 days at  $2-8^{\circ}\text{C}$  and  $32^{\circ}\text{C}$  storage for testing with the **cobas**<sup>®</sup> EGFR Mutation Test v2.

**b. Extracted DNA From FFPET Specimens**

Stability of DNA extracted from NSCLC FFPET specimens was evaluated using one EGFR wild-type specimen, one T790M and L858R dual mutant specimen (31.73% and 28.69% mutation), and one L861Q mutant specimen (16.16% mutation). DNA extracts obtained from each NSCLC FFPET specimen was tested as follows:

1. after storage at -20°C for 15, 31 or 61 days;
2. after storage at 2 to 8°C for 0, 15, 31, or 61 days;
3. after storage at 32°C for 2, 4, or 8 days;
4. after one, two, or three freeze-thaw cycles consisting of storage at -20°C, thawing, re-freezing and sampling at the specified -20°C time points.

After storage at -20°C, 2 to 8°C, or 32°C, results from the specimens matched the expected results (based on sequencing results) at each of the time points, indicating that DNA extracted from NSCLC FFPET specimens using the **cobas**<sup>®</sup> DNA Specimen Preparation Kit is stable for at least 61 days when stored at 2-8°C or -20°C. The results also indicated that the extracted DNA is stable for at least 8 days when stored at 32°C, and up to three freeze-thaw cycles when stored at -20°C. No trend in Ct values was detected over these testing conditions.

**c. Working (Activated) Master Mix**

To evaluate the stability of **cobas**<sup>®</sup> EGFR Mutation Test v2 Working (activated) Master Mixes stored at 2-8°C and 32°C for up to 125 minutes, three NSCLC FFPET specimens (two EGFR mutation-positive and one EGFR wild-type), were tested using 1 lot of reagent. The three NSCLC FFPET specimens were the same as those used in the extracted DNA stability study. Working (activated) Master Mixes were prepared by adding magnesium acetate to each EGFR Master Mix, and then stored at 2-8°C for 0, 35, 65, and 125 minutes, and at 32°C for 0, 35, 65, and 125 minutes. Ten 5-µm sections were obtained from each of the NSCLC FFPET specimens. Each of the sections was processed to isolate DNA using the **cobas**<sup>®</sup> DNA Sample Preparation Kit. DNA obtained from a single specimen was combined, resulting in a pool of extracted DNA for each specimen. After the indicated storage time, duplicate samples of DNA extracts from each of the NSCLC specimens were combined with the Working Master Mixes and amplified and detected using the **cobas**<sup>®</sup> EGFR Mutation Test v2. All valid specimen results matched the expected results at each of the time points, indicating that **cobas**<sup>®</sup> EGFR Mutation Test v2 working (activated) Master Mixes are stable for at least two hours when stored at 2-8°C or 32°C

**d. Extracted DNA Plus Working (Activated) Master Mix**

To evaluate the stability of the combination of extracted DNA from NSCLC

FFPET specimens and **cobas**<sup>®</sup> EGFR Mutation Test v2 Working (activated) Master Mixes, three NSCLC FFPET specimens were tested using 1 lot of reagent. The three NSCLC FFPET specimens were the same as those used in the extracted DNA stability study. DNA was extracted from each of the NSCLC FFPET specimens using the **cobas**<sup>®</sup> DNA Specimen Preparation Kit, combined with Working (activated) Master Mixes, and stored at 2-8°C for 0, 35, 65, and 125 minutes, and at 32°C for 0, 35, 65, and 125 minutes. After the indicated storage time, the combined DNA extract/Working Master Mixes were amplified and detected using the **cobas**<sup>®</sup> EGFR Mutation Test v2. Results from the specimens matched the expected result (based on sequencing results) at each of the time points after storage at 2-8°C or 32°C. No trend in Ct values was detected over these testing conditions. These results indicated that DNA extracted from NSCLC FFPET specimens using the **cobas**<sup>®</sup> DNA Specimen Preparation Kit combined with Working (activated) the **cobas**<sup>®</sup> EGFR Mutation Test v2 Working Master Mixes is stable for up to 125 minutes when stored at 2-8°C or 32°C prior to the start of amplification.

**e. Open Vial, cobas<sup>®</sup> EGFR Mutation Test v2 Kit Reagents**

To determine the open vial stability of the reagents in the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit, two kits were used to test three NSCLC FFPET specimens. The three NSCLC FFPET specimens were the same as those used in the extracted DNA stability study. One kit was tested on Days 0, 15, 21, and 31 and the second kit was tested on Days 0, 45, 61, and 91. The study was conducted to demonstrate the open vial stability of the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit reagents up to 30 days and 90 days with up to 4 uses per kit. Ten 5-µm sections were obtained from each NSCLC FFPET specimen. All results from the six specimens matched the expected result when the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit reagents were used 4 times over 91 days when stored at 2-8°C between uses. No trend in Ct values was detected over these open-vial storage periods. The results indicate that the open vial stability of the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit reagents is at least 91 days.

**f. cobas<sup>®</sup> EGFR Mutation Test v2**

Stability of the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit and its components were assessed at various time points after storage at 2-8°C (real-time) in upright and inverted orientations using three lots of the kit reagents. The test samples were the EGFR Mutant Control (EGFR MC) and the DNA Specimen Diluent (DNA SD), which serve as a positive control and negative control, respectively, in the **cobas**<sup>®</sup> EGFR Mutation Test v2. Eight replicates of the EGFR MC and DNA SD were tested at each storage condition. Stability was evaluated by performing functional testing at 4 weeks, 8 weeks, 3 months, 6 months, 9 months, 12 months, 13 months, 18 months, 19 months, 24 months, and 25 months. For a given storage condition at any time point to pass, the eight replicates of the EGFR MC and DNA SD must be within the pre-

specified ranges of Ct, which are identical to the Ct values for assessing validity of a run and assigning mutation status. To date, testing has been completed and met the acceptance criteria through 18 months storage at 2-8°C for all three lots of the kit reagents. Current real-time stability data support stability of the **cobas**<sup>®</sup> EGFR Mutation Test v2 at 2-8°C for 18 months. Real-time stability studies are ongoing to support the 24 months expiry.

**g. cobas<sup>®</sup> DNA Sample Preparation Kit**

Stability of the **cobas**<sup>®</sup> DNA Sample Preparation Kit, including open-vial stability, was demonstrated in P110020 approval of the **cobas**<sup>®</sup> 4800 BRAF V600 Mutation Test.

**h. Shipping**

Shipping stability was established under the **cobas**<sup>®</sup> EGFR Mutation Test (v1) and is not expected to be different for the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit.

**16. Antimicrobial Effectiveness Testing (AET)**

To assess the effectiveness of the preservatives in the **cobas**<sup>®</sup> EGFR Mutation Test v2 kit components, a total of five microorganisms (*Staphylococcus aureus*, *Candida albicans*, *Aspergillus niger*, *Pseudomonas aeruginosa* and *Escherichia coli*) were individually spiked into each of the kit components on Day 0, and the colony forming units (CFU) were counted in log<sub>10</sub> on Day 14 and Day 28. There is no impact of microbial contamination on the functional performance of the **cobas**<sup>®</sup> EGFR Mutation Test v2 when stored for up to 28 days at 25°C.

**B. Animal Studies**

None.

**C. Additional Studies**

None.

**X. SUMMARY OF PRIMARY CLINICAL STUDY**

The AURA2 study (D5160C00002) was a global phase II, open-label, single-arm study conducted by AstraZeneca Pharmaceuticals LP to assess the safety and efficacy of osimertinib as a second or ≥ third-line therapy in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV), who had progressed following prior therapy with an approved EGFR TKI agent and whose tumor specimens demonstrated a T790M positive result. The AURA2 study began with the first patient dosed on June 13, 2014 and completed, with the last patient dosed on October 27, 2014. The study was submitted for

approval with two other related studies to support efficacy of osimertinib under NDA 208065, but not used to support PMA approval.

In the AURA2 study, patients' EGFR mutation status was determined at one of three central laboratories using an investigational use only (IUO) version of the **cobas**<sup>®</sup> EGFR Mutation Test (v1), which identified mutations masked in the previously approved version of the kit, in order to identify those patients with a T790M mutation. All specimens were later retested using the **cobas**<sup>®</sup> EGFR Mutation Test v2. To establish the clinical utility of the **cobas**<sup>®</sup> EGFR Mutation Test v2, objective response rate (ORR) according to RECIST 1.1 by blinded independent central review (BICR) was estimated for all patients enrolled for enrollment who were determined to be T790M positive by both versions of the **cobas**<sup>®</sup> EGFR Mutation Test. A summary of the clinical study is presented below. Retrospective testing with the **cobas**<sup>®</sup> EGFR Mutation Test v2 was conducted under protocol COB-EGFR-341 which was approved under IDE G140034 on April 3, 2014. The study was completed with the last sample tested on March 25, 2015.

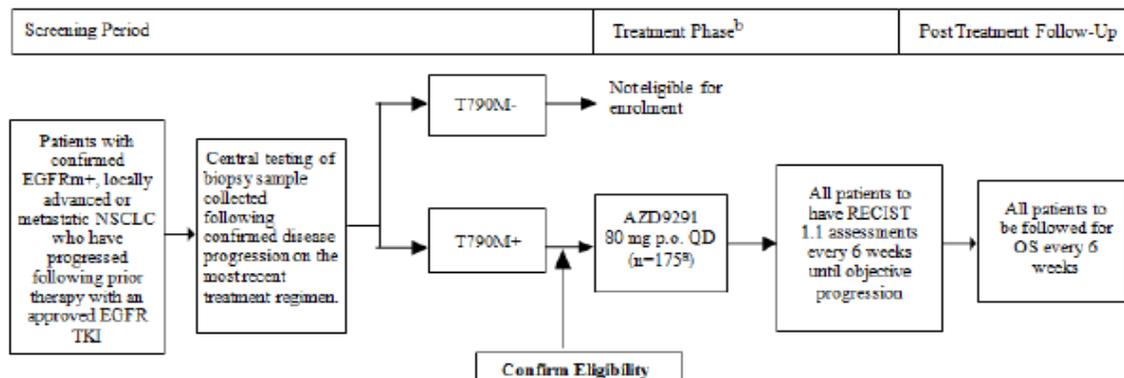
#### **A. Study Design**

The AURA2 study was a global phase II, open-label, single-arm study, assessing the safety and efficacy of osimertinib as a second or  $\geq$  third-line therapy in patients with locally advanced or metastatic NSCLC (Stage IIIB-IV), who had progressed following prior therapy with an approved EGFR TKI agent and whose tumor specimens demonstrated a T790M positive result. The study was conducted at 44 centers in 8 countries. A mandatory biopsy was required for central testing of EGFR T790M mutation status following confirmed disease progression on the most recent treatment regimen. The EGFR T790M mutation status of the patient's tumor was prospectively determined using the **cobas**<sup>®</sup> EGFR Mutation Test (v1) by one of three designated central laboratories, located in the US, Belgium, and Singapore. The study consisted of two cohorts:

1. Second-line therapy cohort: patients whose disease had progressed following first line therapy with an EGFR TKI agent but who had not received further treatment.
2.  $\geq$  third-line therapy cohort: patients whose disease had progressed following treatment with both an EGFR TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment).

A graphical representation of the study is shown in Figure 1 below:

**Figure 1 Study flow chart**



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

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

## 1. Clinical Inclusion and Exclusion Criteria

Patients enrolled in the AURA2 study continued on treatment with osimertinib until RECIST 1.1-defined progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment as patients could continue to receive osimertinib beyond RECIST 1.1-defined progression as long as they continued to show clinical benefit, as judged by the investigator. Prospective patients were required to meet all inclusion and exclusion criteria listed below.

### Inclusion Criteria

1. Provision of signed and dated, written informed consent prior to any study-specific procedures, sampling and analyses. If a patient declined to participate in any voluntary exploratory research and/or genetic component of the study, there was no penalty or loss of benefit to the patient and he or she was not to be excluded from other aspects of the study.
2. Male or female, aged at least 18 years. Patients from Japan aged at least 20 years.
3. Histological or cytological confirmation diagnosis of NSCLC.
4. Locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy.
5. Radiological documentation of disease progression: following first line EGFR TKI treatment but who had not received further treatment OR following prior therapy with an EGFR TKI and a platinum-based doublet chemotherapy.

Patients may have also received additional lines of treatment. All patients had to have documented radiological progression on the last treatment administered prior to enrolling in the study.

6. Confirmation that the tumor harbored an EGFR mutation known to be associated with EGFR TKI sensitivity (including G719X, Ex. 19del, L858R, L861Q).
7. Patients had to have central confirmation of tumor EGFR T790M mutation positive status from a biopsy sample taken after confirmation of disease progression on the most recent treatment regimen.
8. World Health Organization (WHO) performance status 0 to 1 with no deterioration over the previous 2 weeks and a minimum life expectancy of 12 weeks.
9. At least 1 lesion, not previously irradiated and not chosen for biopsy during the study screening period, that could be accurately measured at baseline as  $\geq 10$  mm in the longest diameter (except lymph nodes which had to have short axis  $\geq 15$  mm) with computerized tomography (CT) or magnetic resonance imaging that was suitable for accurate repeated measurements.
10. Females were to be using adequate contraceptive measures, were not to be breastfeeding and had to have a negative pregnancy test prior to the start of dosing if of childbearing potential, or had to have evidence of non-childbearing potential by fulfilling one of the following criteria at screening:
  - Post-menopausal defined as aged more than 50 years and amenorrheic for at least 12 months following cessation of all exogenous hormonal treatments.
  - Women under 50 years old were considered post-menopausal if they had been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution.
  - Documentation of irreversible surgical sterilization by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation.
11. Male patients were to be willing to use barrier contraception (i.e., condoms)
12. For inclusion in the optional genetics research, study patients had to provide informed consent for genetic research.

#### Exclusion criteria

1. Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study center).
2. Treatment with any of the following:
  - Treatment with an EGFR TKI (e.g., erlotinib, gefitinib or afatinib) within 8 days or approximately 5 half-lives, whichever was the longer, of the first dose of study treatment. (If sufficient washout time had not occurred due to the schedule or PK properties, an alternative appropriate washout time based on known duration and time to reversibility of drug-related AEs could be agreed upon by AstraZeneca and the investigator.)

- Any cytotoxic chemotherapy, investigational agent or other anti-cancer drugs from a previous treatment regimen or clinical study within 14 days of the first dose of study treatment.
  - Prior treatment with osimertinib or a third generation EGFR TKI (e.g., CO-1686).
  - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study treatment.
  - Radiotherapy treatment to more than 30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study treatment.
  - Patients currently receiving (or unable to stop use at least 1 week prior to receiving the first dose of study treatment) medications or herbal supplements known to be potent inhibitors or inducers of cytochrome P450 3A4 (CYP3A4) (see Appendix F of the CSP).
3. Any unresolved toxicities from prior therapy greater than CTCAE grade 1 at the time of starting study treatment with the exception of alopecia and grade 2, prior platinum therapy-related neuropath.
  4. Spinal cord compression or brain metastases unless asymptomatic, stable and not requiring steroids for at least 4 weeks prior to the start of study treatment.
  5. Any evidence of severe or uncontrolled systemic diseases, including uncontrolled hypertension and active bleeding diatheses which, in the investigator's opinion, made it undesirable for the patient to participate in the study or which would jeopardize compliance with the protocol, or active infection including hepatitis B, hepatitis C and human immunodeficiency virus. Screening for chronic conditions was not required.
  6. Refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of osimertinib.
  7. Any of specified cardiac criteria related to QTc, arrhythmia, or abnormalities in rhythm, conduction or morphology of resting ECG (e.g., complete left bundle-branch block, second- or third-degree heart block, partial response (PR) interval).
  8. Past medical history of interstitial lung disease (ILD), drug-induced ILD, radiation pneumonitis that required steroid treatment, or any evidence of clinically active ILD.
  9. Inadequate bone marrow reserve or organ function, as demonstrated by specified laboratory values regarding: absolute neutrophil and platelet count, and levels of hemoglobin, ALT, AST, total bilirubin, and creatinine.
  10. History of hypersensitivity to active or inactive excipients of osimertinib or drugs with a similar chemical structure or class to osimertinib.
  11. Women who were breastfeeding.
  12. Judgment by the investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions and requirements.

## 2. Follow-up Schedule

All patients were followed every six weeks from the date of first dose for RESIST 1.1 assessments until objective progression and every six weeks for overall survival assessment. Adverse events were assessed at treatment and all follow-up visits.

## 3. Clinical Endpoints

The AURA2 study's primary efficacy endpoint variable was the objective response rate (ORR) according to RECIST 1.1 by blinded independent central review (BICR) using the Full Analysis Set (FAS). FAS was defined as all T790M+ patients by the **cobas**<sup>®</sup> EGFR Test (v1) who received at least 1 dose of osimertinib. The ORR was defined as the number (%) of patients with at least 1 visit response of complete response (CR) or partial response (PR) that was confirmed at least 4 weeks later (i.e., a best objective response [BOR] of CR or PR).

Secondary objectives were to:

- Further assess the efficacy of osimertinib in terms of duration of response (DoR), disease control rate (DCR), tumour shrinkage, progression-free survival (PFS) and OS.
- Assess the safety and tolerability profile of osimertinib.
- Investigate the effect of AZD9291 on QT interval corrected for heart rate (QTc) interval after oral dosing to NSCLC patients.
- Assess the impact of osimertinib on patients' disease-related symptoms and health-related quality of life (HRQoL).
- Characterize the pharmacokinetics of osimertinib and its metabolites (AZ5104 and AZ7550).

## 4. Bridging Study:

A total of 472 patients who had progressed following an EGFR TKI were screened for enrollment into the AURA2 study. Fifty-five of the 472 patients screened did not meet eligibility criteria for pathology assessment, and 383 had successful pathology assessment and were eligible for **cobas**<sup>®</sup> EGFR Mutation Test (v1) testing. Of these, 233 test results were T790M mutation positive (60.8%), 140 test results were T790M negative (36.6%), and 10 test results were invalid (2.6% invalid rate). Of the 233 T790M mutation positive patients, 210 received osimertinib. All specimens with successful pathology assessment (n = 383) were tested with the **cobas**<sup>®</sup> EGFR Mutation Test v2. Of these, 231 test results were T790M mutation positive (60.3%), 139 test results were T790M negative (36.3%), and 13 test results were invalid (3.4% invalid rate). Of 383 specimens tested with NGS, 261 were T790M mutation positive (68.2%), 118 were T790M negative (30.8%), and 4 were invalid (1.0%).

Agreement was determined between the two **cobas**<sup>®</sup> EGFR Mutation Test versions which is shown in Table 11. Additionally a three-way comparison

table (Table 12) shows the results between the two **cobas**<sup>®</sup> EGFR Mutation Test versions and the NGS reference method.

**Table 11. cobas<sup>®</sup> EGFR Mutation Test v1 vs. v2 Using AURA2 Specimens**

		cobas <sup>®</sup> EGFR Mutation Test v1 (CTA)			
		Exon T790M Deletion			
		MD	MND	Invalid	Total
cobas <sup>®</sup> EGFR Mutation Test v2 Result	MD	225	5	1	231
	MND	8	131	0	139
	Invalid	0	4	9	13
	Total	233	140	10	383
Without Invalid Results	PPA (95% CI)	225/233 = 96.6% (93.4%, 98.3%)			
	NPA (95% CI)	131/136 = 96.3% (91.7%, 98.4%)			
	OPA (95% CI)	(225+131)/369 = 96.5% (94.1%, 97.9%)			
With Invalid Result	PPA (95% CI)	225/242 = 93% (89%, 95.6%)			
	NPA (95% CI)	131/150 = 87.3% (81.1%, 91.7%)			
	OPA (95% CI)	(225+131)/383 = 93% (89.9%, 95.1%)			

Note: Estimates with invalid results assume that the results invalid by both methods are discordant with the reference method (worst case scenario)

**Table 12. Three-way Summary of Results by cobas<sup>®</sup> EGFR Test v1, v2, and NGS**

cobas <sup>®</sup> EGFR Mutation Test Result (v1) <sup>1</sup>	cobas <sup>®</sup> EGFR Mutation Test Result (v2) <sup>1</sup>	NGS Result <sup>1</sup>			Total
		Mutation Detected	No Mutation Detected	Invalid	
		N = 261	N = 118	N = 4	
MD (n=233)	MD (n=225)	222	1	2	225
	NMD (n=8)	7	1	0	8
	Invalid (n=0)	0	0	0	0
NMD (n=140)	MD (n=5)	3	2	0	5
	NMD (n=131)	23	108	0	131
	Invalid (n=4)	1	3	0	4
Invalid (n=10)	MD (n=1)	1	0	0	1
	NMD (n=0)	0	0	0	0
	Invalid (n=9)	4	3	2	9

<sup>1</sup>Mutation Detected indicates the presence of EGFR T790M, as identified by the testing method.

No Mutation Detected indicates the absence of the EGFR T790M as identified by the testing method.

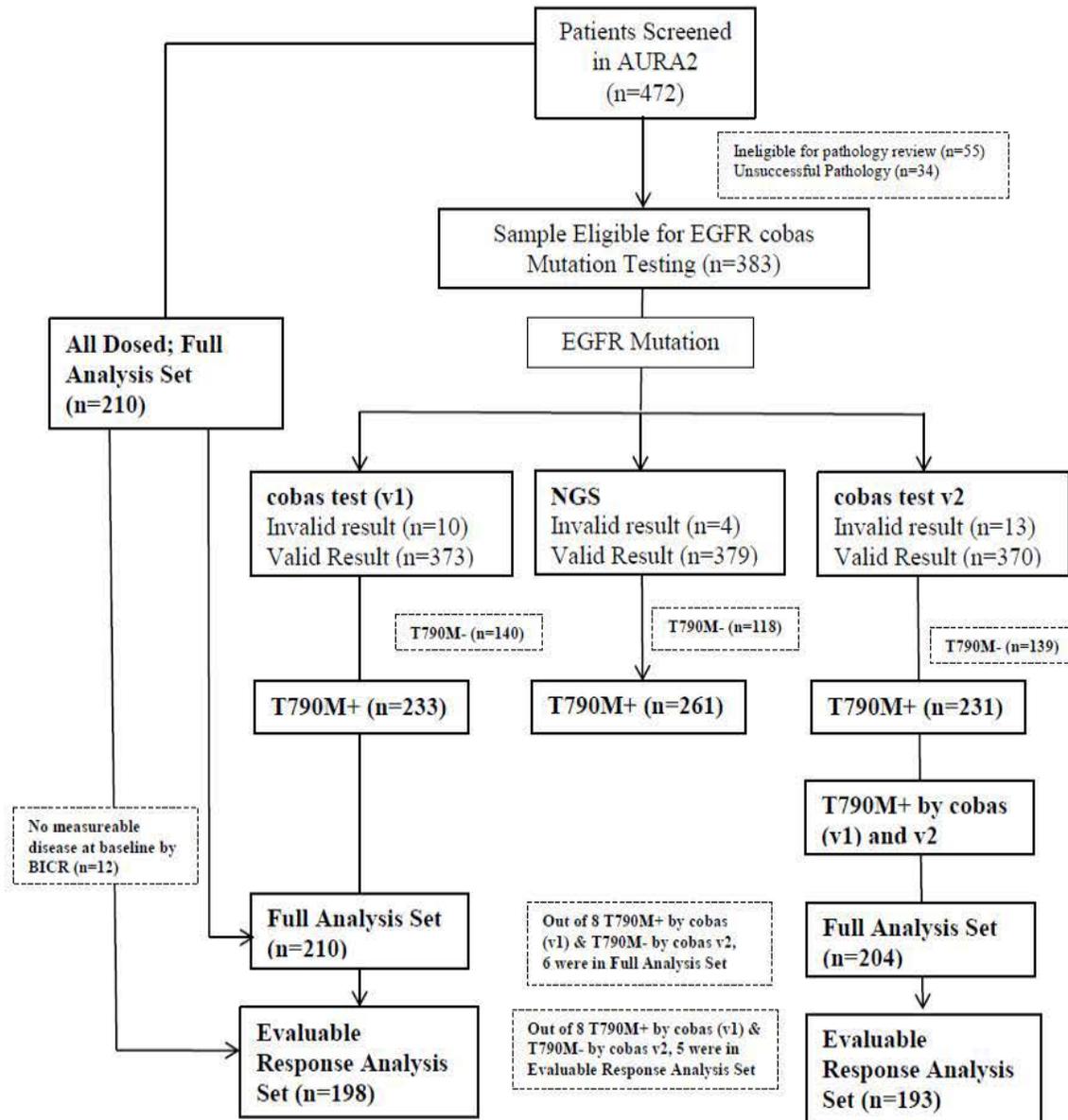
NGS = Next generation sequencing.

## **B. Accountability of the PMA Cohort**

The disposition of patients/specimens and test results are described in Figure 2. Briefly, of the 472 patients screened, 383 patients were eligible for testing with the **cobas**<sup>®</sup> EGFR Mutation Test (v1). Among the 383 patients, 233 T790M+ NSCLC patients were recruited for AURA2 to use Tagrisso<sup>®</sup> (osimertinib). The Full Analysis

Set (FAS) was defined as all T790M+ patients by the **cobas**<sup>®</sup> EGFR Mutation Test (v1) who received at least 1 dose of osimertinib (n = 210 patients).

**Figure 2 Patients/Specimens and Test Results Disposition**



AURA2 = AstraZeneca, Inc. Study D5160C00002; cobas test (v1) = cobas EGFR Mutation Test (v1); cobas v2 = cobas EGFR Mutation Test v2; BICR = blinded independent central review; EGFR = epidermal growth factor receptor; NGS = next generation sequencing.

**C. Study Population Demographics and Baseline Parameters**

The median age of the FAS was 64 years, included nearly twice as many females as males, and the majority of patients had metastatic disease. Justification for the acceptance of foreign data was included in the NDA 208065 submission. A summary

of patient demographic information and disease characteristics are shown in Tables 13 and 14, respectively.

**Table 13. Patient Demographics (AURA2)**

Demographic Characteristics		Second-line	≥ Third-line	Total
	N	68	142	210
Age (years)	Mean	64.0	62.4	62.9
	SD	11.76	10.48	10.91
	Median	64.5	63.5	64.0
	Min	36	35	35
	Max	88	84	88
Age group (years) n (%)	<50	5 (7.4)	15 (10.6)	20 (9.5)
	≥50 to <65	29 (42.6)	59 (41.5)	88 (41.9)
	≥65 to <75	20 (29.4)	49 (34.5)	69 (32.9)
	≥75	14 (20.6)	19 (13.4)	33 (15.7)
Sex n (%)	Male	24 (35.3)	40 (28.2)	64 (30.5)
	Female	44 (64.7)	102 (71.8)	146 (69.5)
Race n (%) <sup>a</sup>	White	26 (38.2)	46 (32.4)	72 (34.3)
	Black or African American	0	3 (2.1)	3 (1.4)
	Asian	39 (57.4)	93 (65.5)	132 (62.9)
	Native Hawaiian or other Pacific Islander	1 (1.5)	0	1 (0.5)
	Other	2 (2.9)	0	2 (1.0)
Ethnic group, n (%) <sup>b, c</sup>	Hispanic or Latino	2 (3.1)	3 (2.2)	5 (2.5)
	Asian (other than Chinese and Japanese)	17 (26.2)	18 (12.9)	35 (17.2)
	Chinese	12 (18.5)	39 (28.1)	51 (25.0)
	Japanese	10 (15.4)	36 (25.9)	46 (22.5)
	Other	24 (36.9)	43 (30.9)	67 (32.8)

<sup>a</sup> The category of “Other” is as collected on the eCRF; any race data missing on eCRFs was not reported as a category in summaries of RACE data.

<sup>b</sup> Caucasian ethnicity is not presented as it was not offered as a category in the eCRF.

<sup>c</sup> Six patients from the United States did not report an “ethnic population” for ethnicity summaries reported in this table (n=204/210); all 6 patients reported themselves as “non-Hispanic or Latino” and all also reported race as “white” in the eCRF.

Abbreviation: eCRF, electronic case report form. Source: CSR.

**Table 14. Disease Characteristics (AURA2)**

	Second-line (N= 68)	≥ Third-line (N = 142)	Total (N = 210)
EGFR mutations by <b>cobas</b> <sup>®</sup> central test <sup>a</sup>			
T790M	68 (100)	140 (98.6)	208 (99.0)
Ex19Del	45 (66.2)	92 (64.8)	137 (65.2)
L858R	20 (29.4)	47 (33.1)	67 (31.9)
G719X	2 (2.9)	2 (1.4)	4 (1.9)
S768I	1 (1.5)	2 (1.4)	3 (1.4)

	<b>Second-line (N= 68)</b>	<b>≥ Third-line (N = 142)</b>	<b>Total (N = 210)</b>
Ex20Ins	0	1 (0.7)	1 (0.5)
T790M only	1 (1.5)	0	1 (1.5)
<b>Overall disease classification</b>			
Metastatic <sup>b</sup>	64 (94.1)	134 (94.4)	198 (94.3)
Locally advanced only <sup>c</sup>	4 (5.9)	8 (5.6)	12 (5.7)
<b>WHO performance status</b>			
0 (normal activity)	29 (42.6)	54 (38.0)	83 (39.5)
1 (restricted activity)	39 (57.4)	88 (62.0)	127 (60.5)
<b>Baseline target lesion size, (mm)</b>			
N	62	136	198
Mean	52.6	63.3	59.9
SD	37.35	41.56	40.50
Median	44.4	55.7	50.5
Minimum	10	12	10
Maximum	208	218	218
<b>Baseline target lesion size category (mm), n (%)</b>			
<40	26 (38.2)	40 (28.2)	66 (31.4)
40 to 79	23 (33.8)	67 (47.2)	90 (42.9)
80 to 119	10 (14.7)	17 (12.0)	27 (12.9)
≥120	3 (4.4)	12 (8.5)	15 (7.1)
Brain metastases <sup>d</sup>	23 (33.8)	65 (45.8)	88 (41.9)
Visceral metastases <sup>e</sup>	53 (77.9)	115 (81.0)	168 (80.0)

<sup>a</sup> EGFR mutation identified by the central **cobas**<sup>®</sup> EGFR Mutation Test v1 (by biopsy taken after confirmation of disease progression on the most recent treatment regimen).

<sup>b</sup> Metastatic disease (patient had any metastatic site of disease).

<sup>c</sup> Locally advanced (patient had only locally advanced sites of disease).

<sup>d</sup> Brain metastases (patients with metastatic site of brain and/or those that reported radiotherapy in anatomical locations unequivocally in the brain and/or those that reported surgical excision of tumor from anatomical locations unequivocally in the brain).

<sup>e</sup> Visceral metastases (patients in whom the metastatic or locally advanced site was “Brain” or “Hepatic”, those where the metastatic site was “Lymph nodes” and/or those that had specified ‘other sites’ such as stomach, spleen, peritoneum, ascites, renal or adrenal).

Abbreviations: EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; WHO, World Health Organization

Prevalence information of different EGFR mutations as well as T790M co-mutations identified from the AURA2 study by the **cobas**<sup>®</sup> EGFR Mutation Test v2 are shown in the Table 15.

**Table 15. Prevalence of Different EGFR Mutations and Co-Mutations with T790M by cobas<sup>®</sup> EGFR Mutation Test v2 in AURA 2**

<b>Mutation</b>	<b>N (%)</b>	<b>Co-Mutation with T790M</b>	
		<b>Co-Mutation</b>	<b>N (%)</b>
G719X	8 (2.27%)		

Mutation	N (%)	Co-Mutation with T790M	
		Co-Mutation	N (%)
Ex19Del	56 (15.86%)		
Ex19Del; S768I; T790M	1 (0.28%)	Ex. 19del	147 (63.64%)
Ex19Del; T790M	144 (40.79%)		
<i>Ex19Del; T790M; Ex20Ins</i>	2 (0.57%)		
L858R	54 (15.30%)		
L858R; G719X	1 (0.28%)		
L858R; T790M	74 (20.96%)	L858R	77 (33.33%)
<i>L858R; T790M; Ex20Ins</i>	2 (0.57%)		
L858R; T790M; S768I	1 (0.28%)		
Ex. 19del; L858R; T790M	1 (0.28%)	Ex. 19del and L858R	1 (0.43%)
S768I	2 (0.57%)		
S768I; G719X	1 (0.28%)		
S768I; T790M; G719X	1 (0.28%)	S768I/G719X/L861Q	4 (1.73%)
T790M; G719X	2 (0.57%)		
T790M; L861Q; G719X	1 (0.28%)		
T790M	2 (0.57%)	T790M only	2 (0.87%)
Total	353		231

Italicized text indicates change in the number of Ex20Ins from the original 12 after cut-off recalculation.

## D. Safety and Effectiveness Results

### 1. Safety Results

The safety with respect to treatment with Tagrisso<sup>®</sup> (osimertinib) will not be addressed in details in the SSED for the **cobas**<sup>®</sup> EGFR Mutation Test v2. At the initial data cut-off date (DCO) of January 9, 2015 the majority of patients [87.1% (183/210) of patients] continued to receive treatment. At the time of the 90-day safety update (May 1, 2015), no patient had been exposed to osimertinib for longer than 12 months. Adverse reactions (ARs) were reported in 95.2% (200/210) of patients in the study and a total of 79.0% (166/210) of patients had ARs considered by the investigator to be possibly causally related to osimertinib, with the majority of AEs being CTCAE grade 1 or 2. Less than 20% were reported to be grade 3 or above. Patients who experienced a CTCAE grade 3 and/or unacceptable toxicity of any grade that was not attributable to their disease or disease-related processes under investigation and where the investigator considered the AR to be specifically associated with the study treatment, their dosing was to be interrupted. For patients whose AR did not resolve within the three weeks specified by the study protocol or who exhibited corneal ulcerations were permanently withdrawn from the study. In a later update, interstitial lung disease (ILD) was added as a reason for permanent withdrawal.

The most frequent treatment-emergent ARs on osimertinib were diarrhea, rash, dry skin, and nail toxicity. The most frequent fatal ARs were pneumonitis/ILD and pneumonia, which led to the deaths of four patients while on study.

Pneumonia, pulmonary embolism, pneumonitis and abdominal pain were the most common non-fatal serious adverse event occurring in patients. Refer to the drug label for more information.

## 2. Effectiveness Results

An open label, single arm Phase II study, AURA2, was performed to investigate the efficacy of osimertinib by assessment of objective response rate (ORR) by Blinded Independent Central Review (BICR) in patients with a confirmed diagnosis of EGFR mutation positive metastatic NSCLC who had progressed following prior therapy with an approved EGFR TKI agent and whose tumors are positive of the EGFR T790M resistance mutation. The study was submitted to support accelerated approval of osimertinib in a second line or greater setting.

A bridging study was performed to establish effectiveness of the **cobas**<sup>®</sup> EGFR Mutation Test v2 through retrospective testing of all patient specimens which were enrolled into the trial with an IUO version of the test approved under P120019 (**cobas**<sup>®</sup> EGFR Mutation Test v1).

Of the 472 patients screened for the AURA2 study, 383 patients were eligible for testing with the **cobas**<sup>®</sup> EGFR Mutation Test v1. Of those eligible, 233 T790M+ patients were recruited into the AURA2 study, and 210 patients were enrolled and received osimertinib. Table 16 presents the ORR by BICR and investigator assessment in AURA2. Of 198 patients who received at least one dose of osimertinib and had measurable disease confirmed by BICR [Evaluable Response Analysis Set (ERAS)], 127 were confirmed responders by BICR with ORR as 64.1% (95% CI: 57.0%, 70.8%).

Of 210 patients who received at least 1 dose of osimertinib (FAS), 128 were confirmed responders by BICR with ORR as 61.0% (95% CI: 54.0%, 67.6%) and 135 by investigator assessment with ORR as 64.3% (95% CI: 57.4%, 70.8%).

All 383 patients eligible for AURA2 trial, were retested by the **cobas**<sup>®</sup> EGFR Mutation Test v2. Of 233 T790M positive patients recruited into the AURA 2 trial, 225 were T790M+ by the **cobas**<sup>®</sup> EGFR Mutation Test and 204 were in the FAS. Of 204 patients who received at least one dose of Tagrisso<sup>®</sup>, 193 ERAS had measurable disease confirmed by BICR (ERAS). Of 193 patients, 126 were confirmed responders by BICR with ORR as 65.3% (95% CI: 58.1% to 72.0%).

Of 204 patients who received osimertinib (FAS), 126 were confirmed responders by BICR with ORR as 62.3% (95% CI: 55.2% to 68.9%) and 133 by investigator assessment with ORR as 65.2% (95% CI: 58.2% to 71.7%). These data are also included in Table 16.

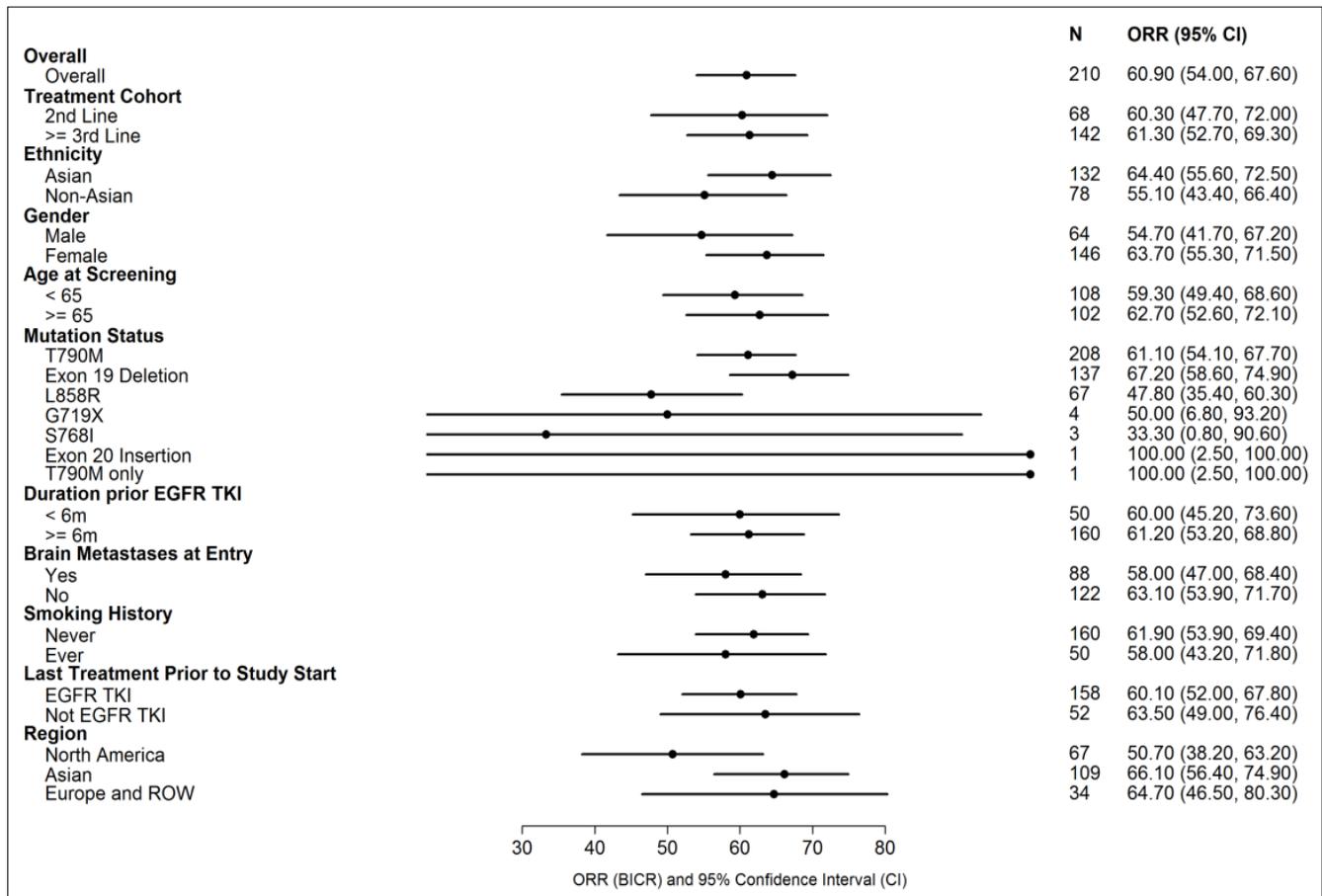
**Table 16. Clinical Benefit of T790M Mutation Positive Patients Tested with the cobas® EGFR Mutation Test v2 in the AURA2 Trial**

Analysis Set	Assessed by	AURA 2			cobas® EGFR Mutation Test v2 T790M Positive		
		N	Number of Confirmed Responders	ORR (95% CI)	N	Number of Confirmed Responders	ORR (95% CI)
FAS	BICR	210	128	61.0% (54.0%, 67.6%)	204	127	62.3% (55.2%, 68.9%)
	Investigator		135	64.3% (57.4%, 70.8%)		133	65.2% (58.2%, 71.1%)

3. Subgroup Analysis

The results of the AURA2 study are based on the cobas® EGFR Mutation Test v1 results. A subgroup analysis was performed which demonstrates the effectiveness of osimertinib in patients whose tumors are positive for the EGFR T790M resistance mutation and is depicted in the Figure 3.

**Figure 3. Subgroup analyses per BICR assessment for AURA2**



## **E. Financial Disclosure**

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

## **XI. PANEL MEETING RECOMMENATION AND FDA'S POST-PANEL ACTION**

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Molecular and Clinical Genetics Panel of Medical Devices, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

## **XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES**

### **A. Effectiveness Conclusions**

The clinical benefit of the **cobas**<sup>®</sup> EGFR Mutation Test v2 was demonstrated in retrospective analyses of patients enrolled in the Phase II AURA2 study for osimertinib. Analytical performance studies with the **cobas**<sup>®</sup> EGFR Mutation Test v2, when used according to the directions provided, demonstrate the ability to detect the T790M mutation with an analytical sensitivity of 3% mutation in DNA extracted from FFPE tissue of patients with advanced non-small cell lung cancer (NSCLC).

The safety and effectiveness of Tagrisso<sup>®</sup> (osimertinib) has not been established in patients whose tumors have G719X, exon 19 deletions, S768I, exon 20 insertions, L858R, or L861Q mutations which are also detected by the **cobas**<sup>®</sup> EGFR Mutation Test v2.

### **B. Safety Conclusions**

The adverse effects of the device are based on data collected in the clinical study conducted to support PMA approval as described above. As a diagnostic test, the **cobas**<sup>®</sup> EGFR Mutation Test v2 involves testing on formalin-fixed, paraffin embedded human NSCLC cancer tissue sections. The risks of the **cobas**<sup>®</sup> EGFR Mutation Test are associated with the potential mismanagement of patients resulting from false results of the test. Failure of the device to perform as expected or failure to correctly interpret test results may lead to incorrect EGFR test results, and consequently improper patient management decisions in NSCLC treatment. A patient with a false positive result may undergo treatment with osimertinib with inappropriate expectation of therapeutic benefit and experience side effects. A patient with a false

negative result may be treated without osimertinib and not experience the potential therapeutic benefit.

### **C. Benefit-Risk Conclusions**

The probable benefits of the device are based on data collected in the AURA2 study, which were used to support PMA approval as described above. The clinical benefit of the **cobas**<sup>®</sup> EGFR Mutation Test v2 was demonstrated in a retrospective analysis of efficacy and safety data obtained from an open-label, single arm study in which Tagrisso<sup>®</sup> (osimertinib) demonstrated a robust objective response rate of 62.3% (95% CI, 55.2%, 68.9%) in the full analysis set based on blinded independent central review (BICR) and the 65.3% (95% CI, 58.1%, 72.0%) in the subset of patient who had measurable disease confirmed by BICR.

The risks of the **cobas**<sup>®</sup> EGFR Mutation Test v2 are associated with the potential mismanagement of patients resulting from erroneous test results. The device is a key part of diagnostic evaluation for non-small cell lung cancer in decisions regarding treatment with erlotinib and osimertinib. There is currently no FDA approved test for the selection of candidate metastatic NSCLC patients for treatment with osimertinib.

In conclusion, given the available information above, the data support the use of the **cobas**<sup>®</sup> EGFR Mutation Test v2 as an aid in selecting NSCLC patients for osimertinib treatment based on a **cobas**<sup>®</sup> EGFR Mutation Test v2 “Mutation Detected” result for the EGFR T790M mutation, and the probable benefits outweigh the probable risks.

### **D. Overall Conclusions**

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Data from the Phase II AURA2 clinical study support the utility of the **cobas**<sup>®</sup> EGFR Mutation Test v2 as an aid in selecting patients with advanced NSCLC for whom Tagrisso<sup>®</sup> (osimertinib), an EGFR tyrosine kinase inhibitor (TKI), is indicated. Tagrisso<sup>®</sup> (osimertinib) demonstrated an objective response rate that appears to be robust and of a magnitude to reasonably predict clinical benefit for osimertinib in patients identified with the **cobas**<sup>®</sup> EGFR Mutation Test v2.

## **XIII. CDRH DECISION**

CDRH issued an approval order on November 13, 2015.

The applicant’s manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## **XIV. APPROVAL SPECIFICATIONS**

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Limitations in the device labeling. Refer to the drug label for Tagrisso<sup>®</sup> (osimertinib) for additional information related to use of the drug.

Post-approval Requirements and Restrictions: See approval order.

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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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KAREN E BIJWAARD

11/12/2015

Official consult memo for CDx device



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

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Food and Drug Administration  
Office of New Drugs, Office of Drug  
Evaluation IV  
Division of Pediatric and Maternal Health  
Silver Spring, MD 20993  
Telephone 301-796-2200  
FAX 301-796-9744

**Division of Pediatric and Maternal Health Review**

**Date:** November 3, 2015    **Consult Received:** June 22, 2015

**From:** Carol H. Kasten, MD, Medical Officer  
Division of Pediatric and Maternal Health, Maternal Health Team  
Office of Drug Evaluation IV (ODE IV)

**Through:** Tamara Johnson, MD, MS, Acting Team Leader  
Maternal Health Team  
Division of Pediatric and Maternal Health, ODE IV

Lynne P. Yao, MD, Director  
Division of Pediatric and Maternal Health, ODE IV

**To:** Division of Oncology Products 2

**Drug:** Tagrisso (osimertinib), NDA 208-065, IND 117-879

**Proposed Indication:** Indicated for the treatment of patients with [REDACTED] (b) (4) metastatic epidermal growth factor receptor (EGFR) T790M mutation-positive non-small cell lung cancer, as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy.

**Sponsor:** AstraZeneca Pharmaceuticals, Inc.

**Subject:** Labeling review

**Consult Request:** Labeling recommendations in compliance with PLLR

**Documents Reviewed:**

- AstraZeneca Patient Risk Management Plan (PRMP) Part II. Data lock January 9, 2015. Module II: Non-Clinical Part of the Safety Specification

- AstraZeneca Response to Information Request, Drug substance: AZD9291, Dated: August 6, 2015

## INTRODUCTION

This original NDA was received from AstraZeneca Pharmaceuticals on June 5, 2015, for Tagrisso (osimertinib), a New Molecular Entity (NME) [REDACTED] (b) (4) Kinase Inhibitor (TKI) drug class. The sponsor's proposed indication is, "for the treatment of patients with [REDACTED] (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 tyrosine kinase inhibitor therapy." The Division of Oncology Products 2 (DOP2) consulted the Division of Pediatric and Maternal Health Staff - Maternal Health Team (DPMH-MHT) to review and provide labeling recommendations for all subsections appropriate for a TKI drug product.

## BACKGROUND

The regulatory history for osimertinib is summarized below.

June 11, 2013	Investigational New Drug (IND) submitted
April 16, 2014	Breakthrough Therapy designation granted
June 5, 2015	Original NDA submission
July 1, 2014	Orphan Drug Designation granted for treatment of EGFR-mutation positive NSCLC
August 4, 2015	Priority Review with an early action reported in 74-Day Filing Letter
February 5, 2016	PDUFA Goal Date

As part of the 74-Day Filing Letter, a DPMH-MHT information request (IR) was included which stated,

*Provide the rationale to support the recommended pregnancy testing and the duration of contraception use proposed in subsection (8.3) Females and Males of Reproductive Potential of the osimertinib full package Insert (FPI).*

The applicant responded on August 14, 2015, and the information is discussed with the labeling recommendations for (8.3) Females and Males of Reproductive Potential.

### Non-Small Cell Lung Cancer (NSCLC)

The leading cause of cancer-related deaths in the U.S. is lung cancer. In 2015, more than 200,000 people will be diagnosed and more than 150,000 will die from either small cell or NSCLC.<sup>1</sup> NSCLC originates in the epithelia of the lungs from the central bronchus to the terminal alveoli. There are three main histological subtypes of NSCLC, squamous cell and large cell carcinomas and adenocarcinoma, the last subtype comprising more

<sup>1</sup> National Cancer Institute (NCI), NIH, Physician Data Query (PDQ) for health professionals, accessed October, 2015, <http://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq>

than half of NSCLC cases.<sup>2</sup> Characterization of NSCLC by genotype has advanced treatment options for some patients. Between 5% and 15% of adenocarcinomas have EGFR mutations while less than 5% of squamous cell tumors harbor them.<sup>3</sup> There are also other genomic changes including the EML4-ALK fusion oncogene,<sup>4</sup> and point mutations in HER2, BRAF, KRAS, PIK3CA, AKT1, MAP2K1 and MET that have all been found in some of NSCLC tumors. Each may respond differently to a particular drug.

The most common NSCLC activating mutations currently known occur in the TK domain of the EGFR gene, producing a deletion of exon 19 or a point mutation of leucine to arginine (L858R) in exon 21.<sup>5</sup> Tumor resistance to the first (gefitinib, erlotinib) and second generation TKIs (afatinib) has been demonstrated.<sup>6</sup> One of the TKI resistance conferring mutations is the threonine to methionine substitution (T790M) in exon 20. Osimertinib is intended to treat NSCLC tumors with both the activating mutations (exon 19 deletion, exon 21 L858R mutation) and the resistance conferring exon 20 (T790M) mutation.

### **Osimertinib Drug Product**

The anti-tumor mechanism of action for osimertinib derives from its ability to prevent phosphorylation of the EGFR protein on tumor cells which have the exon 19 deletion, and the exon 21 (L858R) and exon 20 (T790M) point mutations. The drug is less active against the normal, wild-type EGFR protein. By inhibiting mutant EGFR phosphorylation, the rate of growth of NCSLC tumors is reduced.<sup>7</sup> Based on non-clinical data, osimertinib is not genotoxic<sup>8,9</sup> and has a terminal half-life of 48 hours.

### **Published Literature and Toxicology Database Reviews**

As an NME, there are no publications regarding use of osimertinib in pregnant women. There are also no reviews of osimertinib in the reproductive toxicology databases; however, these databases have reviewed prenatal exposures to erlotinib, another TK1 drug product. With the caveat that erlotinib is not the same drug as osimertinib, a database review of erlotinib is included here. The Reprotox<sup>10</sup> review indicates that based on animal data, erlotinib is not expected to increase the risk of teratogenesis although embryofetal deaths were reported. The Reprotox review suggests that the increased incidence of embryofetal deaths reported with erlotinib may have been caused by

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<sup>2</sup> Pao W, Girard N. New driver mutations in non-small-cell lung cancer, *Lancet Oncol* 2011;12:175–80.

<sup>3</sup> See Pao, *et al.*

<sup>4</sup> Shaw A, Solomon B Anaplastic lymphoma kinase (ALK) fusion oncogene positive NSCLC. [www.Uptodate.com](http://www.Uptodate.com) 2015. Accessed Oct 12, 2015.

<sup>5</sup> Steuer C, Khuri F, Ramalingam S. The Next Generation of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in the Treatment of Lung Cancer, *Cancer* 2015;121:E1-E6, DOI: 10.1002/cncr.29139.

<sup>6</sup> See Steurer, *et al.*

<sup>7</sup> Osimertinib labeling, subsection 12.1 Mechanism of Action

<sup>8</sup> Non-Clinical Pharmacology Toxicology Primary Review Shawna L. Weis, PhD, DOP2, Dated October 8, 2015. DARRTS Reference ID: 3831295.

<sup>9</sup> Supervisory Non-Clinical Pharmacology Toxicology Review, Whitney Helms, PhD, Author, Dated October 8, 2015. DARRTS Reference ID: 3831318.

<sup>10</sup> Reprotox® Website: [www.Reprotox.org](http://www.Reprotox.org). REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed October 12, 2015.

maternal toxicity; of concern is that embryofetal deaths were also reported with osimertinib in the absence of maternal toxicity. Therefore, there is a risk of embryofetal death with prenatal exposure to osimertinib. Erlotinib and osimertinib are different drugs and therefore, the ReproTox review of erlotinib may not be useful for comparison.

## **DISCUSSION**

On December 4, 2014, the Food and Drug Administration (FDA) announced the publication of the “Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling,”<sup>11</sup> also known as the Pregnancy and Lactation Labeling Rule (PLLR). The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and creates a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format will be required for all products that are subject to the 2006 Physicians Labeling Rule<sup>12</sup> format to include information about the risks and benefits of using these products during pregnancy and lactation.

### **Labeling Recommendations: Pregnancy and Lactation**

There are no data on the effects of osimertinib exposures in pregnant women. The rat embryofetal study demonstrated embryoletality when osimertinib was administered prior to implantation and reduced fetal growth when administered during organogenesis. In studies that continued osimertinib administration throughout gestation to early lactation, neonatal deaths were observed. Based on the animal data, there may be a risk of embryofetal toxicity in pregnant women exposed to osimertinib.

There have been no lactation studies with osimertinib to guide a labeling recommendation for lactating women treated with osimertinib. The pre- and postnatal rat study demonstrated neonatal deaths during early lactation. It isn't known if this was secondary to prenatal osimertinib exposure or to adverse effects from the osimertinib administered to the nursing animals. Based on these animal data and the serious adverse events reported in preclinical trials with osimertinib, there may be an adverse effect on the infant if the breastfeeding woman is being treated with osimertinib. Therefore, lactating women should not breastfeed while they are being treated with osimertinib and for 2 weeks following the final dose. The duration of two weeks to avoid breastfeeding is based on six times the drug half-life, at which point the drug concentration in the systemic circulation is expected to be exceedingly low.

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<sup>11</sup> *Content and Format of Labeling for Human Prescription Drug and Biological Products, Requirements for Pregnancy and Lactation Labeling* (79 FR 72063, December 4, 2014).

<sup>12</sup> *Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products*, published in the Federal Register (71 FR 3922; January 24, 2006).

## **Labeling Recommendations: Females and Males of Reproductive Potential** Applicant Response to DOP2-DPMH Information Request<sup>13</sup>

The applicant stated that their recommendations for duration of conception following the final drug dose were based on the (a) pharmacokinetics of osimertinib, and (b) the time thought to be necessary to permit reproductive organ recovery for females and males of reproductive potential. Specifically, the “PK washout period” for osimertinib was identified as 15 days and is equivalent to at least 6 half-lives. The applicant calculated this duration would allow drug levels to fall below the exposures seen at the NOEL/NOAEL<sup>14</sup> for animal reproductive findings.

In repeat dose toxicology studies with female rats, degeneration of corpora lutea and anestrus were observed at one and three months of chronic exposure. In male rats, degeneration of the seminiferous tubules and/or spermatid retention were observed as was reduced fertility at one and three months of chronic exposure. The reduced fertility appeared to have been the result of an increased incidence of preimplantation embryo loss observed in treated males rats mated to untreated females at dose exposures half that expected with the recommended human dose. The mechanism for this apparent reduced fertility in male rats was not elucidated.<sup>15,16</sup>

Following discontinuation of the drug, the pathologic reproductive tract findings were minimal for both sexes of rat, suggesting that given sufficient time off drug, the infertility observed would be expected to be reversible; however, complete reversal of the reproductive organ damage was not observed. The applicant did not provide any data on the presence of the drug in human semen.

The applicant’s recommendations for contraception are:

- Females of reproductive potential should use contraception for 6 weeks after the final dose of osimertinib which provides 15 days for the drug washout period plus approximately four weeks for completion of one menstrual cycle.
- Males should use contraception for (b) (4) after the final dose of osimertinib which provides 15 days for drug washout plus three months for completion of an entire spermatogenic cycle.

### *Reviewer’s comment:*

*Following discussion with our DOP2 Pharmacology Toxicology colleagues, DPMH agrees with the Division’s decision to use six weeks of contraception for women of reproductive potential and four months of contraception for men of reproductive potential following their final osimertinib dose.*

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<sup>13</sup> AstraZeneca Response Document, Drug substance: AZD9291, Response to Agency information request dated 05 August 2015, Rationale for recommended pregnancy testing and duration of contraception. Cover letter dated August 17, 2015, Sequence No. 0027, Jonathan Jazayeri, PharmD, MS, RAC, Regulatory Affairs Director.

<sup>14</sup> No observed effect level (NOEL), No observed adverse effect level (NOAEL).

<sup>15</sup> See Non-Clinical Pharmacology Toxicology Primary Review, DARRTS Reference ID: 3831295.

<sup>16</sup> See Supervisory Non-Clinical Pharmacology Toxicology Review, DARRTS Reference ID: 3831318.

DPMH attended meetings with DOP2 during August, September and October of 2015.

## CONCLUSIONS

- Osimertinib poses a risk of embryofetal harm (reduced fetal growth) or embryofetal death if a woman is exposed during pregnancy.
- Based on the serious adverse events reported with osimertinib, a lactating woman should not breastfeed during treatment with osimertinib and for two weeks after treatment has ended.
- Both women and men of reproductive potential should use contraception during treatment with osimertinib.
  - Women should continue to use contraception until 6 weeks after their final dose.
  - Men should continue to use contraception until 4 months after their final dose.

## RECOMMENDATIONS

The following are the DPMH Maternal Health Team recommendations for the proposed Tagrisso labeling.

## TAGRISSO

**Osimertinib 40 mg, 80 mg tablets**

## HIGHLIGHTS

### -----WARNINGS AND PRECAUTIONS-----

- Embryofetal Toxicity (b) (4) cause fetal harm. Advise females of potential risk to the fetus and to use effective contraception during treatment with TAGRISSO and for 6 weeks after final dose. (5.3, 8.1, 8.3)

### -----USE IN SPECIFIC POPULATIONS-----

Lactation: Do not breastfeed. (8.2)

(b) (4)

## FULL PRESCRIBING INFORMATION: CONTENTS\*

### 5 WARNINGS AND PRECAUTIONS

5.3 Embryofetal Toxicity

### 8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.3 Females and Males of Reproductive Potential

## FULL PRESCRIBING INFORMATION

### ----- INDICATIONS AND USAGE -----

TAGRISSO is indicated 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. (1)

## 5 WARNINGS AND PRECAUTIONS

### 5.3 Embryofetal Toxicity

Based on animal studies and its mechanism of action, TAGRISSO (b) (4) cause fetal harm when administered to a pregnant woman. In animal reproduction studies, osimertinib caused post-implantation fetal loss at a dose exposure 1.5 times the exposure at the recommended human dose. When males were treated prior to mating with untreated females, there was an increase in preimplantation embryonic loss at plasma exposures of approximately 0.5 times those observed in patients at the 80 mg dose level. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose. Advise males of reproductive potential to use effective contraception during treatment with TAGRISSO and for 4 months following their final dose [see *Use in Specific Populations* (8.1, 8.3) and *Clinical Pharmacology* (12.1, 12.3)].

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### *Risk Summary*

Based on animal studies and its mechanism of action TAGRISSO may cause fetal harm when administered to a pregnant woman [see *Clinical Pharmacology* (12.1)]. There are no available data on TAGRISSO use in pregnant women. Administration of osimertinib to pregnant rats (b) (4) was associated with embryolethality and reduced fetal growth at dose exposures 1.5 times the exposure at the recommended human dose [see *Data*]. Advise pregnant women of the potential risk to a fetus.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

#### *Data*

##### Animal Data

When administered to pregnant rats prior to embryonic implantation through the end of organogenesis (gestation days 2 to 20) at a dose of 20 mg/kg/day, which produced plasma exposures of approximately 1.5 times the clinical (b) (4), osimertinib caused post-implantation loss and early embryonic death. When administered from implantation through the closure of the hard palate, at doses of 1 mg/kg/day and above (0.1-times the

AUC observed in patients at the recommended dose of 80 mg), an equivocal increase in the rate of fetal malformations and variations was observed in treated litters relative to those of concurrent controls. When administered to pregnant dams at doses of 30 mg/kg/day during organogenesis through lactation Day 6, osimertinib caused an increase in including total litter loss and postnatal death. At a dose of 20 mg/kg/day, osimertinib administration during the same period resulted in increased postnatal death as well as a slight reduction in mean pup weight at birth that increased in magnitude between lactation days 4 and 6.

## 8.2 Lactation

### *Risk Summary*

There are no data on the presence of osimertinib in human milk or the effects of osimertinib on the breastfed infant or on milk production. Administration of osimertinib to rats during gestation and early lactation was associated with adverse effects, including reduced growth rates and neonatal death [*Use in Specific Populations (8.1)*]. Because of the potential for serious adverse reactions in breastfed infants from osimertinib, advise a lactating woman not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

## 8.3 Females and Males of Reproductive Potential

(b) (4)

### *Contraception*

#### Females

Advise females of reproductive potential to use effective contraception during treatment with TAGRISSO and for 6 weeks after the final dose [*see Use in Specific Populations (8.1)*].

#### Males

Advise male patients with female partners of reproductive potential to use effective contraception during and for 4 months following the final dose of TAGRISSO (b) (4)

(b) (4)

### *Infertility*

Based on animal studies, TAGRISSO may impair fertility in females and males of reproductive potential. It is not known if the effects on fertility are reversible [*see Nonclinical Toxicology (13.1)*].

## 17 PATIENT COUNSELING INFORMATION

(b) (4)

*Embryofetal Toxicity*

*[see Use in Specific Populations (8.1, 8.3)]*

- TAGRISSO may cause fetal harm if taken during pregnancy. Advise pregnant women of the potential risk to a fetus.
- [REDACTED] (b) (4)
- Advise females [REDACTED] (b) (4) to inform their healthcare provider if they become pregnant or if pregnancy is suspected, while taking TAGRISSO.
- [REDACTED] (b) (4)

*Lactation*

*[See Use in Specific Populations (8.2)]*

- Advise women not to breastfeed during treatment with TAGRISSO and for 2 weeks after the final dose.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

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/s/  
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CAROL H KASTEN  
11/03/2015

TAMARA N JOHNSON  
11/05/2015

LYNNE P YAO  
11/06/2015

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## MEMORANDUM

### REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

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**Date of This Memorandum:** November 5, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 208065  
**Product Name and Strength:** Tagrisso (osimertinib) Tablets, 40 mg and 80 mg  
**Submission Date:** October 22, 2015  
**Applicant/Sponsor Name:** AstraZeneca  
**OSE RCM #:** 2015-450-1  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

---

#### 1 PURPOSE OF MEMORANDUM

DOP2 requested that we review the revised container labels for Tagrisso (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.<sup>1</sup>

#### 2 CONCLUSION

The revised container label for the Tagrisso 80 mg tablet is acceptable from a medication error perspective. However, the revised container label for the Tagrisso 40 mg tablet is unacceptable from a medication error perspective. In our previous review we recommended that the Applicant not use sequential product codes (middle digits) as part of the National Drug Code as it is error-prone. In response, the Applicant proposed increasing the font size of the product code. We find this strategy acceptable. This change was made for the proposed 80 mg container label, but not for the proposed 40 mg container label.

<sup>1</sup> Townsend, O. Label and Labeling Review for Tagrisso (NDA 208065). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 SEP 08. 7 p. OSE RCM No.: 2015-450.

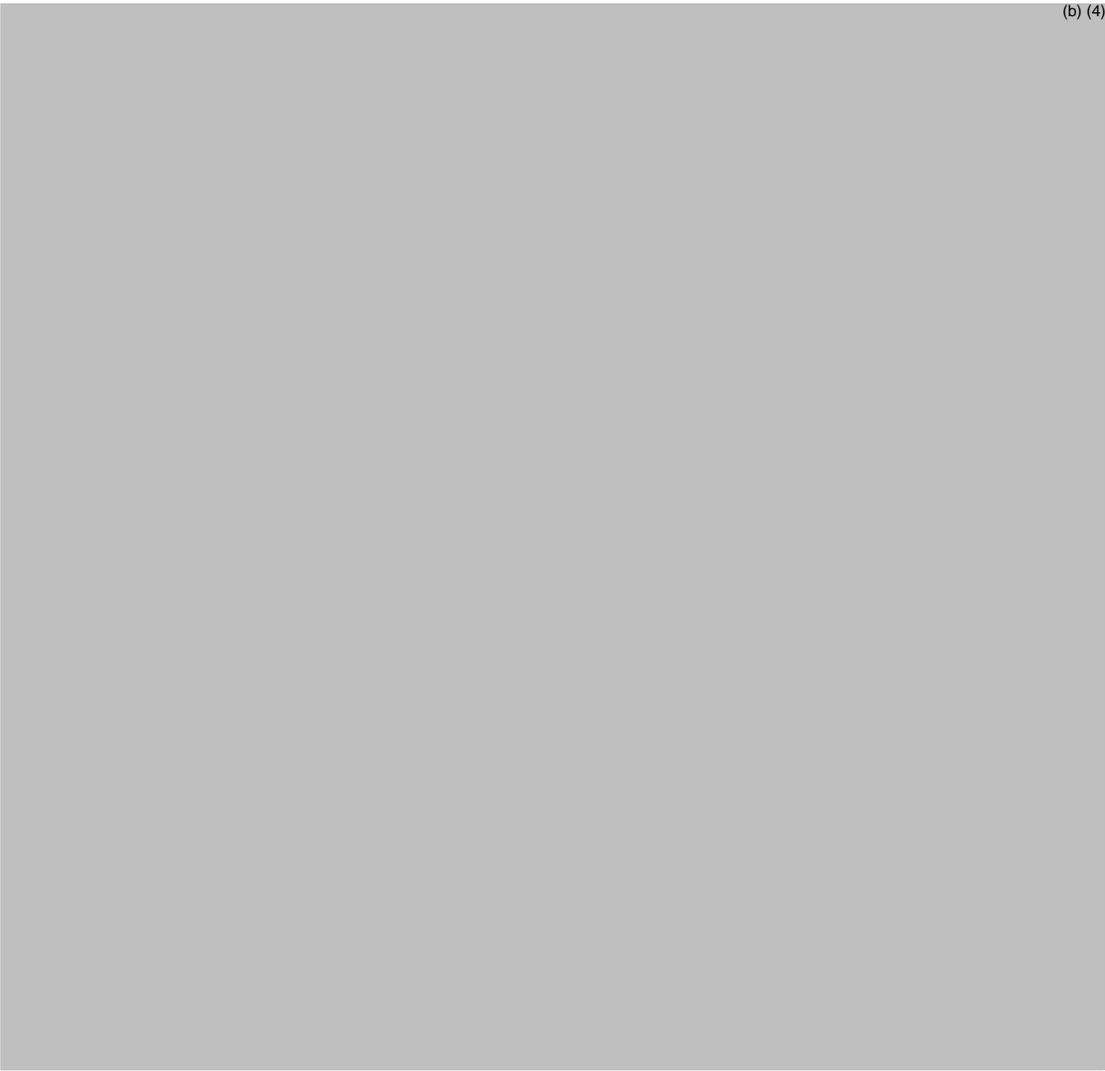
### **3 RECOMMENDATIONS FOR ASTRA ZENECA**

We recommend the following be implemented prior to approval of this NDA:

- A. In your October 22, 2015 Response Document, you proposed increasing the size of the four middle digits (product code) of the National Drug Code (NDC) on the Tagrisso container labels as a strategy to address the risk of confusion between the 40 mg and 80 mg tablets. We note you have incorporated this strategy in the proposed container label for the 80 mg product; however, we note this same strategy was not used for the proposed container label for the 40 mg product. Therefore, we request that you use the same size and style font used for the product code of the NDC for the proposed 80 mg container label to print the product code on the proposed 40 mg container label..

**APPENDIX A. LABEL AND LABELING SUBMITTED ON OCTOBER 22, 2015**

(b) (4)



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/s/  
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OTTO L TOWNSEND  
11/05/2015

CHI-MING TU  
11/05/2015

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion**

**\*\*\*\*Pre-decisional Agency Information**

**Memorandum**

**Date:** 10/28/15

**To:** Ingrid Fan  
Regulatory Project Manager  
Division of Oncology Products 2  
Office of Hematology and Oncology Products

**From:** Nazia Fatima, Pharm.D, MBA, RAC  
Regulatory Review Officer  
Office of Prescription Drug Promotion

**Subject:** Tagrisso (osimertinib) tablets  
**NDA 208065**

Office of Prescription Drug Promotion Comments on proposed labeling (PI)

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Office of Prescription Drug Promotion (OPDP) has reviewed the package insert (PI) for osimertinib as requested in a consult from Division of Oncology Products 2 (DOP2) dated June 15, 2015.

OPDP's review of the proposed PI is based on the substantially completed draft labeling titled, "NDA 208065 Osimertinib PI-PPI" sent via electronic mail on October 16, 2015 to OPDP (Nazia Fatima) from DOP2 (Ingrid Fan). OPDP's comments are provided directly on the marked-up version of the label attached below. Combined OPDP and Division of Medical Policy Programs (DMPP) comments on the proposed PPI were provided under a separate cover on October 27, 2015.

If you have any questions please feel free to contact me, Nazia Fatima at 240-402-5041 or at [Nazia.Fatima@fda.hhs.gov](mailto:Nazia.Fatima@fda.hhs.gov). Thank you! OPDP appreciates the opportunity to provide comments on these materials.

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/s/  
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NAZIA FATIMA  
10/28/2015

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Medical Policy**

**PATIENT LABELING REVIEW**

Date: October 27, 2015

To: Patricia Keegan, MD  
Director  
**Division of Oncology Products 2 (DOP2)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN  
Associate Director for Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

Barbara Fuller, RN, MSN, CWOCN  
Team Leader, Patient Labeling  
**Division of Medical Policy Programs (DMPP)**

From: Nathan Caulk, MS, BSN, RN  
Patient Labeling Reviewer  
**Division of Medical Policy Programs (DMPP)**

Nazia Fatima, Pharm.D, MBA, RAC  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Patient Package Insert (PPI)

Drug Name (established name): TAGRISSO (osimertinib)

Dosage Form and Route: tablets, for oral use

Application Type/Number: NDA 208065

Applicant: AstraZeneca Pharmaceuticals LP

## 1 INTRODUCTION

On June 5, 2015, AstraZeneca Pharmaceuticals LP submitted for the Agency's review the final portion of a rolling submission for an original New Drug Application (NDA) 208065 for TAGRISSO (osimertinib) tablets indicated 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.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Oncology Products 2 (DOP2) on June 15, 2015, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) for TAGRISSO (osimertinib) tablets.

## 2 MATERIAL REVIEWED

- Draft TAGRISSO (osimertinib) tablets PPI received on June 5, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 16, 2015.
- Draft TAGRISSO (osimertinib) tablets Prescribing Information (PI) received on June 5, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on October 16, 2015.
- Approved IRESSA (gefitinib) comparator labeling dated July 13, 2015.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> grade reading level. In our review of the PPI the target reading level is at or below an 8<sup>th</sup> grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We have reformatted the PPI document using the Arial font, size 10.

In our collaborative review of the PPI we have:

- simplified wording and clarified concepts where possible
- ensured that the PPI is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the PPI is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The PPI is acceptable with our recommended changes.

#### **5 RECOMMENDATIONS**

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI.

Please let us know if you have any questions.

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/s/  
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NATHAN P CAULK  
10/27/2015

NAZIA FATIMA  
10/27/2015

BARBARA A FULLER  
10/27/2015

LASHAWN M GRIFFITHS  
10/27/2015

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

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**CLINICAL INSPECTION SUMMARY**

DATE: October 6, 2015

TO: Ingrid Fan, Regulatory Project Manager  
Sean Khozin, M.D., M.P.H., Medical Reviewer  
Division of Oncology Products 2

FROM: Lauren Iacono-Connors, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

THROUGH: Susan D. Thompson, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.  
Branch Chief  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: #208065

APPLICANT: AstraZeneca Pharmaceuticals, LP.

DRUG: Tagrisso (AZD 9291)

NME: Yes

THERAPEUTIC CLASSIFICATION: Priority

INDICATION: Treatment for patients with (b) (4) metastatic Epidermal Growth Factor Receptor (EGFR) T790M mutation-positive non-small cell lung cancer (NSCLC) who have received prior EGFR TKI therapy.

CONSULTATION REQUEST DATE: June 11, 2015  
INSPECTION SUMMARY GOAL DATE: October 9, 2015  
DIVISION ACTION GOAL DATE: November 15, 2015  
PDUFA DATE: February 5, 2016

## I. BACKGROUND:

AstraZeneca Pharmaceuticals, LP seeks approval to market Tagrisso (AZD 9291) 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 tyrosine kinase inhibitor (TKI) therapy. AZD9291 is a potent irreversible inhibitor of both EGFR<sup>m+</sup> (TKI-sensitivity conferring mutations) and T790M<sup>+</sup> (TKI-resistance conferring mutation) receptor forms of EGFR.

Study D5160C00001 (AURA) and Study D5160C00002 are the two key studies supporting this application. Each required a mandatory biopsy for central testing of EGFR T790M mutation status following confirmed disease progression on the most recent treatment regimen for enrollment.

Study D5160C00001 (AURA) is a Phase I/II, open-label, multicenter study of AZD9291 administered orally in patients with advanced non-small cell lung cancer (NSCLC) who had progressed on or after therapy with an epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) agent (with or without additional anti-cancer regimens). The AURA study consisted of 3 components: the dose escalation and dose expansion components in the Phase I part of the study and the Phase II extension component with the tablet formulation at the recommended Phase II 80 mg once daily dose in patients with a centrally confirmed tumor positive for the TKI-resistance conferring mutation T790M (EGFR T790M mutation positive). Of the 401 patients screened, 201 patients received treatment in 40 centers in 10 countries.

Study D5160C00002 (AURA2) is a Phase II, open-label, single-arm study, assessing the safety and efficacy of AZD9291 in patients with a confirmed diagnosis of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-sensitising mutation (EGFR<sup>m</sup>) locally advanced or metastatic non-small cell lung cancer (NSCLC) (Stage IIIB-IV), who had progressed following prior therapy with an approved EGFR TKI agent. The study was designed to include approximately 175 patients overall, approximately 50 patients in the second-line therapy cohort and approximately 125 patients in the  $\geq$  third-line therapy cohort. Of the 472 patients screened, 210 patients received treatment in 44 centers in 8 countries.

For both Study D5160C0001C (Phase II Extension Study) and Study D5160C00002, the primary efficacy endpoint was the Objective Response Rate (ORR), defined as the percentage of subjects with at least one visit response of complete response (CR) or partial response (PR), per RECIST1.1, that was confirmed at least 4 weeks later (i.e., a best objective response [BOR] of CR or PR). Data obtained up until progression, or the last evaluable assessment in the absence of progression, were included in the assessment of ORR.

Study D5160C0001C (Phase II Extension Study) and Study D5160C00002 used an Independent Central Review (ICR) of protocol-specified imaging, conducted by CRO (b) (4) for determination of tumor response per RECIST1.1. Tumor response data from the ICR was used to derive the primary efficacy endpoint variable of ORR for all subjects in Study D5160C0001C (Phase II Extension Study) and Study D5160C00002.

Two clinical sites were chosen for inspection: Site 7800 (Dr. Pasi Janne, Boston, MA) for Study D5160C0001C (Phase II Extension Study) and Site 7401 (Dr. Chung-Ming Tsai, Taipei, Taiwan) for Study D5160C00002. These 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. The sponsor and one study CRO (IRC Vendor), (b) (4) were also inspected.

## II. RESULTS (by Site):

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
<b>CI#1: Janne, Pasi</b> Dana Farber Cancer Institute 450 Brookline Ave Boston, MA 2115	Protocol: D5160C0001C (Phase II extension component)  Site Number: 7800  Number of Subjects: 18	August 3-7, 2015	Pending  Interim classification: NAI
<b>CI#2: Tsai, Chun-Ming</b> Taipei, Veterans General Hosp., Chest No. 201, Sec. 2, Shih-Pai Rd. Taipei, Fujian 112 Taiwan	Protocol: D5160C00002  Site Number: 7401  Number of Subjects: 23	August 10-14, 2015	Pending  Interim classification: NAI
<b>Sponsor: AstraZeneca</b> Gaithersburg, MD	Protocols: D5160C0001C (Phase II extension component)  And  D5160C00002  Number of Sites: 4 (2 for each protocol)	September 28-29, 2015	Pending  Interim classification: NAI

Name of CI or Sponsor/CRO, Location	Protocol #, Site #, and # of Subjects	Inspection Date	Final Classification
CRO: (b) (4) (b) (4)	Protocols: D5160C0001C (Phase II extension component)  and  D5160C00002  Number of Sites: 5 ( $\geq$ 2 for each protocol)  Total Number of Subjects audited: Approximately 30	(b) (4)	Pending  Interim classification: NAI

Key to Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending.

**1. CI#1: Dr. Pasi Janne**

(Site 7800: Study D5160C0001C (Phase II extension component))

- a. What was inspected:** The site screened forty five subjects, and eighteen subjects were enrolled. The study records of all enrolled subjects were audited. At the time of this inspection there were five subjects still on study and continue to take study drug. Of those five subjects, a total of three have continued study drug without progression and the other two subjects had progressive disease but continued on the study drug (in accordance with the protocol). Of the remaining thirteen subjects no longer on study the final disposition is as follows: seven deaths, two withdrew consent, one lost to follow up, and four in long-term follow-up. The record audit included comparison of source documentation to eCRFs and data listings submitted to NDA 208065, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint verification, and general protocol compliance. The FDA investigator also assessed informed consent documents, test article accountability, monitoring reports, and IRB correspondence.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be good. The inspection revealed no significant

deficiencies. Records and procedures were clear, and generally well organized. The primary efficacy endpoint is based on an ICR imaging review for tumor response per RECIST1.1. Corroborating efficacy documentation reviewed at the site included records of the tumor scans sent to the IRC vendor, (b) (4). In addition, the Clinical Investigator tumor response assessments and tumor measurements included in the data listings submitted to NDA 208065 were verified. There was no evidence of underreporting adverse events. A Form FDA 483 was not issued.

There were two discussion points on minor GCP issues. First, the delegation of authority log was signed by Dr. Janne after study site personnel had already conducted activity with the study. The study personnel who were delegated appeared to be qualified. No issues were noted with the actual delegation. Second, nursing notes did not document the study drug kit numbers when subjects returned unused drug to the study site. However, this was not an issue with this study, because all subjects in the extension phase were on the same drug and dose (80mg tablets daily P.O.).

- c. Assessment of data integrity:** The data for Dr. Janne's site, associated with Study D5160C0001C (Phase II Extension Study) submitted to the Agency in support of NDA 208065, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**2. CI#2: Dr. Chun-Ming Tsai**  
(Site 7401: Study D5160C00002)

- a. What was inspected:** The site screened sixty four subjects, and twenty three subjects were enrolled. The study records of seven enrolled subjects were audited. At the time of this inspection sixteen subjects were still considered on study. The record audit included comparison of source documentation to CRFs and data listings submitted to NDA 208065, focusing on inclusion/exclusion criteria compliance, adverse events, treatment regimens, reporting of AEs in accordance with the protocol, efficacy endpoint assessment, and general protocol compliance. The FDA investigator also assessed informed consent documents, test article accountability, and monitoring reports.
- b. General observations/commentary:** Generally, the investigator's execution of the protocol was found to be adequate. Records and procedures were clear, and generally well organized. The inspection revealed no significant deficiencies. The primary efficacy endpoint is based on an ICR imaging review for tumor response per RECIST1.1. Therefore, corroborating efficacy evidence was reviewed at the site that included records of the tumor scans sent to the IRC vendor, (b) (4). There was no evidence of underreporting of adverse events. There were very minor documentation issues discussed with the Site.

A Form FDA 483 was not issued.

- c. Assessment of data integrity:** The data for Dr. Tsai's site, associated with Study D5160C00002 submitted to the Agency in support of NDA 208065, appear reliable based on available information.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

**3. CRO:** (b) (4) **(ICR Vendor)**

- a. What was inspected:** The inspection focused primarily on assessing the integrity of the tumor response and disease progression source records as it pertains to the contractual obligations of the CRO for Study D5160C0001C (Phase II Extension Study) and Study D5160C00002 per Charter. The CRO provided the Independent Central Review for assessment of radiographic images (Radiologist Review) per RECIST1.1.

Inspectional coverage included review of the following areas: (1) organization and personnel; (2) training, education, and qualifications of reviewers (radiologists); (3) quality assurance; (4) fulfillment of contractual agreement and charter to conduct radiological image evaluation; (5) subject records/source documents; and (6) data management and transfer.

- b. General observations/commentary:** Generally, records and procedures were adequate, and well organized. The primary efficacy endpoint support data, PFS/tumor response per RECIST1.1 were verified for five clinical sites (including the Sites 7800 and 7401 identified as above). At least 2 Sites audited were selected from each study targeted for inspection, and included a total of not less than 30 Subjects' records audited. Specifically, Radiologist 1 and Radiologist 2 assessments, along with that of an adjudicator if needed for PFS/tumor response and time to progression (from randomization date to confirmed event), were compared to the datalistings submitted to the supplement application. There were no discrepancies. No Form FDA 483 was issued.
- c. Assessment of data integrity:** Based upon review of select subject data as described above, the data from this CRO, associated with Study D5160C0001C (Phase II Extension Study) and Study D5160C00002 and submitted by the sponsor to the Agency in support of NDA 208065, appear reliable.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

#### 4. Sponsor: AstraZeneca

- a. What was inspected:** The inspection focused on four study sites; two for each study. The inspection included but was not limited to test article accountability records, site monitoring, and all AEs for those four sites and written agreements with all CROs and contractors for duties delegated to them by the study sponsor AstraZeneca. The audit also included, in part, assessment of selected SOPs, including monitoring procedures and monitoring plans for the two studies, Clinical Investigator site qualification, study specific training for investigators and monitors, Form FDA 1572 and investigator agreements.
- b. General observations/commentary:** Records and procedures were clear, and generally well organized. The sponsor maintained adequate oversight over the study. There was no evidence of under-reporting of AEs/SAEs by the sponsor. The primary efficacy endpoint was a derived efficacy outcome measure, based upon tumor response per RECIST1.1 determined by the CRO, (b) (4). Compliance with the investigational plan appeared to be adequate. Monitoring appeared adequate. No study sites were closed due to GCP non-compliance. No Form FDA 483 was issued.
- c. Assessment of data integrity:** The data from this sponsor submitted to the Agency associated with Study D5160C0001C (Phase II Extension Study) and Study D5160C00002 submitted by the sponsor to the Agency in support of NDA 208065, appear reliable.

**Note:** The general observations and actions on inspection are based on preliminary communications with the FDA field investigator. An inspection summary addendum will be generated if conclusions change upon receipt and review of the final EIR.

### III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Tumor response data from the ICR was used to derive the primary efficacy endpoint variable of ORR for all subjects in Study D5160C0001C (Phase II Extension Study) and Study D5160C00002. The primary efficacy outcome measures reported in the application were verified with the source records generated at the sites. There were no trends in underreporting adverse events.

Based on the review of preliminary inspectional findings for clinical investigators Dr. Pasi Janne (Site 7800: Study D5160C0001C), Dr. Chun-Ming Tsai (Site 7401: Study D5160C00002), the CRO (b) (4), and the study sponsor of Study D5160C0001C and Study D5160C00002, data submitted to the Agency in support of NDA 208065, appear reliable and can be used in support of the application.

**Note:** Observations noted above are based on the preliminary communications provided by the FDA field investigators. An inspection summary addendum will be generated if conclusions change significantly upon receipt and complete review of the EIRs.

{See appended electronic signature page}

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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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LAUREN C IACONO-CONNORS  
10/06/2015

SUSAN D THOMPSON  
10/06/2015

KASSA AYALEW  
10/06/2015

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>IND or NDA</b>	NDA 208065
<b>Brand Name</b>	Not decided
<b>Generic Name</b>	Osimertinib (AZD9291)
<b>Sponsor</b>	AstraZeneca Pharmaceuticals
<b>Indication</b>	Non-Small Cell Lung Cancer
<b>Dosage Form</b>	Tablet
<b>Drug Class</b>	Tyrosine kinase inhibitor
<b>Therapeutic Dosing Regimen</b>	80 mg once daily
<b>Duration of Therapeutic Use</b>	(b) (4)
<b>Maximum Tolerated Dose</b>	Not identified
<b>Submission Number and Date</b>	SDN 009; 5 Jun 2015
<b>Review Division</b>	DOP2

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

### 1 SUMMARY

#### 1.1 OVERALL SUMMARY OF FINDINGS

A large change in QTc (i.e., >20 ms) was not detected in this trial following single dose or multiple doses of AZD9291. Significant QT prolongation at steady-state was observed with the maximum mean change from baseline (with the upper bound of the two-sided 90% CI) in QTcF of 16.2 (17.6) ms. A pharmacokinetic/pharmacodynamic analysis suggested a concentration-dependent QTc interval prolongation at 80 mg of 14 ms with an upper bound of 16 ms (90% CI).

This drug is highly unlikely to be a hERG blocker, and, at least over the concentration range observed, would suggest there will be no further interference with repolarization at high exposure. Its modest effect likely conveys some incremental

risk, although only in conjunction with other repolarization blockers, particularly real hERG blockers.

In this phase II, open-label, single-arm study, 210 patients with locally advanced/metastatic non small cell lung cancer received AZD9291 80 mg. Overall summary of findings is presented in Table 1.

**Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for AZD9291 80 mg (FDA Analysis)**

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

The dose tested in the trial, which represents the anticipated therapeutic dose, is reasonable for the QT evaluation.

## 2 PROPOSED LABEL

The following is the sponsor’s proposed labeling language related to QT.

### 2.3 Dose Modification for Adverse Reactions

**Table 2: Recommended Dose Modifications for TRADENAME**

Target Organ	Adverse Reaction <sup>a</sup>	Dose Modification
<i>Cardiac</i>	QTc interval greater than 500 msec on at least 2 separate ECGs	Withhold TRADENAME until QTc interval is less than 481 msec or recovery to baseline if baseline QTc is greater than or equal to 481 msec, then restart at a reduced dose (40 mg)
	QTc interval prolongation with signs/symptoms of (b) (4)	Permanently discontinue TRADENAME

(b) (4)

## 12.2 Pharmacodynamics

### Cardiac Electrophysiology

The QT interval prolongation potential of TRADENAME was assessed in 210 patients who received INN 80 mg daily in Study 2. (b) (4)

*QT-IRT's proposed labeling language is a suggestion only. We defer final labeling decisions to the Division.*

The proposed labeling in Section 2.3 and 5.2 are acceptable.

## 12.2 Pharmacodynamics

### Cardiac Electrophysiology

The QT interval prolongation potential of TRADENAME was assessed in 210 patients who received INN 80 mg daily in Study 2. (b) (4)

A central tendency analysis of the QTcF data at steady-state demonstrated that the maximum mean change from baseline (b) (4) A pharmacokinetic/pharmacodynamic analysis with TRADENAME suggested a concentration-dependent QTc interval prolongation (b) (4)

### 3 BACKGROUND

#### 3.1 PRODUCT INFORMATION

AZD9291 is a potent irreversible inhibitor of both the single epidermal growth factor receptor mutation positive (EGFRm) (tyrosine kinase inhibitor [TKI] sensitivity-conferring mutation) and dual EGFRm/T790M mutation positive (T790M) (TKI resistance-conferring mutation) receptor forms of EGFR but designed to have limited activity against wild type EGFR. Therefore, AZD9291 has the potential to provide clinical benefit to patients with (b) (4) non-small cell lung carcinoma/cancer (NSCLC) (b) (4) following prior therapy with an epidermal growth factor receptor-tyrosine kinase inhibitor (EGFR TKI).

#### 3.2 MARKET APPROVAL STATUS

AZD9291 is not approved for marketing in any country.

#### 3.3 PRECLINICAL INFORMATION

AZD9291 and its metabolites, AZ5104, and AZ7550, were found to inhibit the function of the hERG channel *in vitro* with IC<sub>50</sub> values of 0.69 (GLP assay), 17.48, and >33 µM (non-GLP assay for the metabolites), respectively.

In the GLP dog cardiovascular study (study number 1352ZD), administration of single oral doses of AZD9291 (0, 6, 20 and 60 mg/kg) to conscious telemetered dogs was associated with marginal differences in QTcR (up to 7% increase) and heart rate (up to 20% decrease) compared to the vehicle control. These changes were small in magnitude, transient, not dose-related and are considered to be of limited biological significance. There were no notable effects on cardiovascular parameters in the GLP repeat dose toxicity studies in dogs.

In a non-GLP investigative study in the anaesthetised guinea pig (study number 0264SG), intravenous infusion of AZD9291 was associated with small decreases in heart rate (up to 7%) and +ve dP/dtmax (an index of cardiac contractility; up to 18%) and increases in left ventricular systolic pressure (up to 10%), PR interval (up to 7%), QTcB interval (up to 7%) and QRS duration (up to 26%). These findings were only seen at very high exposures (total plasma concentrations of 22.87 µM) and not at the lower dose of 5 mg/kg (total plasma concentrations of 4.76 µM) therefore they are considered unlikely to be of clinical relevance.

#### 3.4 PREVIOUS CLINICAL EXPERIENCE

See Appendix 6.1.

#### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of AZD9291 clinical pharmacology.

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT did not review the protocol prior to conducting this study. The sponsor submitted the study report D5160C00002 for AZD9291, including electronic datasets and waveforms to the ECG warehouse.

### 4.2 QT STUDY

#### 4.2.1 Title

A phase II, open label, single-arm study to assess the safety and efficacy of AZD9291 in patients with locally advanced/metastatic non small cell lung cancer whose disease has progressed with previous epidermal growth factor receptor tyrosine kinase inhibitor therapy and whose tumours are epidermal growth factor receptor mutation and T790M mutation positive (AURA2)

#### 4.2.2 Protocol Number

D5160C00002

#### 4.2.3 Study Dates

28 Apr 2014 -- 9 Jan 2015

#### 4.2.4 Objectives

Primary objective:

The primary objective of the study was to investigate the efficacy of AZD9291 by assessment of objective response rate (ORR).

Secondary objectives:

- To further assess the efficacy of AZD9291 in terms of duration of response (DoR), disease control rate (DCR), tumour shrinkage, progression-free survival (PFS) and OS.
- To assess the safety and tolerability profile of AZD9291.
- To investigate the effect of AZD9291 on QT interval corrected for heart rate (QTc) interval after oral dosing to NSCLC patients.
- To assess the impact of AZD9291 on patients' disease-related symptoms and health-related quality of life (HRQoL).
- To characterise the pharmacokinetics of AZD9291 and its metabolites (AZ5104 and AZ7550).

## 4.2.5 Study Description

### 4.2.5.1 Design

This is a phase II, open-label, single-arm study. The study consisted of 2 cohorts:

- Second-line therapy cohort: patients whose disease had progressed following first-line therapy with 1 EGFR TKI agent but who had not received further treatment
- Third-line therapy cohort: patients whose disease had progressed following treatment with both EGFR TKI and a platinum-based doublet chemotherapy (patients may have also received additional lines of treatment)

### 4.2.5.2 Controls

There were no placebo and positive (moxifloxacin) controls.

### 4.2.5.3 Blinding

The study was open-label.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

The study was a single-arm trial. AZD9291 80 mg was administered orally as a single daily dose.

A 21-day treatment period was defined as a cycle. Patients continued on treatment with AZD9291 until RECIST 1:1-defined progression or until a treatment discontinuation criterion was met. There was no maximum duration of treatment as patients could continue to receive AZD9291 beyond RECIST 1:1-defined progression as long as they continued to show clinical benefit, as judged by the investigator.

### 4.2.6.2 Sponsor's Justification for Doses

Responses have been observed in patients with T790M mutation positive tumours in dose-ranging study (D5160C00001 Phase I, 20 mg to 240 mg), with no obvious increase in response rate above 80 mg.

No dose-limiting toxicities (DLTs) were reported at any dose level in the escalation cohorts during the 21-day DLT evaluation period, and therefore a maximum tolerated dose (MTD) has not been defined. During the dose expansion phase, there was a dose-related increase in the incidence of classical EGFR TKI toxicities of rash and diarrhoea at doses of 160 mg and above

Additionally, the patients with the lowest AZD9291 exposure after dosing with either the capsule or tablet formulation at 80 mg once daily have AZD9291 exposures that are

approximately twice the geometric mean AUC(0-24) of 1965 nM.h observed at steady-state for the 20 mg once-daily dose (the lowest dose tested). Thus, choosing the 80 mg dose ensures all patients will attain exposures that have been shown to result in a high response rate and are well above the exposures that have been observed after dosing with the initial starting dose of 20 mg once daily, while minimizing the dose-related increase in the incidence and severity of the classical EGFR TKI toxicity of rash and diarrhoea that was apparent at a dose of 160 mg and above.

*Reviewer's Comment: 80 mg once daily is the proposed therapeutic dose. The sponsor's rationale for dose selection is reasonable.*

#### **4.2.6.3 Instructions with Regard to Meals**

AZD9291 is recommended to be taken with or without regard to food. In Study D5160C00005, AZD9291 AUC and C<sub>max</sub> were increased approximately 19% and 14%, respectively, following administration of AZD9291 20 mg Phase 1 tablet to healthy volunteers with a high-fat meal (800 to 1000 calories) compared to fasted conditions while food had no effect on AZ5104 (metabolite) AUC and C<sub>max</sub> compared to fasted conditions.

Based on the dose proportional pharmacokinetics observed between 20 mg and 240 mg and the observation that dissolution is not rate limiting for AZD9291 absorption, the likelihood that food will impact AZD9291 drug exposure differently at 80 mg is low. (b) (4)

*Reviewer's Comment: AZD9291 is recommended to be taken with or without regard to food. (b) (4)*

*based on the result of food effect on dose of 20 mg and PK characteristics of AZD9291, it appears to be acceptable.*

#### **4.2.6.4 ECG and PK Assessments**

Per protocol, patients recruited into AURA2 had centrally read triplicate dECGs performed over a 24-hour period at screening (baseline), after a single dose of 80 mg of AZD9291 (Cycle 1 Day 1), and after multiple doses of once-daily dosing with 80-mg AZD9291 (Cycle 2 Day 1 and Cycle 3 Day 1) as shown in Table 3.

At each time point for assessment, 3 ECG recordings were taken. To obtain a single value of QT, RR, PR, and QRS at each specified time point, the mean of the triplicate values at that time point was used. The mean value was used in the analyses.

**Table 3: Scheduled Digital Electrocardiographic (ECG) Recordings**

Time relative to dose	Screening (baseline)	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1
Pre-dose ( $\pm 5$ min)	X <sup>a</sup>	X	X	X
1 hour ( $\pm 5$ min)	X	X		X
2 hours ( $\pm 10$ min)	X	X		X
4 hours ( $\pm 10$ min)	X	X		X
6 hours ( $\pm 10$ min)	X	X		X
8 hours ( $\pm 10$ min)	X	X		X
10 hours ( $\pm 10$ min)	X			X
12 hours ( $\pm 1$ hour)	X			X
24 hours ( $\pm 1$ hour)	X			X (Day 2, pre-dose)

<sup>a</sup> Since there is no dosing at screening, ECG recordings should start at a time that would be consistent with planned dosing times at Cycle 1 Day 1, Cycle 2 Day 1, and Cycle 3 Day 1 (for baseline purposes).

Source: *QT modeling and simulation report, Page 18, Table 1*

All patients recruited into AURA2 had PK samples collected at matching time points at Cycle 1 Day 1, Cycle 2 Day 1 (pre-dose), and Cycle 3 Day 1, as detailed in Table 4. However, 1 patient had digital ECGs performed and PK samples collected at matching time points at Cycle 6 due to dose interruptions.

**Table 4: Pharmacokinetic Blood Sample Schedule**

Time relative to dose	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1
Pre-dose ( $\pm 5$ min)	X	X	X
1 hour ( $\pm 5$ min)	X		X
2 hours ( $\pm 10$ min)	X		X
4 hours ( $\pm 10$ min)	X		X
6 hours ( $\pm 10$ min)	X		X
8 hours ( $\pm 10$ min)	X		X
10 hours ( $\pm 10$ min)			X
12 hours ( $\pm 1$ hour)			X
24 hours ( $\pm 1$ hour)			X (Day 2, pre-dose)

Source: *QT modeling and simulation report, Page 19, Table 2*

*Reviewer's Comment: The sampling time points are acceptable. PK and ECG measurements were collected to cover median  $T_{max}$  (6-8 hours) and up to 24 hours post-dose at steady state for Day 1 of Cycle 3. The PK and ECG profiles on Day 1 of Cycle 3 are anticipated to be flat because (1) the effective half-life is 48 hours, and (2) the drug is given once daily.*

#### 4.2.6.5 Baseline

Time-matched QT/QTc values at screening visit were used as baselines.

## 4.2.7 ECG Collection

Digital ECGs were obtained while patients were resting.

## 4.2.8 Sponsor's Results

### 4.2.8.1 Study Subjects

A total of 210 patients who received at least 1 dose of AZD9291 were included in the full analysis set. The QTc analysis set included all 210 patients in the full analysis set.

Of the 210 patients who received treatment with AZD9291 80 mg, the median age was 64 years (range 35 to 88 years) at study entry, with 33 patients (15.7%) aged  $\geq 75$  years.

Across all patients, 69.5% were female. Approximately two-thirds of patients were of Asian racial origin (62.9%); the remainder were mainly white (34.3%) with 3 (1.4%) black/African American patients.

### 4.2.8.2 Statistical Analyses

#### 4.2.8.2.1 Primary Analysis

Table 5 shows the sponsor's summary of ANCOVA to assess mean QTcF interval at certain time points for AZD9291 at 6 weeks. An increase from baseline in average QTcF values was observed, which reached a plateau by Week 6. The mean time-matched change from baseline in QTcF at Week 6 ranged from 12.5 ms to 16.1 ms across the 8 time points throughout the dosing interval. The upper 90% CIs (2 sided) ranged from 13.9 ms to 17.5 ms.

**Table 5: Summary of Analysis of Covariance to Assess Mean QTcF interval at Certain Time Points for AZD9291 at 6 Weeks (Sponsor's Results Based on QTc Analysis Set)**

Nominal time point	N	Multiple dose AZD9291	Control (Baseline)	Treatment effect	
		LS mean	LS mean	Difference in LS means (AZD9291 minus baseline)	90% CI
1 hour post dose	198	428.68	412.58	16.10	14.698, 17.502
2 hours post dose	198	429.10	413.54	15.56	14.155, 16.960
4 hours post dose	200	427.87	415.35	12.52	11.123, 13.921
6 hours post dose	200	427.59	414.30	13.29	11.892, 14.690
8 hours post dose	197	428.06	413.05	15.01	13.609, 16.417
10 hours post dose	194	428.55	413.94	14.62	13.207, 16.027
12 hours post dose	184	429.89	413.95	15.94	14.505, 17.372
24 hours post dose	187	425.53	412.51	13.01	11.585, 14.438
Overall	200	428.16	413.65	14.51	14.003, 15.010

The analysis was performed using analysis of covariance with factors for the treatment effect (AZD9291 [after 6 weeks]/control) and time, interaction terms between treatment and time, and patient as a random effect.

The LS mean is the adjusted mean QTcF interval.

Fridericia's correction was used for QTc.

Abbreviations: CI, confidence interval; LS, least squares; QTcF, QTc Fridericia.

Source: clinical study report D5160C00002, Table 25, page 126

*Reviewer's Comments: please see the reviewer's analysis in section 5.2.*

#### **4.2.8.2.2 Assay Sensitivity**

Not Applicable.

#### **4.2.8.2.3 Categorical Analysis**

A total of 29% (61/210) of patients had a QTcF value >450 ms at any time during treatment; of these 61 patients, 8 patients (3.8% [8/210] of patients) had a QTcF >480 ms and 1 patient (0.5% [1/210] of patients) had a QTcF >500 ms (E7401212, QTcF 501 ms). Per protocol, exclusion criterion 7 excluded patients with baseline QTc >470 ms. Eight patients had QTcF values >450 ms at baseline, and 2 of these patients had an increase to QTcF values >480 ms.

In total, 38.6% (81/210) of patients had increases of >30 ms from baseline at any time during treatment; of these 81 patients, 37 patients (17.6% [37/210] of patients) had increases of >30 ms to a QTcF of >450 ms. Six patients (2.9% [6/210] of patients) had increases of >60 ms from baseline at any time during treatment. Of those 6 patients, 2 patients (1.0% [2/210] of patients) had an increase of >90 ms from baseline. One of these 2 patients (E7401212) was the only patient in the >500 ms and >60 ms from baseline category.

#### **4.2.8.3 Safety Analysis**

Fatal adverse events were reported in 3 of the 210 patients (1.4%), 1 of which was considered by the investigator to be possibly related to AZD9291. Serious adverse events were reported in 26 patients (12.4%); 8 of those 26 patients (3.8%) had a SAE considered by the investigator to be possibly related to AZD9291. Eight patients (3.8%) discontinued from the study due to adverse events.

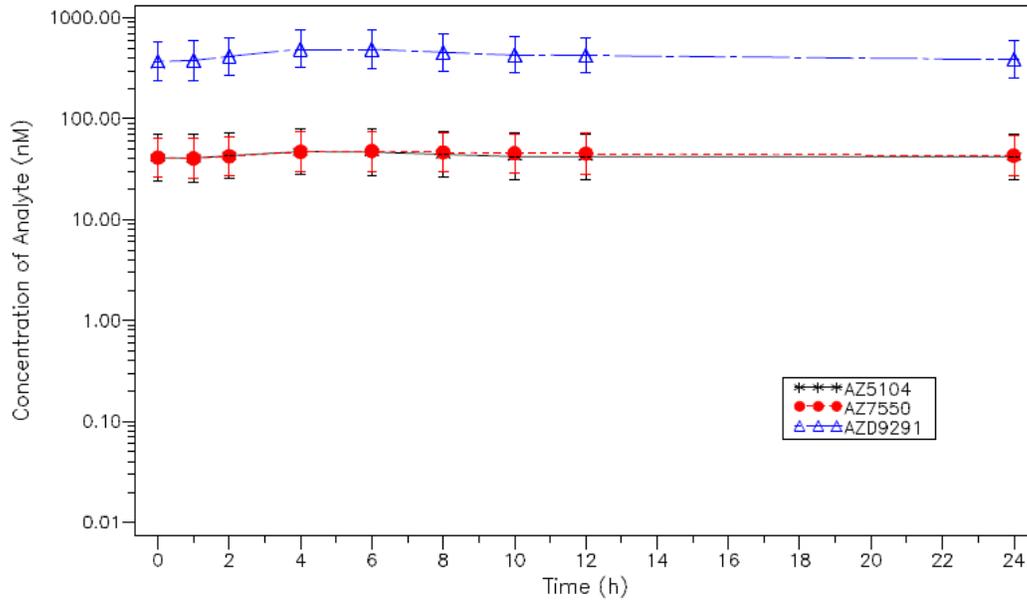
There were no AEs reported of PTs in the cardiac failure or cardiomyopathy standard MedDRA queries (SMQs). Adverse events with PTs in the QT prolongation SMQ category were reported in 7 of the 210 patients (3.3%); all reported PTs were electrocardiogram QT prolonged.

#### **4.2.8.4 Clinical Pharmacology**

##### **4.2.8.4.1 Pharmacokinetic Analysis**

Mean plasma concentration-time profiles of AZD9291 and its major metabolites at Cycle 3 Day 1 are presented in Figure 1. The summary statistics of the pharmacokinetics of AZD9291 in Table 6.

**Figure 1: Mean Concentration-Time Profiles for AZD9291 and Its Metabolites at Cycle 3 Day 1 at 80 mg Once Daily**



Source: Sponsor's summary of clinical pharmacology, Page 54, Figure 7

**Table 6: Geometric Mean (%GCV) of Steady State PK Parameters of AZD9291 at 80 mg Dose in T790M Mutation Positive Patients**

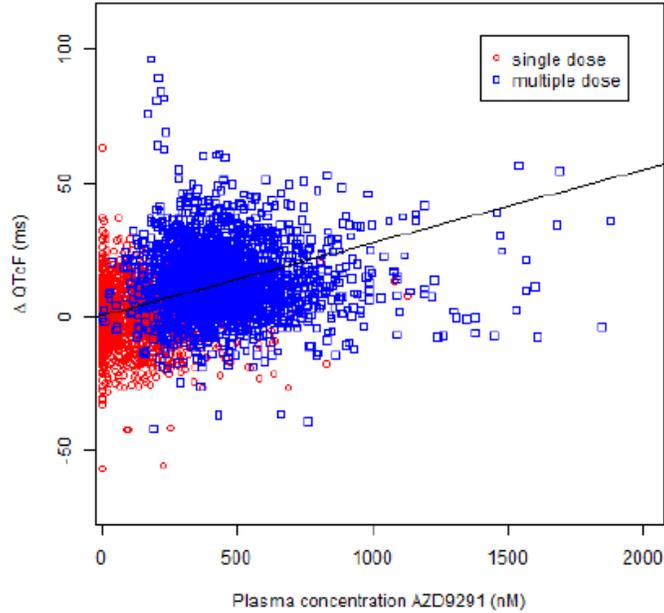
Parameters	AURA 2
Formulation	Film-coated tablet
Cycle/Day	C3/D1
N	192
Tmax (h)	6 (1-23)
Css, min (nM)	533 (43)
Css, max (nM)	332 (49)
AUCss (nM*h)	10180 (42)

Source: Sponsor's summary of clinical pharmacology, Page 52, Table 9

#### 4.2.8.4.2 Exposure-Response Analysis

Figure 2 summarises the correlation between AZD9291 plasma concentrations and  $\Delta$ QTcF, suggesting an increasing trend in  $\Delta$ QTcF with increasing AZD9291 concentrations.

**Figure 2: Scatterplot of  $\Delta$ QTcF vs Plasma Concentration of AZD9291 with the Fitted Regression Line Obtained with the Linear Mixed Effects Model**



Source: Sponsor’s QT modeling and simulation report, Page 30, Figure 3

The result is shown in Table 7, which is consistent with this visual assessment, the linear mixed effects model identified a significant linear relationship between the change from baseline in QTcF and the AZD9291 plasma concentrations ( $P < 0.0001$ ). The mean increase in QTcF adjusted for timematched baseline was estimated to be 0.271 milliseconds per 10-nM increase in AZD9291 plasma levels with a 2-sided 90% confidence interval of 0.241 to 0.301 milliseconds. Nominal time after dose did have a significant effect on  $\Delta$ QTcF and was included as a covariate into the model ( $P < 0.0001$ ). Gender did not have a significant effect on  $\Delta$ QTcF when added to the model ( $P = .97$ ).

**Table 7: Parameter estimates from the linear mixed effects model for AZD9291**

Parameter (unit)	Estimate (90% CI)	P-value	BSV (90% CI)
Intercept (ms)	0.77 (-0.38–1.92)	.27	61.0 (48.3–79.8)
Slope (ms/nM)	0.0271 (0.0241–0.0301)	<.0001	0.0004 (0.0003–0.0005)

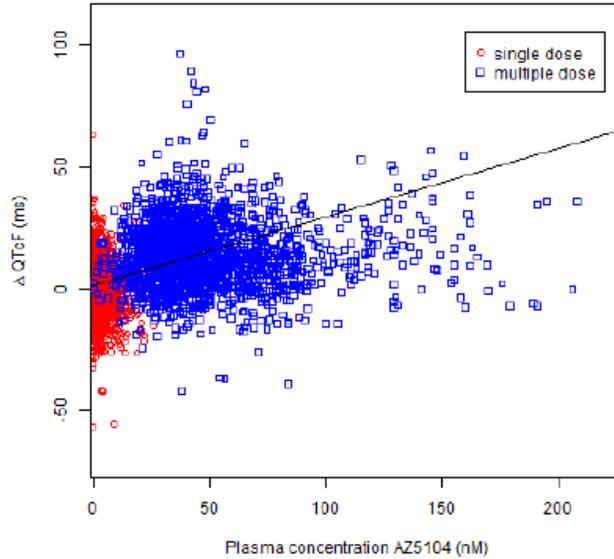
Source: nmqt.xpt (data), LMEmodel\_NOM.sas (analysis), BaseModel-NOM.rtf (output).

Abbreviations: BSV = between-subject variability, CI = confidence interval, ms = milliseconds

Source: Sponsor’s QT modeling and simulation report, Page 31, Table 8

Figure 3 summarises the correlation between plasma concentrations of the metabolite AZ5104 and  $\Delta$ QTcF, suggesting a similar increasing trend as observed for the parent compound.

**Figure 3: Scatterplot of  $\Delta$ QTcF vs plasma concentration of AZ5104 with the fitted regression line obtained with the linear mixed effects model**



Source: Sponsor’s QT modeling and simulation report, Page 31, Figure 4

The result is shown in Table 8 that the linear mixed effects model identified a significant linear relationship between the change-from-baseline QTcF and the AZ5104 plasma concentrations ( $P < 0.0001$ ). The mean increase in QTcF adjusted for time-matched baseline was estimated to be 2.81 milliseconds per 10-nM increase in AZ5104 plasma levels with a 2-sided 90% confidence interval of 2.50 to 3.12 ms. Similar to the model for the parent drug, nominal time after dose was significant ( $P < 0.0001$ ) and added to the model while gender was not significant when added to the model ( $P = 0.67$ ).

**Table 8: Parameter estimates from the linear mixed effects model for AZ5104**

Parameter (unit)	Estimate (90% CI)	P-value	BSV (90% CI)
Intercept (ms)	1.42 (0.47–2.38)	.01	43.2 (34.5–55.9)
Slope (ms/nM)	0.281 (0.250–0.312)	<.0001	0.048 (0.037–0.063)

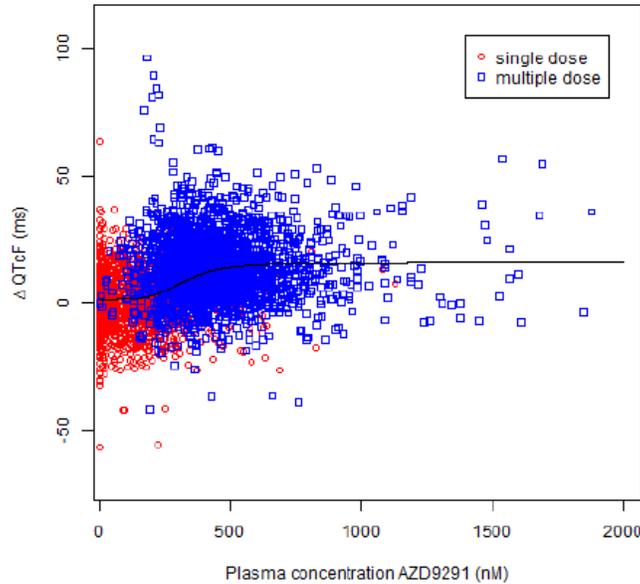
Source: nmqt.xpt (data), LMEmodel\_NOM.sas (analysis), BaseModel-NOM.rtf (output).

Abbreviations: BSV = between-subject variability, CI = confidence interval, ms = milliseconds

Source: Sponsor’s QT modeling and simulation report, Page 32, Table 9

An alternative models for c-QTcF relationship was tested by sponsor. Figure 4 illustrates the correlation between AZD9291 plasma concentrations and  $\Delta$ QTcF together with the fit of the sigmoid Emax model. Based on visual inspection such a model appears to provide an adequate description of the data.

**Figure 4: Scatterplot of  $\Delta$ QTcF vs AZD9291 Plasma Concentration with the Regression Line Obtained with the Non-Linear Mixed Effects Emax Model**



Source: Sponsor’s QT modeling and simulation report, Page 32, Figure 5

The result is shown in Table 9, a maximum effect on  $\Delta$ QTcF was estimated to be 14.6 milliseconds with 2-sided 90% CI of 12.9 to 16.2 milliseconds.

**Table 9: Parameter Estimates from the Non-Linear Mixed Effects Model for AZD9291**

Parameter (unit)	Estimate (90% CI)	P-value	BSV (90% CI)
$E_0$ (ms)	1.42 (0.44–2.39)	0.02	49.3 (34.5–64.2)
$E_{max}$ (ms)	14.6 (12.9–16.2)	<.0001	212 (137–287)
$EC_{50}$ (nM)	325 (309–342)	<.0001	127 (-405–660)
$\gamma$	4.64 (4.13–5.14)	<.0001	191 (102–281)

Source: nmqt.xpt (data), NLMEmodel\_Emax.sas (analysis), EmaxModel\_Hill-random.rtf (output).  
Abbreviations: BSV = between-subject variability, CI = confidence interval, ms = milliseconds

Source: Sponsor’s QT modeling and simulation report, Page 33, Table 10

The AIC of the linear mixed effects model for AZD9291 is similar to that of the alternative Emax model: 25055 (linear model) vs 25038 (Emax model). However, the BSV estimate of  $EC_{50}$  from the Emax model is imprecise.

The AIC of the linear mixed effect model for AZD9291 is higher than that of the linear mixed effect model for AZ5104 (25055 vs 24791). However, the linear mixed effect model for AZ5104 was not selected as the final model to predict the expected QTcF effect at the 80-mg therapeutic dose because it does not include the parent drug concentration in the model.

Thus, the linear mixed effect model using plasma concentration of AZD9291 and nominal time after dose as covariates was selected as final model for prediction of expected QTcF effects at the 80-mg therapeutic dose.

The observed geometric mean steady-state  $C_{max}$  of the therapeutic dose (80 mg) of AZD9291 was 525 nM. Applying the previous linear mixed effects model, the predicted mean QTcF interval prolongation at steady-state  $C_{max}$  of 80 mg of AZD9291 would be 14.2 ms with an upper bound of 15.8 ms (upper bound of the 2-sided 90% CI of the predicted mean).

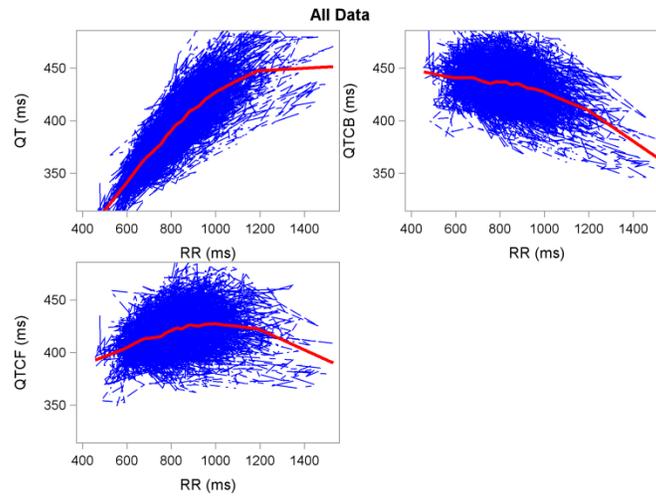
*Reviewer's Analysis An independent exposure-response analysis was conducted.*

## **5 REVIEWERS' ASSESSMENT**

### **5.1 EVALUATION OF THE QT/RR CORRECTION METHOD**

The relationship between different correction methods and RR is presented in Figure 5. This statistical reviewer used QTcF for the primary statistical analysis.

**Figure 5: QT, QTcB, and QTcF vs. RR (Each Subject's Data Points are Connected with a Line)**



## 5.2 STATISTICAL ASSESSMENTS

### 5.2.1 QTc Analysis

#### 5.2.1.1 The Primary Analysis for AZD9291 80 mg

The statistical reviewer used mixed model to analyze the  $\Delta$ QTcF effect. The model includes treatment (time-matched baseline was treated as control), time and treatment by time as fixed effects and subject as a random effect. The analysis results are listed in the following tables.

**Table 10: Analysis Results of  $\Delta$ QTcF for AZD9291 80 mg x 6 Weeks  
(Cycle 3 Day 1)**

<b>Time (hour)</b>	<b>QTcF (ms) AZD9291 80 mg</b>	<b>QTcF (ms) Baseline</b>	<b><math>\Delta</math>QTcF (ms) AZD9291 80 mg</b>	
	<b>LSmean</b>	<b>LSmean</b>	<b>LSmean</b>	<b>90% CI</b>
0	428.2	412.0	16.2	(14.8, 17.6)
1	428.7	412.5	16.1	(14.7, 17.5)
2	429.2	413.6	15.6	(14.2, 17.0)
4	428.0	415.4	12.5	(11.1, 13.9)
6	427.7	414.4	13.3	(11.9, 14.7)
8	428.1	413.2	14.9	(13.5, 16.4)
10	428.7	414.1	14.6	(13.2, 16.0)
12	430.0	414.8	16.0	(14.5, 17.4)
24	425.7	412.8	13.0	(11.5, 14.4)

**Table 11: Analysis Results of  $\Delta$ QTcF for AZD9291 80 mg Single Dose  
(Cycle 1 Day 1)**

	<b>QTcF (ms) AZD9291 80 mg</b>	<b>QTcF (ms) Baseline</b>	<b><math>\Delta</math>QTcF (ms) AZD9291 80 mg</b>	
<b>Time (hour)</b>	<b>LSmean</b>	<b>LSmean</b>	<b>LSmean</b>	<b>90% CI</b>
1	414.2	412.5	1.5	(0.3, 2.8)
2	415.7	413.6	2.1	(0.8, 3.3)
4	414.6	415.4	-0.9	(-2.2, 0.3)
6	413.0	414.4	-1.5	(-2.7, -0.2)
8	413.2	413.2	-0.1	(-1.2, 0.9)

The largest upper bound of the 2-sided 90% CI for the QTcF mean differences between AZD9291 80 mg x 6 weeks and baseline was 17.6 ms.

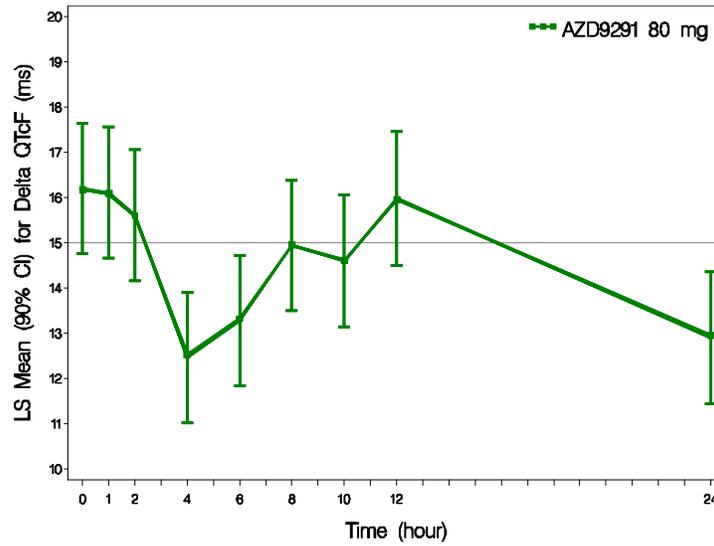
#### **5.2.1.2 Assay Sensitivity Analysis**

Not Applicable.

#### **5.2.1.3 Graph of $\Delta$ QTcF Over Time**

Figure 6 displays the time profile of  $\Delta$ QTcF for AZD9291 80 mg x 6 weeks.

**Figure 6: Mean and 90% CI  $\Delta$ QTcF Timecourse**



#### 5.2.1.4 Categorical Analysis

Table 12 lists the number of subjects as well as the number of observations whose QTcF values were  $\leq 450$  ms, between 450 ms and 480 ms, between 480 ms and 500 ms, and  $>500$  ms.

**Table 12: Categorical Analysis for QTcF**

Treatment Group	Total N		QTcF ≤ 450 ms		450 < QTcF ≤ 480 ms		480 < QTcF ≤ 500 ms		QTcF > 500 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	210	1862	191 (91.0%)	1793 (96.3%)	19 (9.0%)	69 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 1 Day 1 (Single Dose)	210	1256	198 (94.3%)	1216 (96.8%)	12 (5.7%)	40 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cycle 1 Day 8 & 15 Predose	208	410	197 (94.7%)	395 (96.3%)	11 (5.3%)	15 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
> Cycle 1	204	2631	147 (72.1%)	2300 (87.4%)	52 (25.5%)	318 (12.1%)	4 (2.0%)	12 (0.5%)	1 (0.5%)	1 (0.0%)

Table 13 and Table 14 list the categorical analysis results for  $\Delta$ QTcF.

**Table 13: Categorical Analysis of  $\Delta$ QTcF**

Treatment Group	Total N		$\Delta$ QTcF $\leq$ 30 ms		30 $<$ $\Delta$ QTcF $\leq$ 60 ms		$\Delta$ QTcF $>$ 60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Cycle 1 Day 1 (Single Dose)	210	1251	203 (96.7%)	1242 (99.3%)	6 (2.9%)	8 (0.6%)	1 (0.5%)	1 (0.1%)
Cycle 1 Day 8 & Day 15 Predose	208	410	202 (97.1%)	402 (98.0%)	5 (2.4%)	7 (1.7%)	1 (0.5%)	1 (0.2%)
> Cycle 1	204	2608	109 (53.4%)	2293 (87.9%)	90 (44.1%)	299 (11.5%)	5 (2.5%)	16 (0.6%)

**Table 14: Categorical Analysis of  $\Delta$ QTcF (Decrease)**

Treatment Group	Total N		-60 ms $\leq$ $\Delta$ QTcF $<$ -30 ms		$\Delta$ QTcF $<$ -60 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Cycle 1 Day 1 (Single Dose)	210	1251	8 (3.8%)	8 (0.6%)	0 (0.0%)	0 (0.0%)
Cycle 1 Day 8 & Day 15 Predose	208	410	4 (1.9%)	4 (1.0%)	0 (0.0%)	0 (0.0%)
> Cycle 1	204	2608	4 (2.0%)	4(0.2%)	0 (0.0%)	0 (0.0%)

### 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 15 and Table 16. The largest time-matched HR mean difference between AZD9291 80 mg x 6 weeks and baseline was -5.9 bpm with a 90% CI of -7.0 to -4.8 bpm, indicating a small heart rate lowering effect at steady state.

The outlier analysis results for HR are presented in Table 17.

**Table 15: Analysis Results of  $\Delta$ HR for AZD9291 80 mg x 6 Weeks  
(Cycle 3 Day 1)**

Time (hour)	HR (bpm) AZD9291 80 mg	HR (bpm) Baseline	$\Delta$ HR (bpm) AZD9291 80 mg	
	LSmean	LSmean	LSmean	90% CI
0	71.0	77.4	-5.9	(-7.0, -4.8)
1	68.7	74.9	-5.7	(-6.8, -4.6)
2	69.7	74.2	-4.0	(-5.1, -2.9)
4	74.4	76.8	-2.0	(-3.0, -0.9)
6	73.0	76.6	-3.2	(-4.2, -2.1)
8	72.5	75.9	-3.0	(-4.0, -1.9)
10	72.7	76.7	-3.7	(-4.8, -2.6)
12	71.2	75.3	-4.0	(-5.1, -2.9)
24	73.2	78.0	-4.3	(-5.3, -3.2)

**Table 16: Analysis Results of  $\Delta$ HR for AZD9291 80 mg Single Dose  
(Cycle 1 Day 1)**

	<b>HR (bpm) AZD9291 80 mg</b>	<b>HR (bpm) Baseline</b>	<b><math>\Delta</math>HR (bpm) AZD9291 80 mg</b>	
<b>Time (hour)</b>	<b>LSmean</b>	<b>LSmean</b>	<b>LSmean</b>	<b>90% CI</b>
1	74.4	74.9	-0.5	(-1.4, 0.4)
2	74.8	74.2	0.6	(-0.3, 1.5)
4	79.6	76.8	2.9	(2.0, 3.8)
6	77.7	76.6	1.2	(0.3, 2.1)
8	76.9	75.9	1.0	(-0.0, 2.0)

**Table 17: Categorical Analysis for HR**

	<b>Total N</b>	<b>HR<math>\leq</math>100 bpm</b>	<b>HR<math>&gt;</math>100 bpm</b>	<b>HR<math>&gt;</math>45 bpm</b>	<b>HR<math>\leq</math>45 bpm</b>
<b>Treatment Group</b>	<b>Subj. #</b>	<b>Subj. #</b>	<b>Subj. #</b>	<b>Subj. #</b>	<b>Subj. #</b>
Baseline	210	185 (88.1%)	25 (11.9%)	208 (99.0%)	2 (1.0%)
Cycle 1 Day 1 (Single Dose)	210	178 (84.8%)	32 (15.2%)	207 (98.6%)	3 (1.4%)
Cycle 1 Day 8 & 15 Predose	208	199 (95.7%)	9 (4.3%)	206 (99.0%)	2 (1.0%)
> Cycle 1	204	180 (88.2%)	24 (11.8%)	200 (98.0%)	4 (2.0%)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 18 (results for cycle 1 day 1 were not posted). The largest upper limit of 90% CI for the PR mean differences between AZD9291 80 mg x 6 weeks and baseline was 1.8 ms.

The outlier analysis results for PR are presented in Table 19.

**Table 18: Analysis Results of  $\Delta$ PR for AZD9291 80 mg x 6 Weeks (Cycle 3 Day 1)**

Time (hour)	PR (ms) AZD9291 80 mg	PR (ms) Baseline	$\Delta$ PR (ms) AZD9291 80 mg	
	LSmean	LSmean	LSmean	90% CI
0	163.5	162.6	0.5	(-0.7, 1.7)
1	165.1	164.4	0.3	(-0.9, 1.5)
2	164.7	165.4	-1.0	(-2.2, 0.2)
4	163.4	163.7	-0.7	(-1.9, 0.5)
6	163.0	163.8	-1.2	(-2.4, 0.0)
8	163.6	163.8	-0.4	(-1.6, 0.8)
10	163.5	164.0	-0.9	(-2.1, 0.3)
12	164.7	164.6	0.3	(-0.9, 1.5)
24	162.5	161.8	0.5	(-0.7, 1.8)

**Table 19: Categorical Analysis for PR**

Treatment Group	Total N		PR≤200 ms		PR>200 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	209	1852	181 (86.6%)	1714 (92.5%)	28 (13.4%)	138 (7.5%)
Cycle 1 Day 1 (Single Dose)	209	1248	185 (88.5%)	1155 (92.5%)	24 (11.5%)	93 (7.5%)
Cycle 1 Day 8 & 15 Predose	207	408	192 (92.8%)	384 (94.1%)	15 (7.2%)	24 (5.9%)
> Cycle 1	203	2616	175 (86.2%)	2447 (93.5%)	28 (13.8%)	169 (6.5%)

#### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 20 (results for cycle 1 day 1 were not posted). The largest upper limit of 90% CI for the QRS mean differences between AZD9291 80 mg x 6 weeks and baseline was 0.9 ms.

The outlier analysis results for QRS are presented in Table 21.

**Table 20: Analysis Results of  $\Delta$ QRS for AZD9291 80 mg x 6 Weeks  
(Cycle 3 Day 1)**

	<b>QRS (ms) AZD9291 80 mg</b>	<b>QRS (ms) Baseline</b>	<b><math>\Delta</math>QRS (ms) AZD9291 80 mg</b>	
<b>Time (hour)</b>	<b>LSmean</b>	<b>LSmean</b>	<b>LSmean</b>	<b>90% CI</b>
0	91.9	91.7	0.1	(-0.4, 0.7)
1	91.8	91.6	0.1	(-0.5, 0.6)
2	91.7	91.5	0.1	(-0.5, 0.7)
4	91.5	92.0	-0.6	(-1.2, -0.0)
6	91.7	91.3	0.3	(-0.2, 0.9)
8	91.4	91.1	0.2	(-0.4, 0.7)
10	91.8	92.0	-0.2	(-0.7, 0.4)
12	91.9	91.9	-0.4	(-1.0, 0.2)
24	91.9	91.8	-0.1	(-0.6, 0.4)

**Table 21: Categorical Analysis for QRS**

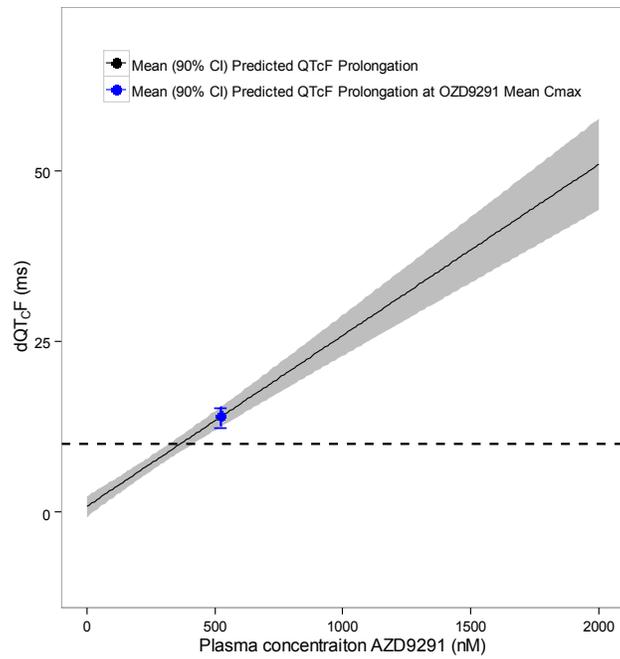
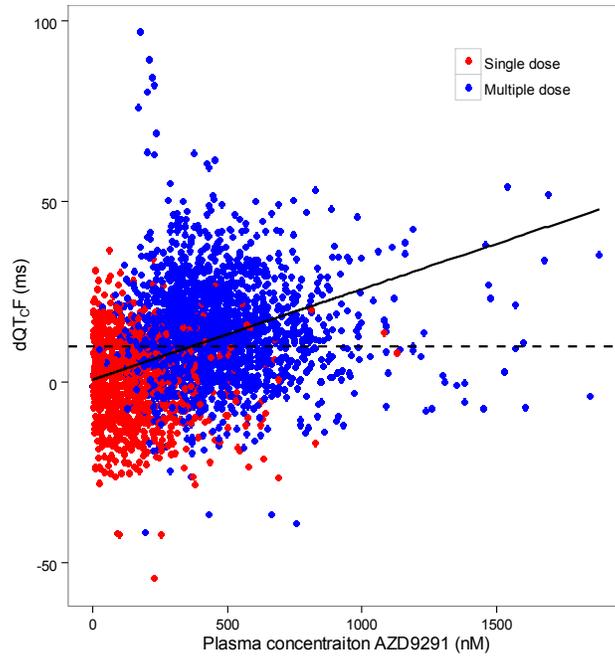
Treatment Group	Total N		QRS≤110 ms		QRS>110 ms	
	Subj. #	Obs. #	Subj. #	Obs. #	Subj. #	Obs. #
Baseline	210	1862	203 (96.7%)	1819 (97.7%)	7 (3.3%)	43 (2.3%)
Cycle 1 Day 1 (Single Dose)	210	1256	200 (95.2%)	1216 (96.8%)	10 (4.8%)	40 (3.2%)
Cycle 1 Day 8 & 15 Predose	208	410	201 (96.6%)	400 (97.6%)	7 (3.4%)	10 (2.4%)
> Cycle 1	204	2632	197 (96.6%)	2562 (97.3%)	7 (3.4%)	70 (2.7%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile at steady state is illustrated in Figure 1.

The relationship between  $\Delta$ QTcF and AZD9291 concentrations was investigated by linear regression modeling (Model 1) and Emax model (Model 2). The relationships between  $\Delta\Delta$ QTcF and drug concentrations are visualized in Figure 7 and Figure 8 with positive exposure-response relationship.

**Figure 7:  $\Delta$ QTcF vs. AZD9291 Concentration**



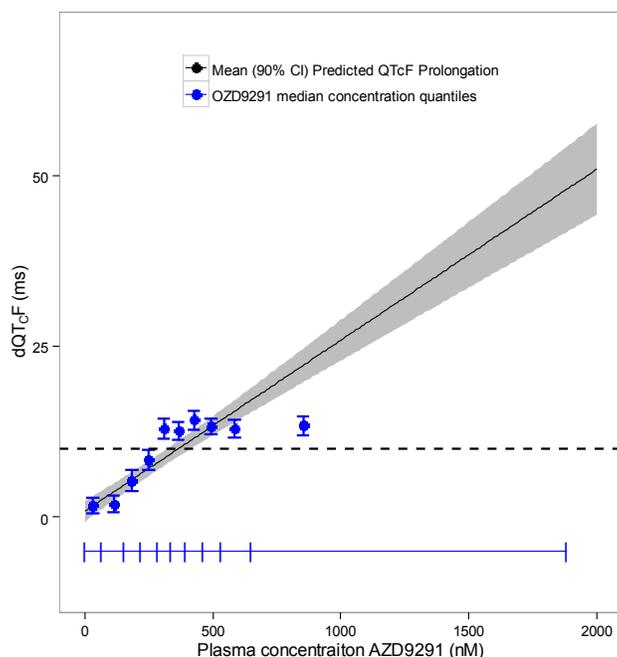


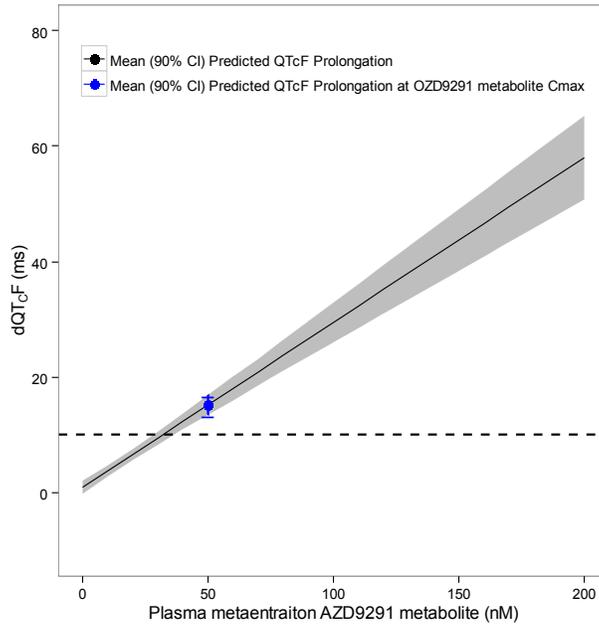
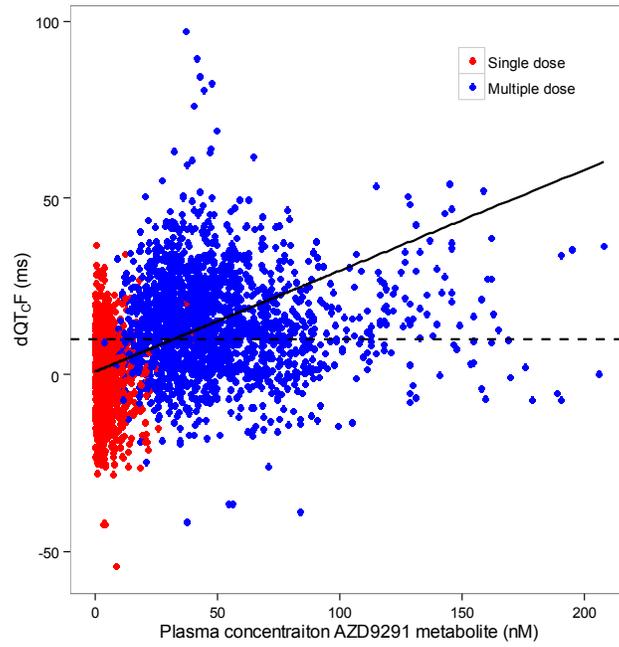
Table 22 summarizes the result for AZD9291 concentration-  $\Delta$ QTcF analysis from linear regression model. The slope of exposure-response relationship is significantly positive. The mean increase in QTcF adjusted for timematched baseline was estimated to be 0.25 milliseconds per 10-nM increase in AZD9291 plasma levels with a 2-sided 90% confidence interval of 0.219 to 0.289 ms.

**Table 22: Parameter Estimates from the Linear Mixed Effects Model for AZD9291**

Parameter (unit)	Estimate (90% CI)	BSV
Intercept (ms)	0.79 (-0.48-2.06)	73.1
Slope (ms/nM)	0.0251 (0.0219-0.0283)	0.0004

Since the two metabolites have parallel concentration profiles (Figure 1), only one metabolite was further tested by reviewer for the exposure-QTc relationship.

**Figure 8:  $\Delta$ QTcF vs. AZD9291 Metabolite Concentration**



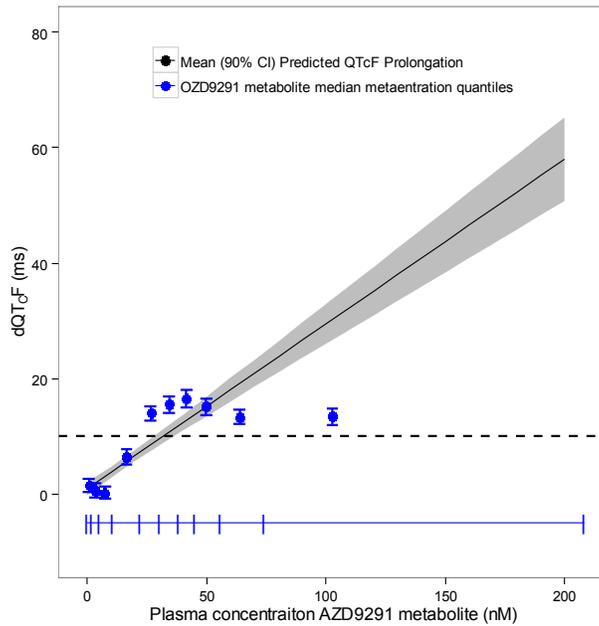


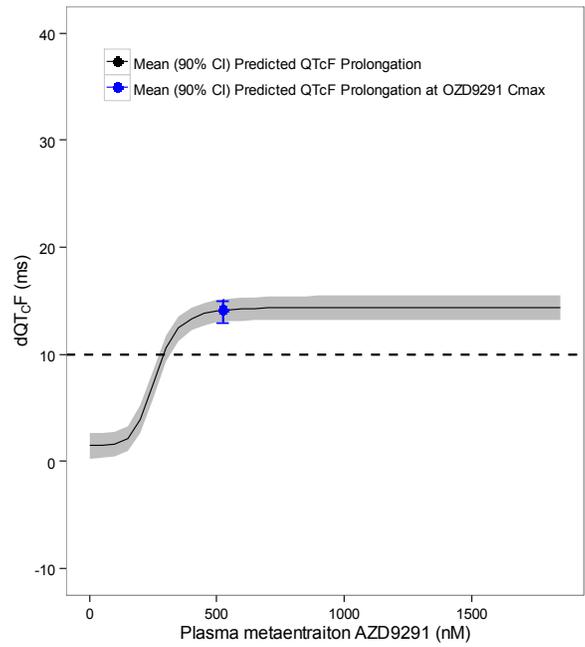
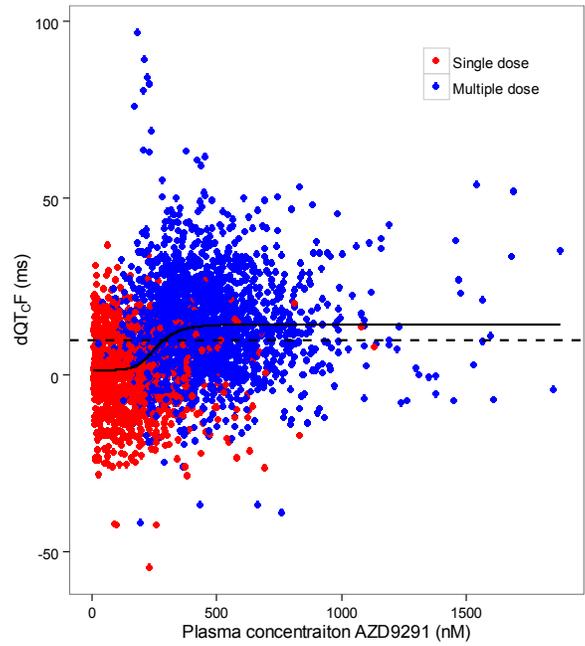
Table 23 summarizes the result for AZD9291 metabolite concentration-  $\Delta$ QTcF analysis from linear regression model. The slope of exposure-response relationship is significantly positive. The mean increase in QTcF adjusted for timematched baseline was estimated to be 2.9 ms per 10-nM increase in AZD9291 metabolite plasma levels with a 2-sided 90% confidence interval of 0.254 to 0.317 ms.

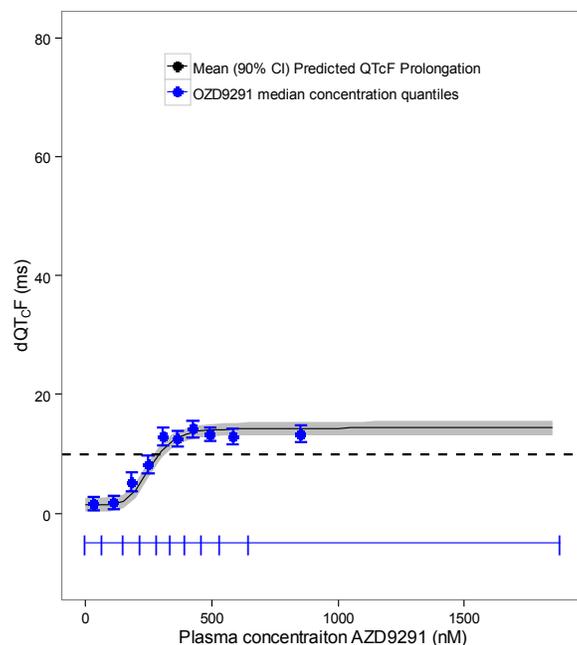
**Table 23: Parameter estimates from the linear mixed effects model for AZD9291 metabolite**

Parameter (unit)	Estimate (90% CI)	BSV
Intercept (ms)	0.88 (-0.07-1.83)	41.8
Slope (ms/nM)	0.286 (0.254-0.317)	0.05

The non-linear mixed effect model was also investigated by reviewer. Since the concentration of AZD9291 is also paralleled to that of metabolites, only AZD9291 concentration is tested. The result is shown in Figure 9.

**Figure 9:  $\Delta$ QTcF vs. AZD9291 Concentration**





The result is shown in Table 24, a maximum effect on  $\Delta\text{QTcF}$  was estimated to be 12.9 ms with a 2-sided 90% CI of 11.6 to 14.2 ms.

**Table 24: Parameter estimates from the linear mixed effects model for AZD9291**

Parameter (unit)	Estimate (90% CI)	BSV
$E_0$ (ms)	1.46 (0.26-2.66)	52.2
$E_{\max}$ (ms)	12.9 (11.6-14.2)	<0.0001
$EC_{50}$ (nM)	258 (240-275)	<0.0001
$\gamma$	5.92 (3.85-7.99)	<0.0001

The result shows that non-linear mixed effect model ( $E_{\max}$ ) model is able to describe the exposure-response relationship better than the linear mixed effect model. Based on the non-linear mixed effect model, the  $\Delta\text{QTcF}$  is reaching the plateau after AZD9291 concentration is higher than 500 nM and the maximum effect is around 13 ms.

## **5.4 CLINICAL ASSESSMENTS**

### **5.4.1 Safety assessments**

None of the events identified to be of clinical importance per the ICH E 14 guidelines (i.e., syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

### **5.4.2 ECG assessments**

Overall ECG acquisition and interpretation in this study appears acceptable.

### **5.4.3 PR and QRS Interval**

There is no clinically relevant effect on PR or QRS.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	80 mg daily for the treatment of patients with (b) (4) metastatic NSCLC whose disease has progressed on previous EGFR TKI therapy (b) (4)	
Maximum tolerated dose	MTD not identified, 240 mg daily maximum dose investigated, with no dose-limiting toxicities reported at this dose	
Principal adverse events	215/232 (93%) patients have reported an adverse event (AE) during the study. Less than 25% of adverse events were CTCAE grade 3 or higher. The most common adverse events have been diarrhoea, rash (grouped terms) and nausea, occurring in 39%, 36% and 18% of patients respectively. There have been 10 patients (4%) who discontinued study treatment due to adverse events and 4 patients (2%) who required dose reductions due to adverse event. There have been 44 patients (19%) who required dose interruptions due to AEs. There were no dose limiting toxicities reported in the 28-day DLT evaluation period in the dose escalation cohorts at any dose level.	
Maximum dose tested	Single Dose	240 mg daily
	Multiple Dose	240 mg daily maximum duration is 283 days as of 7 <sup>th</sup> August 2014
Exposures Achieved at Maximum Tested Dose	Single Dose	C <sub>max</sub> : 458.4 nM (77.7 %) and AUC: 29810 nM.h (73.2) <sup>a,b</sup>
	Multiple Dose	C <sub>max</sub> : 1460 nM (55.0 %) and AUC <sub>(0-24)</sub> : 27950 nM.h (59.0) <sup>a,b</sup>
Range of linear PK	20 - 240 mg single dose and once daily dosing based on visual assessment <sup>a</sup>	
Accumulation at steady state	4.48 (75.2%) once daily dosing <sup>a,b</sup>	
Metabolites	ADME study is ongoing and has not reported data. Two potentially active metabolites (AZ5104 and AZ7550) have been measured in the current clinical program and are present at approximately (b) (4), each of AZD9291 at steady-state based on AUC <sub>ss</sub> <sup>a</sup>	
Absorption	Absolute/Relative Bioavailability	Absolute Bioavailability study not performed. Relative bioavailability @ 20 mg dose in healthy volunteers showed the bioavailability of the capsule, solution and tablet formulations was similar: AZD9291 mean ratio (90% confidence interval): Tablet : Capsule of 1.04 (0.92 – 1.17) and 1.00 (0.86 - 1.15) for AUC and C <sub>max</sub> respectively. Solution : Capsule of 0.98 (0.85 – 1.13) and 0.96 (0.82 - 1.13) for AUC and C <sub>max</sub> respectively.
	Tmax	<ul style="list-style-type: none"> <li>• AZD9291</li> <li>Single dose 6 (3-24) hours<sup>a</sup></li> <li>Multiple dose 6 (1-24) hours<sup>a</sup></li> <li>• AZ5104</li> <li>Single dose 24 (4-72) hours<sup>a</sup></li> <li>Multiple dose 6 (0-24) hours<sup>a</sup></li> <li>• AZ7550</li> <li>Single dose 24 (6-72) hours<sup>a</sup></li> </ul>

		Multiple dose 8 (0-24) hours <sup>a</sup>
Distribution	Vd/F or Vd	$V_z/F = 1503 \text{ L (51.3)}^a$
	% bound	To date it has not been possible to determine the plasma protein binding of AZD9291 due to instability in plasma.
Elimination	Route	ADME study is ongoing and has not reported data, elimination is expected to be mainly hepatic (metabolic)
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• AZD9291: 55.06 hours (44.0%)<sup>a</sup></li> <li>• AZ5104: 48.93 hours (19.1%)<sup>c</sup></li> <li>• AZ7550: 72.98 hours (19.2%)<sup>c</sup></li> </ul>
	CL/F or CL	$CL/F = 20.27 \text{ L/h (54.5)}^a$ $CL_{ss}/F = 17.63 \text{ L/h (84.9)}^a$
Intrinsic Factors	Age	Based on visual assessment there is no suggestion of an age impact on AZD9291 exposure
	Sex	Based on visual assessment there is no suggestion of a gender impact on AZD9291 exposure
	Race	Visual inspection suggests that the PK of AZD9291 is consistent in Asian and non-Asian patients
	Hepatic & Renal Impairment	Not yet studied
Extrinsic Factors	Drug interactions	Not yet studied
	Food Effects	Not yet studied at proposed therapeutic dose
Expected High Clinical Exposure Scenario	Co-administration with strong CYP3A4 inhibitors and/or in patients with hepatic dysfunction is likely to lead to increased exposure	
Preclinical Cardiac Safety	<p>AZD9291 and its two metabolites, AZ5104 and AZ7550, inhibited the function of the hERG channel in vitro with IC<sub>50</sub> values of 0.69 μM (GLP assay), 17.48 μM and &gt;33 μM (non-GLP assay for the metabolites), respectively.</p> <p>In the GLP dog cardiovascular study (study number 1352ZD), administration of single oral doses of AZD9291 (0, 6, 20 and 60 mg/kg) to conscious telemetered dogs was associated with marginal differences in QTcR (up to 7% increase) and heart rate (up to 20% decrease) compared to the vehicle control. These changes were transient, not dose-related and are considered to be of limited biological significance: therefore 60 mg/kg was considered to be the NOAEL. There were no notable effects on cardiovascular parameters in the GLP repeat dose toxicity studies. In a non-GLP investigative study in the anaesthetized guinea pig (study number 0264SG), intravenous infusion of AZD9291 was associated with increases in the QTcB interval at 40 mg/kg (no changes in QTcB present at the lower dose of 5 mg/kg). Since the magnitude of these QT changes were below the statistical power of this study and they were only seen at very high exposures in an anaesthetised model (AZD9291 group mean total plasma concentration of 22.87 μM at 40 mg/kg), these findings are considered to be of limited biological significance.</p>	
Clinical Cardiac Safety	<p>In Study D5160C00001 (AURA Phase I), as of 2 April 2014, 232 NSCLC patients (2<sup>nd</sup> line or greater) have been dosed with AZD9291 across a range of doses (20, 40, 80, 160, 240mg).</p> <p>Across the study, as of 2 April 2014, there have been 4 events of “elctrocardiogram QT prolonged” reported: 1 grade 1 event (1.4%) at 80mg, and 3 events (5%) at 160mg – 2 Grade 1 and 1 Grade 2, with none at other doses. These events were not associated with clinical symptoms and with no trend of increase in QT over time.</p>	

	<p>There have been two Grade 2 AEs of Atrial Fibrillation (1 at 40mg, 1 at 160mg). There have been no other post-dose cardiac adverse events, with no trend observed in LVEF or QTc, and no signal detected across the program to date.</p> <p>There have been 2 SAEs relating to reduced cardiac function in patients who had received AZD9291. Both of these events were at the 160 mg dose, above the recommended 80 mg dose being studied in the ongoing clinical program. These two events, described below, do not constitute a safety signal, and all safety data continue to be monitored across the program.</p> <ol style="list-style-type: none"> <li>1. A 39 year-old Chinese patient with medical history of thyroidectomy and hypocalcaemia started dosing with 160 mg AZD9291 in (b) (6), with a baseline LVEF measured at 54%. The patient suffered heart failure after 4 months dosing with AZD9291 (LVEF drop to 31%). The patient was discontinued from AZD9291 in (b) (6) with a slow recovery of LVEF observed (to 35% in (b) (6); 52% in (b) (6)). Prior history of hypocalcaemia offers an alternative explanation for these events.</li> <li>2. A 51 year-old Caucasian patient started dosing 160 mg AZD9291 in (b) (6). The patient suffered Takotsubo cardiomyopathy in (b) (6), one day after objective disease progression. Disease progression was considered to be the most likely cause of the event.</li> </ol> <p>In Study D5160C00001 (AURA Phase I), in US patients, LVEF data have been collected at baseline and every 12 weeks after first dose, and at discontinuation. As of 2 April 2014, there have been no LVEF decreases to below 50% and no absolute decreases of 10 percentage points or more.</p>
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- <sup>a</sup> D5160C00001, preliminary patient PK data is presented which was calculated using nominal sampling times is draft, unvalidated and subject to change. Data from (b) (4) (on behalf of AZ) analysis of 02 April 2014
- <sup>b</sup> Geometric mean
- <sup>c</sup> D5160C00005, preliminary healthy volunteer PK data is presented which was calculated using nominal sampling times is draft, unvalidated and subject to change. Data from (b) (4) (on behalf of AZ) analysis of 13 March 2014

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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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HUIFANG CHEN  
09/08/2015

QIANYU DANG  
09/08/2015

LUNING ZHUANG  
09/08/2015

JIANG LIU  
09/08/2015

MICHAEL Y LI  
09/08/2015

NORMAN L STOCKBRIDGE  
09/08/2015

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**LABL AND LABELING REVIEW**

Division of Medication Error Prevention and Analysis (DMEPA)  
Office of Medication Error Prevention and Risk Management (OMEPRM)  
Office of Surveillance and Epidemiology (OSE)  
Center for Drug Evaluation and Research (CDER)

**\*\*\* This document contains proprietary information that cannot be released to the public\*\*\***

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**Date of This Review:** September 8, 2015  
**Requesting Office or Division:** Division of Oncology Products 2 (DOP2)  
**Application Type and Number:** NDA 208065  
**Product Name and Strength:** Tagrisso (osimertinib) Tablet, 40 mg and 80 mg  
**Product Type:** Single Ingredient Product  
**Rx or OTC:** Rx  
**Applicant/Sponsor Name:** AstraZeneca Pharmaceuticals LP (AstraZeneca)  
**Submission Date:** June 5, 2015, July 2, 2015, and August 19, 2015  
**OSE RCM #:** 2015-450  
**DMEPA Primary Reviewer:** Otto L. Townsend, PharmD  
**DMEPA Team Leader:** Chi-Ming (Alice) Tu, PharmD

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## 1 REASON FOR REVIEW

As part of the NDA review process for Tagrisso, DOP2 requested that we review the proposed container labels and Prescribing Information for areas that may lead to medication errors.

## 2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A
Human Factors Study	C – N/A
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Other	F – N/A
Labels and Labeling	G

N/A=not applicable for this review

\*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

## 3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our review of the proposed PI found the preparation and administration instructions for patients with difficulty swallowing in (b) (4) should be retained in the Prescribing Information (PI) because this informs healthcare professionals or caregivers when caring for patients who cannot swallow the tablets whole.

The container labels submitted by AstraZeneca have issues that need to be addressed prior to approval of the NDA. These issues include:

- Do not contain the proposed proprietary name or the established name for the drug product. The Applicant will need to ensure final container labels contain the approved proprietary name Tagrisso and established name Osimertinib Tablets. The proprietary and established names should appear in the font style and size as illustrated on the submitted container label drafts.
- Contain a graphic that competes in prominence with the proprietary and established names
- Does not contain the finished dosage form (i.e., tablets) following the established name
- Sequential National Drug Codes (NDC) that are prone to error

## 4 CONCLUSION & RECOMMENDATIONS

The proposed prescribing information (PI) and container labels can be improved to promote the safe use of the product.

### 4.1 RECOMMENDATIONS FOR THE DIVISION

#### Prescribing Information

1. We note in the Filing Communication to AstraZeneca dated August 4, 2015, the Agency advised the removal of preparation and administration instructions for patients with difficulty swallowing in (b) (4). In response to the Agency, AstraZeneca conveyed that they would like to retain this information in (b) (4). These are important preparation and administration instructions that can inform healthcare professionals or caregivers when caring for patients who cannot swallow the tablets whole. We have seen postmarketing reports where patients or caregivers would incorrectly manipulate solid oral dosage forms in order to administer the drug to patients who cannot swallow solid dosage forms. Therefore, from a medication error prevention perspective, we recommend retention of these preparation and administration instructions for patients with difficulty swallowing as long as AstraZeneca has provided data to support the dispersion of the proposed drug in water. We defer to the Review Team on efficacy and safety evaluation of dispersing the proposed drug in water (e.g. absorption, etc.).
2. To maintain consistency with labeling recently approved for (b) (4), consider changing the missed dose statement in section 2.2 to read "If a dose of TAGRISSO is missed, (b) (4)"

### 4.2 RECOMMENDATIONS FOR ASTRAZENECA

We recommend the following changes to container labels be implemented prior to approval of this NDA:

1. Ensure final container labels contain both the approved proprietary and established names. The proprietary and established names should appear in the same font style and size as illustrated on the June 5, 2015 submitted container label drafts.
2. The graphic located to the left of the proprietary and established names on the Principal Display Panel (PDP) competes in prominence with both the proprietary and established names. Delete the graphic or decrease its size and relocate it so that it does not compete in prominence with the proprietary and established names.
3. Include the finished dosage form (i.e., tablets) in the established name.

4. Assigning National Drug Codes (NDC) with sequential drug product codes (middle digits) for different strengths of the same drug product do not adequately distinguish the products (e.g., 40 mg – 0310-1349-30 versus 80 mg – 0310-1350-30). To better differentiate National Drug Codes, we recommend changing the product codes (middle digits) so that they are not sequential.
5. Change the 'Usual Dose' Statement to read, "USUAL ADULT DOSAGE: See Prescribing Information"

6.



## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Tagrisso that AstraZeneca submitted on June 5, 2015 and August 19, 2015.

<b>Table 2. Relevant Product Information for Tagrisso</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Osimertinib
<b>Indication</b>	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.
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Tablets
<b>Strength</b>	40 mg and 80 mg
<b>Dose and Frequency</b>	80 mg orally once daily, with or without food.
<b>How Supplied</b>	Bottles of 30 tablets
<b>Storage</b>	25°C (77°F). Excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].
<b>Container Closure</b>	(b) (4) bottle made of white, high-density polyethylene (HDPE) (b) (4)

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>1</sup> along with postmarket medication error data, we reviewed the following Tagrisso labels and labeling submitted by Astra Zeneca.

- Container Labels (June 5, 2015)
- Prescribing Information (July 2, 2015 and August 19, 2015)

### **G.2 Label and Labeling Images**

#### Container Labels



(b) (4)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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<sup>1</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/  
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OTTO L TOWNSEND  
09/08/2015

CHI-MING TU  
09/08/2015

## RPM FILING REVIEW

(Including Memo of Filing Meeting)

**To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]**

Application Information		
NDA # 208065 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: Tagrisso Established/Proper Name: osimertinib Dosage Form: Tablet Strengths: 40 mg / 80 mg		
Applicant: AstraZeneca Pharmaceuticals LP Agent for Applicant (if applicable):		
Date of Application: June 5, 2015 Date of Receipt: June 5, 2015 Date clock started after UN: N/A		
PDUFA/BsUFA Goal Date: 02/05/2016		Action Goal Date (if different): 11/15/2015
Filing Date: 08/04/2015		Date of Filing Meeting: 07/06/2015
Chemical Classification (original NDAs only) : <input checked="" type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): For the treatment of patients with <span style="background-color: #cccccc; color: #cccccc;">(b) (4)</span> <span style="background-color: #cccccc; color: #cccccc;">(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.		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<b><i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i></b> <a href="http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499">http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499</a>		

Type of BLA	<input type="checkbox"/> 351(a) <input type="checkbox"/> 351(k)
<b>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</b>	
Review Classification:	<input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority
<b>The application will be a priority review if:</b>	<input type="checkbox"/> Pediatric WR <input type="checkbox"/> QIDP <input type="checkbox"/> Tropical Disease Priority Review Voucher <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher
<ul style="list-style-type: none"> <li>• <b>A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)</b></li> <li>• <b>The product is a Qualified Infectious Disease Product (QIDP)</b></li> <li>• <b>A Tropical Disease Priority Review Voucher was submitted</b></li> <li>• <b>A Pediatric Rare Disease Priority Review Voucher was submitted</b></li> </ul>	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)
<b>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</b>	

<input type="checkbox"/> Fast Track Designation <input checked="" type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input checked="" type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan Designation  <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC  Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies (FDCA Section 505B) <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
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Collaborative Review Division (if OTC product):

List referenced IND Number(s): IND 117879

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA and Action Goal dates correct in tracking system?  <b>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the established/proper and applicant names correct in tracking system?  <b>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name</b>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> <a href="http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm">http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</a> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Application Integrity Policy</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at:</i> <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<b>If yes, explain in comment column.</b>				
<b>If affected by AIP, has OC been notified of the submission?</b> <b>If yes, date notified:</b>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>User Fees</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i>	Payment for this application ( <i>check daily email from <a href="mailto:UserFeeAR@fda.hhs.gov">UserFeeAR@fda.hhs.gov</a></i> ): <input type="checkbox"/> Paid <input checked="" type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required			
<i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf</a>	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
<b>505(b)(2) (NDAs/NDA Efficacy Supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is the application a 505(b)(2) NDA? ( <i>Check the 356h form,</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

cover letter, and annotated labeling). <b>If yes</b> , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].		<input type="checkbox"/>	<input type="checkbox"/>		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<b>Check the Electronic Orange Book at:</b> <a href="http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm">http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</a>					
<b>If yes</b> , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i>					
<b>Exclusivity</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>	
Does another product (same active moiety) have orphan exclusivity for the same indication? <b>Check the Orphan Drug Designations and Approvals list at:</b> <a href="http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm">http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm</a>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
<b>If another product has orphan exclusivity</b> , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
<b>NDAs/NDA efficacy supplements only:</b> Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>If yes</b> , # years requested: 5 year					
<b>Note:</b> An applicant can receive exclusivity without requesting it;					

<i>therefore, requesting exclusivity is not required.</i>				
<b>NDAs only:</b> Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>If yes,</b> did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)?  <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>BLAs only:</b> Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act?  <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</i>  <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

<b>Format and Content</b>				
<i>Do not check mixed submission if the only electronic component is the content of labeling (COL).</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic <input type="checkbox"/> Mixed (paper/electronic)			
	<input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
<b>If mixed (paper/electronic) submission,</b> which parts of the application are submitted in electronic format?				
<b>Overall Format/Content</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>If electronic submission,</b> does it follow the eCTD guidance? <sup>1</sup> <b>If not,</b> explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Index:</b> Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including:	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

<input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only)				
<b>If no, explain.</b>				
<b>BLAs only:</b> Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If yes, BLA #</b>				
<b>Forms and Certifications</b>				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
<b>Application Form</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
Are all establishments and their registration numbers listed on the form/attached to the form?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Patent Information (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Financial Disclosure</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		The current information in DARRTS cannot be opened. AZ will submit an amendment to the NDA
<i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i>				
<i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>				
<b>Clinical Trials Database</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i>				

<i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>				
<b>Debarment Certification</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a correctly worded Debarment Certification included with authorized signature?  <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, both the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i>  <i>Note: Debarment Certification should use wording in FD&amp;C Act Section 306(k)(1) i.e., “[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.” Applicant may not use wording such as, “To the best of my knowledge...”</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Field Copy Certification (NDAs/NDA efficacy supplements only)</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b>For paper submissions only:</b> Is a Field Copy Certification (that it is a true copy of the CMC technical section) included?  <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i>  <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Controlled Substance/Product with Abuse Potential</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)?  <i>If yes, date consult sent to the Controlled Substance Staff:</i>  <u>For non-NMEs:</u> <i>Date of consult sent to Controlled Substance Staff:</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>Pediatrics</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
<b><u>PREA</u></b> Does the application trigger PREA?  <i>If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting<sup>2</sup></i>  <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		Orphan Designation was granted on September 4, 2014.

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027829.htm>

Version: 6/15/2015

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<i>(including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver &amp; deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>				
<b>If the application triggers PREA</b> , is there an agreed Initial Pediatric Study Plan (iPSP)?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>If required by the agreed iPSP</b> , are the pediatric studies outlined in the agreed iPSP completed and included in the application?  <i>If no, may be an RTF issue - contact DPMH for advice.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b><u>BPCA:</u></b>  Is this submission a complete response to a pediatric Written Request?  <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)<sup>3</sup></i>	<input type="checkbox"/>	<input type="checkbox"/>		
<b>Proprietary Name</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a proposed proprietary name submitted?  <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>REMS</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is a REMS submitted?  <i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<b>Prescription Labeling</b>	<input type="checkbox"/> <b>Not applicable</b>			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input checked="" type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is Electronic Content of Labeling (COL) submitted in SPL format?  <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<sup>3</sup>

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/PediatricandMaternalHealthStaff/ucm027837.htm>

Is the PI submitted in PLR format? <sup>4</sup>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<b>If PI not submitted in PLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015:</b> Is the PI submitted in PLLR format? <sup>5</sup>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<b>For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format</b> , was a waiver or deferral requested before the application was received or in the submission? <b>If requested before application was submitted</b> , what is the status of the request?  <i>If no waiver or deferral, request applicant to submit labeling in PLR/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>OTC Labeling</b>	<input checked="" type="checkbox"/> <b>Not Applicable</b>			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Is electronic content of labeling (COL) submitted?  <i>If no, request in 74-day letter.</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

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<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging sent to OSE/DMEPA?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<b>Other Consults</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
<b>Meeting Minutes/SPAs</b>	<b>YES</b>	<b>NO</b>	<b>NA</b>	<b>Comment</b>
End-of Phase 2 meeting(s)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		BT initial comprehensive meeting was held on 10/02/2014
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? <b>Date(s):</b> 12/09/2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? <b>Date(s):</b>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

**MEMO OF FILING MEETING**

**DATE:** July 6, 2015

**BACKGROUND:** This NDA proposes the use of osimertinib tablets 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. Fast track designation, under IND 117879, was granted on November 6, 2013 and a breakthrough therapy designation for this indication was granted on April 16, 2014. An interdisciplinary pre-NDA meeting was held on December 9, 2014 where an agreement on the content and format of the proposed NDA was reached. On October 28, 2014, AstraZeneca submitted a request for rolling submission and this request, for submitting portions of the proposed application, was amended on December 16, 2014. FDA accepted the request and their plan for submitting portions of the proposed application on January 16, 2015. The first submission, containing nonclinical, CMC and Clinical portion of the NDA was received on January 26, 2015, the second piece containing clinical information was received on April 30, 2015 and the last piece, containing clinical and CMC information was received on June 5, 2015.

**Summary of Discussion:**

- CMC stated that facility inspection is not needed for this application.
- No filing issues were discussed or identified by any of the review divisions during this meeting; however, although not potential filing issues, CMC would like to include comment(s) in the Day 60 communications (review issues).

**REVIEW TEAM:**

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Ingrid Fan, Mimi Biabile covered filing meeting	Y
	CPMS/TL:	Melanie Pierce	Y
Cross-Discipline Team Leader (CDTL)	Gideon Blumenthal, M.D.		Y
Division Director/Deputy	Patricia Keegan, M.D.		Y
Office Director/Deputy	Richard Pazdur, M.D.		N
Clinical	Reviewer:	Sean Khozin, M.D.	N
	Reviewer:	Chana Weinstock, M.D.	Y
	TL:	Gideon Blumenthal, M.D.	Y
Clinical Pharmacology	Reviewer:	Jun Yang, Ph.D.	Y

	TL:	Hong Zhao, Ph.D.	Y
• Genomics	Reviewer:	Sarah Dorff, Ph.D.,	Y
	TL:	Rosane Charlab Orbach, Ph.D.	Y
• Pharmacometrics	Reviewer:	Hongshan Li, Ph.D.	Y
	TL:	Yaning Wang, Ph.D.	Y
Biostatistics	Reviewer:	Joyce Cheng, Ph.D.	Y
	TL:	Kun He, Ph.D.	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Shawn Weis, Ph.D.	Y
	TL:	Whitney Helms, Ph.D.	Y
Product Quality (CMC) Review Team:	ATL:	Olen Stephens, Ph.D.	Y
	RBPM:	Rabiya Laiq	Y
• Drug Substance	Reviewer:	Charles Jewell, Ph.D.	Y
• Drug Product	Reviewer:	Mike Adams, Ph.D.	Y
• Process	Reviewer:	Ying Zhang, Ph.D.	Y
• Microbiology	Reviewer:		
• Facility	Reviewer:		
• Biopharmaceutics	Reviewer:	Gerlie Gieser, Ph.D.	Y
• Immunogenicity	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)		Liang Zhou, Ph.D.	Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:	Nathan Caulk, M.S.	N
	TL:	Barbara Fuller	
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:	Nazia Fatima, Pharm.D.	Y
	TL:	Jessica Clerk Derenick	N
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:	Otto Townsend	Y
	TL:	Alice (Chi-Ming) Tu	N
OSE/DRISK (REMS)	Reviewer:	Carolyn L Yancey	Y
	TL:	Naomi Redd	N
Bioresearch Monitoring (OSI)	Reviewer:	Lauren Iacono-Connors, Ph.D.	Y
	TL:	Susan Thompson	

Other reviewers/disciplines		
<ul style="list-style-type: none"> <li><b>Discipline</b></li> </ul> <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:	
	TL:	
Other attendees	CDR Latonia Ford, MBA, BSN, RN, OSE RPM	Y
	Shaily Arora, Pharm.D. OSE/DPV	Y
		Y
	Karen Bijwaard , CDRH	Y
	*For additional lines, right click here and select "insert rows below"	

**FILING MEETING DISCUSSION:**

<p><b>GENERAL</b></p> <ul style="list-style-type: none"> <li>505(b)(2) filing issues: <ul style="list-style-type: none"> <li>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</li> <li>Did the applicant provide a scientific "bridge" demonstrating the relationship between the proposed product and the referenced product(s)/published literature?</li> </ul> </li> </ul> <p>Describe the scientific bridge (e.g., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</p>	<input checked="" type="checkbox"/> Not Applicable  <input type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Per reviewers, are all parts in English or English translation?</li> </ul> <p><b>If no</b>, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Electronic Submission comments</li> </ul> <p><b>List comments:</b></p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> No comments

<p><b>CLINICAL</b></p> <p><b>Comments:</b> No comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical study site(s) inspections(s) needed?</li> </ul> <p><b>If no, explain:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>Advisory Committee Meeting needed?</li> </ul> <p><b>Comments:</b></p> <p><i>If no, for an NME NDA or original BLA, include the reason. For example:</i></p> <ul style="list-style-type: none"> <li><i>this drug/biologic is not the first in its class</i></li> <li><i>the clinical study design was acceptable</i></li> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>	<input type="checkbox"/> YES Date if known: <input checked="" type="checkbox"/> NO <input type="checkbox"/> To be determined Reason: <ul style="list-style-type: none"> <li><i>the application did not raise significant safety or efficacy issues</i></li> <li><i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i></li> </ul>
<ul style="list-style-type: none"> <li>If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b>CONTROLLED SUBSTANCE STAFF</b></p> <ul style="list-style-type: none"> <li>Abuse Liability/Potential</li> </ul> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CLINICAL MICROBIOLOGY</b></p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p><b>CLINICAL PHARMACOLOGY</b></p> <p><b>Comments:</b> No comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> <li>Clinical pharmacology study site(s) inspections(s) needed?</li> </ul>	<input type="checkbox"/> YES <input checked="" type="checkbox"/> NO
<p><b>BIOSTATISTICS</b></p> <p><b>Comments:</b> No comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</b></p> <p><b>Comments:</b> No comments</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b>PRODUCT QUALITY (CMC)</b></p> <p><b>Comments:</b> Comments to be included in the Day 60 letter</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE  <input type="checkbox"/> Review issues for 74-day letter
<p><b><u>New Molecular Entity (NDAs only)</u></b></p> <ul style="list-style-type: none"> <li>Is the product an NME?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Environmental Assessment</u></b></p> <ul style="list-style-type: none"> <li>Categorical exclusion for environmental assessment (EA) requested?</li> </ul> <p><b>If no,</b> was a complete EA submitted?</p> <p><b>Comments:</b></p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO  <input type="checkbox"/> YES <input type="checkbox"/> NO
<p><b><u>Facility Inspection</u></b></p> <ul style="list-style-type: none"> <li>Establishment(s) ready for inspection?</li> </ul> <p><b>Comments:</b> Not needed per Olen Stephens</p>	<input type="checkbox"/> Not Applicable  <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<p><b>Facility/Microbiology Review (BLAs only)</b></p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><b>CMC Labeling Review (BLAs only)</b></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p><b>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</b></p> <ul style="list-style-type: none"> <li>• Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application?</li> <li>• If so, were the late submission components all submitted within 30 days?</li> </ul>	<input type="checkbox"/> N/A <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• What late submission components, if any, arrived after 30 days?</li> </ul>	
<ul style="list-style-type: none"> <li>• Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all clinical sites included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> <li>• Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application?</li> </ul>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

## REGULATORY PROJECT MANAGEMENT

**Signatory Authority:** Richard Pazdur, M.D.

**Date of Mid-Cycle Meeting** (for NME NDAs/BLAs in “the Program” PDUFA V): September 2, 2015

**21<sup>st</sup> Century Review Milestones (see attached)** (listing review milestones in this document is optional):

- Send proposed labeling/PMR/PMC/REMS to applicant: end of Sept. or early Oct.
- Late Cycle Meeting: Oct. 13
- Wrap-up Meeting: Oct. 20

**Comments:** This application is under expedited review.

## REGULATORY CONCLUSIONS/DEFICIENCIES

<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	<p>The application, on its face, appears to be suitable for filing.</p> <p><u>Review Issues:</u></p> <p><input type="checkbox"/> No review issues have been identified for the 74-day letter.  <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter.</p> <p><u>Review Classification:</u></p> <p><input type="checkbox"/> Standard Review  <input checked="" type="checkbox"/> Priority Review cl</p>

## ACTION ITEMS

<input checked="" type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input checked="" type="checkbox"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input checked="" type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input checked="" type="checkbox"/>	Update the PDUFA V DARRTS page (for applications in the Program)

<input type="checkbox"/>	Other
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Annual review of template by OND ADRAAs completed: September 2014

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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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INGRID Y FAN  
08/04/2015

MELANIE B PIERCE  
08/04/2015

# REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

**Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements**

**Application:** NDA 208065

**Application Type:** New NDA

**Name of Drug/Dosage Form:** Osimertinib tablets, 40 mg and 80 mg

**Applicant:** AstraZeneca Pharmaceuticals LP (AstraZeneca)

**Receipt Date:** June 5, 2015

**Goal Date:** February 5, 2016

## 1. Regulatory History and Applicant's Main Proposals

This NDA proposes the use of osimertinib tablets 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. Fast track designation, under IND 117879, was granted on November 6, 2013 and a breakthrough therapy designation for this indication was granted on April 16, 2014. An interdisciplinary pre-NDA meeting was held on December 9, 2014 where an agreement on the content and format of the proposed NDA was reached. On October 28, 2014, AstraZeneca submitted a request for rolling submission and this request, for submitting portions of the proposed application, was amended on December 16, 2014. FDA accepted the request and AstraZeneca's plan for submitting portions of the proposed application on January 16, 2015. The first submission, containing nonclinical, CMC and Clinical portion of the NDA was received on January 26, 2015, the second piece containing clinical information was received on April 30, 2015 and the last piece, containing clinical and CMC information was received on June 5, 2015.

## 2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

## 3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix. In addition, several labeling content issues were identified by Dr. Jennie Chang. These issues are described in track changes and using the track changes "comment" function within the text of the attached PI.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 60-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by August 14, 2015. The resubmitted PI will be used for further labeling review.

# Selected Requirements of Prescribing Information

## Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

## Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

### HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.  
*Comment: No comments.*
- YES** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement.  
Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.  
*Comment: No comments.*
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.  
*Comment: No comments.*
- YES** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.  
*Comment: No comments.*
- YES** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.  
*Comment: No comments.*
- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.  
*Comment: No comments.*
- NO** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required

## Selected Requirements of Prescribing Information

• <b>Initial U.S. Approval</b>	Required
• <b>Boxed Warning</b>	Required if a BOXED WARNING is in the FPI
• <b>Recent Major Changes</b>	Required for only certain changes to PI*
• <b>Indications and Usage</b>	Required
• <b>Dosage and Administration</b>	Required
• <b>Dosage Forms and Strengths</b>	Required
• <b>Contraindications</b>	Required (if no contraindications must state “None.”)
• <b>Warnings and Precautions</b>	Not required by regulation, but should be present
• <b>Adverse Reactions</b>	Required
• <b>Drug Interactions</b>	Optional
• <b>Use in Specific Populations</b>	Optional
• <b>Patient Counseling Information Statement</b>	Required
• <b>Revision Date</b>	Required

\* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

**Comment:** *Product title is missing.*

### HIGHLIGHTS DETAILS

#### Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: “**HIGHLIGHTS OF PRESCRIBING INFORMATION**”.

**Comment:** *No comments.*

#### Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: “**These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).**” The name of drug product should appear in UPPER CASE letters.

**Comment:** *Insert name of drug product.*

#### Product Title in Highlights

- NO** 10. Product title must be **bolded**.

**Comment:** *Product title is missing.*

#### Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement “**Initial U.S. Approval:**” followed by the **4-digit year**.

**Comment:** *No comments.*

#### Boxed Warning (BW) in Highlights

- N/A** 12. All text in the BW must be **bolded**.

**Comment:** *N/A.*

- N/A** 13. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”). The BW heading should be centered.

## Selected Requirements of Prescribing Information

**Comment:** N/A

- N/A** 14. The BW must always have the verbatim statement “*See full prescribing information for complete boxed warning.*” This statement should be centered immediately beneath the heading and appear in *italics*.

**Comment:** N/A

- N/A** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

**Comment:** N/A

### Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

**Comment:** N/A

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

**Comment:** N/A

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

**Comment:** N/A

### Indications and Usage in Highlights

- NO** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

**Comment:** *The product title and pharmacologic class are missing*

### Dosage Forms and Strengths in Highlights

- YES** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

**Comment:** *No comments.*

### Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

**Comment:** *No comments.*

## Selected Requirements of Prescribing Information

### Adverse Reactions in Highlights

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

**Comment:** *No comments.*

### Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

**Comment:** *No comments.*

### Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

**Comment:** *No comments.*

## Selected Requirements of Prescribing Information

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### Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.  
***Comment:** No comments.*
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.  
***Comment:** No comments.*
- N/A** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.  
***Comment:** N/A*
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.  
***Comment:** No comments.*
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].  
***Comment:** No comments.*
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.  
***Comment:** No comments.*
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “\*Sections or subsections omitted from the full prescribing information are not listed.”  
***Comment:** No comments.*

## Selected Requirements of Prescribing Information

### Full Prescribing Information (FPI)

#### FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

<b>BOXED WARNING</b>
<b>1 INDICATIONS AND USAGE</b>
<b>2 DOSAGE AND ADMINISTRATION</b>
<b>3 DOSAGE FORMS AND STRENGTHS</b>
<b>4 CONTRAINDICATIONS</b>
<b>5 WARNINGS AND PRECAUTIONS</b>
<b>6 ADVERSE REACTIONS</b>
<b>7 DRUG INTERACTIONS</b>
<b>8 USE IN SPECIFIC POPULATIONS</b>
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
<b>9 DRUG ABUSE AND DEPENDENCE</b>
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
<b>10 OVERDOSAGE</b>
<b>11 DESCRIPTION</b>
<b>12 CLINICAL PHARMACOLOGY</b>
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
<b>13 NONCLINICAL TOXICOLOGY</b>
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
<b>14 CLINICAL STUDIES</b>
<b>15 REFERENCES</b>
<b>16 HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>17 PATIENT COUNSELING INFORMATION</b>

**Comment:** No comments.

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

**Comment:** No comments.

## Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

**Comment:** N/A

### FULL PRESCRIBING INFORMATION DETAILS

#### FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

**Comment:** *The font for this statement is in Arial while the rest of the FPI is in Times New Roman. A comment to be sent to sponsor while labeling review.*

#### BOXED WARNING Section in the FPI

- N/A** 36. In the BW, all text should be **bolded**.

**Comment:** N/A

- N/A** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

**Comment:** N/A

#### CONTRAINDICATIONS Section in the FPI

- YES** 38. If no Contraindications are known, this section must state “None.”

**Comment:** *No comments.*

#### ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

**Comment:** *No comments.*

- N/A** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

**Comment:** *No comments.*

#### PATIENT COUNSELING INFORMATION Section in the FPI

**YES**

## Selected Requirements of Prescribing Information

41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

**Comment:** *No comments.*

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

**Comment:** *No comments.*

# Selected Requirements of Prescribing Information

## Appendix A: Format of the Highlights and Table of Contents

### HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]  
Initial U.S. Approval: [year]

**WARNING: [SUBJECT OF WARNING]**

*See full prescribing information for complete boxed warning.*

- [text]
- [text]

### RECENT MAJOR CHANGES

[section (X.X)] [m/year]  
[section (X.X)] [m/year]

### INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

### DOSAGE AND ADMINISTRATION

- [text]
- [text]

### DOSAGE FORMS AND STRENGTHS

[text]

### CONTRAINDICATIONS

- [text]
- [text]

### WARNINGS AND PRECAUTIONS

- [text]
- [text]

### ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### DRUG INTERACTIONS

- [text]
- [text]

### USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

### FULL PRESCRIBING INFORMATION: CONTENTS\*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

\*Sections or subsections omitted from the full prescribing information are not listed.

20 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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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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MISSIRATCH BIABLE  
07/30/2015